

Inadequate Lymph Node Yield: An Inadequate Indication for Adjuvant Chemotherapy in Stage II Colon Cancer

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Background: Optimal therapy for stage II colon cancer remains unclear, and national guidelines recommend “consideration” of adjuvant chemotherapy (ACT) in the presence of high-risk features, including inadequate lymph node yield (LNY, <12 nodes). This study aims to determine whether the survival benefit of ACT in stage II disease varies based on the adequacy of LNY.

Methods: We used the National Cancer Database (NCDB) to identify adults who underwent resection for a single primary T3 or T4 colon cancer between 2006 and 2018. Multivariable logistic regression tested for associations between ACT and prespecified demographic and clinical characteristics, including the adequacy of LNY. We used Cox proportional hazards models to assess overall survival and restricted cubic splines to estimate the optimal LNY threshold to dichotomize patients based on overall survival.

Results: Unadjusted 5- and 10-year survival rates were 84% and 75%, respectively, among patients who received ACT and 70% and 50% among patients who did not (log-rank $P < 0.01$). Inadequate LNY was independently associated with both receipt of ACT (odds ratios, 1.50; $P < 0.01$) and decreased overall survival [hazard ratio (HR), 1.56; $P < 0.01$]. ACT was independently associated with improved survival (HR, 0.67; $P < 0.01$); this effect size did not change based on the adequacy of LNY (interaction $P = 0.41$). Results were robust to re-analysis with our cohort-optimized threshold of 18 lymph nodes.

Conclusions: Consistent with contemporary guidelines, patients with inadequate LNY are more likely to receive ACT. LNY adequacy is an independent prognostic factor but, in isolation, should not dictate whether patients receive ACT.

Keywords: colorectal cancer, Colon cancer, lymphadenectomy, chemotherapy

INTRODUCTION

Colorectal cancer is the third most common cancer worldwide; in the United States, the estimated annual incidence is 145,000, contributing to over 50,000 deaths per year.¹⁻³ Approximately two-thirds of these cancers are in the colon; one-third are rectal. For nonmetastatic colon cancers, that is, stage I-III, upfront surgical resection is the mainstay of treatment, with selective adjuvant chemotherapy (ACT) guided by the American Joint Committee on Cancer tumor node metastasis staging.⁴

Combined studies of stage II and III colon cancer show that ACT reduces both recurrence and mortality by approximately

30%.⁵ However, the survival benefit of ACT in stage II disease alone is less clear. In the absence of strong supporting evidence, postoperative recommendations from the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) remain broad. Acceptable options range from observation (no chemotherapy) for low-risk stage II tumors to consideration of ACT (FOLFOX/CAPOX) or clinical trials for high-risk disease.⁶ These higher-risk features include local invasion, perforation, poorly differentiated histology, and inadequate lymph node yield (LNY), defined as fewer than 12 nodes on pathological examination. The NCCN and ASCO (from now on referred to as “societies”) only definitively recommend ACT for stage III colon cancer, which is node-positive on pathologic examination.⁶

Given this broad range of possible recommendations for postoperative stage II colon cancer patients, each with concomitant risks, it is important to refine which surgical-pathological features should be considered indications for ACT. It is also important to evaluate society’s recommendations against real-world data to determine if they continue to be relevant. Thus, we sought to use a large, nationally representative database to examine the receipt of ACT and overall survival in stage II colon cancer based on the presence of high-risk features. We hypothesized that (1) individual high-risk features, as defined below, are independently associated with both receipt of ACT and decreased overall survival; (2) ACT is independently associated with improved overall survival; and (3) the survival benefit of ACT does not vary based on the adequacy of LNY.

METHODS

Data were obtained from the National Cancer Database (NCDB), a collaborative program between the American

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The authors declare that they have nothing to disclose.

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Cancer Society and the Commission on Cancer of the American College of Surgeons. The NCDB collects information from over 1500 facilities, all of which are accredited by the Commission on Cancer, capturing approximately 70% of new cancer diagnoses in the United States, as well as associated clinicopathologic features, treatment, and outcomes.

