Prognostic value of neoadjuvant treatment response in locally advanced esophageal adenocarcinoma

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ABSTRACT

Objective: To determine the association between neoadjuvant chemotherapy and chemoradiation therapy on completeness of pathologic response and to assess the impact of primary tumor versus nodal response on survival after esophagectomy.

Methods: Patients aged 18 to 80 years in the National Cancer Data Base (2006-2016) with clinically staged, locally advanced (cT2-4 or cN+) esophageal adenocarcinoma who underwent an R0 esophagectomy after neoadjuvant chemotherapy or chemoradiation therapy were included. Multivariable Cox proportional hazards regression models were constructed to assess the association between treatment response and survival.

Results: Among 2870 patients, there was a significant dose-response association between completeness of response and overall survival: no response (reference), partial response (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.72-0.91), and complete response (HR, 0.55; 95% CI, 0.47-0.65). Compared with neoadjuvant chemotherapy alone, neoadjuvant chemoradiation was associated with higher pathologic primary tumor (33.9% vs 21.3%; $P < .001$) and pathologic nodal response rates (55.9% vs 32.7%; $P < .001$). Both a primary and nodal response were associated with improved survival. However, among patients with a primary but no nodal response, primary tumor response was not associated with risk of death (HR, 0.88; 95% CI, 0.69-1.11). In contrast, among patients who had a nodal but no primary response, the survival benefit of a nodal response was maintained (HR, 0.66; 95% CI, 0.58-0.76).

Conclusions: Pathologic nodal (rather than primary tumor) response to neoadjuvant therapy is associated with improved survival. These data suggest a need to optimize neoadjuvant strategies associated with more complete nodal response rates and to consider more aggressive adjuvant treatment for patients with residual nodal disease after esophagectomy. (J Thorac Cardiovasc Surg 2019;157:1682-1693)

Nodal response to neoadjuvant therapy is independently associated with survival.

Central Message

Pathologic nodal (rather than primary tumor) response to neoadjuvant therapy for esophageal adenocarcinoma is an independent determinant of survival after esophagectomy with negative margins.

Perspective

Pathologic nodal (rather than primary tumor) response to neoadjuvant therapy for locally advanced esophageal adenocarcinoma is the principal determinant of survival after a margin-negative esophagectomy. Thus, neoadjuvant therapy should be optimized to maximize nodal response rates, and adjuvant systemic therapy should be considered for patients with residual nodal disease.

See Commentary on page 1694.

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There have been numerous contemporaneous improvements to the management of esophageal cancer, including endoscopic resection of early-stage tumors, the introduction of biomarker-directed systemic therapies (ie, Her-2, mismatch repair deficiency, microsatellite instability-high, and programmed death-ligand 1), increasing sophistication

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Abbreviations and Acronyms

CI	= confidence interval
CoC	= Commission on Cancer
HR	= hazard ratio
NCDB	= National Cancer Data Base
OS	= overall survival
RRR	= relative risk ratio

of radiation techniques, and surgical and technologic advances such as minimally invasive approaches to radical resection. Despite these and other refinements to cancer-directed therapy, survival for patients with esophageal cancer has improved little over the past several decades. Even with aggressive multimodal therapy incorporating chemotherapy, radiation therapy, and esophagectomy, the 5-year survival remains 30% to 50%.¹⁻³ Two important factors have been identified that positively affect the outcome of patients diagnosed with esophageal cancer: (1) use of multimodal therapy and (2) disease response to neoadjuvant therapy.

Compared with surgery alone, the addition of neoadjuvant therapy prior to esophagectomy is associated with higher margin negative resection rates, lower recurrence rates, and improved survival.¹⁻³ In addition, the degree of pathologic response to neoadjuvant therapy has significant prognostic implications—a complete pathologic response to neoadjuvant therapy is independently associated with improved survival.⁴⁻⁹ However, these data regarding the association between pathologic response to neoadjuvant treatment and survival are primarily limited to single-institution studies.¹⁰ Furthermore, prior studies evaluated treatment response as a binary outcome (complete vs incomplete response) with little information available about the impact of partial, as compared with no or complete pathologic response. Furthermore, given a paucity of data from the general community, the generalizability of the prognostic value of pathologic response remains unclear.

The objectives of this study were to evaluate the association between the degree of pathologic response and the overall survival (OS) and to characterize the relative impact of primary tumor response and nodal response on survival after esophagectomy following neoadjuvant therapy. We hypothesize that the degree of pathologic response (eg, no, partial, or complete) to neoadjuvant treatment is associated with survival and that pathologic nodal response to neoadjuvant therapy has a more significant impact on survival than a primary tumor response.

