Original Article

Assessment of a collaborative treatment model for trimodal management of esophageal cancer

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Background: Patients with esophageal cancer often receive care in a collaborative (multi-institutional) treatment model as opposed to a single institutional model. The effect of a collaborative model on the quality of trimodality therapy and survival is unknown.

Methods: The National Cancer Database (NCDB) was used to identify patients receiving neoadjuvant chemoradiotherapy (CRT) followed by esophagectomy for esophageal cancer between 2012–2017. Patients who received neoadjuvant therapy and surgery at a single institution were compared to those that received collaborative treatment across multiple institutions. Outcomes included adherence to guideline recommended multiagent chemotherapy, receipt of 41.4–50.4 Gy of radiation, R0 resection, pathologic complete response (pCR), and 5-year survival. Sociodemographics, comorbidities, and tumor characteristics were assessed in bivariate and multivariable analysis.

Results: Among 8,396 patients identified, 39% received treatment at a single institution, while 61% received collaborative treatment. Median travel distance to the site of esophagectomy was two times greater for patients receiving collaborative treatment (30 *vs.* 15 miles; P<0.001). Patients in the collaborative cohort were less likely to receive guideline-recommended multiagent chemotherapy (85% *vs.* 96%; P<0.001) and 41.4–50.4 Gy of radiation (89% *vs.* 91%; P=0.01). R0 resection rates were similar (94.4% *vs.* 93.7%; P=0.17). Patients who received collaborative treatment had an increased rate of pCR (24% *vs.* 22%; P=0.02). Overall, 90-day and 5-year survival were 92.9% and 42.6% respectively and did not differ significantly between the two groups.

Conclusions: Collaborative trimodality treatment of esophageal cancer is a common and reasonable practice model, which may alleviate patient travel burden with only a modest impact on the quality of CRT, pCR, 90-day survival, and 5-year survival.

Keywords: Esophageal cancer; neoadjuvant treatment; chemoradiotherapy (CRT); esophagectomy; trimodality therapy

Submitted Mar 08, 2023. Accepted for publication Jul 10, 2023. Published online Aug 25, 2023.
doi: 10.21037/jtd-23-346
View this article at: https://dx.doi.org/10.21037/jtd-23-346

Introduction

Multimodal therapy is the standard of care in patients with loco-regional esophageal adenocarcinoma and squamous cell carcinoma. The combination of neoadjuvant chemoradiotherapy (CRT) and surgical resection increases R0 resection rates, decreases local and systemic recurrence, and improves disease-specific and overall survival (1). At the same time, high-volume highly-specialized centers have consistently been associated with improved operative outcomes for complex oncologic resections, including esophagectomy (2,3).

While regionalization and evolving neoadjuvant treatment regimens have led to a nearly 50% five-year survival in patients with resectable disease, they can represent a major burden to patients and their caregivers in terms of travel, time, and cost (4,5). One strategy to reduce the burden on patients and their families is to consider a collaborative (multi-institutional) treatment model—neoadjuvant CRT at a local center and operative resection at a regional high-volume center.

The effect of collaborative treatment on the quality of CRT and long-term survival are unknown. In this study, we sought to understand treatment practices and their association with short and long-term outcomes using the National Cancer Database (NCDB). In this analysis, we compared compliance with guideline recommendations for multiagent chemotherapy, receipt of 41.4–50.4 Gy of radiation, R0 resection, pathologic complete response (pCR), and survival in patients receiving single institution or multi-institutional collaborative treatment (6). We hypothesized that patients who received collaborative treatment would have a decreased rate of guideline compliant CRT compared to patients receiving single institution treatment. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-346/rc).

Highlight box

Key findings

- A collaborative treatment model—chemoradiotherapy (CRT) at local center, followed by esophagectomy at regional center—is associated with a reduction in travel, but similar 90-day and 5-year survival compared to treatment at a single institution.

What is known and what is new?

- Concentration of complex surgeries at high-volume centers improves outcomes, but can place a significant travel burden on patients.
- Delivery of neoadjuvant CRT at local centers can reduce this burden, with minimal impact on the quality of trimodality therapy or long-term survival.

What is the implication, and what should change now?

- A collaborative treatment model is a common and reasonable approach to delivery of trimodality therapy for patients with resectable esophageal cancer that should be offered to patients to alleviate travel burden.

Methods

Data source

Retrospective cohort study using the NCDB, a robust hospital-based tumor registry maintained by the Commission on Cancer of the American College of Surgeons and the American Cancer Society (7). The Commission on Cancer of the American College of Surgeons and the American Cancer Society have not verified and are not responsible for the statistical validity of the data. Given the use of the NCDB this study was exempted from further approval by the institutional review board. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Inclusion criteria and exclusion criteria

The database was queried for patients diagnosed with esophageal cancer between 2012 and 2017. Patients were included if they were over the age of 18, had an invasive malignancy (as opposed to carcinoma *in situ*), received neoadjuvant treatment (chemotherapy and radiotherapy), and underwent an esophagectomy. Patients with incomplete clinical staging, incomplete pathologic staging, and known stage IV disease at time of esophagectomy were excluded. In addition, patients with missing follow-up or mortality data or unknown site of CRT were excluded.

