Omission of Adjuvant Therapy After Gastric Cancer Resection: Development of a Validated Risk Model

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Abstract

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Gastric Cancer recommend adjuvant chemotherapy with or without radiotherapy following after resection of gastric adenocarcinoma (GA) for patients who have not received neoadjuvant therapy. Despite frequent noncompliance with NCCN Guidelines nationally, risk factors underlying adjuvant therapy omission (ATom) have not been well characterized. We developed an internally validated preoperative instrument stratifying patients by incremental risk of ATom. The National Cancer Data Base was queried for patients with stage IB–III GA undergoing gastrectomy; those receiving neoadjuvant therapy were excluded. Multivariable models identified factors associated with ATom between 2006 and 2011. Internal validation was performed using bootstrap analysis; model discrimination and calibration were assessed using *k*-fold cross-validation and Hosmer-Lemeshow procedures, respectively. Using weighted β-coefficients, a simplified Omission Risk Score (ORS) was created to stratify ATom risk. The impact of ATom on overall survival (OS) was examined in ORS risk-stratified cohorts. In 4,728 patients (median age, 70 years; 64.8% male), 53.7% had ATom. The bootstrap-validated model identified advancing age, comorbidity, underinsured/uninsured status, proximal tumor location, and clinical T1/2 and N0 tumors as independent ATom predictors, demonstrating good discrimination. The simplified ORS, stratifying patients into low-, moderate-, and high-risk categories, predicted incremental risk of ATom (30% vs 53% vs 80%, respectively) and progressive delay to adjuvant therapy initiation (median time, 51 vs 55 vs 61 days, respectively). Patients at moderate/high-risk of ATom demonstrated worsening risk-adjusted mortality compared with low-risk patients (median OS, 26.4 vs 29.2 months). This ORS may aid in rational selection of multimodality treatment sequence in GA. (J Natl Compr Canc Netw 2015;13:531–541)

Gastric adenocarcinoma (GA) is the second leading cause of cancer-related mortality worldwide.[1] In the United States, an estimated 10,990 deaths were attributed to GA in 2014.[2] Margin-negative surgical resection (R0) is the only potentially curative treatment for GA. Even after curative-intent gastrectomy, however, the 5-year survival rate remains approximately 28%.[2,3]

Despite these dismal statistics, surgery alone remained the mainstay of therapy in the United States until publication of results from the Intergroup 0116 (INT-0116) trial in May 2000. This phase III randomized controlled trial evaluated the impact of postoperative chemoradiotherapy (CRT) for patients with resected stomach/gastroesophageal junction adenocarcinoma. Patients receiving adjuvant CRT demonstrated significantly improved median disease-free survival (DFS; 30 vs 19 months; $P<.001$) and overall survival (OS; 36 vs 27 months; $P=.005$) compared with those undergoing surgery alone.[4] This survival benefit persisted on longitudinal (ie, >10-year) follow-up.[5] Despite criticism that CRT may have compensated for inadequate surgery[6] (only 10% of patients underwent D2 lymphadenectomy, whereas 54% received D0 resections[4]), use of adjuvant multimodality therapy has since been incorporated into practice guidelines for GA management in the United States. Subsequently, several retrospective population-based studies have reaffirmed the benefit of adjuvant therapy in patients undergoing curative-intent gastrectomy.[7–9]

Based on these data, current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Gastric Cancer[10] recommend postoperative CRT for

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Submitted September 3, 2014; accepted for publication January 21, 2015.

The authors have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors.

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patients with localized GA[4] or postoperative chemotherapy after D2 (to view the most recent version of these guidelines, visit NCCN.org).[11] The latter recommendation reflects findings from the CLASSIC trial; specifically, improved DFS and OS in patients receiving adjuvant chemotherapy (capecitabine/oxaliplatin) compared with those undergoing surgery alone.[11] Alternatively, patients may receive neoadjuvant chemotherapy, drawing on results from the MAGIC trial, which demonstrated a survival advantage with perioperative chemotherapy versus surgery alone comparable with that achieved from adjuvant CRT in INT-0116.[12] Importantly, in patients selected to undergo a surgery-first approach, clinical adoption of these NCCN Guidelines has remained inadequate. A recent National Cancer Data Base (NCDB) study revealed that use of adjuvant therapy in eligible patients by INT-0116 criteria plateaued at approximately 40% per year between 2003 and 2007. Alarmingly, a substantial proportion of INT-0116–eligible patients (nearly 40% of cases per year) underwent surgery alone in 2007.[13] Risk factors for the omission of adjuvant multimodality therapy in eligible patients have not been well characterized.

Using a contemporary cohort from the NCDB, we (1) assessed temporal trends in use of adjuvant multimodality therapy after surgical resection; (2) identified demographic and clinical factors predicting omission of guideline-appropriate adjuvant therapy; and (3) developed an internally validated preoperative risk stratification model discriminating patients at low, moderate, and high risk for adjuvant therapy omission (ATom) after gastrectomy. This tool identifies vulnerable populations in whom delivery of cancer care could be improved, allowing for a more rational selection of treatment strategy.

Methods

Data Source

After Institutional Review Board approval, data from 1998 through 2011 were acquired from the esophagogastric participant use file of the NCDB, a collaborative effort between the American Cancer Society and the American College of Surgeons' Commission on Cancer (CoC). Established in 1989, the NCDB is a comprehensive oncology surveillance program that captures approximately 70% of new cancer diagnoses from more than 1500 CoC-approved centers.[14] Data available in the NCDB include site-specific operative codes, AJCC clinical/pathologic TNM staging (5th–7th editions), and multimodality treatment sequence.