MATERIALS AND METHODS**Study Subjects**

This was a retrospective cohort study using the National Cancer Data Base (NCDB). The NCDB is a jointly sponsored project of the Commission on Cancer (CoC) of the American College of Surgeons and the American

Cancer Society. It is a prospectively maintained hospital-based cancer registry containing information on more than 70% of incident malignancies diagnosed in the United States annually at more than 1500 CoC-accredited centers.

We selected patients aged 18 to 80 years from the NCDB for inclusion in our study using International Classification Disease for Oncology, 3rd Edition codes for esophageal adenocarcinoma. Patients diagnosed with locally advanced (cT2-4 or cN+) esophageal adenocarcinoma between 2006 and 2012 and who underwent neoadjuvant chemotherapy or chemoradiation therapy followed by esophagectomy were included.

Exclusion criteria for our cohort are shown in Figure 1. Patients with esophageal squamous cell carcinoma were excluded because it accounts for the minority of esophageal cancer diagnoses in the United States and because of its notable differences in response rate to neoadjuvant therapy compared with adenocarcinoma.¹ We excluded patients who had a positive or unknown resection margin (n = 393). We also excluded patients who were treated outside of the reporting facility to improve the accuracy of the ascertainment of the receipt all neoadjuvant and adjuvant therapies.

This study was approved by the Human Subjects Committee of the Baylor College of Medicine Institutional Review Board and the Michael E. DeBakey VA Medical Center Research and Development Committee.

Definitions

Disease response to neoadjuvant therapy was the main variable of interest in this study. Response rates were classified on the basis of the degree of response: 1. complete response (ypT0N0); 2. partial response—primary tumor or nodal downstaging (specifically, cT3 to ypTis-1 or cT4 to ypTis-2 regardless of pathologic nodal status, cN+ to ypN0 with residual primary tumor, or ypN+ with a complete primary response); 3. no response. This definition for primary tumor response was chosen because it should conservatively bias results toward the null. Patients were also categorized on the basis of the type of neoadjuvant treatment received. The NCDB does not provide information to differentiate between patients treated with neoadjuvant concurrent chemoradiation therapy and neoadjuvant sequential chemotherapy and (chemo)radiation therapy. All patients in our cohort were treated with neoadjuvant chemotherapy. Consequently, patients were classified as having been treated with neoadjuvant radiation or not.

Statistical Analysis

Continuous and categorical variable distributions were evaluated with standard descriptive statistics. The primary outcome was OS, and distributions across disease response categories were evaluated using the Kaplan-Meier method and log-rank test. The association between the use of neoadjuvant radiation and the disease response was evaluated using multivariable, multinomial regression. Multivariable Poisson regression was used to evaluate the association between the use of neoadjuvant radiation and the primary tumor and nodal responses separately.¹¹⁻¹⁴ The association between risk of death and pathologic disease response was examined with multivariable Cox regression. The proportional hazards assumption was evaluated graphically. Because 90.7% of patients in the study cohort received neoadjuvant radiation and NCDB does not provide information pertaining to the reasons a patient was treated with chemotherapy alone, Cox models were limited to patients who received neoadjuvant radiation. To evaluate the relative impact of primary tumor response and nodal response on risk of death, we separately evaluated patients who had a primary tumor response (with and without nodal response) and patients who had a nodal response (with and without primary tumor response). In all models, covariates were empirically selected nonparsimoniously and included age, sex, race, insurance status, income, education, rurality, Charlson comorbidity score, type of treating facility, tumor grade, and receipt of adjuvant therapy. All models included an adjustment for clustering of patients within hospitals through the use of robust standard errors.

FIGURE 1. Flow diagram illustrating the inclusion and exclusion criteria that were used to arrive at the final study cohort from all patients with esophageal cancer in the NCDB (2004-2012).

Four additional sensitivity analyses were performed. First, because prior work has demonstrated a benefit for the use of adjuvant therapy in select patients, we restricted our Cox models to those who did not receive any adjuvant treatment ($n = 2569$).¹⁵ Second, to address the potential impact of the quality of surgery and the accuracy of pathologic nodal staging, we also restricted our models to patients who had 15 or more lymph nodes pathologically evaluated ($n = 1092$).¹⁶ Third, to ensure that our findings were not explained by early deaths among patients with no response or partial response, we applied a 90-day landmark analysis to the overall Cox model.¹⁷ Finally, to address possible secular trends in care that may

have been associated with improved outcomes, year of diagnosis was included as a model covariate.

