Original Article

‘CROSS’-ing into the ‘Real World’: a retrospective cohort study of patients receiving trimodality and bimodality therapy for esophageal cancer

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Background: A standard of care for nonmetastatic esophageal cancer is trimodality therapy consisting of neoadjuvant chemoradiation and esophagectomy, with evidence for improved overall survival versus surgery alone in the ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) trial. Patients who receive treatment with curative intent but are poor candidates for or decline surgery receive definitive bimodality therapy. Literature characterizing patients who receive bimodality therapy compared to trimodality therapy, and their relative outcomes, is sparse, especially among patients who are too old or too frail to qualify for clinical trials. In this study, we assess a single-institution real-world dataset of patients receiving bimodality and trimodality management.

Methods: Patients treated for clinically resectable, nonmetastatic esophageal cancer between 2009 and 2019 who received bimodality or trimodality therapy were reviewed, generating a dataset of 95 patients. Clinical variables and patient characteristics were assessed for association with modality on multivariable logistic regression. Overall, relapse-free, and disease-free survival were assessed with Kaplan-Meier analyses and Cox proportional modeling. For patients nonadherent to planned esophagectomy, reasons for nonadherence were recorded.

Results: Bimodality therapy was associated with greater age-adjusted comorbidity index, worse performance status, higher N-stage, presenting symptom other than dysphagia, and held chemotherapy cycles on multivariable analysis. Compared to bimodality therapy, trimodality therapy was associated with higher overall (3-year: 62% *vs.* 18%, P<0.001), relapse-free (3-year: 71% *vs.* 18%, P<0.001), and disease-free (3-year: 58% *vs.* 12%, P<0.001) survival. Similar results were observed among patients who did not meet CROSS trial qualifying criteria. Only treatment modality was associated with overall survival after adjusting for covariates (HR 0.37, P<0.001, reference group: bimodality). Patient choice accounted for 40% of surgery nonadherence in our population.

Conclusions: Patients receiving trimodality therapy were observed to have superior overall survival compared to bimodality therapy. Patient preference for organ-preserving therapies appears to impact

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resection rate; further characterization of patient decision-making may be helpful. Our results suggest patients who wish to prioritize overall survival should be encouraged to pursue trimodality therapy and obtain early consultation with surgery. Development of evidence-based interventions to physiologically prepare patients before and during neoadjuvant therapy as well as efforts to optimize the tolerability of the chemoradiation plan are warranted.

Keywords: Esophageal neoplasms; neoadjuvant therapy; esophagectomy

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Introduction

A standard of care for resectable esophageal cancer is trimodality therapy (TMT), consisting of neoadjuvant chemoradiation followed by esophagectomy, with definitive chemoradiation (bimodality therapy, BMT) preferred for patients who would not tolerate surgery, have inoperable disease, or decline surgery (1,2). This standard is evidenced by the phase III ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) trial, which found that, compared to surgery alone, TMT increased overall survival (OS) and progression-free survival (PFS) without negatively impacting health-related quality of life postoperatively (3-5). The smaller Cancer and Leukemia Group B (CALGB) 9781 trial also found OS and PFS benefit with TMT compared to surgery alone but closed early due to poor accrual (6). Survival benefits of TMT have been characterized primarily in literature comparing TMT to surgery alone, and direct comparisons of TMT and BMT are sparse.

Given the demonstrated benefits of surgery, establishing strategies to maximize TMT adherence and address drivers of nonadherence is imperative to bolstering survivorship, while weighing the toxicities of TMT and patient preferences. However, factors driving successful completion of TMT have yet to be fully characterized, especially in patients with classically unfavorable clinical traits and demography, such as those who are older, carry more comorbidities, and have worse performance status. CROSS trial authors did complete a subsequent retrospective ("post-CROSS") analysis of patients significantly older and more vulnerable than the CROSS trial cohort. Although they found no difference in OS benefit and treatment toxicity compared to the healthier trial cohort, the study excluded patients nonadherent to TMT, which accounted for approximately 16% of patients assessed (7). These data suggest that nonadherence to TMT is both prevalent and not fully predictable at timepoint of initial assessment, and there is little literature to characterize survival for patients who are nonadherent to TMT.

Real world data (RWD) can improve the generalizability of evidence generated through randomized controlled trials (RCTs), especially in clinical practice and community settings (8,9). Here, we present an analysis of RWD from a single-institution retrospective review of patients with clinically resectable esophageal cancer. We aim to explore generalizability of existing evidence for the survival

Highlight box

Key findings
- We observed worse overall, disease-free, and relapse-free survival among patients receiving bimodality therapy (BMT) in comparison to trimodality therapy (TMT).
- BMT was associated with presenting symptoms, comorbidity, performance status, N-stage, and treatment toxicity.
- Patient choice accounted for 40% of TMT nonadherence.

What is known and what is new?
- Phase III data demonstrate survival benefit for TMT compared to surgery alone; however, BMT is standard treatment for patients with resectable disease who do not undergo esophagectomy.
- We assess a real-world dataset to describe drivers of treatment modality (TMT *vs.* BMT) and to further contextualize with assessments of survival.

