

National Cancer Institute Designation Predicts Improved Outcomes in Colorectal Cancer Surgery

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Background: Although National Cancer Institute (NCI) designation as a cancer center is based almost solely on research activities, it is often viewed, by patients and referring providers, as an indication of clinical excellence.

Objective: To compare the short- and long-term outcomes of colon and rectal cancer surgery performed at NCI-designated centers to the outcomes after resection at non-NCI-designated hospitals.

Methods: We performed a retrospective cohort study of Survival, Epidemiology, and End Results (SEER)-Medicare database patients undergoing segmental colectomy (n = 33,969) or proctectomy (n = 8591) for cancer from 1996–2003. Multivariate logistic regression, with and without propensity scores, and matched conditional regression were performed to evaluate the relationship between NCI status and postoperative mortality (in-hospital or 30-day death). The log-rank test, Kaplan-Meier curves, and Cox regression compared survival between hospital types.

Results: We evaluated 33,969 colectomy and 8591 proctectomy patients. Postoperative mortality after colectomy was 6.7% at non-NCI and 3.2% at NCI centers. Mortality after proctectomy was 5.0% and 1.9%, respectively. These differences were significant when adjusted for patient and hospital characteristics. For both colon and rectal cancer patients, long-term mortality was significantly improved after resection at NCI centers (HR 0.84, $P < 0.001$; HR 0.85, $P = 0.02$, respectively).

Conclusion: NCI designation is associated with lower risk of postoperative death and improved long-term survival. Possible factors responsible for these benefits include surgeon training, multidisciplinary care, and adherence to treatment guidelines. Studies are underway to elucidate the factors leading to improved patient outcomes.

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In 2006, there were over 106,000 cases of colon cancer and 41,000 cases of rectal cancer diagnosed in the United States. During the same year, almost 56,000 people died of one of these 2 diseases. This makes colorectal cancer the third most commonly diagnosed cancer in both genders, the second leading cause of cancer death in men and the third leading cause of cancer death in women.¹

The importance of quality measures in cancer outcomes is increasingly recognized but difficult to define. Multiple studies have demonstrated significant variation in the processes and outcomes of care for cancer patients, including variations by patient race, age, and gender. This variation has also been demonstrated at the level of provider, hospital, and even geographic region.

Postoperative mortality after colon and rectal cancer procedures is approximately 3% to 6%. Although not insignificant, these risks are substantially lower than those of esophageal or pancreatic resections where postoperative mortality can be as high as 10% to 15%. Perhaps not surprisingly, most of the literature examining the determinants of variation in postoperative mortality has focused on high-risk procedures, rather than colon and rectal cancer surgery. Absolute differences in mortality attributable to hospital and patient characteristics are likely to be of smaller magnitude for colon and rectal cancer than for other cancers with higher postoperative mortality. However, many more people are diagnosed with colorectal cancer than esophageal or pancreatic cancer, and, of those diagnosed, a substantially greater proportion of patients with colon or rectal cancer undergo surgery than patients with esophageal or pancreatic cancer. Thus, even small differences in mortality after surgical treatment of colorectal cancer affect large numbers of patients. For example, if 100,000 colon resections are performed each year, a 2% decrease in postoperative mortality (6%–4%) would result in 2000 lives saved.

National Cancer Institute Designation. The term “cancer center” is used in a broad variety of contexts when describing institutions delivering cancer care. In 1971, the National Cancer Act established the Cancer Centers Branch of the National Cancer Institute (NCI) thereby formalizing the establishment of NCI-designated cancer centers. Today, the NCI recognizes 22 cancer centers and 39 comprehensive

cancer centers as meeting their rigorous standards for research accomplishments.²

Although NCI designations are awarded almost solely based on research activities,² there are several reasons to hypothesize that clinical centers recognized by the NCI as cancer centers may have better cancer patient outcomes than nondesignated centers. NCI-designated centers bring together specialists from all fields of cancer treatment, which should facilitate the multimodality care common to most neoplasms. These centers are involved in both basic science and clinical research with the ultimate goal of moving novel therapies and technologies from bench to bedside. NCI comprehensive cancer centers also encompass efforts in population-based research including epidemiology and outcomes research, which may support efforts in quality improvement. NCI centers also may maintain institutional databases such as tissue banks or tumor registries that could be used both to contribute to basic science and to track outcomes.

To date, however, there has been very little empiric evidence supporting the superiority of patient outcomes in NCI-designated cancer centers over nondesignated centers that perform similar volumes of cancer surgery. One study compared the outcomes for 6 different cancers treated surgically at NCI centers to those treated at non-NCI designated, volume matched hospitals. These authors reported a slightly lower surgical mortality but very little advantage in long-term survival at the NCI-designated centers.³

This study evaluates the association between NCI cancer center designation and outcomes after surgical resection for colon and rectal cancer. More specifically, we compare postoperative mortality and long-term survival after surgery at NCI-designated cancer centers and non-NCI-designated hospitals. This difference was examined in the context of varying patient, hospital, and regional characteristics.

METHODS

Study Population

We obtained data from the Survival, Epidemiology, and End Results (SEER)-Medicare files (1996–2005) for patients diagnosed with colon or rectal cancer between 1996 and 2002. The SEER-Medicare database brings together Medicare administrative claims data with detailed clinical tumor registry data.^{4,5} The SEER program collects data about cancer incidence, treatment, and mortality in a representative sample of the US population. The SEER coverage area, which includes 14 sites encompassing wide geographic and population variation, is estimated to include approximately 14% of the US population.⁴ In SEER, cancer cases are identified primarily from hospital records. Tumor characteristics, initial courses of therapy, and sociodemographic information come from medical records. With the exception of individuals who are enrolled in health maintenance organizations (HMOs) or do not have part B coverage, Medicare data provides information about all inpatient and outpatient utilization of medical care for residents of the United States 65 years of age and older. In this database, survival is determined by Medicare vital statistics and SEER linkage to

death certificates (National Death Index), medical records, voter registration, and other public records.