Patient Selection

We used the NCDB to identify adult patients who underwent surgery for a single primary pathologic stage T3 or T4, N0 (stage II) colon cancer over a 13-year period (2006–2018). We excluded patients with nodal or distant metastases (stage III or IV), mitigating coding inaccuracies by correlating the overall stage variable with the T stage variable and the number of pathologically positive nodes (recorded as an integer value in NCDB). In keeping with society's recommendations, high-risk tumors were defined by the presence of lymphovascular/perineural invasion, positive margins, poorly differentiated histology, or inadequate LNY. Data on other high-risk features (microsatellite instability, tumor budding, and malignant intestinal obstruction/perforation) were unavailable.

Outcomes and Statistical Analysis

The primary outcomes were the receipt of ACT and overall survival from the time of diagnosis. We evaluated the effects of prespecified demographic characteristics (age, sex, race, ethnicity, and insurance status) as well as clinicopathologic factors (Charlson comorbidity index, pathologic T stage, tumor location within the colon, adequacy of LNY, margin status, histologic differentiation, and lymphovascular/perineural invasion) on the primary outcomes.

Unadjusted χ^2 tests were applied to assess the association between categorical variables and the receipt of ACT. To evaluate the strength of associations and to control for confounding, multivariable logistic regression models were applied, estimating the odds ratios (ORs) with confidence intervals (CI) for the receipt of ACT. We adjusted for prespecified demographic and clinical characteristics, including age, sex, race, ethnicity, comorbidity burden, pathologic T stage, tumor location, and several histopathologic features defined as high risk by the NCCN. We used multivariate Cox proportional hazards

models to assess the effects of these covariates on overall mortality. To test for interaction, we repeated the analysis after stratifying the cohort by (1) adequacy of LNY and by (2) presence of high-risk features. Only complete cases (no missing data) were included in our analysis. We checked the proportional hazard assumption by plotting the cumulative sums of Schoenfeld residuals against follow-up times for each covariate; there were no departures from a horizontal line to suggest nonproportional hazards. Our findings were reproducible on parametric accelerated failure time models, which do not rely on the proportional hazards assumption. The study was adequately powered at 95% with a one-sided significance level of 0.05 to detect a hazard ratio difference of 0.1.

To verify whether the established LNY threshold of 12 would best dichotomize patients based on survival in our NCDB cohort, we applied a multivariable Cox proportional hazards model with restricted cubic splines to identify the optimal threshold based on our data (Material, <http://links.lww.com/AOSO/A253> and Figure 1, <http://links.lww.com/AOSO/A253>). The adjusted survival analysis was then repeated for validation, using the new lymph node threshold optimized for our cohort. All statistical analyses were performed using R, version 4.2.1 (R Core Team 2022, R Foundation for Statistical Computing, Vienna, Austria). The data used in this study are deidentified, and the study was exempted by the University of California, San Francisco Institutional Review Board.

RESULTS

Of the 122,678 patients who met inclusion criteria, 52.5% were female, 83.8% were white, 52.1% were ≥ 70 years old, and 35.5% had at least one high-risk feature (Tables 1–3). Over a median follow-up of 54 months, unadjusted 5- and 10-year survival rates were 84% and 75%, respectively, among the 20,146 patients (16.4% of total) who received ACT, and 70% and 50% among those who did not (log-rank $P < 0.01$, Fig. 1).

Associations with Use of Adjuvant Chemotherapy

To determine which patient factors were independently associated with receipt of ACT, we used a multivariable model that

TABLE 1.

Demographic Features of Patients With Stage II (T3–4, N0 or NX) Colon Cancer, Overall and Based on Receipt of Adjuvant Chemotherapy (ACT), 2006–2018