Missing covariate data were present for 19.6% of the cohort. However, 5-year OS was not significantly different between those who did and did not have missing data in the overall cohort (log-rank, $P = .31$) or among those with varying degrees of disease response (no response—log-rank, $P = .41$; partial response—log-rank, $P = .40$; complete response—log-rank, $P = .37$). To address missing values, models were run using a case-complete approach and after multiple imputation by chained equations. Results of both approaches were similar, and results from the

TABLE 1. Demographic and clinical characteristics of the study cohort stratified by type of pathologic response to neoadjuvant treatment

	No response (n = 1383)	Incomplete response (n = 991)	Complete response (n = 496)	P value
Demographic				
Mean age ± SD, y	60.3 ± 9.3	61.0 ± 9.2	61.3 ± 9.1	.02
Age, y (%)				.07
≤55	30.1	26.9	24.2	
56-60	17.9	17.6	15.7	
61-65	21.6	21.8	23.4	
>65	30.4	33.7	36.7	
Male sex (%)	89.6	90.3	90.3	.81
Race (%)				.28
White	95.8	96.3	97.0	
Nonwhite	2.6	2.9	2.4	
Missing	1.6	0.8	0.6	
Insurance status (%)				.16
Insured	55.8	55.6	56.1	
Medicare/Medicaid	39.3	40.0	40.9	
Other	3.8	4.0	2.8	
Missing	1.2	0.4	0.2	
Income (%)*				.63
≥\$63,000	32.8	34.6	32.1	
Missing	1.6	1.9	1.2	
Education (%)*				.08
<7%	26.0	28.4	32.5	
Missing	1.6	1.8	1.2	
Rurality (%)				.22
Metropolitan	45.0	47.8	44.8	
Urban	31.2	32.1	34.3	
Rural	20.6	16.5	17.7	
Missing	3.2	3.6	3.2	
Comorbidity index (%)				.26
0	74.8	73.7	78.0	
1	20.6	21.4	19.2	
≥2	4.6	4.9	2.8	
Facility				
Hospital type (%)				.004
Academic/research	58.1	62.4	65.7	
Comprehensive cancer center	28.7	27.7	26.8	
Other	11.3	8.3	5.7	
Missing	2.0	1.7	1.8	
Clinical				
Grade (%)				<.001
Well/moderate	37.6	40.2	34.9	
Poor/undifferentiated	51.7	46.6	43.6	
Missing	10.7	13.2	21.6	
Clinical T stage (%)				<.001
1	2.3	2.8	2.8	
2	22.1	15.4	26.0	
3	73.3	77.1	67.5	
4	2.4	4.6	3.6	
Clinical N stage (%)				<.001
Positive	54.0	86.5	66.9	

(Continued)

TABLE 1. Continued

	No response (n = 1383)	Incomplete response (n = 991)	Complete response (n = 496)	P value
Pathologic T stage (%)				<.001
0	0	9.0	100	
In situ	0	2.8	0	
1	7.6	38.2	0	
2	26.6	22.3	0	
3	64.6	27.3	0	
4	1.2	0.4	0	
Pathologic N+ (%)				<.001
Positive	69.1	17.6	0	
Neoadjuvant treatment (%)				<.001
Radiation therapy used	87.3	92.6	96.2	
Chemotherapy only	12.7	7.4	3.8	
Chemotherapy regimen (%)				.24
Single-agent	5.2	3.9	4.4	
Multi-agent	83.5	86.9	83.1	
Chemotherapy administered, NOS	11.2	9.2	12.5	
Adjuvant treatment (%)				<.001
Radiation therapy used	1.5	0.1	0	
Chemotherapy only	12.9	8.2	4.0	

SD, Standard deviation; NOS, not otherwise specified; . *Based on 2008-2012 American Community Survey data. For income, the percentage of patients whose area of residence (based on ZIP code) had a median household income \$63,000 or greater (adjusted for 2012 inflation) is presented. For education, the percentage of patients whose area of residence (based on ZIP code) had less than 7% adults who did not attain a high school education is presented.

imputed models are presented. Analyses were performed using STATA version 14.0 (StataCorp, LP, College Station, Tex).

RESULTS

Study Cohort

The characteristics of the 2870 patients included in the cohort are presented in Table 1. Overall, 17.3% had a complete response, 34.5% had a partial response, and 48.2% had no response. The majority of patients in all disease response categories received a multi-agent

chemotherapy regimen. Among those treated with neoadjuvant chemotherapy alone, 79.5% received a multi-agent regimen. Adjuvant therapy was used less frequently as the degree of pathologic response to neoadjuvant therapy increased (no response, 14.4%; partial response, 8.3%; complete response, 4.0%). There was no significant difference in the 30-day (neoadjuvant radiation, 2.9%; neoadjuvant chemotherapy, 2.2%; $P = .52$) or 90-day (neoadjuvant radiation, 7.0%; neoadjuvant chemotherapy, 5.6%; $P = .38$) mortality between neoadjuvant treatment types.