We used the Medicare Provider Analysis and Review (MEDPAR) files and the Physician/Supplier (NCH) files to identify those patients who underwent colon or rectal resection based on appropriate ICD-9 (the International Classification of Diseases, Ninth Revision) and CPT (Current Procedural Terminology, 2006) procedure codes. Initially, we identified 46,136 colon cancer and 13,570 rectal cancer patients who were diagnosed between 1996 and 2004 and underwent surgical resection of their tumor. We only included patients with histologic diagnosis of adenocarcinoma based on the SEER documentation. We excluded patients from the study who were enrolled HMO during the 6 months before and 3 months after their diagnosis (colon: $n = 3367$; rectal: $n = 1034$). We excluded these patients because HMOs do not submit detailed claims itemizing patient care to Medicare. We then excluded patients who were younger than 66 and older than 99 years old (colon: $n = 3920$; rectal: $n = 1457$). Patients younger than 65 in the Medicare data consist of patients who are disabled or have end-stage renal disease. Because of their unusual characteristics, we did not include them in our analysis, a common practice when using Medicare claims data. To ensure a yearlong look-back period for the purposes of determining comorbidity, we also excluded 65-year-old patients as they would not have a year of prior Medicare records. Finally, we excluded patients who underwent only local excision of their rectal tumor ($n = 989$). A total of 38,849 patients met criteria for colectomy and 10,090 patients met the criteria for rectal resection. From this cohort, we excluded patients for whom no stage information was available (colon: $N = 1461$; rectal: $N = 784$) or who had missing socioeconomic (colon: $N = 3329$; rectal: $N = 699$) or admission type information (colon: $N = 90$; rectal: $N = 16$). The final colon cancer cohort comprised 33,969 subjects who underwent colectomy for colon cancer, whereas the rectal cohort included 8591 subjects who underwent radical rectal resection for rectal cancer. All subsequent analyses were performed separately on the colon and rectal populations.

Outcome Measure

Our primary outcome was postoperative mortality, defined as death within 30 days of colon or rectal resection or death during the hospitalization in which the primary surgical procedure was performed. We also examined differences in long-term survival for each cohort of patients. We calculated survival time as the number of days from the primary surgical procedure to death or until December 31, 2005, whichever came first. We censored observations of patients who were alive at the end of follow-up.

Predictor Variable

The primary predictor of interest was the NCI status of the hospital where each patient's surgical resection was performed. NCI status was obtained from the hospital file provided by the SEER-Medicare program.

Covariates

Before the data analysis, we identified potential confounders of the association between NCI status with the

outcome variables; postoperative mortality and long-term survival. These included patient characteristics (ie, age, race, sex, Charlson comorbidity score, tumor stage, acuity of admission, and zip code-based socioeconomic status) and hospital characteristics (eg, case-specific surgical volume, hospital bed volume, and teaching status).

Tumor Stage. To determine cancer stage, we used the American Joint Committee on Cancer (AJCC) overall cancer stage (0-IV) provided in the SEER files for each patient. As mentioned above, patients who had an unknown tumor stage were not included in the final analysis, whereas stage 0 and stage 1 patients were combined into 1 category.

Comorbidity. Patient comorbidity was assessed using the Romano modification of the Charlson comorbidity index.⁶ The Charlson index, which has been used extensively in prior literature, uses ICD-9 diagnosis and procedure codes from Medicare records to give a weighted, risk-adjusted comorbidity index value per patient.⁷ The Charlson index takes into consideration any comorbid conditions that meet the inclusion criteria as defined by the index parameters and that occurred within a year before diagnosis. The Romano modification excludes cancer diagnoses in determining comorbidity, and thus is used frequently in cancer outcomes research. Because of the small number of patients with Romano-Charlson scores greater than 2, we collapsed the values into 3 categories: 0 (low; no pre-existing comorbid conditions), 1 (moderate; at least 1 comorbid condition), and 2 or greater (high; greater number of, or more severe, comorbid conditions). This is a common practice in the surgical literature, as patients with extensive comorbid illnesses often do not undergo high-risk surgical procedures.⁸⁻¹¹ As an additional measure of patient illness, we included the acuity of admission based on the MEDPAR file (ie, elective, urgent, or emergent).

Sociodemographic Characteristics. Age at diagnosis, race, gender, and socioeconomic status were determined from SEER and MEDPAR data. Age was assessed as a categorical variable (patient age 65-69, 70-74, 75-79, 80-85, and 85 and above). Patient race was initially evaluated using 6 categories: white, black, other, Asian, Hispanic, and Native American. The majority of the patients in the cohort, however, were white (85%). Seven percent of the patients were black with smaller percentages being accounted for by the other racial groups. Because of the small number of nonwhite patients, we collapsed race into 3 categories, white, black, and other. Because SEER-Medicare does not collect individual patient level socioeconomic status information, we used the percentage of persons who lived below the poverty line in the patient's census tract (2000 census information) as a proxy for an individual patient's socioeconomic status.

Hospital Characteristics. For the purpose of this study, we defined hospital surgical volume as the average number of either colon or rectal resections performed on patients living in a SEER region at each hospital in the dataset per year. Hospital information provided in the MEDPAR file identified

a total of 1162 distinct centers at which colectomies and 890 distinct centers at which rectal resections were performed in this cohort. The total number of colon or rectal resections performed on our patient cohort per center was divided by 8, the number of years in our study period. This number was used as a continuous variable in multivariate analyses. For use in stratified analysis, the facilities were then distributed into volume tertiles. For colon cancer, high volume was defined as 16 or more, medium volume as 7 to 15, and low volume as 6 or fewer colectomies per year on SEER-Medicare patients. For rectal cancer, high volume was defined as 5 or more, medium volume as 3 to 4, and low volume as 1 to 2 rectal resections per year.

A similar method was used to define hospital bed volume. Total bed volume was obtained for each center from the hospital file provided by SEER. The hospitals were then divided into tertiles of bed volume designated low, medium, and high. Teaching status for each center was obtained directly from the hospital file.

Statistical Analysis

Univariate associations between type of hospital (NCI or Non-NCI) and clinical and demographic factors were assessed using χ^2 tests for categorical variables and *t* tests for continuous variables. Multivariate logistic regression was used to analyze the association of hospital NCI status and postoperative mortality while adjusting for important patient and hospital characteristics. The final logistic model included: NCI status; hospital surgical volume, bed volume, and teaching status; socioeconomic status and categorical patient age, race, gender, Romano-Charlson score, tumor stage, and admission type. The significance of all pair-wise interaction terms for both colon and rectal models were evaluated using the likelihood ratio test. Interactions between pairs of variables were included in the models if they were significant at a *P* value based on the Bonferroni correction for number of pairs evaluated (55 pairs, significant *P* < 0.0009). No interactions were significant at this level; thus, no interaction terms were included in the final models.

Because the number of patients treated at NCI hospitals was much smaller than the number of patients at non-NCI hospitals, we were concerned that, despite adjusting for the patient level characteristics described above, there may be imbalance in these covariates between patients being treated at NCI versus non-NCI centers. To address this concern, propensity score methods were used to measure the likelihood that a patient would be treated at an NCI hospital based on demographic and clinical factors. We used a logistic regression model to evaluate the relationship between patient factors (age, race, sex, comorbidity score, tumor stage, and admission type) and undergoing surgery at an NCI center. The propensity score for each subject was his/her probability of receiving treatment at an NCI hospital given his/her values for the variables in the logistic regression model. The propensity score was then used in place of these patient variables in the original logistic regressions. Also included in this logistic model was socioeconomic status, as measured by the

percent of person living below the poverty level in a patient's given census tract and the hospital characteristics.