	No ACT	Received ACT	Overall	P Value
Number of patients	102,532 (83.6%)	20,146 (16.4%)	122,678	
Female sex	54,586 (53.2%)	9840 (48.8%)	64,426 (52.5%)	<0.01
Age (years)				<0.01
18–49	6544 (60.9%)	4205 (39.1%)	10,749 (8.7%)	
50–59	13,574 (70.3%)	5735 (29.7%)	19,309 (15.7%)	
60–69	22,782 (79.5%)	5878 (21.5%)	28,660 (23.3%)	
70–79	28,127 (88.9%)	3527 (11.1%)	31,654 (25.8%)	
80+	31,505 (97.5%)	801 (2.5%)	32,306 (26.3%)	
Race				<0.01
White	85,593 (84.2%)	16,444 (82.1%)	102,037 (83.8%)	
Black	11,626 (11.4%)	2593 (12.9%)	14,219 (11.7%)	
Native American	313 (0.3%)	81 (0.4%)	394 (0.3%)	
(South) East Asian	1973 (1.9%)	422 (2.1%)	2395 (2.0%)	
Indian and Pakistani	380 (0.4%)	99 (0.5%)	479 (0.4%)	
Other Asian	788 (0.8%)	154 (0.8%)	942 (0.8%)	
Pacific Islander	138 (0.1%)	28 (0.1%)	166 (0.1%)	
Other	869 (0.9%)	210 (1.0%)	1079 (0.9%)	
Hispanic Ethnicity	9936 (9.7%)	2463 (12.2%)	12,399 (10.1%)	<0.01

Percentages are based on column totals, except for patient number and the age variable, which use row totals. ACT indicates adjuvant chemotherapy.

TABLE 2.**Socioeconomic Features of Patients With Stage II (T3-4, N0 or NX) Colon Cancer, Overall and Based on Receipt of Adjuvant Chemotherapy (ACT), 2006–2018**

	No ACT	Received ACT	Overall	P Value
Number of patients	102,532 (83.6%)	20,146 (16.4%)	122,678	
Insurance				<0.01
Uninsured	3020 (3.0%)	1120 (5.6%)	4140 (3.4%)	
Governmental	70,853 (70.0%)	8679 (43.7%)	79,532 (65.7%)	
Private	27,411 (27.1%)	10,059 (50.7%)	37,470 (30.9%)	
Income quartile				0.67
Q1	17,946 (19.2%)	3627 (19.9%)	21,573 (19.3%)	
Q2	21,242 (22.8%)	4047 (22.2%)	25,289 (22.7%)	
Q3	21,829 (23.4%)	4199 (23.0%)	26,028 (23.3%)	
Q4	32,257 (34.6%)	6365 (34.9%)	38,622 (34.6%)	
Education quartile				<0.01
Q1	20,423 (21.9%)	4246 (23.3%)	24,669 (22.1%)	
Q2	24,844 (26.6%)	4864 (26.7%)	29,708 (26.6%)	
Q3	26,239 (28.1%)	4911 (26.9%)	31,150 (27.9%)	
Q4	21,803 (23.4%)	4225 (23.2%)	26,028 (23.3%)	
Geographic area				0.19
Metropolitan	85,382 (85.2%)	16,926 (85.7%)	102,308 (85.3%)	
Urban	12,896 (12.9%)	2451 (12.4%)	15,347 (12.8%)	
Rural	1938 (1.9%)	373 (1.9%)	2311 (1.9%)	
Facility type				<0.01
Community Cancer Program	9693 (9.6%)	1855 (9.8%)	11,548 (9.6%)	
Comprehensive Community Cancer Program	44,345 (43.9%)	8267 (43.5%)	52,612 (43.9%)	
Integrated Network Cancer Program	22,182 (22.0%)	3988 (21.0%)	26,170 (21.8%)	
Academic Program	24,693 (24.5%)	4896 (25.8%)	29,589 (24.7%)	
Distance travelled				
<12.5 min	61,741 (66.1%)	12,067 (66.1%)	73,808 (66.1%)	
12.5–49 min	24,803 (26.6%)	5123 (28.1%)	29,926 (26.8%)	
50–249 min	6055 (6.5%)	979 (5.4%)	7034 (6.3%)	
>250 min	742 (0.8%)	79 (0.4%)	821 (0.7%)	

Percentages are based on column totals, except for patient number, which uses row totals.

adjusted for sex, age, race, Hispanic ethnicity, facility type, insurance status, comorbidity score, pathologic T stage, tumor location, and high-risk features (Table 4). A total of 68,675 patients had complete data across all variables; only these patients were included in the model. Notably, patients who received ACT were more likely younger ($P < 0.01$), with higher-stage tumors (pT4 *vs* pT3: OR, 5.65; 95% CI, 5.34–5.98; $P < 0.01$) and more distal tumors (left *vs* right colon: OR, 1.28; 95% CI, 1.18–1.38; $P < 0.01$; sigmoid *vs* right colon: OR, 1.39; 95% CI, 1.31–1.47; $P < 0.01$). Inadequate LNY was independently associated with receiving ACT (OR, 1.50; 95% CI, 1.37–1.64; $P < 0.01$).

