THE COMPARATIVE EFFECTIVENESS OF TRIMODAL THERAPY VERSUS DEFINITIVE CHEMORADIATION IN OLDER ADULTS WITH LOCALLY ADVANCED ESOPHAGEAL CANCER

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A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology in the Gillings School of Global Public Health.

Chapel Hill
2022

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ABSTRACT

Charles Earle Gaber: The Comparative Effectiveness of Trimodal Therapy Versus Definitive Chemoradiation in Older Adults with Locally Advanced Esophageal Cancer
(Under the direction of Jennifer L. Lund)

Esophageal cancer has a poor prognosis. For locally advanced tumors, neoadjuvant chemoradiation followed by esophagectomy (trimodal therapy) and definitive chemoradiation are both endorsed by clinical practice guidelines. The existing evidence describing the use and comparative effectiveness of these therapies in older adults is out-of-date and impacted by strong bias. To address these limitations, our aims were to, in a population of older adults with locally advanced esophageal cancer, (1) describe temporal trends in, and factors related to, treatment receipt and (2) assess the comparative effectiveness and harms of trimodal therapy compared to definitive chemoradiation.

We conducted two cohort studies using the Surveillance Epidemiology and End Results (SEER) cancer registry linked with Medicare administrative claims. In the first study, we found that the use of trimodal therapy increased from 2004 to 2017 for adenocarcinomas (annual percent change = 8.2; 95% CI: 4.8 – 11.7) and was stable for squamous cell carcinomas (annual percent change = 0.4; 95% CI: -4.1 – 5.1). Definitive chemoradiation increased during this time and became the dominant treatment strategy. Use of trimodal therapy decreased with increasing age, comorbidity burden, and frailty across both histologic subtypes. Use of carboplatin-based chemoradiation regimens increased over time, largely replacing cisplatin-based regimens. In the second study, we found that trimodal therapy decreased the risk of five-year overall mortality for adenocarcinomas (Risk Ratio (RR) = 0.88; 95% CI: 0.82 – 0.95) and squamous cell carcinomas (RR= 0.87; 95% CI: 0.70 – 1.01). Similar effect estimates were seen

for cancer-specific mortality. However, trimodal therapy was found to increase the one-year cumulative incidence of functional adverse events for adenocarcinomas (RR= 1.40; 95% CI: 1.22 – 1.65) and squamous cell carcinomas (RR= 1.21; 95% CI: 1.00 – 1.49). Trimodal therapy was associated with about 165 added healthy days at home over a five-year span compared to definitive chemoradiation.

In conclusion, the majority of older adults with locally advanced esophageal cancer receive definitive chemoradiation. Trimodal therapy is associated with longer survival, but the benefits are smaller than prior studies suggest. Given this benefit-risk profile and patient preferences, definitive chemoradiation may be appropriate for many in this population.

Dedicated to my wife, Jennifer Gaber, a truly brilliant and kind person whose support is found in every page that follows.

ACKNOWLEDGEMENTS

I would like to begin by thanking my dissertation committee. Assembling and working with this team of experts has been the greatest professional privilege of my career. I am grateful for the wisdom, guidance, and encouragement of Nick Shaheen, Bob Sandler, Jess Edwards, Hazel Nichols, and my advisor and dissertation chair, Jenny Lund. In August 2020, Nick Shaheen generously met with me to discuss my broad interest in gastrointestinal cancers. What came out of our discussion was an exciting doctoral dissertation idea that I would run with for the next 18 months. Nick has provided encouragement and direction throughout this project. Over the years, Bob has offered comprehensive mentorship on everything from identifying sound scientific questions and writing with intention, to formulating a long-term plan as a researcher. He is a stellar mentor whose dedication to developing young investigators is extraordinary. Jess has had a profound impact on my methodologic training as an epidemiologist. Jess taught me to break down complex analytic tasks into their component parts and how to embrace the journey of learning new epidemiologic methods. Hazel has fostered my development as a cancer researcher both through her cancer outcomes course and guidance during this dissertation. Hazel has consistently helped me maintain my focus on generating interpretable, impactful research for cancer patients—the lives behind the data. Lastly, over the past 5 years, my advisor Jenny Lund has been a pivotal force in shaping my professional life. I believe that identifying and emulating role models can be transformative. I cannot think of a better role model than Jenny. She helped me develop not only as a scholar, but also as a person. Jenny encourages students, teaches us to have confidence and persistence when learning new research methods, and emphasizes personal well-being. She cares deeply about the academic success of her students and has always been available and happy to offer

guidance and support. Jenny accomplishes this all while conducting rigorous pharmacoepidemiologic research that has shaped our field. Her mentorship has meant the world to me.

I would additionally like to thank my funding sources that have supported me throughout my career as a doctoral student. In my first two years of the program, I was supported by the Department of Surgery through a Research Assistantship with Jen-Jen Yeh and Paula Strassle. It was in this role that I benefited immensely from the close instruction and mentorship of Paula. From the summer of 2019 to date, I have been funded by the NIH T32 Digestive Disease Epidemiology training grant (NIH T32DK007634). Bob Sandler brought me on as a trainee and it has offered me financial support and crucial opportunities for academic development through multiple projects, including the doctoral dissertation.

Beyond the committee membership, numerous individuals at UNC have contributed to either the success of this dissertation or my growth as a scholar. Alan Kinlaw has been monumental in encouraging my passion for pharmacoepidemiology and helping me navigate the complexities involved in producing high quality work. He is a wonderful mentor and friend. Anne Peery and Evan Dellon were instrumental in providing research opportunities and mentorship through our work on diverticulitis and achalasia. They encompass the spirit of team science in their collaborations. Hanna Sanoff offered crucial clinical context that shaped dissertation study design decisions. I'd also like to thank the Lund research group, whose past and current membership has always been supportive and felt like a family. The clone-censor-weight working group of Emilie Duchesneau, Jeff Yang, and Rachael Ross helped me hurdle the most analytically challenging piece of this dissertation. Thank you to the Department of Epidemiology for your stellar instruction and collaborative environment. Over the years, Virginia Pate and Sharon Peacock-Hinton were incredibly helpful, patient, and generous when it came to teaching me SAS coding techniques. I would like to acknowledge the tireless efforts of Valerie Hudock, Lena Hudock, and Jennifer Moore whom all have provided critical assistance

coordinating and managing academic and administrative aspects of life as a student in the department.

I would like to extend my heartfelt gratitude to my family and friends out of state who have been a steady source of encouragement from afar. My parents, Rick and Patty, have supported me my entire life. I have been able to count on them for words of wisdom whenever I needed it. Their genuine care for each other and dedication to making the world a kinder place inspire me every day. My parents taught me that challenging pursuits are often the most worthwhile. I would also like to thank Rikki, Sean, Vivienne, Genevieve, Kathy, Joe, Joseph, Marie, and Roni. You visited us in North Carolina, opened your homes to us, and celebrated reaching PhD program milestones. Your love and generosity was felt from many states away.

Finally, none of the work presented herein could have been accomplished without the unwavering support of my dear wife and best friend, Jen Gaber. The rigors of this program have led to professional growth and a deeper passion for epidemiology, but have also naturally presented challenges, stress, and moments of doubt. When these occurred, it was Jen's helping hand that pulled me up. She encouraged me to press on and believe in myself. She is a compassionate and strong person who opens her heart and brilliant mind to everyone. Our conversations, serious and silly, sustained me throughout the marathon that is a PhD program. As did our walks together with Willow. I cannot imagine a better partner to have in life.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AAPC	Average annual percent change
AJCC	American Joint Committee on Cancer
APC	Annual percent change
ASCO	American Society of Clinical Oncology
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
CROSS	Chemoradiotherapy for Esophageal Cancer Followed by Surgery Study
ECOG	Eastern Cooperative Oncology Group
EGJ	Esophagogastric junction
ESMO	European Society of Medical Oncology
FFCD	Federation Francophone de Cancerologie Digestive
GERD	Gastroesophageal reflux disease
HCPCS	Healthcare Common Procedure Coding System
HR	Hazard ratio
HRQL	Health-related quality of life
ICD	International Classification of Diseases
IPCW	Inverse probability of censoring weight
MCCD	Mean cumulative count difference

MCCR	Mean cumulative count ratio
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Database
NCI	National Cancer Institute
OR	Odds ratio
PCR	Pathologic complete response
RCT	Randomized clinical trial
RD	Risk difference
RR	Risk ratio
SEER	Surveillance Epidemiology and End Results
SMD	Standardized mean difference
TNM	Tumor, Node, Metastasis
US	United States

CHAPTER 1 – SPECIFIC AIMS

1.1 Specific Aims

Esophageal cancer is a lethal malignancy with a five-year survival rate of 18%.[1] In the United States (US), esophageal cancer is a significant contributor to cancer-related mortality, causing over 15,500 deaths annually.[2] At diagnosis, most patients already have locally advanced or metastatic disease. Clinical treatment guidelines have endorsed neoadjuvant chemoradiation followed by surgery (trimodal therapy) as the standard of care for patients with locally advanced esophageal cancer.[3,4] These guidelines were influenced by the results of the ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) randomized clinical trial (RCT), which demonstrated increased survival in patients receiving trimodal therapy compared to surgery alone.[5,6] However, this trial had strict eligibility criteria and a younger patient population, hindering the generalizability of results to older adults. Moreover, the reference group of surgery alone is less relevant to older adults with locally advanced disease. Older adults have a higher burden of comorbidity and frailty than younger adults. Consequently, many older patients may receive definitive chemoradiation, forgoing resection. For the older adult population, clinical decision making for therapies with curative intent is primarily concerned with whether to include surgery in treatment or opt for definitive chemoradiation. Randomized evidence considering this comparison is scant and the current observational comparative effectiveness research lacks methodologic rigor.

It is unknown if practice patterns for older adults have changed over the past two decades and how receipt of trimodal therapy is distributed across patient-level factors. Additionally, amongst older adults who *are* surgical candidates, the comparative effectiveness and harms of trimodal therapy compared to definitive chemoradiation are poorly characterized.

The lack of clarity regarding comparative effectiveness of these two treatment modalities for older adults is meaningful, given that, in the general US population, the median age at diagnosis of esophageal cancer is 68 years.[7] The following specific aims will address these uncertainties using data from the Surveillance Epidemiology and End Results (SEER) cancer registries linked with administrative claims and enrollment data from the Medicare program.

1.1.1 Specific Aim 1

Aim: Describe temporal trends in, and factors related to, treatment receipt amongst a population of older adults with incident locally advanced esophageal cancer. To accomplish this aim, three objectives will be met. The first objective is to report calendar year trends in the annual age-standardized percentage of individuals receiving trimodal therapy, definitive chemoradiation, surgery alone or other surgery-based multimodal therapy, palliative treatment, and no treatment from 2004-2017. The second objective is to describe the distribution of treatment receipt according to individual-level demographic and clinical characteristics using bivariate statistics and descriptive measures of association. The third objective is to, among the subpopulation receiving either definitive chemoradiation or trimodal therapy, characterize temporal trends in the use of specific chemotherapy regimens, including cisplatin-based, carboplatin-based, and other chemotherapeutic regimens.

1.1.2 Specific Aim 2

Aim: Assess the comparative effectiveness and harms of trimodal therapy compared to definitive chemoradiation in a population of older adults with locally advanced esophageal cancer. To accomplish this aim, four objectives will be met. The first and second objectives are to estimate the effect of trimodal therapy compared to definitive chemoradiation on the five-year cumulative incidence of overall mortality and esophageal cancer-specific mortality, respectively. The third objective is to estimate the effect of trimodal therapy compared to definitive

chemoradiation on the one-year cumulative incidence of functional adverse events. The fourth objective is to estimate the effect of trimodal therapy compared to definitive chemoradiation on the five-year mean cumulative count of healthy days at home, a novel metric quantifying time spent alive but not hospitalized or receiving intensive health care services.

1.1.3 Hypotheses

For the first aim, we hypothesize that trimodal therapy increased over the past two decades, but that definitive chemoradiation will remain the dominant treatment strategy in this population. For the second aim, we hypothesize that trimodal therapy will have a beneficial effect on overall and cause-specific mortality compared to definitive chemoradiation. However, due to prior studies suffering from immortal times bias that conferred an artificial advantage to trimodal therapy, and our explicit focus on an older adult target population, we expect that the gains from trimodal therapy will be meaningfully smaller in our work than previously stated. We additionally hypothesize that individuals treated with trimodal therapy will have a higher one-year risk of functional adverse events and fewer healthy days at home over five-years compared to individuals treated with definitive chemoradiation. In tandem with the small survival benefits, these harms from surgery may position definitive chemoradiation near a place of non-inferiority for clinical decision making.

1.1.4 Rationale and Public Health Impact

This research will impact clinical practice and public health. Older adults are frequently excluded from oncology trials, creating uncertainty regarding the use and effectiveness of treatment strategies in this medically complex population. Quantitatively assessing practice patterns, deploying modern bias-reducing epidemiologic methods, and evaluating a range of outcomes specifically relevant to older adults will provide a richer characterization of the comparative effectiveness and harms of trimodal therapy and definitive chemoradiation. The

generation of evidence tailored to older adults is harmonious with the national imperative of delivering patient-centered, evidence-based medicine.

CHAPTER 2 – REVIEW OF THE LITERATURE

2.1 Overview

The US population is rapidly aging. Demographic data suggest that by 2040 there will be nearly 80 million Americans 65 years of age or older, representing 20% of the total population.[8] The incidence of esophageal cancer increases with advancing age and the median age at diagnosis is 68 years.[9] Thus, the national number of adults diagnosed with esophageal cancer is expected to dramatically increase—a phenomenon that, across malignancies, has been termed the "survivorship tsunami".[10,11] This wave is particularly concerning given that the most appropriate treatment for older adults with esophageal cancer is obfuscated by lack of representation in clinical trials. Older adults have a greater burden of comorbidities, comedications, and frailty compared to younger oncology trial populations. These features complicate clinical decision making for this population faced with a poor prognosis cancer. Herein, an orientation is provided to the clinical aspects (section 2.2) and public health impact of esophageal cancer (section 2.3). To close the chapter, the current state of the literature is presented regarding treatment patterns and the comparative effectiveness of trimodal therapy versus definitive chemoradiation for older adults with locally advanced esophageal cancer (section 2.4).

2.2 Clinical Aspects of Esophageal Cancer

2.2.1 Anatomy of the Esophagus and Esophageal Cancer Biology

Esophageal cancer is an aggressive gastrointestinal malignancy with the primary site of the tumor originating in the esophagus, the muscular tube responsible for movement of food from the pharynx to the stomach. The esophagus extends from the upper esophageal sphincter

to the esophagogastric junction (EGJ), with zones from top to bottom consisting of the cervical esophagus, thoracic, and abdominal esophagus.[12] Cross-sectionally, the esophageal wall is composed of four layers of tissue: mucosa (innermost), submucosa, muscularis propria, and the adventitia.[13] As esophageal tumors grow, they start from the mucosa and penetrate deeper into the subsequent layers, with possible metastasis to other tissues and organs. Esophageal cancer is a carcinoma with two distinct histologic subtypes that classify the cancer according to the type of cell from which the tumor originated: esophageal squamous cell carcinoma and esophageal adenocarcinoma. Squamous cell carcinomas arise from the epithelial squamous cells that line the mucosal layer of the esophagus. These tumors typically present in the upper, proximal regions of the esophagus.[12,14] In contrast, adenocarcinomas arise from the glandular goblet cells that form on the esophagus after the occurrence of intestinal metaplasia characteristic of Barrett's esophagus. Adenocarcinomas typically present in the lower, distal region of the esophagus.

2.2.2 Diagnosis and Staging of Locally Advanced Esophageal Cancer

Esophageal cancer is typically diagnosed via endoscopy and biopsy in patients experiencing difficulty swallowing (dysphagia), unexpected weight loss, or gastric bleeding.[15] In endoscopy, a narrow tube is inserted into the esophagus, allowing the gastroenterologist to view the lining of the organ and biopsy any abnormal tissue. Pathologists examine the biopsied cells microscopically and determine whether there is cancer, and, if present, the histologic subtype of cancer. This pathologic confirmation of malignancy is referred to as a histologically confirmed diagnosis and is crucial to accurately staging the cancer and planning appropriate treatment. Stage is a measurement of how advanced the cancer is and carries important information for prognosis and treatment options. Stage can be assessed clinically and pathologically (also known as anatomic stage). Clinical stage is determined before treatment has been initiated and reflects the results of endoscopy and biopsy as well as radiologic imaging. Imaging typically

consists of computed tomography and positron emission tomography scans, which help determine the depth of tumor growth locally and whether the tumor has spread to other regional and distant locations in the body. The pathologic stage is determined by examining the resected surgical specimen and any lymph nodes that were removed during surgery—if surgery was part of the treatment course. The added information from anatomic examination of the removed specimen includes a more accurate look at lymph node involvement and depth of the tumor growth. Thus, it is possible if not probable for clinical stage to differ from pathologic stage, with both upstaging (pathologic stage worse than clinical stage) and downstaging (pathologic stage better than clinical stage) occurring in some patients. Downstaging can occur with inaccurate clinical assessment but may also be the result of pre-surgical therapy having an intended beneficial impact on decreasing tumor burden through shrinking the tumor and removing cancerous tissue on lymph nodes.

In the US, cancer stage is determined using the Tumor, Node, and Metastasis (TNM) classification scheme of the American Joint Committee on Cancer (AJCC). T (“tumor”) staging determines the size of the primary tumor and the extent to which it has spread into the four layers of the esophagus. N (“node”) staging focuses on ascertaining the degree to which the tumors has spread to nearby and distant lymph nodes. M (“metastasis”) staging assigns a value of 0 if the tumor has not spread to other organs, and a 1 if it has metastasized. Intuitively, smaller tumors with few or no spread to lymph nodes that have not metastasized carry a more favorable prognosis. The T, N, and M characteristics of the tumor can be used collectively to classify the cancer into *stage groups* I through IV according to the AJCC staging manual. How the TNM characteristics map to stage groups varies across histologic subtypes and depends on what edition of the AJCC staging manual is used. Due to this variation, construction of stage groups across years of data that use different AJCC editions should be re-built using the individual TNM components to a common edition across years. Tumor grade refers to the extent to which the cancer cells appear abnormal in their shape and formation compared to normal,

healthy cells using microscopy. High grade tumors are expected to grow and spread at a faster rate than low grade tumors. Lastly, tumor behavior indicates whether the growth is benign or malignant.

Locally advanced cancers, the subject of our work, are intermediate tumors in which there has been cancerous growth extending to regional tissue and/or lymph nodes. However, these tumors have not yet metastasized to other organs and do not classify as distant disease. In practice, exactly what constitutes a locally advanced tumor varies by individual clinician, institution, professional society, and country. Our work used the definition provided by current treatment guidelines from the American Society of Clinical Oncology (ASCO), which defines locally advanced cancer as M0 tumors with at least either ≥T2 or ≥N1.[4] For both ACs and SCCs, this corresponds to AJCC 7th edition stage groupings of IB, IIA, IIB, IIIA, IIIB, and IIIC.

2.2.3 Treatment Strategies for Older Adults with Locally Advanced Esophageal Cancer

Older adults with locally advanced esophageal cancer may receive several different treatments, including definitive chemoradiation and neoadjuvant chemoradiation followed by surgery (trimodal therapy). Definitive chemoradiation therapy entails receipt of chemotherapy and concurrent radiation without any planned surgical resection afterward. Typically, multiple chemotherapeutic agents are used; cisplatin and 5-fluorouracil or carboplatin and paclitaxel are common chemotherapy regimens. This modality is used by more than 73% of older adults with locally advanced cancers who receive any type of treatment, though the data is not contemporary (cases diagnosed between 2001-2009).[16] While definitive chemoradiation is an option for patients deemed not fit for surgery, it is also received by patients who decide to forgo surgery (even if eligible) or are not offered it by their providers. In trimodal therapy, patients are given chemotherapy with concurrent radiation treatment upfront, followed by planned esophagectomy within several months of completing chemoradiation. Esophagectomy is a major surgery involving removal of the tumor and surrounding portions of esophagus. Trimodal

therapy has, in the general population, become accepted as the most aggressive treatment associated with the highest five-year survival rates. This standard reflects the results of a landmark RCT (reviewed in depth in section 2.4) that demonstrated increased survival (49.4 months versus 24.0 months) in patients who receive trimodal therapy compared to surgery alone.[5,6] Clinical treatment guidelines from the National Comprehensive Cancer Network (NCCN), ASCO, and the European Society of Medical Oncology (ESMO) have all endorsed the use of multimodal therapy over surgery alone for locally advanced tumors of both histologic subtypes.[3,4,17] The use of trimodal therapy for locally advanced tumors is prominently featured in their evidence-based guidelines, although definitive chemoradiation is also considered a viable option in patients with squamous cell carcinomas, those who are not medically fit for surgery, and those who prefer not to undergo surgery.

Despite treatment guidelines favoring trimodal therapy, it is likely that most older adults do not receive this aggressive modality. Potential influences of treatment utilization patterns are explored further in section 2.2.4. This variation in real-world receipt of therapies allows for the estimation of treatment effects outside of the clinical trial setting that may help inform patient choice during the treatment decision making process.

2.2.4 Factors that Influence Treatment and Prognosis

An array of patient characteristics may simultaneously drive treatment decisions and survival outcomes, acting as confounders in comparative effectiveness studies estimating treatment effects. The patient-level factors consist of tumor, demographic, and clinical characteristics. Tumor characteristics encompass histologic subtype, grade, site, size, and clinical assessments of the extent of tumor invasion and nodal involvement. Demographic characteristics include age, sex, and race and ethnicity. Lastly, clinical characteristics include comorbidities and patient frailty. The common thread of these elements is that literature suggests they have a prognostic role in terms of overall survival, with many of these factors

additionally imbalanced in cohorts of trimodal therapy and definitive and chemoradiation patients. The current literature on these prognostic factors are reviewed in the subsections below.

Histologic subtype

Squamous cell carcinomas have a poorer prognosis compared to adenocarcinoma tumors. Analysis of SEER cancer registry data from 2004-2009 documented a 5-year cause-specific survival of 23.4% in adenocarcinomas and 18.9% in squamous cell carcinomas.[18] Other analyses of the SEER data in slightly different years have also documented lower survival in squamous cell carcinoma tumors.[19,20] While both trimodal therapy and definitive chemoradiation are used across histologic subtypes, population-based and institutional studies indicate squamous cell carcinomas are more likely to receive definitive chemoradiation.[21] In a National Cancer Database (NCDB) study comparing the two modalities, 82% of trimodal patients were adenocarcinomas, compared to 58.5% of definitive chemoradiation patients.[22] A separate NCDB analysis that exclusively examined treatments in patients at least 70 years of age found that patients with adenocarcinoma tumors were more likely to receive trimodal therapy (instead of definitive chemoradiation) than patients with squamous cell tumors (Odds Ratio (OR) = 2.10, 95% confidence interval (CI): 1.80 – 2.45).[23] With strong simultaneous influence on prognosis and treatment received, histology is a strong confounder that needs to be accounted for in comparative population studies either through statistical control or complete stratification of results by histologic subtype.

In addition to being a confounder of the treatment and survival relationship, histologic subtype may also be a strong effect measure modifier. The CROSS randomized trial found important heterogeneity in the effect of trimodal therapy by histologic subtype. While the trial had a different reference group (surgery alone), the heterogeneity has implications for the comparison of trimodal therapy versus definitive chemoradiation. The effect of trimodal therapy

versus surgery alone on overall mortality was markedly stronger in squamous cell carcinomas (Hazard Ratio (HR) = 0.42, 95% CI: 0.23 – 0.79) compared to adenocarcinomas (HR= 0.74, 95% CI: 0.54 – 1.02).[5] This heterogeneity translated into clinically important differences in survival benefit. In squamous cell carcinomas, the median overall survival was 81.6 months in the trimodal therapy arm and 21.1 months in the surgery alone group (survival benefit of 5 years). In adenocarcinomas, the median overall survival was 43.2 months in the trimodal therapy arm and 27.1 months in the surgery alone group (survival benefit of 16 months). Unfortunately, this subgroup analysis had low power, and despite the substantively different point estimates, the authors concluded there was no effect modification by histology because the interaction term was not significant. A randomized trial from Australia comparing surgery alone with trimodal therapy stratified results by histology and similarly found a stronger effect of trimodal therapy in squamous cell carcinomas (HR=0.69, 95% CI: 0.42 – 1.15) than adenocarcinomas (HR=1.04, 95% CI: 0.74 – 1.48).[24]

To the extent that squamous cell carcinomas have poorer prognosis, there may be greater room for treatment benefit from trimodal therapy over definitive chemoradiation. On the other hand, in the CROSS trial, tumor clinical response to chemoradiation was higher in squamous cell carcinomas (49%) compared to adenocarcinomas (23%). The higher response rates support the hypothesis that chemoradiation may reduce pre-surgery tumor burden to an extent where surgery may not be critical for squamous cell carcinomas; under this scenario, a smaller benefit of trimodal therapy would be observed amongst individuals diagnosed with squamous cell carcinomas.