Treatment exposure, covariates, and outcomes

All analysis was performed at the patient level. Patients who received neoadjuvant treatment and esophagectomy at a single NCDB reporting institution and associated outpatient clinics (single institutional treatment) were compared to those that received at least part of their CRT at an institution separate from the site of their esophagectomy (collaborative treatment). Outside

institutions were identified based on the NCDB variables "RAD_LOCATION_OF_RX", "RX_SUMM_CHEMO", and "RX_HOSP_CHEMO" and defined as another commission on cancer accredited facility that independently reports to the NCDB.

Independent variables included sociodemographics, Charlson-Deyo comorbidity index, tumor histology, clinical stage, operative approach, facility type (academic *vs.* non-academic), geographic location, and year of diagnosis. Travel distance to the site of esophagectomy was included and categorized into tertiles. Based on work by Metzger *et al.*, an annual esophagectomy volume of 20 was used to identify high-volume centers (8). Primary outcomes included compliance with guideline recommendations for multiagent chemotherapy (*vs.* single agent), receipt of 41.4–50.4 Gy of radiation (*vs.* out of recommended range), pCR, R0 resection, 90-day mortality, and 5-year survival (6). Subgroup analysis was performed stratifying patients by clinical stage.

Statistical analysis

Descriptive analysis of the distribution of patient characteristics and outcomes was performed by treatment model (single institution *vs.* collaborative). Statistically significant differences in these distributions were identified using the χ^2 test or Fisher exact test for categorical variables, and the *t*-test or Mann-Whitney *U* test for continuous variables. An inclusive multivariable logistic regression model was used to assess factors associated with receiving collaborative treatment and expressed in odds ratios (ORs) with 95% confidence intervals (95% CIs). The missing rate for radiation doses was 17.8%. A survey performed to identify patterns in the missing data found that these data appeared to be missing at random. A complete case analysis was performed.

To provide estimates for the overall survival of patients who did and did not receive collaborative treatment, Kaplan-Meier estimates were generated. The survival benefit associated with multi-institutional treatment was analyzed in a Cox proportional hazard models stratified by stage and expressed as a hazard ratio (HR). These models included age as a continuous variable, race, ethnicity, insurance status, median income quartile based on the zip code of the patient's residence, facility type and location, patient area of residence, year of diagnosis, Charlson-Deyo comorbidity index, and travel distance as categorical variables. In addition, a hospital-specific random effect to account for clustering at the hospital level was included. A sensitivity analysis including only patients receiving guideline concordant CRT was performed to determine any effect on survival. All statistical tests were 2-sided with a P value of 0.05 as the threshold for statistical significance. Analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata software, version 15.1 (StataCorp, College Station, TX, USA).

Results

Patient characteristics

Among the 8,396 patients who met inclusion criteria, 3,276 (39%) received single-institution treatment, while 5,113 (61%) received collaborative treatment (*Figure 1*). Patients who received collaborative treatment were more likely to be older, White, and to have Medicare insurance; however, none of these variables differed by more than 5% (*Table 1*). Similarly, Charlson-Deyo comorbidity index, clinical T status, and clinical N status all differed by less than 3% between the two treatment groups. Patients who received collaborative treatment were more likely to originate from a non-academic center (40.7% *vs.* 36.5%; P<0.001), and to live in the Southern or Western United States. The percentage of patients receiving collaborative treatment increased from 56.7% in 2012 to 60.2% in 2017. Slightly more patients in the single-institution group received an esophagectomy at a high-volume center (72.5% *vs.* 69.7%; P=0.01).

The greatest relative difference between the two groups was in travel distance to the primary treatment center: those receiving collaborative treatment traveled twice the median distance to where they received their esophagectomy (30.5 *vs.* 15.1 miles; P<0.001) compared to single institution treatment. When categorized in tertiles, the lowest, middle, and highest groups traveled a median of 6.1, 23.2, and 84.3 miles respectively. In the collaborative treatment model, 40.3% of patients were in the highest tertile as opposed to 22.7% of patients in the single institution treatment model (P<0.001).

Multivariable logistic regression

Variables associated with a collaborative treatment model were assessed in a multivariable logistic regression (*Table 2*). Esophagectomy at a non-academic center was associated with a collaborative treatment model. Esophagectomy at a high-volume center trended toward significance but did

