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Adjuvant Chemotherapy is Associated with Improved Survival After Esophagectomy without Induction Therapy for Node-positive Adenocarcinoma

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Abstract

Background—This study investigated adjuvant chemotherapy(AC) use after esophagectomy without induction therapy for node-positive (pN+) adenocarcinoma using the National Cancer Database (NCDB), including the impact of complications related to surgery (CRS) on outcomes.

Methods—Predictors of AC use in 1,694 patients in the NCDB who underwent R0 esophagectomy from 2003-2011 without induction therapy for pN+ adenocarcinoma of the middle or lower esophagus and survived >30 days were identified with multivariable logistic regression. The impact of AC on survival was estimated using Kaplan-Meier and Cox-proportional hazards methods.

Results—AC was given to 874/1,694 (51.6%) patients; 618 (70.7%) AC patients received radiation. Older age (AOR 0.58/decade, p<.001), longer travel distance (AOR 0.78/100 miles, p=.03) and CRS (AOR 0.45, p<.001) predicted that AC was not used. Patients given AC had better 5-year survival than patients not given AC (24.2% vs 14.9%, p<.001), and AC use predicted improved survival in multivariate analysis (HR 0.67, p=0.008, Table). Receiving radiation in addition to AC did not improve survival (p=0.35). Although CRS was associated with worse survival, patients who had CRS but received AC had superior survival compared to patients who did not have CRS or get AC (p=.016).

Conclusions—AC following esophagectomy is associated with improved survival but was only used in half of patients with pN+ esophageal adenocarcinoma. We also found that the addition of radiation to AC was not associated with a survival benefit. CRS predict worse long-term survival and lower the chance of getting AC, but even patients with CRS had improved survival when given AC.

Keywords

esophageal cancer; adjuvant chemotherapy; post-operative complications

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Introduction

Approximately 57% of all esophageal cancers in the United States are adenocarcinomas, with an increasing incidence in recent years.[1-6] Esophageal adenocarcinomas are found in the distal esophagus in three quarters of cases.[2] Overall approximately 32% of esophageal cancer patients have regional disease at the time of diagnosis.[1,2,7] The treatment for locally advanced esophageal cancer that does not have distant metastases and is potentially resectable (T3-4aN0, T1-4aN1M0) is highly variable in practice.[8] However, recent evidence suggests that induction chemoradiation followed by surgical resection is the optimal treatment for patients with nodal disease (pN+).[9-15] For patients with pN+ adenocarcinoma who are treated primarily with surgical resection, the National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant chemoradiation.[16]

However, the use of adjuvant therapy after esophagectomy for adenocarcinoma has not been well characterized. Recommendations related to adjuvant therapy for esophageal adenocarcinoma are derived from trials that exclusively or predominantly included patients with gastric carcinoma.[17-23] One potential difficulty with translating results from those studies is that a patient's ability to tolerate adjuvant treatment may differ between gastrectomyand esophagectomy. Esophagectomy is associated with significant morbidity despite improvements over time, and complications can more than double already long hospital stays and overall recovery periods.[24-31] Both patients and their providers may be reluctant to consider potential risks associated with adjuvant therapy after esophagectomy, especially if the patient had a difficult perioperative course. Currently the paucity of data regarding the use of adjuvant therapy limits clinicians' ability to appropriately counsel patients on the risks and benefits. This study was undertaken to examine the role of adjuvant therapy following surgical resection for adenocarcinoma of the esophagus using a large national clinical database and attempt to improve the available level of evidence, particularly with regard to the potential benefits of adjuvant oncologic therapy in patients with postoperative complications.

Methods

This retrospective analysis of patients in the National Cancer Data Base (NCDB) undergoing esophagectomy for esophageal cancer from 2003-2011 was approved by the Duke University Institutional Review Board. The NCDB currently contains over 30 million records by collecting data from more than 1,500 CoC-approved facilities across the United States, and is estimated to capture approximately 70% of all newly diagnosed U.S. cases of cancer annually. Patients with adenocarcinoma of the mid- and distal third of the esophagus were identified using International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) topography and histology codes. Pathologic TNM staging data was directly extracted using the American Joint Commission on Cancer (AJCC) 6th and 7th edition staging manuals depending on year of diagnosis, and only patients with N+ disease were kept for analysis. As our primary predictor variable was the use of adjuvant chemotherapy (AC) following oncologic resection, only patients with negative (R0) margins who survived at least 30 days postoperatively were included. Patients who received induction therapy of

any kind were excluded, as were patients with missing data regarding the specific timing of chemoradiation therapies.

