Original Article

# Efficacy of Adjuvant Chemotherapy for Small Bowel Adenocarcinoma: A Propensity Score–Matched Analysis

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**BACKGROUND:** The role of adjuvant chemotherapy (AC) in the treatment of small bowel adenocarcinoma is poorly defined. Previous analyses have been limited by small sample sizes and have failed to demonstrate a survival advantage. **METHODS:** Patients with resected small bowel adenocarcinoma (American Joint Committee on Cancer [AJCC] pathologic stage I-III) who were receiving AC (n = 1674) or surgery alone (SA; n = 3072) were identified in the NCDB (1998-2011). Cox regression identified covariates associated with overall survival (OS). AC and SA cohorts were matched (1:1) by propensity scores based on the likelihood of receiving AC or the survival hazard from Cox modeling. OS was compared with Kaplan-Meier estimates. **RESULTS:** The omission of AC conferred an increased risk of death (hazard ratio, 1.36; 95% confidence interval, 1.24-1.50; $P < .001$). After propensity score matching, there was a nonsignificant trend toward improved OS with AC in AJCC stage I patients (158.8 vs 110.7 months; $P = .226$) and AJCC stage II patients (104.0 vs 79.6 months; $P = .185$), including the subset with a T4 tumor classification (64.0 vs 47.4 months; $P = .130$) or a positive resection margin (44.4 vs 31.0 months; $P = .333$). Median OS was superior for patients with AJCC stage III disease who were receiving AC versus SA (42.4 vs 26.1 months; $P < .001$). **CONCLUSIONS:** These data support the use of AC for resected stage III small bowel adenocarcinoma. The trend toward improved OS for patients without nodal metastasis, including those who have T4 tumors or have undergone positive-margin resection, may justify the use of AC in select patients with earlier stage disease. ***Cancer* 2016;122:693-701.** © *2015 American Cancer Society.*

**KEYWORDS:** adenocarcinoma, adjuvant therapy, chemotherapy, node positivity, propensity score, small bowel cancer.

## INTRODUCTION

Although the small bowel accounts for the majority of the absorptive surface area of the gastrointestinal tract, small bowel malignancies are rare. It has been estimated that 9410 new cases of small bowel cancer and 1260 deaths from small bowel cancer occur annually in the United States.[1] Small bowel adenocarcinoma accounts for approximately 3140 new cases annually, the majority of which present with locoregional disease.[2] Surgical resection remains the primary component of treatment; however, distant recurrence is frequent after surgical resection,[3-6] and this suggests a role for adjuvant systemic therapy.

Utilization of adjuvant chemotherapy (AC) has increased substantially over the last 2 decades for patients with small bowel adenocarcinoma.[7] This has likely been driven by the survival trends observed for patients with adenocarcinoma of the large intestine, for whom chemotherapy is associated with improved long-term survival for node-positive disease.[8,9] To date, no randomized controlled studies have assessed the survival benefit of AC for small bowel adenocarcinoma,[10] whereas single-center, retrospective studies have not demonstrated an improvement in overall survival (OS) with AC.[6,11-14]

Using the National Cancer Data Base (NCDB), a large population-representative cancer registry, we compared the survival impact of AC and surgery alone (SA) in patients with small bowel adenocarcinoma undergoing curative-intent resection. A propensity score matching methodology was used to minimize the effects of confounding by indication in different treatment groups.[15]

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## MATERIALS AND METHODS

### Data Source

After institutional review board approval, data from 1998 to 2012 were acquired from the small bowel participant use file of the NCDB, a collaborative effort between the American Cancer Society and the American College of Surgeons' Commission on Cancer. Established in 1989, the NCDB is a comprehensive oncology surveillance program that captures approximately 70% of all new cancer diagnoses in the United States from more than 1500 Commission on Cancer–approved centers.[16]

### Patient Selection

Patients with invasive small bowel adenocarcinoma (defined as topography codes C17.0-C17.9 from *International Classification of Diseases for Oncology*, 3rd edition[17] who had undergone curative-intent resection for American Joint Committee on Cancer (AJCC) pathologic stage I to III disease between 1998 and 2011 were identified. Patients were excluded if they had received neoadjuvant chemotherapy, had received radiotherapy at any time, had undergone palliative therapy, or had died within the first 90 days after surgery. Patients diagnosed in 2012 were excluded to ensure at least 1 year of follow-up for all patients.