What is the implication, and what should change now?
- Evidenced interventions to mitigate toxicity and to best condition patients for surgery are necessary to optimize patients for esophagectomy.
- Early multidisciplinary consultation and presentation of real-world outcomes to patients may influence adherence in patients who are otherwise fit for surgery.

outcomes with TMT noted in CROSS. Utilization of RWD inclusive of patients older and more vulnerable than RCT populations enables the assessment of differences in outcomes between CROSS-eligible and CROSS-ineligible patients based on published criteria. To our knowledge, there are no data comparing outcomes of patients treated with BMT *vs.* TMT categorized by violation of CROSS exclusion criteria except for one analysis that looked singularly at age (10). Additionally, we aim to characterize and explore documented reasons for nonadherence in our cohort, purposefully including patients nonadherent to TMT as a population of interest, in contrast to the "Post-CROSS" analysis. While previous studies have examined TMT nonadherence in BMT patients, we offer further insight through assessment of clinical factors for association with BMT (*vs.* TMT) alongside reasons for nonadherence through analysis of a dataset inclusive of both BMT and TMT patients (11,12). We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-633/rc).

Methods

Patients

We conducted a single institution retrospective review of consecutive patients with non-metastatic surgically resectable esophageal cancer who presented to University of Vermont Medical Center division of Radiation Oncology between 2009–2019. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of the University of Vermont (IRB00000485) and individual consent for this retrospective analysis was waived. Patients were identified from radiation oncology's MOSAIQ electronic medical record (EMR) system. Patients with biopsy-proven nonmetastatic esophageal adenocarcinoma or squamous cell carcinoma were screened for inclusion in the study.

Patients receiving therapies other than definitive BMT or TMT were excluded. Patients with tumor location in the cervical esophagus were excluded. Patients with Siewert type III tumors (tumor centroid located 2 cm or more below the gastroesophageal junction) were excluded (13). Treatment on a research protocol was not a criterion for exclusion. We did not exclude patients who received a part of their treatment outside our health network, such that patients who received consultation and/or esophagectomy at a higher-volume cancer center were included in our cohort.

Assessment of clinical characteristics

Detailed chart review was conducted using the MOSAIQ and Epic EMR systems. All patients were re-staged utilizing the American Joint Committee on Cancer (AJCC) 8th edition staging manual (14). All patients were analyzed for CROSS trial eligibility based on reported criteria (15). Patients receiving ≥2 chemotherapy treatments prior to chemoradiation were considered to have received induction chemotherapy. For our primary presenting symptom categorical variable, a primary complaint of dysphagia was compared to those presenting with other symptoms including gastrointestinal (GI) bleed/anemia, odynophagia, or asymptomatic incidental discovery. For patients who planned for TMT therapy and did not receive surgery, reasons for nonadherence were recorded based on clear rationale documented in a patient's medical record. To align with prior studies, categories included personal choice, poor general condition, disease progression, death, unresectable disease on preoperative assessment, and unresectable disease intraoperatively (11,12).

Assessment of efficacy and safety outcomes

For our study, we defined TMT as completed esophagectomy after neoadjuvant chemoradiation. Surgery dates were recorded for all applicable patients, and post-operative mortality within 30 and 90 days from surgery was assessed.

Follow-up

For each patient, the date of most recent follow-up and date of death were recorded as applicable. The reverse Kaplan-Meier (KM) method was used to calculate median follow up (16,17). Patients were assessed for recurrence, which was recorded as the day of clinical evidence of recurrence.

Statistical analysis

Clinical variables were analyzed for association with BMT using univariable logistic regression and multivariable logistic regression. CROSS trial eligibility was excluded from multivariable analysis to prevent collinearity with

Table 1 Baseline demographics and clinical characteristics for patients treated with TMT or BMT

Characteristics	TMT, n [%]	BMT, n [%]	P value
Patients included in study	51	44	–
Age (years), median [IQR]	63 [58–69.5]	72.5 [62–79]	0.007†
Sex			
Female	6 [12]	7 [16]	0.57
Male	45 [88]	37 [84]	
Weight loss at presentation			
<5%	25 [49]	14 [32]	0.1
≥5%	26 [51]	30 [68]	
ECOG performance			
0	25 [57]	10 [25]	0.002
1	17 [39]	19 [48]	
2	2 [05]	11 [28]	
Age-adjusted CCI			
2–4	23 [45]	9 [20]	0.006
5–7	25 [49]	24 [55]	
8–10	3 [6]	11 [25]	
Primary presenting symptom			
Dysphagia	39 [76]	26 [59]	0.08
Other	12 [24]	18 [41]	
Tumor histology			
AC	44 [86]	36 [82]	0.58
SCC	7 [14]	8 [18]	
Tumor location			
Upper/middle	7 [14]	9 [20]	0.42
Lower/GEJ	44 [86]	35 [80]	
Tumor stage (AJCC 8th Ed.)			
I	1 [2]	2 [5]	0.06
II	5 [10]	5 [12]	
IIB	7 [14]	0 [0]	
III	35 [69]	30 [70]	
IVA	3 [6]	6 [14]	
T-stage			
cT1	1 [2]	2 [5]	0.12
cT2	11 [22]	3 [7]	
cT3	39 [76]	38 [88]	
N-stage			
cN0	28 [55]	22 [51]	0.69
cN1	19 [37]	15 [35]	
cN2-3	4 [8]	6 [14]	
Tumor grade			
G1	4 [8]	3 [9]	0.33
G2	29 [60]	15 [44]	
G3	15 [31]	16 [47]	
History of neoplasm			
No	42 [82]	30 [68]	0.15
Yes	9 [18]	14 [32]	
Qualify for CROSS trial			
Eligible	24 [47]	3 [7]	<0.001
Ineligible	27 [53]	41 [73]	
Distance from radiation treatment			
<30 miles	24 [57]	24 [55]	0.54
≥30 miles	27 [53]	20 [45]	
Rurality by Zip Code (RUCA)			
Non-rural	39 [76]	28 [64]	0.19
Rural	12 [24]	16 [36]	