To further test our results, we created a matched dataset. Patients were matched on relevant patient-level characteristics (age category, race, sex, tumor stage, comorbidity score, and admission type). A conditional logistic regression was run using postoperative mortality as the outcome, NCI status as the main predictor variable and the patient group as the matching variable. This further addresses the issue of possible imbalance of covariates between patients treated at NCI and non-NCI centers. Odds ratios for the original logistic regressions, the propensity score, and the conditional logistic models are reported separately for the colon and rectal cancer cohorts.

To investigate overall mortality, we generated Kaplan-Meier survival curves for each cohort and for each cancer stage strata and compared NCI to non-NCI centers with log-rank tests. The overall hazard ratio for NCI status was estimated using a Cox proportional hazards model adjusting for above described patient and hospital characteristics.

Sensitivity Analysis

In nonrandomized studies, an observed association between treatment (here, NCI status) and outcome may reflect effects of unknown or unmeasured confounders. We conducted a sensitivity analysis of the effects of an unmeasured binary confounder on the estimated propensity score-adjusted hazard ratio for NCI versus non-NCI centers in the colon cancer cohort.^{12,13} We assumed, for this analysis, that the confounder represented patient functional status (binary: poor and good). This is not captured in administrative data and could be associated with use of an NCI center if patients with poor functional status prefer to go to their local hospital rather than travel, if necessary, to an NCI cancer center for treatment. As poor functional status is likely to be associated with worse short- and long-term outcomes, this would make non-NCI centers look worse. In our analysis, we systematically varied both the prevalence of poor functional status in the patients treated at NCI and non-NCI hospitals and the relative hazard of death associated with poor functional status.

For all of the logistic and Cox proportional hazards models, we adjusted for the clustering of patients in individual hospitals using robust variance estimators. Two tailed tests were used for all analyses, and, with the exception of the evaluation for interaction, statistical significance was set at $P < 0.05$. All analyses were conducted using the statistical software STATA 8.0 (STATA Inc, College Station, TX) and R version 2.6.0 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics and Univariate Analysis

The final cohorts consisted of 33,969 patients who underwent colectomy for colon cancer and 8591 patients who underwent rectal resection for rectal cancer. Nine hundred thirty-four (3.0%) of the colon cancer patients and 365 (4.3%) of the rectal cancer patients had their surgery at an NCI

cancer center. The baseline characteristics of the colon and rectal cohorts and the results of the univariate association between patient and hospital characteristics and NCI status are shown in Tables 1 and 2. Patients with colon cancer treated at NCI centers tended to be younger, black, and from lower socioeconomic regions. They are also more likely to have stage IV disease and were less likely to be admitted on an emergent or urgent basis. Similarly, rectal cancer patients treated at NCI centers were younger and more likely to be black and treated on an elective basis. The rectal cancer patients treated at NCI centers also had a lower comorbidity burden than those treated at non-NCI centers. As expected, NCI centers tended to have larger bed and surgical volume than non-NCI centers. Also, all NCI centers in this study were designated as teaching hospitals.

Postoperative Mortality – Colon Cancer

Postoperative mortality after colon resection for colon cancer was 6.7% and 3.2% at non-NCI and NCI centers, respectively. When adjusted for patient and hospital characteristics in the described logistic model, NCI status remained significantly associated with postoperative mortality. Patients undergoing resection at an NCI center were slightly less than half as likely to die in the postoperative period as patients undergoing resection at a non-NCI center (OR, 0.58; $P = 0.008$). When propensity score was included in the logistic model, both the point estimate and significance of the association remained unchanged (OR 0.55, $P = 0.007$).

The results of the matched analysis yielded similar results. The exact matching algorithm created 340 groups of patients each with identical characteristics. When the analysis was conditioned on these matched groups, the association of NCI status and lower odds of postoperative mortality remained essentially unchanged (OR, 0.56; $P = 0.004$).

Finally, the association of NCI center and postoperative mortality was evaluated using the original logistic regression limited to high volume hospitals, those that performed 16 or more colectomies for cancer in our patient cohort per year. In this limited cohort, the OR for the association of NCI center and postoperative mortality rose slightly to 0.67 ($P = 0.02$). NCI centers were still clearly associated with a much lower risk of postoperative death, even in this high volume sample. When limited to low volume centers, the OR remained essentially unchanged (0.55, $P = 0.04$). The OR and P values for each separate model are shown in Table 3.

Postoperative Mortality – Rectal Cancer

Postoperative mortality after resection for rectal cancer was 5.0% and 1.9% at non-NCI and NCI centers, respectively. When adjusted for patient and hospital characteristics in the described logistic model, NCI status remained significantly associated with postoperative mortality (Table 3). Patients undergoing rectal resection at an NCI center were half as likely to die in the postoperative period as patients undergoing resection at a non-NCI center (OR, 0.50; $P = 0.05$). Again, the use of propensity score to adjust for patient characteristics in the model did not change the results (OR, 0.49; $P = 0.049$).

Applying the matching algorithm to the rectal cancer cohort resulted in 140 matched patients groups for analysis.

TABLE 1. Patient Characteristics and Univariate Analysis of Characteristics and NCI Status: Colon Cancer

