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Article

Trimodality Therapy vs Definitive Chemoradiation in Older Adults With Locally Advanced Esophageal Cancer

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Abstract

Background: The comparative effectiveness of trimodality therapy vs definitive chemoradiation for treating locally advanced esophageal cancer in older adults is uncertain. Existing trials lack generalizability to older adults, a population with heightened frailty. We sought to emulate a hypothetical trial comparing these treatments using real-world data. **Methods:** A cohort of adults aged 66-79 years diagnosed with locally advanced esophageal cancer between 2004 and 2017 was identified in the Surveillance Epidemiology and End Results–Medicare database. The clone-censor-weight method was leveraged to eliminate time-related biases when comparing outcomes between treatments. Outcomes included overall mortality, esophageal cancer–specific mortality, functional adverse events, and healthy days at home. **Results:** A total of 1240 individuals with adenocarcinomas and 661 with squamous cell carcinomas were identified. For adenocarcinomas, the standardized 5-year risk of mortality was 73.4% for trimodality therapy and 83.8% for definitive chemoradiation (relative risk [RR] = 0.88, 95% confidence interval [CI] = 0.82 to 0.95). Trimodality therapy was associated with mortality risk reduction for squamous cell carcinomas (RR = 0.87, 95% CI = 0.70 to 1.01). The 1-year incidence of functional adverse events was higher in the trimodality group (adenocarcinomas RR = 1.40, 95% CI = 1.22 to 1.65; squamous cell carcinomas RR = 1.21, 95% CI = 1.00 to 1.49). Over 5 years, trimodality therapy was associated with 160 (95% CI = 67 to 229) and 177 (95% CI = 51 to 313) additional home days in individuals with adenocarcinomas and squamous cell carcinomas, respectively. **Conclusions:** Compared with definitive chemoradiation, trimodality therapy was associated with reduced mortality but increased risk of function-related adverse events. Discussing these tradeoffs may help optimize care plans.

Esophageal cancer has a poor prognosis, with 80% of individuals experiencing mortality within 5 years of diagnosis (1). In the United States, more than 15 500 deaths are attributed to esophageal cancer annually (2). As the United States undergoes an aging demographic shift, the burden of disease will rise considerably (3,4). Most older adults diagnosed with esophageal cancer present with locally advanced tumors for which the current evidence base pertaining to treatment is deficient.

For older adults diagnosed with locally advanced cancers, the comparative effectiveness of neoadjuvant chemoradiation followed by esophagectomy (trimodality therapy) vs definitive chemoradiation is uncertain. Both treatments are considered viable options by practice guidelines (5,6). Two randomized control trials (RCTs) have directly compared these treatments; however, these studies focused on squamous cell carcinomas, and older adults were underrepresented (7,8). Compared with younger individuals, older adults have higher comorbidity and frailty burdens, which can cause poorer outcomes after surgery and may alter the benefit–risk profile of trimodality therapy (9-11).

In the absence of applicable trial data, observational evidence comparing trimodality therapy and definitive chemoradiation may provide insight (12-20). However, most observational studies making this comparison are vulnerable to immortal time bias—an analytic error wherein exposure information during follow-up is used to classify exposure status at baseline, guaranteeing survival up to the surgery for the trimodality group. Additionally, most published observational studies

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were conducted using data from before the introduction of the Chemoradiotherapy for Esophageal Cancer Followed by Surgery Study trial regimen in 2012 (21). A recent meta-analysis described the overall quality of existing studies as low (22).

The primary objective of this study was to assess the comparative effectiveness of trimodality therapy vs definitive chemoradiation in a population of older US adults using a rigorous study design that avoids immortal time bias.

Methods

Data Source

We used data from the Surveillance Epidemiology and End Results (SEER)–Medicare–linked database to identify individuals diagnosed with esophageal cancer from 2004 to 2017. Supported by the National Cancer Institute, SEER is a population-based cancer registry covering 28% of the US population (23). Medicare is a federal program that provides health insurance to adults aged 65 years and older, as well as those with disabilities and/or end-stage renal disease.

Study Design

We designed our study using the target trial approach, which maintains that observational studies can maximize their internal validity by emulating a hypothetical RCT (24,25). Through emulation, this approach facilitates the comparison of well-defined interventions and can avoid many common pitfalls in observational research (26). Supplementary Table 1 (available online) details the target trial and how the trial was emulated using the SEER-Medicare data; a design schematic is presented in Supplementary Figure 1 (available online) (27).

Our study population consisted of older adults aged 66-79 years newly diagnosed with locally advanced esophageal cancer. Individuals were required to have a noncervical tumor site and have adenocarcinoma or squamous cell carcinoma histology. We used the tumor (T), node (N), and metastasis (M) definitions from the American Joint Committee on Cancer (AJCC) seventh edition staging manual to identify cancers of interest. All cancers were required to be nonmetastatic (M0). There were 2 T and N combination groups that met inclusion criteria: node negative (N0) tumors that were T2, T3, or T4a and node positive tumors (N1-N3) from T1-T4a. These requirements translated to stage groups of IB-IIIC.

