## Title

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



## Journal

Annals of Surgery Open, 4(4)

## ISSN

2691-3593

## Authors

Zambeli-Ljepović, Alan
Hoffman, Daniel
Barnes, Katherine E
et al.

## Publication Date

2023-10-12

## DOI

10.1097/as9.0000000000000338

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

**Running Head:** Lymph Node Yield in Stage II Colon Cancer

Alan Zambeli-Ljepović, MD, MHS[1]; Daniel B. Hoffman, MD[1]; Katherine E. Barnes, BS[1]; Fernanda Romero-Hernandez, MD[1]; Amir Ashraf Ganjouei, MD, MPH[1]; Mohamed A. Adam, MD[1]; Ankit Sarin, MD, MHA[2]

[1]Department of Surgery, University of California, San Francisco, San Francisco, CA
[2]Department of Surgery, University of California Davis, Sacramento, CA

**Corresponding Author:**
Ankit Sarin

**Corresponding Address:**
Ankit Sarin, MD, MHA, FACS, FASCRS
Associate Professor and Chief of Colorectal Surgery
Department of Surgery | UC Davis School of Medicine
6th Floor, 2335 Stockton Blvd., Sacramento, CA 95817
axsarin@ucdavis.edu

**Disclosures:** The authors have no disclosures relevant to this work.

**Synopsis** (limit 40 words)

This retrospective study of stage II colon cancer patients confirms that patients with inadequate lymphadenectomy (<12 nodes) have decreased survival. Adjuvant chemotherapy prolongs survival in these patients, but no more than for those with an adequate lymphadenectomy.

**Abstract:** (limit 250 words)

**Background:** Optimal therapy for stage II colon cancer remains unclear, and national guidelines recommend "consideration" of adjuvant chemotherapy 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 adjuvant chemotherapy (ACT) in stage II disease varies based on 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 2006-2018. Multivariable logistic regression tested for associations between ACT and prespecified demographic and clinical characteristics, including 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 (OR 1.50, $p<0.01$) and decreased overall survival (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 adequacy of LNY (interaction $p=0.41$). Results were robust to re-analysis with our cohort-optimized threshold of 18 lymph nodes.

**Conclusion:** 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.

## 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 non-metastatic colon cancers, i.e., Stage I-III, upfront surgical resection is the mainstay of treatment, with selective adjuvant chemotherapy (ACT) guided by the American Joint Committee on Cancer (AJCC) tumor node metastasis (TNM) 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 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 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 adequacy of LNY.

## Methods

Data were obtained from the National Cancer Database (NCDB), a collaborative program between the American Cancer Society and the Commission on Cancer of the American College of Surgeons. The NCDB collects information from over 1,500 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 integer value in NCDB). In keeping with society 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 receipt of ACT and overall survival from time of diagnosis. We evaluated the effects of prespecified demographic characteristics (age, sex, race and 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 chi-square 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 and ethnicity, comorbidity burden, pathologic T stage, tumor location, and several histopathologic features defined as high risk by NCCN (Tables 2 and 3). 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 non-proportional 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 (RCS) to identify the optimal threshold based on our data (Supplemental Text, Supplemental Figure 1). The adjusted survival analysis was then repeated for validation, using the new LN 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). 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 (Table 1). 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 $p<0.01$, Figure 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 adjusted for sex, age, race, Hispanic ethnicity, facility type, insurance status, comorbidity score, pathologic T stage, tumor location, and high-risk features (Table 2). A total of 68675 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 = 68667) 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 3]. 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 vs. inadequate LNY, once again, the survival benefit of ACT was not significantly different: aHR 0.66 [95% CI (0.63, 0.70)] vs. 0.70 [95% CI (0.62, 0.81)]. There was no evidence of interaction between 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)] vs. 0.67 [95% CI (0.63, 0.71)], respectively, interaction $p=0.17$.

*Re-evaluating 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 RCS demonstrated that the LNY that maximized the log-rank statistic was 18 nodes (Figure 2, Supplemental Text). Using this threshold to redefine adequate vs. 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 vs. 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 survival benefit in the stage III subgroup. [8–12] Studies focused on stage II tumors have been unable to consistently demonstrate 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 adjustment for these high-risk features as well as T stage, our data showed an overall survival benefit with administration of ACT in stage II disease, with an aHR of 0.67. This is notably higher than the 3% improvement in five-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 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 ACT.[14] In keeping with society recommendations, patients with 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 NCDB),[15,16,17] this finding also demonstrates reasonable real-world application of society 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 vs. 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 related to adequacy of LNY. One explanation may come from Lal et al., 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 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 T lymphocytes[19] and microsatellite instability,[20] a predictor of response to checkpoint blockade. In the context of current literature,[21] our results indicate that adequacy of LNY – in absence of other high-risk features – may not be a sufficient indication for ACT.

