

# Association of Hospital Procedure Volume and Outcomes in Patients with Colon Cancer at High Risk for Recurrence

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**Background:** Studies that use registry data have demonstrated superior long-term overall survival after curative surgical resection of colon cancer at hospitals where the volume of such surgeries is high. However, because such administrative data lack information on cancer recurrence, the true nature of this relation remains uncertain.

**Objective:** To determine whether hospital procedure volume predicts long-term outcomes of colon cancer surgery.

**Design:** Nested cohort study within a randomized clinical trial.

**Setting:** Intergroup 0089 national adjuvant colon cancer study conducted between 1988 and 1992.

**Patients:** 3161 patients with high-risk stage II and stage III colon cancer.

**Measurements:** Overall survival and recurrence-free survival, by hospital procedure volume as defined by Medicare claims data.

**Results:** With a median follow-up of 9.4 years, 5-year overall survival significantly differed across tertiles of hospital procedure volume (63.8% for patients who had resection at low-volume

hospitals compared with 67.3% at high-volume hospitals;  $P = 0.04$ ). After adjustment for other predictors of colon cancer outcome, the hazard ratio for overall mortality in patients treated at low-volume centers was 1.16 (95% CI, 1.03 to 1.32). However, the risk for cancer recurrence was not associated with hospital procedure volume. Five-year recurrence-free survival was 63.9% for patients who had resection at low-volume hospitals compared with 63.0% at high-volume hospitals (adjusted hazard ratio, 1.03 [CI, 0.89 to 1.18]). These findings did not materially change after stratification by other potential demographic and clinical predictors of outcome.

**Conclusions:** According to prospectively recorded data from a large clinical trial, patients whose colon cancer was resected at low-volume hospitals experienced a higher risk for long-term mortality; however, this increased mortality was not attributable to differences in colon cancer recurrences.

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Hospital procedure volume has been used as a proxy for institutional proficiency (1) and has been studied extensively as a predictor of clinical outcomes in complex medical and surgical procedures (1–15). Outcomes after less complex cancer surgeries, including operations for colon and breast cancer, also seem to be improved at high-volume centers (12, 13, 16, 17). Most of these studies have relied on administrative claims-based sources. Such studies, which rely on administrative data and even hybrid sources, such as the linkage of Medicare and the Surveillance, Epidemiology, and End Results (SEER) data, lack detailed information about patient and tumor characteristics. Moreover, because data on cancer relapse are often not available, it remains unclear whether the influence of lower hospital procedure volume on survival is directly related to a higher rate of cancer recurrence.

A recent analysis of Medicare beneficiaries in the SEER registry found diminished long-term survival among patients who underwent colon cancer surgery at low-volume hospitals (13). This survival difference persisted after adjustment for perioperative mortality and the use of postoperative adjuvant chemotherapy. The authors concluded that, after adjustment for other factors, colon cancer surgery at high-volume hospitals improves colon cancer outcomes, possibly because of greater oncologic surgical expertise at high-volume surgical hospitals. However, because complete data on cancer recurrence were not available in

the SEER–Medicare database, this study could not address whether hospital procedure volume predicted any differences in colon cancer recurrence. Consequently, the underlying mechanism for the observed volume–outcome relation in colon cancer remained uncertain.

We therefore used data from a large randomized trial of patients with stage II and stage III colon cancer to examine the influence of hospital procedure volume on long-term outcome. Because patients were identified for this trial 4 to 6 weeks after colon cancer surgery, surgery was performed before study enrollment at various hospitals that had a wide range of surgical volume. Since all patients in this trial received standard postoperative adjuvant chemotherapy and follow-up, we could isolate the influence of hospital surgical volume beyond other potential confounding variables. Finally, because data on cancer recurrence and cancer-specific survival were available for all patients, we examined any differences in cancer recurrence rates across hospital surgical volume.

## METHODS

### Study Sample

Patients for this analysis were drawn from the National Cancer Institute–sponsored Intergroup 0089 (INT-0089) randomized trial of adjuvant chemotherapy for stage II and stage III colon cancer, which was conducted be-

**Context**

Evidence suggests that long-term survival is worst when patients have colorectal cancer surgery at hospitals that perform a small volume of these procedures. However, these studies have not examined cancer-specific outcomes.

**Contribution**

Among patients in a randomized trial of adjuvant chemotherapy, lower long-term survival at low-volume hospitals was not due to higher rates of colorectal cancer recurrence or cancer-specific death.