Patients were stratified into two groups based on the use of AC versus postoperative observation. Baseline patient characteristics and postoperative outcomes were compared using the Mann Whitney U test for continuous variables and Pearson's chi-square test for discrete variables. Trends over time were examined with the Cochran-Armitage trend test. Since the NCDB does not contain data regarding specific perioperative morbidity, we defined postoperative complications as cases that involved either an unplanned readmission, or a length of stay of at least 20 days following esophagectomy. Predictors of AC were identified using multivariable logistic regression modeling, which included age, sex, race, Charlson/Deyo comorbidity score, median census tract education and income levels, TNM pathologic T-stage, patient distance from treatment facility, and presence of a postoperative complication as defined above.

The Kaplan-Meier method was used to estimate overall survival, which was defined as time from diagnosis to death or censor. Cancer-specific survival is not available in the NCDB. To estimate the independent effect of AC on survival, a Cox proportional hazards model was developed that included age, sex, race, comorbidity burden, pathologic T stage, and treatment facility volume. To examine whether postoperative complications were confounding any potential differences between the treatment groups, we conducted a subgroup analysis of assessing long-term survival only for those patients who did not experience a complicated course. Likewise, we explored survival among patients who received AC, stratified by the presence of postoperative complications, focusing on how rescue from such complications affects survival for patients who received AC, compared to patients receiving AC in the setting of no major complications.

We made an affirmative decision to control for type I error at the level of each comparison. A p-value <0.05 was considered statistically significant for all comparisons. Missing data was handled with complete case analysis given the substantial completeness of the NCDB for the study population investigated. All statistical analyses were performed using R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Of 1,694 node-positive patients in the NCDB who did not receive induction therapy and survived at least 30 days after surgery, 874 (51.6%) were treated with AC, and 618 of these (70.7%) also received radiation therapy post-operatively. Use of chemotherapy significantly increased over time, from 45% of patients in 2003 to 57% in 2011, $p<0.001$ (Figure 1). Baseline unadjusted characteristics are shown in Table 1, with the patients who received adjuvant therapy being younger, with lower comorbidity burden, were more likely to have private insurance, and had significantly shorter hospital length of stays following esophagectomy. Following multivariable adjustment, older age (adjusted odds ratio [AOR] 0.58/decade, $p<.001$), longer travel distance (AOR 0.78/100 miles, $p=.03$) and presence of postoperative complications (AOR 0.45, $p<.001$) predicted that AC was not used (Table 2). A total of 1,470 (86.8%) patients had complete data regarding unplanned readmission and

hospital length of stay. Of patients not experiencing post-operative complications, 587 (54.4%) were treated with AC, while among patients who experienced a complication, only 130 (33.3%) went on to received AC.

Median survival for patients given AC was 24.8 months versus 16.7 months for patients treated with surgery alone (p<.001, Figure 2A). Patients given AC had better 5-year survival than patients not given AC (24.2% versus 14.9%), and AC use predicted improved survival in multivariable analysis (hazard ratio [HR] 0.67, p=0.008, Table 3). Although postoperative complications were associated with worse survival (HR 1.5, p=0.01), adjuvant therapy use was still associated with a significant survival advantage after excluding all patients who experienced a postoperative complication (5-year survival: 24.7% versus 16.0%, p<.001; Figure 2B). More importantly, patients who experienced postoperative complications and were subsequently rescued to receive intended AC had similar survival compared to patients who received AC in the absence of complications (p=0.78, Figure 3A), but had superior survival compared to patients who did not experience complications but also did not get AC (p=.016, Figure 3B). In an exploratory analysis examining the effect of adding adjuvant radiation therapy to AC, no significant improvement in survival was found between patients who were given AC and radiation compared to patients who were only given AC (p=0.35).

Discussion

In this study, we found that the use of AC following esophagectomy is associated with significantly improved survival for patients for pN+ esophageal adenocarcinoma not treated with induction therapy. Despite increasing rates of AC use over time, we found that only approximately half of patients treated with esophagectomy without induction therapy for pN + esophageal adenocarcinoma in the NCDB ultimately received AC treatment postoperatively. While complications related to surgery both significantly lower the probability of treatment with AC and predict worse long-term survival overall, patients who adequately recover from complications and subsequently receive AC do derive benefits with respect to long-term survival.