### Variables

The demographic and clinical NCDB variables used in this study have been defined previously.[18-22] Our primary outcome, OS, was defined as the interval between the date of diagnosis and the date of death or last contact. AC was defined as the receipt of either single-agent or multiagent chemotherapy without a documented history of neoadjuvant or perioperative treatment. Salvage chemotherapy, defined as the initiation of chemotherapy more than 6 months after the operation, was excluded.

### Statistical Analysis

Descriptive statistics are presented as frequencies for categorical variables and as medians and interquartile ranges (IQRs) for continuous variables. Pearson's $\chi^2$ test or Fisher's exact test and the Wilcoxon rank-sum test were used to analyze categorical and continuous variables, respectively. Variables significantly associated with chemotherapy receipt in the univariate analysis ($P \leq .05$) were entered into a stepwise, logistic regression model ($P \leq .05$ for entry, $P > .10$ for removal) to identify independent predictors of chemotherapy utilization. OS was analyzed with Cox proportional hazards modeling with backwards stepwise selection ($P \leq .05$ for entry, $P > .10$ for removal).

Propensity scores were developed that accounted for all factors significantly associated with either the receipt of AC or the survival hazard from Cox modeling.[15] Individual scores were calculated through logistic regression modeling on the basis of the following 11 covariates: age, median income (dichotomized at $48,000), population density (urban vs rural), academic affiliation of the treating facility, year of diagnosis, tumor location (duodenum vs jejunoileal), AJCC pathologic stage, T stage classification, nodal involvement, histologic grade, and margin status. Subjects receiving either SA or AC were matched 1:1 with these propensity scores via the greedy nearest neighbor matching algorithm without replacement.[23] A caliper size of 0.1 times the logarithm of the standard deviation of the propensity score was used to minimize treatment bias.[24] Standardized differences were estimated before and after matching to evaluate the balance of covariates; small absolute values ($<0.1$) indicated balance between the treatment groups. After propensity score matching, OS of SA and AC patients was examined with Kaplan-Meier estimates via the Klein-Moeschberger methodology.[25] $P$ values $\leq .05$ were considered statistically significant; all tests were 2-sided. Analyses were performed with SPSS 22.0 (IBM Corporation, Armonk, NY).

## RESULTS

### Treatment Trends

The utilization of chemotherapy steadily increased over the study period ($P < .001$). The proportion of AJCC stage I to III patients who received AC increased by 19.2% (from 24.2% in 1998 to 43.4% in 2011). The majority of patients received multiagent chemotherapy (59.4%) versus single-agent chemotherapy (29.9%) or an unknown regimen (10.7%).

### Utilization of AC

Before propensity score matching, 4746 patients—3072 SA patients (64.7%) and 1674 AC patients (35.3%)—met the study criteria. The median age was 66 years (IQR, 55-75 years), 53.2% of the patients were male, and 81.3% of the patients were white. A univariate analysis demonstrated significant differences in patient and tumor features in the SA and AC cohorts (age, median income, facility type, year of diagnosis, tumor location, AJCC pathologic stage, pathologic T-stage classification, nodal involvement, tumor size, histologic grade, and margin status). Race, insurance status, and location (both geographic region and population density) were not associated with

**TABLE 1.** Multivariate Cox Proportional Hazards Modeling for Overall Survival in Unmatched Patients Receiving Adjuvant Chemotherapy or Surgery Alone (n = 4746)