Associations with Survival

As in the logistic regression model, we included only complete cases ($N = 68,667$) in our survival analysis. After adjustment for the same confounders as in the logistic regression described above, overall survival was lower in the presence of any known high-risk feature [adjusted hazard ratio (aHR), 1.31; 95% CI, 1.29–1.34; Table 5]. In particular, the aHR of inadequate LNY was 1.56 (95% CI, 1.49–1.63; $P < 0.01$). After adjustment for these high-risk features, ACT remained independently associated with improved survival (aHR, 0.67; 95% CI, 0.63–0.71; $P < 0.01$). When the cohort was stratified into adequate versus inadequate LNY, once again, the survival benefit of ACT was not significantly different: aHR 0.66 (95% CI, 0.63–0.70) versus 0.70 (95% CI, 0.62–0.81). There was no evidence of interaction between the adequacy of LNY and receipt of ACT ($P = 0.41$). Similarly, when the cohort was stratified by risk status (high- *vs* low-risk), the survival benefit associated with ACT was similar: aHR 0.70 (95% CI,

0.67–0.74) versus 0.67 (95% CI, 0.63–0.71), respectively, interaction $P = 0.17$.

Reevaluating the Optimal LNY Threshold

This study was originally conducted using the established definition of adequate LNY: 12 nodes identified on pathological examination. However, further analysis of survival data in our cohort using a Cox proportional hazards model with restricted cubic splines demonstrated that the LNY that maximized the log-rank statistic was 18 nodes (Fig. 2 and Material, <http://links.lww.com/AOSO/A253>). Using this threshold to redefine adequate versus inadequate LNY in multivariable analysis resulted in similar findings: adjuvant chemotherapy was independently associated with improved survival (aHR, 0.68; 95% CI, 0.64–0.71).

DISCUSSION

In our national, retrospective analysis of 122,678 patients treated for stage II colon cancer over a span of 13 years, we found that ACT was more likely to be given in high-risk disease and was independently associated with improved survival. Inadequate LNY, an established high-risk feature, was independently associated with decreased survival. Notably, however, the survival benefit attributable to ACT was no different between those who had an adequate versus inadequate LNY.

To date, this is the largest study using real-world data to examine the effect of ACT on stage II colon cancer. The current recommendations for ACT in stage II and III disease rely on data that has only definitively demonstrated a survival benefit in the stage III subgroup.^{7–12} Studies focused on stage II tumors

TABLE 3.
Clinical Features of Patients with Stage II (T3-4, N0 or NX) Colon Cancer, Overall and Based on Receipt of Adjuvant Chemotherapy (ACT), 2006–2018

