

Original Investigation

A Novel Risk-Adjusted Nomogram for Rectal Cancer Surgery Outcomes

Maria C. Russell, MD; Y. Nancy You, MD, MHSc; Chung-Yuan Hu, MPH, PhD; Janice N. Cormier, MD, MPH; Barry W. Feig, MD; John M. Skibber, MD; Miguel A. Rodriguez-Bigas, MD; Heidi Nelson, MD; George J. Chang, MD, MS

IMPORTANCE The circumferential resection margin is the primary determinant of local recurrence and a major factor in survival in rectal cancer. Neither chemotherapy nor chemoradiation compensates for a margin positive for cancer.

OBJECTIVE To identify treatment-related factors associated with hospital margin-positive resection and to develop a tool that could be used by individual hospitals to assess their outcomes based on their unique mix of patient and tumor characteristics.

DESIGN Retrospective review of the National Cancer Data Base, 1998-2007.

SETTINGS Community and academic/research hospitals.

PARTICIPANTS Individuals with histologically confirmed localized rectal/rectosigmoid adenocarcinoma.

EXPOSURE All individuals underwent radical resection for rectal cancer with or without neoadjuvant therapy.

MAIN OUTCOMES AND MEASURES Rate of margin positivity determined and adjusted for patient- and tumor-related factors to calculate expected margin positivity per hospital. An observed to expected ratio was calculated based on patient- and tumor-related factors to identify treatment-associated variation.

RESULTS The overall margin-positive resection rate was 5.2%. Patients with margins positive for cancer were more likely to be older, male, and African American; not have private insurance; and have their cancer diagnosed later in the study period. Associated tumor-related factors include rectal location, higher American Joint Committee on Cancer stage, signet/mucinous histology, and poor/undifferentiated grade. Among hospitals that were significantly low outliers, 47% were comprehensive community hospitals, and 43.9% were academic/research hospitals; of those that were significantly high outliers, 52.3% were comprehensive community hospitals, and 17.8% were academic/research hospitals. High-volume centers made up 80% of significantly low outlier hospitals and 17% of significantly high outlier hospitals. The rates of chemotherapy and radiation were similar, but low outlier hospitals gave more neoadjuvant radiation (26.3% vs 17%).

CONCLUSIONS AND RELEVANCE After adjustment for patient- and tumor-related factors, we identified both low and high outlier hospitals for margin positivity at resection, as well as potentially modifiable risk factors. The nomogram created in this model allows for the evaluation of observed and expected event rates for individual hospitals, providing a hospital self-assessment tool for identifying targets for improvement.

JAMA Surg. 2013;148(8):769-777. doi:10.1001/jamasurg.2013.2136
Published online June 26, 2013.

← Invited Commentary page 778

+ Supplemental content at
jamasurgery.com

Author Affiliations: Department of Surgical Oncology, Emory University, Atlanta, Georgia (Russell); Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston (You, Hu, Cormier, Feig, Skibber, Rodriguez-Bigas, Chang); Department of Surgery, Mayo Clinic College of Medicine, Rochester, Minnesota (Nelson).

Corresponding Author: George J. Chang, MD, MS, Department of Surgical Oncology; University of Texas MD Anderson Cancer Center, 1400 Pressler St, FCT 17.6000, Houston, TX 77030 (gchang@mdanderson.org).

In 2012, there were an estimated 40 290 cases of rectal cancer diagnosed in the United States. Colorectal cancer is the second leading cause of US cancer death, with rectal cancer accounting for approximately one-third of colorectal cancer deaths.¹ For cases without metastases, the primary treatment is radical resection with proctectomy and en bloc radical lymphadenectomy; for locally advanced cases, primary treatment is perioperative radiation and chemotherapy. The widespread adoption of sharp total mesorectal excision has improved local control and survival by improving radical lymph node clearance and decreasing the risk for a surgical margin positive for cancer (hereafter referred to as a positive margin). Accordingly, local recurrence rates have decreased to 5% to 10% from as high as 50%.²⁻⁴ Circumferential resection margin status has been identified as one of the most important determinants of local recurrence risk. Positive resection margins are associated with metastatic disease and decreased survival.^{5,6} Unfortunately, neither radiation nor chemotherapy can compensate for a positive margin in rectal cancer.^{7,8} Therefore, the achievement of a negative resection margin is a primary goal of surgery for rectal cancer.

A number of tumor-related factors are associated with the risk for margin positivity at rectal cancer resection. Tumor location in the distal third of the rectum, T4 status, advanced local nodal stage, need for abdominoperineal resection, and anteriorly located tumors are associated with a higher risk of margin positivity. Patient- and treatment-related factors have also been identified, including American Joint Committee on Cancer (AJCC) stage and advanced age.^{7,9-14}

Factors influencing the risk for margin positivity at resection can be categorized as patient-, tumor-, and treatment-related factors. To further investigate these relationships, we used a large hospital-based national database to examine risk factors for margin-positive resection of rectal cancer. We specifically sought to identify treatment-related factors associated with margin-positive resection and to develop a tool that could be used by individual hospitals to assess their outcomes based on their unique mix of patient and tumor characteristics.

Methods

Data Source

Data from the National Cancer Data Base (NCDB) were used for our study. The NCDB is a joint program of the Commission on Cancer of the American College of Surgeons and the American Cancer Society and is used as a surveillance tool to assess patterns of care for patients with cancer.¹⁵ More than 1500 cancer programs in the United States are accredited by the Commission on Cancer of the American College of Surgeons; the NCDB captures approximately 76% of newly diagnosed cancer cases. Hospitals contributing to the NCDB are classified as academic/research hospital cancer programs, comprehensive cancer programs, or community hospital cancer programs. Data collected for each cancer case include patient characteristics, cancer staging, tumor characteristics, types of treatment administered, and outcomes.