P values are generated using Fisher's exact test except †age, which utilized a two-sample *t*-test. TMT, trimodality therapy; BMT, bimodality therapy; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; CCI, Charlson Comorbidity Index; AC, adenocarcinoma; SCC, squamous cell carcinoma; GEJ, gastroesophageal junction; AJCC, American Joint Committee on Cancer; CROSS, ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study; RUCA, rural-urban commuting area codes.

Table 2 Treatment characteristics for patients treated with TMT or BMT

Characteristics	TMT, n [%]	BMT, n [%]	P value
Total dose of radiotherapy (Gy), median (IQR)	50.4 (47.7–50.4)	50.4 (50.4–50.4)	0.27†
Chemo held during treatment			
No	25 [68]	12 [30]	0.001
Yes	12 [32]	28 [70]	
Induction chemotherapy			
No	33 [79]	33 [89]	0.24
Yes	9 [21]	4 [11]	
On clinical trial			
No	37 [80]	35 [85]	0.37
Yes	9 [20]	6 [15]	
Lodging wraparound service			
Utilized	27 [56]	30 [71]	0.19
Not utilized	21 [44]	12 [29]	

P values are generated using Fisher's exact test except †radiotherapy dose, which utilized a two-sample *t*-test. TMT, trimodality therapy; BMT, bimodality therapy; IQR, interquartile range.

variables included in criteria. Similarly, age was excluded from multivariable analysis in favor of age-adjusted Charlson Comorbidity Index (CCI), given that these were highly correlated (18).

OS was analyzed using log-rank test and Cox proportional hazards regression, with initial timepoint recorded as the diagnostic biopsy date of the tumor. The proportional hazards assumption was validated graphically by using log-log survival plots. Disease-free survival (DFS) and relapse-free survival (RFS) were generated in the same fashion. Multivariate logistic regression was utilized to assess variables, including modality, for association with OS.

All data analysis was conducted using STATA/SE 16.1 software (Stata, RRID:SCR_012763) of dataset generated as described above (19).

Results

Analysis of clinical variables for association with BMT

Of 186 patients identified from 2009–2019, 95 patients qualified for inclusion, of whom 51 (54%) received TMT. Patient demographics and clinical data at presentation can be found in *Table 1*. On average, BMT patients had a significantly higher age, higher Eastern Cooperative Oncology Group (ECOG) performance status, and higher age-adjusted CCI. Additionally, a lower proportion of BMT patients met CROSS trial criteria. Tumor location and histology were similar in TMT and BMT patients. There was no significant difference between distance to radiation treatment center and rurality of patient residences between TMT and BMT patients.

Radiation dose, participation in clinical trial, utilization of induction chemotherapy, and utilization of lodging wraparound services were similar between TMT and BMT patients (see *Table 2*). Additional characterization of patients receiving induction chemotherapy and chemotherapy agents utilized in all study participants is available in the Tables S1,S2. Only 12% (6/50) of patients receiving TMT received lower-dose radiation therapy (LDRT, dose ≤48.85 Gy_{10}), all receiving the CROSS-regimen dose of 41.4 Gy in 23 fractions. Among BMT patients, 7% (3/43) received LDRT, all of whom did not complete their treatment plan and received 21.33, 28.8, or 41.4 Gy.

A larger proportion of BMT patients had ≥1 chemotherapy cycle held compared to TMT patients (P=0.001). Among BMT patients, 28 (70%) had ≥1 cycle of chemotherapy held. Indication for withholding chemotherapy included cytopenia (15, 54%), poor performance or fatigue (6, 21%), GI toxicity (2, 7%), and other reasons (6, 21%). One patient had multiple documented reasons for holding chemotherapy. Among TMT patients, 12 (32%) patients had ≥1 cycle of chemotherapy held. Indication for withholding chemotherapy included cytopenia (7, 58%), poor performance/fatigue (2, 17%), GI toxicity (1, 8%), and other reasons (2, 17%). There were insufficient data to reliably compare the incidence of individual toxicities between patients receiving BMT and TMT.

On multivariable logistic regression, higher age-adjusted CCI, higher ECOG performance status at presentation, higher N-stage, presentation with a chief complaint other than dysphagia, and held chemotherapy cycles were all significantly associated with BMT (see *Table 3*).