Tumor Grade

High-grade, poorly-differentiated tumors are associated with decreased survival compared to low or moderate grade tumors in patients with esophageal cancer. A Mayo clinic study of 796 patients with adenocarcinomas followed up after surgical resection found that

compared to individuals with grade 1 or 2 tumors, those with grade 4 tumors had increased risk of overall-mortality (HR= 1.60, 95% CI: 1.19 – 2.16) and cancer-specific mortality (HR=1.64, 95% CI: 1.20 – 2.24) even after adjustment for other tumor prognostic measures.[25] This relationship holds in patients receiving chemoradiation prior to surgery. A retrospective cohort study of 238 patients receiving trimodal therapy examined predictors of one-year mortality and found that 23% of patients with high grade tumors died within one year of treatment compared to only 8% of those with low to moderate grade tumors.[26] The association stood in multivariate modeling, with a HR of 2.67 (95% CI: 1.14 – 6.21) comparing poorly differentiated to low-grade tumors. A propensity-matched cohort study comparing survival in patients receiving trimodal therapy versus definitive chemoradiation found that prior to matching, 42% of definitive chemoradiation patients had poorly differentiated tumors compared to only 33% of trimodal therapy patients, suggesting the presence of a relationship between grade and elected treatment modality.[27]

Tumor locations

Esophageal cancers can develop anywhere within the length of the esophagus. Studies have found that the specific anatomic site of the tumor—the topography—is associated with cancer prognosis. Tumors that begin in the distal, lower third of the esophagus typically have worse prognosis than those in higher portions of the organ. A survival analysis of SEER data found that patients with localized tumors originating in the lower one-third had increased mortality (HR=1.55, 95% CI: 1.24 – 1.93) compared to those with cervical or upper two-thirds thoracic tumors.[28] A retrospective study of 130 patients with locally advanced tumors found that 60% of trimodal therapy patients had tumors in the lower third of the esophagus, compared to 33% of definitive chemoradiation patients.[29] Thus, tumor topography may be a factor that channels patients towards or away from trimodal therapy. However, it is difficult to disentangle prognostic impacts of histology from tumor location as adenocarcinomas typically originate in

the lower esophagus. This treatment channeling impact of tumor location requires further exploration in a large, national US cohort.

Tumor size

Multiple institutional and database observational studies have reported an association between tumor length and prognosis, with larger tumors resulting in lower patient survival. A cohort study of 113 esophageal cancer patients who underwent surgery investigated the prognostic role of tumor length, independent of the well-known TNM criteria. Tumors that were >3 cm in length had worse disease-free survival (HR=2.88, 95% CI: 1.39 – 2.98) compared to those <3 cm.[30] Other studies have reported a similar association. In a cohort of 309 patients who received surgical resection, median survival of patients with tumors ≤ 3.5 cm was 30 months (95% CI: 19.4 – 40.6) compared to 14 months (95% CI: 11.7 – 16.3) in those with tumors > 3.5 cm, with a corresponding HR of 1.41 (95% CI: 1.04 – 1.90) in a multivariate Cox model.[31] Quantitatively similar results were reported from a cohort study of 244 squamous cell carcinoma patients in Taiwan undergoing resection, with diagnosis of tumors > 4 cm associated with an increased risk of all-cause mortality (HR= 1.82, 95% CI: 1.18 – 2.79) compared to tumors ≤ 4 cm.[32]

Extent of tumor invasion

The depth of tumor invasion at the primary site of the lesion is associated with prognosis. Tumors that display more extensive tissue invasion are associated with worse prognosis. This association is unsurprising given that extent of invasion is the “T” characteristic of the AJCC TNM staging system, which is designed to be prognostically informative. Multiple observational studies have compared the survival of patients according to their T status with simultaneous adjustment for other tumor features and patient clinical characteristics. In the Mayo clinic cohort, compared to patients with T1 tumors, patients with T2 (HR=1.63 , 95% CI:

1.10 – 2.43) and T3 or T4 (HR= 1.83 , 95% CI: 1.25 – 2.66) tumors had worse overall survival.[25] Substantively similar HR point estimates were reported in the cohort study of squamous cell carcinoma patients in Taiwan, though precision was lower.[32] An institutional cohort study reported higher percentage of T4 cancers in definitive chemoradiation patients (27.4%) than trimodal therapy patients (11.9%),[33] although an analysis of NCDB data restricted to cases with T1-T3 clinical T stage found more trimodal patients had T3 (74%) tumors than did definitive chemoradiation patients (65%).[34]

Nodal involvement

Regional lymph node involvement is an additional TNM staging characteristic ("N") that is expectedly associated with prognosis. As the number of positive regional lymph nodes increases, survival worsens. In the Mayo clinic cohort, compared to patients with N0 tumors, patients with N1 (HR= 2.78, 95% CI: 2.05 – 3.77), N2 (HR= 4.49, 95% CI: 3.30 – 6.09), or N3 (HR=5.94, 95% CI: 4.26 – 8.27) tumors had worse cancer-specific survival.[25] In a cohort of 116 patients in Turkey who underwent esophagectomy, the five-year survival of patients with N0 tumors was 45% compared to only 15% and 6% in patients with N2 and N3 tumors, respectively.[30]

Age

Patients with more advanced age at diagnosis of esophageal cancer have worse prognosis in terms of overall survival. This is empirically confirmed in several of the same studies that examined tumor characteristics associated with prognosis. The Mayo Clinic cohort found that patients >76 years of age had an increased risk of overall mortality (HR=1.64, 95% CI: 1.27 – 2.12) compared to those ≤ 76 years of age.[25] In the cohort based in Taiwan, a one-year increase in age had a HR of 1.03 (95% CI: 1.01 – 1.04; converting to 10 year age increase the HR=1.28).[32] In the United Kingdom study of 309 EC patients, patients younger than 65 had

a median survival of 30 months (95% CI: 22.1 – 37.9), whereas those ≥ 65 years had a median survival of 14 months (95% CI: 9.1 – 18.9). Age is also a strong predictor of treatment received, with advanced age patients being less likely to receive aggressive trimodal therapy. A SEER-Medicare cohort of EC cases from 2004-2013 found that compared to individuals aged 66-69, adults aged 70-74 (Odds ratio (OR)= 0.63, 95% CI: 0.49 – 0.80), 75-79 (OR=0.43, 95% CI: 0.33 – 0.57), and 80+ (OR=0.09, 95% CI: 0.06 – 0.13) were less likely to receive trimodal therapy.[35] In real-world settings, there is likely substantial variation across providers in how age is factored into treatment recommendations. Chronological age and functional age are not synonymous, and studies demonstrating high survival after trimodal therapy in selected older adults have challenged the notion that chronological age alone should be a contraindication for surgery.[36–42]

Sex

While male sex is a well-known risk factor for development of esophageal cancer, the prognostic influence of sex conditional on diagnosis of cancer is less established. The common theme in the existing literature is that female sex is likely associated with longer survival, but poor precision due to small number of female patients in esophageal cancer cohorts limits the conclusions that can be drawn. For instance, in the Mayo clinic cohort female sex was associated with decreased risk of overall mortality in univariate analysis (HR= 0.82, 95% CI: 0.62 – 1.09).[25] A stronger association (using a male reference group) was demonstrated in the Taiwanese cohort study, as male sex was associated with increased overall mortality (HR= 1.84, 95% CI: 0.85 – 3.95).[32] Importantly, both studies had imprecise estimates with confidence intervals compatible with a null effect of sex on survival. The SEER-Medicare study of cases from 2004-2013 found that 34.3% of men received induction therapy and surgery compared to 20.9% of women.[35] Other cohorts have also demonstrated undertreatment in women compared to men.[16]

Comorbidities

A higher comorbidity burden is associated with greater risk of mortality in esophageal cancer patients. Marked survival differences are observed according to comorbidity burden, despite esophageal cancer being considered a uniformly poor prognosis malignancy. A nationwide retrospective cohort study of esophageal cancer patients diagnosed between 1990-2013 using data form the Swedish Cancer Registry found that patients with 2 comorbidities or greater at the time of their surgery had higher 5-year overall mortality compared to those with no comorbidities (HR= 1.27, 95% CI: 1.15 – 1.40).[43] A cohort study of 122 patients in Japan who underwent esophagectomy found that patients in the lowest age-adjusted Charlson comorbidity index category had a three year survival of 64.2%, while those in the highest category had a three-year survival rate of 42.3%.[44] In multivariable analysis, the hazard ratio was 1.93 (95% CI: 1.13 – 3.31). Studies of US populations have yielded similar findings, with an NCDB analysis of esophageal patients reporting an overall mortality HR of 1.26 (95% CI: 1.08 – 1.47) comparing patients with a Charlson-Deyo score of 2 or greater to those with a score of zero.[45] Differences in survival by comorbidity likely reflect that those with a higher comorbidity burden are less likely to receive aggressive treatment and are more likely to experience complications and recurrences post-surgery.[46] In a study of SEER-Medicare data, patients with a Charlson Comorbidity Index score of 2 or greater had odds of receiving treatment that were 60% lower than patients with a Charlson score of 0 (OR= 0.40, 95% CI: 0.33 – 0.49).[16]

Performance-status

In geriatric oncology populations, clinically assessed performance status is highly associated with overall survival. A single institution study of 238 patients who received trimodal therapy examined prognostic markers of survival and observed that 25% of patients with a higher (worse) performance status score died within one year compared to only 11% of patients with a performance score of 0 (multivariable adjusted HR= 2.19, 95% CI: 1.02 – 4.69).[26] In a

cohort study of patients with locally advanced esophageal cancer receiving definitive chemoradiation, patients with an Eastern Cooperative Oncology Group (ECOG) score of 2 (more difficulty independently functioning) had increased risk of overall mortality (HR= 1.73, 95% CI: 1.19 – 2.52) compared to those with an ECOG score of 0 or 1.[47] Institutional clinical cohort studies that have access to data on patient performance status have demonstrated that patients with worse performance status are less likely to receive trimodal therapy.[29] To date, studies have not examined the relationship between frailty, treatment selection, and outcomes in locally advanced esophageal cancer. Frailty measurement encompasses a broader range of functional health than performance status.

2.3 Public Health Impact of Esophageal Cancer in the US Older Adult Population

2.3.1 Incidence and Mortality Rates of Esophageal Cancer

Esophageal cancer incidence and mortality rates rise precipitously with advancing age. Figure 2.1 displays the incidence and mortality rates according to five year age increments using data and visuals from the SEER program.[48] Diagnosis of esophageal cancer is exceedingly rare in young adults; however, by age 65-69, the incidence rate is 17.7 cases per 100,000 individuals. The increasing incidence rate continues within the 65+ population, with an incidence rate of 22.1, 24.0, and 26.2 in adults 70-74, 75-79, and 80-84 years of age, respectively. The esophageal cancer mortality rate increases with advancing age. The mortality rate is 15.3 deaths per 100,000 adults 65-69 years of age, and increases to 19.3, 22.6, and 26.3 in those 70-74, 75-79, and 80-84 years of age, respectively. In the US, there are projected to be 19,260 new cases of esophageal cancer and 15,530 esophageal-cancer attributable deaths in 2021, making it the sixth most common cause of cancer-related death and responsible for 2.7% of all cancer deaths.[2]

The US population is rapidly aging, and the expected cancer burden will grow correspondingly. Demographic data estimate that by 2040 over 20% of the population will be 65

years of age or older.[8] Given that the esophageal cancer burden dramatically increases over the lifespan, the national number of adults diagnosed with malignancy is logically expected to markedly increase.[10] Projections derived from a pairing of SEER incidence trend data and US Census Bureau population estimates suggest that older adults will represent 70% of all cancers diagnosed in 2030 and that poor prognosis cancers will have the largest relative increase in mortality.[49] Even when taking demographic transition into account, age-standardized rates demonstrate that esophageal cancer incidence in older adults has risen steadily over the past four decades, with distinct trends emerging by histologic subtype.[50] Since the 1970s, esophageal adenocarcinoma has the fastest growing incidence of all malignancies in US.[51] The incidence of adenocarcinoma surpassed squamous cell carcinoma in the late 1990s. These underlying trends have been attributed to a decrease in smoking (a strong risk factor for squamous cell carcinoma) and an increase in obesity, gastroesophageal reflux disease (GERD), and Barrett's esophagus (strong risk factors for adenocarcinoma).[52] The growing burden of esophageal cancer in older adults will necessitate comparative effectiveness research to elucidate optimal treatment strategies for this large and medically complex population that is chronically underrepresented in clinical trials.

2.3.2 Post-Diagnosis Survival

Esophageal cancer has a dismal prognosis because most older adults are diagnosed with advanced disease. At diagnosis, 31.5% of cancers are regional and 32.2% are distant among adults 65 years of age and older.[50] The five-year survival rate drops abruptly with increasing stage of cancer: localized tumors are associated with a 47.1% five-year survival rate, whereas survival is substantially lower for regional (25.2%) and distant (4.9%) tumors. Contributing to the advanced stage distribution is the fact that no accepted routine screening modalities exist for esophageal cancer that would facilitate early detection in the general population. When the tumor has already spread to lymph nodes, nearby tissues, and other

organs of the body, treatment options are limited and focus mainly on improving survival as opposed to absolute cure or restoration of pre-cancer life expectancy. Older adults have worse prognosis compared to younger patients: patients 75 and older have a 12.4% five-year survival rate compared to 20.0% in patients aged 50-64 (Figure 2.2).[50] Relative survival, also known as net cancer survival, is a statistic that eliminates the influence of non-cancer "competing" causes of death by calculating the overall survival for cancer patients relative to overall survival for a population without cancer without relying explicitly on cause-of-death records.[53,54] Esophageal cancer has a relative survival rate of 20%; only pancreatic cancer (9%) has a substantively lower rate.[55]

2.3.3 Treatment-Related Decreases in Health Related Quality of Life

Esophagectomy is a major surgical procedure with considerable morbidity and mortality risks that are heightened in older adults. It is common for esophagectomy patients to experience anastomotic complications and dysphagia, with 35%-45% of patients requiring a subsequent endoscopic dilation; other treatment sequalae include aspiration pneumonia, esophageal stricture, and psychological distress.[56–63] Due to the complexity and invasiveness of the procedure, the overall operative mortality rate is 4%, though low-volume centers have been associated with rates as high as 20%.[64,65] An analysis of Medicare patients with non-metastatic cancers who received esophagectomy reported that 30% of patients had a hospitalization or adverse event within two months of the procedure and 4% of patients died within this short-term window.[64] A cohort study of patients undergoing esophagectomy using the National Inpatient Sample demonstrated sharp increases in the operative mortality rate as the age of the patient increased (1.5% in those 40 years old to 7.0% in those 80-years-old).[66] Patient age ≥70 was associated with a higher probability of inpatient mortality compared to age <70 (OR=1.84, 95% CI: 1.39, 2.45), along with higher probability of postoperative renal failure, cardiac failure, respiratory failure, and length of stay.

The side effects, complications, and adverse events from cancer and treatment are damaging to health-related quality of life (HRQL) in older adults. Several studies have documented that treatment-related adverse effects from esophagectomy decrease HRQL. Importantly, these decrements to HRQL are placed on top of an already lowered HRQL due to underlying cancer symptoms, diagnostic workup, and chemoradiation. Given that most esophageal cancers are diagnosed symptomatically, patients are often dealing with a high symptom burden at diagnosis including dysphagia, regurgitation, fatigue, and weight loss.[67] Several studies have demonstrated that health-related quality of life (HRQL) is already low at the time of diagnosis for many esophageal cancer patients, as these symptoms erode patient functioning and wellbeing.[67–69] The diagnostic phase also places significant burden on patients who undergo a litany of imaging and staging procedures before eventually being diagnosed with a poor-prognosis cancer.[70] The post-diagnosis, pre-treatment prevalence of anxiety and depression is high, with one cross-sectional study reporting that 34% of esophageal patients had probable anxiety or depression.[71] Additional drops in HRQL due to adding surgery to the treatment plan have clinical implications. In older patients for whom the expected benefit of trimodal therapy is small, nonexistent, or even harmful, the potential exists to avoid decreases in HRQL by forgoing surgery and electing to be treated with definitive chemoradiation. Thus, the decision to elect trimodal therapy over definitive chemoradiation has critical ramifications for patient well-being. Currently, comparative effectiveness research contrasting outcomes in these modalities have strong limitations (detailed in section 2.4).

2.3.4 Costs Attributed to Esophageal Cancer

The economic impacts of esophageal cancer on the patient and health care system are substantial. From the societal perspective, the total national direct cost of esophageal cancer care in the US exceeded $1.3 billion in 2010.[72] Given the increasing incidence of esophageal cancer and the intensive treatment options, national costs are expected to increase

substantially. At the patient level, health care costs depend on stage of disease and phase of care. A cohort study of older adults conducted in the SEER-Medicare database of esophageal cancer cases diagnosed between 1998-2013 estimated the costs of care stratified by stage of disease and phase of care.[73] The highest monthly cost was during the terminal phase six months prior to death, at $18,150 ($1,433 in patient liability costs). The staging ($8,953 total) and initial treatment ($7,731 total) phases also carried substantial financial burden. Esophagectomy is a highly complex procedure and 51% of adults 65 years and older experience a complication after surgery, including intraoperative, pulmonary, wound, and systemic complications.[74] Surgical complications of cancer resections are expensive to the patient and healthcare system.[75] Given that older adults are more likely to experience complications from esophagectomy, they may incur higher costs post-operatively compared to younger esophageal cancer patients.

2.4 Current Treatment Practice and Critical Gaps in the Literature

2.4.1 Establishment of Trimodal Therapy as Standard of Care

Trimodal therapy has been established as the highest standard of care for locally advanced tumors; however, the RCTs endowing this superiority mostly excluded older adults and compared trimodal therapy to surgery alone instead of definitive chemoradiation.[5,6,24,76–86] In general, studies prior to the CROSS trial were small single-institution studies and only two were conducted in a US population. Seven (58%) of the twelve trials comparing trimodal therapy to surgery alone only enrolled one of the two main histologic subtypes of esophageal cancer. The limitations of these early trials include strict exclusion criteria, study drop-out,[79] low radiation doses in the trimodal arm not in line with contemporary practice,[78] and lack of exploration of heterogenous treatment effects according to patient characteristics such as age.

CROSS was a landmark phase III RCT conducted in the Netherlands that compared overall survival in patients with locally advanced esophageal cancer randomized to trimodal

therapy (n=178) with patients randomized to surgery alone (n=188).[5] Eligibility criteria included esophageal cancer patients aged 18-75 with either histologic subtype. Eligible patients were additionally required to have a WHO performance status of 2 or lower (out of 5, lower number denoting better performance status). Median overall survival was substantially higher in the neoadjuvant chemoradiation group (49.4 months) compared to surgery alone group (24.0 months) (HR= 0.66, 95% CI: 0.50, 0.87). CROSS was instrumental in demonstrating the potential advantage conferred by aggressive therapy. However, the mean age in the CROSS trial was 60, while the mean age at diagnosis of esophageal cancer is nearly 70.

In addition to its younger study population, CROSS's reference group of surgery alone now lacks relevance for the older adult population with locally advanced tumors. Surgery alone is no longer a recommended treatment modality for locally advanced esophageal cancer in any of the major treatment guidelines. For older adults, treatment uncertainty now centers around whether to include surgery via trimodal therapy or instead opt for definitive chemoradiation. Definitive chemoradiation is a recommended treatment for those not fit for surgery, but also those who do not want surgery. Guidelines additionally present definitive chemoradiation as a viable option for squamous cell carcinoma tumors, which are more sensitive (beneficially) to chemoradiation.

Older cancer patients have a higher burden of comorbidities, frailty, functional impairments, and concomitant medication use that complicate therapeutic decision making because these characteristics can negate many of the purported treatment benefits of surgery, especially when taking quality of life into account.[87–90] However, advanced age itself does not guarantee a negation of treatment benefit from trimodal therapy and should not be considered a universal contraindication for aggressive treatment.[42] Geriatric oncology has embraced the concept that chronological age is not synonymous with functional age and that decision making is best made considering individual characteristics.[91,92] The potential benefit of trimodal therapy is reflected in multiple clinical cohorts of older adults receiving trimodal therapy that, when

carefully selected for surgery, have experienced long-term survival similar to younger patients.[93] Thus, in the older adult population, there is considerable uncertainty surrounding the use of trimodal therapy and the average treatment effect compared to definitive chemoradiation.

2.4.2 Overview of the Critical Gaps in the Literature and Implications for Practice

While the results of CROSS were groundbreaking, important questions remain that require further investigation to optimize patient care in older adults. First, no existing studies have thoroughly documented patterns of care among older US adults with locally advanced esophageal cancer. It is unknown whether the CROSS results have impacted practice patterns in geriatric oncology, or what patient characteristics are associated with receipt of trimodal therapy. Any well-conducted comparative effectiveness study will require a detailed mapping of how concepts such as comorbidity burden and frailty may be channeling older patients away from aggressive trimodal therapy. The second gap is that existing randomized and observational studies that compare outcomes of trimodal therapy to definitive chemoradiation have strong methodologic flaws and are not comprehensive of outcomes relevant to the decision-making process of older adults. In the following two subsections (2.4.3 and 2.4.4) these gaps are discussed in further detail.

2.4.3 Patterns of Care in Older Adults Incompletely Described

There are no contemporary population-level estimates that quantify the patterns of care in older US adults diagnosed with locally advanced esophageal cancer. Correspondingly, it is uncertain whether the use of trimodal therapy has increased compared to other treatments and how treatment receipt is distributed across patient-level factors. Practice patterns may have shifted in the wake of the CROSS trial, potentially impacting not only the use of trimodal therapy but also the selection of specific chemotherapeutic agents used during chemoradiation.

Several database studies have examined treatment patterns, but mostly contain data from ten to twenty years ago. A SEER-Medicare study from an earlier era of care (cases diagnosed between 1992-2002) demonstrated that 24% of patients with non-metastatic, pathologically confirmed esophageal cancer did not receive any care at all.[94] Amongst the treated cohort, 40% received definitive chemoradiation, 30% underwent surgery alone, while only 7% received trimodal therapy. While this study was conducted before large trials established the survival benefits of trimodal therapy for the average patient, it suggests that most older patients may generally be less likely to receive aggressive care. A slightly more recent SEER-Medicare analysis of practice patterns of cases diagnosed from 2001-2009 (still prior to CROSS results) confirmed these findings, as only 5.4% of the cohort received trimodal therapy and over 35% received no care at all.[16] An analysis of treatment trends in the NCDB found that trimodal therapy usage did increase in a cohort of those 75 years of age and older, from 6.7% of treatments in 2006 to 13.6% of treatments in 2012.[23] However, 2012 was still early in the post-CROSS timeline and whether adoption further increased in older adults is unknown. Additionally, the NCDB is a hospital-based not population-based registry and may not be nationally representative of treatment trends.

Current demographic and clinical stratum-specific estimates of trimodal therapy utilization in older adults with esophageal cancer are also lacking, along with corresponding analysis of how these factors influence treatment patterns. In the earlier of the two previously mentioned SEER-Medicare studies, comorbidities appeared to be negatively associated with receipt of trimodal therapy; 54% of the surgery alone group belonged to the healthiest Charlson Comorbidity Index group (score of 0: mild comorbidities), compared to 73% of the trimodal therapy group.[94] The second study provided a closer look at the association between patient-level characteristics and treatment receipt.[16] Regionally, individuals from the West (OR= 2.59) and South (OR=1.49) SEER regions were more likely to not receive therapy of any kind compared to patients in the Northeast. Older age groups compared to those 65-69 were also

more likely to receive no treatment, as were individuals in the lowest quartile of zip-code defined education. These association estimates are helpful; however, they may change using data from more current years when trimodal therapy had been reinforced by large trial results. In addition to overall utilization of trimodal therapy in older adults with esophageal cancer, stratum-specific estimates of utilization by age, sex, comorbidity burden, and frailty index are important for two reasons. First, they help identify subgroups with potential underuse of trimodal therapy. Second, analysis of factors related to trimodal receipt help uncover treatment channeling that will be important to consider in observational comparative effectiveness studies faced with confounding. If these channeling factors also influence survival, they will need to be accounted for to facilitate a fair comparison of treatments.

Contemporary studies from other cancer sites where trimodal therapy is considered the most effective treatment have reported low utilization of this aggressive therapy in older populations. For instance, a SEER-Medicare study of bladder cancer patients who received radical cystectomy found that only 6.4% of patients received neoadjuvant chemoradiation prior to their surgery.[95] Uptake increased over time, but across study years older age strata were associated with lower utilization of trimodal therapy (75-79 age group compared to 66-69 OR= 0.7, 95% CI: 0.5 – 1.0). A survey asking member physicians from the Society of Urologic Oncology about major concerns they had in recommending trimodal therapy to their patients found that 54.4% of respondents indicated age and comorbidities and 32.8% indicated marginal benefit as major concerns.[96] Factors for lower use of trimodal therapy in bladder cancer may be similar in esophageal cancer patients, especially comorbidities in an older patient population. Although these data come from a different cancer site, they suggest that similarly low uptake of trimodal therapy may exist in older adults with esophageal cancer.

2.4.4 Comparative Effectiveness of Treatments Uncertain in Older Adults

Trimodal therapy may lead to increased survival compared to definitive chemoradiation through improved local control of the tumor. Locally advanced esophageal cancers are known to have high risk of relapse through local, regional, and distant recurrences.[97] Some patients will have tumors that are resistant to chemoradiation, while other tumors are more sensitive to the beneficial effect of chemoradiation. Thus, omission of surgery via definitive chemoradiation has the potential to leave residual tumor behind in some patients, increasing the risk of recurrence and subsequently lowering survival.[98] This hypothesis is supported by empirical data comparing disease control after treatments. A propensity-matched institutional cohort study found 5-year risks of local and regional recurrence in definitive chemoradiation patients of 38% and 19%, respectively. In comparison, these local and regional recurrence rates were 0% and 18% in patients receiving trimodal therapy.[27]

In contrast, trimodal therapy may have no effect or even decrease survival compared to definitive chemoradiation for some individuals. Amongst patients who experience a pathologic complete response (PCR) from chemoradiation, additional surgery may not contribute additional survival benefit. PCR occurs when there is no evidence of viable cancer cells in the tissue that is removed during resection due to successful destruction of cancerous tissue by chemotherapy and radiation. Thus, while patients treated by trimodal and definitive chemoradiation can both experience PCR, it can only reliably be documented in trimodal patients because a surgically resected specimen is needed for confirmation. Current literature estimates that between 24-31% of patients receiving trimodal therapy experience a PCR and that this percentage is higher in patients with squamous cell carcinomas compared to those with adenocarcinomas.[99–101] Multiple studies have demonstrated that achievement of PCR results in lower recurrence rates and confers a survival advantage. A retrospective cohort study of esophageal cancer patients receiving neoadjuvant chemoradiation found that patients who experienced PCR had a 5-year survival of 47.2%, compared to 27.3% in patients who did not experience PCR.[102] Other studies

have demonstrated a similar magnitude of survival benefits from PCR,[103–109] though it must be reiterated that PCR may entail longer survival but not cure, as up to 33% of patients with PCR still experience a cancer recurrence.[110,111] Acceptance of PCR as a strong predictor of survival has solidified, with one randomized trial that compared neoadjuvant therapies using PCR as a primary outcome indicating therapeutic success.[112] The influence of PCR on survival has led to research trying to build predictive models of PCR using pre-treatment variables to identify patients who could defer surgery.[113] The evidence that a quarter of patients experience PCR after chemoradiation has called into question whether additional planned surgery is needed for all patients.[114] If PCR could be validly predicted before treatment, patients with a high probability of PCR could forgo surgery and opt for the less invasive modality of definitive chemoradiation.