| Variable | | Hazard Ratio[a] | 95% Confidence Interval | *P* |
|---|---|---|---|---|
| Age | ≤65 y | Reference | — | <.001 |
| | 66-74 y | 1.33 | 1.21-1.47 | <.001 |
| | >74 y | 1.78 | 1.62-1.96 | <.001 |
| Income | ≥$48,000 | Reference | — | — |
| | <$48,000 | 1.14 | 1.04-1.24 | .003 |
| Population density | Metro | Reference | — | <.001 |
| | Urban | 1.20 | 1.06-1.34 | .003 |
| | Rural | 1.49 | 1.13-1.96 | .004 |
| Facility type | Nonacademic | Reference | — | — |
| | Academic | 1.15 | 1.06-1.25 | .001 |
| Tumor location | Jejunoileal | Reference | — | <.001 |
| | Duodenum | 1.13 | 1.03-1.24 | .010 |
| | Overlapping/unknown | 1.36 | 1.22-1.52 | <.001 |
| Pathologic T classification | pT1-pT2 | Reference | — | — |
| | pT3-pT4 | 1.62 | 1.42-1.84 | <.001 |
| Pathologic N classification | Node-negative | Reference | — | — |
| | Node-positive | 1.81 | 1.66-1.98 | <.001 |
| Grade | Well/moderately differentiated | Reference | — | — |
| | Poorly differentiated/undifferentiated or anaplastic | 1.25 | 1.15-1.36 | <.001 |
| Resection margin | Negative (R0) | Reference | — | — |
| | Positive (R1-R2) | 1.98 | 1.73-2.28 | <.001 |
| Chemotherapy | Surgery + chemotherapy | Reference | — | — |
| | Surgery alone | 1.36 | 1.24-1.50 | <.001 |

[a] The hazard ratios indicate the relative hazard for death and have been adjusted for all variables included.

the administration of AC. Variables significantly associated with chemotherapy receipt in the univariate analysis ($P \leq .05$) were entered into a multivariate model to identify independent predictors of chemotherapy utilization. Factors independently associated with chemotherapy receipt included the following: younger age (odds ratio [OR] for ≤ 65 years, 5.66; 95% confidence interval [CI], 4.67-6.87; $P < .001$; OR for 66-74 years, 2.65; 95% CI, 2.13-3.29; $P < .001$), median income ≥ $48,000 (OR, 1.30; 95% CI, 1.13-1.50; $P < .001$), facility type (OR for nonacademic/research facility, 1.20; 95% CI, 1.04-1.38; $P = .014$), increasing year of diagnosis (OR, 1.07; 95% CI, 1.05-1.09; $P < .001$), tumor location (OR for jejunoileal location, 2.17; 95% CI, 1.85-2.54; $P < .001$), advancing AJCC pathologic stage (OR for stage II, 2.99; 95% CI, 1.83-4.91; $P < .001$; OR for stage III, 11.7; 95% CI, 7.26-19.0; $P < .001$), increasing pathologic T-stage classification (OR for T3-T4, 1.54; 95% CI, 1.07-2.20; $P = .019$), and positive-margin resection (OR, 1.35; 95% CI, 1.04-1.74; $P = .022$). Nodal involvement, tumor size, and histologic grade were not independently associated with the utilization of chemotherapy.

### *Effect of AC on Survival in the Unmatched Cohort*

The impact of adjuvant therapy on OS between 1998 and 2011 was examined in the unmatched cohort (n = 4746) with Cox proportional hazards modeling. Variables significantly associated with OS in the univariate analysis (ie, age, race, Hispanic ethnicity, median income, population density, facility type, year of diagnosis, tumor location, AJCC pathologic stage, pathologic T-stage classification, nodal status, histologic grade, margin status, and administration of chemotherapy) were entered into a multivariate Cox regression. After adjustments for potential confounders, the omission of chemotherapy (HR 1.36, 95% CI 1.24-1.50, $p < 0.001$) as well as several other factors (Table 1) conferred an increased risk of death. Race, Hispanic ethnicity, year of diagnosis, and AJCC pathologic stage—in a model including pathologic T-stage classification and nodal involvement—were not associated with risk-adjusted OS.

### *Effect of Adjuvant Therapy on Survival in the Propensity Score–Matched Cohort*

To better control for the treatment bias associated with the administration of AC, patients were matched 1:1 according to the likelihood of receiving chemotherapy or factors associated with the survival hazard in the unmatched cohort. The resulting propensity score–matched cohort included 2297 patients: 1155 (50.3%) in the SA group and 1142 (49.7%) in the AC group (Fig. 1). Previously observed differences between cohorts with respect to age, median income, population density,