Our study contained exclusion criteria. Individuals diagnosed at death or autopsy were excluded. A minimum of 1 year of continuous enrollment in Medicare Part A and Part B insurance prior to first chemotherapy infusion was required. Claims in the year prior to the first infusion were used to measure comorbidities and frailty using the National Cancer Institute adaptation of the Charlson comorbidity score (28,29) and Kim frailty index (30), respectively. We sought to identify a population eligible for surgery and excluded individuals with a high comorbidity burden (Charlson score >5), those categorized as frail (Kim frailty index ≥ 0.35), and individuals aged older than 79 years to limit confounding (31). We excluded individuals who were diagnosed with other cancers in the year prior to their first esophageal cancer diagnosis.

Treatments compared consisted of trimodality therapy or definitive chemoradiation. Trimodality therapy was defined as starting chemotherapy within 120 days of cancer diagnosis, radiation on the same day or up to 7 days after chemotherapy, followed by receipt of esophagectomy at a maximum of 6 months after the first chemotherapy treatment. Definitive chemoradiation was defined the same, except not receiving esophagectomy within 6 months of the first chemotherapy treatment. Chemotherapy consisted of outpatient infusion-based chemotherapy. Radiation consisted of any external-beam radiation delivery code. Health-care codes used to identify treatments are included in Supplementary Table 2 (available online). A sensitivity analysis explored the impact of shortening the surgery window to 3 months.

Unlike the target trial, individuals were not randomly assigned to treatment in our study. We accounted for the following confounders in our statistical analysis: age, sex, race and ethnicity, geographic region, year of diagnosis, census-tract poverty level, histologic subtype, tumor location, tumor grade, tumor stage, comorbidity score, frailty score, number of prior cancers diagnosed at least a year before esophageal cancer, and number of hospitalizations and emergency department visits in the year prior to first infusion. Race and ethnicity were determined using registry variables, the data from which come from chart abstraction by tumor registrars and may vary in original collection method between medical records. The “other race and ethnicity” category included American Indian and Alaska Native and Asian or Pacific Islander.

Study outcomes included the 5-year risks of overall and esophageal cancer–specific mortality, the 1-year risk of functional adverse events, and the 5-year mean cumulative count of days at home. Functional adverse events were defined using a claims-based algorithm that identifies incident claims for durable medical equipment and skilled care, meant to signal a potential decline in functional status from treatment (32). Days at home were defined using a recently developed quality measure (33).

Statistical Analysis

Data were analyzed using the clone-censor-weight method, a technique that properly handles complex, sequential interventions such as trimodality therapy (34-38). The method avoids immortal time bias (39), wherein individuals would be classified into trimodality therapy at the start of chemoradiation based on future knowledge about receipt of esophagectomy. Individuals were duplicated (cloned) at first chemotherapy treatment within 120 days of cancer diagnosis. One copy was assigned to trimodality therapy, and the other to definitive chemoradiation. When the observed treatment data of the copy were no longer consistent with the assigned treatment strategy, that observation was analytically censored. Figure 1 depicts this process for 4 example individuals.

After cloning and analytic censoring of individuals when they deviated from their assigned treatment group, inverse probability of censoring weights was implemented to account for the confounders causing deviation. Censoring weights were calculated using pooled logistic regression (40).

Descriptive statistics of the eligible study population were calculated prior to cloning individuals. Balance in confounders at 6 months before and after weighting was assessed using standardized mean differences. The 5-year cumulative incidence of overall mortality was calculated using the complement of the Kaplan-Meier estimator. The 5-year cumulative incidence of esophageal cancer–specific mortality and functional adverse events were estimated using the Aalen-Johansen estimator (41). The Dong-Yasui estimator was used to quantify the mean