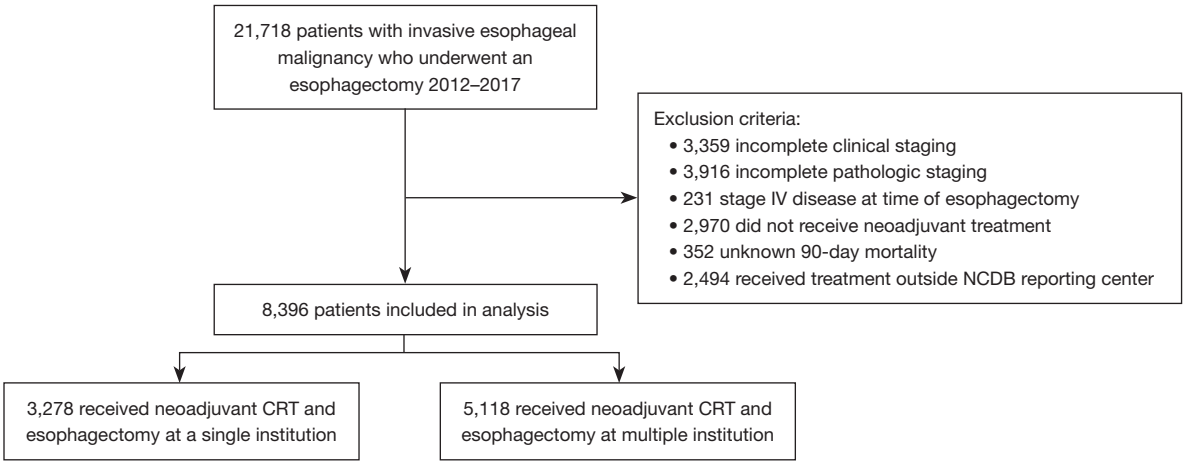

Figure 1 Cohort selection. NCDB, National Cancer Database; CRT, chemoradiotherapy.

not cross the predetermined threshold for significance. Increasing travel distance from the site of esophagectomy was associated with a stepwise increase in the receipt of multi-institutional treatment. In contrast, residence within urban areas and rural (as opposed to more densely population metropolitan areas) was associated with single institutional treatment. In a sensitivity analysis this trend was reversed if travel distance was not included in the model (Table S1). Similarly, when controlling for travel distance, geographic location lost its significance.

Multimodal therapy, R0 resection, pCR, and 90-day mortality

Patients in the collaborative treatment model were less likely to receive dual agent chemotherapy (84.6% *vs.* 96.5%; P<0.001) compared to patients who received single-institution treatment (*Figure 2*). In addition, patients who received collaborative treatment were less likely to receive guideline recommended 41.4–50.4 Gy of radiation (89.3% *vs.* 91.1%; P=0.01). Patients who received collaborative treatment were slightly more likely to have a pCR at time of esophagectomy (24.3% *vs.* 22.0%; P=0.02). However, there was no significant difference in R0 resection between patients treated in a collaborative treatment and single-institution treatment (94.4% *vs.* 93.7%; P=0.17). Lastly, there were no statistically or clinically significant differences in 90-day mortality between the two groups (7.1% *vs.* 7.1%; P=0.96). When stratified by clinical stage these effects were maintained, with the exception of pCR and R0 resection, which lost their significance in patients with clinical stage I and stage II disease (Table S2). Other quality markers including days from diagnosis to initiation of chemotherapy, radiotherapy, and operative resection were evaluated. For these events, the median difference in timing between the two groups was less than or equal to 5 days (Table S3).

5-year survival and cox-proportional hazard model

Overall, 5-year survival was 42.6% and did not differ significantly between patients in the single institution or collaborative treatment groups (*Figure 3A*). This relationship was preserved in the Cox proportional hazard model. Variables associated with worse survival included older age, male sex, lack of insurance, increasing Charlson-Deyo comorbidity index, esophagectomy at a low-volume center, and increasing clinical stage (*Table 3*). When stratified by clinical stage, there was no difference in 5-year survival in patients with stage I and stage III disease who received multi-modal treatment at a single institution or multiple institutions. However, there was a 5-year survival advantage in patients with clinical stage II disease who received treatment at a single institution (49.2% *vs.* 44.1%; P=0.01) (*Figure 3B-3D*). This effect was maintained in the Cox-proportional hazard model (HR =1.23; 95% CI: 1.09–1.34; P<0.01) (Tables S4-S6). Finally, in a sensitivity analysis including only patients receiving guideline concordant CRT, there was no qualitative difference in survival compared to the overall cohort (*Figure 4*).

Discussion

In this study of more than 8,000 patients receiving trimodal

Table 1 Characteristics of patients who received multi-modal therapy at a single institution versus those receiving treatment in a collaborative (multiple institutional) model