TMT adherence

Of patients who ultimately received BMT, only 14 (32%) planned to receive definitive chemoradiation without surgery from the start of treatment. Among patients without planned definitive BMT, we observed 63%

Table 3 Univariable and multivariable analyses of clinical variables for association with BMT

Variable	Univariable analysis			Multivariable analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age at diagnosis	0.92	0.88–0.97	0.001	–	–	–
Not CROSS eligible	0.08	0.02–0.30	<0.001	–	–	–
CCI						
5–7	0.41	0.16–1.06	0.07	0.18	0.042–0.79	0.02
≥8	0.11	0.02–0.47	0.003	0.036	0.003–0.38	0.006
ECOG PS at presentation						
1	0.36	0.13–0.96	0.04	0.45	0.11–1.89	0.28
≥2	0.07	0.01–0.39	0.002	0.12	0.015–0.96	0.05
N stage						
1	1.34	0.44–1.47	0.28	0.70	0.18–2.73	0.61
≥2	0.81	0.79–2.30	0.48	0.023	0.001–0.45	0.01
Presentation, no dysphagia	0.44	0.18–1.07	0.07	0.11	0.018–0.74	0.02
Held chemotherapy cycle(s)	0.21	0.08–0.54	0.001	0.074	0.015–0.36	0.003

OR greater than one indicates greater odds of trimodality therapy. BMT, bimodality therapy; OR, odds ratio; CI, confidence interval; CROSS, ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study; CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Table 4 Reasons for nonadherence to treatment among patients without plan for definitive BMT at start of treatment, compared to previously published studies of TMT adherence (11,12)

Reason for nonadherence	N, current series	%, Current series	%, Rahmani *et al.*	%, Depypere *et al.*
Personal choice	12	40.0	25.8	13.2
Poor general condition	9	30.0	12.9	22.8
Disease progression	4	13.3	32.3	43.9
Expired	2	6.7	6.5	7.9
Unresectable	2	6.7	–	12.3
Unresectable intraoperatively	1	3.3	14.5	–

TMT, trimodality therapy; BMT, bimodality therapy.

adherence to TMT. A large portion of nonadherent patients (40%) declined surgical treatment. Reasons for patient nonadherence to TMT are recorded in *Table 4* alongside findings from two similar analyses of nonadherence (11,12). Among the 12 patients who declined surgery, 6 (50%) patients cited preference for non-surgical management, 3 (25%) patients cited concern for morbidity, 2 (17%) patients cited advanced age, and 1 (8%) patient cited optimism based on response to chemoradiation. One patient with preference for non-operative management also cited the lack of a support system to enable post-operative recovery. Of BMT patients receiving induction chemotherapy, 2 (50%) declined surgical treatment, 1 (25%) expired, and 1 (25%) had poor general condition. Notably, among the 27 patients who met CROSS criteria, we observed an 89% resection rate which compares favorably with the 94% rate noted in the CROSS data and 84% in the post-CROSS data (5,7).