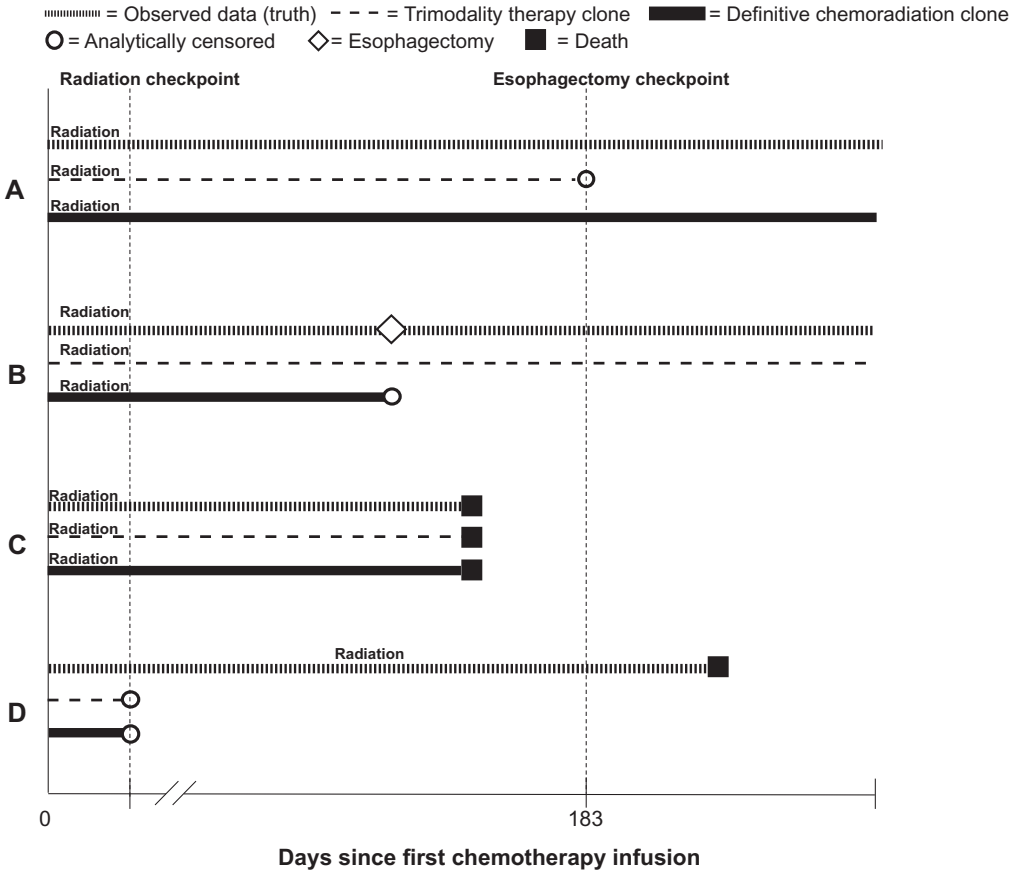

Figure 1. Cloning and censoring analytic schema for 4 example individuals. Individual A receives radiation the day after the first chemotherapy infusion and then never receives an esophagectomy; the trimodal clone for this individual is analytically censored at 183 days because at that point, for the first time, data is inconsistent with the trimodal therapy intervention. The definitive chemoradiation clone is never analytically censored because it is always following the definitive chemoradiation treatment strategy. Individual B receives radiation 5 days after the first chemotherapy infusion and an esophagectomy within 183 days; the trimodal clone is never analytically censored because the individual's data was always consistent with trimodal therapy, whereas the definitive chemoradiation clone is censored at the time of esophagectomy. Individual C receives radiation on the same day as the first chemotherapy infusion and dies before 183 days; neither the trimodal clone nor the definitive chemoradiation clone are analytically censored as the individual is following both treatment strategies until death. Individual D receives radiation more than 7 days after the first chemotherapy infusion; the trimodal clone and the definitive chemoradiation clone are analytically censored at 7 days as the individual is no longer consistent with respective treatment strategies at day 7.

cumulative count of days at home in the 5 years after the index date (42). Bootstrapping was performed to generate all 95% confidence intervals (CIs) for all estimates within and between treatment groups.

This study was approved by the University of North Carolina at Chapel Hill institutional review board (21-1217). All analyses were performed using SAS 9.4 (Cary, NC, USA).

Results

Study Population

The study population consisted of 1901 adults (Figure 2). Descriptive characteristics stratified by histologic subtype are presented in Table 1. The median age was 72 years for both histologic subtypes. Nearly 88% of adenocarcinomas were diagnosed in males compared with only 55% of squamous cell carcinomas. Most tumors were stage IIB and IIIA and had an intermediate or high grade. About half of the study population was prefrail, and roughly 17% had a Charlson comorbidity score between 3 and 5. Given that a substantial number of individuals had either missing tumor stage data or could not be staged to the AJCC seventh edition, an attrition table was generated that displayed the distribution of demographic and tumor characteristics before and after those with missing stage were excluded (Supplementary Table 3, available online); only minor changes were observed.

Balance of confounders was assessed at the end of the 6-month grace period in the unweighted and weighted data using standardized mean differences (Supplementary Figures 2 and 3, available online). After weighting, the absolute standardized mean difference was less than 0.10 for all measured confounders, a threshold indicating adequate confounder balance (43).

Overall Mortality and Cause-Specific Mortality

The standardized cumulative incidence curves for 5-year overall mortality and esophageal cancer–specific mortality, by treatment group, are presented in Figure 3 and Table 2. All results are stratified by histologic subtype.