The use of adjuvant therapy after esophagectomy for adenocarcinoma is poorly characterized. Recommendations related to adjuvant therapy for esophageal adenocarcinoma are derived from trials that exclusively or predominantly included patients with gastric carcinoma.[17-23] The NCCN recommendations for adjuvant chemoradiation therapy after esophagectomy are primarily based on the Intergroup-0116 study. In this study of 556 patients with adenocarcinoma of the stomach or cardia, 85% of whom had pathologic nodal disease, patients given adjuvant chemoradiation (45 Gy combined with 5-FU and leucovorin) had significantly better three year survival compared to patients treated with surgery alone (50% versus 41%, hazard ratio 1.32, p=0.0046).[17, 18] However, only 20% of these patients had cancer in the proximal stomach or gastroesophageal (GE) junction area. Similarly, the ARTIST trial compared adjuvant chemoradiation (2 cycles cisplatin and capecitabine then 46 Gy with capecitabine for 5 weeks and then 2 more cycles of cisplatin and capecitabine) and chemotherapy alone (6 cycles of cisplatin and capecitabine) in 458 patients with adenocarcinona of the stomach or GE junction, and found chemoradiation was associated with improved disease-free survival in the subgroup of patients who had

pathologic lymph node metastases at the time of surgery, but overall no difference in 3 year disease-free survival.[19] Pathological nodal disease was present in 86% of the patients, but only 5% of patients had GE junction tumors. Similarly, studies of adjuvant chemotherapy have also included very limited numbers of esophageal cancer patients. The Asian Phase III Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) was a study of 1059 Japanese patients with gastric adenocarcinoma, most of whom were stage II or III, that found adjuvant chemotherapy (one year of the oral fluoropyrimidineS-1) was associated with better survival than surgery alone (71.7% versus 61.1%, hazard ratio 0.669).[20, 21] However, this study only included patients with stomach cancer and involved a drug that is not widely used outside of Asia. The CLASSIC study did include patients with GE junction adenocarcinomas and found patients that were given adjuvant chemotherapy (8 cycles capecitabine and oxaliplatin) had better overall five year survival compared to patients treated with surgery alone (78% vesus 69%, p=0.0029).[22, 23] This Asian trial of 1035 patients included 90% who had nodal disease, but 98% of included patients had gastric cancer with only the remaining 2% having GE junction cancers.

Using data related to gastric adenocarcinoma to guide treatment of esophageal adenocarcinoma does have some validity. Adenocarcinoma of the GE junction (GEJ) is treated and staged similarly to more proximal esophageal cancers of the proximal esophagus, but is considered to be significantly less radiosensitive than other esophageal cancers and is biologically more closely related to gastric adenocarcinoma.[32] However, surgical resection and subsequent reconstruction of gastrointestinal continuity for esophageal cancer is more complex than that for gastric cancer, which can impact the ability to tolerate additional therapy postoperatively and therefore limit the ability to extrapolate gastric adenocarcinoma treatment data to patients with esophageal cancer. Our current study quantifies the impact of postoperative complications on outcomes and the use of adjuvant chemotherapy among patients with esophageal cancer. Although the NCDB does not have specific data available regarding postoperative morbidity, our definition based on unplanned readmission within 30 days or a length of stay of three weeks or greater captures patients who did not have a completely uneventful postoperative course. Importantly, our study shows that patients who have postoperative complications but still receive AC have survival that is similar to that of those patients who have an uncomplicated course and are treated with AC as planned, and is markedly better than for patients who do not experience a complication but are also not treated with AC. This data can guide patient counseling, as patients reluctant to consider additional therapy may be more amenable if the potential benefits of improved survival are better quantified.