**Implications**

Poor long-term survival in hospitals with low rates of colorectal cancer surgery may be due to the poor general health of populations cared for at low-volume hospitals rather than to low-quality cancer surgery.

—The Editors

tween August 1988 and July 1992 (18, 19). The study had a nationwide enrollment of 3759 patients, with participation by institutions affiliated with 1 of the following cooperative groups: Eastern Cooperative Oncology Group (ECOG; the coordinating group), Southwest Oncology Group (SWOG), and Cancer and Leukemia Group B (CALGB).

Eligible patients had histologically proven adenocarcinoma of the colon that had been resected en bloc without evidence of residual gross or microscopic disease. The inferior margin of the primary tumor must have been above the peritoneal reflection. Patients were eligible if there was evidence of spread of tumor to regional lymph nodes (Dukes C or tumor, node, metastasis [TNM] classification system stage III tumor). In addition, patients with penetration of the tumor into or through the bowel serosa without regional lymph node spread (Dukes B2 or TNM stage II) were eligible if there was evidence of bowel obstruction, bowel perforation, peritoneal implants, or adherence to or invasion of adjacent organs by the primary tumor.

All patients were required to give written informed consent and were randomly assigned between 21 and 35 days after surgery. Patients must have had an ECOG performance status of 2 or less (ambulatory for at least 50% of the day or better) (20). Patients were also required to have adequate bone marrow, renal, and hepatic function (leukocyte count  $\geq 3.5 \times 10^9$  cells/L; platelet count  $\geq 100 \times 10^9$  cells/L; serum creatinine level  $\leq 3$  times the upper limit of normal; and bilirubin, aspartate aminotransferase, and alkaline phosphatase levels  $\leq 3$  times the upper limit of normal). Pregnant or lactating women were not eligible for enrollment. In addition, patients with a concurrent malignant disease or any malignant tumor within the previous 3 years (except for superficial squamous- or basal-cell carcinoma of the skin or in situ carcinoma of the cervix) were

ineligible. Patients receiving any concurrent radiation or chemotherapy, previous radiation or chemotherapy for the cancer present at enrollment, or previous exposure to 5-fluorouracil were also not eligible for entry into this trial. All participating centers were required to obtain institutional review board approval before the start of the trial. The treatment groups for the trial have been previously described (18, 19, 21, 22).

For our analysis, study staff, who were blinded to patient outcome, reviewed the operative reports of all eligible patients (198 patients in the treatment trial were ineligible and excluded from this cohort; reasons for exclusion have been previously described [21]) to identify the hospital where primary colon cancer surgery was performed. We also excluded patients who were missing sufficient information to identify the hospital of surgery ( $n = 51$ ). In addition, because hospital procedure volume rankings were derived from U.S. Medicare claims, we excluded patients who underwent surgery at a Veterans Administration or military hospital ( $n = 303$ ) or a hospital outside of the United States ( $n = 46$ ). After these exclusions, 3161 patients were eligible for the analysis.

**Medicare Hospital Procedure Volume**

Using the U.S. Medicare claims database, we ranked hospitals by volume according to the number of primary colon cancer surgeries performed on all Medicare-enrolled patients between 1988 and 1993, the enrollment period inclusive of the clinical trial (13). Primary colon cancer surgeries were defined by using an International Classification of Diseases, 9th revision (ICD-9), diagnosis code of 153.x (colon cancer) or 154.x (rectal cancer) and an ICD-9 procedure code of either 45.7x or 45.8x (colon surgeries), or 48.4x, 48.5x, or 48.7x (rectal surgeries) for a particular hospitalization. Our results did not change when we used hospital volume rankings according to only colon cancer surgery (ICD-9 diagnosis code of 153.x and ICD-9 procedure code of either 45.7x or 45.8x), as the 2 rankings were highly correlated ( $r = 0.99$ ).