Patient Selection

Patients with invasive GA (defined by ICD-O-3[15]) undergoing curative-intent resection for AJCC pathologic stage IB–III disease were identified. Patients receiving neoadjuvant chemotherapy and/or radiotherapy were excluded from the analysis. Patients were also excluded if they did not undergo at least a partial gastrectomy, received an indeterminate lymph node (LN) harvest, underwent palliative resection, or died within 30 days postoperatively.

Variables

The demographic/clinical NCDB variables used in this study (Table 1) have been defined previously.[16] Non–privately insured (Medicare/Medicaid) patients were combined with uninsured patients to dichotomize the insurance variable for ease of incorporation into the risk model. Pre–INT-0116 (1998–2000) and post–INT-0116 (2001–2011) eras were defined to compare temporal differences in treatment utilization rates. The primary outcome of interest—ATom—was defined as nonreceipt of adjuvant chemotherapy or CRT (C±RT) in resected INT-0116–eligible patients selected to undergo a surgery-first approach. The remainder of patients received adjuvant C±RT. A variable representing duration to adjuvant therapy commencement was created by calculating the difference between duration to chemotherapy initiation and duration to gastrectomy (both from date of diagnosis). OS was defined as the interval between date of diagnosis and date of death/last contact.

Statistical Analysis

Descriptive statistics were performed. Simple linear regression was used to analyze temporal trends in adjuvant C±RT use. Bivariate analysis of independent variables by outcome of interest (ie, ATom) was performed. Pearson-χ^2 or Fisher exact test and unpaired Student *t* tests were used to analyze categorical and continuous variables, respectively. Candidate predictive variables were entered via backward stepwise regression ($P<.05$ for entry); those variables demonstrating no independent association ($P>.10$) with ATom were removed. Covariates yielding a *P* value less than .10 were included in a bootstrap internal validation procedure, wherein 1000 random samples were generated with replacement.[17] Each sample was

Table 1 Demographic and Clinical Characteristics of the Analytic Cohort (n=4,728) and Univariate Comparison Between ATom and Adjuvant C±RT Cohorts

Characteristic	Overall Cohort (%) (2006–2011)	Patients With ATom (%)	Patients Receiving Adjuvant C±RT (%)	Univariate *P* Value
All patients	4,728 (100)	2,535 (53.6)	2,193 (46.4)	–
Demographic				
Age quartiles (y)[a]				<.001
<56	770 (25.0)	231 (9.1)	539 (25.0)	
56–66	1,100 (23.5)	461 (18.2)	649 (29.6)	
67–76	1,430 (30.2)	752 (29.7)	678 (30.9)	
>76	1,418 (30.0)	1,091 (43.0)	327 (14.9)	
Sex[a]				.005
Male	3,064 (64.8)	1,597 (63.0)	1,467 (66.9)	
Female	1,664 (35.2)	938 (37.0)	726 (33.1)	
Race[a]				<.001
White	3,456 (73.1)	1,926 (76.0)	1,530 (69.8)	
Asian	333 (7.0)	165 (6.5)	168 (7.7)	
Black/other (eg, American Indian, Pacific Islander)	939 (19.9)	444 (17.5)	495 (22.6)	
Hispanic ethnicity[a]				.001
No	4,229 (89.4)	2,304 (90.9)	1,925 (87.8)	
Yes	499 (10.6)	231 (9.1)	268 (12.2)	
Charlson/Deyo comorbidity index[a]				<.001
0	3,145 (66.5)	1,580 (62.3)	1,565 (71.4)	
≥1	1,583 (33.5)	955 (37.7)	628 (28.6)	
Insurance type[a,b]				<.001
Private	1,462 (31.4)	588 (23.5)	874 (40.5)	
Nonprivate/uninsured	3,199 (68.6)	1,916 (76.5)	1,283 (59.5)	
Median income[a,b]				.499
≥$46,000	1,663 (37.3)	1,501 (63.1)	1,290 (62.1)	
<$46,000	2,791 (62.7)	877 (36.9)	786 (37.9)	
Facility location[a]				.699
Northeast	1,164 (24.6)	612 (24.1)	552 (25.2)	
West	845 (17.9)	445 (17.6)	400 (18.2)	
Midwest	1,108 (23.4)	601 (23.7)	507 (23.1)	
South	1,611 (34.1)	877 (34.6)	734 (33.5)	
Urban/rural[a,b]				.588
Metro/Urban	4,335 (98.0)	2,310 (97.9)	2,025 (98.1)	
Rural	89 (2.0)	50 (2.1)	39 (1.9)	
Facility type[a]				.107
Academic/research	1,956 (41.4)	1,076 (42.4)	880 (40.1)	
Nonacademic	2,772 (58.6)	1,459 (57.6)	1,313 (59.9)	
Anatomic/Pathologic				
Primary tumor location[a]				<.001
Distal/lesser or greater curvature	3,120 (66.0)	1,604 (63.3)	1,516 (69.1)	
Proximal[c]	1,608 (34.0)	931 (36.7)	677 (30.9)	
Clinical T classification[a]				<.001
T 1/2	2,807 (59.4)	1,605 (63.3)	1,202 (54.8)	
T 3/4	1,921 (40.6)	930 (36.7)	991 (45.2)	
Clinical N classification[a]				<.001
Node-negative (N0)	2,835 (60.2)	1,702 (67.1)	1,133 (51.7)	
Node-positive (N1–3)	1,893 (40.0)	833 (32.9)	1,060 (48.3)	

Abbreviations: ATom, adjuvant therapy omission; C±RT, chemotherapy with or without radiotherapy.
[a]Indicates preoperatively known variables included in final multivariable logistic regression model.
[b]Missing data: Insurance: 67 patients; Median income: 274 patients; Urban/rural: 304 patients; Tumor size: 335 patients; Tumor grade: 136 patients; Duration of postoperative stay: 498 patients; 30-day readmission: 144 patients.
[c]73.4% of patients with proximal tumors underwent near total/total gastrectomy with or without partial esophageal resection.