For adenocarcinomas, the 5-year cumulative incidence of overall mortality was 73.4% (95% CI = 69.1% to 77.4%) in the trimodality group and 83.8% (95% CI = 78.6% to 87.2%) in the definitive chemoradiation group, corresponding to a risk difference

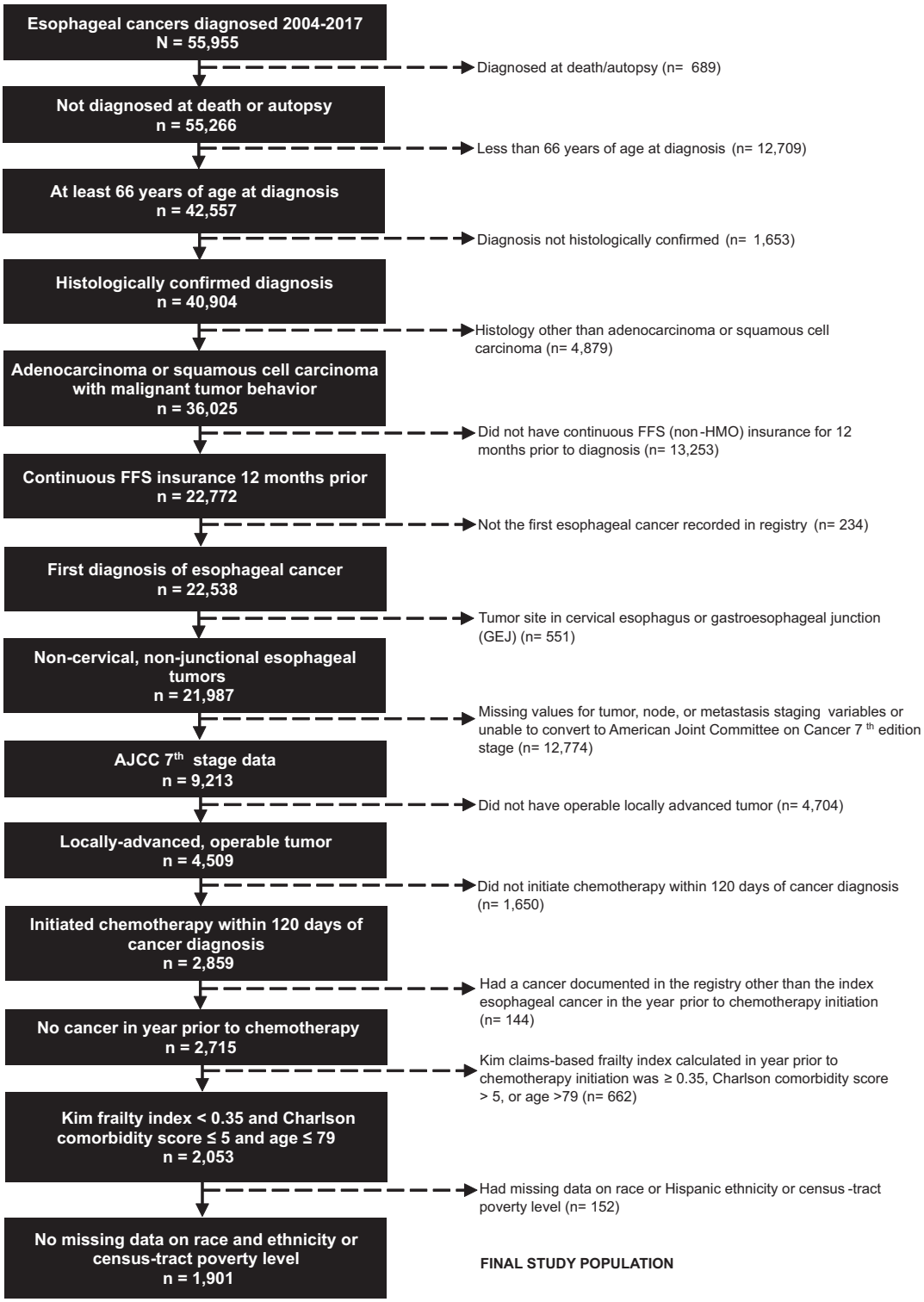

Figure 2. Flowchart depicting selection of study population. AJCC = American Joint Committee on Cancer; FFS (non-HMO) = Fee-for-service Medicare Part A and Part B insurance.

of −10.4 (95% CI = −15.6 to −3.9) percentage points and a risk ratio of 0.88 (95% CI = 0.82 to 0.95) comparing trimodality therapy with definitive chemoradiation. The 5-year cumulative incidence of esophageal cancer–specific mortality was 61.2% (95% CI = 55.8% to 66.2%) in the trimodality therapy group and 71.0% (95% CI = 64.9% to 75.9%) in the definitive chemoradiation group, corresponding to a risk difference of −9.8 (95% CI = −17.2 to −1.5) percentage points and a risk ratio of 0.86 (95% CI = 0.77 to 0.98).