Population

Rectal or rectosigmoid cancers (*International Classification of Disease for Oncology* codes C199 and C209) were identified within the NCDB between 1998 and 2007 (Figure 1). All patients with histologically confirmed adenocarcinoma who had undergone a partial or complete proctectomy (excluding cases of local tumor excision/destruction), were 18 to 90 years of age, and had received no prior cancer diagnosis were included. Patients who died within 30 days of cancer diagnosis, had stage IV disease, or had an unknown margin status were excluded. Finally, hospitals reporting a margin-positive rate of 0 were excluded because they may have been subject to either very low procedure volume or coding discrepancies that precluded analysis.

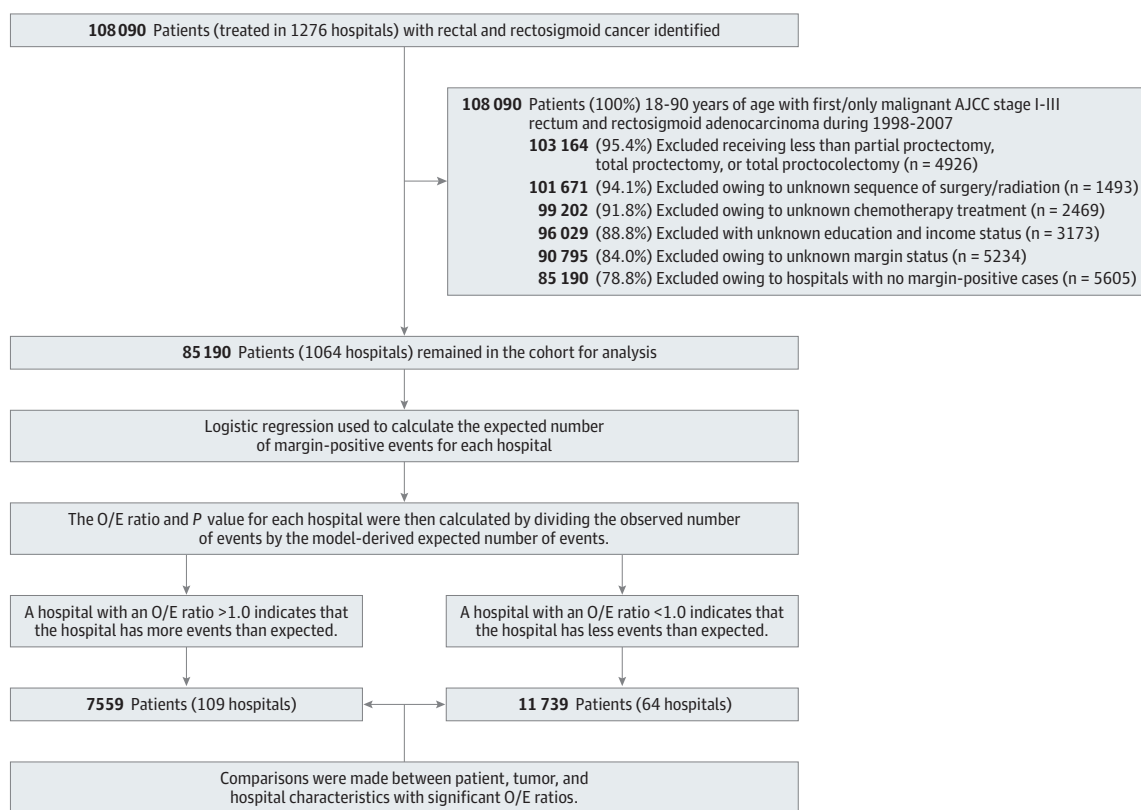
Statistical Analysis

We analyzed data on the basis of patient-, tumor-, and treatment/hospital-related variables. The primary outcome measure was the individual hospital rate of margin-positive resection adjusted for patient- and tumor-related risk factors. Demographic data included patient age (categorized in groups as 18-49, 50-75, and 76-90 years), sex, race, year of diagnosis, insurance status, median quartile income, percentage of residents in the patient's neighborhood without a high school diploma, and area-based measures of residence as metropolitan, urban, or rural. The patients' educational and income levels were assessed by matching patients' zip codes to files derived from 2000 US Census data coded as quartiles. Tumor characteristics included anatomic location (rectosigmoid vs rectum), AJCC (sixth edition) tumor stage, tumor size, histology, and grade. Treatment-related variables included type of facility (community cancer program, comprehensive community cancer program, or academic/research program), yearly hospital surgical volumes categorized by quartiles, receipt of chemotherapy or radiotherapy and the sequence of treatment, and specific type of surgery (low anterior resection, coloanal anastomosis, or abdominoperineal resection).

We sought to ascertain the hospital rate of margin positivity after adjustment for patient- and tumor-related risk factors in order to identify potentially modifiable treatment-related factors. We first developed a patient-level multivariable risk model for margin positivity using multiple logistic regression analysis incorporating important patient- and tumor-related clinical variables, leaving the treatment-related factors unadjusted in the model for post hoc comparison.

This risk model was used to calculate the expected number of patients with a positive margin for each hospital by summing all patients' risk estimates by hospital. The observed number of margin-positive cases was then divided by the expected number of events (based on patient- and tumor-related factors) to create an observed to expected (O/E) ratio for each hospital. To estimate the significance of the O/E ratio, the probability (P) that a hospital had exactly the observed number of events ($X = k$) was determined based on the binomial function $P(X = k)$, where k denotes the actual number of events observed within the hospital, n denotes the hospital volume, and P denotes the model-

Figure 1. Study Design



AJCC indicates American Joint Committee on Cancer, sixth edition; O/E ratio, observed to expected ratio.

derived expected probability of the event.¹⁶ Finally, hospital- and treatment-related factors were compared on the basis of statistically significant outlier status.

Nomogram

A nomogram was constructed using multivariate logistic regression analysis and internally validated for model discrimination and calibration by bootstrapping with 200 resamples. Model discrimination was first quantified using the concordance index to measure the predictive accuracy of the model by analyzing all possible pairs of patients. After quantifying the model discrimination, the model calibration was graphically assessed using a calibration plot.¹⁷

All statistical analyses were performed using Stata MP software version 11.0 (release 2010), and the R software (www.r-project.org/) with the RMS package was used to construct the nomogram. Because the analysis used preexisting data with no personal identifiers, it was exempt from review by our institutional review board.