FIGURE 2. Disease response rates to neoadjuvant chemotherapy alone (chemotherapy) versus neoadjuvant chemoradiation therapy (radiation therapy), defined as complete response (ypT0N0), partial response (primary tumor or nodal downstaging, specifically, cT3 to ypTis-1 or cT4 to ypTis-2 regardless of pathologic nodal status, cN+ to ypN0 with residual primary tumor, or ypN+ with a complete primary response), and no response. Primary response rates were ascertained among node-negative patients. Nodal response rates were ascertained among clinically node-positive patients.

FIGURE 3. OS (and 95% CIs) based on the degree of pathologic response to neoadjuvant therapy, defined as complete response (ypT0N0), partial response (primary tumor or nodal downstaging, specifically, cT3 to ypTis-1 or cT4 to ypTis-2 regardless of pathologic nodal status, cN+ to ypN0 with residual primary tumor, or ypN+ with a complete primary response), and no response.

Association Between Neoadjuvant Therapy and Response to Therapy

Higher rates of complete (18.3% vs 7.1%, $P < .001$) and partial response (35.3% vs 27.2%, $P = .008$) were observed with neoadjuvant radiation compared with chemotherapy alone (Figure 2). In addition, primary tumor response rates were higher in patients who received neoadjuvant radiation compared with neoadjuvant chemotherapy alone (33.9% vs 21.3%, $P < .001$). Furthermore, among patients with clinically node positive disease, nodal downstaging was more common after neoadjuvant radiation compared with chemotherapy alone (55.9% vs 32.7%, $P < .001$). Compared with patients who received neoadjuvant radiation, patients who received neoadjuvant chemotherapy alone were less likely to have a partial (relative risk ratio [RRR], 0.52; 95% confidence interval [CI], 0.40-0.68) or complete response (RRR, 0.26; 95% CI, 0.16-0.42). Compared with patients who received neoadjuvant radiation, patients who received neoadjuvant chemotherapy alone were less likely to have a complete primary tumor response (RRR, 0.63; 95% CI, 0.48-0.81) or a complete nodal response (RRR, 0.56; 95% CI, 0.46-0.69).

Association Between Response to Therapy and Survival

For patients who were treated with neoadjuvant radiation therapy, the 5-year OS increased with the degree of treatment response (no response 29.3%; partial response 37.8%; complete response 49.9%; $P < .001$) (Figure 3). Even after adjusting for potential confounding variables, complete (hazard ratio [HR], 0.54; 95% CI, 0.46-0.63)

and partial (HR, 0.80; 95% CI, 0.71-0.91) pathologic responses were associated with a significantly decreased overall risk of death compared with patients who had no response (Table 2). These findings were similar when limiting the analysis to patients who did not receive any adjuvant therapy, those who had an adequate lymphadenectomy, in the landmark analysis, and when adjusting for year of diagnosis (data not shown).

Relative Contribution of Primary Tumor Response Versus Nodal Response on Overall Survival

Patients with a primary tumor response had a better 5-year OS than patients without a primary tumor response (44.3% vs 31.6%, log-rank, $P < .001$). However, among patients with residual nodal disease, primary tumor response was not associated with improved unadjusted 5-year OS (27.0% vs 21.9%, log-rank, $P = .19$). After adjusting for potential confounding variables, the overall risk of death was significantly lower among those who had a complete primary tumor response (HR, 0.71; 95% CI, 0.63-0.79), but the magnitude of this association was mitigated among those who did not have a pathologically complete nodal response (HR, 0.88; 95% CI, 0.69-1.12) (Table 2). Compared with patients who had residual nodal disease, clinically node positive patients who achieved a complete nodal response had better 5-year OS (42.3% vs 21.8%; log-rank, $P < .001$), even among those patients who did not have a complete primary tumor response (37.5% vs 21.0%; log-rank, $P < .001$). After adjusting for potential confounding variables, the risk of death was also significant lower in those who had a complete nodal response (HR, 0.60; 95% CI, 0.54-0.67), regardless of whether there

TABLE 2. Association between degree and type of disease response and overall risk of death among patients who underwent a margin-negative esophagectomy after neoadjuvant chemotherapy and radiation for locally advanced esophageal adenocarcinoma*

	Hazard ratio (95% CI)
Overall cohort	
No response	Reference
Partial response	0.80 (0.71-0.91)
Complete response	0.54 (0.46-0.63)
No adjuvant therapy	
No response	Reference
Partial response	0.81 (0.71-0.93)
Complete response	0.54 (0.46-0.63)
≥15 lymph nodes examined	
No response	Reference
Partial response	0.72 (0.58-0.91)
Complete response	0.55 (0.42-0.73)
Primary tumor response	
Incomplete primary response	Reference
Complete primary response	0.70 (0.62-0.79)
Primary tumor response and no nodal response	
Incomplete primary response	Reference
Complete primary response	0.88 (0.70-1.12)
Nodal response	
No nodal response	Reference
Nodal response	0.58 (0.52-0.65)
Node response and no primary response	
No nodal response	Reference
Nodal response	0.64 (0.55-0.74)

CI, Confidence interval. *All models were adjusted for age, sex, race, insurance status, income, education, rurality, Charlson comorbidity score, type of treating facility, tumor grade, and receipt of adjuvant therapy. The full model for the overall cohort is provided in Table E1.

was a complete primary response (HR, 0.66; 95% CI, 0.57-0.76) (Table 2).