For squamous cell carcinomas, the 5-year cumulative incidence of overall mortality was 62.6% (95% CI = 50.9% to 73.5%) in the trimodality therapy group and 72.3% (95% CI = 67.6% to

Table 1. Study population descriptive statistics, among Medicare-enrolled older adults diagnosed with locally advanced esophageal cancer

Characteristics	Adenocarcinomas (n = 1240)	Squamous cell carcinomas (n = 661)
Age, median (IQR), y	72 (68-75)	72 (69-75)
Sex, No. (%)		
Male	1090 (87.9)	366 (55.3)
Female	150 (12.1)	295 (44.6)
Race, No. (%)[a]		
Black	19 (1.5)	98 (14.8)
Other race and ethnicity	18 (1.5)	52 (7.9)
White Hispanic	37 (3.0)	37 (5.6)
White non-Hispanic	1166 (94.0)	474 (71.7)
Year of diagnosis, No. (%)		
2004-2008	215 (17.3)	124 (18.8)
2009-2013	475 (38.3)	277 (41.9)
2014-2017	550 (44.4)	260 (39.3)
Registry region, No. (%)[b]		
West	490 (39.5)	293 (44.3)
South	225 (18.2)	149 (22.5)
Northeast	312 (25.2)	148 (22.4)
Midwest	213 (17.2)	71 (10.7)
Tumor grade, No. (%)		
Low grade	40 (3.2)	34 (5.1)
Intermediate grade	460 (37.1)	273 (41.3)
High grade	580 (46.8)	244 (36.9)
Grade cannot be assessed	160 (12.9)	110 (16.6)
Tumor location, No. (%)		
Upper and middle esophagus	73 (5.9)	414 (62.6)
Lower esophagus	1092 (88.1)	188 (28.4)
Overlapping lesion or NOS	75 (6.0)	59 (8.9)
Stage group, No. (%)		
IB	98 (7.9)	16 (2.4)
IIA	51 (4.1)	105 (15.9)
IIB	435 (35.1)	246 (37.2)
IIIA	498 (40.2)	232 (35.1)
IIIB	104 (8.4)	37 (5.6)
IIIC	54 (4.4)	25 (3.8)
Charlson comorbidity score, No. (%)		
0	482 (38.9)	257 (38.9)
1-2	544 (43.9)	298 (45.1)
3-5	214 (17.3)	106 (16.0)
Kim Frailty Index, No. (%)		
Robust, <0.15	542 (43.7)	255 (38.6)
Prefrail, 0.15-0.24	617 (49.8)	337 (51.0)
Mildly frail, 0.25-0.34	81 (6.5)	69 (10.4)
Prior nonesophageal cancer diagnosis, No. (%)		
No	1019 (82.2)	526 (79.6)
Yes	221 (17.8)	135 (20.4)
Hospitalizations in past year, No. (%)		
0	823 (66.4)	400 (60.5)
1	304 (24.5)	185 (28.0)
≥2	113 (9.1)	76 (11.5)
Emergency department visits in past year, No. (%)		
0	913 (73.6)	460 (69.6)
1	237 (19.1)	135 (20.4)
≥2	90 (7.3)	66 (10.0)
Census-tract poverty level, No. (%)		
0% to <5%	345 (27.8)	154 (23.3)
5% to <10%	373 (30.1)	189 (28.6)
10% to <20%	343 (27.7)	180 (27.2)
20% to 100%	179 (14.4)	138 (20.9)

[a]"Other race and ethnicity" defined using cancer registry variable and includes American Indian and Alaska Native and Asian or Pacific Islander. IQR = interquartile range; NOS = not otherwise specified.
[b]West consisted of California, Hawaii, New Mexico, Utah, and Seattle. Northeast consisted of Connecticut and New Jersey. Midwest consisted of Iowa and Detroit. South consisted of Georgia, Kentucky, and Louisiana.

76.3%) in the definitive chemoradiation group, corresponding to a risk difference of −9.6 (95% CI = −21.6 to 0.8) percentage points and a risk ratio of 0.87 (95% CI = 0.70 to 1.01) comparing trimodality therapy with definitive chemoradiation. The 5-year cumulative incidence of esophageal cancer–specific mortality was 51.0% (95% CI = 40.5% to 61.5%) in the trimodality therapy arm and 58.1% (95% CI = 52.1% to 63.2%) in the definitive chemoradiation arm, corresponding to a risk difference of −7.1 (95% CI = −18.9 to 4.4) percentage points and a risk ratio of 0.88 (95% CI = 0.68 to 1.07). The sensitivity analysis found that the benefit of trimodality therapy was slightly stronger when the time-to-surgery requirement was shortened to 90 days (Supplementary Table 4, available online).

Functional Adverse Events

The standardized 1-year cumulative incidence of functional adverse events, by treatment group, is presented in Table 3. For adenocarcinomas, the 1-year cumulative incidence of experiencing a functional adverse event was 57.9% (95% CI = 53.3% to 61.6%) in the group receiving trimodality therapy and 41.3% (95% CI = 34.6% to 46.1%) in the definitive chemoradiation group, corresponding to a risk difference of 16.5 (95% CI = 9.8 to 23.3) percentage points and a risk ratio of 1.40 (95% CI = 1.22 to 1.65). For squamous cell carcinomas, the 1-year cumulative incidence of experiencing a functional adverse event was 46.8% (95% CI = 37.4% to 54.9%) in the trimodality therapy group and 38.5% (95% CI = 32.3% to 43.6%) in the definitive chemoradiation arm, corresponding to a risk difference of 8.2 (95% CI = 0.0 to 17.5) percentage points and a risk ratio of 1.21 (95% CI = 1.00 to 1.49).