Results

A total of 85 190 patients (treated in 1064 hospitals) met the study criteria and were eligible for analysis. The identifica-

tion of cases and a flowchart of the analysis are shown in Figure 1. Demographic and tumor data for all patients are summarized in our Table. The overall rate of margin-positive resections for the entire cohort was 5.2%. Patients with a margin-positive resection were more likely to be older, male, and African American; to have their disease diagnosed in the more recent years of the study period (2004-2007); and to not have private insurance. Other demographic factors, including median income quartile, educational level, and residence (rural vs urban), were not associated with risk of margin positivity.

Baseline patient and tumor characteristics and margin status are summarized in our Table. Tumors located in the rectum with a higher AJCC stage (final pathology stage), signet or mucinous histology, or classified as poorly differentiated or undifferentiated were associated with a higher risk for positive margin. Tumor size was not associated with margin status.

Adjusted Risk Model

An adjusted risk model for margin positivity was developed based on patient and tumor characteristics. Nearly 64% of patients in the patient sample were between 40 and 75 years of age. The margin-positive rate was lowest in this group. On multivariate analysis, patient-related factors associated with a small to moderate increased risk for margin positivity (adjusted odds ratio [AOR] 1.0-1.50) included age older than 75 years, male sex,

Table. Margin-Positive Rate and Adjusted Risk of Margin Positivity for Patients With Surgically Treated Rectal and Rectosigmoid Adenocarcinoma, 1998-2007

Characteristics	Patients, No. (%)	Margin-Positive Patients, %	AOR (95% CI)
Overall	85 190 (100.0)	5.2	
Age at diagnosis, y			
18-49	11 932 (14.0)	5.9	1 [Reference]
50-75	54 416 (63.9)	4.9	0.96 (0.88-1.05)
76-90	18 842 (22.1)	5.7	1.18 (1.07-1.32)
Sex			
Female	37 203 (43.7)	5.1	1 [Reference]
Male	47 987 (56.3)	5.3	1.07 (1.01-1.15)
Race			
White	75 134 (88.2)	5.1	1 [Reference]
Black	5951 (7.0)	6.6	1.21 (1.08-1.36)
Other	4105 (4.8)	5.6	1.04 (0.90-1.19)
Year of diagnosis			
1998-1999	15 683 (18.4)	4.7	1 [Reference]
2000-2001	16 504 (19.4)	4.3	0.92 (0.83-1.03)
2002-2003	17 234 (20.2)	5.0	1.06 (0.95-1.17)
2004-2005	18 120 (21.3)	5.8	1.23 (1.11-1.36)
2006-2007	17 649 (20.7)	6.1	1.31 (1.19-1.45)
Insurance status			
Private insurance	13 138 (15.4)	4.7	1 [Reference]
Not insured	2254 (2.6)	8.5	1.54 (1.29-1.84)
Government	67 733 (79.5)	5.2	1.10 (1.00-1.21)
Unknown	2065 (2.4)	5.6	1.15 (0.93-1.42)
Median income quartile, \$			
<30 000	11 239 (13.2)	5.6	1 [Reference]
30 000-34 999	15 761 (18.5)	5.4	1.04 (0.93-1.17)
35 000-45 999	24 247 (28.5)	5.3	1.05 (0.94-1.18)
≥46 000	33 943 (39.8)	4.9	0.99 (0.87-1.13)
Patients without high school degree, ^a %			
<14.0	14 022 (16.5)	5.5	1 [Reference]
14.0-19.9	20 493 (24.1)	5.5	1.04 (0.94-1.15)
20.0-28.9	21 345 (25.1)	5.2	1.02 (0.91-1.14)
≥29	29 330 (34.4)	4.9	1.00 (0.88-1.13)
Population density of residence			
Metro area	69 087 (81.1)	5.1	1 [Reference]
Urban area	12 879 (15.1)	5.5	1.02 (0.93-1.11)
Rural area	3224 (3.8)	5.4	0.97 (0.83-1.14)
Tumor location			
Rectosigmoid	32 294 (37.9)	4.9	1 [Reference]
Rectum	52 896 (62.1)	5.4	1.19 (1.11-1.27)
AJCC tumor stage			
I	26 978 (31.7)	1.3	1 [Reference]
IIA	22 748 (26.7)	3.9	2.90 (2.55-3.30)
IIB	1988 (2.3)	23.6	21.80 (18.74-25.36)
IIIA	5954 (7.0)	2.2	1.70 (1.39-2.08)
IIIB	14 747 (17.3)	7.7	5.93 (5.24-6.71)
IIIC	12 775 (15.0)	11.5	8.33 (7.36-9.42)
Tumor size, mm			
≤10	2874 (3.4)	2.6	1 [Reference]

(continued)

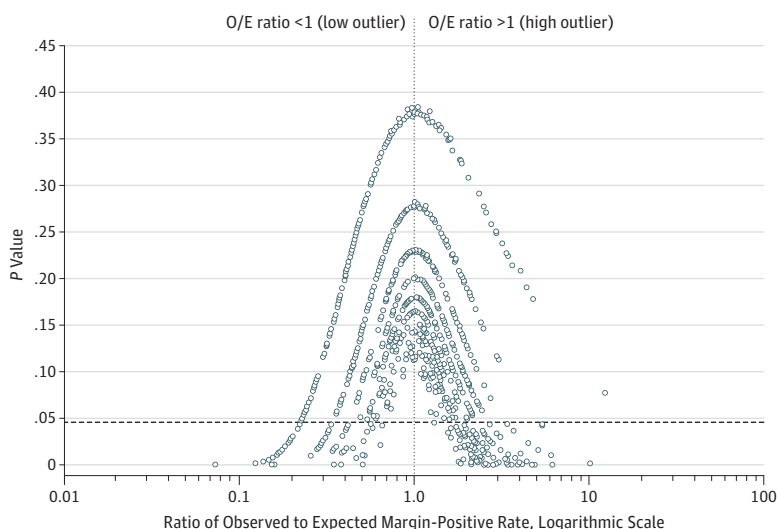
Table. Margin-Positive Rate and Adjusted Risk of Margin Positivity for Patients With Surgically Treated Rectal and Rectosigmoid Adenocarcinoma, 1998-2007 (continued)