Table 1 Demographic and Clinical Characteristics of the Analytic Cohort (n=4,728) and Univariate Comparison Between ATom and Adjuvant C±RT Cohorts (cont.)

Characteristic	Overall Cohort (%) (2006–2011)	Patients With ATom (%)	Patients Receiving Adjuvant C±RT (%)	Univariate *P* Value
Tumor size (cm)[b]				<.001
<2	629 (14.3)	434 (18.3)	195 (9.7)	
2–5	2,195 (50.0)	1137 (47.8)	1,058 (52.5)	
>5	1,569 (35.7)	806 (33.9)	763 (37.8)	
Tumor grade[b]				<.001
Well/moderately differentiated	1,790 (39.0)	1,062 (43.1)	728 (34.2)	
Poorly/undifferentiated or anaplastic	2,802 (61.0)	1,404 (56.9)	1,398 (65.8)	
Operative/Postoperative				
Type of gastrectomy				.004
Near total/total/combined with partial esophageal resection	1,824 (38.6)	980 (38.7)	844 (38.4)	
Subtotal/partial	2,496 (52.8)	1362 (53.7)	1,134 (51.7)	
Multivisceral/en bloc	408 (8.6)	193 (7.6)	215 (9.8)	
Resection margin				<.001
R0	4,065 (86.0)	2245 (88.6)	1,820 (83.0)	
R1	338 (7.1)	146 (5.8)	192 (8.8)	
R2	24 (0.5)	14 (0.6)	10 (0.5)	
Indeterminate	301 (6.4)	130 (5.1)	171 (7.8)	
Adequacy of lymph node staging				<.001
Inadequate (<15 lymph nodes)	2,437 (51.5)	1,398 (55.1)	1,039 (47.4)	
Adequate (≥15 lymph nodes)	2,291 (48.5)	1,137 (44.9)	1,154 (52.6)	
Duration of postoperative stay (days)[b]				<.001
≤7	1,625 (38.4)	752 (29.7)	873 (45.9)	
8–14	1,742 (41.2)	968 (38.2)	774 (40.7)	
15–21	372 (8.8)	237 (9.3)	135 (7.1)	
>21	491 (11.6)	370 (14.6)	121 (6.3)	
30-day readmission[b]				<.001
No readmission	4,155 (90.6)	2,226 (87.8)	1,929 (91.6)	
Any unplanned readmission	308 (6.7)	202 (8.0)	106 (5.0)	
Planned readmission	121 (2.6)	50 (2.0)	71 (3.4)	

Abbreviations: ATom, adjuvant therapy omission; C±RT, chemotherapy with or without radiotherapy.
[a]Indicates preoperatively known variables included in final multivariable logistic regression model.
[b]Missing data: Insurance: 67 patients; Median income: 274 patients; Urban/rural: 304 patients; Tumor size: 335 patients; Tumor grade: 136 patients; Duration of postoperative stay: 498 patients; 30-day readmission: 144 patients.
[c]73.4% of patients with proximal tumors underwent near total/total gastrectomy with or without partial esophageal resection.

then subjected to multivariable regression. Predictors occurring in 50% or more of bootstrap models were retained in the final regression.

Model performance was evaluated using *k*-fold cross-validation, which split the dataset into 10 exclusive subsets of equal size, with 90% and 10% of subsets used for model training and testing, respectively.[18] Results were used to calculate a bias-corrected C statistic comparable with the area under the receiver operating characteristic curve. A value of 0.5 demonstrates poor predictive capacity, whereas 1.0 demonstrates perfect model discrimination. Model calibration was performed via Hosmer-Lemeshow goodness-of-fit tests.[19]

A simplified risk stratification tool—the adjuvant therapy Omission Risk Score (ORS)— was created by assigning discrete numerical values to each risk factor based on β coefficients derived from the bootstrapped model. The referent for each variable was assigned a value of zero. For the remaining values, point assignments proportional to the lowest β coefficient were made. The aggregate of these values generated a composite risk score for each patient. Clinically applicable risk zones were developed using categorical regression of composite ORS.

The Kaplan-Meier method was used to estimate survival function.[20] Univariate comparisons between

treatment groups were performed by the log-rank test. Cox proportional hazards regression of covariates was performed using backward elimination. All tests were 2-sided. A *P* value of .05 or less was considered statistically significant. Analysis was conducted using SPSS V22.0 (Chicago, IL) and SAS 9.3 (Cary, NC).

Results

Descriptive Statistics and Temporal Trends in Treatment Utilization

The NCDB gastric cohort included 141,760 patients with invasive GA treated between 1998 and 2011. Structured queries allowed exclusion of patients with metastatic (n=19,732) or unknown stage (n=70,382) disease, as well as those who received preoperative C±RT (n=6,845), underwent indeterminate LN harvest (n=1,126), did not undergo gastrectomy (n=10,874), required palliative resection (n=108), died within 30 postoperative days (n=1,773), or had unknown clinical T-/N-classification data (n=22,666). Temporal treatment trends were analyzed in this cohort (n=8,254).