Characteristics	Treatment at single institution (n=3,276)	Treatment at multiple institutions (n=5,113)	P value
Age, median [IQR]	63 [57, 69]	64 [57, 69]	0.03
Male, n (%)	2,735 (83.5)	4,308 (84.3)	0.34
Travel distance[†], miles, median (IQR)	15.1 (6.5, 38.1)	30.5 (11.7, 70.2)	<0.001
<12.5 miles, n (%)	1,293 (44.3)	1,164 (26.4)	<0.001
12.6–42.6 miles, n (%)	964 (33.0)	1,466 (33.3)	
>42.6 miles, n (%)	661 (22.7)	1,774 (40.3)	
Race, n (%)			0.34
White	3,023 (92.3)	4,784 (93.5)	
Black	147 (4.5)	166 (3.3)	
Asian	62 (1.9)	85 (1.7)	
Other	24 (0.7)	46 (0.9)	
Unknown	20 (0.6)	32 (0.64)	
Hispanic, n (%)	104 (3.2)	141 (2.8)	0.53
Insurance, n (%)			<0.001
Private	1,527 (46.6)	2,271 (44.4)	
Medicaid	207 (6.3)	290 (5.7)	
Medicare	1,372 (41.9)	2,298 (44.9)	
Other government insurance	44 (1.3)	121 (2.4)	
Uninsured	75 (2.3)	79 (1.5)	
Unknown	51 (1.6)	54 (1.1)	
Income quartiles[‡], n (%)			<0.001
<$40,227	441 (13.5)	664 (13.0)	
$40,227–$50,353	612 (18.7)	1,038 (20.4)	
$50,354–$63,332	709 (21.6)	1,090 (21.3)	
≥$63,333	1,121 (34.2)	1,568 (30.7)	
Unknown	393 (1.6)	753 (14.7)	
Population density[§], n (%)			<0.001
Metropolitan	2,570 (78.5)	3,817 (74.7)	
Urban	474 (14.5)	937 (18.3)	
Rural	52 (1.6)	103 (2.01)	
Unknown	180 (5.4)	256 (5.0)	
Facility type, n (%)			<0.001
Non-academic	1,194 (36.5)	2,082 (40.7)	
Academic	2,029 (61.9)	2,978 (58.2)	
Unknown	53 (1.6)	53 (1.0)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Treatment at single institution (n=3,276)	Treatment at multiple institutions (n=5,113)	P value
Esophagectomy at high-volume center[¶], n (%)	2,375 (72.5)	3,565 (69.7)	0.01
Facility location, n (%)			<0.001
Northeast	911 (27.8)	1063 (20.8)	
Midwest	1,040 (31.7)	1,552 (30.3)	
South	856 (26.1)	1,697 (33.2)	
West	416 (12.7)	748 (14.6)	
Unknown	53 (1.6)	53 (1.0)	
Year of diagnosis, n (%)			<0.001
2012	514 (15.7)	672 (13.2)	
2013	549 (16.8)	794 (15.5)	
2014	524 (16.0)	892 (17.5)	
2015	555 (17.0)	935 (18.3)	
2016	529 (16.1)	904 (17.7)	
2017	606 (18.5)	916 (17.9)	
Charlson-Deyo comorbidity index, n (%)			0.03
0	2,315 (70.7)	3,498 (68.4)	
1	712 (21.8)	1,151 (22.5)	
≥2	249 (7.6)	464 (9.1)	
Squamous cell carcinoma, n (%)	517 (15.8)	731 (14.3)	0.14
Clinical stage, n (%)			0.09
I	248 (7.6)	438 (8.6)	
II	1,209 (36.9)	1,946 (38.1)	
III	1,819 (55.5)	2,729 (53.4)	

[†], from hospital at which esophagectomy is performed; [‡], average income in patient's residing zip code; [§], metropolitan defined at population >20,000 within residing county, rural defined at population <2,500 within residing county; [¶], greater than or equal to 20 esophagectomies per year. Facility refers to the institution in which the esophagectomy was performed. IQR, interquartile range.

treatment for esophageal cancer, we found that 61% of patients received part of their care at a different institution than where they ultimately underwent esophagectomy. A collaborative treatment model across multiple institutions was associated with slightly decreased rates of guideline concordant CRT but was not associated with a decrease in pCR, 90-day survival, or 5-year survival. This finding is important because it demonstrates CRT can be effectively coordinated for patients receiving complex oncologic care across multiple institutions with only a modest effect on quality.

As popularized by Birkmeyer *et al.* in 2002, concentration of complex operations such as esophagectomy among high-volume, high-quality centers has the potential to improve operative morbidity and mortality (9). The association between improved surgical quality and higher volume specialty cancer centers has been demonstrated in multiple studies over the past 20 years and regionalization of complex surgery, including esophagectomy, has been advocated for by leaders in the field (10-13). Recent studies focused on esophageal cancer have shown that both short-term and long-term outcomes are improved by regionalization

Table 2 Logistic regression for receiving care in a collaborative (multi-institutional) model