DISCUSSION

Compared with surgery alone, there is a clear benefit associated with esophagectomy as part of a multimodal treatment strategy (along with chemotherapy with or without radiation therapy) for patients with locally advanced esophageal adenocarcinoma.^{1-3,18-20} Largely based on the results of the CROSS trial, concurrent neoadjuvant chemoradiation therapy followed by esophagectomy has become the preferred treatment strategy of most centers in the United States for patients with locally advanced disease. The findings of our national cohort of patients with esophageal adenocarcinoma support several important observations with regard to patients who undergo neoadjuvant therapy followed by an esophagectomy with negative margins.

First, compared with neoadjuvant chemotherapy alone, the combination of neoadjuvant chemotherapy and radiation therapy is associated with higher pathologic

response rates. Samson and colleagues⁹ also used data from the NCBD and found that the use of neoadjuvant radiation was associated with higher pathologic complete response rates (17.2%) compared with neoadjuvant chemotherapy alone (6.4%). In contrast to the study by Samson and colleagues⁹ and other single institution studies⁴⁻⁸ that have examined pathologic response as a binary outcome (complete response vs no/partial response), we noted a clear dose-response relationship between the degree of pathologic response (no, partial, and complete response) and OS. This dose-response observation has potentially important implications for patient care by providing more detailed prognostic information for counseling patients, personalizing the amount of neoadjuvant chemotherapy, selecting patients who may benefit from adjuvant therapy, and guiding post-treatment surveillance.

Second, independent of primary tumor response, nodal response to neoadjuvant chemotherapy and radiation therapy appears to be the principle determinant of survival after an R0 esophagectomy. These findings are consistent with recently published follow-up data from the MAGIC trial, which compared perioperative chemotherapy and surgery versus surgery alone for resectable gastroesophageal adenocarcinomas, 24% of which were distal esophageal or gastroesophageal junction tumors. The authors of this trial found that the presence of lymph node metastasis was the only independent predictor of OS (HR, 3.36; 95% CI, 1.70-6.63).²¹ Data from other observational studies^{10,22-25} and clinical trials¹⁸ confirm the association between lymphovascular invasion or residual nodal disease and poorer survival. However, compared with data from clinical trials or quaternary referral centers, our data are derived from the general population, which enhances the generalizability of these findings.

Higher recurrence rates likely underlie the association between residual nodal disease and poorer survival.^{22,23} Indeed, results from a phase II clinical trial comparing perioperative chemotherapy and surgery with surgery alone for distal esophageal or gastroesophageal junction carcinomas demonstrated recurrence was more common in node-positive (55%) than in node-negative (22%) patients.²⁶ In particular, a multivariate analysis of CROSS trial data demonstrated that pathologic nodal status, not primary tumor stage, was independently associated with an approximately 3-fold increased risk of locoregional recurrence.¹⁹ Unfortunately, the NCDB does not provide recurrence data to researchers for us to further assess the impact of nodal disease on recurrence rates.

In the context of these data, our results could have several important implications for clinical practice. At present, the role of adjuvant chemotherapy for patients who undergo an R0 esophagectomy after neoadjuvant therapy is unclear.²³ However, our data are consistent with previous work

suggesting patients with residual nodal disease are at a higher risk of recurrence and lower survival and suggest that these patients may benefit from more aggressive systemic therapy.^{22,27} Indeed, although there are presently no published randomized data regarding the selection of patients for adjuvant therapy, our group previously demonstrated a survival benefit associated with adjuvant chemotherapy limited to patients who have residual nodal disease after neoadjuvant chemoradiation therapy.¹⁵