What constitutes an "adequate" lymph node resection, anyway? The threshold of 12 lymph nodes was established by Scott et al. in 1989, based on a sample of 62 colon and 41 rectal cancer specimens.[22] 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 re-evaluate 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 vs. ≥ 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 effort 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 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.

## Conclusion

There is a lack of evidence to guide adjuvant therapy for stage II colon cancer. ASCO and NCCN recommendations 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 adequacy of lymphadenectomy. The longstanding definition and implications of inadequate lymphadenectomy warrant reexamination.

## Acknowledgements

We thank Sy Han Chiou in the USCF Department of Surgery Biostatistics Core for reviewing and verifying our statistical analysis.

**References**


1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209-249. doi:10.3322/caac.21660

2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7-33. doi:10.3322/caac.21708

3. Colorectal Cancer - Statistics. Cancer.Net. Published June 25, 2012. Accessed September 21, 2022. https://www.cancer.net/cancer-types/colorectal-cancer/statistics

4. Benson AB, Venook AP, Al-Hawary MM, et al. NCCN Guidelines Insights: Colon Cancer, Version 2.2018. *J Natl Compr Canc Netw*. 2018;16(4):359-369. doi:10.6004/jnccn.2018.0021

5. Sargent D, Sobrero A, Grothey A, et al. Evidence for Cure by Adjuvant Therapy in Colon Cancer: Observations Based on Individual Patient Data From 20,898 Patients on 18 Randomized Trials. *J Clin Oncol*. 2009;27(6):872-877. doi:10.1200/JCO.2008.19.5362

6. Baxter NN, Kennedy EB, Bergsland E, et al. Adjuvant Therapy for Stage II Colon Cancer: ASCO Guideline Update. *J Clin Oncol Off J Am Soc Clin Oncol*. 2022;40(8):892-910. doi:10.1200/JCO.21.02538

7. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and Fluorouracil for Adjuvant Therapy of Resected Colon Carcinoma. *N Engl J Med*. 1990;322(6):352-358. doi:10.1056/NEJM199002083220602

8. Gill S, Loprinzi CL, Sargent DJ, et al. Pooled Analysis of Fluorouracil-Based Adjuvant Therapy for Stage II and III Colon Cancer: Who Benefits and by How Much? *J Clin Oncol*. 2004;22(10):1797-1806. doi:10.1200/JCO.2004.09.059

9. Laurie JA, Moertel CG, Fleming TR, et al. Surgical adjuvant therapy of large-bowel carcinoma: an evaluation of levamisole and the combination of levamisole and fluorouracil. The North Central Cancer Treatment Group and the Mayo Clinic. *J Clin Oncol*. 1989;7(10):1447-1456. doi:10.1200/JCO.1989.7.10.1447

10. QUASAR Collaborative Group. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *The Lancet*. 2007;370(9604):2020-2029. doi:10.1016/S0140-6736(07)61866-2

11. O'Connor ES, Greenblatt DY, LoConte NK, et al. Adjuvant Chemotherapy for Stage II Colon Cancer With Poor Prognostic Features. *J Clin Oncol*. 2011;29(25):3381-3388. doi:10.1200/JCO.2010.34.3426

12. Buyse M, Piedbois P. Should Dukes' B patients receive adjuvant therapy? A statistical perspective. *Semin Oncol*. 2001;28:20-24. doi:10.1016/S0093-7754(01)90247-7

13. Iveson TJ, Sobrero AF, Yoshino T, et al. Duration of adjuvant doublet chemotherapy (3 or 6 months) in patients with high-risk stage II colorectal cancer. Published online 2021. doi:10.1200/jco.20.01330

14. Ayanian JZ, Zaslavsky AM, Fuchs CS, et al. Use of Adjuvant Chemotherapy and Radiation Therapy for Colorectal Cancer in a Population-Based Cohort. *J Clin Oncol*. 2003;21(7):1293-1300. doi:10.1200/JCO.2003.06.178

15. Weiss JM, Pfau PR, O'Connor ES, et al. Mortality by Stage for Right- Versus Left-Sided Colon Cancer: Analysis of Surveillance, Epidemiology, and End Results–Medicare Data. *J Clin Oncol*. 2011;29(33):4401-4409. doi:10.1200/JCO.2011.36.4414

16. Glebov OK, Rodriguez LM, Nakahara K, et al. Distinguishing Right from Left Colon by the Pattern of Gene Expression1. *Cancer Epidemiol Biomarkers Prev*. 2003;12(8):755-762.