Characteristics	Patients, No. (%)	Margin-Positive Patients, %	AOR (95% CI)
11-20	8178 (9.6)	2.9	0.92 (0.70-1.20)
21-998	62 055 (72.8)	5.6	1.09 (0.86-1.38)
Unknown	12 083 (14.2)	5.3	1.30 (1.01-1.66)
Histology			
Adenocarcinoma	78 580 (92.2)	4.7	1 [Reference]
Signet ring	586 (0.7)	22.4	2.49 (2.02-3.07)
Mucinous	6024 (7.1)	9.6	1.51 (1.38-1.67)
Tumor grade			
Well or moderately differentiated	68 940 (80.9)	4.5	1 [Reference]
Poorly differentiated or undifferentiated	11 902 (14.0)	9.4	1.44 (1.33-1.56)
Unknown	4348 (5.1)	4.7	0.95 (0.82-1.11)

Abbreviations: AJCC, American Joint Committee on Cancer, sixth edition; AOR, adjusted odds ratio.

^a Assessed by matching patients' zip codes to files derived from 2000 US Census data coded as quartiles.

Figure 2. Ratio of Observed to Expected Margin-Positive Rates (ie, Rates of Margins That Are Positive for Cancer)



O/E ratio indicates observed to expected ratio.

African American race, and more recent year of diagnosis (2004-2005 and 2006-2007). A stronger association was observed with lack of private insurance with a 63% relative increase in margin positivity (8.5%; AOR, 1.54 [95% CI, 1.29-1.84]).

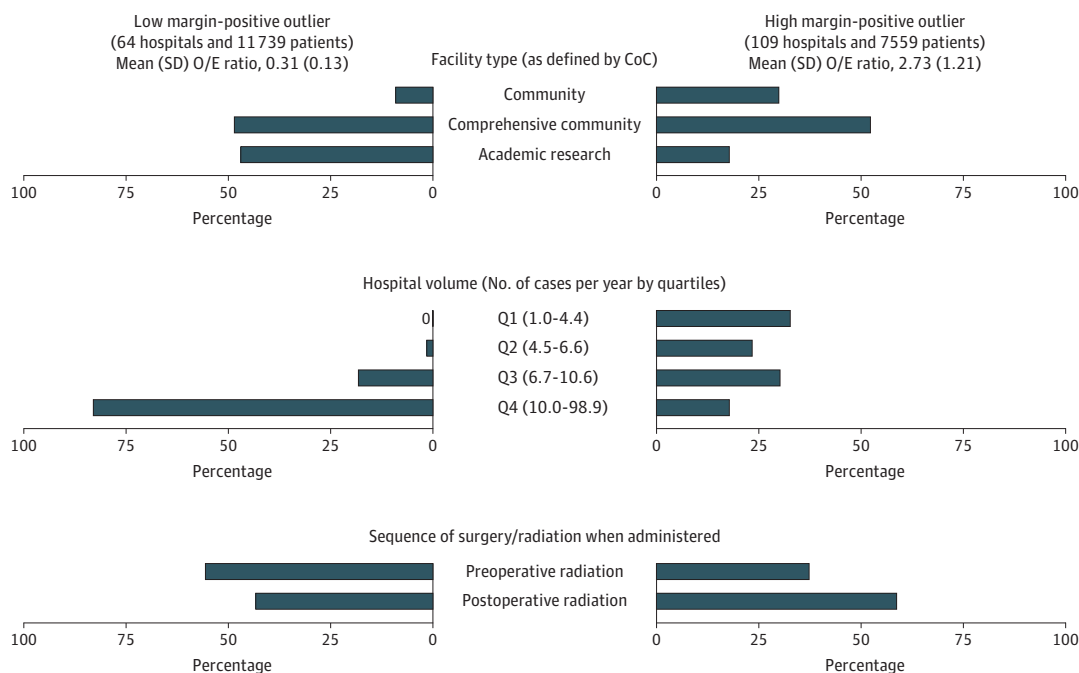
Tumor-specific factors were evaluated on the final pathologic specimen. Factors significantly associated with a moderately increased risk for margin positivity included poorly differentiated grade and tumor location in the rectum. Stronger associations were observed for signet ring cell or mucinous histologic type, and more advanced T or N category. The highest rates of margin-positive resection were associated with AJCC stage IIB tumors (margin-positive rate, 23.6%; AOR, 21.8 [95% CI, 18.74-25.36] vs stage I tumors) and signet ring histology (22.4%; AOR, 2.49 [95% CI, 2.02-3.07] vs non-signet ring, non-mucinous adenocarcinomas) (Table). Notably, 24% of patients with stage IIB cancer received neoadjuvant radiation, and 20.3% of these patients had a positive margin at resection. As expected, the margin-positivity rate for the adjuvant group was higher at 31.5%.

Observed to Expected Rates

The O/E ratio of margin-positive resection was determined for individual hospitals (Figure 2) and plotted logarithmically to compare the ratios of observed to expected margin-positive resection rates according to the model-derived expected probabilities. Hospitals with an O/E ratio of 1 had exactly the same number of observed margin-positive cases as expected according to patient and tumor characteristics. Those with an O/E ratio of more than 1 had a greater number of observed margin-positive tumors than expected; those with an O/E ratio of less than 1 had fewer observed margin-positive tumors than expected. These were further designated as significantly high (referred to as “high outliers”) and significantly low outliers (referred to as “low outliers”) on the basis of the probability of H₀: O = E, defined by P < .05. This allowed us to make comparisons among the hospitals on the basis of outlier status, taking into account hospital characteristics and treatment patterns.