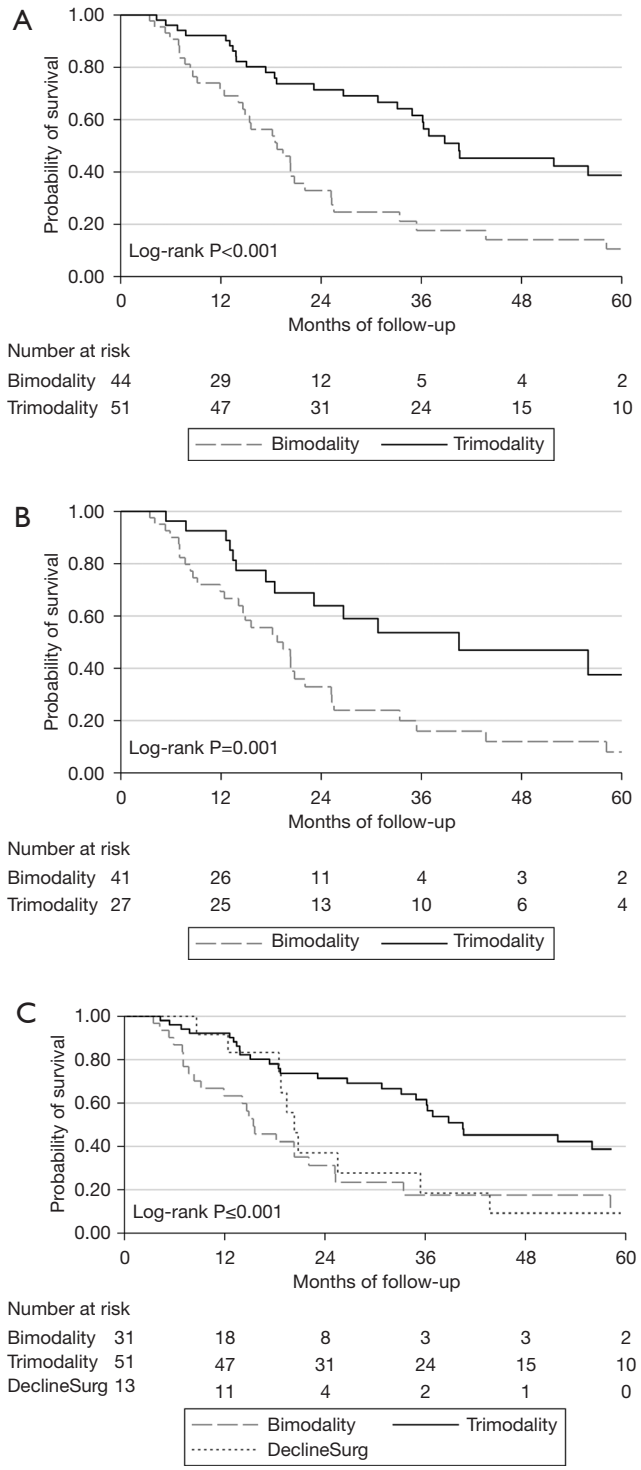

Figure 1 Kaplan-Meier overall survival stratified by (A) treatment modality, (B) treatment modality among CROSS ineligible patients and (C) separated from other BMT patients, with P value comparing TMT patients and BMT patients who declined surgery. CROSS, ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study; BMT, bimodality therapy; TMT, trimodality therapy.

Survival

Median follow-up was 69 (95% CI: 58.3–89.9) months. In the overall cohort, median OS was 26.7 (95% CI: 20.3–36.3) months. As shown in *Figure 1A*, TMT was associated with a significantly higher OS, with median and 3-yr OS at 40.5 months (95% CI: 33.1–83.1) and 62% (95% CI: 46–74%). For patients receiving BMT, median and 3-yr OS was 18.7 months (95% CI: 14.6–22.1) and 18% (95% CI: 7–32%). Similar outcomes were observed when including only patients who did not meet criteria for the CROSS trial, with an observed median OS for TMT of 40.5 (95% CI: 18.4–not reached) months and 19.4 (95% CI: 12.4–22.1) months for BMT, as shown in *Figure 1B*. As characterized in *Figure 1C*, for patients declining esophagectomy resulting in BMT, OS was initially similar to TMT patients. However, by 2 years OS was similar to patients with BMT planned from the start of therapy (P=non-significant) while being significantly worse than TMT.

Only treatment modality was associated with improved OS on multivariable Cox regression (TMT *vs.* BMT: HR 0.34; 95% CI: 0.20–0.57) with 63 death events observed. Univariable and multivariable analysis of OS can be found in the Table S3. Landmark assessments of 6 and 12 months were completed as a sensitivity analysis for immortal time bias introduced by patients who expired during neoadjuvant therapy; however, patterns of OS were similar to analyses of the whole cohort.

RFS was significantly higher for patients receiving TMT with median and 3-yr RFS at 83.1 months (95% CI: 36.9–not reached) and 71% (95% CI: 54–83%) in contrast to 20.3 months (95% CI: 15.4–25.2) and 18% (95% CI: 7–33%) for patients receiving BMT (see *Figure 2A*). DFS was significantly higher for patients receiving TMT, with median and 3-yr DFS at 38.8 months (95% CI: 30.8–83.1) and 58% (95% CI: 43–71%) in contrast to 18.5 months (95% CI: 12.4–20.4) and 12% (95% CI: 4–24%) among patients receiving BMT (see *Figure 2B*).

For TMT patients, 30 and 90-day postoperative mortality was low, observed to be 2.0% and 3.9%, respectively. All patients who expired before 90 days (n=2) were ≥69 years old.

Discussion

Survival benefits of TMT

In our dataset, only TMT was associated with improved OS after adjusting for covariates. Even when excluding patients who met published criteria for the CROSS trial, TMT

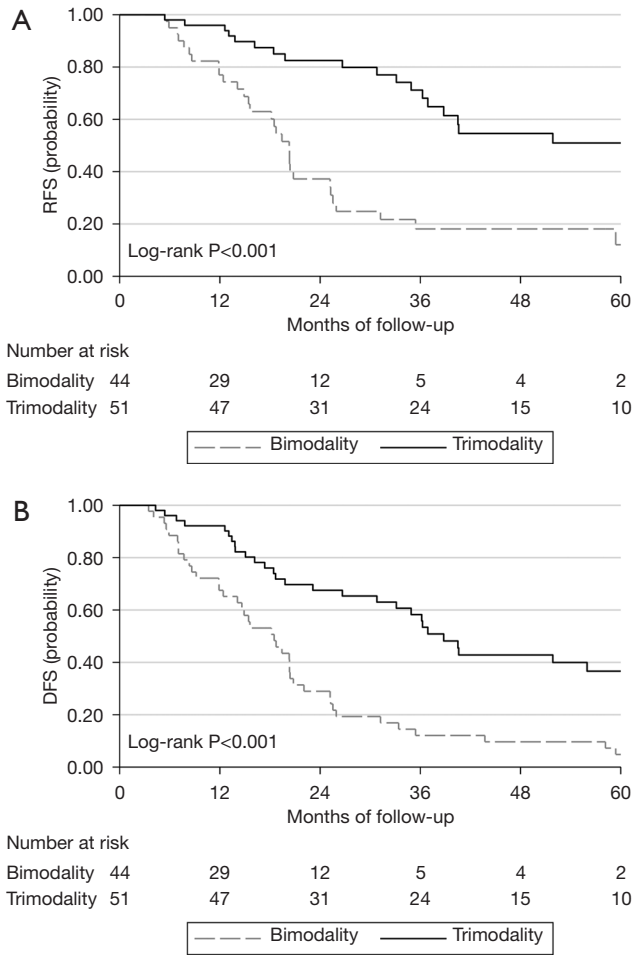

Figure 2 Kaplan-Meier (A) RFS and (B) DFS stratified by treatment modality. RFS, relapse-free survival; DFS, disease-free survival.

continued to be associated with improved OS. Although these data reflect composite criteria, further characterization of individual criteria may translate into more precise patient selection for TMT.