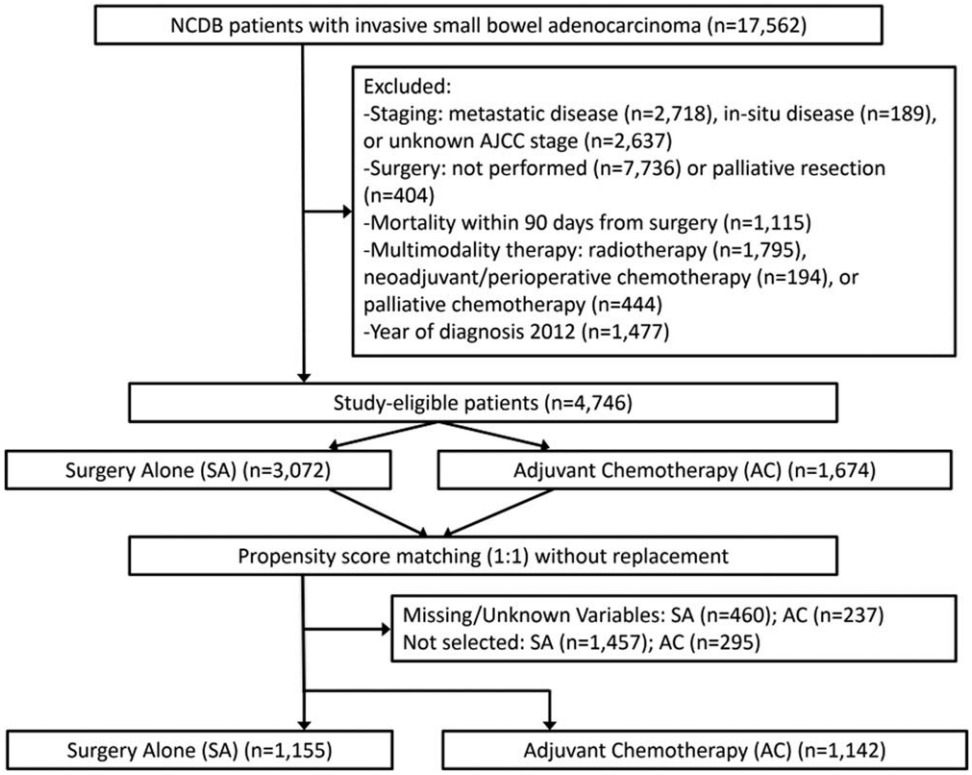


**Figure 1.** Patient selection flow diagram. AC indicates adjuvant chemotherapy; AJCC, American Joint Committee on Cancer; NCDB, National Cancer Data Base; SA, surgery alone.

academic affiliation of the treating institution, year of diagnosis, AJCC pathologic stage, pathologic T-stage classification, nodal involvement, and margin-positive resection were successfully balanced after matching (Table 2). There was, however, a persistent difference in tumor location between the propensity-matched cohorts ($P < .001$).

At a median follow-up of 66.7 months (IQR, 35.5-104.5 months), the median OS of the propensity-matched cohort was 53.3 months (IQR, 20.0-161.3 months). There was a significant survival advantage for patients who received AC versus SA (median OS, 63.2 vs 44.5 months; $P < .001$; HR, 0.77; 95% CI, 0.68-0.86; Fig. 2). With stratification by the pathologic stage, there was no significant survival benefit after AC for AJCC stage I patients (n = 73) in terms of median survival (158.8 vs 110.7 months; $P = .226$; HR, 0.59; 95% CI, 0.24-1.41) or actuarial survival (84.0% vs 76.0% at 3 years and 52.0% vs 46.0% at 5 years; $P = .255$). There was no significant survival benefit from AC in stage II patients (n = 1003; median OS, 104.0 vs 79.6 months; $P = .185$; HR, 0.88; 95% CI, 0.72-1.07). There was no significant difference in 3- (73.0% vs 73.0%) or 5-year actuarial survival (42.0% vs 36.0%; $P = .492$). AJCC stage III patients who received AC (n = 622) had significantly improved OS in comparison with SA patients (n = 599) in terms of median survival (42.4 vs 26.1 months; $P < .001$; HR, 0.66; 95% CI, 0.58-0.77) and actuarial survival (55.0% vs 41.0% at 3 years and 25.0% vs 17.0% at 5 years; $P < .001$).