Variables	OR (95% CI)	P value
Age	1.00 (0.99–1.00)	0.42
Female	1.00 (0.87–1.16)	0.96
Median travel distance in miles[†]		
≤12.5	Ref.	
12.6–42.6	1.96 (1.66–2.31)	<0.001
≥42.7	4.81 (3.43–6.74)	<0.001
Race		
White	Ref.	
Black	0.90 (0.65–1.13)	0.27
Asian	1.27 (0.82–1.97)	0.29
Other	1.14 (0.68–1.95)	0.61
Unknown	1.25 (0.60–2.62)	0.55
Hispanic	0.89 (0.62–1.30)	0.57
Insurance status		
Private	Ref.	
Medicaid	1.00 (0.78–1.29)	0.97
Medicare	1.11 (0.96–1.29)	0.15
Other government insurance	1.52 (0.93–2.50)	0.10
Uninsured	0.61 (0.42–1.01)	0.05
Unknown	0.52 (0.23–1.15)	0.11
Income quartiles[‡]		
≥$63,333	Ref.	
<$40,227	0.78 (0.65–1.18)	0.07
$40,227–$50,353	0.90 (0.76–1.21)	0.33
$50,354–$63,332	0.94 (0.77–1.15)	0.54
Unknown income	0.70 (0.44–1.11)	0.13
Population density[§]		
Metropolitan	Ref.	
Urban	0.66 (0.50–0.83)	<0.01
Rural	0.52 (0.35–0.77)	<0.01
Unknown	0.89 (0.71–1.12)	0.13
Facility type		
Academic	Ref.	
Non-academic	1.11 (1.05–1.22)	0.01
Unknown	0.68 (0.49–1.03)	0.08
Esophagectomy at high-volume center[¶]	0.76 (0.58–1.00)	0.05
Facility location		
Northeast	Ref.	
Midwest	1.16 (0.67–1.99)	0.59
South	1.60 (0.98–2.61)	0.06
West	1.49 (0.82–2.67)	0.19
Year of diagnosis		
2012	Ref.	
2013	1.11 (0.92–1.35)	0.22
2014	1.28 (1.04–1.52)	0.02
2015	1.24 (0.96–1.49)	0.08
2016	1.22 (0.98–1.50)	0.10
2017	1.11 (0.82–1.30)	0.85
Charlson-Deyo comorbidity index		
0	Ref.	
1	1.09 (0.92–1.30)	0.67
≥2	1.27 (0.99–1.60)	0.05
Squamous cell carcinoma	0.98 (0.83–1.15)	0.81
Clinical stage		
Stage I	Ref.	
Stage II	0.88 (0.72–1.07)	0.20
Stage III	0.84 (0.68–1.04)	0.11

[†], from hospital at which esophagectomy is performed; [‡], average income in patient's residing zip code; [§], metropolitan defined at population >20,000 within residing county, rural defined at population <2,500 within residing county; [¶], greater than or equal to 20 esophagectomies per year. Facility refers to the institution in which the esophagectomy was performed. OR, odds ratio; CI, confidence interval.

of care to high-volume centers (14,15). However, the downside of regional care includes increased cost and travel burden on patients, which can represent significant barriers (5,16-18). These barriers help explain a lack spontaneous regionalization found specifically in high-risk patients with comorbidities who might otherwise benefit the most from treatment at high-volume centers (19).

In our study, the most striking difference between patients who received collaborative treatment compared

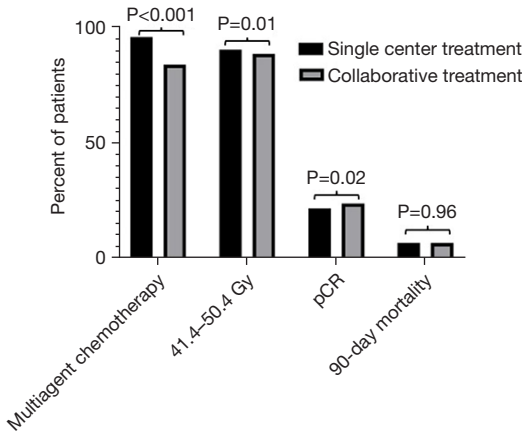

Figure 2 Comparison of guideline recommended chemoradiotherapy, pCR, and 90-day mortality post-esophagectomy in patients receiving trimodal therapy for esophageal cancer between single center and collaborative (multi-institutional) treatment models. pCR, pathologic complete response.

to those who received single-institutional treatment was the travel distance to the site of their esophagectomy. On average, patients who received collaborative treatment traveled almost twice as far as single institution patients. Nearly 1 in 5 patients in the collaborate treatment model traveled a median of 80 miles to the site of esophagectomy. By receiving CRT at local institutions, these patients are potentially spared a significant travel burden without a demonstratable impact on pCR or overall survival. Given that neoadjuvant CRT requires multiple encounters at an infusion/radiation treatment center, this represents a major benefit for patients and their caregivers.

Recently, Rhodin *et al.* demonstrated the efficacy of multi-institutional treatment of esophageal cancer in the NCDB (20). We build on that work by including more recent data and focusing on patients receiving standard neoadjuvant regiments of CRT rather than just chemotherapy. Our study shows that even when accounting for the added complexity of coordinating radiotherapy