Between 1998 and 2011, the relative proportion of ATom patients decreased from 71.5% to 51.9%, whereas those receiving adjuvant C±RT increased by 68.8%, from 28.5% to 48.1% (both, *P*<.001). The largest annual change in undergoing ATom (67.9%–59.5%) or use of adjuvant C±RT (32.1%–40.5%) occurred between 1999 and 2000. Compared with the pre–INT-0116 era, the relative proportion of ATom patients decreased significantly in the post–INT-0116 era (54.0% vs 70.6%; *P*<.001). Nevertheless, as of 2011 in the United States, NCCN Guideline–appropriate[10] adjuvant therapy was omitted in 51.9% of INT-0116–eligible patients selected for a surgery-first approach.

A contemporary subset of patients diagnosed between 2006 and 2011 was used to derive the ORS model (n=4,728). In this cohort, ATom was observed in 2,535 (53.6%) of patients; 2,193 (46.4%) received adjuvant C±RT (CRT, 1,546 [70.5%]; chemotherapy alone, 647 [29.5%]). The median age was 70 years (interquartile range [IQR], 60–78 years); a majority of patients were male (64.8%) and white (73.1%). Most patients held nonprivate (Medicare/Medicaid) insurance (66.7%), and a minority (1.9%) were uninsured. Facility type and location with the highest case representation were nonacademic centers (58.6%) and southern region (34.1%), respectively. Most tumors were larger than 2 cm (85.7%) and had poorly differentiated/undifferentiated histology (61.0%). Proximal tumor location accounted for 34.0% of cases; most (73.4%) required total gastrectomy. Microscopically negative margins (R0) and adequate LN staging (≥15 LNs examined[10]) were achieved in 86.0% and only 48.5% of cases, respectively. Median duration of postoperative stay was 9 days (IQR, 6–13 days), and the 30-day readmission rate was less than 10% (Table 1).

Factors Predicting ATom

Univariate comparison between adjuvant C±RT and ATom cohorts is presented in Table 1. Significantly different preoperative demographic/clinical variables (ie, age, sex, race, Hispanic ethnicity, Charlson/Deyo comorbidity index, insurance, tumor location, and clinical T/N classification) were entered in the final multivariable regression model. AJCC clinical stage, income, facility location or type, and urban/rural treatment status did not achieve statistical significance.

Predictors determined by backward stepwise regression to be significantly associated with ATom were advancing age (56–66 years: odds ratio [OR], 1.48, *P*<.001; 67–76 years: OR, 2.19, *P*<.001; >76 years: OR, 7.06, *P*<.001), Charlson/Deyo comorbidity index (score ≥1: OR, 1.35; *P*<.001), nonprivate insurance/uninsured (OR, 1.20; *P*=.02), proximal tumor location (OR, 1.63; *P*<.001), clinical T1/2 classification (OR, 1.20; *P*=.006), and clinical N0 classification (OR, 1.83; *P*<.001).

Risk Model Generation and Validation

Performance of the model was internally validated using a bootstrap procedure, an approach that minimizes the inherent bias (or optimism) toward an overestimated performance in the derivation dataset,[17] yielding the following regression equation:

> lnR/(1 + lnR) = –1.590 + (0.389 x age 56–66 y) + (0.780 x age 67–76 y) + (1.962 x age ≥76 y) + (0.296 x Charlson score ≥ 1) + (0.187 x nonprivate insurance) + (0.464 x proximal tumor location) + (0.185 x clinical T1/T2) + (0.604 x clinical N0), where *lnR/(1+lnR)* represents the logarithm of the odds of ATom

Regression β coefficients, adjusted ORs, and bias-corrected 95% CIs are detailed in Table 2. The C statistic

Table 2 Independent Variables in Bootstrap-Validated Logistic Regression Model Predicting ATom in Intergroup-0116–Eligible Patients

Variable	β Coefficient	Standard Error	Adjusted OR	95% Wald CI	*P* Value
Intercept	–1.590	0.106			
Age (y)					
<56	–	–	Ref	–	–
56–66	0.389	0.103	1.48	1.20–1.78	<.001
67–76	0.780	0.106	2.18	1.78–2.70	<.001
>76	1.962	0.113	7.11	5.77 9.07	<.001
Charlson/Deyo comorbidity index					
0	–	–	Ref	–	–
≥1	0.296	0.068	1.34	1.17–1.54	<.001
Insurance type					
Private	–	–	Ref	–	–
Nonprivate/uninsured	0.187	0.079	1.21	1.01–1.39	.023
Primary tumor location					
Distal/lesser or greater curvature	–	–	Ref	–	–
Proximal	0.464	0.069	1.59	1.38–1.84	<.001
AJCC clinical T classification					
T 3/4	–	–	Ref	–	–
T 1/2	0.185	0.069	1.20	1.05–1.38	.010
AJCC clinical N classification					
Node-positive (N1–3)	–	–	Ref	–	–
Node-negative (N0)	0.604	0.068	1.83	1.60–2.08	<.001

Abbreviations: ATom, adjuvant therapy omission; OR, odds ratio.

of the original regression was 0.73 (Figure 1A), with a bias-corrected C statistic of 0.72, indicating good discrimination. The calibration of this model was acceptable by Hosmer-Lemeshow goodness-of-fit testing (8.28, *P*=0.41; Figure 1B).