Because of the imbalance in tumor location between the cohorts after propensity score matching, a survival analysis was performed separately for the subset of duodenal and jejunoileal tumors. The survival benefit of AC for AJCC stage III patients was observed for tumors located in the duodenum (n = 547; median OS, 34.1 vs 24.3 months; $P = .002$; HR, 0.71; 95% CI, 0.57-0.88) as well as the jejunum and ileum (n = 476; median OS, 52.6 vs 29.6 months; $P = .003$; HR, 0.70; 95% CI, 0.55-0.89; Fig. 3). Likewise, no significant improvements in OS were observed for stage II patients who received AC, regardless of the tumor location (n = 255 for the duodenal group; median OS, 110.3 vs 75.5 months; $P = .323$; HR, 0.81; 95% CI, 0.54-1.23; n = 482 for the jejunoileal group; median OS, 152.3 vs 88.1 months; $P = .099$; HR, 0.78; 95% CI, 0.58-1.05; Fig. 3).

**TABLE 2.** Demographic and Clinicopathologic Variables of the Propensity Score–Matched Cohort and Univariate Comparison of Patients Receiving Adjuvant Chemotherapy and Patients Receiving Surgery Alone (n = 2297)

| Variable | | Surgery Alone (n = 1155), No. (%) | Adjuvant Chemotherapy (n = 1142), No. (%) | *P* |
|---|---|---|---|---|
| Age | ≤65 y | 705 (61.0) | 676 (59.2) | .289 |
| | 66-74 y | 280 (24.2) | 309 (27.1) | |
| | >74 y | 170 (14.7) | 157 (13.7) | |
| Income | <$48,000 | 482 (41.7) | 489 (42.8) | .598 |
| | ≥$48,000 | 673 (58.3) | 653 (57.2) | |
| Population density | Metro | 981 (84.9) | 956 (83.7) | .532 |
| | Urban | 157 (13.6) | 135 (14.3) | |
| | Rural | 17 (1.5) | 23 (2.0) | |
| Facility type | Nonacademic | 709 (61.4) | 681 (59.6) | .390 |
| | Academic | 446 (38.6) | 461 (40.4) | |
| Year of diagnosis | | — | — | .220 |
| Tumor location | Duodenum | 469 (40.6) | 358 (31.3) | <.001 |
| | Jejunoileal | 423 (36.6) | 565 (49.5) | |
| | Overlapping/other | 263 (22.8) | 219 (19.2) | |
| AJCC pathologic stage | I | 38 (3.3) | 35 (3.1) | .456 |
| | II | 518 (44.8) | 485 (42.5) | |
| | III | 599 (51.9) | 622 (54.5) | |
| Pathologic T classification | pT1-pT2 | 78 (6.8) | 75 (6.6) | .858 |
| | pT3-pT4 | 1077 (93.2) | 1067 (93.4) | |
| Pathologic N classification | Node-negative | 557 (48.2) | 522 (45.7) | .227 |
| | Node-positive | 598 (51.8) | 620 (54.3) | |
| Grade | Well/moderately differentiated | 757 (65.5) | 741 (64.9) | .742 |
| | Poorly differentiated/undifferentiated or anaplastic | 398 (34.5) | 401 (35.1) | |
| Resection margin | Negative (R0) | 1062 (91.9) | 1035 (90.6) | .263 |
| | Positive (R1-R2) | 93 (8.1) | 107 (9.4) | |

Abbreviation: AJCC, American Joint Committee on Cancer.