Variable	Total N (%)	Non-NCI n (%)	NCI n (%)	P
Overall	33,969	33,036	934	
Postop mortality				<0.001
Yes	2237 (6.5)	2206 (6.7)	31 (3.3)	
No	31,732 (93.5)	30,829 (93.3)	903 (96.7)	
Age				<0.001
65–69	4717 (13.9)	4550 (13.8)	167 (17.9)	
70–74	7669 (22.6)	7426 (22.5)	243 (26.0)	
75–79	8334 (24.5)	8099 (24.5)	235 (25.1)	
80–84	7079 (20.8)	6913 (20.9)	166 (17.8)	
85+	6170 (18.2)	6047 (18.3)	123 (13.2)	
Stage				0.02
0/I	8290 (24.4)	8045 (24.4)	245 (26.2)	
II	12,178 (35.9)	11,878 (35.9)	300 (32.1)	
III	9082 (26.7)	8839 (26.8)	243 (26.0)	
IV	4419 (13.0)	4273 (12.9)	146 (15.7)	
Charlson score				0.095
0	22,327 (65.7)	21,686 (65.6)	641 (68.6)	
1	7232 (21.3)	7041 (21.3)	191 (20.5)	
2+	4410 (12.0)	4308 (13.1)	102 (10.9)	
Admit type				<0.001
Elective	19,244 (56.7)	18,554 (56.2)	690 (73.9)	
Urgent	7714 (22.7)	7642 (23.1)	72 (7.7)	
Emergent	7011 (60.6)	6839 (20.7)	172 (18.4)	
Sex				0.292
M	14,702 (43.3)	14,282 (43.2)	420 (45.0)	
F	19,267 (56.7)	18,753 (56.8)	514 (55.0)	
Race				<0.001
White	29,133 (85.8)	28,398 (86.0)	735 (78.7)	
Black	2622 (7.7)	2460 (7.4)	162 (17.3)	
Other	2214 (6.5)	2177 (6.6)	37 (4.0)	
SES				0.01
Mean % below poverty level (95% CI)	10.8 (10.7, 10.9)	10.81 (10.7, 10.9)	11.6 (10.9, 12.3)	
Hospital surgical volume				0.034
Low	12,019 (35.4)	11,668 (35.3)	351 (37.6)	
Medium	11,269 (33.2)	10,995 (33.3)	273 (29.2)	
High	10,681 (31.4)	10,371 (31.4)	310 (33.2)	
Hospital bed volume				<0.001
Low	10,621 (31.3)	10,524 (31.9)	97 (10.4)	
Medium	10,598 (31.2)	10,591 (32.1)	7 (0.8)	
High	10,604 (31.2)	9811 (29.7)	793 (85.9)	
Unknown	2146 (6.3)	2109 (6.3)	37 (3.9)	
Teaching status				<0.001
Nonteaching	14,157 (41.7)	14,157 (42.9)	0 (0.0)	
Teaching	17,662 (52.0)	16,765 (50.7)	897 (96.0)	
Unknown	2150 (6.3)	2113 (6.4)	37 (4.0)	

NCI remained associated with a lower odds of postoperative mortality when a conditional logistic regression model was applied to these patients groups (OR, 0.52; $P = 0.1$). The point estimate of the odds ratio remained unchanged; however, the P value is no longer significant. This is due to the substantially smaller sample size ($n = 3935$) used in the matched analysis. The fact that the odds ratio itself does not

change, however, supports the findings from the other models that included the entire cohort, discussed above.

Finally, similarly to the colon cancer cohort, the association was evaluated in only high volume hospitals, those that performed 5 or more radical rectal resections per year. Here, again, the association remained essentially stable (OR, 0.54; $P = 0.2$). When limited to low volume centers, the OR

TABLE 2. Patient Characteristics and Univariate Analysis of Characteristics and NCI Status: Rectal Cancer

Variable	Total N (%)	Non-NCI n (%)	NCI n (%)	P
Overall	8591	8226	365	
Postop mortality				0.008
Yes	417 (4.9)	410 (5.0)	7 (1.9)	
No	8174 (95.1)	7816 (95.0)	358 (98.1)	
Age				<0.001
65–69	1602 (18.7)	1502 (18.3)	100 (27.4)	
70–74	2281 (26.5)	2173 (26.4)	108 (29.6)	
75–79	2177 (25.3)	2094 (25.5)	83 (22.7)	
80–84	1520 (17.7)	1468 (17.8)	52 (14.3)	
85+	1011 (11.8)	989 (12.0)	22 (6.0)	
Stage				0.155
0/I	2573 (30.0)	2461 (29.9)	112 (30.7)	
II	2501 (29.1)	2413 (29.3)	88 (24.1)	
III	2572 (29.9)	2,449 (29.8)	123 (22.7)	
IV	945 (11.0)	903 (11.0)	42 (11.5)	
Charlson score				0.027
0	6137 (71.4)	5855 (71.2)	282 (77.3)	
1	1643 (19.1)	1583 (19.2)	60 (16.4)	
2+	811 (9.5)	788 (9.6)	23 (6.3)	
Admit type				<0.001
Elective	6126 (71.3)	5801 (70.5)	325 (89.0)	
Urgent	1464 (17.0)	1447 (17.6)	17 (4.7)	
Emergent	1001 (11.7)	978 (11.9)	23 (6.3)	
Sex				0.852
M	4513 (52.5)	4323 (52.6)	190 (52.1)	
F	4078 (47.5)	3903 (47.4)	175 (47.9)	
Race				<0.001
White	7412 (86.3)	7105 (86.4)	307 (84.1)	
Black	482 (5.6)	445 (5.4)	37 (10.1)	
Other	697 (8.1)	676 (8.2)	21 (5.8)	
SER				0.34
Mean % below poverty level (95% CI)	10.8 (10.6, 11.0)	10.7 (10.6, 11.0)	10.3 (9.2, 11.4)	
Hospital surgical volume				<0.001
Low	3120 (36.3)	3060 (37.2)	60 (16.4)	
Medium	2730 (31.8)	2610 (31.7)	120 (32.9)	
High	2741 (31.9)	2556 (31.1)	185 (50.7)	
Hospital bed volume				<0.001
Low	2721 (31.7)	2663 (32.4)	58 (15.9)	
Medium	2688 (31.3)	2670 (32.5)	18 (4.9)	
High	2667 (31.0)	2386 (29.0)	281 (77.0)	
Unknown	515 (6.0)	507 (6.1)	8 (2.2)	
Hospital teaching status				<0.001
Nonteaching	3405 (39.6)	3405 (41.4)	0 (0.0)	
Teaching	4671 (54.4)	4314 (52.4)	357 (97.8)	
Unknown	515 (6.0)	507 (6.2)	8 (2.2)	

TABLE 3. Association of NCI Status and Postoperative Mortality, Odds Ratio (P Value)

	Logistic Model				
	Original	Propensity Score	Matched	High Volume	Low Volume
Colon	0.58 (0.008)	0.55 (0.007)	0.56 (0.004)	0.64 (0.005)	0.53 (0.04)
Rectal	0.50 (0.05)	0.49 (0.05)	0.52 (0.1)	0.54 (0.2)	0.49 (0.4)