ORS Derivation and Risk Stratification

A simplified ORS was derived, wherein an individual patient's overall score could range from 0 to 12 (Table 3). Along a continuum, the frequency of ATom correlated significantly with progressively increasing ORS (*P*<.001; Figure 2A). The simplified model retained the ability to predict ATom as effectively as the original model (C statistic 0.72; Hosmer-Lemeshow 7.65, *P*=.37; Figure 1B).

Risk stratification using composite ORS is illustrated in Figure 2B. Patients in the low-risk (ORS, 0–3; n=325) and moderate-risk (ORS, 4–7; n=1,137) zones demonstrated a 30% and 53% risk of ATom, respectively; however, 80% of patients stratified as high risk (ORS, 8–12; n=1,042) did not receive adjuvant therapy.

Association of ORS With Duration to Adjuvant Therapy

We hypothesized that increasing ORS may also predict a delay in multimodality therapy initiation after gastrectomy. In 1,878 patients (85.6%) evaluable for this analysis, median duration to commencement of adjuvant chemotherapy rose incrementally from 51 days (IQR, 38–70 days) in low-risk patients, 55 days (IQR, 41–74 days) in moderate-risk patients, and 61 days (42.0–78.8 days) in high-risk patients (*P*=.001; Figure 2C). Moreover, a strong linear relationship was observed between mean duration to adjuvant C±RT and ORS, when plotted along a risk continuum (*P*=.001). Next, in accordance with the INT-0116 schedule, delay to adjuvant therapy was defined as treatment commencement greater than 6 weeks after gastrectomy. The ORS retained the ability to predict delay; the proportion of patients initiating adjuvant therapy more than 6 weeks after gastrectomy increased from 68.5% (low-risk) to 74.6% (moderate-risk) to 77.6% (high-risk; *P*=.005).

ORS Risk Stratification and Survival

The impact of ORS risk stratification on OS was examined. Survival analysis included 1,717 patients from 1998 through 2006 with minimum 5-year follow-up.[14] Within this cohort, median survival was 35.7 months and 1- and 5-year survival rates were 79.6% and 38.3%, respectively. Each patient was assigned a composite ORS score and categorized into low- (ORS, 0–3) or

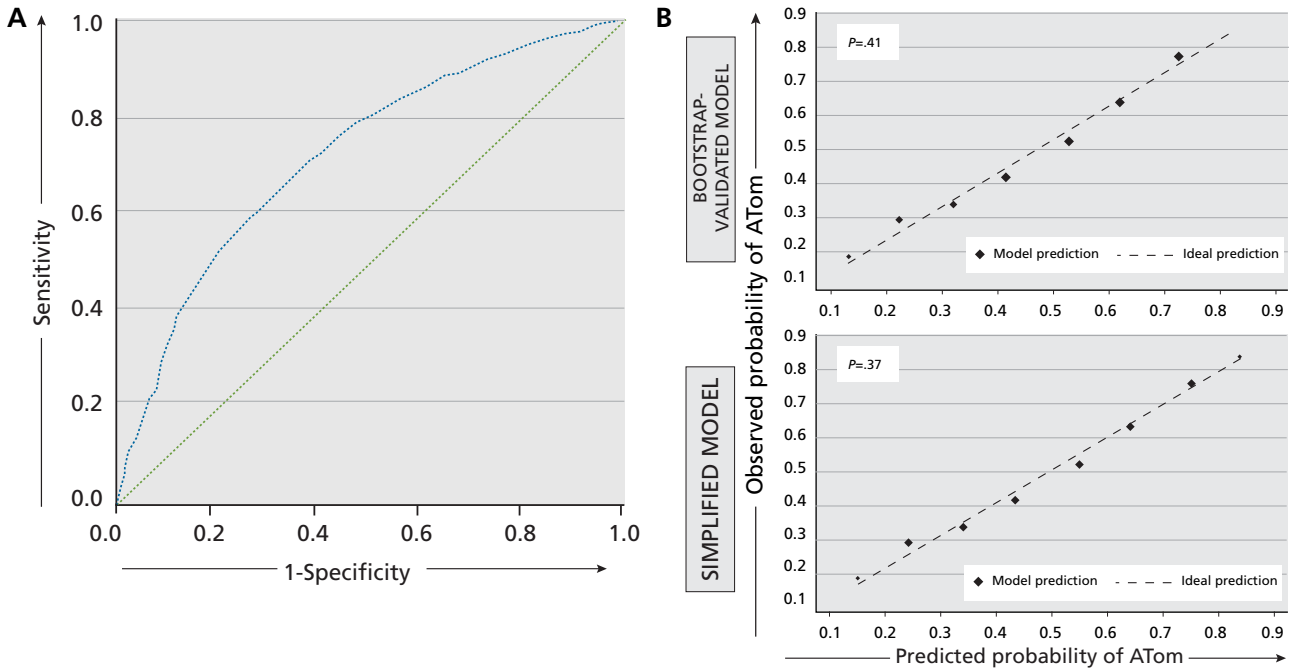

Figure 1 (A) Receiver operating characteristic (ROC) curve plotting capacity of the bootstrap-validated regression model to predict adjuvant therapy omission (ATom; blue curve). The C statistic (area under ROC curve) of the model is 0.73, indicating good model discrimination. (B) Hosmer-Lemeshow goodness-of-fit calibration plots depicting correlation between observed and predicted probabilities of ATom in bootstrap-validated (upper panel) and simplified (lower panel) models.