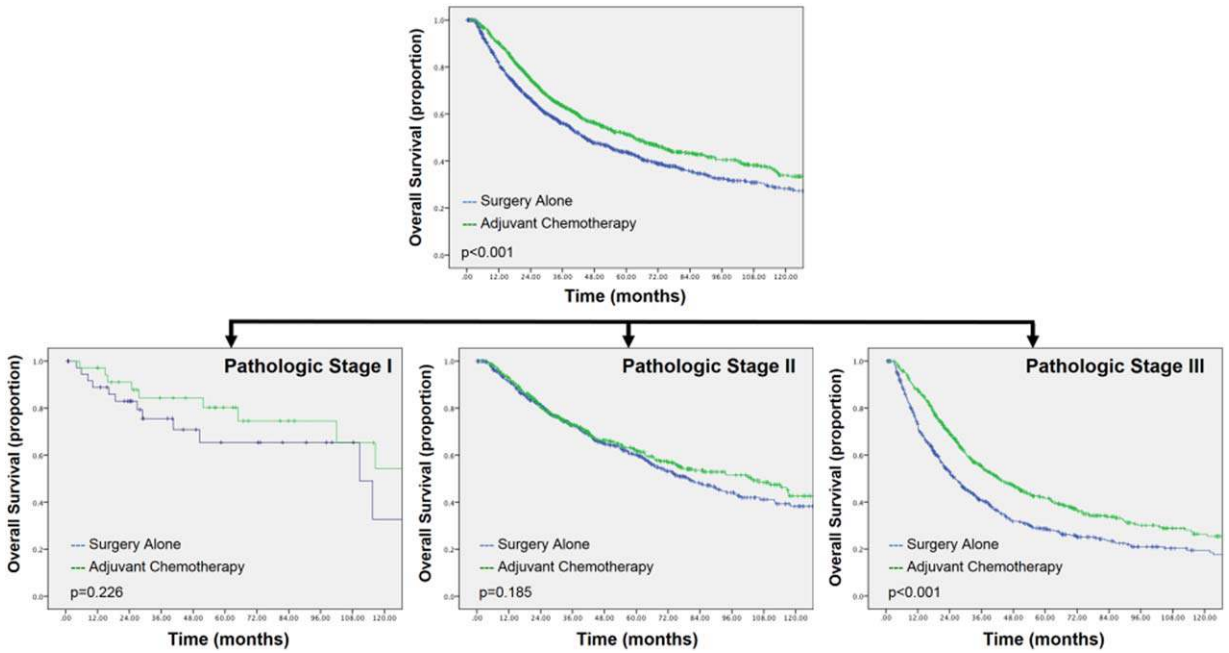


**Figure 2.** Comparative effect of adjuvant chemotherapy versus surgery alone on overall survival in the propensity-matched cohorts with resected stage I to III small bowel adenocarcinoma stratified by the pathologic stage.