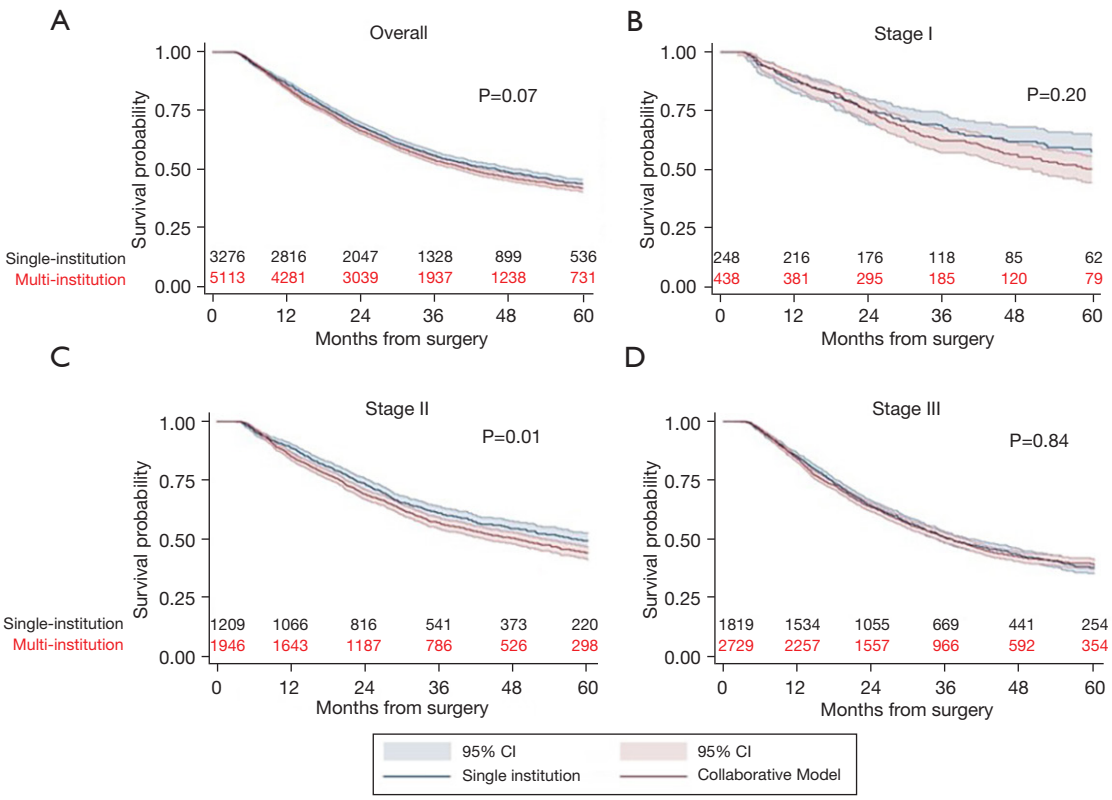

Figure 3 Kaplan-Meier survival curve in patients with locally advanced esophageal cancer who receive all care at a single institution compared to those receiving collaborative care across multiple institutions overall (A) and stratified by clinical stage (B-D). CI, confidence interval.

Table 3 Cox regression for mortality

Variables	HR (95% CI)	P value
Collaborative (multi-institutional) treatment	1.04 (0.98–1.17)	0.09
Age	1.02 (1.01–1.02)	<0.001
Female	0.81 (0.73–0.89)	<0.001
Travel distance in miles[†]		
≤12.5	Ref.	
12.6–42.6	0.98 (0.91–1.09)	0.87
≥42.7	1.00 (0.89–1.13)	0.89
Race		
White	Ref.	
Black	0.94 (0.80–1.13)	0.54
Asian	0.97 (0.76–1.24)	0.64
Other	1.07 (0.72–1.39)	0.96
Unknown	0.92 (0.66–1.48)	0.94
Hispanic	0.87 (0.71–1.08)	0.20
Insurance status		
Private	Ref	
Medicaid	1.14 (0.98–1.31)	0.07
Medicare	1.01 (0.98–1.32)	0.77
Other government insurance	1.01 (0.93–1.11)	0.78
Uninsured	1.30 (1.01–1.66)	0.04
Unknown	1.07 (0.81–1.40)	0.62
Income quartiles[‡]		
≥$63,333	Ref.	
<$40,227	1.18 (1.03–1.27)	0.01
$40,227–$50,353	1.06 (0.94–1.13)	0.28
$50,354–$63,332	1.13 (1.04–1.22)	0.01
Unknown	1.16 (0.83–1.64)	0.38
Facility type		
Academic	Ref.	
Non-Academic	1.05 (0.94–1.16)	0.48
Unknown	1.03 (0.42–1.81)	0.70
Esophagectomy at high-volume center[§]	0.93 (0.85–0.99)	0.04
Facility location		
Midwest	Ref.	
Northeast	1.05 (0.91–1.21)	0.50
South	1.03 (0.95–1.12)	0.45
West	0.84 (0.74–0.96)	0.01
Population density[¶], n (%)		
Metropolitan	Ref.	
Urban	1.14 (1.04–1.24)	0.003
Rural	1.16 (0.93–1.44)	0.18
Unknown	0.66 (0.56–0.77)	<0.001
Year of diagnosis		
2012	Ref.	
2013	1.03 (0.89–1.08)	0.60
2014	0.96 (0.81–0.98)	0.03
2015	0.99 (0.88–1.07)	0.48
2016	0.89 (0.82–1.00)	0.05
2017	0.78 (0.74–0.96)	0.01
Charlson-Deyo comorbidity index		
0	Ref.	
1	1.08 (1.01–1.15)	0.04
≥2	1.25 (1.15–1.41)	<0.001
Squamous cell carcinoma	0.94 (0.85–1.06)	0.26
Clinical stage		
Stage I	Ref.	
Stage II	1.23 (1.04–1.45)	<0.01
Stage III	1.54 (1.31–1.81)	<0.001

[†], from hospital at which esophagectomy is performed; [‡], average income in patient's residing zip code; [§], greater than or equal to 20 esophagectomies per year. Facility refers to the institution in which the esophagectomy was performed; [¶], metropolitan defined at population >20,000 within residing county, rural defined at population <2,500 within residing county. HR, hazard ratio; CI, confidence interval.