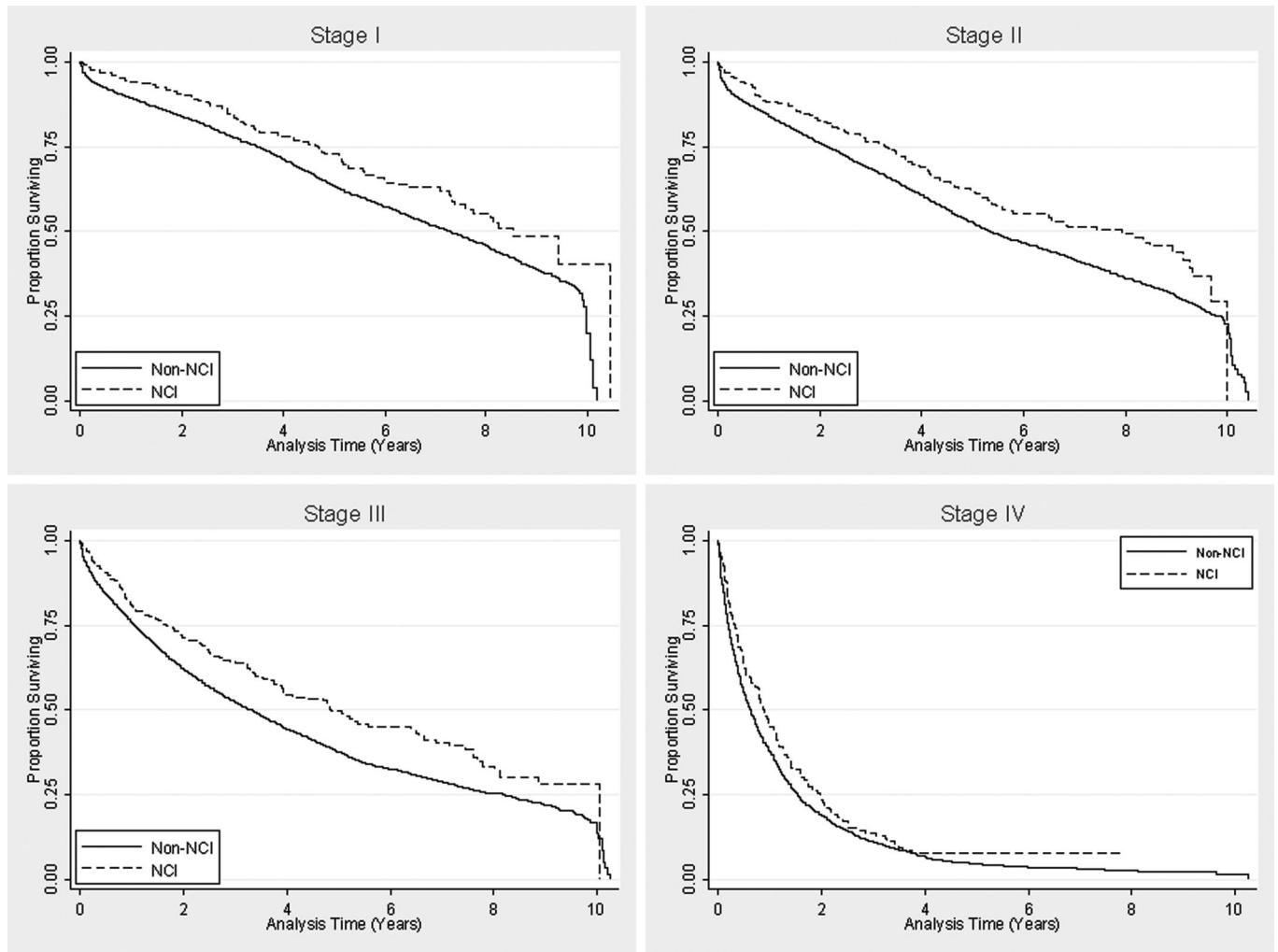


FIGURE 1. Kaplan Meier survival estimates: colon cancer, stages I-IV.

decreased to 0.48 ($P = 0.4$). Again, the point estimates for the association do not change, but the small sample size in the select analyses limits the statistical significance of these values.

Survival Analysis – Colon Cancer

The unadjusted Kaplan Meier curves for the each colon cancer stage are shown in Figure 1. Univariate analysis using the log-rank test indicates that NCI status is significantly associated with improved long-term survival (Table 4). The

TABLE 4. Median Survival (Yrs) After Surgery for Colon Cancer

	Non-NCI	NCI	<i>P</i> *
All stages	4.3	5.4	<0.001
Stage I	7.3	8.5	0.003
Stage II	5.3	7.9	<0.001
Stage III	3.3	4.9	<0.001
Stage IV	0.6	0.9	0.05

**P* value from log rank test.

median survival for all stage patients treated at NCI centers was 5.4 years, compared with only 4.3 years for patients who underwent surgery at non-NCI centers ($P < 0.001$). The difference was most pronounced in stage II and III patients who had median survival times of 7.9 and 4.9 years when treated at NCI centers and 5.3 and 3.3 years, otherwise ($P < 0.001$).

NCI status was included in a Cox proportional hazards model that adjusted for patient and hospital characteristics. When adjusted for these factors, NCI status remained significantly associated with improved survival (HR, 0.83; $P < 0.001$). When limited to high volume centers, the HR actually decreased slightly (HR = 0.78).

Survival Analysis – Rectal Cancer

The unadjusted Kaplan Meier curves for each stage of the rectal cancer cohort are shown in Figure 2. Univariate analysis using the log-rank test indicates that NCI status is significantly associated with improved long-term survival for rectal cancer patients (Table 5). The median survival for all stage patients treated at NCI centers was 5.2 years, compared with 4.4 years for patients who underwent surgery at non-