Of the total 1064 hospitals examined, 173 were significant low or high outliers. Of the low outliers (significantly fewer than

Figure 3. Percentage of Significantly Low and High Margin-Positive Outliers by Facility Type, Hospital Volume, and Surgery/Radiation Sequence



CoC indicates Commission on Cancer of the American College of Surgeons and the American Cancer Society; O/E ratio, observed to expected ratio; Q1-Q4, 4 quartiles. The grey bars represent percentages within each category.

expected margin-positive resections), 9.1% were community cancer programs, 47% were comprehensive community hospitals, and 43.9% were academic/research hospitals (Figure 3). Of the high outlier hospitals (significantly greater than expected margin-positive resections), 29.9% were community cancer programs, 52.3% were comprehensive community hospitals, and 17.8% were academic/research institutions.

Hospitals were stratified by yearly surgical volume into quartiles, and differences in positive-margin rates between significantly high- and low-volume hospitals were assessed (Figure 3). Among the low outlier hospitals, more than 80% were the highest quartile for volume (10.7-98.9 cases per year). No hospitals from the lowest quartile for volume (1.0-4.4 cases per year) were low outliers. However, high volume did not preclude high outlier status because 17.8% of the high margin-positive outliers were high-volume hospitals, whereas the remaining hospitals were fairly evenly distributed among mid-high-volume (32.7%), mid-low-volume (23.4%), and low-volume (26.2%) quartiles.

The treatment-related variables assessed included receipt of chemotherapy or radiation therapy and their sequence. We also examined type of surgery (low anterior resection, coloanal anastomosis, or abdominoperineal resection) to examine differences between the significant outlier groups. Rates of chemotherapy (54.1% vs 54%) or radiation therapy (46.5% vs 45.8%) between the low and high outlier hospitals did not differ meaningfully. However, there were notable differences in the sequence of surgery and radiation. Among low outlier hospitals, 56.6% of the patients who received radiation received it prior to surgery, whereas among high outlier

hospitals, only 37.3% of patients received radiation prior to surgery. Finally, there was little difference between the low and high outlier groups with regard to specific operation. The majority underwent a low anterior resection, whereas coloanal anastomosis was a more common procedure in the low outlier hospitals (8.5%) than in the high outlier hospitals (5.5%).

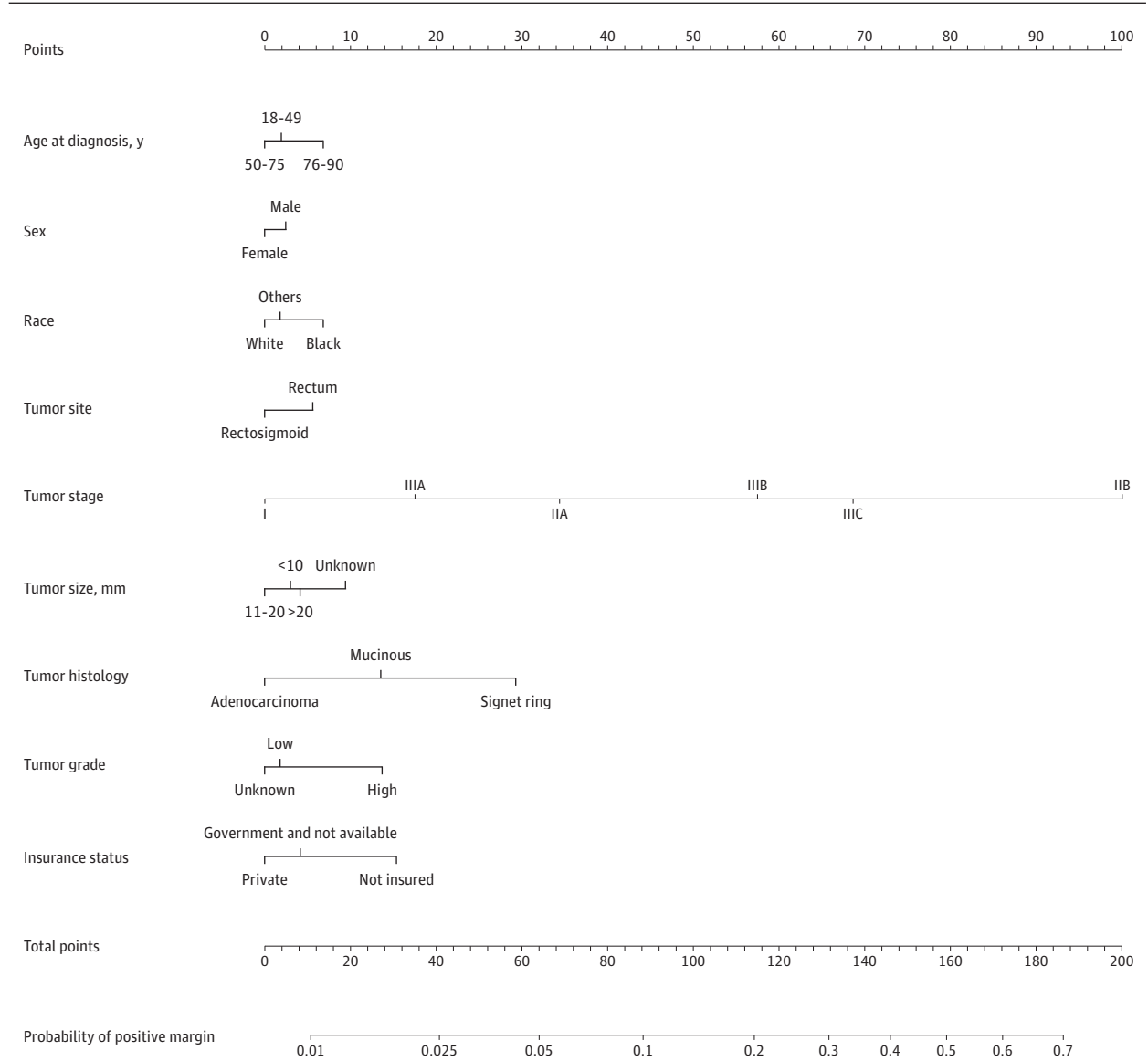
Nomogram

We used the logistic regression model (Table) to construct a nomogram for determining the expected rate of margin positivity for a given hospital (Figure 4). The nomogram has a bootstrap-corrected concordance index of 0.7474 (eFigure in Supplement), indicating good performance. The calibration plot demonstrates that the predicted probability derived from the nomogram corresponds well with the observed probability and is slightly overestimated only when greater than 0.3. This nomogram can thus be used to determine an individual hospital’s expected rate of margin-positive resection for comparison with its observed rate within the NCDB.