17. Birkenkamp-Demtroder K, Olesen SH, Sørensen FB, et al. Differential gene expression in colon cancer of the caecum versus the sigmoid and rectosigmoid. *Gut*. 2005;54(3):374-384. doi:10.1136/gut.2003.036848

18. Lal N, Chan DKH, Ng ME, Vermeulen L, Buczacki SJA. Primary tumour immune response and lymph node yields in colon cancer. *Br J Cancer*. 2022;126(8):1178-1185. doi:10.1038/s41416-022-01700-1

19. Märkl B, Wieberneit J, Kretsinger H, et al. Number of Intratumoral T Lymphocytes Is Associated With Lymph Node Size, Lymph Node Harvest, and Outcome in Node-Negative Colon Cancer. *Am J Clin Pathol*. 2016;145(6):826-836. doi:10.1093/ajcp/aqw074

20. Berg M, Guriby M, Nordgård O, et al. Influence of Microsatellite Instability and KRAS and BRAF Mutations on Lymph Node Harvest in Stage I–III Colon Cancers. *Mol Med*. 2013;19(1):286-293. doi:10.2119/molmed.2013.00049

21. Märkl B, Schaller T, Kokot Y, et al. Lymph node size as a simple prognostic factor in node negative colon cancer and an alternative thesis to stage migration. *Am J Surg*. 2016;212(4):775-780. doi:10.1016/j.amjsurg.2015.05.026

22. Scott KW, Grace RH. Detection of lymph node metastases in colorectal carcinoma before and after fat clearance. *Br J Surg*. 1989;76(11):1165-1167. doi:10.1002/bjs.1800761118

23. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(3):145-164. doi:10.3322/caac.21601

**Table 1.** Demographic and 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** | 102532 (83.6%) | 20146 (16.4%) | 122678 | |
| **Female sex** | 54586 (53.2%) | 9840 (48.8%) | 64426 (52.5%) | < 0.01 |
| **Age (years)** | | | | < 0.01 |
| 18 – 49 | 6544 (60.9%) | 4205 (39.1%) | 10749 | |
| 50 – 59 | 13574 (70.3%) | 5735 (29.7%) | 19309 | |
| 60 – 69 | 22782 (79.5%) | 5878 (21.5%) | 28660 | |
| 70 – 79 | 28127 (88.9%) | 3527 (11.1%) | 31654 | |
| 80+ | 31505 (97.5%) | 801 (2.5%) | 32306 | |
| **Race** | | | | < 0.01 |
| White | 85593 (84.2%) | 16444 (82.1%) | 102037 (83.8%) | |
| Black | 11626 (11.4%) | 2593 (12.9%) | 14219 (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%) | 12399 (10.1%) | < 0.01 |
| **Comorbidity Score** | | | | < 0.01 |
| 0 | 66137 (64.5%) | 15098 (74.9%) | 81235 (66.2%) | |
| 1 | 23343 (22.8%) | 3822 (19.0%) | 27165 (22.1%) | |
| 2 | 8059 (7.9%) | 864 (4.3%) | 8923 (7.3%) | |
| 3+ | 4993 (4.9%) | 362 (1.8%) | 5355 (4.4%) | |
| **Insurance** | | | | < 0.01 |
| Uninsured | 3020 (3.0%) | 1120 (5.6%) | 4140 (3.4%) | |
| Governmental | 70853 (70.0%) | 8679 (43.7%) | 79532 (65.7%) | |
| Private | 27411 (27.1%) | 10059 (50.7%) | 37470 (30.9%) | |
| **Income Quartile** | | | | 0.67 |
| Q1 | 17946 (19.2%) | 3627 (19.9%) | 21573 (19.3%) | |
| Q2 | 21242 (22.8%) | 4047 (22.2%) | 25289 (22.7%) | |
| Q3 | 21829 (23.4%) | 4199 (23.0%) | 26028 (23.3%) | |
| Q4 | 32257 (34.6%) | 6365 (34.9%) | 38622 (34.6%) | |
| **Education Quartile** | | | | < 0.01 |
| Q1 | 20423 (21.9%) | 4246 (23.3%) | 24669 (22.1%) | |
| Q2 | 24844 (26.6%) | 4864 (26.7%) | 29708 (26.6%) | |
| Q3 | 26239 (28.1%) | 4911 (26.9%) | 31150 (27.9%) | |