moderate/high- (ORS 4-12) risk categories. Risk-stratified univariate survival of ATom and adjuvant C±RT cohorts is illustrated in Figure 3. Although median OS between ATom and C±RT cohorts differed significantly (29.2 vs 43.1 months; *P*=.03) in low-risk patients, this survival disparity widened appreciably (26.4 vs 42.3 months; *P*<.001) in moderate/high-risk populations. Compared with adjuvant C±RT, ATom conferred an increased risk of death in low-risk (hazard ratio [HR], 1.80; 95% CI, 1.06–3.06; *P*=.029) and moderate/high-risk (HR, 1.49; 95% CI, 1.10–2.02; *P*=.011) groups on Cox proportional hazards modeling. Clinical LN positivity (N1–N3), tumor T classification 3/4, and margin positivity (R1/R2) were other strong predictors of risk-adjusted mortality in low- and moderate/high-risk populations (Table 4).

Discussion

The current study proposes a novel preoperative tool to stratify patients according to risk of ATom following curative-intent gastrectomy for GA. Using

Table 3 Simplified Adjuvant Therapy Omission Risk Score

Variable	Logistic β Coefficient	Rounded Score
Age 56–66 y	0.389	1
Age 67–76 y	0.780	2
Age >76 y	1.962	6
Charlson/Deyo comorbidity score ≥1	0.296	1
Nonprivate insurance or uninsured	0.187	1
Proximal tumor location	0.464	1
Clinical T 1/2	0.185	1
Clinical node-negative (N0)	0.604	2

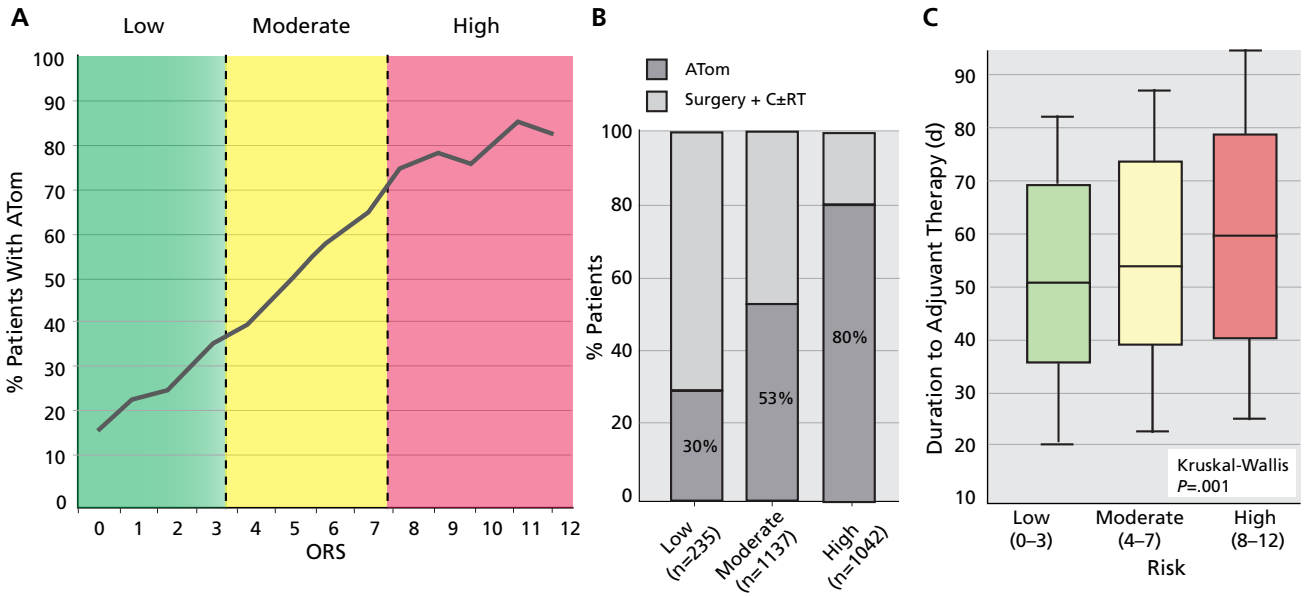

Figure 2 (A) Relationship between proportion of patients with adjuvant therapy omission (ATom) and simplified omission risk score (ORS) along a continuum. This linear trend was highly significant (*P*<.001). (B) Stratification into low-, moderate-, and high-risk zones using composite ORS scores. The incidence of ATom increases significantly in higher risk categories. (C) Ability of ORS to predict delay to adjuvant therapy initiation after gastrectomy. The box-and-whisker plot illustrates median (± interquartile range) duration to commencement of adjuvant therapy in low-, moderate-, and high-risk patient groups. Abbreviation: C±RT, chemotherapy with or without radiotherapy.

bootstrap-validated risk modeling, advancing age, comorbidity, non–privately insured/uninsured status, proximal tumor location, and clinically "early" tumor-related characteristics were independently associated with ATom. Good model discrimination and calibration were verified by a bias-corrected bootstrap,[18] *k*-fold cross validation, and Hosmer-Lemeshow procedures.[19] A simplified ORS instrument,