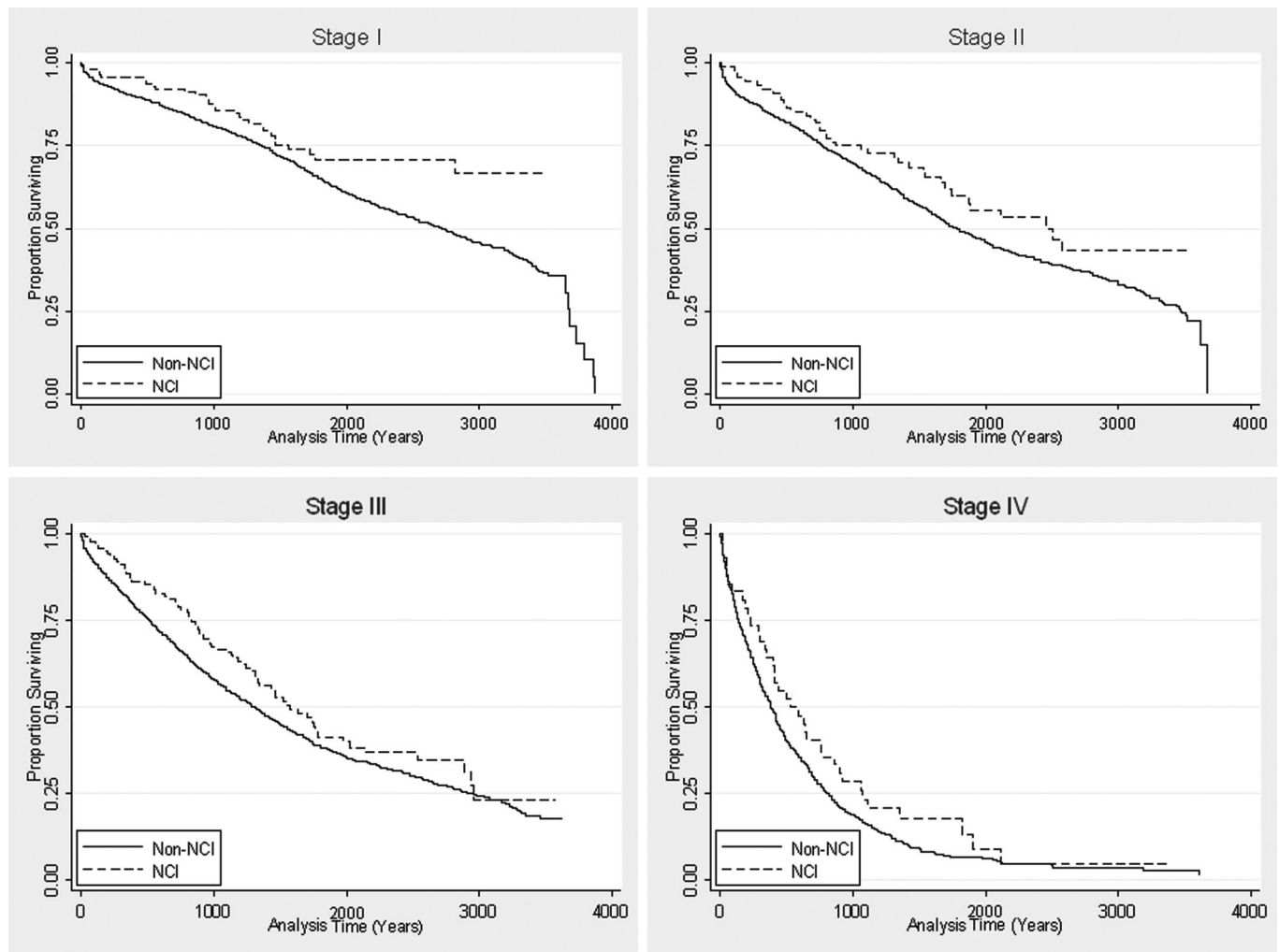


FIGURE 2. Kaplan Meier survival estimates: rectal cancer, stages I-IV.

TABLE 5. Median Survival (Yrs) After Surgery for Rectal Cancer

	Non-NCI	NCI	<i>P</i> *
All stages	4.4	5.2	<0.001
Stage I	7.5	†	0.009
Stage II	4.9	6.9	0.04
Stage III	3.6	4.3	0.05
Stage IV	1.0	1.4	0.09

**P* value from log rank test.

†Greater than 50% of patients alive at end of follow-up.

NCI centers ($P < 0.001$). Although median survival was longer at NCI centers for all stages, the effect was most pronounced in stage II patients. In this group, median survival after resection at an NCI center 6.9 years, whereas it was 4.9 years at non-NCI centers ($P = 0.04$).

As for colon cancer, the association of NCI status and long-term outcome was evaluated while adjusting for relevant patient and hospital characteristics. When adjusted for these

characteristics, NCI status remained significantly associated with improved survival after surgical resection for rectal cancer (HR, 0.84; $P = 0.02$). In addition, limiting the analysis to high volume centers did not affect the observed association between NCI centers and improved long term survival (HR = 0.85).

Sensitivity Analysis

In the sensitivity analysis, we used functional status as an example of an unmeasured confounder affecting the association of NCI status and outcome. We chose the prevalence of the confounder at NCI centers based on the comorbidity data in our cohort. Only 10% of patients at NCI centers had a Charlson score of 2 or greater. We hypothesized that patients with poor functional status would have a Charlson of at least 2. For the purposes of this analysis, we evaluated the effect of this confounder at prevalence rates of 5% and 10% in the NCI cohort. We varied the prevalence of this unmeasured confounder in the non-NCI group to determine the extent to which its distribution would need to be imbalanced to influence the statistical significance of the results (ie, the

TABLE 6. Sensitivity Analysis Estimating the Effect of an Unmeasured Confounder on the Hazard Ratio of Death

Prevalence at Non-NCI Centers	Prevalence at NCI Centers	Unmeasured Confounder HR	NCI HR Adjusting for Unmeasured Confounder (95% CI)
0.10	0.05	1.25	0.84 (0.75–0.95)
0.10	0.05	1.5	0.85 (0.76–0.96)
0.10	0.05	1.75	0.86 (0.77–0.97)
0.15	0.05	1.25	0.85 (0.76–0.96)
0.15	0.05	1.5	0.87 (0.77–0.98)
0.15	0.05	1.75	0.89 (0.79–1.00)
0.15	0.1	1.25	0.85 (0.75–0.95)
0.15	0.1	1.5	0.85 (0.75–0.96)
0.15	0.1	1.75	0.86 (0.77–0.97)
0.2	0.1	1.25	0.85 (0.76–0.96)
0.2	0.1	1.5	0.87 (0.77–0.98)
0.2	0.1	1.75	0.88 (0.79–1.00)

upper bound of the 95% CI crosses 1). For instance, as shown in Table 6, if poor functional status had a prevalence of 5% in the NCI group and a hazard ratio of 1.75, the prevalence of poor functional status in the non-NCI group would need to be 3 times that of the NCI group, or 15%. Based on the analysis of this cohort, it is unlikely that there is an unmeasured patient characteristic that is 3 times as likely in 1 cohort of patients and that the hazard of death associated with that unmeasured confounder is considerable.

DISCUSSION

Our results indicate that undergoing surgical treatment for colon and rectal cancer at an NCI-designated cancer institute is associated with both lower postoperative mortality and improved long-term survival. To our knowledge, only one other study has attempted to look at the association of NCI center and outcome after surgery for 6 different types of cancer, including colon cancer.³ This study, like ours, found a significant difference in the postoperative mortality and long-term survival between NCI and non-NCI centers for colon cancer resection, although the magnitude of the difference was smaller than that observed in this study. Rectal cancer was not separately considered. Interestingly, they did not observe a long-term survival benefit after higher risk procedures such as esophagectomy or pancreatectomy. This contrasts to our results for rectal resections (which are more technically challenging and higher risk than colectomies), where we observed both short- and long-term benefit after resection at an NCI center. The conclusion of this prior article was that NCI status should not be an important factor in deciding where to go for surgical treatment, particularly when examining long-term outcomes. In contrast, our results suggest that undergoing colon or rectal resection at an NCI-designated cancer center confers both short-term and long-term survival benefit.