**Validation of Medicare Procedure Volume**

In previous studies, Medicare case volume was highly correlated with total hospital procedure volume (2). To validate our Medicare procedure volume rankings for colorectal cancer surgery, we used the Nationwide Inpatient Sample (NIS) database from 1988 to 1992. The NIS database consists of a random sample of 750 to 900 hospitals per year from 11 states, approximating a 20% sample of U.S. community hospitals. Using the NIS database, we identified the total number of colorectal cancer surgeries performed using the same ICD-9 diagnostic and procedure codes, as described earlier, and created a parallel annual volume ranking for all hospitals that were represented in our cohort. Among hospitals that were jointly represented in our cohort study and the NIS database (255 hospitals), the Spearman rank correlation coefficient for annual colorectal cancer surgery volume, as measured by the Medicare

Table 1. Baseline Characteristics by Tertile of Hospital Procedure Volume\*

Characteristic	Low Volume	Medium Volume	High Volume	P Value†
Patients, <i>n</i>	1050	1058	1053	
Different hospitals, <i>n</i>	530	334	214	
Annual case volume (based on annual Medicare patient volume), <i>n</i>	≤46	47–84	≥85	
Mean age, <i>y</i>	61.3	62.3	61.9	0.12‡
Men, %	50.6	52.6	52.9	>0.2
Race/ethnicity, %				<0.001
White	81.6	90.2	87.4	
African-American	12.3	7.7	8.3	
Other	6.1	2.1	4.3	
ECOG performance status, %§				>0.2
0	66.3	67.2	68.8	
1	30.4	29.2	28.9	
2	3.3	3.6	2.3	
Bowel obstruction at presentation, %	32.7	31.5	30.0	>0.2
Bowel perforation at presentation, %	7.2	6.3	5.2	0.16
Grade of differentiation, %				<0.001
Well	12.1	7.6	7.5	
Moderate	67.6	68.4	68.2	
Poor	20.3	24.0	24.3	
Peritoneal implants at surgery, %	9.3	8.0	7.6	>0.2
Tumor stage/depth of tumor penetration, %				0.0014
T1	1.1	1.5	3.3	
T2	8.6	9.4	9.3	
T3	62.0	62.8	64.6	
T4	28.3	26.3	22.8	
Node stage (positive lymph nodes), %				0.005
0 nodes	20.7	21.1	16.5	
1–4 nodes	58.7	58.7	65.6	
≥5 nodes	20.6	20.2	17.9	
Dukes stage, %				0.022
B1/B2 (stage II)	12.4	14.0	9.8	
B3 (stage II)	8.3	7.1	6.7	
C (stage III)	79.3	78.9	83.5	
Location of primary tumor, %				>0.2
Right colon	49.3	50.2	50.7	
Left colon	50.3	49.1	49.0	
Both	0.4	0.7	0.3	
Treatment group, %¶				>0.2
B: LDLV	27.2	26.5	27.2	
C: HDLV	26.8	27.1	26.4	
E: LEV	24.1	23.5	23.3	
F: LEV + LDLV	21.8	22.9	23.2	
Institution affiliation, %**				<0.001
Main member center	28.4	16.8	21.0	
CCOP	18.8	21.3	19.3	
CGOP	49.6	58.5	58.1	
Other	3.2	3.4	1.6	
Completed adjuvant therapy, %				>0.2
Yes	76.4	78.0	78.6	
No	23.4	22.0	21.4	

\* CCOP = Community Clinical Oncology Program; CGOP = Cooperative Group Outreach Program; ECOG = Eastern Cooperative Oncology Group; HDLV = high-dose leucovorin; LDLV = low-dose leucovorin; LEV = levamisole.

† Chi-square test unless otherwise noted.

‡ Wilcoxon rank-sum test.

§ 0 = full active; 1 = restricted in physically strenuous activity but ambulatory and able to carry out light work; 2 = ambulatory, capable of all self-care, but unable to carry out any work activities, up and about more than 50% of waking hours.

|| Right-sided tumors arise in the cecum, ascending colon, hepatic flexure, or transverse colon; left-sided tumors arise in the splenic flexure, descending colon, sigmoid colon, or rectosigmoid colon.

¶ See references 18, 19, 21, 22 for further explanation of chemotherapy regimens.