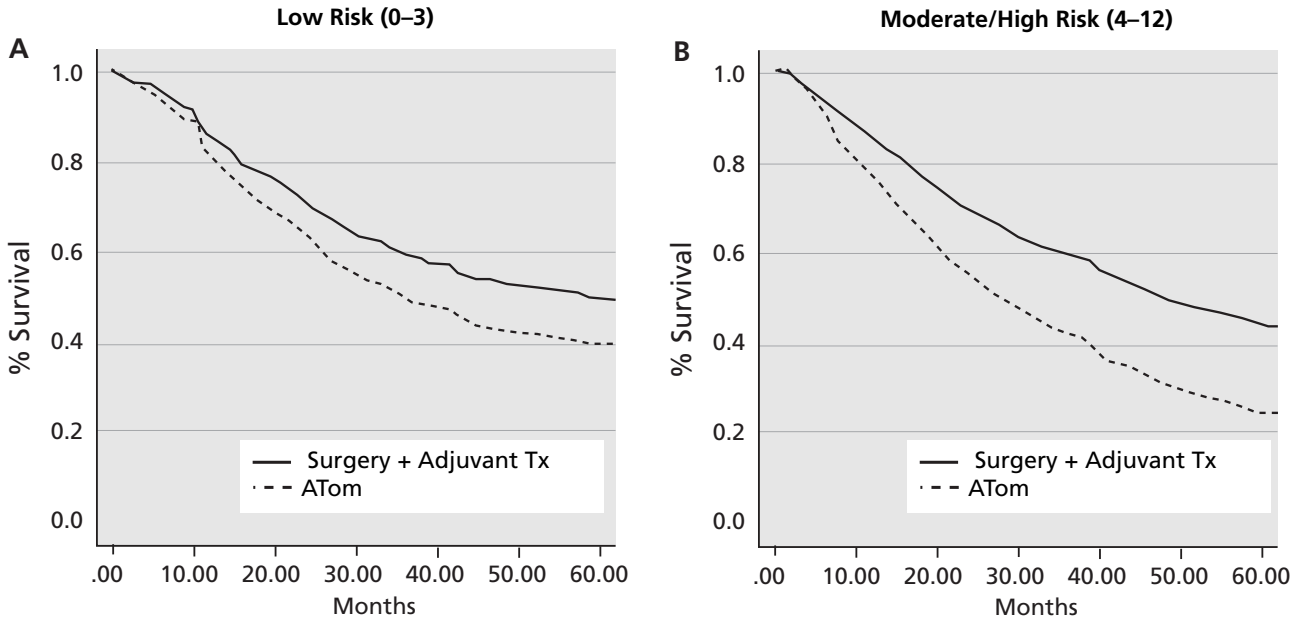

Figure 3 Impact of adjuvant therapy omission (ATom) on overall survival (OS) in gastric adenocarcinoma from 1998 to 2006 (n=1,717), stratified by omission risk score category. OS is significantly worse in patients with ATom compared with those receiving adjuvant chemotherapy with or without radiotherapy in (A) low-risk, and (B) moderate/high-risk categories. The survival disadvantage conferred by ATom is exacerbated in moderate/high-risk versus low-risk patients.

Table 4 Cox Proportional Hazards Model for Overall Survival in Patients Stratified Into Low- and Moderate/High-Risk ORS Cohorts (n=1,717)

Variable	Hazard Ratio	95% CI	*P* Value
Low Risk (ORS 0–3)			
Race			
White	Ref	–	–
Black/Other (eg, American Indian, Pacific Islander)	1.15	0.67–1.97	.609
Asian	0.34	0.12–0.96	.042
Multimodality therapy			
Adjuvant C±RT	Ref	–	–
ATom	1.80	1.06–3.06	.029
AJCC clinical T classification			
T 1/2	Ref	–	–
T 3/4	2.10	1.20–3.68	.009
Resection margin			
Margin negative (R0)	Ref	–	–
Margin positive (R1/R2)	2.04	1.00–4.17	.049
Indeterminate	1.72	0.87–3.40	.116
Moderate-/High-Risk (ORS 4–12)			
Age (y)			
<56	–	–	–
56–66	1.74	0.60–5.03	.307
67–76	1.73	0.62–4.82	.298
>76	2.90	1.03–8.15	.043
Sex			
Female	–	–	–
Male	1.49	1.11–1.99	.008
Facility location			
Northeast	–	–	–
West	0.96	0.63–1.46	.845
Midwest	1.13	0.76–1.67	.541
South	1.66	1.13–2.44	.009
Multimodality therapy			
Adjuvant C±RT	–	–	–
ATom	1.49	1.10–2.02	.011
AJCC clinical T classification			
T 1/2	–	–	–
T 3/4	1.83	1.34–2.50	<.001
AJCC clinical N classification			
Node-negative (N0)	–	–	–
Node-positive (N1–3)	1.55	1.14–2.09	.005
Resection margin			
Margin negative (R0)	–	–	–
Margin positive (R1/R2)	2.23	1.36–3.66	.002
Indeterminate	1.52	0.94–2.47	.087
Adequacy of LNS			
Adequate LNS (≥15 LN)	–	–	–
Inadequate LNS (<15 LN)	1.37	1.02–1.84	.034

Abbreviations: ATom, adjuvant therapy omission; C±RT, chemotherapy with or without radiotherapy; LN, lymph node; LNS, lymph node staging; ORS, omission risk score.

demonstrating equivalent predictive accuracy, was created to facilitate clinical application. Stratification of patients into low-, moderate-, and high-risk zones predicted incremental risk of ATom and progressive delay to adjuvant therapy commencement. Moreover, moderate-/high-risk–stratified ATom patients demonstrated worsening risk-adjusted mortality compared with low-risk counterparts.