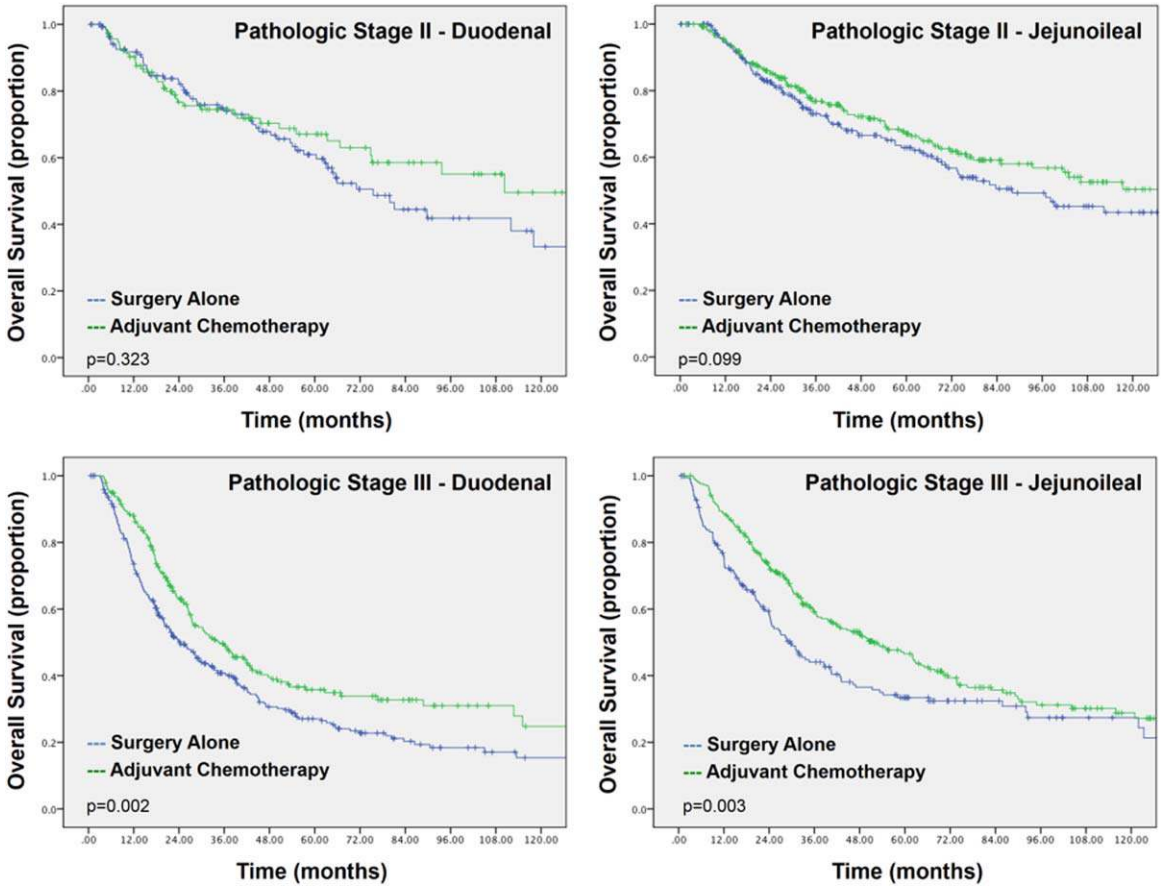


**Figure 3.** Impact of adjuvant chemotherapy versus surgery alone on overall survival for patients with resected stage II to III small bowel adenocarcinoma stratified by the tumor location.

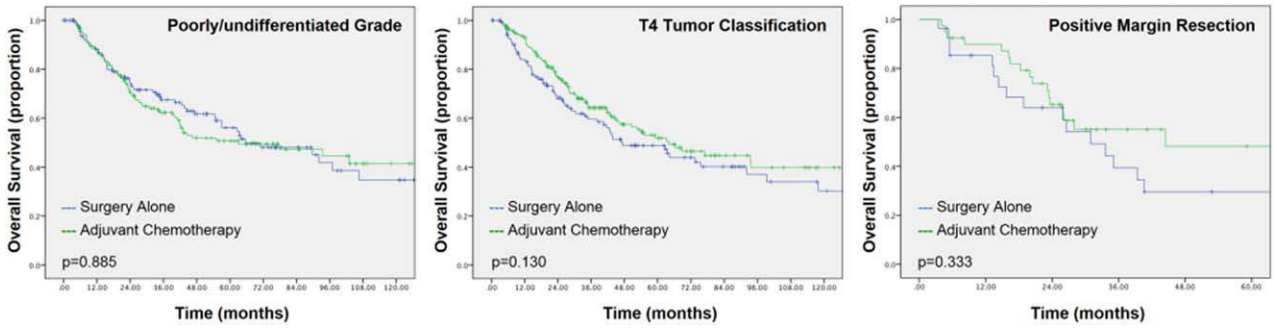


**Figure 4.** Impact of adjuvant chemotherapy versus surgery alone on overall survival for patients with resected stage II small bowel adenocarcinoma with high-risk characteristics: poorly differentiated/undifferentiated histology, T4 tumor classification, and positive-margin resection.

Lastly, the impact of AC on AJCC stage II patients with select adverse pathologic characteristics was analyzed. Equivalent survival between the AC and SA groups was observed in the presence of poorly differentiated histology (n = 272; median OS, 63.2 vs 65.6 months; $P = .885$; HR, 1.03; 95% CI, 0.72-1.47). There was a trend of improved OS in AC patients with a T4 tumor classification (n = 312; median OS, 64.0 vs 47.4 months; $P = .130$; HR, 0.77; 95% CI, 0.55-1.08) or a positive-margin resection (n = 68; median OS,

44.4 vs 31.0 months; $P = .333$; HR, 0.72; 95% CI, 0.38-1.39; Fig. 4).

## DISCUSSION

Using a large population-based registry of patients with resected small bowel adenocarcinoma, the current study indicates an improvement in OS with AC versus SA. The absolute survival benefit was most pronounced in AJCC stage III patients; nonsignificant improvements in survival were observed for patients without nodal metastasis.

We observed increasing utilization of AC for small bowel adenocarcinoma despite limited available data to support this strategy. Although palliative chemotherapy for metastatic disease may improve survival in patients with small bowel adenocarcinoma,[26-28] studies defining its role in the adjuvant setting have been limited by small sample sizes and a single-center design.[11-14] In a retrospective analysis of patients who received chemotherapy, radiotherapy, or chemoradiotherapy, Overman et al[11] observed an improvement in OS for certain AJCC stage III patients with a lymph node ratio $> 0.1$; however, the inclusion of patients receiving radiotherapy made an assessment of the impact of chemotherapy more difficult.