Our study differed from the prior study of NCI designation in several ways that could account for some of these discrepancies. First, we evaluated rectal cancer resections, which were not included in their analysis. It is possible that

had they looked at outcomes for rectal cancer, they would have found a long term survival benefit at NCI centers. Second, our analysis adjusted for more patient level characteristics, including acuity of admission and, most importantly, based on the SEER data, stage of the tumor. In our cohort, NCI centers treated a significantly greater percentage of patients who had stage IV disease. Patients with stage IV disease clearly have worse long-term survival than patients with stage I, II, or III disease. If stage is not adjusted for in the analyses, the benefit attributed to NCI centers appears diminished.

Third, our study examined patients treated more recently, 1996–2005, whereas as the previous study examined patients treated between 1994–1999. It is possible that the benefit of undergoing treatment at an NCI center has increased over time, perhaps because of the preferential adoption of new medical and surgical treatments by NCI centers. For example, the use of neoadjuvant chemotherapy and radiation for the treatment of advanced stage rectal cancer may have been adopted earlier and more widely at NCI centers. Patients treated surgically at NCI centers may be more likely to receive neoadjuvant care and thus have improved outcomes. Further investigation is necessary to evaluate the patterns of treatment across hospital types in an attempt to better understand our observed results.

Because our study used an observational cohort rather than a randomized controlled trial design, there is concern that the results we observed could be due to selection bias. In other words, it is possible that the benefit we observed is secondary to the underlying characteristics of the patients being treated at NCI centers, instead of the treatment rendered at these centers. For example, if patients treated at NCI cancer centers are “healthier” than patients who are not and we are unable to adjust for this difference, NCI centers may seem to reduce mortality when the difference is actually attributable to treatment of patients less likely to die. Several factors, however, reduce the likelihood that the observed benefit is solely due to selection bias. First, the SEER–Medicare-linked database provides extensive information on patient characteristics such as demographic information, comorbidities, reason for admission, and cancer stage. When we adjusted for all of these patient level factors, the benefit associated with NCI designation persisted.

Second, we performed multiple secondary analyses in an attempt to address the effect of potential selection bias. We used a propensity score model, which is a useful method to adjust for confounding by multiple covariates.¹⁴ In addition, we performed a matched analysis in which patients were matched on patient level characteristics. Patients within each group were the same age category, sex, and race and had the same tumor stage, acuity of admission, and comorbidity burden. In each of these analyses, the benefit of NCI status remained unchanged.

Lastly, our sensitivity analysis demonstrates that our main result is robust even if an unknown and unbalanced confounder were present. For example, using a baseline prevalence rate of 5% in the NCI group and an increased risk of death of 1.75, the unmeasured confounder would need to be 3 times more common, 15%, in the non-NCI group to

eliminate a statistically significant association of NCI designation and improved survival in colon cancer patients. Based on the distribution of covariates in this cohort, it is unlikely that there is a patient-level confounder present in such disparate rates between the 2 patient populations.

Our study has several limitations. First, when using administrative claims data, there is always the possibility of misclassification due to miscoding. The SEER-Medicare data, however, have been well-validated for studying outcomes of cancer surgery and have been used in numerous other such studies.^{5,15} Second, because we restricted our study population to patients over 65 for reasons delineated above, we cannot generalize our results to younger patients. The average age of colorectal cancer diagnosis in the United States, however, is 72, with the majority of patients being diagnosed after the age of 65. Given the demographics of colorectal cancer, it is reasonable and appropriate to study the disease in the Medicare population.

Third, the center surgical volumes determined using the methods above are based solely on numbers of procedures performed at each hospital on patients living in a SEER region. They are not total hospital procedure volumes. The use of SEER-Medicare volume as a proxy for total hospital procedure volume, however, has been validated by studies comparing ranking of hospitals based on Medicare volume versus ranking based on total volume. Medicare case volume, in these reports, has been shown to correlate highly with total volume, and numerous prior studies using the SEER database use this proxy approach.^{10,11,16,17}

Despite this, we were still concerned that some high volume NCI centers might be misclassified as low volume centers. Patients living in SEER areas might travel outside of their area to undergo treatment at one of these referral-based cancer centers. Based on our volume calculation, only the patients living in a SEER region treated at these NCI centers would count towards volume. This could result in misclassification of some of the high-volume NCI centers as low volume. As high volume is known to be a predictor of improved outcomes after many types of cancer surgery, these centers might look better when the results are adjusted for volume (the “low volume” NCI centers will look better compared with the low volume non-NCI centers). To address this issue, we evaluated postoperative mortality in 1 model limited to high volume centers and another limited to low volume centers. As discussed in the results, when limited to high volume centers, the effect of NCI center was slightly attenuated; when limited to low-volume centers, the benefit of NCI designation was more pronounced. Despite this, NCI designation remained associated with a significantly lower hazard of death, even in the high volume only cohort. This indicates that although volume may account for a small portion of the benefit seen at NCI centers, it does not account for the majority of the benefit.

Although our study did not examine the pathways by which treatment at an NCI center may lead to improved outcomes, there are several plausible potential reasons for this association. NCI centers may have services, such as advanced ICUs, trained code teams, and certain diagnostic capabilities

associated with lower postoperative mortality rates. The presence of these types of sophisticated services is shown to be a significant predictor of postoperative mortality.^{9,18,19} In general, these services are associated with high volume centers, and it is speculated that they account for much of the mortality benefit observed at high volume institutions.⁹ In this study, however, postoperative mortality was lower at NCI Centers even when only high volume hospitals were evaluated.

In addition, surgeons at NCI centers may be more likely to concentrate their area of focus through fellowship training in colorectal surgery or surgical oncology. High case-specific volume and repetition of technically complex procedures are well described factors influencing improved colorectal outcomes and may impact individual patient outcomes to a far greater degree than hospital volume alone.^{9,20–22} In addition to volume, surgeon specialization has been shown to be associated with lower postoperative mortality rates and improved long-term survival.^{22–24}

Additionally, NCI centers may be more likely to treat patients based on the most current guidelines. For example, as discussed above, patients with stage II or III rectal cancer may be more likely to get appropriate neoadjuvant chemoradiation at an NCI center and postoperative referrals to medical oncology. In addition, it is reasonable to speculate that patients operated on at an NCI center may be more likely to have appropriate and timely surveillance for recurrence. This adherence to the most current guidelines for treatment and follow-up should result in improved long-term survival.