Days at Home

The standardized 5-year mean cumulative count of days at home for each histology, by treatment, is presented in Table 4. For adenocarcinomas, the 5-year (1826 days) mean cumulative count of days at home was 840.1 (95% CI = 779.9 to 901.6) days for the trimodality therapy strategy and 680.3 (95% CI = 634.8 to 762.0) days for the definitive chemoradiation strategy, corresponding to a mean cumulative count difference of 159.8 (95% CI = 67.3 to 229.2) days and a mean cumulative count ratio of 1.23 (95% CI = 1.09 to 1.36).

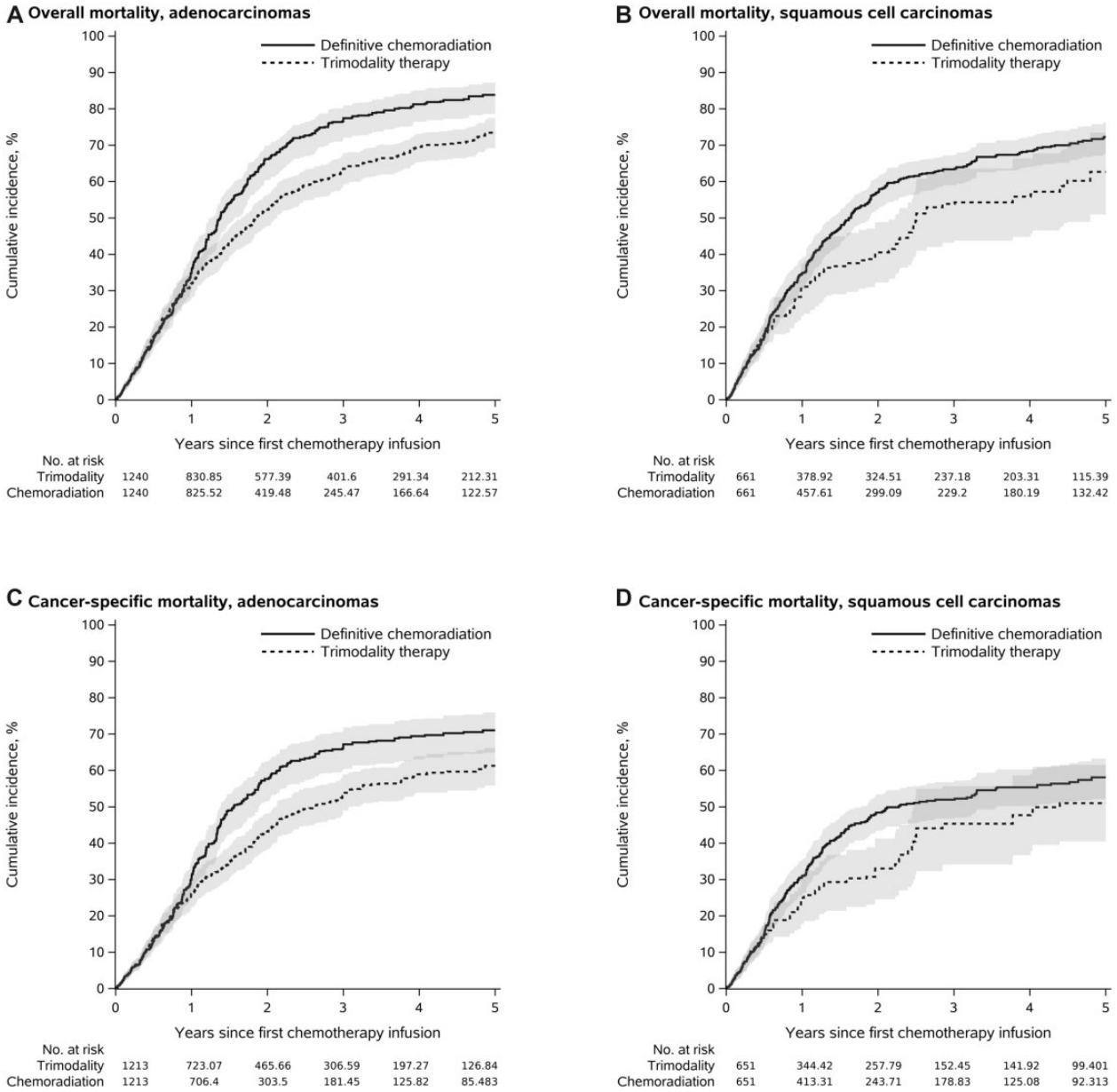

Figure 3. Five-year standardized cumulative incidence of overall and esophageal cancer–specific mortality. **A)** and **(B)** present overall mortality for adenocarcinomas and squamous cell carcinomas, respectively. **C)** and **(D)** present esophageal cancer–specific mortality for adenocarcinomas and squamous cell carcinomas, respectively.