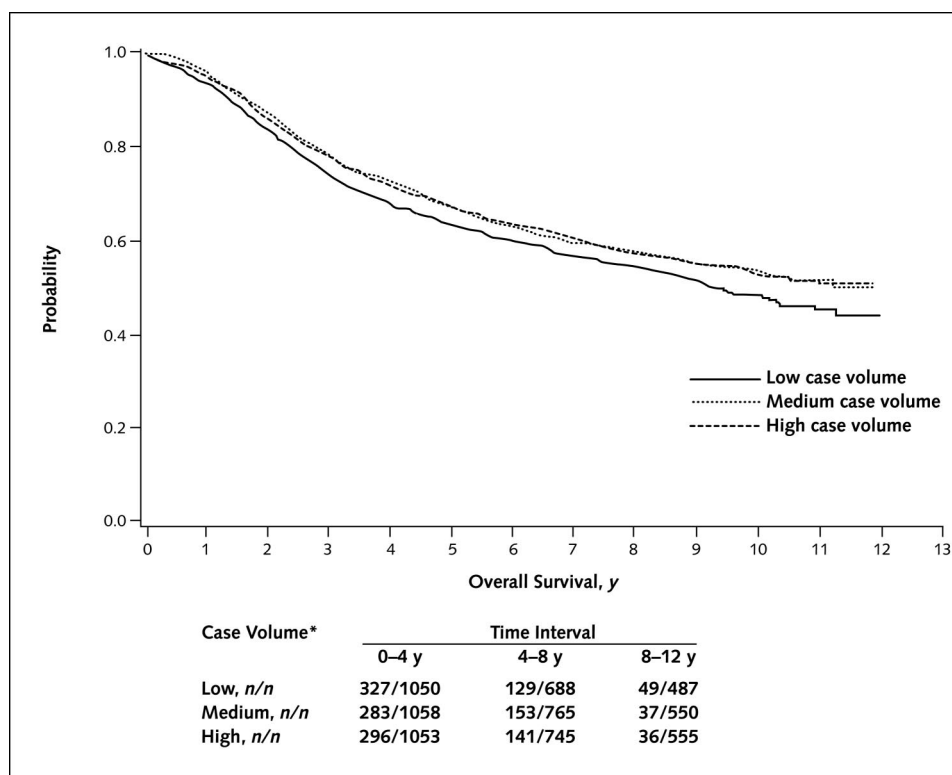
\*\* Center of chemotherapy treatment (not necessarily center where surgery performed). Main member center = main participating cooperative group institution; other = unfunded CCOP with or without CGOP funding, high-priority institution, minority-based institution, or consortium main.

claims database and the NIS database, was 0.92 ( $P < 0.001$ ). This high correlation supports the use of procedure volume for colorectal surgery, as calculated from the Medicare claims database, as a valid measure of relative overall hospital procedure volume.

## Follow-up

Patients were followed at least every 3 months from time of study entry for 1 year (for year-long treatment groups, more frequent provider visits and evaluations were required), then every 6 months for 5 years, and then an-

Figure 1. Overall survival for patients with colon cancer by hospital procedure volume.



\*Values are number of events/number of patients at risk.

nually until death. Because 95% of colon cancer recurrences occur within 5 years after surgery, data for treatment outcomes and therapeutic efficacy from INT-0089 have reached maturity as of the time of this analysis. The median follow-up time for patients included in this report is 9.4 years.

### Statistical Analysis

The distribution of baseline characteristics across hospital procedure volume tertiles was evaluated by using chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Overall and recurrence-free survival rates were examined by using the Kaplan–Meier method (23), and differences among tertiles were assessed by using the log-rank test. Overall survival was defined as time from study entry to death from any cause. Recurrence-free survival was defined as time from study entry to tumor recurrence or occurrence of a new primary tumor. In recurrence-free survival analyses, patients who died without known tumor recurrence were censored at the last documented evaluation by the treating provider. Cancer-specific survival was defined as time from study entry to time of death for patients with documented recurrences; patients who died without a documented recurrence were censored at the time of death, as were patients alive at the time of our analysis. The entire cohort was analyzed by using Cox proportional hazards regression (24); a priori, the model included age, sex, race, bowel obstruction at

presentation, bowel perforation at presentation, performance status, stage of disease, and peritoneal implants. In addition, on the basis of differences in baseline characteristics, tumor differentiation was included in the models.