Recent evidence suggests that induction chemoradiation followed by surgical resection is the optimal treatment for patients with locally advanced but resectable esophageal cancer.[9-15] There are several potential reasons why patients in this current study may not have been given induction therapy. First, the patients may have been treated at institutions where induction therapy was not routinely considered. Second, induction therapy may been considered inappropriate do to specific patient characteristics, such as medical comorbidities or previous chemotherapy or radiation therapy. Third, the patients may have been understaged pre-therapy due to limitations of current staging modalities.[33-38] Our study does suggest that adjuvant therapy likely provides benefit to patients who are primarily

treated with surgery due to initial understaging. However, clinicians may want to more strongly consider induction therapy prior to esophagectomy whenever there is suggestion of nodal or more advanced disease, considering our finding that only about half of patients get AC and therefore all of the recommended treatment when nodal disease is discovered after primary therapy with esophagectomy.

Younger age and the absence of a complicated postoperative course were both strongly associated with the use of AC, though interestingly Charlson/Deyo comorbidity score did not appear to alter its use. However, it is likely that considerable co-linearity between higher comorbidity scores and likelihood of postoperative complications, both of which were included in our statistical model, may explain the lack of significance. Socioeconomic factors including race, income and education level do not appear to have an independent effect on the use of AC, however longer distance to the treatment facility lowered the odds of receiving AC. While this could be related to geographic and center-level variation, it more likely represents a logistical burden for patients who are required to travel longer distances to receive their care.

While the primary purpose of this study was to examine adjuvant chemotherapy use, we also examined the addition of radiation therapy to AC. In an exploratory Cox proportional hazards model, the addition of radiation therapy to the model resulted in neither adjuvant radiation nor chemotherapy having an independent association with long-term survival. As this was likely due to significant co-linearity between the two variables (71% of the AC patients also received radiation therapy), we then conducted a comparison of survival among patients treated with only AC versus combined adjuvant chemoradiation, and found no significant difference between the two groups. These results suggest that the substantial survival advantage associated with adjuvant therapy is due to chemotherapy. Although radiation may confer some benefits in terms of local control as evidenced by the studies that investigated adjuvant therapy for gastric cancer, these benefits may be offset by complications related to treatment of the conduit after esophageal cancer resection. Our results suggest that among patients with node-positive disease following esophagectomy, radiation does not effect overall survival. Given these findings, more study is needed regarding the impact of postoperative radiation therapy on patients recently treated with esophagectomy.

The NCDB offers significant advantages over existing studies due to its large size and population-based nature. Regardless, the database does have inherent limitations. First, this was a retrospective study, and as such is subject to intrinsic selection bias. While our patient population was defined by fairly strict criteria regarding indications for AC (R0 resection and node-positive disease, in the absence of induction treatment), it is possible that some patients were not treated with AC due to comorbidities or the belief that they would not safely tolerate chemotherapy following the expected insult of an esophagectomy. Second, the NCDB does not provide specific complication data such as anastomotic leak, pneumonia, or sepsis, and therefore our definition of postoperative complications is based on measured indicators. While we felt that an unplanned readmission or length of stay >20 days was clearly related to a non-routine postoperative course, it is possible that the actual complication rate was much higher, and we were simply unable to detect less severe

occurrences based on the criteria used. Lastly, cancer-specific survival and recurrence data are not available in the NCDB, both of which may be particularly important in our analyses of patients experiencing postoperative complications.

In conclusion, adjuvant chemotherapy is associated with a substantial survival advantage for patients with positive nodal disease following esophagectomy. Esophagectomy remains a highly morbid procedure with considerable risk of postoperative complications. Patients who can be rescued to proceed to AC despite complications fare as well as patients treated with AC but who had an uncomplicated course. In light of the meaningful survival benefit associated with AC despite complications, great effort should be made to ensure that patients who experience a complicated course following esophagectomy are given strong consideration for treatment with AC if at all possible.