| | | | | |
|---|---|---|---|---|
| Q4 | 21803 (23.4%) | 4225 (23.2%) | 26028 (23.3%) | |
| **Geographic Area** | | | | 0.19 |
| Metropolitan | 85382 (85.2%) | 16926 (85.7%) | 102308 (85.3%) | |
| Urban | 12896 (12.9%) | 2451 (12.4%) | 15347 (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%) | 11548 (9.6%) | |
| Comprehensive Community Cancer Program | 44345 (43.9%) | 8267 (43.5%) | 52612 (43.9%) | |
| Integrated Network Cancer Program | 22182 (22.0%) | 3988 (21.0%) | 26170 (21.8%) | |
| Academic Program | 24693 (24.5%) | 4896 (25.8%) | 29589 (24.7%) | |
| **Distance Travelled** | | | | |
| <12.5 mi | 61741 (66.1%) | 12067 (66.1%) | 73808 (66.1%) | |
| 12.5 – 49 mi | 24803 (26.6%) | 5123 (28.1%) | 29926 (26.8%) | |
| 50 – 249 mi | 6055 (6.5%) | 979 (5.4%) | 7034 (6.3%) | |
| >250 mi | 742 (0.8%) | 79 (0.4%) | 821 (0.7%) | |
| **Pathologic T Stage** | | | | < 0.01 |
| pT3 | 91423 (89.2%) | 13126 (65.2%) | 104549 (85.2%) | |
| pT4 | 11109 (10.8%) | 7020 (34.8%) | 18129 (14.8%) | |
| **Tumor Location** | | | | < 0.01 |
| Right Colon | 55742 (54.4%) | 8507 (42.2%) | 64249 (52.4%) | |
| Transverse Colon | 11807 (11.5%) | 1994 (9.9%) | 13801 (11.2%) | |
| Left Colon | 9689 (9.4%) | 2496 (12.4%) | 12185 (9.9%) | |
| Sigmoid Colon | 22510 (22.0%) | 6552 (32.5%) | 29062 (23.7%) | |
| Colon NOS[1] | 2784 (2.7%) | 597 (3.0%) | 3381 (2.8%) | |
| **Surgical Approach** | | | | < 0.01 |
| Open/Unspecified | 58490 (57.0%) | 13063 (64.8%) | 71553 (58.3%) | |
| Laparoscopic | 33710 (32.9%) | 5058 (25.1%) | 38768 (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[2]** | 34219 (33.4%) | 9282 (46.1%) | 43501 (35.5%) | < 0.01 |
| Inadequate Lymphadenectomy | 9377 (9.2%) | 2206 (11.0%) | 11583 (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%) | 12903 (14.5%) | < 0.01 |
| Perineural Invasion | 4419 (6.6%) | 1475 (12.2%) | 5894 (7.4%) | < 0.01 |
| Poorly Differentiated | 16237 (16.1%) | 4042 (20.5%) | 20279 (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[3] >7 Days** | 2029 (1.9%) | 72 (0.5%) | 2101 (1.7%) | < 0.01 |
| **Median follow-up (months)** | 52 | 64 | 54 | < 0.01 |
| **Overall Mortality** | 42433 (31.6%) | 3792 (20.1%) | 46225 (30.2%) | < 0.01 |

Percentages based on column totals, except for patient number and the age variable, which use row totals.
[1]NOS: not otherwise specified
[2]High-risk tumors defined by one or more of the following: poorly differentiated histological features, perineural invasion, lymphovascular invasion, positive margins, inadequate lymph node yield (<12 lymph nodes on pathologic examination).
[3]LOS: length of stay

**Table 2.** 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] | 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.

[1]High-risk tumors defined by one or more of the following: poorly differentiated histological features, perineural invasion, lymphovascular invasion, positive margins, 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.