In the absence of data specific for small bowel adenocarcinoma, indications for AC have previously been extrapolated from colon cancer. This study confirms that similarly to the treatment of adenocarcinoma of the large intestine, adjuvant systemic chemotherapy improves survival for AJCC stage III patients. The use of AC for resected AJCC stage II colon cancer patients, even for those with poor prognostic clinicopathologic characteristics, remains controversial.[29,30] Although consensus guidelines from the American Society of Clinical Oncology discourage the routine administration of AC for stage II patients, a role in select high-risk patients has been suggested.[31] Similarly, we failed to identify high-risk clinicopathologic features associated with a significant survival advantage for AJCC stage II small bowel adenocarcinoma patients receiving AC. The prognosis following a curative resection for stage II disease is typically excellent; before propensity score matching, we observed a median OS of 66.4 months for stage II patients managed with SA, and this was similar to previously published data.[2,32] Thus, surgical resection is likely curative for many of these patients, and any added benefit of AC must be weighed against potential toxicities of treatment. Stage II patients, including those with a T4 tumor classification or a positive-margin resection, derived an absolute, though not statistically significant, benefit.

Another notable finding of this study was the discrepancy between the tumor location and the receipt of adjuvant systemic therapy. When analyzing OS by tumor location, we observed worse survival with duodenal lesions versus jejunoileal lesions. A duodenal tumor location has been associated with a poorer prognosis in several other studies.[2,5,33] Yet, in this national cohort of patients, AC was less frequently used for tumors located in the duodenum to such an extent that tumor location was the only covariate that remained statistically unbalanced between the treatment arms after propensity score matching. It is possible that the increased perioperative morbidity associated with the more extensive resection (ie, pancreaticoduodenectomy) for proximal duodenal lesions may prohibit the timely initiation of adjuvant therapy. Regardless, these results underscore opportunities for improvement in care whether through improved surgical outcomes or the application of neoadjuvant approaches.

Several limitations, particularly those inherent to retrospective database analyses, warrant emphasis. First, although extensive measures were undertaken to ensure quality control, miscoding and data omission remain possibilities. Certain inadequacies of the database, namely, the specific chemotherapeutics and dosing schedules, limited nuanced analyses of adjuvant therapy regimens. Although this is speculative, it is likely that oxaliplatin-based regimens, with either infusional 5-fluorouracil or capecitabine, were the predominant chemotherapeutics used because of the support for these regimens in the literature.[11,26] Also unavailable were medical comorbidity data for all years of the study cohort, and this prohibited inclusion of the Charlson comorbidity score as a variable in the statistical models. The increased mortality observed for patients who received care at academic centers may be explained by referral patterns: more complex cases or patients with more significant comorbidity may have been referred to academic centers with the resources to care for these patients. In addition, disease-specific mortality is not captured by the NCDB; however, the majority of patients in the propensity score–matched cohort were 65 years old or younger, and OS may closely parallel disease-specific survival for these patients. Second, the results of any observational cohort study are subject to the immortal time bias: those patients who die before the initiation of therapy are placed into the control arm, and this may exaggerate the apparent benefits seen in the treatment arm. By excluding patients who died within the first 90 days after surgery, we attempted to minimize this bias. Moreover, the exclusion of patients who died within 90 days

reduced the selection bias because this subgroup likely suffered early mortality from postoperative complications unrelated to the cancer. Third, adequate lymph node examination has prognostic significance for many gastrointestinal malignancies, for which lymph node bench marks have been proposed to ensure adequate staging.[34-36] Moreover, in the case of colorectal cancer, patients with stage II disease and inadequate lymph node staging are considered to be high-risk patients who may benefit from AC.[31,37] Further efforts to define the optimal extent of lymph node identification in small bowel adenocarcinoma patients are crucial before inadequate lymph node assessment can be considered an indication for chemotherapy in node-negative patients.

In summary, these data support the use of AC for patients with resected stage III small bowel adenocarcinoma. Future investigations, perhaps incorporating genomic, proteomic, or immunologic predictors of response, will help to identify stage I or II patients who might benefit from multimodality therapy.

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