There are two other mechanisms by which trimodal therapy may not be beneficial to older adults, beyond the concept of PCR: limited life expectancy and high surgical risks. Limited life expectancy in advanced age due to comorbid conditions and frailty may render trimodal therapy less beneficial (in absolute survival time gained) to the average older adult than younger adults. Despite being a very poor prognosis cancer, data suggests that a non-negligible percentage (24%) of Medicare-enrolled esophageal cancer patients will die from non-cancer causes.[73] A limited life expectancy will significantly diminish the chance of large survival gains from aggressive trimodal therapy if a patient has a high pre-surgery risk of mortality due to comorbid conditions. A systematic review of older cancer patients found that pre-operative frailty strongly increases the risk of complications and mortality during surgical resection, extends length of stay during hospitalization, and decreases quality of life.[115] Older adults have increased operative mortality and perioperative morbidity from esophagectomy, which could hypothetically dampen the benefit of trimodal therapy. Esophagectomy is a complicated surgical procedure with major risks of morbidity and mortality. These risks are heightened with age, as the physiologic reserve of patients wanes and with it the ability to handle the physical toll of a drastic surgical procedure.[38] To the extent that surgical resection is more dangerous in older

patients, with higher operative mortality,[66] the survival advantage thought to be conferred by trimodal therapy may be substantially lessened.

Only two randomized trials have been conducted that compared trimodal therapy to definitive chemoradiation and they have features that limit their applicability to a modern cohort of older adults debating which of these treatments to undergo. The first trial, Federation Francophone de Cancerologie Digestive (FFCD) 9102, was a single-center study in France that randomized patients with locally advanced tumors who had completed chemoradiation with a positive response to either continue with chemoradiation (n=130) or have surgery (n=129).[116] The 2-year overall survival was 40% in the group that continued chemoradiation and 34% in the surgery group (Definitive chemoradiation versus trimodal therapy HR=0.88, 95% CI: 0.59 – 1.31). While no meaningful differences in survival were found, the trimodal therapy arm experienced better local disease control (66.4% compared to 57%) but also higher rates of treatment-related short-term mortality. The second trial, conducted in Germany and published in 2005, randomized 172 patients to receive either induction chemotherapy followed by chemoradiation and surgery (n=86) or induction chemotherapy followed by chemoradiation (n=86).[117] The two-year survival was statistically and clinically equivalent in the trimodal therapy arm (39.9%, 95% CI: 29.4%, 50.4%) compared to the dCRT arm (35.4%, 95% CI: 25.2%, 45.6%), though two-year progression-free survival was higher in the surgery arm (64.3% compared to 40.7%).

A handful of characteristics of these trials limit their applicability to the decision making of older adults in present times. The French trial has been criticized for only randomizing positive responders to the first round of chemoradiation, as positive response to chemoradiation would select patients more likely to benefit from further chemoradiation. All patients received induction chemotherapy and the majority (66%) of patients received split-course radiation therapy with a low dose, both of which are not standard, recommended treatments. In current practice, a higher radiation dose is given to patients receiving definitive chemoradiation.

Generalizability to current older US adults is also lacking, as FFCD 9102 was a single-center study conducted in 2007 in a younger patient population. The mean patient age of 58 in FFCD 9102 and fact that 90% of tumors were of squamous cell carcinomas render the results less useful to a population of older adults with predominantly adenocarcinomas. The German trial similarly used induction therapy, had a median age of 57, and only included squamous cell carcinomas. Interestingly, in both the German and French trials, local control of tumor was better (fewer recurrences) in the trimodal group, but this did not translate into improved survival. Treatment-related mortality was significantly higher in the trimodal therapy group.

Observational studies have mostly found that trimodal therapy increases survival, however they differ in reported magnitude of benefit and contain strong biases due to methodologic flaws. Appendix 1 displays the key design attributes and findings from thirteen observational studies conducted from 2010 onward that compared trimodal therapy and definitive chemoradiation in patients with local or regional esophageal cancer.[21–23,27,29,33,34,118–122] Briefly, total study population size ranged from 95 to 8,064. Six of the studies were conducted within the US. The largest effect comparing trimodal therapy to definitive chemoradiation was HR=0.45 (95% CI: 0.40 – 0.51).[33] On the other side of the spectrum, two studies found no survival difference between groups; unfortunately, these studies only report the median survival times with a non-statistically significant p-value instead of a contrast measure such as the risk difference. Only three of the studies were explicitly focused on older adult target populations. Heterogeneity in results across studies can be attributed to several factors. Study populations varied in histologic subtypes considered, age and stage eligibility, eras of diagnosis, and country. To the extent that these factors impact outcomes and treatment effects, one would expect the average treatment effect reported by these studies to vary in accord. Beyond wide differences in reported effect, this evidence base is fraught with methodologic issues that diminish the enthusiasm for applying these findings to clinical practice. These flaws consist of

immortal time bias, selection bias, lack of adequate confounding control, and reporting measures of association that have troublesome statistical and interpretability properties.

Immortal time bias was pervasive in the twelve observational studies comparing modalities, being a major limitation in ten. The common motif in the studies afflicted by this bias is that outcome follow-up began at the date of cancer diagnosis, but exposure-defining events such as receipt of surgery occurred sometime after the origin (time zero). Three of the four studies that used data from the NCDB conditioned on future exposure to define treatment groups at baseline, reporting highly protective effects of trimodal therapy (median survival advantage of trimodal group 8 to 20 months).[22,23,34] By requiring the patient to survive long enough to have their surgery noted in the records, these patients are precluded from experiencing mortality any time between the date of diagnosis and the date of their surgery. If they did experience an event in this time frame, it would have been prior to their surgery and the outcome would be attributed to exposure to definitive chemoradiation. Thus, the trimodal therapy group is erroneously afforded a major survival advantage over the definitive chemoradiation group, pushing the hazard ratio downward and away from the null. Immortal time bias is considered rampant in the medical literature, with many implausible protective effects of drugs or procedures being attributed chiefly to this validity concern.[123–130] It is particularly problematic in applications with the precise profile of a comparison of trimodal versus definitive chemoradiation, where the comparison resides in contrasting one intervention with a second intervention that takes longer to be experienced in full. Proper techniques to handle immortal-time bias include partitioning exposure time appropriately within individuals in Poisson regression models,[131] time-dependent Cox regression models,[132–135] landmark analysis,[136] and the clone-censor-weight technique.[137–140] Notably, two of the studies assuaged concerns about immortal time bias by using time-dependent Cox models wherein individuals in the trimodal therapy group did not contribute at-risk person-time in that group until their surgery took place.[27,121]

Intimately connected to the immortal time bias in these studies is the selection bias that is induced by requiring the complete exposure to all components that constitute trimodal therapy in order to contribute *any* amount of follow-up data to the trimodal arm. Even when three of the four statistical methods are used to appropriately handle immortal time (partitioned Poisson model, landmark analysis, time-dependent Cox model), selection bias remains an issue because to make it into the trimodal therapy group the patient had to be healthy enough to complete the whole therapy.[141] The subset of patients assigned to trimodal therapy that complete the full treatment course without dying before surgery will be a healthier subset, inducing a selection bias. This occurs even if follow-up starts on the day of surgery instead of the day of cancer diagnosis to handle immortal time bias. This is not just a theoretical issue, as empirical evidence suggests that a substantial number of individuals intended to receive trimodal therapy do not ultimately receive esophagectomy, the final phase of their treatment. In the appropriately named study *Analysis of patients scheduled for neoadjuvant therapy followed by surgery for esophageal cancer, who never made it to esophagectomy*, the authors examined a cohort of 679 patients who planned to receive trimodal therapy and reported on the proportion of patients who ultimately did not receive surgery and the reasons associated with surgical omission.[142] In the cohort, 16.8% of trimodal-scheduled patients did not ultimately receive surgery; of these, disease progression (43.9%), patient's own decision (13.2%) and mortality during the neoadjuvant therapy (7.9%) were cited as the most prevalent reasons behind forgoing esophagectomy.

Uncontrolled confounding is a major limitation in the existing observational studies that have compared trimodal therapy to definitive chemoradiation. Comparing trimodal therapy to definitive chemoradiation will certainly have less confounding than a comparison of trimodal therapy to no treatment, due to using an active comparator instead of an untreated referent.[143–145] Yet, the decision of whether to provide major surgery in older adults is likely susceptible to strong channeling based on patient comorbidity, frailty, and life expectancy. In the collected

literature, there was a noticeable tradeoff between sample size and level of clinical detail that had ramifications for precision and confounding control. For instance, a strength of the single-center studies in the United Kingdom and Germany was the availability of performance status in their institutional data, but small sample sizes and center-specific practices hinder drawing stable, generalizable conclusions to a US population.[21,29] In contrast, the database studies using the NCDB offer large study populations but do not have access to measures of frailty.

While several larger database studies did carefully control measured confounding through propensity score matching, the concern remains high for residual confounding. Ultimately, these patient factors will either be entirely unmeasured or imperfectly measured in registries and healthcare databases. For instance, the NCDB is limited in its ability to fully capture patient comorbidity burden. It contains the Charlson Comorbidity Index score for patients, but this is based on discharge abstracts and billing data related to the cancer diagnosis and treatment, rather than being drawn from comprehensive past medical history. Validation studies have demonstrated that NCDB capture of comorbidities can have strong measurement error. A study comparing the Charlson score from the NCDB with SEER-Medicare (using 12 months prior of claims history) found that 18.2% of non-small-cell lung cancer patients had a Charlson score of 2 or greater in the NCDB, compared to 33.1% in SEER-Medicare.[146] However, there are data sources and methodologic study design best practices that can reduce confounding given constraints. SEER-Medicare, for instance, links cancer registry data with longitudinal provider claims for medical services and prescription drugs. The ability to use a patient's past claims history, often consisting of many years of data, facilitates a more comprehensive characterization of comorbidity burden at the time of cancer diagnosis. Methodologically, longer claims history assessment periods have been shown to have higher sensitivity for detecting comorbidities. One of the existing studies used only a 6-month lookback period for assessing comorbidities, likely leaving some degree of measurable confounding uncontrolled.[122]

Though not statistically invalid, the existing observational studies uniformly reported a hazard ratio as the measure of effect, which has troublesome statistical and interpretability issues. Cox proportional hazards regression is a staple of time-to-event analysis and is often the default survival analysis technique. However, there are several notable issues with the hazard ratio: the requirement of proportional hazards, assumption of uniformity of effect over follow-up time, non-collapsibility, and low interpretability.[147–149] The first two can be addressed with time-varying coefficients through interaction terms of non-proportional culprit variables with time. However, non-collapsibility and low interpretability are properties of the HR that cannot be remedied. An effective strategy for avoiding these problems is to report contrasts of risk: either the risk difference (RD) or risk ratio (RR) at one or several timepoints during follow-up. Risk, expressed as the estimated percentage of patients who will experience the outcome by a timepoint of interest, is a foundational estimand in epidemiology and is easier to communicate to patients than hazards.[150] This more meaningful contrast can be generated using several methods including inverse-probability of treatment weighted Kaplan-Meier survival curves.[151] A patient-centered contrast in the absolute risk of an outcome that could be experienced under two competing treatment alternatives is absent from the literature. Thus, the existing evidence base contains problematic features including immortal time bias, selection bias, unmeasured confounding, and interpretability issues. However, beyond study design and statistical considerations, there is also the issue that the comparative effectiveness of these treatments is not fully characterized in terms of scope of outcomes evaluated.

The existing comparative effectiveness literature focuses solely on overall survival differences between individuals receiving trimodal therapy and definitive chemoradiation, offering a restricted profile of the outcomes that older adults find relevant in their treatment decision making. To the older adult with limited life expectancy recently diagnosed with a poor-prognosis cancer, quality of remaining life is a critical component surrounding treatment decision making. There is a paucity of data on how trimodal therapy and definitive

chemoradiation differ in their impacts on quality of life in patients of advanced age. While patient-reported quality of life is not contained in most large administrative claims databases, there are important outcome events that reflect quality of life that can be measured in these data sources. Patient-centered outcome measures include functional adverse events and healthy days at home. No quantitative estimates exist comparing these important outcomes between trimodal therapy and definitive chemoradiation. The International Society of Geriatric Oncology has advocated for trials to include alternative endpoints related to patient functioning to increase relevance of findings for older adults.[152] A wider consideration of patient outcomes beyond mortality naturally extends to observational research. Older adults and cancer care providers would benefit immensely from data on outcomes that are pertinent to quality of life.

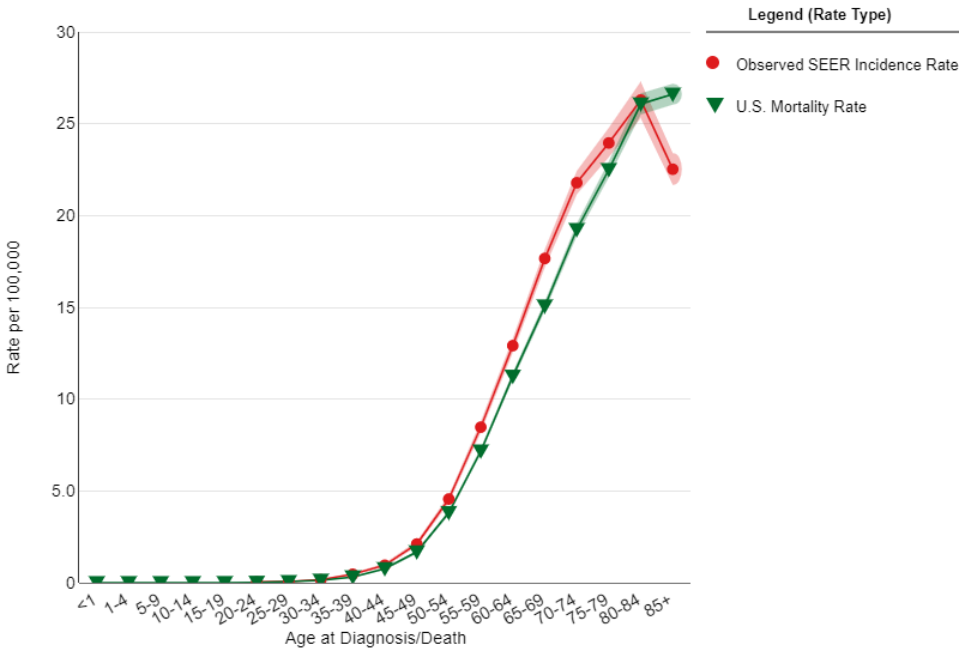
2.5 Summary

Esophageal cancer is a poor prognosis cancer with increasing incidence and mortality rates and a large burden of disease concentrated in older adults. A devasting diagnosis, esophageal cancer leads to a high risk of mortality, decreased health-related quality of life and large economic costs to the patient and healthcare system. In the past decade, trimodal therapy has become the standard of care embraced by treatment guidelines for patients with locally advanced tumors. However, treatment guidelines were largely the result of the CROSS trial, which had a younger study population and compared trimodal therapy to surgery alone—a less relevant comparison arm for older adults. As a result, there are critical gaps in the geriatric oncology literature regarding the use and effects of trimodal therapy in the older adult population. First, it is uncertain how the uptake of trimodal therapy in clinical practice has changed in older adults after the results of the CROSS trial; the median age in CROSS was 8 years younger than the median age at diagnosis in the general US population. Second, the comparative effectiveness and harms of trimodal therapy compared to definitive chemoradiation are poorly characterized, relying heavily on two randomized trials with generalizability concerns

and a suite of observational studies that contain strong biases. The current observational research is riddled with immortal time bias and does not consider outcomes beyond mortality that may influence the decision making of older adults. Addressing these limitations will help clinicians and patients shift from a landscape of uncertainty to one where decisions are based on less biased results, wider consideration of outcomes relevant to older adults, and increased applicability of effect estimates. The third chapter introduces the methodological strategies that were employed to accomplish our specific aims.

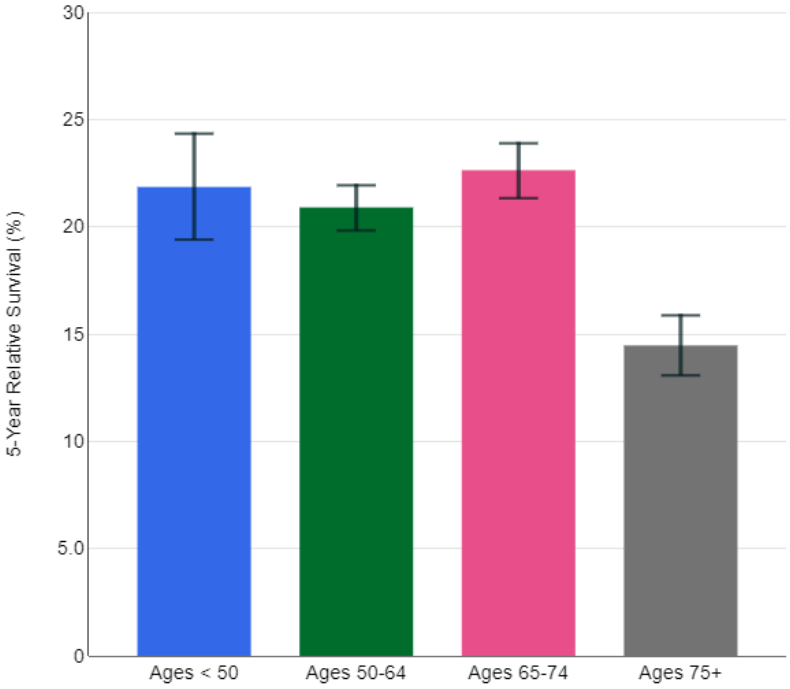
2.6 Tables and Figures

Figure 2.1 Incidence and mortality rates of esophageal cancer by age



Graphic generated using SEER*Explorer and data from cases diagnosed between 2000-2019. Available from https://seer.cancer.gov/explorer/.

Figure 2.2 Five-year relative survival of esophageal cancer by age



Graphic generated using SEER*Explorer and data from cases diagnosed between 2011-2017. Available from https://seer.cancer.gov/explorer/.

CHAPTER 3 – METHODS

3.1 Data Sources

Analyses for the two specific aims were performed using data obtained from the SEER-Medicare database. SEER-Medicare constitutes a data linkage of the SEER system of population-based cancer registries with administrative claims data from the Medicare program. SEER, supported by the National Cancer Institute, reports incident cancers and survival data from 17 population-based registries that collectively cover nearly one third of the US.[153] Trained cancer registrars collect data on patient demographics such as age, race, ethnicity, and sex, as well as tumor information including site, month and year of diagnosis, stage, and histologic subtype. SEER data also contain vital status and cause of death from linked death certificates through the National Center for Health Statistics.[154] The federally funded Medicare program, administered by the Centers for Medicare and Medicaid Services (CMS), provides health insurance to adults 65 years and older, as well as individuals with end-stage-renal-disease and disabilities. Over 96% of individuals 65 years of age and older in the US receive Medicare insurance, though our study uses data only from individuals with fee-for-service Medicare. The administrative database contains information on beneficiary enrollment as well as medical claims data.

The SEER-Medicare linked database contains data from cancer patients living in the SEER area who are eligible and enrolled in the Medicare program. Thus, the linkage represents the overlapping domain of the two sources, as only Medicare data on SEER documented cases are included in the database—although a random 5% sample of non-cancer Medicare beneficiaries is available when matched non-cases are needed. This linkage captures over 94% of patients 65 and older living in the SEER regions. The combined data possess high value for

comparative effectiveness research in geriatric oncology, as the SEER data have detailed tumor information while the claims allow for identification of treatments and outcomes that occur during follow-up.[155]

Older adults constitute a chronically underrepresented population in oncology clinical trials, creating a dearth of evidence to support treatment decision-making. A landmark study published in 1999 documented that, while patients 65 years of age or older represented 63% of the cancer population in SEER data, they represented only 25% of trial-enrolled patients in the Southwest Oncology Group.[156] Some incremental positive developments have occurred in the ensuing two decades, but the overall narrative of underrepresentation has persisted.[157] The SEER-Medicare database, while lacking some important clinical measures (e.g., smoking status), is a critical resource for generating evidence generalizable to older adults.

3.2 Aim I Methods

3.2.1 Aim I Study Population

The study population for the first aim consisted of adults 66 years of age and older diagnosed between 2004-2017 with incident locally advanced esophageal cancer of adenocarcinoma or squamous cell carcinoma histology and non-cervical esophagus topography. Locally advanced esophageal cancer was defined using the ASCO definition which considers locally advanced tumors as non-metastatic tumors (M0) that either have positive nodes (N1-N3) of any T (T1-T4) or negative nodes (N0) with T ≥ 2.[4] For both adenocarcinomas and squamous cell carcinomas this corresponded to AJCC 7th edition stage groupings of IB, IIA, IIB, IIIA, IIIB, and IIIC. Along with TNM variables, ICD-O-3 site and histology codes (Appendix 2) from the SEER-Medicare Cancer File were used to identify cases meeting tumor topography and histology inclusion criteria. Both specific aims focused on incident esophageal cancers; the SEER-Medicare Cancer File was used to identify the first esophageal cancer diagnosis for an individual.

Individuals were excluded from the study if their cancer was not histologically confirmed, was diagnosed at death or autopsy, or did not have malignant tumor behavior. Additionally, we excluded those who had non-esophageal cancers that were diagnosed within the year before esophageal cancer diagnosis, because for such individuals it would be difficult to attribute treatment observed in claims data to a specific primary cancer. The SEER-Medicare Cancer File was used to identify any non-esophageal cancer diagnoses within one year prior to the incident esophageal cancer diagnosis. We did not restrict the cohort to first primary esophageal cancer (i.e., an individual was allowed to have been diagnosed with lung cancer 5 years ago) because a significant proportion of older adults may have a history of cancer, especially considering that smoking is a strong risk factor for esophageal cancer. Though 65-year-old adults are Medicare eligible, a one-year claims lookback period was used to construct comorbidity and frailty variables. Thus, in practice, the youngest an individual could be at diagnosis to meet this requirement was 66. This study population was broader than the study population for aim two, because treatment patterns were characterized rather than identifying a target sub-population receiving either trimodal therapy or definitive chemoradiation. In other words, patients that receive treatments outside of trimodal therapy and definitive chemoradiation (e.g., surgery alone) or no treatment at all were included in this analysis of practice patterns.

3.2.2 Aim I Exposure Assessment

What constituted the exposure (independent variable) for the first specific aim varied between the three objectives of the aim. Objective one examined temporal trends in treatment received; thus, the independent variable of interest was the calendar year of cancer diagnosis.

The second objective considered the individual-level characteristics of the study population (i.e., demographic and clinical variables) as the independent variables, focusing on simple bivariate relationships with treatment received (bar charts and unadjusted risk ratios).

Demographic characteristics consisted of age, sex, race and ethnicity, geographic region, census-tract poverty level, and rurality.

All of the demographic variables considered in objective two were ascertained from the SEER cancer registry side of the linkage. Age was categorized into 66-70, 71-75, and ≥76 years of age. The race and ethnicity variable was created by combining information from the race and Hispanic ethnicity variables. The cell size suppression policy in the data use agreement mandated that, for confidentiality protection, no cell sizes less than 11 could be directly reported or deduced from other cells. This necessitated collapsing the race and ethnicity variable in places, resulting in a final variable with possible values of non-Hispanic white, Hispanic white, black, and other race and ethnicity. Given that "other race and ethnicity" is definitionally a highly heterogenous group racially and ethnically (that was simultaneously small in sample size), stratified estimates were reported only for non-Hispanic white, Hispanic white, and black individuals for interpretability and confidentiality purposes. We created the geographic region variable by determining the state location of the reporting registry and forming groups that consisted of Northeast, Midwest, South, and West. Census-tract poverty level is provided in the SEER data and is a categorical variable that reports the percentage of individuals living below the federal poverty line in the diagnosed individual's census tract of residence.[158] Rurality was determined using Rural-Urban Continuum codes and further classified into metro, urban, and rural areas.

Tumor clinical variables considered in objective two were ascertained from the SEER registry. Tumor characteristics consisted of histology, grade, tumor location, and stage. Histology was a binary variable indicating whether the tumor was an adenocarcinoma or a squamous cell carcinoma. Grade was categorized as low grade (well-differentiated tumors), intermediate grade, high grade (poorly-differentiated and undifferentiated), and grade undetermined. Location was classified into upper and middle esophagus, lower esophagus, and overlapping or not otherwise specified lesions. Stage was determined using the TNM

information of the tumor and classified into stage groups based on the seventh edition of the AJCC staging manual. A particular advantage of the seventh edition is that T4 tumors, in which the extension of the tumor invades adjacent structures, are subclassified into T4a and T4b tumors. T4b tumors invade adjacent structures such as the aorta or trachea and are considered unresectable.[159] This distinction was pivotal because we were interested in treatment patterns for individuals with tumors amenable to resection; we were able to use this data to exclude T4b tumors that would not be eligible for resection. Thus, while we may have reduced our sample size by excluding tumors that could not be re-staged to the seventh edition, the bias reduction achieved through purposeful selection of tumors that had the possibility of resection was paramount.