Although patients with residual nodal disease may theoretically benefit from adjuvant chemotherapy, many such patients never receive it. Among patients in the MAGIC trial assigned to the perioperative chemotherapy arm, only 42% completed all assigned treatments, and 34% of patients who completed neoadjuvant therapy and surgery did not receive adjuvant chemotherapy because of early disease progression, postoperative complications, or patient refusal.² Likewise, in a Federation Nationale des Centres de Lutte Contre Le Cancer/Federation Francophone de Cancerologie multicenter phase III trial, which compared perioperative chemotherapy and surgery versus surgery alone for resectable gastroesophageal adenocarcinomas, only 50% of patients assigned to perioperative chemotherapy received at least 1 cycle of adjuvant chemotherapy and only 39% completed all assigned treatments.³ Because of similar limitations in administering adjuvant therapy in the treatment of patients with other locally advanced, resectable gastrointestinal malignancies, there is increasing interest in more aggressive “total upfront” neoadjuvant strategies in pancreatic ductal adenocarcinoma,²⁸ gastric adenocarcinoma,²⁹ and rectal adenocarcinoma.³⁰ Given the aggressive nature of esophageal cancer, our inability to predict which patients will respond to neoadjuvant therapy, and the morbidity associated with surgical resection that currently limits the number of patients who are able to receive adjuvant treatment, certain patients with locally advanced esophageal adenocarcinoma may also benefit from this “total upfront” approach before esophagectomy. Most cancer-related deaths from esophageal carcinoma are due to systemic disease. For patients who would likely benefit from systemic therapy, history has taught us that most patients (~60%) cannot complete a full planned course of adjuvant chemotherapy using currently available regimens. Therefore, consideration should be given to optimizing nodal response rates in the neoadjuvant setting.

Given the existing data regarding the importance of pathologic nodal status, one possible approach could be to use a given patient’s nodal status to guide the use of additional therapy in the neoadjuvant setting. For example, if a clinically node-positive patient was treated with neoadjuvant chemoradiation and on restaging found have residual nodal disease, consideration could be given to providing additional systemic therapy in an effort to convert

VIDEO 1. Dr Shawn Groth summarizing the findings of this study. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)33307-5/fulltext](https://www.jtcvs.org/article/S0022-5223(18)33307-5/fulltext).

that patient to node-negative disease rather than proceeding immediately to esophagectomy. Likewise, for patients who are initially clinically node negative but demonstrate progressive disease after neoadjuvant therapy, consideration could be given to providing additional systemic treatment (perhaps an alternative regimen or targeted therapy) before proceeding with radical resection. Cancer and Leukemia Group B (Alliance) 80803 is a cooperative group trial that is evaluating the concept of adjusting neoadjuvant chemotherapy before esophagectomy based on the patient’s clinical response.³¹ Perhaps patients who are nonresponders would benefit from biomarker-directed neoadjuvant targeted therapy or immunotherapy. A clinical trial to further evaluate such strategies is in order.

Study Limitations

There are several limitations of our study. The NCDB does not provide information on clinical decision-making; thus, we could not ascertain the reasons patients were treated with neoadjuvant chemotherapy alone or with radiation. Therefore, selection bias is a potential limitation of our study. Although unmeasured differences in performance status (which is not available in NCDB) may have played a role in treatment decisions or eventual outcome, we noted no difference in 30- or 90-day mortality rates between patients treated with either type of neoadjuvant therapy. Furthermore, the consistency of our results across all sensitivity analyses and in our landmark analysis speaks to the robustness of our findings to varying assumptions. To assess treatment response, we compared pretreatment clinical staging with pathologic staging. The limitations of clinical staging could introduce error into our analysis in patients who had a partial response. Therefore, we chose a relatively conservative definition for partial response to conservatively bias our results toward the null. The NCDB does not collect information on several patient factors that are associated with survival, such as margin length,³² local and distant recurrence,³³ and

performance status before and after treatment. In addition, the NCDB does not collect data on postoperative complications, which may affect cancer-specific survival.³⁴ Although detailed data on the specific chemotherapy regimen and number of cycles administered are not provided, the majority of patients in our cohort were treated with multi-agent chemotherapy, which would be consistent with the regimens used in the MAGIC or CROSS trials. Information on the cause of death is not provided; thus, cancer-specific survival could not be calculated. Data regarding the staging modalities used to ascertain clinical stage are not available. Finally, the NCDB only collects data from CoC-accredited hospitals, which could affect the generalizability of our findings.^{35,36}

CONCLUSIONS

Pathologic nodal (rather than primary tumor) response to neoadjuvant therapy for locally advanced esophageal adenocarcinoma is the principal determinant of survival after an esophagectomy with negative margins (Video 1).

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/18May01/25ABC%202.General%20Thoracic%20SS/S91%20-%20Part%202/S91_3_webcast_043607106.mp4.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: esophageal neoplasms, esophagectomy, neoadjuvant therapy, pathology

Discussion

Dr Siva Raja (Cleveland, Ohio). I thank the Association for the invitation to discuss the work.

I have no relevant disclosures. The facts that esophageal adenocarcinoma is an aggressive disease and the treatment is morbid are not in question. What is in question is what population

we currently do not help and how can we do a better job. In this study, the authors use the NCDB data set to examine the impact of response to neoadjuvant therapy on long-term survival. They show a graded improvement of survival with a graded increase in response to therapy. They also show that nodal status trumps response in primary therapy. However, with big data we could have big holes in the data,

and this is primarily due to a lack of granularity and the retrospective nature of the data set.