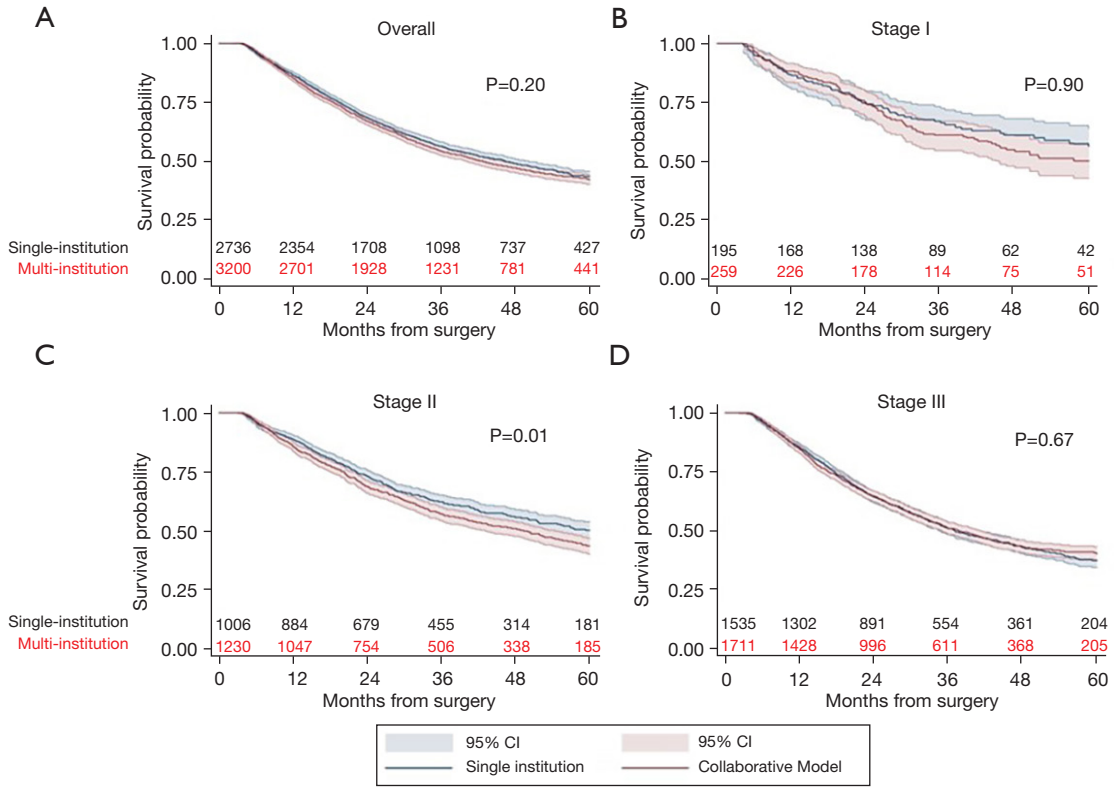

Figure 4 Sensitivity analysis including only patients who received guideline recommended chemoradiotherapy both overall (A) and stratified by stage (B-D). CI, confidence interval.

long-term survival is maintained. Equally important, our study uniquely describes the quality of neoadjuvant therapy and the performance of guideline concordant treatments. Additionally, by categorizing travel distance we show a powerful association between travel distance and collaborative treatment that has not previously been recognized. Prior associations with geographic location (e.g., Northeast, South, etc.) become insignificant when controlling for travel distance in this manner.

While we demonstrated that complex oncologic care can be coordinated among multiple centers without a significant decrease in overall 90-day or 5-year survival; we did note there was a slight decrease in the rate of appropriate radiotherapy dosing (89% *vs.* 91%) among patients who received collaborative treatment. In addition, there was a more significant drop in the rate of multiagent chemotherapy treatment (85% *vs.* 97%). There are several explanations for this finding. First, patients who received collaborative treatment had a higher co-morbidity burden as demonstrated by Charlson-Deyo comorbidity index and this may have limited their ability to tolerate multimodal therapy. Second, these patients tended to be older than those receiving all their care at a single institution, and this may have further limited their ability to tolerate more toxic neoadjuvant regimens. Interestingly, despite this relative decrease in standard-of-care CRT, the population that received collaborative care had a small increase in cPR (24% *vs.* 22%). This rate of cPR was similar to that reported in the CROSS trial and other studies evaluating the utility of neoadjuvant multimodal therapy (21,22). It is surprising the patients in the collaborative treatment model had a greater rate cPR despite slightly lower rates of guideline concordant CRT. This result may reflect slight differences in the population in each treatment arm; however, the clinical impact of this ~2% difference in cPR is unclear. More importantly, the 90-day or 5-year survival did not differ between the two treatment groups.