We believe we have captured a cohort that is more inclusive of patients who are older and more vulnerable compared to available literature, thus making our results potentially more generalizable to the typical range of esophageal cancer patients. For example, in the previously cited "post-CROSS" analysis of consecutive patients regardless of age or performance status, significant differences between the "post-CROSS" and CROSS cohort were of small absolute difference and nearly every patient in the cohort had a Karnofsky Performance Scale ≥90, the mean age was 62, and every patient had an unadjusted CCI ≤2 (7). The post-CROSS cohort reported similar 3-year DFS (54% *vs.* 58%) and median OS (44.2 *vs.* 40.5 months) compared to our TMT population, indicating generalizability of expected results (7). Limitations of generalizability for our study are discussed below in 'limitations'.

Additional analyses of older patients undergoing esophagectomy have similar long-term control benefits of TMT and tolerability of neoadjuvant chemoradiation for selected patients, with some conflicting findings of increased post-operative mortality in elderly patients (defined as ≥65–70 years old) (20-22). In our cohort we observed notably low postoperative mortality despite being a low-volume hospital (~10 esophagectomies/year), with two patients expiring <90 days postoperatively. Both patients were ≥69 years of age, an age group representing 11.8% of TMT patients in our cohort.

Our study period predated standard use of nivolumab for TMT patients based on CheckMate577 trial which found improved DFS with adjuvant nivolumab after TMT; thus, no patients received adjuvant nivolumab in our cohort (23). Integration of neoadjuvant immunotherapy is currently under study in ECOG 2174, a double randomized phase II/III trial evaluating the addition of nivolumab during neoadjuvant chemoradiation and the use of single agent *vs.* doublet adjuvant immunotherapy (NCT 03604991). Further characterizing those expected to respond to immunotherapy in the neoadjuvant, adjuvant, or definitive treatment setting may further change standard systemic therapy options for esophageal cancer patients (24). Evidence of non-inferiority for peri-operative chemotherapy compared to the CROSS regimen in terms of OS has been observed in the Neoadjuvant trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study (NEO-AEGIS) trial, but precise analysis by Siewert class and comparison to survival outcomes with addition of immunotherapy are needed to determine appropriate patients for consideration of omission of radiation and to compare with updated practice following CheckMate577 (25).

Clinical variables associated with BMT

Of the five variables independently associated with BMT on multivariable analysis, four (comorbidities, performance status, N-stage, and chief complaint) are assessable at presentation or with initial work-up. Additionally, held chemotherapy treatments were significantly associated with

BMT and were the only treatment variable independently associated with BMT. Notably, these factors were associated with BMT, but were not independently associated with decreased overall survival after adjusting for covariates (including treatment modality).

Prehabilitation therapies administered during neoadjuvant treatment may serve to mitigate the effects of comorbidities and performance status, reduce patient decompensation, and bolster TMT adherence. Previously described interventions include supervised intensive inspiratory muscle training and a "walk and eat" intervention; however, further characterization of interventions and patients who derive benefit is needed, and should be contextualized with adherence to treatment (26,27). For patients presenting with dysphagia, neoadjuvant therapy with either chemoradiation or chemotherapy may provide symptomatic relief and help to bolster nutritional status (28). In patients presenting without dysphagia who develop odynophagia secondary to neoadjuvant therapy, additional nutritional support may be associated with increased rates of resection. Individualized consultation with a dietician following diagnosis may help optimize nutrition status and tolerability of chemoradiation, and should be the standard of care for all patients (29,30).

Interrupted chemotherapy administration may serve as a rough proxy for toxicity status during neoadjuvant chemoradiation. Our study was limited due to insufficient data to assess individual toxicities despite exhaustive review of available records. TMT patients who completed the CROSS LDRT regimen and do not receive a full five cycles of chemotherapy have been observed to have worse overall survival (39 *vs.* 18 months), although similar outcomes do not appear to be previously studied in BMT (31). Robust prospective data exploring both toxicities and interventions to mitigate their effects on patient's ability or willingness to undergo esophagectomy is needed. Re-examination of the optimal duration of concurrent chemotherapy may be warranted with the addition of adjuvant nivolumab to the current standard of care.

We did not observe any significant association between tumor histology and modality, possibly due to a large proportion of patients with adenocarcinoma. In patients with squamous cell histology, multiple studies demonstrate noninferiority of BMT compared to TMT (32,33). We included patients with squamous histology in our final analysis, as TMT is the current standard of practice due to the challenges and potential morbidity associated with salvage surgery (2).