Discussion

Resection margin status is a primary determinant of long-term oncologic outcome among patients with rectal cancer. In our study, we used the NCDB to investigate the relationship between patient-, tumor-, and treatment-related variables and the risk for margin positivity during resection for rectal cancer. The analysis demonstrates a number of patient-related risk factors for margin-positive resection, including older age, male

Figure 4. Nomogram for Predicting the Probability of Margin Positivity



To calculate the probability of a positive margin (ie, a margin positive for cancer), first obtain the value for each predictor by drawing a vertical line straight upward from that factor to the points' axis, then sum the points

achieved for each predictor, and locate this sum on the total points' axis of the nomogram where the probability of a positive margin can be located by drawing a vertical line downward.

sex, African American race, and public insurance. Tumor-related risk factors include more advanced AJCC stage (especially T category), signet or mucinous histology, and poor/undifferentiated grade.

Using the adjusted risk model, we determined the ratio of observed to expected rates of margin positivity and identified 173 of 1064 hospitals that were significant high or low outliers. High outlier status was associated with a lower rate of neoadjuvant radiotherapy, lower hospital volume, and non-academic/research hospital type, whereas low outlier status was associated with a higher rate of neoadjuvant radiotherapy, high hospital volume, and academic/research hospi-

tal type. However, it was highly notable that neither academic/research hospital type nor high hospital volume precluded high outlier status.

The historically high rates of local failure following resection of rectal cancer were dramatically improved with the widespread adoption of the sharp total mesorectal excision technique.^{4,7,18,19} Total mesorectal excision improves the clearance of regional lymph nodes and the achievement of negative circumferential resection margins. Previous studies^{14,20-22} of risk factors for circumferential resection margin positivity have focused on tumor-related factors such as T and N categories, tumor size and location, vascular invasion, and the

need for abdominoperineal resection. Other studies²³⁻²⁵ have reported associations between higher provider and hospital volumes and improved outcomes for oncologic procedures. In the present analysis, we have identified additional patient- and tumor-related factors associated with an underlying risk for margin-positive resection. In addition, we have identified the use of preoperative radiotherapy and treating facility characteristics as important treatment-related factors accounting for outlier status and significant variance from risk-adjusted expected rates of margin positivity. We then developed a nomogram that individual hospitals can use to determine their own risk-adjusted expected margin-positivity rates. With this nomogram, individual hospital-based cancer programs can use their own previously abstracted data to determine their expected rate of margin-positive resection and compare it with the benchmark-expected rate based on their individual patient and tumor mix. If significant variance is identified, it can alert the cancer program to consider quality improvement initiatives to decrease their rates of margin positivity.

Resection margins have a significant effect on both local recurrence and disease-free survival.^{5,6,26-28} Neither preoperative radiotherapy nor adjuvant chemotherapy can compensate for margin positivity; however, randomized trials²⁹⁻³¹ have demonstrated that neoadjuvant radiotherapy can improve local control. Furthermore, preoperative combined modality chemotherapy and radiation has been associated with improved local control, margin-negative resection, and the potential for sphincter preservation and disease-free survival compared with postoperative therapy.³¹⁻³³ Our analysis indicates that patients who receive preoperative radiation therapy are more likely to have been treated in a low outlier hospital and that those who receive postoperative therapy are more likely to have been treated in a high outlier hospital, thus identifying a simple, key, potentially modifiable treatment-related factor that may help hospitals improve their negative resection margin rates.

In this analysis, we have focused on comparing the ratio of the observed to expected rates of margin positivity within the NCDB. Outlier status was not exclusively predicted by hospital volume, nor by academic/research or nonacademic/research hospital type (ie, no hospital type was exempt from high outlier status, nor could a hospital be ensured low outlier status). Thus, the analysis is applicable and relevant for all types of individual hospitals that want to compare their observed rate to their risk-adjusted expected rate. All facility types may have factors in their practice that may be targeted to improve rectal cancer outcomes. High outlier hospitals can look for modifiable treatment-related factors to alter their clinical practice to improve rates and outcomes. Using the O/E ratio allows a hospital to evaluate itself while controlling for its mix

of patient- and tumor-related risk factors. We have created a simple-to-use nomogram to facilitate this evaluation.

Our study has important limitations, as well as strengths. Analysis of a large database is subject to data constraints, incorrect or missing data, and an inability to account for pathologic or surgical variability. The Commission on Cancer does conduct abstraction training, as well as annual quality-control audits, to minimize these errors in the database. We also noted that the rate of margin positivity was higher during the later years of the study, suggesting a secular trend in reporting bias as the importance of margin status has become increasingly recognized. However, the analysis remains valid for individual hospitals during the reporting period because their individual patient and tumor characteristics served as the basis for the model. Moreover, our study includes only data from Commission on Cancer hospitals, so hospital selection bias may exist. The percentage of minorities in our study is smaller than expected (7% African American in our study vs 12.6% in the 2010 US Census), suggesting this potential for bias. Information regarding provider specialty or experience was not available, and the NCDB did not collect data on comorbid conditions until 2003; therefore, the effect of these variables is unknown. However, while less surgeon familiarity with rectal cancer surgery may have been associated with margin positivity, being an academic/research or higher-volume program did not preclude high outlier status. Finally, while the nomogram was not independently validated, the information is taken from the NCDB, which collects data on approximately 76% of incident cancer cases in the United States and thus represents the majority of the US population with rectal cancer. For internal validation, we did perform bootstrapping and identified good performance with a concordance index of 0.75. The calibration plot also demonstrates that the predicted probability derived from the nomogram corresponds well with the observed probability.