Patient clinical variables considered in objective two were ascertained from the SEER registry data and Medicare claims, and consisted of number of prior malignancies, comorbidity burden, and frailty. The Cancer File from the registry data was used to determine the number of previously diagnosed (and registered) cancers. While patients were excluded from analyses if they had a recent cancer (diagnosed within the one year prior to incident esophageal cancer diagnosis), patients were eligible for study if their other primary cancers were diagnosed further back in their medical history.

Medicare claims from the one-year prior to esophageal cancer diagnoses were used to calculate claims-based proxies for comorbidity burden and frailty using the NCI adaptation of the Charlson Comorbidity Index[160,161] and the Kim frailty index,[162] respectively. The NCI Comorbidity Index is a modification by Klabunde et al. to the well-known Charlson Comorbidity Index and allows health services researchers to quantify the Charlson Comorbidity Index score using administrative claims data and exclude cancer-related conditions in the score calculation.[160,161] The predictive validity of the NCI Comorbidity Index in terms of accurately predicting non-cancer death has been confirmed in prior research.[163] The content validity of the NCI Comorbidity Index has also been demonstrated; in a cohort study, the percentage of prostate cancer patients

reporting poor health status increased with higher index scores.[164] In analyses, we categorized the NCI Charlson Comorbidity Index into four levels: 0, 1-2, 3-5, and ≥6. The Kim frailty index is a validated claims-based index that is based on the deficit-accumulation model of frailty.[162,165–167] The Kim frailty index was categorized into four levels: robust (<0.15), prefrail (0.15-0.24), mildly frail (0.25-0.34), and moderately-to-severely frail (≥0.35), a categorization that has been used by the developers of the index.

The third (final) objective of aim one returns to using calendar time as the independent predictor, as temporal trends in chemotherapeutic regimens used by trimodal and definitive chemoradiation patients are estimated.

3.2.3 Aim I Outcome Assessment

Similar to the exposure(s), what constituted the outcome (dependent variable) changed according to the objectives within aim 1. In the first objective, temporal trends in treatment received were examined; thus, treatment received was the outcome. Treatment received was measured using Medicare fee-for-service medical claims in the nine months following cancer diagnosis. Given that a considerable number of study population individuals were expected to die prior to completion of this nine-month window, survival for the whole window was not required. However, we did require that individuals possess continuous Medicare fee-for-service insurance up until the earliest of death or nine-months post-diagnosis. A sensitivity analysis examined treatment trends in the subset of individuals who lived for at least 9 months post diagnosis. The medical claims in this assessment window were searched for International Classification of Disease (ICD) 9 and 10 procedure codes, Healthcare Common Procedure Coding System (HCPCS) codes, and Current Procedural Terminology (CPT) codes that corresponded to esophagectomy, delivery of external beam radiation, and intravenous chemotherapy. A full listing of the codes used to identify these treatments is supplied in Appendix 2. The occurrence and sequence of these procedures were used to define treatment

groups of interest. Treatment groups consisted of trimodal therapy, definitive chemoradiation, surgery alone or other surgery-based multimodal therapy (e.g., surgery with adjuvant chemotherapy), palliative treatment (chemotherapy alone or radiation alone), or no treatment. To meet the definition for trimodal therapy, chemotherapy receipt had to be followed by radiation delivery and then surgery.

In objective two, we explored the relationships between individual-level factors and receipt of treatment. Therefore, treatment received again served as the outcome variable. We reported the percentages of individuals receiving each treatment group, stratified by the demographic and clinical factors. In a supplemental analysis, we collapsed treatment received into trimodal therapy versus all other treatment groups. This was done to contrast the probability of receiving trimodal therapy between levels of the individual-level factors with descriptive, unadjusted risk ratios.

In the third objective, we assessed temporal trends in chemotherapy regimen received by individuals treated with either trimodal therapy or definitive chemoradiation. Chemotherapy regimens were determined by identifying which specific chemotherapy agents were delivered within 28 days of the first documented chemotherapy infusion. If delivery of cisplatin or carboplatin was identified within this time window, the regimens were classified as cisplatin-based and carboplatin-based, respectively. If neither of these agents were identified, the regimen was classified as other chemotherapy.

3.2.4 Aim I Statistical Analysis

In objective one, we examined temporal trends in the age-standardized percentage of individuals receiving each treatment. We began by using direct standardization to account for potential variation in the age distribution across years, using the age distribution of individuals diagnosed in 2017 as the standard population.[168,169] Given the small sample size, age was stratified into three groups: 66-72, 73-79, and ≥80. We calculated age-strata-specific

percentages of individuals receiving each treatment group in each year from 2004-2017. We then standardized these percentages to the age distribution of the standard population. After we calculated age-standardized treatment percentages, each set of annual standardized treatment percentages was analyzed using the *Joinpoint Regression* program (National Cancer Institute) to examine trends over time.[170] Joinpoint regression is a flexible, data-adaptive technique that detects the existence of trends and quantifies their magnitude while allowing for non-linearities in trends over the period considered. This technique has been applied across a variety of settings in epidemiologic research.[171,172] Joinpoint accommodates non-linearities across the time period considered by allowing there to be multiple, smaller segments with their own linear trends within the time period.[173] Our analyses considered the time period of 2004-2017 with annual measurements.

In joinpoint regression, within a given regression segment, the percentage of patients receiving a given treatment is modelled on the log-linear scale:

$$\text{Log(percentage of patients receiving treatment)} = \beta_0 + \beta_1(\text{year of diagnosis}) + \text{error}$$

Year of diagnosis was entered as a continuous variable. From this model we derived the annual percent change (APC), which represents the change (increase or decrease) on the multiplicative scale that was experienced during a segment from year-to-year in the segment. The APC was calculated as:

$$\text{APC} = (e^{\beta_1} - 1) \times 100$$

The average annual percent change (AAPC) takes a weighted average of the detected segments. Each segment has a weight w_i that corresponds to the length of the segment and a coefficient for the slope, β_i.[173] The AAPC is calculated as:

$$\text{AAPC} = \left\{ e^{\frac{\sum w_i \beta_i}{\sum w_i}} - 1 \right\} \times 100$$

Though the AAPC was of less interest than characterizing the separate segment trends, we reported it for trends in addition to the APC because it provides a single numeric summary of the increase or decrease. If no join points are detected for a given trend analysis, there is just one slope and the AAPC is equivalent to the APC. In all trend models a maximum of two join points (three trends) was considered, and the permutation statistical test was used to select the final model.[174]

The second objective provided a simple descriptive breakdown of the treatments received according to levels of demographic and clinical variables. We calculated cross-tabulations between these characteristics and treatment received. Relationships were presented with bar graphs. We additionally performed a supplementary analysis where treatment received was dichotomized into trimodal therapy versus all other treatment groups. We calculated unadjusted risk ratios that contrast the probability of individuals receiving trimodal therapy between levels of the demographic and clinical variables. These risk ratios were descriptive (non-causal) in nature, as they were calculated to compare levels of trimodal therapy receipt across values of the independent variables.

The decision to present unadjusted risk ratios merits further discussion. Historically, statistical models have been categorized by their intent: etiologic models and predictive models.[175,176] Etiologic models seek to isolate the causal effect of an exposure variable on an outcome of interest. In contrast, predictive models are not concerned with the “effect” of a single variable, but rather how well a group of variables together can accurately estimate the probability that an event will occur. Somewhere between these two goals lies the often ill-defined “risk factor analysis” that places a set of variables together in the model and reports a measure of association (e.g., risk ratio) for each variable that is mutually adjusted for all others in the model. Interpreting the statistical output causally from such a model has been termed the Table 2 Fallacy,[177] with one of the primary reasons being that a mutual adjustment strategy is unlikely to successfully differentiate between confounders, mediators, and colliders. What

constitutes a confounder for one exposure variable may not have the same role for another exposure variable in the global set of potential risk factors. A growing literature highlights the importance of appropriately matching the task (descriptive, predictive, explanatory) with the right statistical tools,[178] and that if the goal is descriptive, unadjusted measures can be entirely appropriate if not superior.[179,180] For instance, our goal was to describe how often adults 80 years of age and older were treated with trimodal therapy compared to younger adults. We were not focused on isolating a causal effect of being 80, but rather describing distributions. Therefore, the risk ratios accompanied with objective two were unadjusted.

The third and final objective of the first aim was to examine temporal trends in the use of specific chemotherapy regimens amongst the sub-cohort of patients who were treated with either definitive chemoradiation or trimodal therapy. The statistical analysis for this objective employed the same join point regression modelling technique as the first objective, but instead of treatment modality received we modelled the percentages of patients receiving cisplatin-based, carboplatin-based, and other chemotherapeutic regimens.

3.3 Aim II Methods

3.3.1 Target Trial Emulation Framework

The target trial emulation approach was the guiding strategy for the execution of the second aim, which focused on evaluating the comparative effectiveness of trimodal therapy and definitive chemoradiation. Ideally, causal research questions are answered using double-blind randomized clinical trials conducted in large populations with long-term follow-up and little dropout. However, the RCT gold standard is often not possible for a given research question due to expense, feasibility constraints, and ethical concerns.[181–184] Additionally, older patients are often excluded from oncology clinical trials due to comorbidities and health status limiting eligibility. This necessitates the use of results from well-conducted observational studies to arrive at a conclusion in the absence of an RCT.[185,186] The target trial approach posits that

clinical research using observational data can maximize its validity and avoid common design and analytic pitfalls by emulating a well-specified theoretical RCT—the target trial.[187,188] In practice, this entails both a delineation of six key features of the target trial (eligibility criteria, treatment strategies, assignment procedures, outcomes, follow-up, causal contrast of interest), as well as a breakdown of how these features will be best emulated using the available observational data.[189] This approach has quickly gained traction in pharmacoepidemiologic research and brought clarity to several complex research questions.[190] Examples in the literature include studies of whether initiation of postmenopausal hormone therapy is associated with coronary heart disease,[191] if colonoscopy in older adults reduces cancer incidence,[192] and whether the addition of erlotinib to gemcitabine increases survival in pancreatic cancer patients.[137] By specifying how the observed data will be used to emulate a theoretical RCT, the target trial approach facilitates the comparison of well-defined interventions, which is a prerequisite for causal inference.[193–197]

In Aim 2, the target trial was a pragmatic clinical trial of older adults with locally advanced esophageal cancer randomized to either trimodal therapy or definitive chemoradiation. The following subsections detail the features of the target trial and the observational emulation.

3.3.2 Eligible Study Population

In the target pragmatic trial, inclusion criteria would consist of incident diagnosis of histologically-confirmed locally advanced esophageal cancer with malignant tumor behavior, age ≥65, adenocarcinoma or squamous cell carcinoma histology, and non-cervical esophagus site of tumor origin. Patients would undergo a screening questionnaire and rigorous baseline clinical evaluation to evaluate whether they would be considered fit for both treatments they could potentially be randomized to (trimodal therapy or definitive chemoradiation). This evaluation would be critical because patients would be excluded if they had contraindications for

either of the treatments. Contraindications would include severe cardiovascular or respiratory disease, and a frailty or comorbidity burden severe enough to prohibit surgery. This eligibility information would be prospectively ascertained at the time of study enrollment.

In the emulated trial, the eligible study population was identified using patient and tumor data from the SEER cancer registry and past medical diagnoses and procedures from Medicare claims. Diagnosis of non-cervical locally advanced esophageal cancer with adenocarcinoma or squamous cell carcinoma histology was determined using ICD-O-3 site codes (Appendix 2). Tumors were required to have malignant behavior and had to be histologically confirmed. Cases diagnosed at death or autopsy were excluded. SEER data allowed restriction to patients with TNM categories that denoted locally advanced disease: 1) any resectable tumor (T1-T4a) with positive nodes (N1-N3), and 2) more advanced resectable tumors (T2-T4a) with any nodal status (N0-N3). All eligible tumors were required to be non-metastatic (M0). While no baseline clinical assessment was feasible with the secondary data, we attempted to identify a population of older adults that could theoretically be eligible for surgery by calculating measures of comorbidity and frailty burden and restricting our study population to particular levels. Specifically, we used the claims-based NCI adaptation of the Charlson score and the Kim frailty index to measure comorbidity and frailty, respectively. These indices were calculated by detecting the presence of particular conditions in the claims up to one year prior to the first chemotherapy infusion. Individuals with a moderate-to-severe frailty index value (≥ 0.35) or a Charlson score greater than 5 were excluded. These restrictions were put in place to minimize the chance of severe confounding wherein patients with poor health status would be less likely to eventually receive surgical resection. A minimum of one year of continuous insurance enrollment prior to cancer diagnosis was required to ensure a sufficient evaluation period using this one-year fixed lookback period. On account of this one year, eligibility started at age 66. Results from the first aim were used to inform the upper age limit wherein older adults were still

feasibly receiving resection. We implemented a maximum eligible age of 79 at first chemotherapy infusion.

The most important concession made in the observational emulation is that, unlike the target trial, we did not have a baseline clinical visit to evaluate whether a patient was fit for resection. Instead, we relied on claims-based indices calculated using diagnosis and procedure codes in the year prior to the cancer diagnosis to serve as proxies for comorbidity and frailty. These indices, while validated, are imperfect measures. Residual confounding may exist from not detecting prior conditions and not capturing the severity range within a given comorbid condition.

3.3.3 Treatment Strategies

In the target trial, eligible patients would be randomized at baseline to receive either trimodal therapy or definitive chemoradiation. Trimodal therapy would consist of 5 weekly cycles of carboplatin and paclitaxel infusion chemotherapy with 41.4 Gy of concurrent radiation followed by esophagectomy within 6 weeks of completing chemoradiation; these are the therapeutic parameters of the CROSS trial.[5] Definitive chemoradiation would consist of 5 cycles of infusion chemotherapy and 50.4 Gy of concurrent external beam radiation with no planned surgical resection.

In the emulated trial, the courser nature of the observational treatment data meant that the exactitude of the treatments in the target trial could not be perfectly mirrored. For instance, SEER-Medicare does not contain data on the dose of radiation delivered. Trimodal therapy was defined as the following sequence: start infusion chemotherapy within 120 days of cancer diagnosis, start external beam radiation within 7 days of chemotherapy (same day as chemotherapy allowed), and receive esophagectomy after chemotherapy and radiation and within 6 months of the first chemotherapy infusion. Treatments were defined using Medicare claims data from inpatient and outpatient encounters (see Appendix 2 for codes).

Chemotherapy was identified using HCPCS “J-codes” for chemotherapy infusions. Radiation was identified using CPT codes for external beam radiation delivery. Esophagectomy was identified using CPT and ICD procedure codes. Definitive chemoradiation was defined as the following sequence: start infusion chemotherapy within 120 days of cancer diagnosis, start external beam radiation within 7 days of chemotherapy (same day as chemotherapy allowed), and do *not* receive esophagectomy within 6 months of the first chemotherapy infusion.

The timing of resection played a pivotal role in the treatment group definitions and will ultimately leave some degree of exposure misclassification. If the requirement of esophagectomy within six months from chemotherapy infusion were shortened (surgery within 3 months), a number of trimodal therapy patients would be misclassified as definitive chemoradiation because the assessment window was too short. On the other hand, if the requirement were lengthened (e.g., esophagectomy within one year of chemotherapy initiation), one runs the risk of capturing salvage esophagectomies that are not performed with curative intent and were not part of a trimodal therapy treatment plan. Six months was chosen to balance these considerations and was selected based on consultation with an oncologist and health services researcher. A sensitivity analysis explored the impact of shortening this window to 3 months.

3.3.4 Assignment Procedures

In the target trial, eligible patients would be randomized at baseline to either of the two study arms. Each case would be reviewed by a multi-disciplinary tumor board and the eligible and consenting patient would be randomized to a treatment plan. This facilitates a simple follow-up plan that begins at randomization. Confounders would be balanced between treatment groups in expectation given the randomized assignment and large enough sample size.

In the emulated trial, the observational data meant that treatment assignment was not randomized. Additionally, it was not known at the patients first chemotherapy infusion and

radiation treatment whether a post-chemoradiation esophagectomy was planned. To accommodate these features, our emulated trial used the clone-censor-weight method for analysis. Clone-censor-weight is a technique that has gained traction in the applied epidemiologic methods literature due to its handling of complex time-delimited (or sequential) interventions such as trimodal therapy.[137–139,190,198–201] The data of each patient was cloned at first chemotherapy infusion within 120 days of cancer diagnosis and "assigned" analytically to both treatment strategies: trimodal therapy and definitive chemoradiation. When the observed treatment data of the patient was no longer consistent with the assigned treatment strategy, we analytically censored that observation. Thus, the observation contributed to the risk-set while the data still reflect the assigned treatment arm, but did not contribute to the risk-set after deviation from the initial assignment. For both treatments, time zero (the start of follow-up) was the date of the first chemoradiation treatment within 120 days of cancer diagnosis. A clone assigned to the trimodal therapy strategy was analytically censored if that individual reached 7 days after the first chemotherapy infusion without external beam radiation delivery, or 183 days (6 months) after first chemotherapy infusion without receiving an esophagectomy. A clone assigned to the definitive chemoradiation arm was analytically censored if that individual reached 7 days after the first chemotherapy infusion without external beam radiation delivery, or at any point in the 183 days after the first infusion if and when they received esophagectomy.

Figure 3.1 depicts the clone cand censor approach for four example patients (A-D). For each patient in Figure 3.1, there is a cluster of three lines. The top line depicts what was observed in the data pertaining to treatments and outcomes and the two lines below depict how follow-up time is assigned to each of the treatment clones. Patient A received radiation the day after chemotherapy but did not have any surgery within the 6 months after the first chemotherapy infusion. The trimodal clone for Patient A was thus censored at 6 months after the first chemotherapy infusion, because at this timepoint it is known for the first time that they did not get trimodal therapy as defined by the emulated trial. The definitive chemoradiation

clone for Patient A never gets censored because the observed data was always consistent with the definitive chemoradiation treatment. Patient B starts chemoradiation and undergoes esophagectomy 8 weeks after the first chemotherapy infusion. The trimodal clone for Patient B is never censored because the observed data is always consistent with the described trimodal treatment strategy in the emulated trial. The definitive chemoradiation clone for Patient B is censored at the time of esophagectomy because this is the first-time during follow-up at which it is known in the database that they did not receive definitive chemoradiation (they had a surgery). Patient C starts chemoradiation but dies four months after starting chemotherapy. This death is counted towards the mortality outcome for both clones, because at this timepoint it is not yet known whether the patient planned to have definitive chemoradiation or simply died before a planned esophagectomy. Lastly, Patient D never receives radiation within the one week after starting chemotherapy. Patient D is censored at day 7 for both the trimodal therapy clone and the definitive chemoradiation clone.

The reasons for which a clone does not follow each treatment strategy are not random, but rather driven by confounders. For instance, a clone that is analytically censored from the trimodal therapy arm at 6 months—because they have not received an esophagectomy yet—may be older, on average, than patients that receive esophagectomy and remain uncensored. Thus, there is informative, non-random censoring due to confounding factors. To account for the informative nature of the analytic censoring, which creates imbalance in confounders, inverse probability of censoring weights were applied. Further details on the statistical application of the weights are provided in section 3.3.8.

The measured confounders consisted of patient demographic and clinical characteristics. Demographics included age, sex, race and ethnicity, geographic region of diagnosis, year of diagnosis, and census-tract poverty level. Clinical characteristics included histologic subtype, stage, tumor grade, location of tumor within the esophagus, number of previously diagnosed (non-esophageal) cancers, Charlson comorbidity score, and Kim frailty

index. These factors were measured in the same fashion as presented for Aim I (section 3.2.2), with the key difference being that the measures of prior cancers, comorbidity burden, and frailty index were all anchored in relation to the first chemotherapy infusion instead of the date of cancer diagnosis. The Charlson Comorbidity Index and Kim index were calculated using medical claims in the year prior to the first chemotherapy infusion. Prior cancers were measured using all available registered non-esophageal cancers that were diagnosed before the first chemotherapy infusion.

3.3.5 Outcome Assessment

There were four primary outcomes of interest. The first three outcomes were five-year risk of overall mortality, five-year risk of cancer-specific mortality, and one-year risk of functional adverse events. The fourth outcome was the five-year mean cumulative count of days at home, which was different from the first three because it required a recurrent events analysis. These four outcomes are the same between the target trial and the emulated trial, however the outcome measurement strategies differ.

In the target trial, overall and cause-specific mortality would be ascertained by study site personnel with a clinical adjudication panel determining the cause of death. Functional adverse events and days at home would be assessed during follow-up questionnaires at regularly spaced (ex. semi-annual) intervals combined with medical record review.

In the emulated trial, overall mortality was ascertained from the Medicare enrollment files which contain the date of death of each beneficiary. Cause-specific mortality was ascertained from the SEER side of the linkage, using the SEER cause-specific death classification variable that is derived from ICD-10 cause of death codes on death certificates. A functional adverse event was defined using a claims-based algorithm recently used in the geriatric oncology setting: the presence during follow-up of at least one claim for durable medical equipment or skilled care.[202] Durable medical equipment consisted of items such as wheelchairs and home

oxygen supply, while skilled care consisted of skilled nursing facility claims or home health nursing claims. Codes for durable medical equipment and skilled care are listed in Appendix 2. Patients who had a functional adverse event in the year prior to starting chemoradiation were excluded from the analysis of incident functional adverse events.

The mean cumulative count of days at home is built on the concept of home-time, a patient-centered outcome measure that can be calculated in administrative databases.[203] Home-time is the percentage of time during follow-up after an origin of interest that is spent outside of a facility and presumably at home. This metric has been calculated in multiple Medicare-based cohort studies[204–209] and validated as a measure of functioning and quality of life through linkage with survey data.[203] We defined a day at home as any day alive and not spent hospitalized, in the observation unit of a hospital, at a skilled nurse facility, at an inpatient psychiatric hospital, at an inpatient rehabilitation unit, at a long-term hospital, or receiving inpatient hospice care. The statistical advantages of the mean cumulative count as a method for estimating home days are addressed in section 3.3.8.

Competing events preclude the event of interest from happening and were handled explicitly as such in statistical analyses (3.3.8) rather than treating these as censoring events, a practice which can inflate risk estimates.[210–214] The overall mortality outcome does not have any competing events, but cancer-specific mortality has the competing event of non-cancer death, and functional adverse events and days at home have the competing event of all-cause mortality.

3.3.6 Follow-Up

The duration of follow-up for each clone varied according to the outcome analyzed. For the five-year risk of overall mortality outcome, clones were followed from first chemotherapy infusion until the earliest of the following potential events: analytic censoring, death, administrative end of study (12/31/2019), or five years after first infusion. For the five-year risk of

esophageal cancer-specific mortality outcome, clones were followed from first chemotherapy infusion until the earliest of: analytic censoring, death from esophageal cancer, death from a cause other than esophageal cancer, administrative end of study (12/31/2017, two years earlier than all-cause mortality for cause-specific death data from SEER-Medicare), or five years after first infusion. For the one-year risk of functional adverse events outcome, clones were followed from the first chemotherapy infusion until the earliest of: analytic censoring, loss of continuous fee-for-service insurance coverage, death from any cause, functional adverse event occurrence, administrative end of study (12/31/2019), or one year after first infusion. Lastly, for the days at home recurrent event outcome, clones were followed from the first chemotherapy infusion until the earliest of: analytic censoring, loss of continuous fee-for-service insurance coverage, death from any cause, administrative end of study (12/31/2019), or five-years after first infusion. Importantly, for this last outcome, follow-up does not stop at the first occurrence of the recurrent event (a day at home).

3.3.7 Causal Contrast of Interest

In the target trial, both the intent-to-treat and per-protocol effects would be of interest. The intent-to-treat effect would compare outcomes according to the groups to which patients were randomized regardless of final treatment. The per-protocol effect would estimate the effect of completing the interventions in full according to the planned treatment strategies.

In the emulated trial, only the per-protocol effect was estimated due to the inability to ascertain one's baseline "assigned" exposure and the necessity of a grace period to assess whether the exposure was experienced to completion. However, our per-protocol effect was less stringent than the target trial because we counted any amount of chemotherapy and radiation as being compliant with chemoradiation. The emulation estimated the average treatment effect; this represented the contrast in outcomes expected if everybody in the eligible study population had been treated with (any amount of) definitive chemoradiation versus if

everybody had been treated with (any amount of) chemoradiation followed by esophagectomy. Causal effect estimation using marginal contrasts of pseudo-populations (if everybody had been treated versus untreated) are described in the epidemiologic literature.[215]

3.3.8 Statistical Analysis

All statistical analyses were performed stratified by histologic subtype. This decision was influenced by the existing clinical literature, which has embraced the fact that esophageal adenocarcinomas and squamous cell carcinomas represent distinct cancers with varying etiology, pathogenesis, prognosis, and sensitivity to chemoradiation.

We presented descriptive statistics of the entire eligible cohort that initiated chemotherapy prior to cloning individuals, stratified by histologic subtype. Continuous variables such as age were described with medians and interquartile ranges, while categorical variables were described with counts and percentages. This presentation of “total cohort” characteristics instead of characteristics stratified by treatment group (unknown at baseline) has been used in prior studies that implemented the clone-censor weight approach.[199,216]

Inverse probability of censoring weights (IPCWs) were calculated to handle the confounder imbalance that was created by analytic censoring. There are several different methods for calculating IPCWs including pooled logistic regression with spline terms for time measured in days, pooled logistic regression with weights updated at courser intervals (e.g., monthly), and Cox proportional hazards regression models. After implementing several of the methods, we found that a combination of normal and pooled logistic regression models produced the best covariate balance.