We and others have shown that in the setting of primary response to treatment, characterizing percent of viable tumor cells as a continuous variable can allow you to separate the signal from the noise. However, those were individual studies with small patient populations relative to the larger study that you are presenting today.

Because it is easier to critique than do research, I am going to start by congratulating you on a study well done and I have 2 questions for you, Dr Groth. First, information about response to your study only provides answers after being subjected to an esophagectomy. Did you have any sense from the study if there were any predictive factors such as tumor grade, inability to complete treatment, et cetera, that predicted a poor response? It would be nice to know who was not going to respond and think about their algorithm differently from the beginning as opposed to try to change course in the middle like in the anecdote you suggested.

Dr Shawn S. Groth (Houston, Tex).

Thank you, Dr Raja. One of the limitations of this study is an inherent limitation of NCDB—we are only provided with pretreatment clinical staging. We don't have any information on post-treatment clinical staging, which, as you mentioned, would be beneficial in terms of making treatment decisions prior to committing a patient to esophagectomy. Despite this limitation, the accuracy of post-treatment clinical staging is imperfect. By using pathologic staging, we have 100% accuracy regarding post-treatment primary tumor and nodal response. To answer your question, the focus of our study was on the prognostic implications of primary tumor and nodal response to neoadjuvant therapy. In our multivariable models, we adjusted for covariates such as tumor grade, but we did not specifically isolate covariates that predict poor response to therapy.

Dr Raja. The second question is, nodal stage trumps tumor stage. Have you looked at a more refined population such as those with ypN0 to see if there is any response to therapy between chemotherapy only and chemotherapy and radiotherapy to see if in that population the effect on primary tumor has some benefit in long-term survival?

Dr Groth. We didn't look at the effect of tumor and nodal response on survival among patients treated with chemotherapy alone because they comprised only a small percentage of esophageal cancer patients in the NCDB. In terms of response to treatment, yes; there was an association between use of radiation and improved primary tumor response in node-negative patients.

Dr Malcolm M. DeCamp (*Madison, Wis*). Congratulations on an important study. I wanted to get your thoughts about this issue of pathologic response, because that's a snapshot in time and it depends on the timing from completion of therapy to the day you go to the operating room, and it's obviously a biologic continuum. So does the NCDB have data on the interval from when they completed therapy to surgery? There are articles from colleagues across town in Houston that suggest perhaps the adjuvant window can be extended longer from completion of therapy if the goal is to see that true pathologic complete response. Is there a way to assess for those near-complete responders?

Dr Groth. The time interval between the completion of radiation therapy and the date of surgery can be calculated by using NCDB data. However, we did not specifically look at the time interval between completion of chemoradiation therapy and esophagectomy and whether or not longer intervals increased the percentage of complete responders as compared to partial responders.

Unidentified Speaker. You showed 3 curves, right? You have the complete pathologic responders, you have the intermediate, we will say, and then you have the nonresponders, but really there should be 9 curves. What I mean by that is, where you start actually has significant impact on the OS. So if the patient has T3N0 and receives chemoradiation therapy and is a complete responder, the likelihood for cure is a lot better than somebody with TN2 or N3.

So I think what happens is the NCDB database doesn't allow you to do that, but others have shown that if you take T3N0s and give them chemoradiation and they are complete responders, most of those patients will have 50% cure rates or better, whereas in the old staging system it was sort of N1 or N1A, meaning celiac or supraclavicular nodes. If you took a person who had N1 disease, either celiac access or supraclavicular nodes, even if they were "complete pathological responders," their overall failure rate was higher than people who had a T3N0 start.

So I think one of the problems with this database is you won't really know accurately where people started. You only know where they kind of finished when you look at the final pathology, right?

Dr Groth. All that we know from the NCDB is the pretreatment clinical stage and the final pathologic stage. That's all we get. Of course, clinical staging is not 100% accurate.

Unidentified Speaker. But the preoperative staging can vary from institution to institution, in other words, how hard you look.

Dr Groth. Yes, of course. The NCDB isn't granular enough to provide information on what was used, such as

EUS, PET, or staging laparoscopy, to establish the clinical stage. There's no information on the quality of pretreatment staging. It is what it is. That's the nature of the data. Though it may be perceived as a limitation, this is reflective of everyday practice around the country, which makes our results generalizable.