	No ACT	Received ACT	Overall	P Value
Number of patients	102,532 (83.6%)	20,146 (16.4%)	122,678	
Comorbidity score				<0.01
0	66,137 (64.5%)	15,098 (74.9%)	81,235 (66.2%)	
1	23,343 (22.8%)	3822 (19.0%)	27,165 (22.1%)	
2	8059 (7.9%)	864 (4.3%)	8923 (7.3%)	
3+	4993 (4.9%)	362 (1.8%)	5355 (4.4%)	
Pathologic T stage				<0.01
pT3	91,423 (89.2%)	13,126 (65.2%)	104,549 (85.2%)	
pT4	11,109 (10.8%)	7020 (34.8%)	18,129 (14.8%)	
Tumor location				<0.01
Right colon	55,742 (54.4%)	8507 (42.2%)	64,249 (52.4%)	
Transverse colon	11,807 (11.5%)	1994 (9.9%)	13,801 (11.2%)	
Left colon	9689 (9.4%)	2496 (12.4%)	12,185 (9.9%)	
Sigmoid colon	22,510 (22.0%)	6552 (32.5%)	29,062 (23.7%)	
Colon NOS	2784 (2.7%)	597 (3.0%)	3381 (2.8%)	
Surgical approach				<0.01
Open/unspecified	58,490 (57.0%)	13,063 (64.8%)	71,553 (58.3%)	
Laparoscopic	33,710 (32.9%)	5058 (25.1%)	38,768 (31.6%)	
Robotic	5243 (5.1%)	840 (4.2%)	6083 (5.0%)	
Laparoscopic converted to open	4689 (4.6%)	1081 (5.4%)	5770 (4.7%)	
Robotic converted to open	400 (0.4%)	104 (0.5%)	504 (0.4%)	
High-risk features [†]	34,219 (33.4%)	9282 (46.1%)	43,501 (35.5%)	<0.01
Inadequate lymphadenectomy	9377 (9.2%)	2206 (11.0%)	11,583 (9.5%)	<0.01
Positive margin	2725 (2.7%)	1613 (8.1%)	4338 (3.6%)	<0.01
Lymphovascular invasion	9884 (13.1%)	3019 (22.3%)	12,903 (14.5%)	<0.01
Perineural invasion	4419 (6.6%)	1475 (12.2%)	5894 (7.4%)	<0.01
Poorly differentiated	16,237 (16.1%)	4042 (20.5%)	20,279 (16.9%)	<0.01
30-day mortality	4722 (3.6%)	5 (0.0%)	4727 (3.1%)	<0.01
90-day mortality	7249 (5.5%)	71 (0.4%)	7320 (4.9%)	<0.01
Unplanned 30-day readmission	7575 (5.2%)	949 (4.7%)	8524 (5.1%)	0.01
LOS >7 days	2029 (1.9%)	72 (0.5%)	2101 (1.7%)	<0.01
Median follow-up (months)	52	64	54	<0.01
Overall mortality	42,433 (31.6%)	3792 (20.1%)	46,225 (30.2%)	<0.01

Percentages are based on column totals, except for patient number, which uses row totals.

[†]High-risk tumors are defined by one or more of the following: poorly differentiated histological features, perineural invasion, lymphovascular invasion, positive margins, and inadequate lymph node yield (<12 lymph nodes on pathological examination).

LOS indicates length of stay; NOS, not otherwise specified.

have been unable to consistently demonstrate a survival benefit from ACT.^{6,10–12} As a result, current society guidelines only recommend ACT in stage II disease with high-risk features, such as inadequate (<12) LNY, poorly differentiated histology, and lymphovascular/perineural invasion.⁶ Even after adjustment for these high-risk features as well as the T stage, our data showed an overall survival benefit with the administration of ACT in stage II disease, with an aHR of 0.67. This is notably higher than the 3% improvement in 5-year overall survival reported in the 2009 meta-analysis by Sargent et al,⁵ but more similar to the results of the 2022 ASCO meta-analysis, which showed an HR of 0.64 among patients with T4 tumors who received ACT (*vs.* those who did not).⁶ Recognizing our limits in accounting for the complex decision to administer ACT, the choice a specific regimen, and measurement of chemotherapy-related outcomes, these findings do represent real-world patterns of care. There may be a role for shorter and less morbid protocols, as demonstrated in recent studies of the CAPOX regimen,¹³ but ACT should remain a strong consideration for high-risk patients with stage II disease.

Our analysis of factors associated with ACT use confirms that the real-world application of ACT aligns with society's recommendations, which is important when analyzing outcomes outside the confines of clinical trials. Consistent with other

reports, increasing age and comorbidity scores were associated with lower odds of receiving the ACT.¹⁴ In keeping with society's recommendations, patients with a higher T stage and high-risk disease were more likely to receive ACT. Patients with left-sided cancers were also more likely to receive ACT. Considering that left-sided cancers are more likely to present with obstruction or perforation (a high-risk feature not captured in the NCDB),^{15–17} this finding also demonstrates reasonable real-world application of society's recommendations.

In this cohort, inadequate LNY was independently associated with decreased survival—an expected confirmation of an established prognostic factor. However, after stratification into adequate versus inadequate LNY, both groups derived a similar survival benefit from ACT, independently of other risk factors. This suggests that a patient's response to ACT does not appear to be related to the adequacy of LNY. One explanation may come from Lal et al,¹⁸ who found that LNY was associated with tumor biology and overall survival but not with nodal positivity. Therefore, LNY more likely reflects tumor immunogenicity (as opposed to the adequacy of resection), with greater immunogenicity leading to increased LN size and yield.¹⁸ The correlation between LNY and immunogenicity would explain the positive prognostic effects of a higher LNY. This is concordant with prior data associating LNY with increased intra-tumoral

TABLE 4.