In conclusion, the rates of margin positivity have decreased since the introduction of the total mesorectal excision, but margin positivity remains a major determinant of local recurrence, metastases, and overall survival. Our study identified both patient- and tumor-related risk factors for margin positivity, as well as treatment-related factors such as the use of preoperative radiation therapy and facility characteristics, that are associated with rates of positive-margin resection. Although type of hospital and volume were associated with outcomes, no hospital was immune to being a high outlier for margin positivity. The nomogram for determining the risk-adjusted expected rate of margin positivity that has thus been developed in our study permits hospitals to evaluate their own performance and identify potential areas for process improvement.

ARTICLE INFORMATION

Accepted for Publication: February 1, 2013.

Published Online: June 26, 2013.
doi:10.1001/jamasurg.2013.2136.

Author Contributions: *Study concept and design:* Hu, Cormier, Skibber, Nelson, Chang.
Analysis and interpretation of data: Russell, You,

Hu, Cormier, Feig, Rodriguez-Bigas, Chang.
Drafting of the manuscript: Russell, Hu, Cormier, Chang.
Critical revision of the manuscript for important intellectual content: You, Cormier, Feig, Skibber, Rodriguez-Bigas, Nelson, Chang.
Statistical analysis: Russell, Hu, Cormier, Chang.
Obtained funding: Chang.

Administrative, technical, and material support: Russell, Feig, Skibber.
Study supervision: You, Skibber, Nelson, Chang.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by the National Institutes of Health/National Cancer

Institute grants K07-CA133187 (to Dr Chang) and CA016672 (MD Anderson Cancer Center support grant).

Additional Contributions: We thank Kathryn Hale for her assistance with the manuscript editing and Christina Caraway for her technical assistance with manuscript preparation.

REFERENCES

- Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62(1):10-29.
- McCall JL, Cox MR, Wattchow DA. Analysis of local recurrence rates after surgery alone for rectal cancer. *Int J Colorectal Dis*. 1995;10(3):126-132.
- Park IJ, You YN, Agarwal A, et al. Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. *J Clin Oncol*. 2012;30(15):1770-1776.
- Martling AL, Holm T, Rutqvist LE, Moran BJ, Heald RJ, Cedemark B; Stockholm Colorectal Cancer Study Group; Basingstoke Bowel Cancer Research Project. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. *Lancet*. 2000;356(9224):93-96.
- Adam IJ, Mohamdee MO, Martin IG, et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet*. 1994;344(8924):707-711.
- Wibe A, Rendedal PR, Svensson E, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. *Br J Surg*. 2002;89(3):327-334.
- Quirke P, Steele R, Monson J, et al; MRC CR07/NCIC-CTG CO16 Trial Investigators; NCRI Colorectal Cancer Study Group. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet*. 2009;373(9666):821-828.
- Marijnen CA, Nagtegaal ID, Kapiteijn E, et al; Cooperative investigators of the Dutch Colorectal Cancer Group. Radiotherapy does not compensate for positive resection margins in rectal cancer patients: report of a multicenter randomized trial. *Int J Radiat Oncol Biol Phys*. 2003;55(5):1311-1320.
- Baik SH, Kim NK, Lee YC, et al. Prognostic significance of circumferential resection margin following total mesorectal excision and adjuvant chemoradiotherapy in patients with rectal cancer. *Ann Surg Oncol*. 2007;14(2):462-469.
- den Dulk M, Collette L, van de Velde CJ, et al; EORTC Radiation Oncology Group. Quality of surgery in T3-4 rectal cancer: involvement of circumferential resection margin not influenced by preoperative treatment: results from EORTC trial 22921. *Eur J Cancer*. 2007;43(12):1821-1828.
- McArdle CS, Hole D. Impact of variability among surgeons on postoperative morbidity and mortality and ultimate survival. *BMJ*. 1991;302(6791):1501-1505.
- Phillips RK, Hittinger R, Blesovsky L, Fry JS, Fielding LP. Local recurrence following 'curative' surgery for large bowel cancer: II, the rectum and rectosigmoid. *Br J Surg*. 1984;71(1):17-20.
- Phang PT, Kennecke H, McGahan CE, Macfarlane J, McGregor G, Hay JH. Predictors of positive radial margin status in a population-based cohort of patients with rectal cancer. *Curr Oncol*. 2008;15(2):98-103.
- Nagtegaal ID, van de Velde CJ, Marijnen CA, van Krieken JH, Quirke P; Dutch Colorectal Cancer Group; Pathology Review Committee. Low rectal cancer: a call for a change of approach in abdominoperineal resection. *J Clin Oncol*. 2005;23(36):9257-9264.
- Winchester DP, Stewart AK, Bura C, Jones RS. The National Cancer Data Base: a clinical surveillance and quality improvement tool. *J Surg Oncol*. 2004;85(1):1-3.
- Rosner B. *Fundamentals of Biostatistics*. 6th ed. Boston, MA: Duxbury Press; 2005.
- Hosmer D. *Applied Logistic Regression*. 2nd ed. New York, NY: John Wiley and Sons; 2000.
- Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet*. 1986;1(8496):1479-1482.
- Wibe A, Eriksen MT, Syse A, Myrvold HE, Søreide O; Norwegian Rectal Cancer Group. Total mesorectal excision for rectal cancer—what can be achieved by a national audit? *Colorectal Dis*. 2003;5(5):471-477.
- Tilney HS, Tekkis PP, Sains PS, Constantinides VA, Heriot AG; Association of Coloproctology of Great Britain and Ireland. Factors affecting circumferential resection margin involvement after rectal cancer excision. *Dis Colon Rectum*. 2007;50(1):29-36.
- Reshef A, Lavery I, Kiran RP. Factors associated with oncologic outcomes after abdominoperineal resection compared with restorative resection for low rectal cancer: patient- and tumor-related or technical factors only? *Dis Colon Rectum*. 2012;55(1):51-58.
- Marr R, Birbeck K, Garvican J, et al. The modern abdominoperineal excision: the next challenge after total mesorectal excision. *Ann Surg*. 2005;242(1):74-82.
- Killeen SD, O'Sullivan MJ, Coffey JC, Kirwan WO, Redmond HP. Provider volume and outcomes for oncological procedures. *Br J Surg*. 2005;92(4):389-402.
- Konety BR, Dhawan V, Allareddy V, Joslyn SA. Impact of hospital and surgeon volume on in-hospital mortality from radical cystectomy: data from the health care utilization project. *J Urol*. 2005;173(5):1695-1700.
- Ellison LM, Trock BJ, Poe NR, Partin AW. The effect of hospital volume on cancer control after radical prostatectomy. *J Urol*. 2005;173(6):2094-2098.
- Nagtegaal ID, Marijnen CA, Kranenbarg EK, van de Velde CJ, van Krieken JH; Pathology Review Committee; Cooperative Clinical Investigators. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. *Am J Surg Pathol*. 2002;26(3):350-357.
- Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection: histopathological study of lateral tumour spread and surgical excision. *Lancet*. 1986;2(8514):996-999.
- Birbeck KF, Macklin CP, Tiffin NJ, et al. Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. *Ann Surg*. 2002;235(4):449-457.
- van Gijn W, Marijnen CA, Nagtegaal ID, et al; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol*. 2011;12(6):575-582.
- Kapiteijn E, Marijnen CA, Nagtegaal ID, et al; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*. 2001;345(9):638-646.
- Sauer R, Becker H, Hohenberger W, et al; German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004;351(17):1731-1740.
- Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. *J Clin Oncol*. 2009;27(31):5124-5130.
- Silberfein EJ, Kattepogu KM, Hu CY, et al. Long-term survival and recurrence outcomes following surgery for distal rectal cancer. *Ann Surg Oncol*. 2010;17(11):2863-2869.