To avoid the possibility of selecting cut-points that could maximize the associations between volume and outcome, primary statistical analyses were performed by using hospital volume as a continuous variable. Volume had a skewed distribution and therefore was modeled with a square-root transformation to maintain the normality assumption. However, modeling without transforming yearly colorectal volume did not change the results. To facilitate display of our results and to adjust survival and recurrence in a Cox proportional hazards model, we defined tertiles of hospital procedure volume (low [ $\leq 46$  cases per year, based on Medicare volume], medium [47 to 84 cases per year], and high [ $\geq 85$  cases per year]) on the basis of Medicare procedure volume of the hospital where study participants had surgery. According to the method of Lin and Wei (25), we used a robust sandwich estimator to adjust parameter standard errors for the clustering of cases within hospitals. Stratified analyses were conducted to determine whether the influence of hospital procedure volume was modified by various covariates. We used SAS software, version 8.2 (SAS Institute, Inc., Cary, North Carolina), for all statistical analyses. All *P* values are 2-sided.

With a sample size of 3100 patients with colon cancer, we have greater than 90% power to detect a 5% difference in either overall or recurrence-free survival between low- and high-volume hospitals.

### Role of the Funding Sources

The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

## RESULTS

### Baseline Characteristics by Hospital Tertiles

Among the 3161 patients (age range, 18 to 87 years) included in our analysis, primary colon cancer surgery was performed at 1078 U.S. hospitals. Table 1 shows the baseline characteristics of the cohort according to tertiles of hospital volume. Patients who underwent surgical resection at low-volume hospitals were more likely to be African American, to have tumors that invaded or adhered to adjacent structures (T4), and to have 5 or more positive lymph nodes. In contrast, the total number of lymph nodes analyzed in the resection specimen was greater in high-volume centers. Baseline ECOG performance status, rates of bowel obstruction or perforation at the time of surgery, tumor location within the bowel, and chemotherapy assignment within the treatment trial did not differ significantly by tertiles of hospital procedure volume.

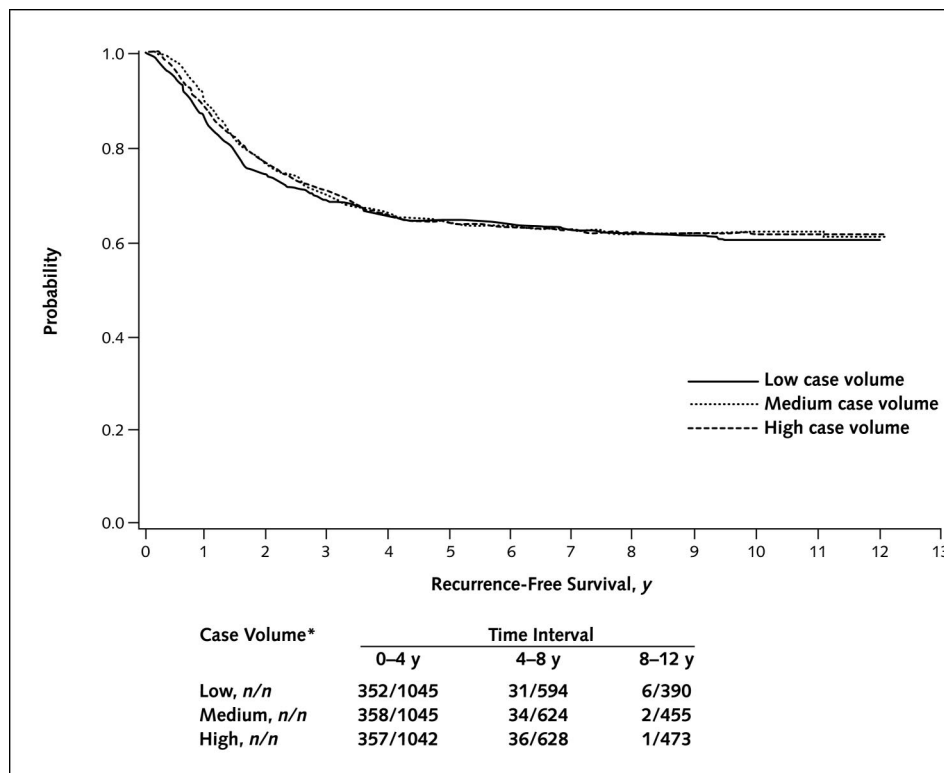
### Survival and Cancer Recurrence by Hospital Procedure Volume

As previously reported, no significant overall survival advantage was observed among any of the 4 treatment groups in the study of adjuvant chemotherapy (18, 19). Consequently, patients in all 4 treatment groups were analyzed jointly according to the procedure volume of the hospital where they had surgery.