In the trimodal therapy clones, two separate logistic regression models were generated to facilitate calculation of IPCWs. The first regression modeled the probability of remaining analytically uncensored at day seven (receiving radiation) given survival to day 6. The second regression modelled the probability of remaining analytically uncensored at day 183 (receiving

surgery) given survival to day 182. The models were used to calculate, using cumulative products, the probability of remaining uncensored at a given time point conditional on confounders. We then took the inverse of this probability to generate the time-varying IPCW. In the definitive chemoradiation clones, a similar logistic regression model was used at day seven. However, a pooled logistic regression with restricted cubic splines for time was used to obtain the probability of remaining uncensored between days 8 and 183—given that a clone could be analytically censored at receipt of surgery anytime between day 8 and 183.

The weighting scheme upweights individuals who remain uncensored (i.e., compliant with their assigned treatment) but, given their covariates, were more likely to have been censored. In parallel, it down weights individuals who are overrepresented in the uncensored population. In effect, the weights allow uncensored individuals to stand in for censored individuals who were similar in terms of confounder values, restoring the confounder distribution to that before censoring. Since the total eligible study population was duplicated at the start, with one copy of each individual assigned to trimodal therapy and one to definitive chemoradiation, restoring the original confounder distribution *within* each arm prior to any censoring creates balance *between* treatment groups. In the final dataset architecture, each clone had a row for each day of follow-up that contained their IPCW for that given day, the values of confounders, and a variable denoting outcome status.

The measured confounders used in the construction of the IPCWs were enumerated in section 3.3.4; herein we discuss the statistical form in which they were entered into the regression models that generated the IPCWs. Age, Kim frailty index, Charlson comorbidity score, and the count of hospitalizations in the prior year were all modelled using restricted cubic spline with 5 knots. The values of the knots were data-adaptive and placed at the 5^{th}, 27.5^{th}, 50^{th}, 72.5^{th}, and 95^{th} percentiles. The following binary indicator variables entered into the model: female sex, Hispanic white race and ethnicity, black race, other race and ethnicity, year of diagnosis between 2009-2013, year of diagnosis between 2014-2017, South geographic region,

Northeast geographic region, Midwest geographic region, 5%-10% census tract poverty level, 10-20% census tract poverty level, >20% census tract poverty level, intermediate tumor grade, high tumor grade, undetermined tumor grade, lower esophagus tumor location, overlapping or not otherwise specified tumor location, stage IIA tumor, stage IIB tumor, stage IIIA tumor, stage IIIB tumor, stage IIIC tumor, and count of emergency department visits in past year. For all categorical variables with more than two response possibilities, the referent group did not have an indicator variable. Referent groups thereby incorporated into the intercept included: white non-Hispanic race and ethnicity, year of diagnosis between 2004 and 2008, West geographic region, 0-5% poverty level, low tumor grade, upper or middle esophageal tumor location, and stage IB tumors.

The balance of the covariates before and after weighting was assessed at the end of the 6-month grace period using standardized mean differences. An absolute standardized mean difference greater than 0.10 was taken to indicate residual confounder imbalance.[217] A plot was constructed to display the impact of weighting on the standardized mean differences. The results of these calculations are presented in Chapter 5.

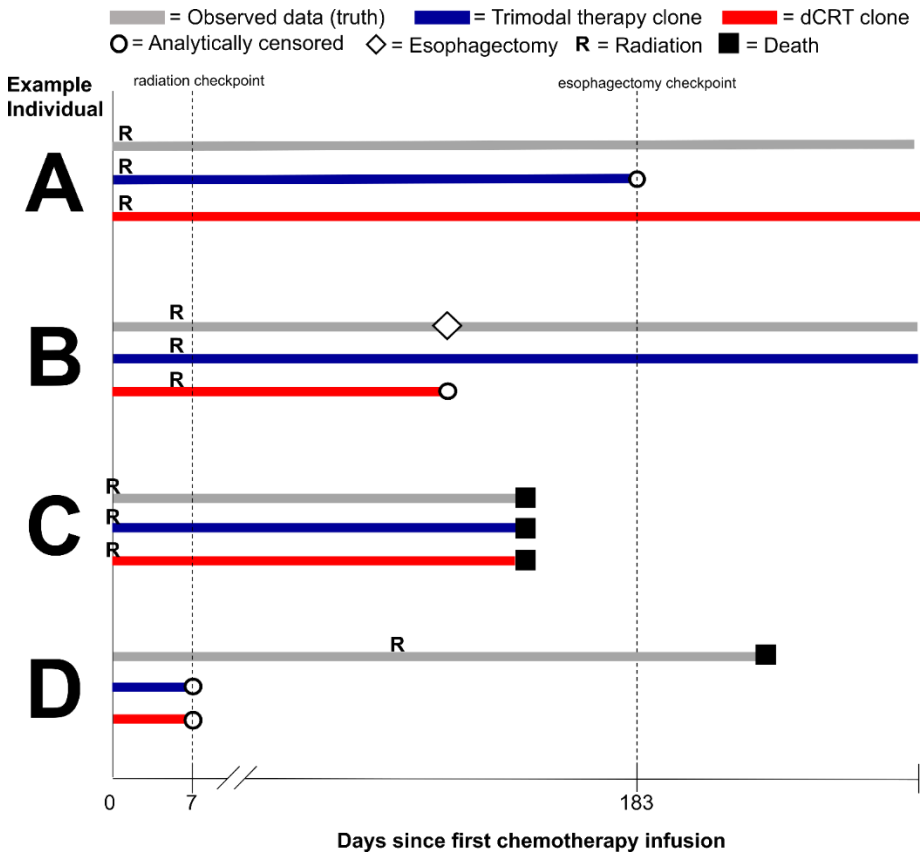
After cloning, censoring, and applying IPCWs, weighted non-parametric estimators were used to estimate the standardized cumulative incidence and standardized mean cumulative count. The standardized cumulative incidence curve for overall mortality was the mathematical complement of the survival function yielded by the Kaplan-Meier estimator. For cancer-specific mortality and functional adverse events, non-cancer mortality and all-cause mortality were treated as competing events, respectively. Thus, we multiplied the discrete hazards by an overall survival function that decreased with the occurrence of events of interest and competing events. Censoring individuals at the time of competing events would have yielded over-inflated estimates of risk.[211,218] The standardized cumulative incidence curves for cancer-specific mortality and functional adverse events were calculated using the weighted Aalen-Johansen

estimator (Appendix 3). The standardized mean cumulative count for days at home was calculated using the weighted Dong estimator (Appendix 3).

To quantify the degree of random error in our estimates, we calculated 95% confidence intervals for all measures of occurrence and association using a non-parametric bootstrap. Measures of occurrence were risks and mean cumulative counts. Measures of association were risk differences, risk ratios, mean cumulative count differences, and mean cumulative count ratios. Using sampling with replacement, we generated 500 bootstrap samples from the original study population of each outcome analyzed. Each bootstrap sample was of the same size as the original population it was drawn from. We then calculated all relevant estimates (e.g., five-year risk of mortality in each group and the risk difference) in each bootstrap sample. Similar to other studies using the clone-censor-weight technique, we used the 2.5^{th} and 97.5^{th} percentiles of the 500 bootstrapped estimates to serve as the lower and upper confidence limits for all measures of occurrence and association.[219] An increase in the number of bootstrap samples to 1,000 or more may have been warranted using the percentile method of confidence interval construction, but the computationally intensive nature of the calculations led to long run times.

3.4 Tables and Figures

Figure 3.1 Cloning and censoring process for four example patients who all received a chemotherapy infusion within 120 days of incident esophageal cancer diagnosis



Individual A receives radiation the day after their 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, their 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 they are following both treatment strategies until death. Individual D receives radiation more than 7 days after the first chemotherapy infusion; both the trimodal clone and the definitive chemoradiation clone are analytically censored at 7 days as they are no longer consistent with their respective treatment strategies at day 7.

CHAPTER 4 – MANUSCRIPT 1: PATTERNS OF CARE AMONG OLDER ADULTS DIAGNOSED WITH LOCALLY ADVANCED ESOPHAGEAL CANCER ELIGIBLE FOR TRIMODAL THERAPY

4.1 Introduction

Esophageal cancer is an aggressive malignancy with a five-year survival rate of 20%.[18] Over 15,000 deaths are attributed to esophageal cancer in the United States annually.[2] The incidence of esophageal adenocarcinoma has risen dramatically over time, potentially attributable to an increase in obesity and gastroesophageal reflux disease.[15,220] Similar to most malignancies, esophageal cancer incidence increases precipitously with advancing age, reaching a peak of 26.2 new cases per 100,000 amongst individuals 80-84 years of age.[50] As the U.S. population ages, the burden of esophageal cancer will continue to increase.[11,52]

At the time of diagnosis, most patients present with locally advanced disease. Treatment regimens for locally advanced cancers recommended by clinical guidelines from the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) include definitive chemoradiation and neoadjuvant chemoradiation followed by surgery (trimodal therapy).[3,4] Trimodal therapy is widely accepted as conferring the longest survival benefit due to the results of the Neoadjuvant Chemoradiotherapy Plus Surgery for Esophageal Cancer (CROSS) trial in 2015, which demonstrated superior overall survival (24.6 months longer median survival) in patients receiving trimodal therapy compared to surgery alone.[5,6,221] However, definitive chemoradiation is also considered an acceptable alternative based on studies showing about 20-30% of trimodal patients experience pathologic complete response.[5,82]

Uptake of trimodal therapy may be limited for older adults, a clinically complex population that was underrepresented in the CROSS trial. The median age of CROSS

participants was 60, whereas the median age at diagnosis of esophageal cancer in the United States is 68. This limits the generalizability of CROSS to older adults, a frequent limitation of randomized trials.[222,223] On average, older patients with cancer have higher comorbidity burdens, increased frailty, and decreased life expectancy compared to younger patients with cancer; in totality these may dampen the potential beneficial effect of trimodal therapy and inflate adverse events, concerns which may influence treatment selection.[88] In light of the morbidity and mortality of esophagectomy, many older adults may instead receive definitive chemoradiation.

Treatment trends over time and factors influencing treatment selection in older adults in the decade after the publication of the CROSS trial results have not been well-characterized. Understanding the treatment landscape is critical for assessing care quality and identifying populations that may be receiving undertreatment and overtreatment. The objective of this study was to describe patterns of initial cancer-directed therapy amongst a population of older adults with locally advanced esophageal cancer.

4.2 Methods

4.2.1 Data Source

This cohort study leveraged data from the Surveillance Epidemiology and End Results (SEER)-Medicare linkage to identify a population of older adults diagnosed with esophageal cancer between 2004-2017. SEER is a system of population-based cancer registries supported by the National Cancer Institute that captures incident cancers from select state and regional registries that collectively cover 28% of the U.S. population.[154] Medicare is the federally-funded governmental program administered by the Center for Medicare and Medicaid Services that provides health insurance to adults 65 years of age and older, as well as individuals with end-stage-renal-disease and disabilities. Over 97% of adults 65 years of age and older are enrolled in Medicare, though our study uses data only from SEER cases with fee-for-service Medicare.[153]

Administrative data from Medicare used in this study include beneficiary enrollment information and medical claims (Medicare Parts A and B).

4.2.2 Study Population

We focused on a population of locally advanced esophageal cancer cases for which trimodal therapy is a recommended treatment option per current NCCN and ASCO guidelines.[3,4] Incident cases diagnosed between 2004 and 2017 were identified using the SEER-Medicare database. We included individuals 66 years of age or older at the time of diagnosis who had a histologically-confirmed incident diagnosis of adenocarcinoma or squamous cell carcinoma not originating in the cervical esophagus (ICD Oncology-3 site codes C15.1-C15.9). Cases diagnosed via death certificate or autopsy were excluded. We used the NCCN and ASCO clinical guidelines coupled with the American Joint Committee on Cancer (AJCC) 7th edition staging manual to identify cancers of interest based on the tumor (T), node (N), and metastasis (M) case data supplied by the registry. All locally advanced cancers were required to be non-metastatic (M0). There were two T and N combination groups eligible amongst the non-metastatic cases: 1) any resectable tumor (T1-T4a) with positive nodes (N1-N3), and 2) more advanced resectable tumors (T2-T4a) with any nodal status (N0-N3). Eligible cases were required to have at least 12 months of continuous fee-for-service Medicare insurance and no managed care enrollment prior to the cancer diagnosis. We further excluded cases who were diagnosed with other cancers (e.g., lung) in the year before their first esophageal cancer diagnosis to ensure that cancer-directed treatments observed in the claims data were for treatment of esophageal cancer.

4.2.3 Patient Characteristics

We assigned the date of diagnosis as the first of the month in which the cancer was diagnosed. The following patient-level characteristics were identified at the date of diagnosis:

age, sex, race and ethnicity, tumor site (location), histologic subtype, tumor stage group, tumor grade, number of previous cancers in the registry (first diagnosed more than a year before incident esophageal cancer), geographic region of the reporting registry, percentage of population living below the federal poverty line in the census tract, and county-level urbanicity. We calculated the NCI adaption of the Charlson comorbidity score[160,161] and the Kim frailty index[167] using medical claims data from the year prior to cancer diagnosis. These claims-based indices serve as proxies of patient comorbidity and frailty, respectively.[165–167,224]

4.2.4 Outcome Assessment: Initial Treatment Received

We were primarily interested in five categories of treatment: trimodal therapy (neoadjuvant chemoradiation followed by surgery), definitive chemoradiation, surgery alone or other surgery-based multimodal therapy (e.g., chemotherapy followed by surgery), palliative therapy (chemotherapy or radiation alone), and no treatment. A nine-month treatment window extending from the date of diagnosis was used to assess the treatments received based on the occurrence and sequence of medical claims corresponding to treatments of interest. Given the lethality of esophageal cancer, a substantial number of cases were anticipated to die prior to completion of the nine-month assessment window. Thus, in our primary analysis we did not require nine months of survival. If an individual received any treatment prior to death within nine months, this treatment information was used to classify the individual into a treatment group using all therapies received prior to death. However, individuals were excluded from the analysis if they lost their fee-for-service insurance coverage within nine months of diagnosis and prior to death, an uncommon occurrence (Figure 4.1). A sensitivity analysis examined treatment trends amongst individuals who lived at least 9 months after diagnosis.

Surgery consisted of resection (esophagectomy) and was identified using International Classification of Disease (ICD)-9 and 10 procedure codes, as well as Current Procedural

Terminology (CPT) codes. Chemotherapy consisted of any intravenous chemotherapy with a corresponding Healthcare Common Procedure Coding System (HCPCS) code. All chemotherapy agents received within 28 days of the first delivery of chemotherapy were used in characterizing different regimens. Radiation consisted of external beam radiation and was identified with radiation treatment delivery CPT codes. Individuals who received chemotherapy and radiation before surgical resection were classified as trimodal therapy patients. Individuals who received chemotherapy and radiation, but no surgery, were categorized as belonging to the definitive chemoradiation treatment group. Individuals receiving only resection or who received either chemotherapy or radiation (but not both before surgery) with surgery were classified in the "surgery or other multimodal" group. Cases receiving only chemotherapy or only radiation were classified in the palliative care group. Lastly, cases not receiving any one of these modalities were classified as no treatment. All codes used to identify treatments are provided in Appendix 2.

4.2.5 Statistical Analysis

Given the differences in etiology, pathogenesis, treatment, and prognosis between adenocarcinomas and squamous cell carcinomas, all analyses were stratified by histologic subtype. Descriptive characteristics were calculated for the study population. The age-standardized annual percentage of individuals in each treatment group was reported across study years of diagnosis (2004-2017). Direct standardization was used to provide age-standardized percentages using the age distribution of individuals diagnosed in 2017 as the standard population.[168]

Joinpoint regression software was used to detect and quantify significant trends in age-standardized percentages for each treatment over calendar time. A maximum of two join points (three trends) was considered, and the permutation statistical test was used to select the final model. Joinpoint regression is a data-adaptive trend analysis method that allows for non-

linearities in data by allowing for separate trend “segments” with distinct slopes across the time being considered in trend analysis. Within each segment, the relationship between year of diagnosis and percentage receiving a given treatment is assumed to be linear on the log scale.[225]

Descriptive statistics of treatment receipt were calculated and represented with bar charts. These graphics presented the proportion of individuals in each treatment category according to values of each respective clinical and demographic characteristic under consideration. Descriptive (non-causal) risk ratios comparing the probability of receiving trimodal therapy versus all other treatment modalities across levels within each variable were calculated using univariable modified Poisson regression.[226]

To evaluate temporal trends in receipt of specific chemotherapy regimens across the study years, another joinpoint regression analysis was performed within the subset of the cohort treated with definitive chemoradiation or trimodal therapy.

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).

4.3 Results

4.3.1 Study Population

After applying study eligibility criteria, the final study population consisted of 4,332 individuals 66 years of age and older with incident locally-advanced esophageal cancer diagnosed between 2004 and 2017 (Figure 4.1). Study population descriptive statistics for demographic and clinical variables are reported in Table 4.1, stratified by histologic subtype. There were 2,801 adenocarcinomas and 1,531 squamous cell carcinomas. The median ages of individuals with adenocarcinomas and squamous cell carcinomas were 74 and 75, respectively. Over 93% of individuals with adenocarcinomas were non-Hispanic white, compared to only 71.8% of squamous cell carcinomas. In both histologic subtypes, less than half of the population

were classified in the robust (healthiest) frailty index category. Combined across adenocarcinomas and squamous cell carcinomas, 1,322 (30.5%) of patients died within 9 months of diagnosis.

4.3.2 Temporal Trends in Treatment Received

Age-standardized percentages of the cohort corresponding to each treatment group are presented in Figure 4.2. Accompanying estimates are presented in Table 4.2. The age-standardized rates are plotted with a trend line produced via joinpoint regression models.

For adenocarcinomas, the age-standardized percentage of adenocarcinomas receiving trimodal therapy increased from 16.7% (95% CI, 10.7 – 22.7%) in 2004 to 26.1% (95% CI, 20.8% – 31.5%) in 2017. The joinpoint regression of these rates found one (increasing) trend for trimodal therapy, with an annual percent change from 2004-2017 of 3.5% (95% CI, 0.7% – 6.4%). The age-standardized percentage of cases receiving definitive chemoradiation increased from 17.7% (95% CI, 11.6% – 23.7%) in 2004 to 49.8 % (95% CI, 43.5% – 56.0%) in 2017, the largest increasing percentage change of any of the therapeutic groups. The corresponding joinpoint regression of these definitive chemoradiation rates found two increasing trends, with annual percent changes from 2004-2010 and 2010-2017 of 14.6% (95% CI, 6.4% – 23.3%) and 3.0% (95% CI, 0.3% – 5.8%), respectively. In contrast to these increases, the percentage of cases receiving surgery or other multimodal therapy decreased over the study period. The percentage of patients receiving palliative treatment and none of these treatments were stable.

For squamous cell carcinomas, the age-standardized percentage of adenocarcinomas receiving trimodal therapy increased minimally from 7.3% (95% CI, 2.5 – 12.0%) in 2004 to 9.1% (95% CI: 4.1% – 14.1%) in 2017. The joinpoint regression of these rates detected no change over time. The age-standardized percentage of cases receiving definitive chemoradiation increased from 25.7% (95% CI, 17.7% – 33.8%) in 2004 to 59.5% (95% CI, 50.8% – 68.2%) in 2017, constituting the largest increasing percentage change of any of the

therapeutic groups. The corresponding joinpoint regression of these definitive chemoradiation rates found two increasing trends, with annual percent changes from 2004-2011 and 2011-2017 of 11.3% (95% CI, 6.4% – 16.5%) and 2.6% (95% CI, -0.8% – 6.1%), respectively. Regarding the other treatment groups, receipt of palliative treatment and surgery or other multimodal therapy decreased over time. The percentage of patients receiving none of these treatments was stable.

The sensitivity analysis that required 9 months of post-diagnosis survival found qualitatively similar temporal trends in the age-standardized percentage of patients receiving each treatment as the primary analysis (Figure 4.3). As expected, the percentages of patients receiving no treatment and palliative treatment decreased with this survival requirement. In adenocarcinomas and squamous cell carcinomas, the age-standardized percentage of patients receiving no treatment in 2017 decreased from 12.9% to 7.6% and 15.7% to 7.0%, respectively.

4.3.3 Relationships Between Patient Characteristics and Treatment Received

The relationships between select demographic and clinical characteristics and treatment received are represented in Figures 4.4-4.7. The numeric estimates for all variables considered can be found in Tables 4.3-4.6. As seen in Figure 4.4, the probability of receiving trimodal therapy decreased with increasing age and increasing comorbidity burden for both histologic subtypes. For instance, among adenocarcinomas, 37.7% of individuals aged 66-70 received trimodal therapy compared to only 27.0% of those aged 71-75 (RR = 0.72; 95% CI, 0.62 – 0.83) and 11.7% of those 76 years of age and older (RR = 0.31; 95% CI, 0.26 – 0.40). Treatment with trimodal therapy was highest in stage IIIB tumors for adenocarcinomas and stage IIIA for squamous cell carcinomas. A comprehensive reporting of the probabilities of receiving trimodal therapy and corresponding descriptive (unadjusted, non-causal) risk ratios are presented in Tables 4.7 and 4.8.

4.3.4 Temporal Trends in Chemotherapeutic Regimens

Temporal trends in the age-standardized percentage of individuals who received cisplatin-based, carboplatin-based, and other chemotherapeutic regimens among those treated with definitive chemoradiation or trimodal therapy are presented in Figure 4.8 and Table 4.9. The age-standardized percentage of individuals with adenocarcinomas and squamous cell carcinomas receiving cisplatin-based therapies decreased at an average annual percent change of -18.0% (95% CI, -24.9% – -10.5%) and -13.7% (95% CI: -19.6% – -7.5%), respectively. This decrease coincided with an increase in the use of carboplatin-based therapies; for instance, amongst individuals with adenocarcinomas there was a 17.8% (95% CI: 7.1 – 29.7) annual percent increase in carboplatin-based therapy between 2008 and 2014.

4.4 Discussion

Our study empirically documented patterns of care in older adults with locally advanced esophageal cancer between 2004 and 2017 using data from SEER-Medicare. Although the use of trimodal therapy increased over time, treatment with definitive chemoradiation increased at a faster rate and is currently the dominant treatment paradigm for older adults in practice. We have shown that receipt of trimodal therapy varies across levels of demographic and clinical characteristics. Among patients receiving definitive chemoradiation or trimodal therapy, we found a strong substitution of cisplatin with carboplatin. This suggests that the chemotherapy regimen used in CROSS (carboplatin and paclitaxel) has been adopted even in non-surgical populations.

The results of our study add to the existing literature. Molena et al. examined esophageal cancer treatment trends in older adults using SEER-Medicare data from 2001 to 2009 and similarly found that definitive chemoradiation was the dominant treatment strategy (48.5% using a denominator of patients who received any chemotherapy, radiation, or surgery),

though the study ended 8 years prior to ours and before the final results of CROSS were disseminated.[16] Our findings that the use of trimodal therapy and definitive chemoradiation have both increased suggests that the CROSS regimen has been adopted by oncologists treating older adults, though many of their patients may not be fit to receive esophagectomy, may not be offered surgery, or may not elect to receive offered surgery. No prior research has documented the trends in use of different chemotherapy regimens in this population, though our finding of a channeling away from cisplatin and towards carboplatin is reflective of studies that document higher rates of grade 3 toxicities in patients receiving cisplatin and 5-fluorouracil compared to carboplatin and paclitaxel.[227]

Our study has numerous strengths. We described contemporary trends in treatment including calendar years after publication of the results from the CROSS trial. Our incorporation of a novel frailty index was germane to the older adult population, providing insight into how patient frailty may impact treatment selection. Detailed understanding of potential confounding factors are a prerequisite for producing a methodologically rigorous comparative effectiveness study. This work provides a detailed, quantitative depiction of factors that may influence treatment selection and prognosis, thereby serving as a roadmap for future studies seeking to compare outcomes across these modalities.

Limitations of the study include the reliance on claims-based proxies for comorbidity and frailty, in place of clinical measurement. Without data on patient preference and the results of geriatric assessment—cornerstones of shared decision making—our study does not determine the appropriateness of treatment received. Future work describing the distribution of treatment according to levels of clinically-assessed frailty and functional status would better illuminate quality of care gaps. The generalizability of our findings is also restricted to those with Medicare fee-for-service. Medicare Advantage beneficiaries tend to have a higher health status,[228] potentially impacting treatment patterns.

In conclusion, the treatment of older adults with locally advanced esophageal cancer has evolved over time. The percentage of individuals receiving definitive chemoradiation and trimodal therapy have both increased since 2004. The larger increase has been in definitive chemoradiation, which remains the dominant form of treatment for older adults in practice. Given the possibility of complete response and the significant morbidity and mortality associated with resection, definitive chemoradiation may be appropriate treatment for some older adults this population. However, despite its prognostic importance, pathologic complete response is notoriously difficult to predict based on clinical parameters.[100,113] Additionally, adenocarcinomas have been demonstrated to have lower rates of pathologic complete response than squamous cell carcinomas.[5,101] Even most recently, less than a third of older adults diagnosed with adenocarcinomas received trimodal therapy, signaling potential undertreatment in the subset of these patients that are candidates for surgery.