Treatment approaches (including radiation dose, chemotherapy regimen, and use of induction chemotherapy) were not significantly associated with treatment modality in our analysis. Thus, these heterogenous approaches were not differentiated. Notably, about 13% of our study cohort received induction chemotherapy as part of a clinical trial. While proceeding to surgery per protocol may have had an impact on treatment course for enrolled patients, we did observe patients disenrolling and declining surgical management after induction chemotherapy.

In a recent systematic review, LDRT in the neoadjuvant setting, most commonly to the CROSS-protocol dose of 41.4 Gy, was found to be associated with significantly improved PFS and OS, improved safety, and lower distant failure rate as well as more favorable side-effect profile compared to higher-dose radiation therapy (HDRT, any dose >48.85 Gy_{10}) (34). Individual studies demonstrate mixed data for differences in pathologic complete response and survival following LDRT compared to HDRT (35,36). While we did not find any association with dose and modality in our series, only 12% (6/51) TMT patients in our series received a neoadjuvant dose of 41.4 Gy, reflecting changing practice over the study period. All 6 patients who received this "CROSS Protocol" of 41.4 Gy proceeded to surgery. This dose a preferred dose per American Radium Society Appropriate Use Criteria guidelines for esophageal adenocarcinoma (1). In patients who are committed to TMT, 41.4 Gy is an appropriate dose with emerging evidence for decreased toxicity with potential to impact adherence, whereas HDRT to 50 or 50.4 Gy may be most appropriate in the definitive setting, including patients undecided about pursuing surgery. Treatment with proton beam therapy (PBT), in comparison to intensity modulated radiation therapy (IMRT), has been observed to be associated with a decrease in the novel metric total toxicity burden (as defined by the authors) with similar PFS and OS (37). However, this study did not utilize LDRT and it is unclear if benefit in toxicity for PBT would be sustained when delivering LDRT in the neoadjuvant setting.

Drivers of TMT nonadherence

In our study, 40% of patients nonadherent to TMT declined surgery. Two prior studies of nonadherence to surgery reported rates of voluntarily declined esophagectomy between 13.2% and 25.8%, with collection periods spanning 2002–2015 and 2007–2016, respectively (11,12). In one study, significant OS benefit

was observed for patients declining surgery when there was a high proportion of complete clinical response (11). Patients declining surgery frequently cited quality of life as their chief concern, but follow up was not conducted to determine if patients felt regret over this decision (12).

A prospective discreet-choice experiment including 100 patients 4-6 weeks after completion of neoadjuvant chemoradiation and before surgery found patients would be willing to trade a 5-year OS reduction of 16% if the chance of needing surgery decreased from 100% to 35% through active surveillance (38). We observed similar OS at 24 months between patients who were offered and declined esophagectomy and patients who were nonadherent to TMT for other reasons. Comparing patients declining esophagectomy and patients receiving TMT, we observed an approximately 40% difference in probability of OS between at 3 years, far greater than the acceptable five-year survival difference of 16% in Noordman *et al.*, albeit in a shorter follow-up period.

While the National Comprehensive Cancer Network suggests considering definitive BMT for squamous cell patients if positron emission tomography (PET)/computed tomography (CT) and endoscopy with biopsy show complete response, false negatives may occur and evidence to support active surveillance is still lacking. Radiation Therapy Oncology Group (RTOG) 8501 demonstrated five-year OS of 13% for definitive BMT in patients with adenocarcinoma histology, with only 1 of 23 patients alive with long-term follow up (39). In RTOG 0436, local recurrence rates following definitive BMT approached 50% in both arms, finding no benefit to adding cetuximab and suggesting that many patients recur at a time where development of fibrosis might impair candidacy for salvage esophagectomy (40). Trials have reported rates of resection between 6% and 33% during active surveillance using heterogenous approaches (41). To routinely offer organ-preserving treatment to patients who prioritize OS, strong evidence to support noninferiority of active surveillance is necessary (42). Multiple ongoing trials comparing TMT to active surveillance may provide clarity over the next several years (43-45). Circulating tumor DNA (ctDNA) has demonstrated association with recurrence and survival and may become an additional tool for prognostication and identification of patients for whom nonsurgical management carries lower risk (46,47). Information is needed to characterize the quantity of patients declining esophagectomy beyond single-institution data and comprehensively assess patient decision-making.

Disease progression noted during restaging post-chemoradiation was the most common reason for TMT nonadherence in previous studies (comprising 43.9% and 32.3%) (11,12). We observed far lower rates of TMT nonadherence attributable to disease progression (13.3%). Due to many patients declining surgery in our series, results are skewed away from other factors in favor of personal choice.

Poor general condition was the second highest reason for nonadherence at 30% in our analysis. Our findings are more consistent with the literature for this measure. Prehabilitation, as discussed previously, may reduce decompensation as a driver of nonadherence. Additionally, LDRT has demonstrated superior benefit with improved therapeutic ratio and should be considered to support patients in completing TMT (34).