CONCLUSIONS

The results of our study indicate that NCI cancer center designation is associated with a lower risk of postoperative death and improved long-term survival. NCI designation most likely serves as a proxy for some complement of hospital and staff characteristics found at these centers that positively impact patient outcome. Most NCI centers are high volume institutions. Volume alone, however, does not explain the observed benefit. Cancer care involves operative success and a complicated and rigorous perioperative treatment algorithm involving a wide spectrum of medical and surgical personnel. It is plausible to assume that NCI cancer centers, in addition to being high volume surgery centers, are more adept at coordinating and managing complex cancer care. Most likely, it is an intricate combination of multidisciplinary team meetings; surgeon, oncologist, and pathologist specialization and volume; and familiarity with and adherence to treatment guidelines that mediate the improved patient outcomes seen at NCI centers. Future studies are underway in an attempt to further elucidate the specific factors leading to these improved patient results.

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Discussions

DR. BRUCE G. WOLFF (ROCHESTER, MINNESOTA): The issue of quality in surgery and its determinants is one of the most controversial we face. In general, there are thought to be 2 ways of achieving good outcomes. One is through a multidisciplinary systematic management of a disease pro-

cess and the other is through establishing process markers and requirements, such as timely administration of perioperative prophylactic antibiotics.

The latter is fairly simple to measure and relatively inexpensive, at least for the reviewing parties, and is favored by stakeholders such as CMS, insurance companies, the National Quality Forum, and even the American College of Surgeons. However, there is ample evidence from studies that the administration of prophylactic antibiotics in the VA population shows no positive effect on surgical site infections, and several studies show problems with the 12 lymph node harvest criterion in colorectal cancer. Thus, process determinants may not reflect quality in terms of better outcomes, and this calls into question the validity of the whole pay-for-performance program.

The authors have done us a great service by bringing us further information that quality is complex and multifactorial, and that quality markers are not likely to be simple isolated measurements.

I have just one very difficult question for you to answer, and that is: What now?

Can NCI designated centers possibly deal with 150,000 new colorectal cancer patients every year and the ongoing treatment of patients? Having given credence to a systematic approach to colorectal cancer, what suggestions can the authors provide for those regional non-NCI-designated centers with more limited resources to bring their outcomes into line? Or, as in Scandinavia and Europe, are we headed for treatment of all colorectal cancer patients in regional centers of excellence?

DR. FREDERICK L. GREENE (CHARLOTTE, NORTH CAROLINA): For the last 5 years, I have served as Chairman of the Commission on Cancer of the American College of Surgeons. In that position I oversaw our Approvals Program and its 1480 hospitals. After hearing this presentation, I am saddened and concerned about taking a small group – we do have 32 of the NCI centers in this group – and highlighting care in these institutions. The message we try to give to all of our Approved Hospitals is that all of our approved institutions should achieve a level of care based on certain indicated standards and the achievement of quality benchmarks that are given back to hospitals. One of those benchmarks has been the 12 lymph node count that was just referenced.

Blue Cross and Blue Shield just last month decided to list 85 hospitals chosen to treat rare and complex cancers. If you are not practicing in one of those hospitals, you will be disadvantaged because those patients will not be referred to you. This is a further example of selecting institutions based on arbitrary indicators.

One of my questions relates to risk adjustment. Unfortunately, none of our registry information includes comorbidities and our registrars do not routinely include these data.

I would like to ask whether comorbidity information should be included in the registry information.

Finally, when your article is published in the *Annals of Surgery* and is read by surgeons working in small and medium-sized community hospitals, what is the message that you want surgeons or those hospitals to take away from this study?

DR. NAJIA N. MAHMOUD (PHILADELPHIA, PENNSYLVANIA): I would like to think that this study represents a 30,000-foot view of disparities in care in the treatment of colon and rectal cancer based on differences in short- and long-term mortality. Although NCI centers are commonly viewed as “centers of excellence,” exactly what they are excellent at in the clinical setting is not clear, and is not clarified by these data, nor will it be clarified by studies examining large administrative databases.

Process measurements, such as surgical site infection, DVT prophylaxis, adherence to beta blockade, et cetera, are easy data to measure, compare, and price, which is why they are such attractive targets for governmental and nongovernmental quality organizations, medical societies, payers, insurance buyers, and the public itself.

Cancer care does not fit easily into this category. It is complicated and multifactorial, as we all know. It involves patient participation, choices, and compliance to a much greater degree and it is highly dependent on the timely and accurate transmission of medical information among treating physicians.

It will be much more challenging to examine which specific differences in care result in improved outcomes in the multidisciplinary systematic disease management model that Dr. Wolf suggests is more appropriate for the examination of differences in care in colon and rectal cancer, yet we must try, because I think that this is the most appropriate model in which to consider this disease and the treatment paradigms.

We know from this very well-controlled data that there are differences in outcomes between NCI and non-NCI designated centers. We suspect, but we do not know, that these outcomes are not confined to just NCI centers. We have not

parsed this out in this study, and we suspect that NCI-like clinical centers with high surgeon volume, not just hospital volume, and specialization without the basic science research component may have similar outcomes. This is supported in the literature and it has been demonstrated by others.

Even so, there are “process measurements” within this multidisciplinary systematic disease management model that we may look to. For example, the controversial 12 lymph node measurement data, adherence to preoperative chemotherapy and radiation protocols for advanced rectal cancer, and the timely referral of your colon and rectal cancer patients with advanced stage disease for postoperative chemotherapy. There are real differences between NCI and non-NCI designated centers in this regard.

We know that our results endure when adjusted for both patient and hospital characteristics like acuity, which gets to the comorbidities question, and volume. There are multiple ways that this can be explored at the institutional level, and that may be where we need to turn for a more comprehensive analysis guided by this overview.

If colon and rectal cancer were treated only at NCI centers, then 147,000 patients in 2007 would be treated only at 62 centers in the United States, which would mean that each center would see 2371 patients per year per center. That is 7 new colorectal cancer patients per day every day of the year. This is not only an impossible scenario for these hospitals; it is an impossible scenario for our patients as well.

Establishing special centers for highly specialized surgery may be possible for other smaller countries, and perhaps even other much more rare cancers and tumors, but it would be very difficult to do this in the United States for a disease that effects so many without envisioning a scenario where care is severely curtailed to a large portion of the population.

Studies like these give us an overview of what is going on to guide investigation into achievable ways to improve care, that are cost effective, data-driven, and that are ultimately meaningful.