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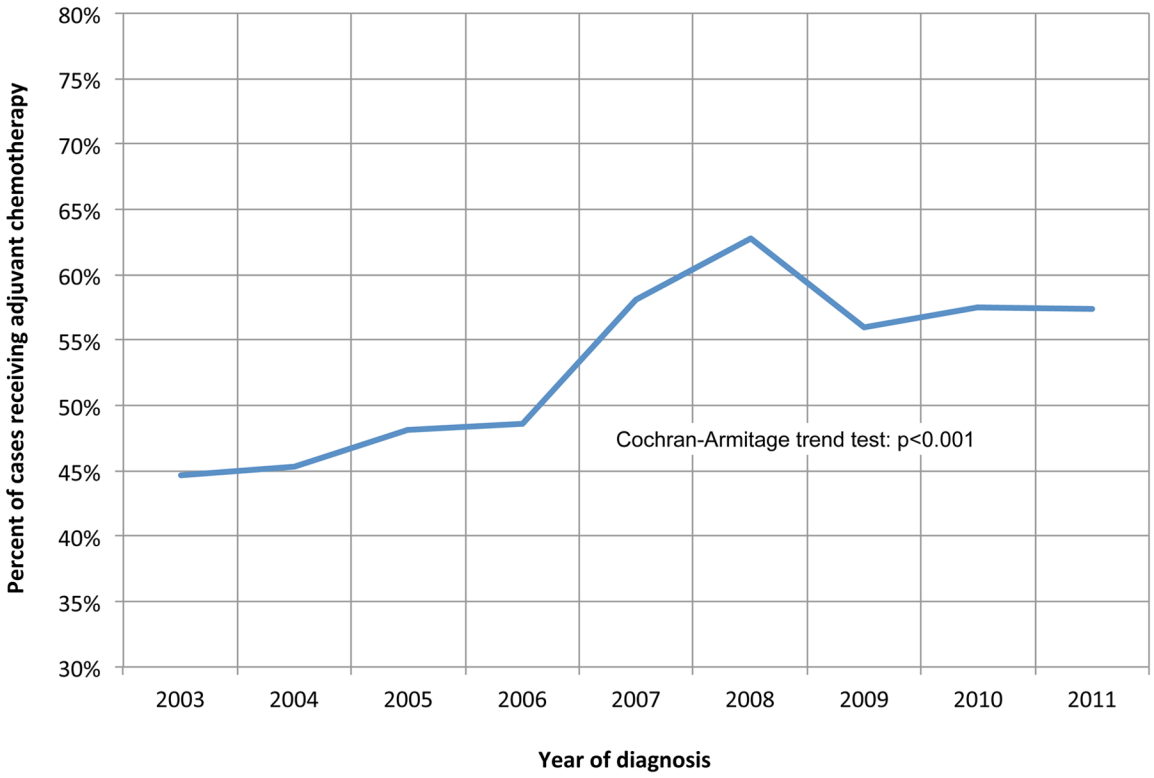

Figure 1. Trends in the use of adjuvant chemotherapy following margin-negative, node-positive esophagectomy