Compliance with NCCN Guidlines recommendations for adjuvant C±RT in resected GA has been poor in the United States. The proportion of eligible patients that had ATom (ie, undergoing surgery alone) approached 60% in 2006, and 50% in 2009 in recent SEER and Oregon State Cancer Registry analyses, respectively.[8,21] The present assessment in a contemporary NCDB cohort suggests that ATom continues to be a pervasive problem nationally. As data from prospective randomized controlled trials suggest, these high ATom rates may be explained partly by attrition from prescribed adjuvant therapy regimens because of treatment-related adverse effects. Treatment cessation was observed in 25% of CRT-randomized INT-0116 patients because of toxicity or noncompliance.[4] Similarly, only 42% of patients completed the designated postoperative component of their perioperative epirubicin/cisplatin/fluorouracil regimen in the MAGIC trial.[12] Concerns about tolerability of adjuvant therapy may be addressed in part by contemporary efforts to apply chemotherapy-only regimens following standardized surgery.

Toxicity-related attrition may also be more pronounced in subsets of patients with high-risk features identified by the ORS model. These include both host- and tumor-related factors—advanced age/comorbidity[22] and proximal tumors necessitating total gastrectomy[23]—which impart substantial risk of perioperative morbidity, suggesting that nonfatal surgical complications may be a major determinant of adjuvant therapy omission/delay in resected GA. Indeed, in other gastrointestinal tumors, perioperative morbidity not only delays and/or precludes initiation of adjuvant therapy,[24,25] but also negatively impacts DFS and OS.[26,27] It is possible, therefore, that the surrogates for worsening operative morbidity in this study may contribute to the deteriorating risk-adjusted survival observed in moderate/high-risk ATom patients.

It should be emphasized that ATom may be appropriate in a subset of patients deemed eligible for adjuvant therapy by clinical staging, barring other ORS-defined high-risk features. Discordance between clinical and pathologic staging is well recognized; discrimination between early T classifications (ie, T1 vs T2) is particularly challenging and may account for appropriate ATom in some cases. Nonetheless, given the reasonable concordance between clinical and pathologic staging in retrospective analyses[28,29] when tumors are grouped as T1/2 versus T3/4 categories, the strong association of clinical T1/2 and N0 tumors with ATom may reflect assumptions regarding the dispensability of adjuvant therapy in "early" disease. Such assumptions have not been supported in the literature; conversely, suboptimal outcomes in US patients with GA, including those with stage IB and II disease,[3] indicate that a multimodality approach should be applied more consistently. In addition, the increased risk of ATom in older/comorbid patients may reflect quality-of-life considerations or risk aversion. Although these risks may outweigh the putative benefits of adjuvant therapy in such populations, they should be balanced against the well-documented risk of morbidity and mortality from gastric resection, and total gastrectomy in particular.[23] Finally, the disproportionate risk of ATom in non–privately insured or uninsured patients point to disparities in access to comprehensive cancer care, which merit further investigation.

Selecting the optimal multimodality treatment sequence for patients with resectable GA remains a considerable challenge.[30] The apparent equipoise between adjuvant and neoadjuvant/perioperative C±RT protocols in the published literature continues to obfuscate treatment priorities. The ORS instrument, which preoperatively assesses individualized risk of adjuvant therapy delay/omission, may aid in clinical decision-making. For instance, a subset of patients at moderate/high ORS risk may be better served by induction therapy before surgery. Advantages of neoadjuvant therapy include tumor downstaging and enhanced tolerability of multimodality therapy.[30] This approach, however, is also associated with a rate of attrition; in intent-to-treat trials, up to 15% of patients who initiate neoadjuvant therapy fail to undergo gastrectomy.[31,32] Importantly, factors that drive attrition during neoadjuvant therapy likely differ from those predicting ATom and may aid more rational application of surgical therapy. Specifically, disease progression during induction therapy identifies patients for whom initial surgery would confer little advantage. Notwithstanding, there are patients for whom surgery provides essential locoregional disease control, and neoadjuvant therapy represents an ineffective detour. Dissecting apart these patient subsets is a logical next step in efforts to optimize multimodality treatment sequencing.

Several study limitations, characteristic of retrospective database analyses, warrant emphasis: (1) bias from missing data, (2) patient misclassifi-

cation, and (3) underreporting of adjuvant C±RT receipt. The last of which may have inflated the prevalence of ATom in this cohort and impacted study findings. Additionally, because determination of treatment intent is not possible with the NCDB data, it remains unclear whether adjuvant therapy was intended but never initiated (eg, related to postoperative complications) or excluded (eg, not considered part of treatment plan[8]). Finally, specifics regarding the C±RT schedules used are not available and the effect of adjuvant therapy may be underestimated or overestimated.

Conclusions

This is the first report of an internally validated risk assessment tool assimilating patient-, tumor-, and provider-associated factors to predict ATom in patients with resected GA. Although the ORS is not intended to supplant nuanced clinical judgment, it does underscore the need for a more personalized approach to multimodality treatment of GA. The not infrequent tensions between optimizing long-term cancer-related outcomes and locoregional control preclude an algorithmic approach to this disease. Above all, the current data highlight shortcomings of the current armamentarium for the treatment of GA. Development of better tolerated and more effective adjuvant approaches, increased utilization of neoadjuvant therapies when appropriate, and more standardized surgery may represent important elements in improving overall GA outcomes in the United States.

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