4.5 Tables and Figures

Figure 4.1 Flowchart depicting selection of study population through application of eligibility criteria

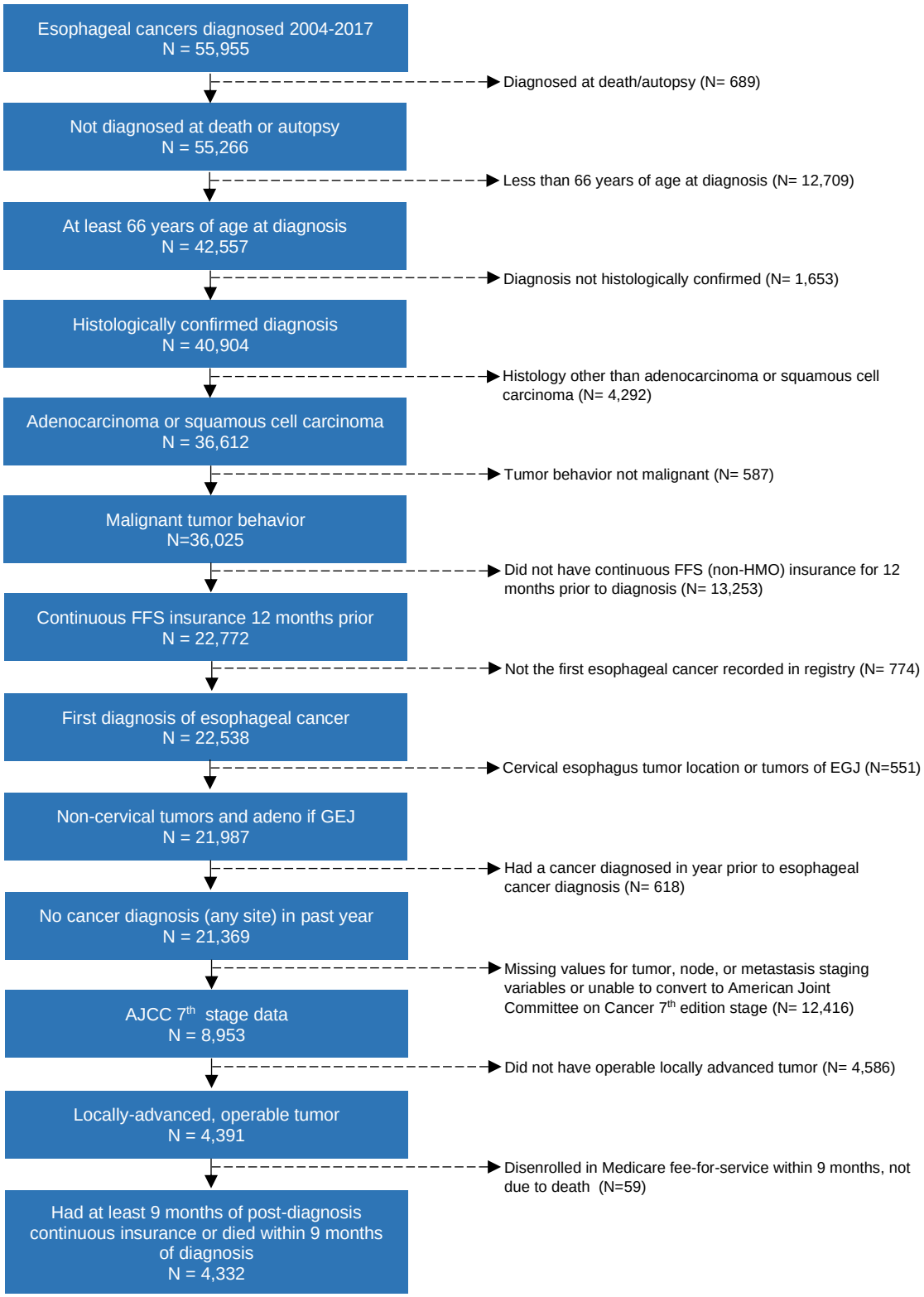
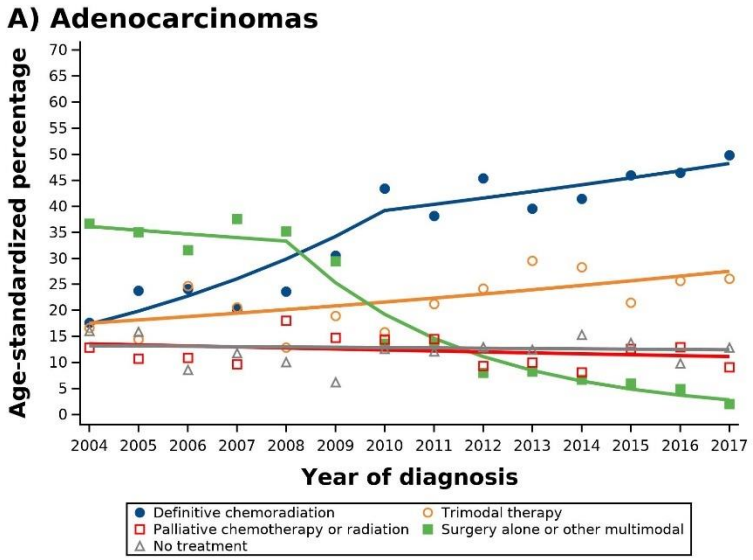


Table 4.1 Study population characteristics, amongst a population of Medicare-enrolled older adults diagnosed with locally advanced esophageal cancer in SEER regions, 2004-2017

	Adenocarcinomas (N = 2,801)	Squamous cell carcinomas (N = 1,531)
Age, median (IQR)	74 (70 - 80)	75 (70 - 80)
Sex		
Male	2,412 (86.1)	855 (55.9)
Female	389 (13.9)	676 (44.2)
Race		
Non-Hispanic white	2,609 (93.2)	1,099 (71.8)
Hispanic white	97 (3.5)	83 (5.4)
Black	54 (1.9)	231 (15.1)
Another race and ethnicity or missing	41 (1.5)	118 (7.7)
Year of diagnosis		
2004-2008	646 (23.1)	381 (24.9)
2009-2013	1,054 (37.6)	631 (41.2)
2014-2017	1,101 (39.3)	519 (33.9)
Registry region[†]		
Northeast	641 (22.9)	348 (22.7)
Midwest	420 (15.0)	165 (10.8)
South	615 (22.0)	350 (22.9)
West	1,125 (40.2)	668 (43.6)
Tumor grade		
Grade I	117 (4.2)	83 (5.4)
Grade II	1,040 (37.1)	630 (41.2)
Grade III	1,238 (44.2)	540 (35.3)
Undetermined differentiation	406 (14.5)	278 (18.2)
Tumor location		
Upper and middle	201 (7.2)	950 (62.0)
Lower	2,394 (85.5)	436 (28.5)
Overlapping or NOS	206 (7.4)	145 (9.5)
Stage group		
IB	286 (10.2)	54 (3.5)
IIA	149 (5.3)	290 (18.9)
IIB	1,095 (39.1)	601 (39.3)
IIIA	936 (33.4)	459 (30.0)
IIIB	207 (7.4)	77 (5.0)
IIIC	128 (4.6)	50 (3.3)
Number of prior non-esophageal cancers		
0	2,313 (82.6)	1,119 (78.3)
1	415 (14.8)	266 (17.4)
≥2	73 (2.6)	66 (4.3)
Charlson comorbidity score		
0	1,218 (43.5)	692 (45.2)
1-2	1,099 (39.2)	591 (38.6)
3-4	326 (11.6)	167 (10.9)
≥5	158 (5.6)	81 (5.3)
Kim Frailty Index		
Robust, <0.15	1,368 (48.8)	692 (45.2)
Prefrail, 0.15-0.24	1,156 (41.3)	674 (44.0)
Mildly frail, 0.25-0.34	224 (8.0)	135 (8.8)
Moderate-to-severely frail, 0.35	53 (1.9)	30 (2.0)
Census tract poverty percent		
0% - <5%	694 (26.8)	330 (22.6)
5%-<10%	782 (30.2)	413 (28.3)
10% - <20%	728 (28.1)	385 (26.4)
20% - 100%	384 (14.8)	333 (22.8)
Missing	213	70
Level of urbanization		
Metropolitan	2,350 (83.9)	1,335 (87.2)
Urban	315 (11.3)	151 (9.9)
Rural	136 (4.9)	45 (2.9)

[†] 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.

Figure 4.2 Modelled temporal trends in the age-standardized percentage of individuals receiving each treatment for a Medicare-enrolled population of adults 66 years of age and older diagnosed with locally advanced esophageal cancer between 2004 and 2017



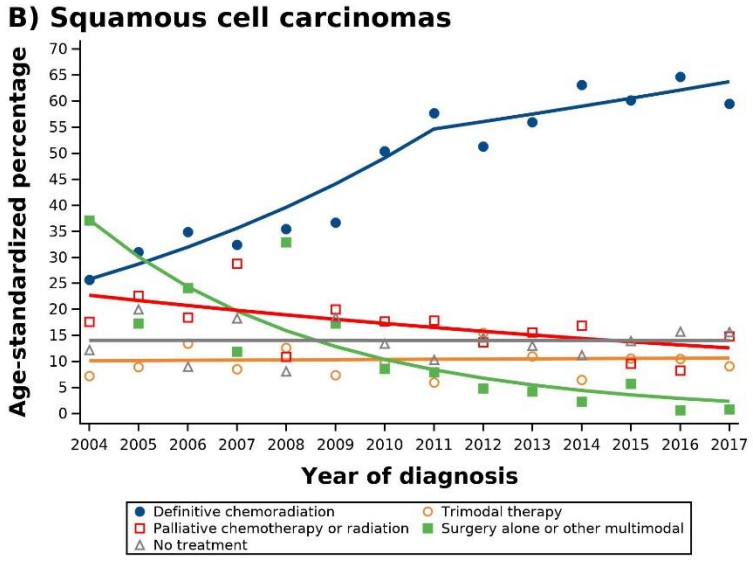
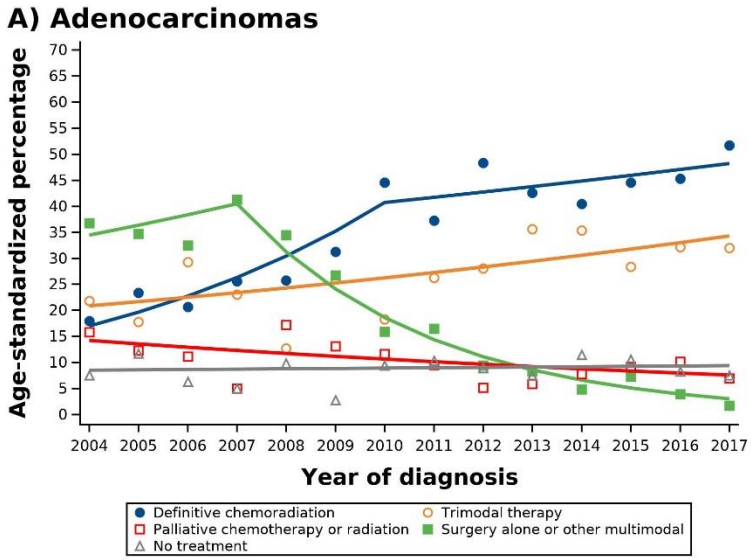


Figure 4.3 Sensitivity analysis presenting temporal trends in the age-standardized percentage of individuals receiving each treatment amongst those who survived at least nine months post-diagnosis



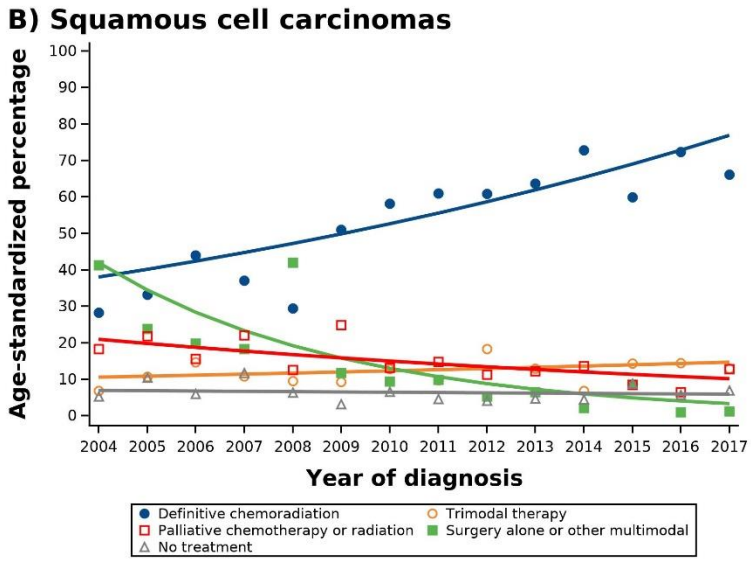
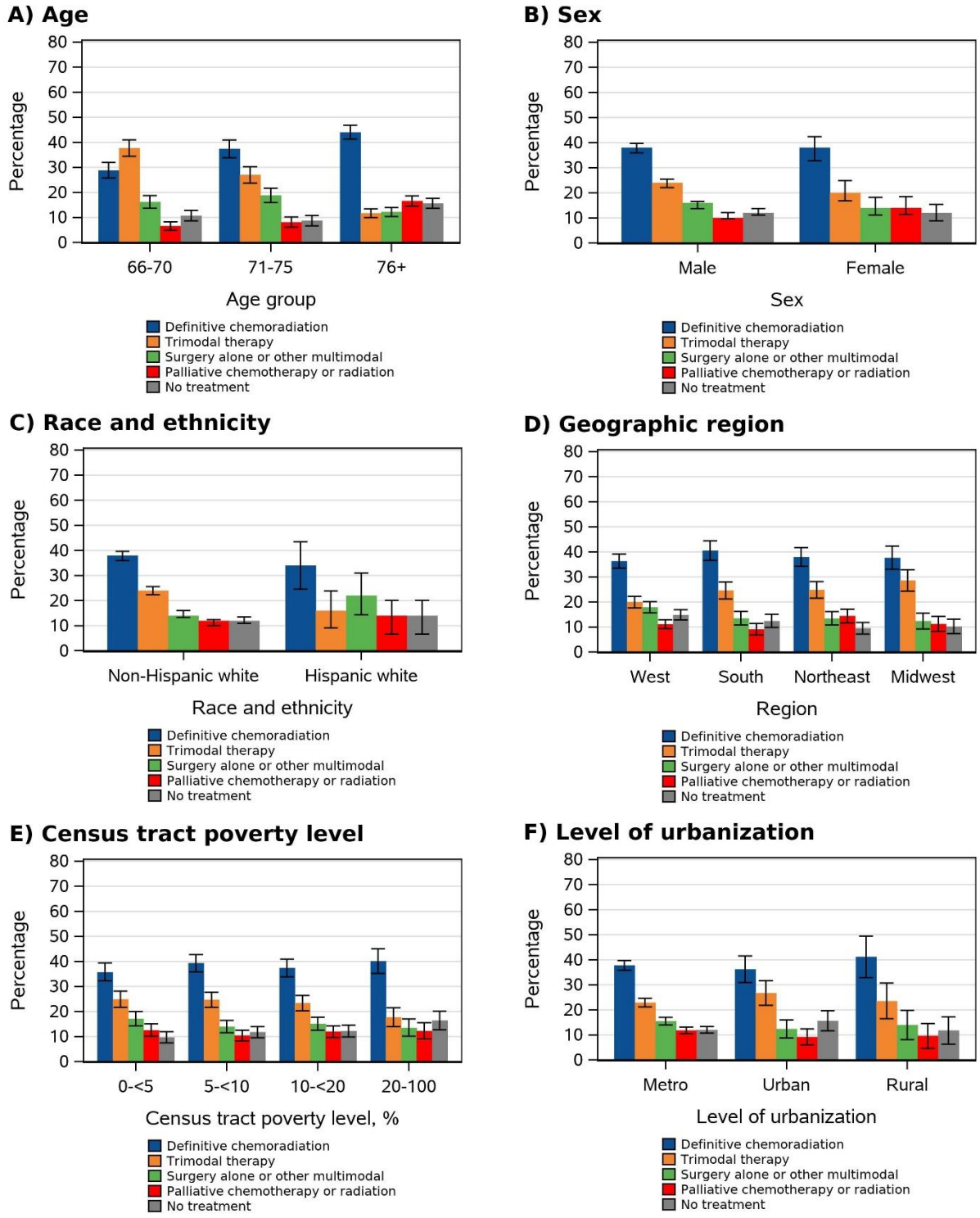


Table 4.2 Temporal trends in treatment received, stratified by histologic subtype, SEER-Medicare 2004-2017

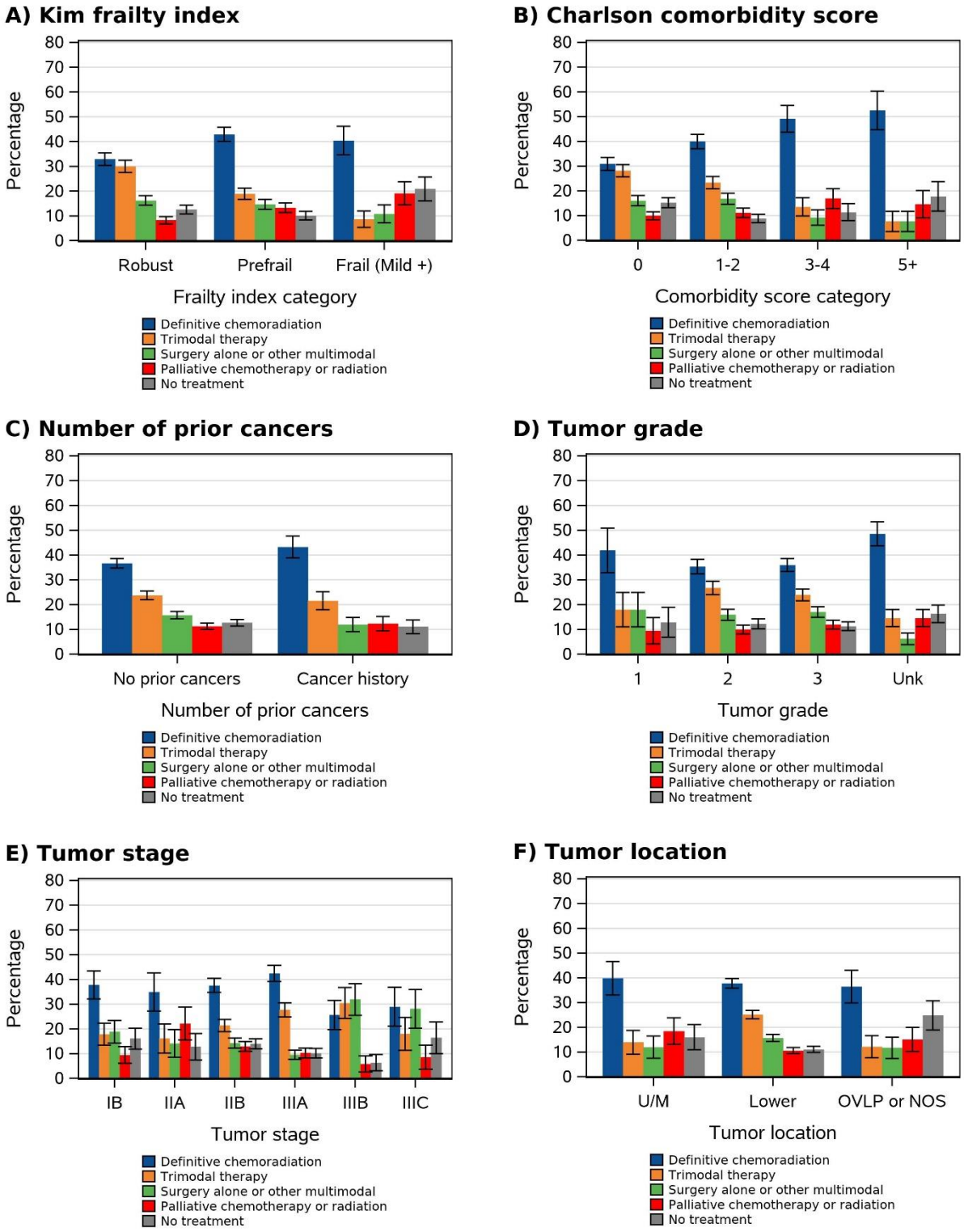
Treatment group	Age-standardized percentage in 2004 (95% CI)	Age-standardized percentage in 2017 (95% CI)	Temporal trend segment	Annual percent change during segment, %	Average annual percent change across all segments, 2004-2017
Adenocarcinomas					
Definitive chemoradiation	17.7 (11.6 – 23.7)	49.8 (43.5 – 56.0)	2004-2010 2010-2017	14.6 (6.4 – 23.3) 3.0 (0.3 – 5.8)	8.2 (4.8 – 11.7)
Trimodal therapy	16.7 (10.7 – 22.7)	26.1 (20.8 – 31.5)	2004-2017	3.5 (0.7 – 6.4)	3.5 (0.7 – 6.4)
Surgery alone or other multimodal	36.7 (28.8 – 44.5)	2.1 (0.9 – 3.9)	2004-2008 2008-2017	-2.0 (-13.4 – 10.9) -29.1 (-18.4 – -8.9)	-17.8 (-22.0 – -13.3)
Palliative chemotherapy or radiation	12.9 (7.5 – 18.3)	9.1 (5.6 – 12.7)	2004-2017	-1.5 (-4.7 – 1.8)	-1.5 (-4.7 – 1.8)
No treatment	16.1 (10.5 – 21.7)	12.9 (8.6 – 17.1)	2004-2017	-0.5 (-3.3 – 2.4)	-0.5 (-3.3 – 2.4)
Squamous cell carcinomas					
Definitive chemoradiation	25.7 (17.7 – 33.8)	59.5 (50.8 – 68.2)	2004-2011 2011-2017	11.3 (6.4 – 16.5) 2.6 (-0.8 – 6.1)	7.2 (4.5 – 10.0)
Trimodal therapy	7.3 (2.5 – 12.0)	9.1 (4.1 – 14.1)	2004-2017	0.4 (-4.1 – 5.1)	0.4 (-4.1 – 5.1)
Surgery alone or other multimodal	37.1 (27.6 – 46.7)	0.8 (0.0 – 2.4)	2004-2017	-19.1 (-24.8 – -13.0)	-19.1 (-24.8 – -13.0)
Palliative chemotherapy or radiation	17.7 (10.1 – 25.2)	14.9 (8.7 – 21.1)	2004-2017	-4.4 (-7.7 – -1.0)	-4.4 (-7.7 – -1.0)
No treatment	12.2 (5.7 – 18.8)	15.7 (9.3 – 22.1)	2004-2017	0.0 (-3.4 – 3.4)	0.0 (-3.4 – 3.4)

Figure 4.4 Distribution of treatment receipt by patient demographics among older adults diagnosed with locally advanced esophageal adenocarcinomas



Cell sizes <11 are suppressed to protect confidentiality, per CMS Cell Size Suppression Policy. This may cause some variable values to not be presented such as the treatment distribution of black individuals diagnosed with esophageal adenocarcinoma.