In subgroup analysis, patients with clinical stage II disease had a decreased 5-year survival in the collaborative treatment model (44% *vs.* 49%). This may be attributed to differences in age or comorbidities, although it remained significant when controlling for these in multivariable

analysis. It is also possible that it became more difficult to care for these patients in the event of late complications. Several authors have shown increased care burden and cost for patients who present to non-index hospitals after a surgical procedure (23,24). We expect that the collaborative treatment group would be more likely to present to an alternative hospital given that on average they lived twice as far away from the site of their esophagectomy. More concerningly, the drop in long-term survival for the stage II patients may be related to the relative decrease in appropriate multimodal therapy. However, in sensitivity analysis including only patients who received guideline concordant CRT these differences persisted. Furthermore, differences in the quality of CRT delivery persisted across all stages.

An additional contributor may be attributed to staging error. Relative to other cancers esophageal cancer is difficult to stage and this is especially true in stage II disease (25). Given the potential challenges in coordinating care, patients treated in the collaborate care model may have been more likely to be under staged, thus resulting in long-term outcomes that appear worse. Regardless, the ~5% decrease in 5-year survival in patients with clinical stage II disease should be considered in the context of their disease and the burdens associated with single institutional care.

There is enormous benefit to neoadjuvant CRT in the treatment of resectable esophageal cancer, but it is associated with significant decreases in quality of life (26). Fortunately, quality of life does improve after completion of neoadjuvant treatment, and post-esophagectomy quality of life is similar between patients who do and do not receive neoadjuvant CRT (27). Getting patients safely through their neoadjuvant treatment and surgery is a priority of the multidisciplinary cancer team. In the treatment of pancreatic adenocarcinoma—a similar cancer requiring coordination of neoadjuvant therapy and surgical resection—sociodemographic barriers are a significant hurdle to patients receiving guideline recommended treatment, most pronounced in under-represented minorities and those of lower socioeconomic status (28,29). These factors may also contribute to distrust for specific healthcare networks and influence a patient's choice to receive single-institution or collaborative treatment. Indeed, we found that patients who received collaborative treatment were more likely to originate from non-academic centers. Further qualitative analysis will be necessary to develop an understanding behind these treatment-decision and will be the focus of ongoing studies. Despite the need for additional studies, decreasing travel time is expected to help increase the number of patients who are able to complete multimodal therapy. The results described above show that collaborative, multi-institutional, treatment can be performed effectively, but will require diligent monitoring and additional study, especially in patients with clinical stage II disease.

Limitations

Limitations of this study include those commonly associated with large retrospective observational studies. We are unable to account for differences in treatment regimens or why certain patients did or did not receive a given therapy. Most importantly, we are unable to accurately identify patients who may have started neoadjuvant treatment but then failed to proceed to surgery. We do not know if these events occurred due to treatment complications, patient preference, or a decision to defer surgery in favor of clinical monitoring. We also do not know the reasons a patient elected for treatment in a single-institution or a collaborative model, or how this may have affected their trust and satisfaction with a given healthcare network. Differences in staging modality and accuracy between patients in the collaborative and single-institution treatment groups could have further biased this study. Unfortunately, the NCDB lacks the granularity to satisfactorily answer these questions, and this will the subject of focused qualitative and quantitative studies.

Likewise, the treatment of esophageal cancer is evolving and increasingly includes immunotherapy. Given the timing and irregular use of immunotherapy during the study time-period, we are unable to accurately assess its role and if this contributed to any difference in outcomes between the study groups. As with other studies using the NCDB, we cannot comment on specific comorbidities, performance, status, nutritional status, and smoking history, which may have influenced neoadjuvant CRT regimens and contributed to long-term survival. There is also a significant amount of missing clinical and pathologic staging data. Exclusion of patients with missing data may bias these results and reduce their generalizability. We do not know the quality of staging, staging modality, or location at which cancer was first diagnosed. These factors may have differed between the study groups and biased the study. Similarly, we were unable to assess cancer specific survival and recurrence rates, which may have provided insight into competing mortality risks (7,30). We are unable to account for care that may have

https://dx.doi.org/10.21037/jtd-23-346

occurred outside of a NCDB reporting center and was not captured in the database. Among patients excluded due to care outside of an NCDB center, we did see a similar ratio of patients receiving single-institution and collaborative treatment. We are also reliant on the NCDB classification of individual centers and their associated outpatient clinics. We cannot make assessments regarding in network versus out of network care or if certain independent institutions have preexisting relationships that enable coordination of complex oncologic treatment.

Conclusions

Multiple institutions commonly collaborate to deliver trimodality treatment to patients with esophageal cancer without an overall reduction in R0 resection, pCR, 90-day survival, or long-term survival. Collaborative care is a reasonable treatment model that can allow patients to receive CRT at local centers and alleviate barriers to accessing guideline recommended care. Collaborative deliver of trimodality treatment should be encouraged as it may allow more patients with esophageal cancer to access and benefit from guideline recommended therapy.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-346/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-346/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-346/coif). DJB was paid a stipend from Iovance to attend a panel discussion on cell-based therapy that was unrelated to this work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Cite this article as: Udelsman BV, Ermer T, Ely S, Canavan ME, Zhan P, Boffa DJ, Blasberg JD. Assessment of a collaborative treatment model for trimodal management of esophageal cancer. J Thorac Dis 2023;15(9):4668-4680. doi: 10.21037/jtd-23-346