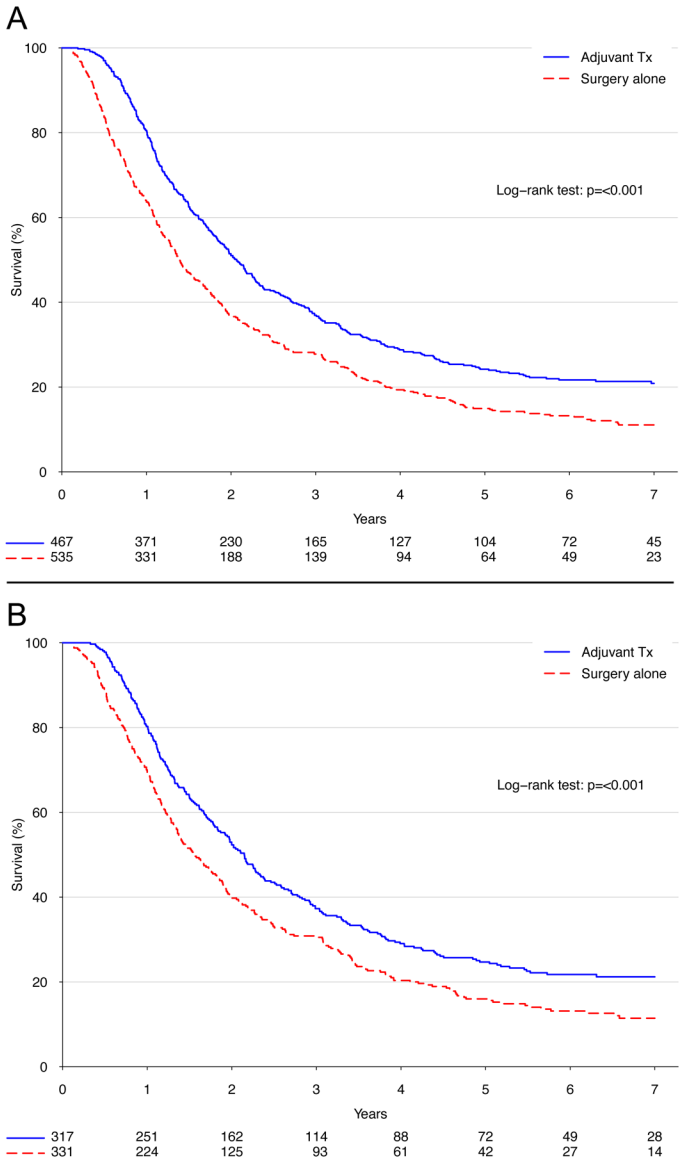

Figure 2.

Kaplan-Meier survival curves for patients (A) treated with versus without adjuvant chemotherapy; and (B) treated with versus without adjuvant chemotherapy and excluding patients experiencing a postoperative complication (defined as an unplanned readmission or length of stay >20 days).

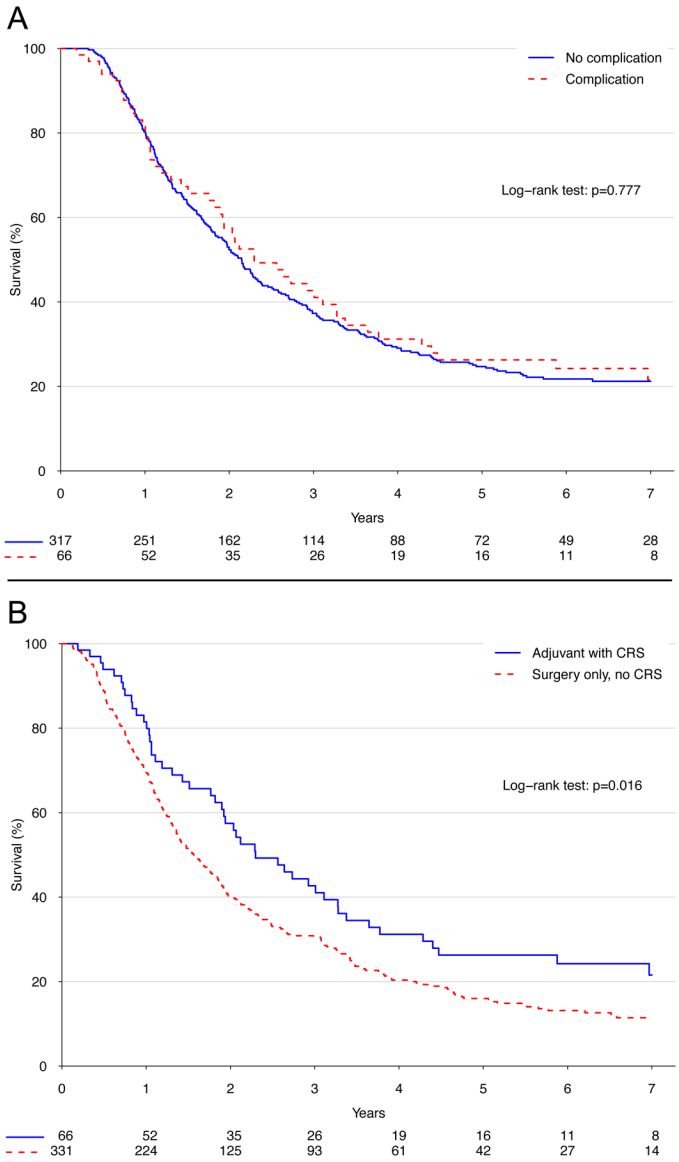

Figure 3.

Kaplan-Meier survival curves for patients who experienced a postoperative complication but were rescued to receive intended adjuvant chemotherapy compared to patients who (A) received adjuvant chemotherapy in the absence of complications; and (B) patients who did not experience complications or get adjuvant therapy.