Multivariable Analysis of Factors Associated with Receipt of Adjuvant Chemotherapy Among Patients with Stage II (T3 and T4, N0 or NX) Colon Cancer, 2006–2018 (N = 68675)

	Adjusted Odds Ratio	95% Confidence Interval	P Value
Female sex	1.07	(1.02–1.12)	0.01
Age (years)			
18–49	—		
50–59	0.69	(0.64–0.75)	<0.01
60–69	0.42	(0.39–0.46)	<0.01
70–79	0.19	(0.18–0.21)	<0.01
≥80	0.03	(0.03–0.04)	<0.01
Race			
White	—		
Other	0.82	(0.67–0.99)	0.04
South/East Asian	0.89	(0.78–1.02)	0.09
Black	0.98	(0.91–1.05)	0.53
Hispanic Ethnicity	1.13	(1.04–1.22)	<0.01
Facility type			
Community Cancer Program	—		
Comprehensive Community Cancer Program	0.94	(0.86–1.02)	0.15
Integrated Network Cancer Program	0.85	(0.77–0.93)	<0.01
Academic Program	0.82	(0.74–0.89)	<0.01
Insurance status			
Uninsured	—		
Governmental	1.07	(0.95–1.20)	0.28
Private	1.29	(1.15–1.44)	<0.01
Comorbidity score			
0	—		
1	0.91	(0.86–0.97)	<0.01
2	0.76	(0.68–0.85)	<0.01
3+	0.45	(0.38–0.53)	<0.01
Pathologic T stage			
pT3	—		
pT4	5.65	(5.34–5.98)	<0.01
Tumor location			
Right colon	—		
Transverse colon	0.99	(0.92–1.08)	0.89
Left colon	1.28	(1.18–1.38)	<0.01
Sigmoid colon	1.39	(1.31–1.47)	<0.01
High-risk features*	1.85	(1.78–1.91)	<0.01
Inadequate lymphadenectomy	1.50	(1.37–1.64)	<0.01
Positive margin	1.69	(1.52–1.88)	<0.01
Lymphovascular invasion	1.67	(1.57–1.78)	<0.01
Perineural invasion	1.43	(1.32–1.56)	<0.01
Poorly differentiated	1.51	(1.42–1.61)	<0.01

Multivariable logistic regression model adjusts for each variable shown. Only patients with complete data across all variables (N = 68675) were included.

*High-risk tumors are defined by one or more of the following: poorly differentiated histological features, perineural invasion, lymphovascular invasion, positive margins, and inadequate lymph node yield (<12 lymph nodes on pathologic examination). The adjusted odds ratio for the high-risk variable was computed using a separate model that did not include the individual components of that variable, to avoid collinearity.

T lymphocytes¹⁹ and microsatellite instability,²⁰ a predictor of response to checkpoint blockade. In the context of current literature,²¹ our results indicate that the adequacy of LNY—in the absence of other high-risk features—may not be a sufficient indication for ACT.

TABLE 5.

Adjusted Overall Survival Among Patients With Stage II (T3 and T4, N0 or NX) Colon Cancer, 2006–2018 (N = 68667)

	Adjusted Hazard Ratio	95% Confidence Interval	P Value
High-risk*	1.31	(1.29–1.34)	<0.01
Inadequate lymphadenectomy	1.56	(1.49–1.63)	<0.01
Positive margin	1.57	(1.48–1.68)	<0.01
Lymphovascular invasion	1.14	(1.09–1.19)	<0.01
Perineural invasion	1.33	(1.26–1.40)	<0.01
Poorly differentiated	1.08	(1.04–1.12)	<0.01
Adjuvant chemotherapy	0.67	(0.63–0.71)	<0.01

The Cox proportional hazards model used to construct this table adjusts for sex, age, race, Hispanic ethnicity, facility type, insurance status, comorbidity score, pathologic T stage, tumor location, and high-risk features. Only patients with complete data across all variables (N = 68667) were included.