**Table 3.** 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] | 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.

[1]High-risk tumors 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.

**Figure 1.** Adjusted survival based on receipt of adjuvant chemotherapy (ACT).

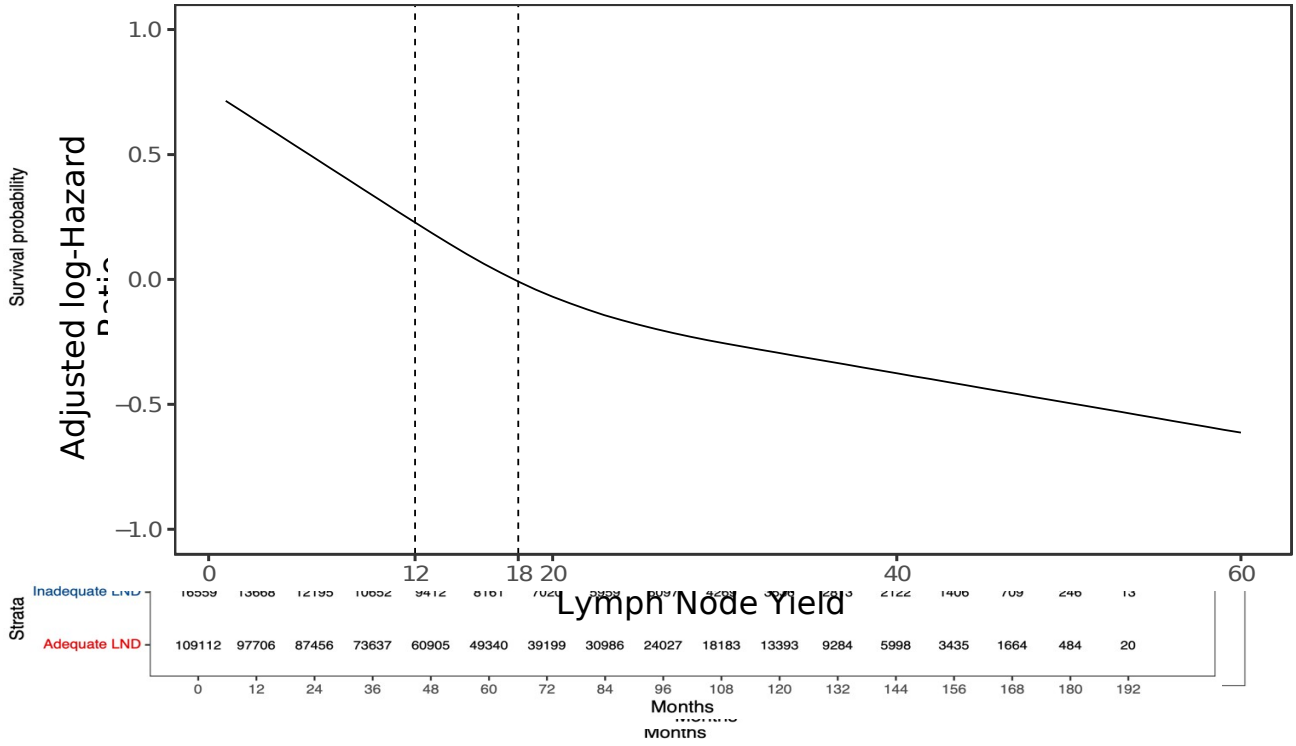
**Figure 2.** Adjusted survival based on adequacy of lymph node yield.

**Supplemental Text**

We used a restricted cubic splines (RCS) method to model the relationship between LNY and adjusted hazard ratio. We determined the number of knots for constructing RCS based on the Akaike information criterion. We then fit the nonlinear RCS curve to the plot of adjusted log hazard ratios vs. LNY. This identified an inflection point in survival at a LNY between 15 and 25 (Supplemental Figure 1).

We then performed an exhaustive series of log-rank tests throughout this range to identify which LNY, if used as the threshold for "adequate lymphadenectomy," would maximizes the difference in survival between the cases that met or exceeded that LNY compared to those that did not. The LNY that maximized the log-rank statistic was 18 nodes.

**eFigure 1**. The adjusted log hazard ratio plotted against lymph node yield.




*The dashed lines represent the previously established lymph node yield of 12 and our cohort-optimized lymph node yield of 18.*