Figure 4.5 Distribution of treatment receipt by patient clinical factors among older adults diagnosed with locally advanced esophageal adenocarcinomas



Abbreviations: NOS, not otherwise specified; OVLP, overlapping; U/M, upper/middle; Unk, undetermined

Table 4.3 Quantitative estimates of treatment receipt by patient demographics among older adults diagnosed with locally advanced esophageal adenocarcinomas

		Definitive chemoradiation		Trimodal therapy		Other multimodal		Palliative chemotherapy or radiation		No treatment	
Variable	**Total stratum size**	N	Treatment Percent (95% CI)	N	Treatment Percent (95% CI)	N	Treatment Percent (95% CI)	N	Treatment Percent (95% CI)	N	Treatment Percent (95% CI)
Age group											
66-70	839	242	28.8 (25.8, 31.9)	316	37.7 (34.4, 40.9)	136	16.2 (13.7, 18.7)	55	6.6 (4.9, 8.2)	90	10.7 (8.6, 12.8)
71-75	712	266	37.4 (33.8, 40.9)	192	27.0 (23.7, 30.2)	134	18.8 (15.9, 21.7)	58	8.1 (6.1, 10.2)	62	8.7 (6.6, 10.8)
76+	1250	550	44.0 (41.2, 46.8)	146	11.7 (9.9, 13.5)	152	12.2 (10.3, 14.0)	207	16.6 (14.5, 18.6)	195	15.6 (13.6, 17.6)
Sex											
Male	2,412	912	37.8 (35.9, 39.7)	573	23.8 (22.1, 25.4)	365	15.1 (13.7, 16.6)	262	10.9 (9.6, 12.1)	300	12.4 (11.1, 13.8)
Female	389	146	37.5 (32.7, 42.3)	81	20.8 (16.8, 24.9)	57	14.7 (11.1, 18.2)	58	14.9 (11.4, 18.4)	47	12.1 (8.8, 15.3)
Race and ethnicity											
NHW	2,609	986	37.8 (35.9, 39.7)	626	24.0 (22.4, 25.6)	384	14.7 (13.4, 16.1)	294	11.3 (10.1, 12.5)	319	12.2 (11.0, 13.5)
HW	97	33	34.0 (24.6, 43.4)	16	16.5 (9.1, 23.9)	22	22.7 (14.3, 31.0)	13	13.4 (6.6, 20.2)	13	13.4 (6.6, 20.2)
Black	54	*	*	*	*	*	*	*	*	*	*
Another race and ethnicity	41	*	*	*	*	*	*	*	*	*	*
Region											
West	1,125	408	36.3 (33.5, 39.1)	224	19.9 (17.6, 22.2)	201	17.9 (15.6, 20.1)	125	11.1 (9.3, 12.9)	167	14.8 (12,8, 16.9)
South	615	249	40.5 (36.6, 44.4)	151	24.6 (21.2, 28.0)	83	13.5 (10.8, 16.2)	56	9.1 (6.8, 11.4)	76	12.4 (9.8, 15)
Northeast	641	243	37.9 (34.2, 41.7)	159	24.8 (21.5, 28.1)	86	13.4 (10.8, 16.1)	92	14.4 (11.6, 17.1)	61	9.5 (7.2, 11.8)
Midwest	420	158	37.6 (33.0, 42.3)	120	28.6 (24.3, 32.9)	52	12.4 (9.2, 15.5)	47	11.2 (8.2, 14.2)	43	10.2 (7.3, 13.1)
Census-tract poverty level											
0% - <5%	694	248	35.7 (32.2, 39.3)	173	24.9 (21.7, 28.1)	119	17.1 (14.3, 20.00	87	12.5 (10.1, 15.0)	67	9.7 (7.5, 11.9)
5% - <10%	782	307	39.3 (35.8, 42.7)	193	24.7 (21.7, 27.7)	109	13.9 (11.5, 16.4)	81	10.4 (8.2, 12.5)	92	11.8 (9.5, 14.0)
10% - <20%	728	272	37.4 (33.8, 40.9)	170	23.4 (20.3, 26.4)	110	15.1 (12.5, 17.7)	87	12.0 (9.6, 14.3)	89	12.2 (9.8, 14.6)
20% - 100%	384	154	40.1 (35.2, 45.0)	68	17.7 (13.9, 21.5)	52	13.5 (10.1, 17.0)	47	12.2 (9.0, 15.5)	63	16.4 (12.7, 20.1)
Urbanization											
Metro	2,350	888	37.8 (35.8, 39.7)	538	22.9 (21.2, 24.6)	364	15.5 (14.0, 17.0)	278	11.8 (10.5, 13.1)	282	12.0 (10.7, 13.3)
Urban	315	114	36.2 (30.9, 41.5)	84	26.7 (21.8, 31.6)	39	12.4 (8.7, 16.0)	29	9.2 (6.0, 12.4)	49	15.6 (11.6, 19.6)
Rural	136	56	41.2 (32.9, 49.4)	32	23.5 (15.4, 30.7)	19	14.0 (8.1, 19.8)	13	9.6 (4.6, 14.5)	16	11.8 (6.3, 17.2)

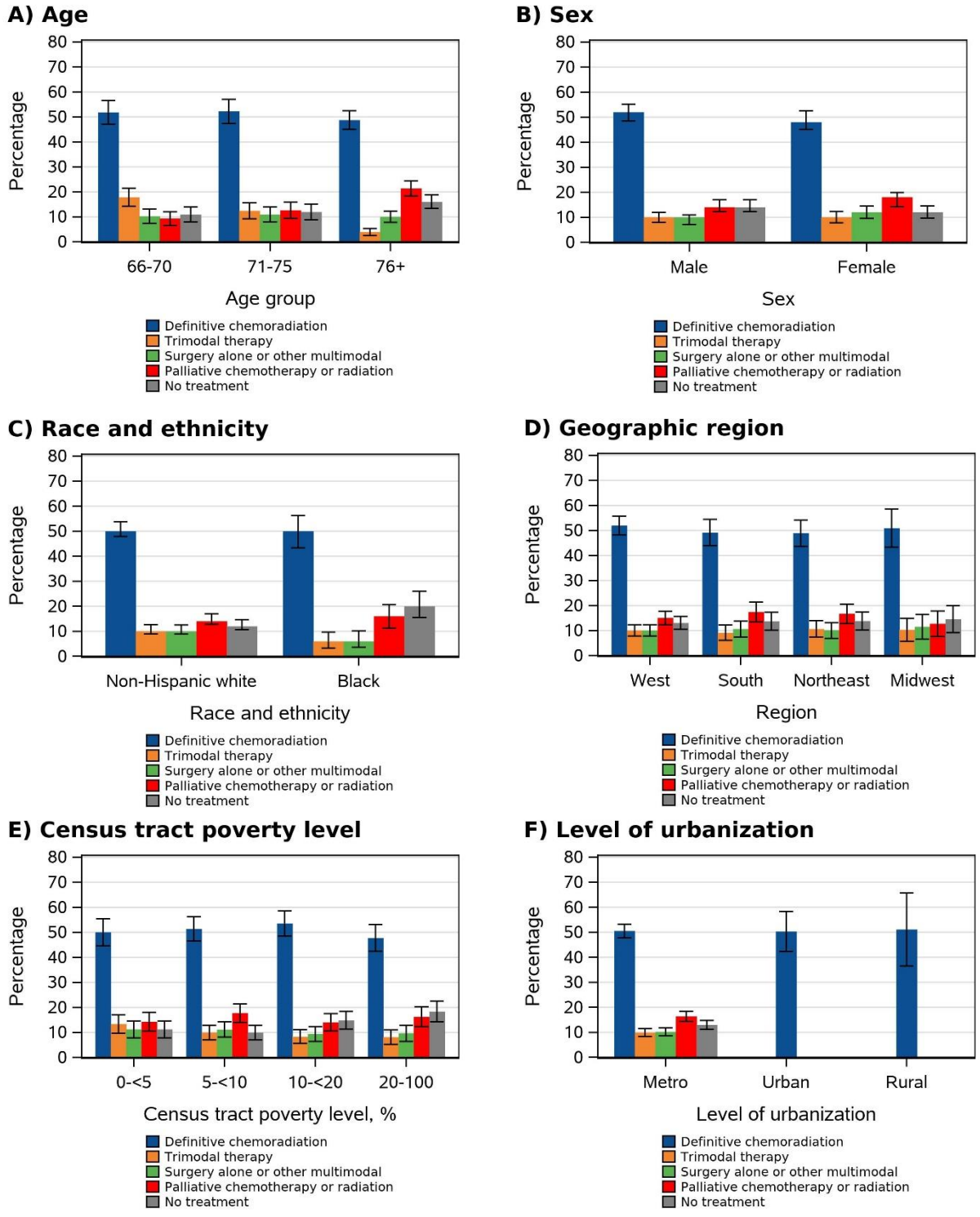
* Cell sizes <11 are suppressed to protect confidentiality, per CMS Cell Size Suppression Policy. Cell sizes greater than 11 may also be suppressed if necessary to ensure small cell sizes cannot be deduced from other cells.

Table 4.4 Quantitative estimates of treatment receipt by patient clinical factors among older adults diagnosed with locally advanced esophageal adenocarcinomas

Variable	Total stratum size	Definitive chemoradiation N	Definitive chemoradiation Treatment Percent (95% CI)	Trimodal therapy N	Trimodal therapy Treatment Percent (95% CI)	Other multimodal N	Other multimodal Treatment Percent (95% CI)	Palliative N	Palliative Treatment Percent (95% CI)	No treatment N	No treatment Treatment Percent (95% CI)
Kim frailty index											
Robust	1,368	450	32.9 (30.4, 35.4)	411	30.0 (27.6, 32.5)	222	16.2 (14.3, 18.2)	113	8.3 (6.8, 9.7)	172	12.6 (10.8, 14.3)
Prefrail	1,156	496	42.9 (40.1, 45.8)	219	18.9 (16.7, 21.2)	170	14.7 (12.7, 16.7)	154	13.3 (11.4, 15.3)	117	10.1 (8.4, 11.9)
Frail (Mild +)	277	112	40.4 (34.7, 46.2)	24	8.7 (5.4, 12.0)	30	10.8 (7.2, 14.5)	53	19.1 (14.5, 23.8)	58	20.9 (16.1, 25.7)
Charlson comorbidity score											
0	1,218	376	30.9 (28.3, 33.5)	342	28.1 (25.6, 30.6)	195	(16.0, 14.0, 18.1)	120	9.9 (8.2, 11.5)	185	15.2 (13.2, 17.2)
1-2	1,099	439	39.9 (37.0, 42.8)	256	23.3 (20.8, 25.8)	185	16.8 (14.6, 19.0)	122	11.1 (9.2, 13.0)	97	8.8 (7.1, 10.5)
3-4	326	160	49.1 (43.7, 54.5)	44	13.5 (9.8, 17.2)	30	9.2 (6.1, 12.3)	55	16.9 (12.8, 20.9)	37	11.3 (7.9, 14.8)
5+	158	83	52.5 (44.7, 60.3)	12	7.6 (3.5, 11.7)	12	7.6 (3.5, 11.7)	23	14.6 (9.1, 20.1)	28	17.7 (11.8, 23.7)
Number of prior cancers											
No prior cancers	2,313	847	36.6 (34.7, 38.6)	549	23.7 (22.0, 25.5)	364	15.7 (14.3, 17.2)	260	11.2 (10.0, 12.5)	293	12.7 (11.3, 14.0)
Cancer history	488	211	43.3 (38.8, 47.6)	105	21.5 (17.9, 25.2)	58	11.9 (9.0, 14.8)	60	12.3 (9.4, 15.2)	54	11.1 (8.3, 13.8)
Tumor grade											
1	117	49	41.9 (32.9, 50.8)	21	17.9 (11.0, 24.9)	21	17.9 (11.0, 24.9)	11	9.4 (4.1, 14.7)	15	12.8 (6.8, 18.9)
2	1,040	367	35.3 (32.4, 38.2)	278	26.7 (24.0, 29.4)	165	15.9 (13.6, 18.1)	103	9.9 (8.1, 11.7)	127	12.2 (10.2, 14.2)
3	1,238	445	35.9 (33.3, 38.6)	296	23.9 (21.5, 26.3)	211	17.0 (14.9, 19.1)	147	11.9 (10.1, 13.7)	139	11.2 (9.5, 13.0)
Undetermined	406	197	48.5 (43.7, 53.4)	59	14.5 (11.1, 18.0)	25	6.2 (3.8, 8.5)	59	14.5 (11.1, 18.0)	66	16.3 (12.7, 19.8)
Tumor stage											
IB	286	108	37.8 (32.1, 43.4)	51	17.8 (13.4, 22.3)	54	18.9 (14.3, 23.4)	27	9.4 (6.1, 12.8)	46	16.1 (11.8, 20.3)
IIA	149	52	34.9 (27.2, 42.6)	24	16.1 (10.2, 22.0)	21	14.1 (8.5, 19.7)	33	22.1 (15.5, 28.8)	19	12.8 (7.4, 18.1)
IIB	1,095	411	37.5 (34.7, 40.4)	234	21.4 (18.9, 23.8)	156	14.2 (12.2, 16.3)	141	12.9 (10.9, 14.9)	153	14.0 (11.9, 16.0)
IIIA	936	397	42.4 (39.2, 45.6)	259	27.7 (24.8, 30.5)	89	9.5 (7.6, 11.4)	96	10.3 (8.3, 12.2)	95	10.1 (8.2, 12.1)
IIIB	207	53	25.6 (19.7, 31.5)	63	30.4 (24.2, 36.7)	66	31.9 (25.5, 28.2)	12	5.8 (2.6, 9.0)	13	6.3 (3.0, 9.6)
IIIC	128	37	28.9 (21.1, 36.8)	23	18.0 (11.3, 24.6)	36	28.1 (20.3, 35.9)	11	8.6 (3.7, 13.4)	21	16.4 (10.0, 22.8)
Tumor location											
Upper and middle	201	80	39.8 (33.0, 46.6)	28	13.9 (9.1, 18.7)	24	11.9 (7.5, 16.4)	37	18.4 (13.1, 23.8)	32	15.9 (10.9, 21.0)
Lower	2,394	903	37.7 (35.8, 39.7)	601	25.1 (23.4, 26.8)	374	15.6 (14.2, 17.1)	252	10.5 (9.3, 11.8)	264	11.0 (9.8, 12.3)
Overlapping or not specified	206	75	36.4 (29.8, 43.0)	25	12.1 (7.7, 16.6)	24	11.7 (7.3, 16.0)	31	15.0 (10.2, 19.9)	51	24.8 (18.9, 30.7)

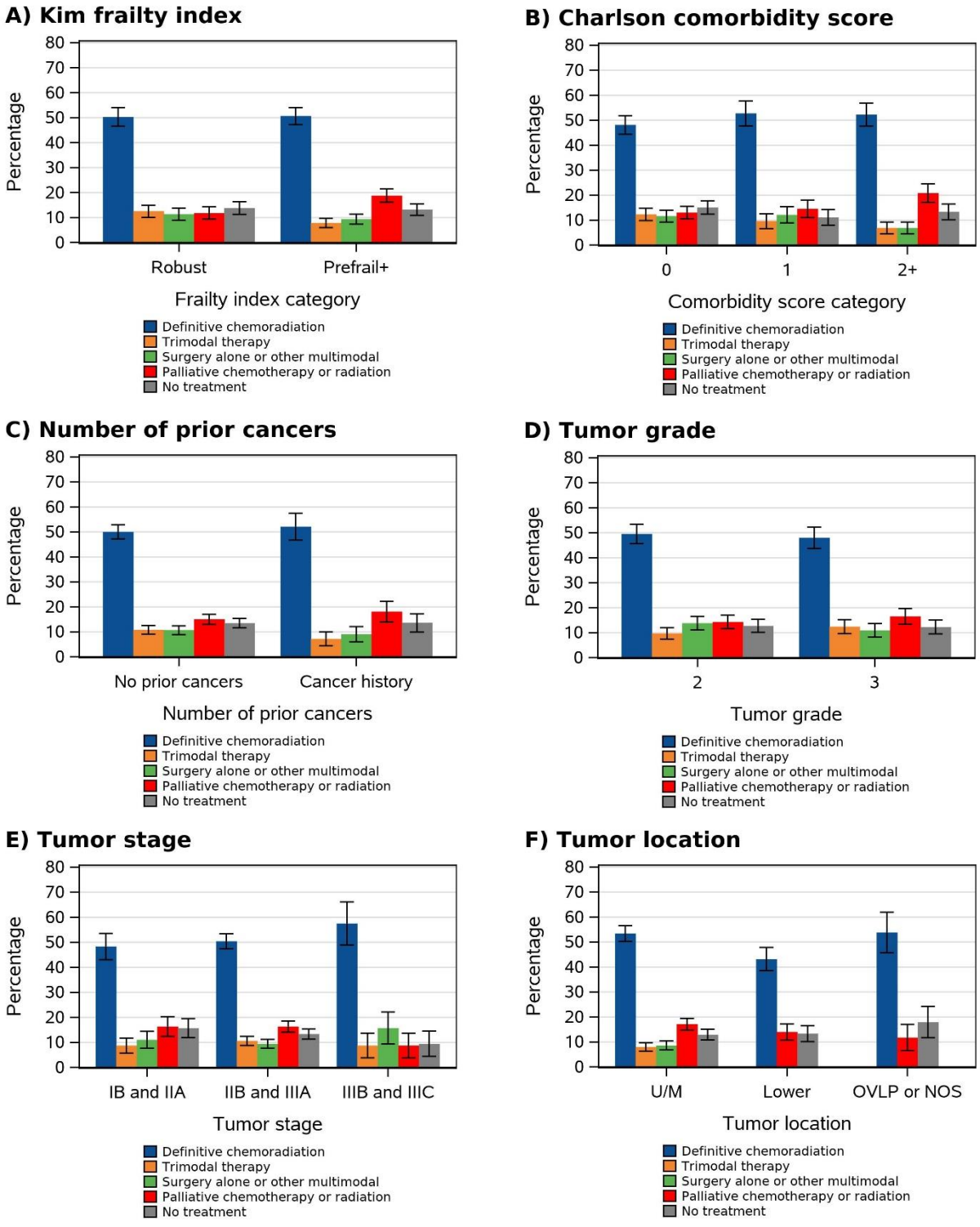
* Cell sizes <11 are suppressed to protect confidentiality, per CMS Cell Size Suppression Policy. Cell sizes greater than 11 may also be suppressed if necessary to ensure small cell sizes cannot be deduced from other cells.

Figure 4.6 Distribution of treatment receipt by patient demographics among older adults diagnosed with locally advanced esophageal squamous cell carcinomas



Cell sizes <11 are suppressed to protect confidentiality, per CMS Cell Size Suppression Policy. This may cause some variable values to not be presented such as the treatment distribution of Hispanic white individuals diagnosed with esophageal squamous cell carcinoma.

Figure 4.7 Distribution of treatment receipt by patient clinical factors among older adults diagnosed with locally advanced esophageal squamous cell carcinomas



Abbreviations: NOS, not otherwise specified; OVLP, overlapping; U/M, upper/middle; Unk, undetermined

Table 4.5 Quantitative estimates of treatment receipt by patient demographics among older adults diagnosed with locally advanced esophageal squamous cell carcinomas

Variable	Total stratum size	Definitive chemoradiation		Trimodal therapy		Other multimodal		Palliative chemo or rad		No treatment	
		N	Treatment Percent (95% CI)	N	Treatment Percent (95% CI)	N	Treatment Percent (95% CI)	N	Treatment Percent (95% CI)	N	Treatment Percent (95% CI)
Age group											
66-70	421	218	51.8 (47.0, 56.6)	75	17.8 (14.2, 21.5)	43	10.2 (7.3, 13.1)	39	9.3 (6.5, 12.0)	46	10.9 (7.9, 13.9)
71-75	412	215	52.2 (47.4, 57.0)	51	12.4 (9.2, 15.6)	45	10.9 (7.9, 13.9)	52	12.6 (9.4, 15.8)	49	11.9 (8.8, 15.0)
76+	698	340	48.7 (45.0, 52.4)	27	3.9 (2.4, 5.3)	70	10.0 (7.8, 12.3)	149	21.3 (18.3, 24.4)	112	16.0 (13.3, 18.8)
Sex											
Male	855	443	51.8 (48.5, 55.2)	85	9.9 (7.9, 11.9)	77	9.0 (7.1, 10.9)	125	14.6 (12.3, 17.0)	125	14.6 (12.3, 17.0)
Female	676	330	48.8 (45.0, 52.6)	68	10.1 (7.8, 12.3)	81	12.0 (9.5, 14.4)	115	17.0 (14.2, 19.8)	82	12.1 (9.7, 14.6)
Race and ethnicity											
NHW	1,099	559	50.9 (47.9, 53.8)	119	10.8 (9.0, 12.7)	118	10.7 (8.9, 12.6)	164	14.9 (12.8, 17.0)	139	12.6 (10.7, 14.6)
HW	83	*	*	*	*	*	*	*	*	*	*
Black	231	115	49.8 (43.3, 56.2)	15	6.5 (2.2, 9.7)	16	6.9 (3.7, 10.2)	37	16.0 (11.3, 20.7)	48	20.8 (15.5, 26.0)
Another race and ethnicity	118	*	*	*	*	*	*	*	*	*	*
Region											
West	668	347	51.9 (48.2, 55.7)	67	10.0 (7.8, 12.3)	67	10.0 (7.8, 12.3)	15	12.3 (17.7)	87	13.0 (10.5, 15.6)
South	350	172	49.1 (43.9, 54.4)	32	9.1 (6.1, 12.2)	37	10.6 (7.4, 13.8)	61	17.4 (13.5, 21.4)	48	13.7 (10.1, 17.3)
Northeast	348	170	48.9 (43.6, 54.1)	37	10.6 (7.4, 13.9)	35	10.1 (6.9, 13.2)	58	16.7 (12.8, 20.6)	48	13.8 (10.2, 17.4)
Midwest	165	84	50.9 (43.3, 58.5)	17	10.3 (5.7, 14.9)	19	11.5 (6.6, 16.4)	21	12.7 (7.6, 17.8)	24	14.5 (9.2, 19.9)
Census-tract poverty level											
0% - <5%	330	165	50.0 (44.6, 55.4)	44	13.3 (9.7, 17.0)	37	11.2 (7.8, 14.6)	47	14.2 (10.5, 18.0)	37	11.2 (7.8, 14.6)
5% - <10%	413	212	51.3 (46.5, 56.2)	41	9.9 (7.0, 12.8)	46	11.1 (8.1, 14.2)	73	17.7 (14.0, 21.4)	41	9.9 (7.0, 12.8)
10% - <20%	385	206	53.5 (48.5, 58.5)	32	8.3 (5.6, 11.1)	36	9.4 (6.4, 12.3)	54	14.0 (10.6, 17.5)	57	14.8 (11.3, 18.4)
20% - 100%	333	159	47.7 (42.4, 53.1)	27	8.1 (5.2, 11.0)	32	9.6 (6.4, 12.8)	54	16.2 (12.3, 20.2)	61	18.3 (14.2, 22.5)
Urbanization											
Metro	1,335	674	50.5 (47.8, 53.2)	132	9.9 (8.3, 11.5)	136	10.2 (8.6, 11.8)	219	16.4 (14.4, 18.4)	174	13.0 (11.2, 14.8)
Urban	151	76	50.3 (42.4, 58.3)	*	*	*	*	*	*	*	*
Rural	45	23	51.1 (36.5, 65.7)	*	*	*	*	*	*	*	*

* Cell sizes <11 are suppressed to protect confidentiality, per CMS Cell Size Suppression Policy. Cell sizes greater than 11 may also be suppressed if necessary to ensure small cell sizes cannot be deduced from other cells.

Table 4.6 Quantitative estimates of treatment receipt by patient clinical factors among older adults diagnosed with locally advanced esophageal squamous cell carcinomas

Variable	Total stratum size	Definitive chemoradiation		Trimodal therapy		Other multimodal		Palliative		No treatment	
		N	Treatment Percent (95% CI)	N	Treatment Percent (95% CI)	N	Treatment Percent (95% CI)	N	Treatment Percent (95% CI)	N	Treatment Percent (95% CI)
Kim frailty index											
Robust	692	348	50.3 (46.6, 54.0)	87	12.6 (10.1, 15.0)	79	11.4 (9.0, 13.8)	82	11.8 (9.4, 14.3)	96	13.9 (11.3, 16.4)
Prefrail +	839	425	50.7 (47.3, 54.0)	66	7.9 (6.0, 9.7)	79	9.4 (7.4, 11.4)	158	18.8 (16.2, 21.5)	111	13.2 (10.9, 15.5)
Charlson comorbidity score											
0	692	333	48.1 (44.4, 51.8)	85	12.3 (9.8, 14.7)	80	11.6 (9.2, 13.9)	90	13.0 (10.5, 15.5)	104	15.0 (12.4, 17.7)
1	387	204	52.7 (47.7, 57.7)	37	9.6 (6.6, 12.5)	47	12.1 (8.9, 15.4)	56	14.5 (11.0, 18.0)	43	11.1 (8.0, 14.2)
2+	452	236	52.2 (47.6, 56.8)	31	6.9 (4.5, 9.2)	31	6.9 (4.5, 9.2)	94	20.8 (17.1, 24.5)	60	13.3 (10.1, 16.4)
Number of prior cancers											
No prior cancers	1,119	600	50.0 (47.2, 52.9)	129	10.8 (9.0, 12.5)	128	10.7 (8.9, 12.4)	180	15.0 (13.0, 17.0)	162	13.5 (11.6, 15.4)
Cancer history	332	173	52.1 (46.7, 57.5)	24	7.2 (4.4, 10.0)	30	18.1 (13.9, 22.2)	60	18.1 (13.9, 22.2)	45	13.6 (9.9, 17.2)
Tumor grade											
1	83	*	*	*	*	*	*	*	*	*	*
2	630	312	49.5 (45.6, 53.4)	61	9.7 (7.4, 12.0)	87	13.8 (11.1, 16.5)	90	14.3 (11.6, 17.0)	80	12.7 (10.1, 15.3)
3	540	259	48.0 (43.7, 52.2)	67	12.4 (9.6, 15.2)	59	10.9 (8.3, 13.6)	89	16.5 (13.4, 19.6)	66	12.2 (9.5, 15.0)
Undetermined	278	*	*	*	*	*	*	*	*	*	*
Tumor stage											
IB and IIA	344	166	48.3 (43.0, 53.5)	30	8.7 (5.7, 11.7)	38	11.0 (7.7, 14.4)	56	16.3 (12.4, 20.2)	54	15.7 (11.9, 19.5)
IIB and IIIA	1,060	534	50.4 (47.4, 53.4)	112	10.6 (8.7, 12.4)	100	9.4 (7.7, 11.2)	173	16.3 (14.1, 18.5)	141	13.3 (11.3, 15.3)
IIIB and IIIC	127	73	57.5 (48.9, 66.1)	11	8.7 (3.8, 13.6)	20	15.7 (9.4, 22.1)	11	8.7 (3.8, 13.6)	12	9.4 (4.4, 14.5)
Tumor location											
Upper and middle	950	507	53.4 (50.2, 56.5)	76	8.0 (6.3, 9.7)	82	8.6 (6.8, 10.4)	162	17.1 (14.7, 19.4)	123	12.9 (10.8, 15.1)
Lower	436	188	43.1 (38.5, 47.8)	*	*	*	*	61	14.0 (10.7, 17.2)	58	13.3 (10.1, 16.5)
Overlapping or not specified	145	78	53.5 (45.7, 61.9)	*	*	*	*	17	11.7 (6.5, 17.0)	26	17.9 (11.7, 24.2)

* Cell sizes <11 are suppressed to protect confidentiality, per CMS Cell Size Suppression Policy. Cell sizes greater than 11 may also be suppressed if necessary to ensure small cell sizes cannot be deduced from other cells.

Table 4.7 Probability of receiving trimodal therapy by demographic and clinical characteristics amongst individuals with locally advanced esophageal adenocarcinomas

	Received trimodal therapy, n (%)	Risk Ratio (95% CI)
Age		
66-70	316 (37.7)	Reference
71-75	192 (27.0)	0.72 (0.62, 0.83)
76+	146 (11.7)	0.31 (0.26, 0.40)
Sex		
Male	573 (23.8)	Reference
Female	81 (20.8)	0.88 (0.71 – 1.08)
Race and ethnicity		
Non-Hispanic white	626 (24.0)	Reference
Hispanic white	16 (16.5)	0.69 (0.44 – 1.08)
Registry region		
West	224 (19.9)	Reference
South	151 (24.6)	1.23 (1.03 – 1.48)
Northeast	159 (24.8)	1.25 (1.04 – 1.49)
Midwest	120 (28.6)	1.43 (1.19 – 1.74)
Tumor grade		
Grade I	21 (17.9)	Reference
Grade II	278 (26.7)	1.49 (1.00 – 2.22)
Grade III	296 (23.9)	1.33 (0.89 – 1.99)
Undetermined differentiation	59 (14.5)	0.81 (0.51 – 1.27)
Tumor location		
Upper and middle	28 (13.9)	Reference
Lower	601 (25.1)	1.80 (1.27 – 2.56)
Overlapping or NOS	25 (12.1)	0.87 (0.53 – 1.44)
Stage group		
IB	51 (17.8)	Reference
IIA	24 (16.1)	0.90 (0.58 – 1.41)
IIB	234 (21.4)	1.20 (0.91 – 1.58)
IIIA	259 (27.7)	1.55 (1.19 – 2.03)
IIIB	63 (30.4)	1.71 (1.24 – 2.36)
IIIC	23 (18.0)	1.01 (0.65 – 1.57)
Number of prior non-esophageal cancers		
No prior cancers	549 (23.7)	Reference
History of cancer	105 (21.5)	0.91 (-0.75, 1.09)
Charlson comorbidity score		
0	342 (28.1)	Reference
1-2	256 (23.3)	0.83 (0.72, 0.95)
3-4	44 (13.5)	0.48 (0.36, 0.64)
≥5	12 (7.6)	0.27 (0.16, 0.47)
Kim Frailty Index		
Robust, <0.15	411 (30.0)	Reference
Prefrail, 0.15-0.24	219 (18.9)	0.63 (0.55 – 0.73)
Mildly frail or greater, ≥0.25		
Census tract poverty percent		
0% - <5%	173 (24.9)	Reference
5%-<10%	193 (24.7)	0.99 (0.83 – 1.18)
10% - <20%	170 (23.4)	0.94 (0.78 – 1.13)
20% - 100%	68 (17.7)	0.71 (0.55 – 0.91)
Level of urbanization		
Metropolitan	538 (22.9)	Reference
Urban	84 (26.7)	1.16 (0.96 – 1.42)
Rural	32 (23.5)	1.03 (0.75 – 1.40)

* Cell sizes <11 are suppressed to protect confidentiality, per CMS Cell Size Suppression Policy. Cell sizes greater than 11 may also be suppressed if necessary to ensure small cell sizes cannot be deduced from other cells.
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.