For squamous cell carcinomas, the 5-year mean cumulative count of days at home was 990.3 (95% CI = 865.7 to 1125.8) days for the trimodality strategy and 813.0 (95% CI = 749.5 to 883.9) days for the definitive chemoradiation strategy, corresponding to a mean cumulative count difference of 177.3 (95% CI = 50.8 to 313.1) days and a ratio of 1.22 (95% CI = 1.06 to 1.40).

Discussion

Older adults diagnosed with locally advanced esophageal cancer face challenges when considering treatment with definitive chemoradiation vs trimodality therapy. Given low rates of complete response to chemoradiation, resection may be warranted to obtain better local control of the tumor. In contrast, esophagectomy may bring complications, decrements to health-related quality of life, and operative mortality.

Our study found that trimodality therapy is associated with decreased risks of 5-year all-cause and cancer-specific mortality compared with definitive chemoradiation for adenocarcinomas and squamous cell carcinomas. We also found that trimodality therapy was associated with more days at home but a greater risk of incident functional adverse events. Of note, trimodality therapy did not surpass the definitive chemoradiation strategy in expected days at home for the first year and a half after starting chemotherapy.

Our estimates can inform decision making. A discrete choice experiment in individuals considering definitive chemoradiation with active surveillance or trimodality therapy found interviewed patients would accept a 16% lower 5-year survival if

Table 2. Five-year standardized risks of overall and esophageal cancer–specific mortality among a cohort of locally advanced esophageal cancer cases identified in SEER-Medicare, 2004-2017[a]

Outcome, by histology and treatment	Risk (95% CI)	Risk difference (95% CI)	Risk ratio (95% CI)
Overall mortality			
Adenocarcinomas			
Definitive chemoradiation	83.8 (78.6 to 87.2)	Referent	Referent
Trimodal therapy	73.4 (69.1 to 77.4)	−10.4 (−15.6 to −3.9)	0.88 (0.82 to 0.95)
Squamous cell carcinomas			
Definitive chemoradiation	72.3 (67.6 to 76.3)	Referent	Referent
Trimodal therapy	62.6 (50.9 to 73.5)	−9.6 (−21.6 to 0.8)	0.87 (0.70 to 1.01)
Esophageal cancer–specific mortality			
Adenocarcinomas			
Definitive chemoradiation	71.0 (64.9 to 75.9)	Referent	Referent
Trimodal therapy	61.2 (55.8 to 66.2)	−9.8 (−17.2 to −1.5)	0.86 (0.77 to 0.98)
Squamous cell carcinomas			
Definitive chemoradiation	58.1 (52.1 to 63.2)	Referent	Referent
Trimodal therapy	51.0 (40.5 to 61.5)	−7.1 (−18.9 to 4.4)	0.88 (0.68 to 1.07)

[a]CI = confidence interval; SEER = Surveillance Epidemiology and End Results.

Table 3. One-year standardized risk of experiencing a functional adverse event among a cohort of patients diagnosed with locally advanced esophageal cancer identified in SEER-Medicare, 2004-2017[a]

Histology and treatment	Risk (95% CI)	Risk difference (95% CI)	Risk ratio (95% CI)
Adenocarcinomas			
Definitive chemoradiation	41.3 (34.6 to 46.1)	Referent	Referent
Trimodal therapy	57.9 (53.3 to 61.6)	16.5 (9.8 to 23.3)	1.40 (1.22 to 1.65)
Squamous cell carcinomas			
Definitive chemoradiation	38.5 (32.3 to 43.6)	Referent	Referent
Trimodal therapy	46.8 (37.4 to 54.9)	8.2 (0.0 to 17.5)	1.21 (1.00 to 1.49)

[a]CI = confidence interval; SEER = Surveillance Epidemiology and End Results.

Table 4. Five-year standardized mean cumulative count of days at home among a cohort of locally advanced esophageal cancer cases identified in SEER-Medicare, 2004-2017[a]

Histology and treatment	MCC (95% CI)	MCC difference (95% CI)	MCC ratio (95% CI)
Adenocarcinomas			
Definitive chemoradiation	680.3 (634.8 to 762.0)	Referent	Referent
Trimodal therapy	840.1 (779.9 to 901.6)	159.8 (67.3 to 229.2)	1.23 (1.09 to 1.36)
Squamous cell carcinomas			
Definitive chemoradiation	813.0 (749.5 to 883.9)	Referent	Referent
Trimodal therapy	990.3 (865.7 to 1125.8)	177.3 (50.8 to 313.1)	1.22 (1.06 to 1.40)

[a]CI = confidence interval; MCC = mean cumulative count; SEER = Surveillance Epidemiology and End Results.

quality of life was at the level associated with definitive chemoradiation instead of the (lower) quality associated with resection (44).

Ideally, an accurate prediction of whether pathologic complete response would be expected after neoadjuvant treatment would inform treatment selection. Unfortunately, predictive models of clinical response to chemoradiation need external validation, and clinical response maps poorly to pathologic response (45-47). The current literature reports that only 20%-40% of individuals who undergo trimodality therapy will achieve a pathologic complete response and that adenocarcinoma is associated with lower rates of response (21,48,49).