At the time of this analysis, median follow-up for the trial was 9.4 years (maximum, 12.7 years). Figures 1 and 2 show Kaplan–Meier curves of overall survival and recurrence-free survival. Five-year overall survival (from date of entry into the adjuvant chemotherapy trial) significantly differed across tertiles of hospital procedure volume (63.8% for patients who had resection at low-volume hospitals compared with 67.3% at high-volume hospitals;  $P = 0.04$ ) (Table 2). However, 5-year recurrence-free survival did not differ significantly across tertiles.

Table 2 shows unadjusted and adjusted hazard ratios and CIs for overall mortality and cancer recurrence for patients according to category of hospital volume. Compared with patients who underwent resection at high-volume hospitals, those treated at low-volume centers had significantly greater adjusted overall mortality (hazard ratio, 1.16 [CI, 1.03 to 1.32]). However, compared with patients who had resection at high-volume hospitals, those treated

Figure 2. Recurrence-free survival for patients with colon cancer by hospital procedure volume.



\*Values are number of events/number of patients at risk.

**Table 2. Unadjusted and Adjusted Risk for Mortality and Recurrence by Tertile of Hospital Procedure Volume**

Volume Tertile	Overall Mortality				Cancer Recurrence			
	Deaths	5-Year Overall Survival	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio* (95% CI)	Recurrences	5-Year Recurrence-Free Survival	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio* (95% CI)
	<i>n</i>	%			<i>n</i>	%		
High volume†	473	67.3	1.00	1.00	394	63.0	1.00	1.00
Medium volume	474	67.3	0.99 (0.88–1.14)	1.01 (0.89–1.14)	394	63.0	0.99 (0.86–1.14)	1.00 (0.87–1.15)
Low volume	505	63.8	1.15 (1.01–1.30)	1.16 (1.03–1.32)	389	63.9	1.03 (0.89–1.18)	1.03 (0.89–1.19)
<i>P</i> value for trend‡		0.04	0.038	0.034		>0.2	>0.2	>0.2

\* Hazard ratio compared with reference group (high volume). Adjusted hazard ratio from Cox proportional hazards with adjustment for age, sex, race, baseline performance status, bowel obstruction, bowel perforation, stage of disease, tumor differentiation, and presence of peritoneal implants.

† Reference group.

‡ *P* value for trend from log-rank test for 5-year overall survival and recurrence-free survival and from model with square root of annual hospital volume as continuous variable.

at low-volume centers did not experience a significant increase in the risk for cancer recurrence (hazard ratio, 1.03 [CI, 0.89 to 1.19]). Although patients without known recurrence could have potentially died with undiagnosed recurrent disease, we defined a cancer-specific mortality end point for this cohort (patients who died with known disease recurrence were considered to have an event at time of death, and other patients were censored at time of death or at time of analysis). Compared with patients treated at high-volume hospitals, cancer-specific mortality did not differ for patients treated at low-volume hospitals (hazard ratio, 1.06 [CI, 0.91 to 1.23]) or at medium-volume hospitals (hazard ratio, 0.98 [CI, 0.98 to 1.13]).

We considered the possibility that differences in cancer recurrence rates may be apparent only at the extreme levels of hospital procedure volume. We therefore repeated our analysis after categorizing hospital volume according to deciles. As compared with patients in the highest decile (134 to 298 cases per year), patients in the lowest decile of hospital volume (0 to 18 cases per year) had an adjusted hazard ratio of 0.99 (CI, 0.75 to 1.29) for cancer recurrence.

### Stratified Analysis of Survival and Recurrence

We also examined the influence of hospital volume on cancer recurrence and overall mortality after stratifying by other potential predictors of outcome (Table 3). Although limited by statistical power, among each subgroup defined by age, race, sex, bowel obstruction or perforation, baseline performance status, and stage of disease, we continued to observe a similar magnitude of increased overall mortality in low-volume centers. However, we did not observe a significant relation between hospital volume and cancer recurrence in any of these substrata. We found similar results when we stratified by whether patients completed the assigned adjuvant chemotherapy and by adjuvant chemotherapy treatment group (data not shown).

To confirm that the institution where patients received chemotherapy did not affect the relation between surgical hospital volume and outcome, we also stratified the analy-

sis by whether adjuvant chemotherapy was delivered at main member institutions (typically university hospital and cancer centers) or an affiliated center (Community Clinical Oncology Program, Cooperative Group Outreach Program, or other). Within both strata of centers delivering chemotherapy, hazard ratios for overall mortality and cancer recurrence were similar to those observed for the entire cohort.