Dr Steven R. DeMeester (*Portland, Ore*). Just a plea for caution. The data are interesting, but for the last decade we have been on this quest of pathologic complete response, centers like MD Anderson cranking up the radiation and trying everything they can to achieve complete pathologic

response. But in reality, most of these patients are dying of systemic disease, and complete pathologic response is kind of a fog, because it depends on how hard you look for it. If you do immunohistochemistry versus just cutting a node and using hematoxylin-eosin or if you go way back to Jerry Sullivan's work and you do bone marrow aspirations on people who supposedly have pathologic complete response, you find viable tumor cells in the bone marrow. So we are chasing after the wind with this pathologic complete response when what we really need is systemic control. I think we have to be careful, because chemotherapy regimens are never going to provide the pathologic complete response rates that we are getting with the addition of radiation treatment, yet radiation doesn't help the systemic disease problem that we are facing.

So I think we have to shift our thinking a bit going forward, and I would like your assessment of systemic disease. Do you have any information on systemic disease in these 2 groups that received chemo only versus chemoradiation?

Dr Groth. To respond to your first point, I wasn't saying that we should target a complete pathologic response before esophagectomy, but we should do the best that we can within reason to try to sterilize their lymph nodes. By no means am I trying to imply that patients who have suspected residual nodal disease be treated with endless cycles of chemotherapy until they sterilize their nodes. As you mentioned, most patients die of systemic disease and better systemic control is needed. However, if we've learned anything from history, the majority of patients who have adjuvant therapy as part of their pretreatment care plan can't complete it. If systemic therapy is part of the treatment plan, we should consider optimizing its use prior to esophagectomy.

Unfortunately, the NCDB does collect information on recurrences, but it doesn't provide those data to researchers because there's a lot of missing data. Consequently, we can't look at systemic failures in patients

treated with chemoradiation therapy versus chemotherapy alone.

Dr Toni Lerut (*Leuven, Belgium*). Excellent presentation, but I think the picture is only complete if you know also, and I don't know whether the database allows you to know that, the dropouts and whether there is a difference between dropouts in the chemo versus chemoradiation. We have the impression that there are more dropouts in the chemo rads than in the chemo.

Dr Groth. We don't have information on dropouts per se with the NCDB. We do have information on missing data, and perhaps some of the patients with missing data didn't complete all of their assigned therapy. We

accounted for missing data with our statistical methods, although we did not directly compare the amount of missing data in the chemotherapy alone versus chemoradiation groups.

Dr Virginia Litle (*Boston, Mass*). I just want to make a little shameless plug for some of our own research that we presented at the Society of Thoracic Surgeons on using circulating cell-free tumor DNA to look at patients who are responding to therapy or for early recurrence. We should be focusing more effort on our biomarkers and identifying the subsets to help in this decision-making treating algorithm. Otherwise we may be just overtreating patients even with unnecessary resection.

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Thoracic: Esophageal Cancer

ORIGINAL SUBMISSION: Delay in Oral Feeding is Associated With a Decrease in Anastomotic Leak Following Transhiatal Esophagectomy. James Speicher. *Semin Thoracic Surg* 2018: Volume 30, Issue 4.

Editorial Commentary: To eat or not to eat: Does delaying oral feeding decrease anastomotic leaks? Jules Lin. *Semin Thoracic Surg* 2018: Volume 30, Issue 4.

ORIGINAL SUBMISSION: Esophagectomy in Patients with Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome: A Viable Option. Michael Mwachiro. *Semin Thoracic Surg* 2018:116-121.

TABLE E1. Complete model results from Cox regression for the overall cohort

	Hazard ratio (95% CI)
Treatment response	
No response	Ref
Partial response	0.80 (0.71-0.91)
Complete response	0.54 (0.46-0.63)
Age, y	
≤55	Ref
56-60	1.04 (0.92-1.19)
61-65	1.14 (0.98-1.32)
>65	1.19 (1.01-1.39)
Female sex	0.86 (0.73-1.01)
Nonwhite race	1.29 (0.92-1.80)
Insurance	
Insured	Ref
Medicare/Medicaid	1.26 (1.10-1.45)
Other	1.39 (1.04-1.87)
Income >\$63,000*	0.93 (0.80-1.09)
Education*	0.83 (0.73-0.96)
Rurality	
Metropolitan	Ref
Urban	1.01 (0.88-1.17)
Rural	1.00 (0.86-1.18)
Charlson index	
0	Ref
1	1.17 (1.05-1.32)
≥2	1.14 (0.90-1.44)
Facility	
Academic/research	Ref
Comprehensive cancer center	1.16 (1.02-1.32)
Other	0.98 (0.83-1.16)
Grade, poor/undifferentiated	1.29 (1.14-1.45)
Adjuvant therapy	0.80 (0.67-0.97)

CI, Confidence interval. *Based on 2008-2012 American Community Survey data. For income, indicates patient had an area of residence (based on ZIP code) with a median household income \$63,000 or greater (adjusted for 2012 inflation). For education, indicates patient had an area of residence (based on ZIP code) where less than 7% adults did not attain a high school education.