The existing experimental evidence comparing trimodal therapy with definitive chemoradiation is limited. Two RCTs found better local control of tumors among those who received trimodality therapy but did not find statistically significant differences in survival (7,8). However, 11.2% of trial participants in one study (7) had adenocarcinomas, and the other (8) was exclusively composed of squamous cell carcinomas. In the United States, adenocarcinomas now have a higher incidence than squamous cell carcinomas (50). The trials have also been criticized for their higher-than-expected operative mortality rates and use of induction chemotherapy and split-course radiotherapy (51,52).

Prior observational studies found strong protective associations from trimodality therapy compared with definitive chemoradiation. For instance, using Los Angeles cancer registry data, McKenzie et al. (12) report a hazard ratio of 0.66 (95% CI =

0.56 to 0.77) comparing trimodal therapy with definitive chemoradiation. Two institutional studies of adenocarcinomas offer similar findings; Shridhar et al. (53) report a contrast of 43.6% vs 35.6%, and Xi et al. (54) report a contrast of 54.7% vs 28.1% comparing 5-year overall survival rates of trimodality vs definitive chemoradiation, respectively. Though these studies offer rich clinical detail on patient baseline health and treatment regimens, these 3 studies are susceptible to immortal time bias because follow-up started at diagnosis but treatment data in the future were used to define the comparison groups at baseline. In practice, nearly 17% of individuals with trimodality-planned treatment do not ultimately receive resection (55). Immortal time bias is particularly prevalent in research of surgical interventions (56).

In their National Cancer Database analysis of adults aged 70 years and older with stage I and II esophageal cancer diagnosed between 1998 and 2012, Vlacich et al. (57) compared survival outcomes between propensity-matched cohorts of individuals receiving definitive chemoradiation and trimodality therapy. Median survival was higher in the trimodality group (27.6, 95% CI = 24.7 to 30.4 months) than the definitive chemoradiation group (15.6, 95% CI = 14.3 to 16.9 months), though immortal time bias was present as baseline exposure group definitions relied on future treatment information. Our study differed in several important ways. Critically, we used a statistical method that eliminated immortal time bias and used a linked data source (SEER-Medicare) that allowed a more sensitive capture of confounders. The National Cancer Database does not offer data on proxies for frailty status, and diagnoses of comorbid conditions are captured less comprehensively than SEER-Medicare (58).

Our study contains numerous strengths. Methodologically, we removed all potential for immortal time bias by using the clone-censor-weight technique. We reported risk differences and ratios, which offer greater interpretability than hazard ratios and have statistical advantages (59,60). We quantified proxy measurements of comorbidity and frailty using validated claims-based indices to identify a population of adults eligible for trimodality therapy and control measured confounding. Lastly, we examined functional adverse events and the novel home days measure, 2 patient-centric outcomes that help define the benefit–risk balance of following chemoradiation with resection.

Limitations of our study include the inability to capture detailed clinical information in the SEER-Medicare database and the potential for misclassification of treatment group. For example, body mass index is not contained in the database and may impact receipt of treatment, tolerability, and survival. Importantly, although the clone-censor-weight technique removes immortal time bias by aligning study eligibility, intervention initiation, and the start of follow-up, it does not possess additional confounding control over classic regression models; unmeasured confounders may still bias the results. Ultimately, such bias would best be handled in a RCT. This comparison of therapies is the subject of the Neoadjuvant Chemoradiotherapy for Esophageal Squamous Cell Carcinoma Versus Definitive Chemoradiotherapy With Salvage Surgery as Needed trial, which has an expected completion date of 2031 (61). Additionally, individuals receiving definitive chemoradiation who did not have an esophagectomy within 6 months of chemoradiation but did shortly after (eg, 6 months and 1 day) were misclassified as definitive chemoradiation. However, a time-point had to be chosen to distinguish between trimodal therapy and an unplanned salvage esophagectomy.

In conclusion, our study suggests that esophagectomy after chemoradiation confers a survival advantage for older adults with locally advanced esophageal cancer, though the benefit is smaller than previously reported and should be interpreted with nuance. The 5-year mortality risk reduction of 12% was not dramatic, especially considering the potential quality-of-life benefits with an organ-preserving approach and increased risk of functional adverse events after resection. Additionally, the mortality reduction reported may be overestimated, as patients with tumor biology favorable for resection may more likely be offered surgery. While the results of randomized trials such as the Neoadjuvant Chemoradiotherapy for Esophageal Squamous Cell Carcinoma Versus Definitive Chemoradiotherapy With Salvage Surgery as Needed are awaited, the findings of our observational study merit consideration by older patients and their providers when discussing care plans and can enhance shared decision making and optimize patient outcomes.

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Data Availability

Data from the SEER-Medicare–linked database are available through application to the National Cancer Institute and a data use agreement.

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