### DISCUSSION

In this large trial of adjuvant chemotherapy in patients with high-risk stage II and stage III colon cancer, overall survival after curative surgery was significantly improved among patients who underwent surgery at a hospital with a high volume of colon cancer surgeries. Nonetheless, despite the 16% increase in overall mortality observed among patients resected at low-volume centers, we saw no significant relation between hospital procedure volume and the risk for cancer recurrence or cancer-specific mortality.

Analyzing Medicare beneficiaries in the SEER registry, Schrag and colleagues (13) found a similar 16% excess risk for long-term overall mortality among patients who had resection at low-volume hospitals (13). Despite adjustments for adjuvant therapy and certain predictors of long-term survival, most of the survival difference between high- and low-volume centers seemed to be the result of events beyond 30 days after surgery. In addition, because data on cancer recurrence were unavailable, the mechanism underlying this relation was unclear.

Using clinical trial data to examine the influence of hospital procedure volume offers several advantages over the use of other data sources and allows for isolation of the effect of surgery on outcomes. First, the stage of disease is comparable within the constraints of the protocol entry criteria. Second, detailed information on prognostic variables, such as the number of positive lymph nodes and performance status, is routinely collected. Most important,

the date and nature of cancer recurrence are prospectively recorded.

Because patients were identified for this clinical trial 4 to 6 weeks after primary surgical resection, perioperative (short-term) morbidity and mortality were not addressed. However, we specifically focused on the influence of hospital surgical volume on long-term colon cancer outcomes. Nonetheless, despite the exclusion of short-term mortality from our analysis, we continued to see an overall survival difference across hospital surgical volumes.

By using data from a prospective clinical trial, our analysis may have eliminated variability in other potential explanatory variables, such as use of adjuvant chemotherapy and other follow-up care. However, differences in survival across hospital surgical volumes reported in the previous SEER–Medicare analysis were observed after adjustment for other covariates, including use of adjuvant

chemotherapy (13). Moreover, we found approximately the same relative hazard for long-term mortality across hospital volume as did the previous SEER–Medicare study. In contrast, we observed no relation between hospital procedure volume and the risk for cancer recurrence or cancer-specific mortality.

Because patients enrolled into a randomized clinical trial may not be representative of the broader population of patients with colon cancer nationwide, the generalizability of our findings could be questioned. However, colon cancer surgery was performed before enrollment into this trial, and we did observe considerable variation in hospital procedure volume within our cohort. In addition, because the study sample included patients in both community and academic medical centers, we believe that the surgical treatment reflects the general U.S. population. Moreover, when we excluded patients who went to main member academic

**Table 3. Adjusted Risk for Overall Mortality and Cancer Recurrence according to Hospital Procedure Volume in Subgroups Defined by Selected Variables\***

Variable	Patients	Overall Mortality				Cancer Recurrence			
		5-Year Overall Survival		Adjusted HR (95% CI) <sup>†</sup>	P Value for Trend <sup>‡</sup>	5-Year Recurrence-Free Survival		Adjusted HR (95% CI) <sup>†</sup>	P Value for Trend <sup>‡</sup>
		High-Volume Hospital	Low-Volume Hospital			High-Volume Hospital	Low-Volume Hospital		
n	%		%		%				
Age									
<65 y	1407	69.7	66.6	1.17 (0.98–1.40)	0.13	65.0	64.0	1.02 (0.84–1.24)	0.15
≥65 y	1753	64.2	60.2	1.14 (0.96–1.37)	0.16	60.3	63.7	0.96 (0.78–1.18)	>0.2
Race/ethnicity									
White	2727	67.2	63.7	1.15 (1.01–1.32)	0.06	62.7	63.6	1.03 (0.89–1.20)	>0.2
African-American and other	427	67.8	63.5	1.26 (0.90–1.78)	0.18	65.3	64.8	1.00 (0.68–1.47)	>0.2
Sex									
Male	1644	65.6	61.8	1.10 (0.92–1.14)	>0.2	62.8	61.8	1.05 (0.86–1.23)	>0.2
Female	1517	69.2	66.0	1.24 (1.02–1.50)	0.05	63.3	66.0	0.98 (0.80–1.21)	>0.2
Bowel obstruction or perforation									
Present	1126	65.9	60.5	1.24 (1.00–1.53)	0.12	60.6	59.8	1.07 (0.77–1.23)	>0.2
Absent	2035	68.0	65.9	1.13 (0.96–1.32)	0.12	64.4	66.3	1.00 (0.84–1.20)	>0.2
ECOG performance status <sup>§</sup>									
0	2035	69.5	66.2	1.16 (0.99–1.37)	0.11	65.0	65.5	1.06 (0.78–1.13)	>0.2
1 or 2	983	63.3	58.9	1.17 (0.98–1.51)	>0.2	59.0	61.4	0.98 (0.77–1.26)	>0.2
Disease stage									
II	614	77.4	77.3	1.17 (0.83–1.66)	>0.2	70.8	76.1	0.97 (0.66–1.42)	>0.2
III	2547	65.3	60.4	1.16 (1.08–1.32)	0.05	61.5	60.8	1.04 (0.89–1.21)	>0.2
Center where adjuvant chemotherapy was administered <sup>  </sup>									
Main member center	697	72.7	65.3	1.31 (1.0–1.71)	0.10	67.0	66.0	1.05 (0.78–1.42)	>0.2
Affiliated centers	2464	65.9	63.3	1.13 (0.98–1.30)	0.08	62.0	63.0	1.04 (0.86–1.17)	>0.2

\* ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio.

<sup>†</sup> Adjusted hazard ratio from Cox proportional hazards analysis with adjustment for age, sex, race, baseline performance status, bowel obstruction, bowel perforation, disease stage, tumor differentiation, and presence of peritoneal implants, excluding the given stratification variable.

<sup>‡</sup> P value for trend for the full cohort of that stratification with annual procedure volume entered in the model as a continuous variable.

<sup>§</sup> 0 = full active; 1 = restricted in physically strenuous activity but ambulatory and able to carry out light work; 2 = ambulatory, capable of all self-care, but unable to carry out any work activities, up and about more than 50% of waking hours.

<sup>||</sup> Main member center = a main participating cooperative group institution; Affiliated centers = Community Clinical Oncology Program, Cooperative Group Outreach Program, or other (unfunded Community Clinical Oncology Program with or without Cooperative Group Outreach Program funding, high-priority institution, minority-based institution, or consortium).

centers for study enrollment and restricted the analysis to patients enrolled at community and affiliated institutions, our findings were unchanged. Nonetheless, underlying differences between patients participating in a clinical trial and the general colon cancer population may limit the external validity of these findings. In addition, our results apply to patients receiving adjuvant therapy and do not address potential volume-related differences in the use of adjuvant therapy in this patient sample.

Our findings suggest that the observed volume–outcome relation may be more reflective of higher rates of non–cancer-related mortality at low-volume centers. The presence of concurrent adverse health conditions, or comorbid conditions, has been shown to increase overall mortality among patients with cancer (26–29). In our analysis, we did not ascertain comprehensive information on baseline noncancer diagnoses, and detailed data on non–cancer-related causes of death are not available. However, our database does record diabetes mellitus, and the percentage of diabetic patients at baseline did not significantly differ by hospital tertile ( $P > 0.2$ ). In addition, a recent analysis of hospital volume demonstrated an increase in Charlson comorbidity score with increasing hospital procedure volume among more than 304 000 Medicare patients, suggesting a higher-risk population at high-volume centers (3). Nonetheless, it is plausible that mortality rates for chronic diseases other than cancer may contribute to the shorter survival among patients who have resection at low-volume centers.

Our study allows for the beginning of an understanding of the processes of care underlying the volume–outcome relationship. Despite uniform use of chemotherapy and potentially more consistent postoperative care in our cohort, patients with stage II and stage III colon cancer having operations at low-volume hospitals had increased long-term mortality, beyond the window of immediate postoperative mortality, but not increased cancer recurrence or cancer-specific mortality. These data suggest that differences between patients served by hospitals with large and small caseloads, outside of tumor-related factors, may explain the association between procedure volume and outcomes observed in claims-based studies. Whether differences exist in the general health status of patients, the use of preventive medicine programs, or the quality of care of non–cancer-related diseases at low-volume centers is beyond the scope of this study. Recent initiatives have focused on regionalization of cancer surgeries to improve patient outcomes (30). Our results should give pause to this growing movement toward regionalization of cancer surgery, as we believe that further research is needed to identify those specific features and processes of care that underlie the volume–outcome relation.

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