*High-risk tumors are defined by one or more of the following: inadequate lymphadenectomy (<12 lymph nodes on pathologic examination), positive pathologic margins, lymphovascular invasion, perineural invasion, and poorly differentiated histological features. The adjusted hazard ratio for the high-risk variable was computed using a separate model that did not include the individual components of that variable, to avoid collinearity.

What constitutes an “adequate” lymph node resection, anyway? The threshold of 12 lymph nodes was established by Scott et al²² in 1989, based on a sample of 62 colons and 41 rectal cancer specimens. The group determined that an LNY of 12 has >90% accuracy in predicting nodal positivity. In light of recent studies questioning the relationship between LNY and nodal positivity,^{18,21} we sought to reevaluate the optimal threshold number. In our cohort, the optimal LNY for discriminating based on survival was 18. When we repeated our adjusted survival analysis using this new threshold for adequacy of LNY, our findings remained the same: the survival benefit of ACT was similar between patients with LNY <18 versus ≥18 nodes.

Although the overall incidence of colorectal cancer is declining, it has been increasing in younger populations (<55 years of age) by 1%–2% per year over the last 30 years.²³ We show that these younger patients are more likely to receive ACT, making it all the more important to identify specific patient factors that predict a good response to ACT. Clarifying these factors can also serve to help select patients for clinical trials of novel adjuvant treatments, including immunotherapy.

Despite its large sample size and long follow-up time, our study has several limitations. Its retrospective nature predisposes data to selection bias and confounding, despite our efforts to statistically control for known potential confounders. Furthermore, although the NCDB records reasons why ACT was not recommended or administered, missingness within this variable was too high to draw meaningful conclusions. Specific chemotherapy regimens and their related complications were also not recorded, limiting our ability to consider the harms associated with ACT. Certain high-risk tumor characteristics, such as the presence of microsatellite instability, tumor budding, and intestinal obstruction or perforation on presentation, were unavailable, precluding a full analysis of the prognostic potential of these features. Despite the imperfect availability of data, the NCDB provides the most comprehensive overview of nationwide practice patterns in cancer care. The definitive way to address these limitations would be through a prospective study with longitudinal outcome data capturing both surgery- and chemotherapy-related morbidity.

CONCLUSIONS

There is a lack of evidence to guide adjuvant therapy for stage II colon cancer. ASCO and NCCN recommendations