Invited Commentary

Multidisciplinary Treatment of Rectal Cancer

The Way of the Future

James W. Fleshman, MD

Russell et al¹ have added more information to the debate over the treatment of rectal cancer in institutions focused on the treatment of rectal cancer. Although the treatment of patients with rectal cancer in higher-volume academic centers with neoadjuvant protocols does not guarantee good surgical outcomes, it seems to help. Because no type of hospital (even a high-volume academic hospital) was immune to high outlier status for circumferential margins positive for cancer, the need for quality assurance and improvement in processes is extremely important for any hospital/institution that treats patients with rectal cancer.

The American Society of Colon and Rectal Surgeons, in conjunction with the Society of Surgical Oncology, the American College of Surgeons, the Society for Surgery of the Alimentary Tract, and the Society of American Gastrointestinal and



Related article page 769

Endoscopic Surgeons, has initiated a project to optimize treatment of rectal cancer; OSTRiCh (Optimizing Surgical Treatment of Rectal Cancer) is a group of interested institutions and individuals attempting to develop a program in the United States similar to that in the United Kingdom, Scandinavia, and Europe. Out of this effort, a set of criteria for centers of excellence should become available. Rather than focusing solely on surgeon credentialing, the OSTRiCh group is embracing the institution with a multidisciplinary approach to rectal cancer. Some of the criteria included dedicated high-volume surgeons using total mesorectal excision of rectal cancer; radiologists experienced in magnetic resonance imaging staging of rectal cancer; medical and radiation oncologists who understand the nuances of neoadjuvant chemoradiation and adjuvant chemotherapy for rectal cancer; pathologists focused on macroscopic specimen grading, circumferential radial margin reporting, and whole-specimen processing for

cross-section mounts; gastroenterologists with high-level endoscopic intervention skills; and genetic counselors, as members of a multidisciplinary team, who manage, evaluate, and assesses every patient treated with colorectal cancer. These criteria should improve the outcomes of patients treated for rectal cancer.

Russell et al¹ have also shown us that a patient's awareness of the appropriate treatment of rectal cancer is important. Older individuals and those without private insurance had a higher likelihood of choosing low-volume, nonteaching hospitals, which have a greater likelihood of high outlier status for radial margins positive for cancer. As patients become more aware and/or educated about rectal cancer, this trend should change.

This study¹ has some issues that may never be resolved, even with the use of a database as sophisticated as the National Cancer Data Base. The patient population included young patients who must, by definition, be considered high risk for hereditary cancer, which behaves differently from sporadic cancer. The inclusion of rectosigmoid cancers, simply because the patients underwent irradiation, may bias or negatively influence the outcomes because only the most advanced rectosigmoid cancers would require neoadjuvant therapy.

The change in the awareness of the requirements for the pathologic evaluation of a rectal cancer specimen began in 2007 and seems to be associated with the increase in circumferential margin positivity. Similarly, surgeons are more aware of the need for total mesorectal excision and the avoidance of circumferential radial margin positivity. The use of a 9% to 10% baseline level of circumferential radial positivity and a 100% complete total mesorectal specimen can become an objective measure of surgical quality for hospitals treating rectal cancer. On the whole, Russell et al¹ are to be congratulated for their superb effort to improve the surgical procedure for and the treatment of rectal cancer.

ARTICLE INFORMATION

Author Affiliation: Department of Surgery, Baylor University Medical Center, Dallas, Texas.

Corresponding Author: Dr Fleshman, Department of Surgery, Baylor University Medical Center, 3500 Gaston Ave, 1st Floor, Dallas, TX 75246 (james.fleshman@baylorhealth.edu).

Published Online: June 26, 2013.
doi:10.1001/jamasurg.2013.2151.

Conflict of Interest Disclosures: None reported.

REFERENCE

1. Russell MC, You YN, Hu C-Y, et al. A novel risk-adjusted nomogram for rectal cancer surgery outcomes. *JAMA Surg*. 2013;147(8):769-777.