Table 1

Baseline characteristics between groups

Variable	Total (n = 1,694)	No chemo (n = 820)	Adjuvant chemo (n = 874)	P-value
Patient characteristics				
Age, yrs (IQR)	64 (56, 72)	67 (59, 75)	61 (54, 68)	< 0.001
Female	201 (11.9%)	106 (12.9%)	95 (10.9%)	0.217
Race				0.496
White	1,631 (97.2%)	790 (97.4%)	841 (97%)	
Black	25 (1.5%)	13 (1.6%)	12 (1.4%)	
Other	22 (1.3%)	8 (1%)	14 (1.6%)	
Charlson Comorbidity Score				< 0.001
0	1,166 (68.8%)	532 (64.9%)	634 (72.5%)	
1	414 (24.4%)	211 (25.7%)	203 (23.2%)	
≥2	114 (6.7%)	77 (9.4%)	37 (4.2%)	
Education above median	1,016 (63.1%)	492 (63.5%)	524 (62.7%)	0.777
Income above median	1,100 (68.3%)	527 (68%)	573 (68.5%)	0.858
Insurance				< 0.001
Private	811 (48.7%)	316 (39%)	495 (58%)	
Medicare	747 (44.9%)	439 (54.2%)	308 (36.1%)	
Medicaid	57 (3.4%)	30 (3.7%)	27 (3.2%)	
Government	18 (1.1%)	8 (1%)	10 (1.2%)	
Uninsured	31 (1.9%)	17 (2.1%)	14 (1.6%)	
Tumor characteristics				
Tumor size				0.48
< 1 cm	39 (2.5%)	19 (2.5%)	20 (2.5%)	
1-1.9 cm	124 (8%)	65 (8.6%)	59 (7.4%)	
2-4.9 cm	889 (57.3%)	440 (58.4%)	449 (56.3%)	
> 4.9 cm	499 (32.2%)	229 (30.4%)	270 (33.8%)	
Pathologic T-stage				0.872
T1	307 (18.3%)	154 (18.9%)	153 (17.7%)	
T2	322 (19.2%)	159 (19.5%)	163 (18.8%)	
T3	999 (59.4%)	477 (58.5%)	522 (60.3%)	
T4	53 (3.2%)	25 (3.1%)	28 (3.2%)	
Facility characteristics				
Distance to cancer center (IQR)	15.6 (6, 39.6)	20.2 (7.4, 54.4)	12.6 (4.8, 30.4)	0.016
Treatment facility				< 0.001
Academic/Research Program	793 (47%)	438 (53.7%)	355 (40.8%)	
Community Program	893 (53%)	377 (46.3%)	516 (59.2%)	
Surgical endpoints				

Variable	Total (n = 1,694)	No chemo (n = 820)	Adjuvant chemo (n = 874)	P-value
Nodes removed (IQR)	13 (8, 19)	13 (8, 19)	13 (9, 20)	0.334
Short-term outcomes				
30-day readmission	129 (8%)	74 (9.4%)	55 (6.7%)	0.064
Hospital LOS (IQR)	11 (8, 16)	13 (9, 21)	10 (8, 14)	< 0.001
Major complication	390 (26.5%)	260 (34.5%)	130 (18.1%)	< 0.001

Table 2
Independent predictors of adjuvant chemotherapy use following esophagectomy

Predictor	Odds ratio	Upper 95% CI	Lower 95% CI	p-value
Age (per decade)	0.58	0.49	0.70	<0.001
Female sex	0.74	0.41	1.33	0.308
Race (ref = White)				
Black	5.77	0.64	52.24	0.119
Other	3.08	0.18	51.50	0.434
Charlson score	0.84	0.62	1.13	0.241
Education above median	1.12	0.72	1.73	0.615
Income above median	0.82	0.52	1.28	0.373
pT stage	0.93	0.76	1.13	0.453
Distance traveled (per 100 miles)	0.78	0.62	0.98	0.032
Complication related to surgery	0.45	0.30	0.67	<0.001

Table 3

Adjusted predictors of long-term mortality, following Cox proportional hazards modeling

Risk factor/Predictor	Hazard ratio	Upper 95% CI	Lower 95% CI	p-value
Adjuvant chemotherapy	0.67	0.50	0.90	0.008
Age (per decade)	1.11	0.97	1.27	0.13
Female sex	0.91	0.56	1.50	0.72
Race (ref = White)				
Black	2.15	0.78	5.94	0.138
Other	8.07	1.08	60.12	0.042
Charlson score	1.16	0.93	1.45	0.198
Pathologic T stage (per unit)	1.57	1.31	1.87	<0.001
Facility volume (per 10 cases)	0.56	0.29	1.07	0.077
Complications related to surgery	1.51	1.10	2.08	0.012