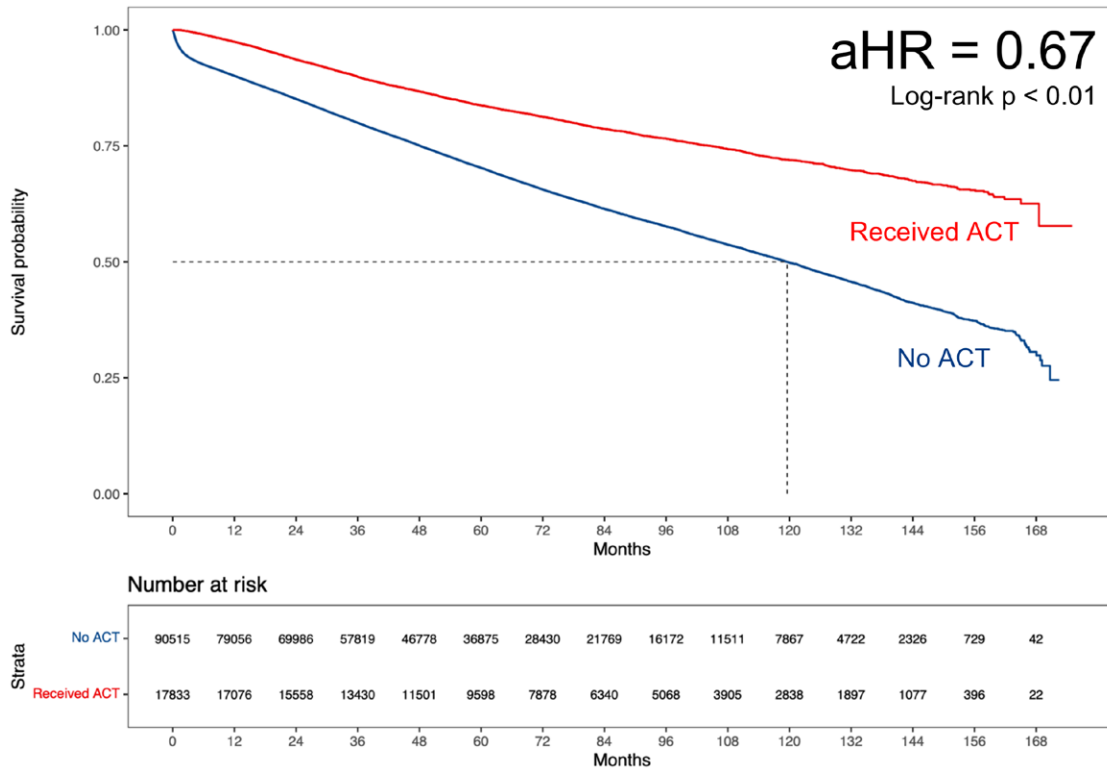


FIGURE 1. Adjusted survival based on receipt of adjuvant chemotherapy (ACT) aHR: adjusted hazard ratio.

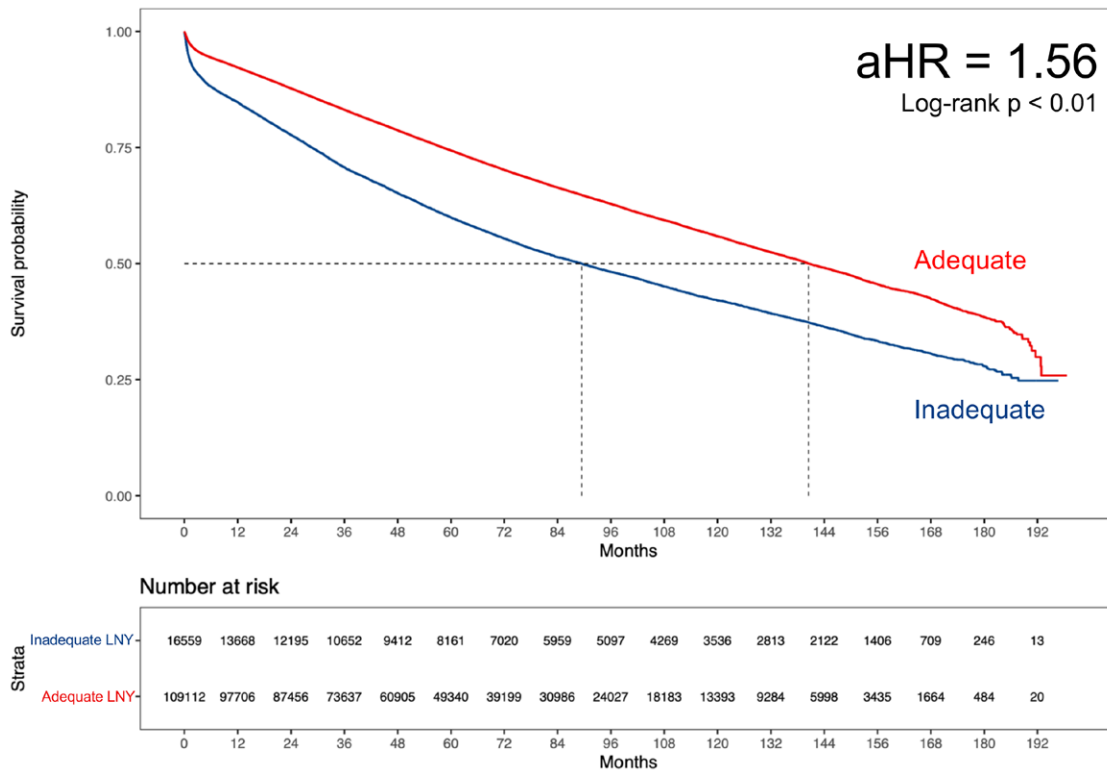


FIGURE 2. Adjusted survival based on the adequacy of lymph node yield. aHR: adjusted hazard ratio.

suggest selective use of ACT for patients with high-risk features, and national practice patterns are aligned with these guidelines. Our retrospective analysis of national data over 13 years indicates that contemporary ACT regimens improve overall survival in stage II colon cancer, regardless of the adequacy of lymphadenectomy. The longstanding definition and implications of inadequate lymphadenectomy warrant reexamination.

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