Limitations

Limitations include those inherent to retrospective analyses. Retrospective analyses present challenges when controlling for differences between cohorts to mitigate effects of selection bias. Through multivariable analysis, we controlled for differences in common prognostic factors between patients receiving TMT and BMT when analyzing for association with survival and other outcomes. Additionally, our exclusion criteria were designed to create a cohort in which patient presentation was both inclusive of patients who were older and with increased frailty, but minimized uncontrollable variation in disease through exclusion of patients receiving treatment without curative intent. However, some patients may have experienced inferior outcomes due to factors for which we did not collect data or had incomplete data, or had complexities difficult to characterize and study in a single-institution retrospective cohort, which may impact the results and associated conclusions of our multivariable analyses and these should be interpreted accordingly.

Our analysis was limited to the content and quality of available data, which commonly impacts analyses of RWD (48). The power of our study was determined by available data, and may have impacted our ability to detect the association of factors additional to treatment modality with overall survival. For patients who received parts of their care outside of our cancer center, we had limited access to records; however, through the inclusion of patients who

received part of their care at a high-volume cancer center, we hope to provide an analysis that is both representative of the patient population at a center with smaller volume and inclusive of patients without means to access a high-volume center. Overall, limited data were available to assess individual treatment toxicities. Few patients received PET scans following neoadjuvant therapies in our cohort; thus, we were unable to analyze PET response for association with BMT or OS.

We included patients who met inclusion criteria but planned for definitive BMT at the start of therapy in our analyses for association of clinical factors with modality and our analyses of survival, but excluded these patients from analyses of adherence. While we were able to record clearly documented plans for definitive BMT, many patients had contingent plans and patients were offered initial consultation with a surgeon at varying timepoints relative to diagnosis and therapy during our study period. For these reasons, analyses of survival based on intent to treat with definitive BMT as compared to the remainder of our cohort is of limited utility and was not included in our findings.

Of patients receiving BMT, two expired during the anticipated nCRT course and one expired during the interval between nCRT and surgery, which may introduce immortal time bias in analyses of modality for association with survival; however, landmark assessments at 6 and 12 months suggest against immortal time bias in our results.

Conclusions

Trimodality therapy was associated with an improved OS, RFS, and DFS for patients with resectable esophageal cancer in our cohort. Further characterizing the patients who derive the greatest benefit from esophagectomy is necessary. Interventions during neoadjuvant therapy may be an important area for future research efforts to identify ways to best physiologically prepare patients to receive surgery. Furthermore, patient preference for organ-preserving therapies appears to have a significant impact on resection rate in our cohort; further characterization of patient decision-making may be helpful to best counsel patients when weighing potential OS benefits versus treatment morbidity. Patients should be given the option to discuss details regarding their expected prognosis with TMT *vs.* BMT, so that they better understand the long-term expectations of both treatment modalities. Therefore, early consultation with a surgeon should be facilitated for all patients with potentially resectable disease. For those patients who wish to pursue TMT, the CROSS protocol involving 41.4 Gy/23 fractions (rather than 50.4 Gy/28 fractions) should be considered to minimize treatment toxicity and support TMT adherence.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-633/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-633/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-633/coif). All authors report that this study received financial support from NNECOS and the UVM LCOM Summer Research Fellowship. Any opinions, findings, and conclusions expressed in this material are those of the author(s) and do not necessarily reflect those of the NNECOS. The authors have no other 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). The study was approved by institutional review board of the University of Vermont (IRB00000485) and individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 Characterization of patients receiving induction chemotherapy by chemotherapy regimen and participation in a clinical trial

Characteristics	TMT, n (%)	BMT, n (%)
Chemotherapy regimen		
Carboplatin and paclitaxel	5 (56)	3 (75)
FOLFOX	1 (11)	0 (0)
Cisplatin and irinotecan	1 (11)	0 (0)
Multiple, per research protocol	2 (22)	0 (0)
Other	0 (0)	1 (25)
On research protocol		
No	1 (11)	0 (0)
Yes	8 (89)	4 (100)

Table S2 Chemotherapy agents utilized in patients receiving BMT and TMT

Chemotherapy regimen	TMT, n (%)	BMT, n (%)
Carboplatin and paclitaxel	37 (73)	34 (77)
Cisplatin and paclitaxel	0 (0)	3 (7)
FOLFOX	1 (2)	0 (0)
Cisplatin and 5-fluorouracil	3 (6)	0 (0)
Cisplatin and irinotecan	4 (8)	1 (2)
Multiple, per research protocol	4 (8)	0 (0)
Other	0 (0)	5 (11)
Data unavailable	2 (4)	1 (2)

Table S3 Univariable and multivariable cox regression of overall survival

Variable	Univariable analysis			Multivariable analysis		
	HR	(95% CI)	P value	HR	(95% CI)	P value
Trimodality therapy	0.31	(0.19–0.51)	<0.001	0.37	(0.21–0.64)	<0.001
History of neoplasm	1.73	(1.01–2.97)	0.03	1.74	(0.97–3.12)	0.06
Age-adjusted CCI						
5–7	1.32	(0.73–2.36)	0.3	0.98	(0.53–1.80)	0.9
8–10	2.35	(1.11–4.96)	0.03	1.32	(0.60–2.91)	0.5
CROSS-Ineligible	1.99	(1.16–3.42)	0.01	–	–	–

Univariable and multivariable cox regression of overall survival. CROSS eligibility was excluded from multivariable regression due to collinearity with history of neoplasm. CCI, Charlson Comorbidity Index.

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