Table 4.8 Probability of receiving trimodal therapy by demographic and clinical characteristics, amongst individuals with locally advanced squamous cell carcinomas

	Received trimodal therapy, n (%)	Risk Ratio (95% CI)
Age		
66-70	75 (17.8)	Reference
71-75	51 (12.4)	0.69 (0.50 – 0.97)
76+	27 (3.9)	0.22 (0.14 – 0.33)
Sex		
Male	85 (9.9)	Reference
Female	68 (10.1)	1.01 (0.75 – 1.37)
Race		
Non-Hispanic white	119 (10.8)	Reference
Black	15 (6.5)	0.60 (0.36 – 1.01)
Registry region		
West	67 (10.0)	Reference
South	32 (9.1)	0.91 (0.61 – 1.36)
Northeast	37 (10.6)	1.06 (0.73 – 1.55)
Midwest	17 (10.3)	1.03 (0.62 – 1.70)
Tumor grade		
Grade II	61 (9.7)	Reference
Grade III	67 (12.4)	1.28 (0.92 – 1.78)
Stage group		
IB and IIA	30 (8.7)	Reference
IIB and IIIA	112 (10.6)	1.21 (0.83 – 1.78)
IIIB and IIIC	11 (8.7)	0.99 (0.51 – 1.92)
Prior non-esophageal cancers		
No prior cancers	129 (10.8)	Reference
History of cancer	24 (7.2)	0.67 (0.44 – 1.02)
Charlson comorbidity score		
0	85 (12.3)	Reference
1	37 (9.6)	0.78 (0.54 – 1.12)
2+	31 (6.9)	0.56 (0.38 – 0.83)
Kim Frailty Index		
Robust, <0.15	87 (12.6)	Reference
Prefrail +, >=0.15	66 (7.9)	0.63 (0.46 – 0.85)
Census tract poverty percent		
0% - <5%	44 (13.3)	Reference
5%-<10%	41 (9.9)	0.74 (0.50 – 1.11)
10% - <20%	32 (8.3)	0.62 (0.41 – 0.96)
20% - 100%	27 (8.1)	0.61 (0.39 – 0.96)

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.

Figure 4.8 Temporal trends in the age-standardized percentage of cases receiving each chemotherapy regimen amongst a population of adults 66 years of age and older diagnosed with locally advanced esophageal cancer who received definitive chemoradiation or trimodal therapy, SEER-Medicare 2004-2017

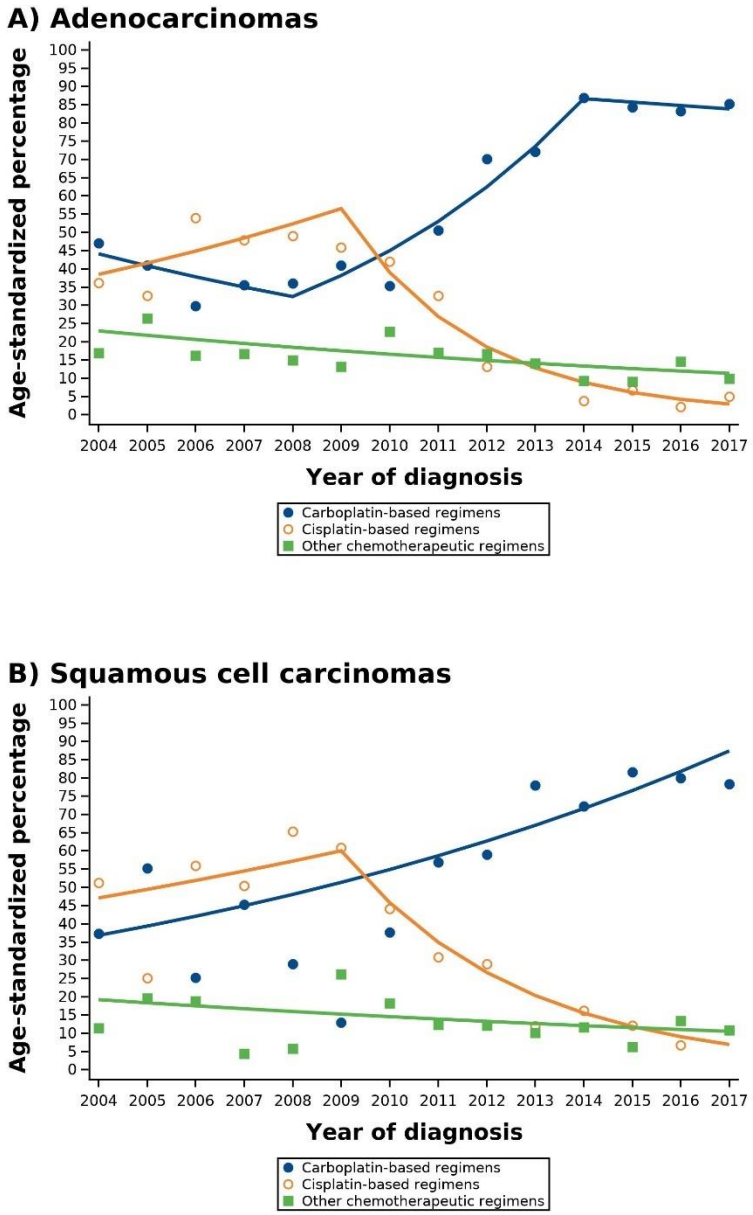


Table 4.9 Temporal trends in chemotherapy-regimen received amongst a cohort of Medicare-enrolled locally advanced esophageal cancer patients treated with either definitive chemoradiation or trimodal therapy, stratified by histologic subtype

Treatment group	Age-standardized percentage in 2004 (95% CI)	Age-standardized percentage in 2017 (95% CI)	Segment	Annual percent change during segment, %	Average annual percent change across all segments, 2004-2017
Adenocarcinomas					
Carboplatin-based regimens	47.0 (33.2 – 60.8)	85.3 (80.1 – 90.3)	2004-2008 2008-2014 2014-2017	-7.4 (-28.0 – 18.9) 17.8 (7.1 – 29.7) -1.1 (-8.0 – 6.3)	5.1 (-2.3 – 13.0)
Cisplatin-based regimens	36.1 (23.0 – 49.2)	4.9 (1.8 – 8.0)	2004-2009 2009-2017	8.0 (-10.5 – 30.3) -31.0 (-38.4 – -22.6)	-18.0 (-24.9 – -10.5)
Other chemotherapy regimens	16.9 (6.9 – 26.9)	9.8 (5.5 – 14.1)	2004-2017	-5.3 (-8.9 – -1.6)	-5.3 (-8.9 – -1.6)
Squamous cell carcinomas					
Carboplatin-based regimens	37.3 (16.3 – 58.3)	78.3 (69.5 – 87.2)	2004-2017	6.9 (3.3 – 10.6)	6.9 (3.3 – 10.6)
Cisplatin-based regimens	51.3 (29.7 – 72.9)	10.8 (4.3 – 17.4)	2004-2009 2009-2017	5.0 (-9.8 – 22.2) -23.7 (-30.3 – -16.4)	-13.7 (-19.6 – -7.5)
Other chemotherapy regimens	11.4 (2.3 – 20.5)	10.8 (4.3 – 17.4)	2004-2017	-4.5 (-9.4 – 0.6)	-4.5 (-9.4 – 0.6)

Abbreviations: CI, confidence interval.

CHAPTER 5 – MANUSCRIPT 2: COMPARATIVE EFFECTIVENESS OF TRIMODAL THERAPY VERSUS DEFINITIVE CHEMORADIATION IN OLDER ADULTS WITH LOCALLY ADVANCED ESOPHAGEAL CANCER

5.1 Introduction

Esophageal cancer is a poor prognosis gastrointestinal malignancy, with 80% of patients experiencing mortality within five years of diagnosis.[48] Globally, esophageal cancer is the sixth leading cause of cancer related death.[229] Within the United States, over 15,500 deaths are attributed to esophageal cancer annually.[2] The incidence of esophageal cancer increases with age (median age at diagnosis of 68), which portends an escalating burden of esophageal cancer as the United States undergoes an aging demographic shift.[11,52] Importantly, the majority of older adults diagnosed with esophageal cancer will 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 (trimodal therapy) versus definitive chemoradiation is uncertain. Both modalities are considered viable options for locally advanced cancers in current treatment guidelines.[3,4] Only two randomized control trials with small samples have been conducted that directly compared these modalities and it is difficult to draw conclusions from these studies on account of their design features, such as use of induction chemotherapy and complete exclusion or underrepresentation of adenocarcinomas.[116,117] Moreover, these trials did not explicitly focus on older adult populations, hampering their generalizability. Older esophageal cancer patients have a higher comorbidity burden and are more likely to be frail, qualities that are associated with poorer outcomes after surgery.[44,88,230] Esophagectomy is a major surgical procedure and the potential for complications and mortality rises with advancing age.[66] Older age and poorer health status alter the benefit-risk profile of

trimodal therapy and complicate treatment decision making.[88] Unsurprisingly, the prior literature has documented low use of trimodal therapy in older adults with locally advanced tumors; the majority of patients receive definitive chemoradiation.[94] In the absence of relevant trial data, the observational evidence comparing trimodal therapy and definitive chemoradiation may provide insight.[21,27,29,34,119–122,231] However, many of the database studies examining this comparison are afflicted by immortal time-bias. Immortal time bias is an analytic error wherein exposure information during the course of follow-up is used to classify exposure status at baseline, which necessitates survival up to the exposure-defining event. A recent meta-analysis described the overall quality of these studies as low and in need of more refined evidence.[232] For older adults, it remains unknown whether planned resection is warranted after chemoradiation.

The primary objective of this study was to assess the comparative effectiveness of trimodal therapy versus definitive chemoradiation in a population of older adults in the United States. Through leveraging a new bias-reducing analytic technique that avoids immortal time bias, we sought to generate rigorous real-world evidence about these therapies for a population underrepresented in clinical trials.

5.2 Methods

5.2.1 Data Source and Study Population

This study used data from the Surveillance Epidemiology and End Results (SEER)-Medicare linked database to identify individuals diagnosed with esophageal cancer between 2004 and 2017. Led by the National Cancer Institute, SEER is a population-based cancer registry program that, during the years of analysis, covered 28% of the U.S. population.[154] The SEER data include patient demographics, tumor features, first course of cancer-directed treatment, vital status, and cause of death from death certificate data. Administered by the Center for Medicare and Medicaid Services, Medicare is a federal program that provides health insurance to adults 65 years of age and older, as well as those with disabilities and/or end-

stage-renal-disease (ESRD). Medicare administrative data used in our study include information pertaining to beneficiary enrollment and medical claims. Broadly, our study focused on a population of older adults who were diagnosed with locally advanced esophageal cancer. Details of the study population are provided in the study design section below, which is oriented around specifying how our study design and analysis choices are made to mirror a hypothetical randomized trial, the "target trial".[187,188]

5.2.2 Study Design

The target trial approach posits that clinical research using observational data can maximize internal validity and avoid common design and analytic pitfalls by emulating a well-specified theoretical RCT—the target trial.[188] By specifying how the observed data will be used to emulate a theoretical RCT with specific treatment arms, the target trial approach facilitates the comparison of well-defined interventions.[194] In practice, this entails both a delineation of six key features of the target trial (eligibility criteria, treatment strategies, assignment procedures, outcomes, follow-up, and causal contrast of interest), as well as a breakdown of how these features will be emulated to the extent possible using the SEER-Medicare data. The features of both the target trial and observational emulation are presented in Table 5.1. Given constraints, we focus the accompanying text on criteria implemented by the performed observational emulation; a corresponding study design schematic using an available template to promote reproducibility is presented in Figure 5.1.[233]

Our study population focused on a population of older adults newly diagnosed with locally advanced esophageal cancer, for which trimodal therapy is a recommended treatment option per clinical practice guidelines.[3,4] Study inclusion criteria included being 66-79 years of age at the first esophageal cancer diagnosis (histologically confirmed) between 2004 and 2017. Tumor site and histology were determined using International Classification of Disease-Oncology-3 (ICD-O-3) codes (Appendix 2). Individuals were required to have a non-cervical site

and have adenocarcinoma or squamous cell carcinoma histologic subtype. We used the tumor (T), node (N), and metastasis (M) definitions from the American Joint Committee on Cancer (AJCC) 7th edition staging manual to identify cancers of interest. All cancers were required to be non-metastatic (M0). There were two 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 to T4a. These requirements translated to eligible stage groups of IB-IIIC.

Individuals diagnosed at death or autopsy were excluded. A minimum of one year of continuous enrollment in Medicare Part A and Part B insurance (non-HMO) prior to cancer diagnosis was required to ensure a sufficient evaluation period for comorbidities and frailty. Claims in the year prior to the cancer diagnosis were used to measure patient comorbidities and frailty using the NCI adaptation of the Charlson comorbidity score[160,161] and Kim frailty index[162], respectively. As we were trying to identify a population eligible for surgery, we excluded individuals with a high comorbidity burden (Charlson score >5), those categorized as frail (Kim frailty index>=0.35), and individuals older than 79 years of age; such restriction can remove a substantial amount of confounding.[234] We excluded individuals who were diagnosed with any other cancer in the year prior to their first esophageal cancer diagnosis to ensure that cancer-directed treatments observed in the claims data were for treatment of the esophageal cancer.

Treatments compared consisted of trimodal therapy or definitive chemoradiation. Trimodal 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 exactly the same, except *not* receiving esophagectomy within 6 months of the first chemotherapy treatment. Chemotherapy was defined as any outpatient infusion-based chemotherapy of carboplatin, paclitaxel, cisplatin, fluorouracil, oxaliplatin, irinotecan, docetaxel, epirubicin, or oral capecitabine. Radiation consisted of any external-beam radiation delivery code. Health care codes used to identify chemotherapy, radiation, and

esophagectomy are included in Appendix 2. A sensitivity analysis explored the impact of shortening this window to 90 days; surgeries occurring within 90 days of the first chemotherapy infusion were considered part of trimodal therapy and surgeries after three months were considered salvage esophagectomies (which were permitted for the definitive chemoradiation treatment arm).

Unlike the target trial, patients were not randomized to treatment in our retrospective cohort study. Therefore, we accounted for the following measured baseline 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 the number of hospitalizations and ED visits in the past year.

Study outcomes included the five-year risks of overall and esophageal cancer-specific mortality, the one-year risk of functional adverse events, and the five-year mean cumulative count of days at home. Cause of death data were obtained from state death certificates gathered by the National Center for Health Statistics. Functional adverse events were identified 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.[202] Days at home were defined using a recently developed quality measure.[209] A day at home was a day alive and not spent in the following locations: inpatient short-stay hospital, inpatient psychiatric hospital, inpatient rehabilitation facility, inpatient long-term hospital, skilled nursing facility, outpatient emergency department, or hospital observation unit. We were interested in the per-protocol effect; the intent-to-treat effect is not estimable in this data as it is unclear at the first chemotherapy infusion using SEER-Medicare data whether the patient was intended to receive definitive chemoradiation or trimodal therapy.

5.2.3 Statistical Analysis

Data were analyzed using the clone-censor-weight method, a technique that is gaining traction in the epidemiologic methods literature due to its proper handling of complex, time-delimited interventions such as trimodal therapy.[137–139] The most salient benefit of the method is that it avoids immortal time bias,[123] wherein patients would be classified into trimodal therapy at the start of chemoradiation based on future knowledge about receipt of esophagectomy. Thus, until an esophagectomy occurred within 6 months of starting chemoradiation the patient's data contributed to both treatment arms. The data of each patient were cloned at first chemotherapy treatment within 120 days of cancer diagnosis and "assigned" analytically to both treatment strategies, trimodal therapy and definitive chemoradiation. When the observed treatment data of the patient was no longer consistent with the assigned treatment strategy, that observation was analytically censored. Thus, the observation contributed to the risk-set while the data still reflect the assigned treatment arm but did not contribute to the risk-set after deviation from the initial assignment. For both treatments, time zero (the start of follow-up) was the date of the first chemoradiation treatment within 120 days of cancer diagnosis. An individual assigned to the trimodal therapy strategy was analytically censored if they did not have radiation within 7 days of chemotherapy or reached 6 months after the first infusion without an esophagectomy. An individual assigned to definitive chemoradiation was analytically censored if they did not have radiation within 7 days of chemotherapy or at the occurrence of esophagectomy within 6 months of the first infusion. Figure 3.1 (methods chapter) depicts this process for four example patients.

Following the cloning and analytic censoring of individuals when they deviated from their assigned treatment group, inverse-probability of censoring weights were implemented to account for the confounders causing deviation. For instance, a higher Charlson score may decrease the chance of receiving esophagectomy, leading to analytic censoring the clones assigned to trimodal therapy. To appropriately balance the Charlson score between treatment

groups, uncensored individuals need to be re-weighted. Censoring weights were calculated using pooled logistic regression.[235]

Descriptive statistics of the entire eligible cohort that initiated chemotherapy within 120 days of cancer diagnosis were calculated prior to cloning individuals. Balance in confounders at six months before and after weighting was assessed using standardized mean differences. The five-year standardized cumulative incidence of overall mortality was calculated as the mathematical complement of the weighted Kaplan-Meier estimator. The five-year standardized cumulative incidence of esophageal cancer-specific mortality was calculated using the weighted Aalen-Johansen estimator to account for the competing event of non-cancer mortality.[211] The Aalen-Johansen estimator was also used to estimate the one-year risk of functional adverse events. Risk differences (RD) and risk ratios (RR) were calculated at five years after the index date for overall and cancer-specific mortality and one-year after the index date for functional adverse events. The weighted Dong estimator was used to quantify the standardized mean cumulative count of days at home in the five years after the index date.[236] The mean cumulative count difference (MCCD) and mean cumulative count ratio (MCCR) were calculated at five years after the index date. Non-parametric bootstrapping was performed to generate all 95% confidence intervals.

5.3 Results

5.3.1 Study Population and Confounder Balance

After applying inclusion and exclusion criteria, the study population consisted of 1,901 adults (Figure 5.2). Descriptive characteristics of the study population stratified by histologic subtype are presented in Table 5.2. The median age was 72 for both adenocarcinomas and squamous cell carcinomas. Nearly 88% of adenocarcinomas were diagnosed in men compared to only 55% of squamous cell carcinomas. The majority of 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 seventh edition (Figure 5.2), an attrition table was generated that displayed the distribution of demographic and tumor characteristics before and after those with missing stage were excluded (Table 5.3). Only minor changes in the distribution of these characteristics were observed.

Amongst the 1,240 target-trial eligible individuals with adenocarcinomas who started chemotherapy (follow-up day zero), 971 received radiation within 7 days of chemotherapy initiation and a further subset of 491 received esophagectomy within 6 months. Amongst the 661 target-trial eligible individuals with squamous cell carcinomas who started chemotherapy (follow-up day zero), 432 received radiation within 7 days of chemotherapy initiation and a further subset of 111 received esophagectomy within 6 months.

Balance of confounders was assessed at the end of the 6-month (183 day) grace period in both the unweighted and weighted data using standardized mean differences. Figures 5.3 and 5.4 display the balance metrics for adenocarcinomas and squamous cell carcinomas, respectively. Importantly, after the weights were applied, the absolute standardized mean difference was below 0.10 for all measured confounders, a commonly used threshold indicating adequate confounder balance.[217]

5.3.2 Overall Mortality and Esophageal-Cancer Specific Mortality

The standardized cumulative incidence curves for five-year overall mortality and esophageal cancer-specific mortality, by treatment group, are presented graphically in Figure 5.5. All results are stratified by histologic subtype. The numeric results at five years are reported in Table 5.3, with contrasts in standardized cumulative incidence by treatment group reported as risk differences and risk ratios.

For adenocarcinomas, the five-year standardized cumulative incidence of overall mortality was 73.4% (95% CI: 69.1% – 77.4%) in the trimodal therapy group and 83.8% (95% CI: 78.6% – 87.2%) in the definitive chemoradiation group, corresponding to a standardized risk difference of -10.4 percentage points (95% CI: -15.6 – -3.9) and a standardized risk ratio of 0.88 (95% CI: 0.82 – 0.95) comparing trimodal therapy to definitive chemoradiation. The five-year standardized cumulative incidence of esophageal cancer-specific mortality was 61.2% (95% CI: 55.8% – 66.2%) in the trimodal therapy group and 71.0% (95% CI: 64.9% – 75.9%) in the definitive chemoradiation group, corresponding to a standardized risk difference of -9.8 percentage points (95% CI: -17.2 – -1.5) and a standardized risk ratio of 0.86 (95% CI: 0.77 – 0.98).

For squamous cell carcinomas, the five-year standardized cumulative incidence of overall mortality was 62.6% (95% CI: 50.9% – 73.5%) in the trimodal therapy group and 72.3% (95% CI: 67.6% – 76.3%) in the definitive chemoradiation group, corresponding to a standardized risk difference of -9.6 percentage points (95% CI: -21.6 – 0.8) and a standardized risk ratio of 0.87 (95% CI: 0.70 – 1.01) comparing trimodal therapy to definitive chemoradiation. The five-year standardized cumulative incidence of esophageal cancer-specific mortality was 51.0% (95% CI: 40.5% – 61.5%) in the trimodal therapy arm and 58.1% (95% CI: 52.1% – 63.2%) in the definitive chemoradiation arm, corresponding to a standardized risk difference of -7.1 percentage points (95% CI: -18.9 – 4.4) and a standardized risk ratio of 0.88 (95% CI: 0.68 – 1.07).

In a sensitivity analysis, shortening the time window from six months to three months for distinguishing surgeries as part of trimodal therapy or salvage resection impacted the results by pushing associations towards the null. In adenocarcinomas, the five-year standardized overall mortality risk was 79.2% (95% CI: 75.4% – 82.4%) in definitive chemoradiation patients and 67.4% (95% CI: 61.1% – 74.7%) in trimodal therapy patients (RD = -11.8, 95% CI: -19.0 – -2.9). In squamous cell carcinomas, the five-year standardized overall mortality risk was 70.8% (95%

CI: 66.6% – 74.7%) in definitive chemoradiation patients and 60.7% (95% CI: 40.3% – 80.7%) in trimodal therapy patients (RD = -10.1, 95% CI: -30.8 – 9.5). However, this shortened 90 day window introduced substantial misclassification; 38.9% of adenocarcinomas and 12.3% of squamous cell carcinomas classified as definitive chemoradiation received an esophagectomy at some point after 90 days. This was expected given that the median time from chemotherapy infusion to surgery was 92 days (interquartile range: 80 – 112) and supported the longer time window (6 months) used in our primary analysis.

5.3.3 Functional Adverse Events

The standardized one-year cumulative incidence of functional adverse events, by treatment group, is presented in Figure 5.5 with numeric results in Table 5.3. For adenocarcinomas, the standardized one-year cumulative incidence of experiencing a functional adverse event was 57.9% (95% CI: 53.3% – 61.6%) in the trimodal therapy group and 41.3% (95% CI: 34.6% – 46.1%) in the definitive chemoradiation arm, corresponding to a standardized risk difference of 16.5 percentage points (95% CI: 9.8 – 23.3) and a standardized risk ratio of 1.40 (95% CI: 1.22 – 1.65). For squamous cell carcinomas, the standardized one-year cumulative incidence of experiencing a functional adverse event was 46.8% (95% CI: 37.4% – 54.9%) in the trimodal therapy group and 38.5% (95% CI: 32.3% – 43.6%) in the definitive chemoradiation arm, corresponding to a standardized risk difference of 8.2 percentage points (95% CI: 0.0 – 17.5) and a standardized risk ratio of 1.21 (95% CI: 1.00 – 1.49).

5.3.4 Days at Home

The standardized five-year mean cumulative count of days at home for each histologic subtype, by treatment group, is presented in Figure 5.6 with numeric results in Table 5.3. For adenocarcinomas, the standardized five-year (1,826 day) mean cumulative count of days at home was 840.1 days (95% CI: 779.9 – 901.6) for the trimodal therapy strategy and 680.3 days

(95% CI: 634.8 – 762.0) for the definitive chemoradiation strategy, corresponding to a standardized mean cumulative count difference of 159.8 days (95% CI: 67.3 – 229.2) and a standardized mean cumulative count ratio of 1.23 (95% CI: 1.09 – 1.36).

For squamous cell carcinomas, the standardized five-year mean cumulative count of days at home was 990.3 days (95% CI: 865.7 – 1,125.8) for the trimodal therapy strategy and 813.0 days (95% CI: 749.5 – 883.9) for the definitive chemoradiation strategy, corresponding to a standardized mean cumulative count difference of 177.3 days (95% CI: 50.8 – 313.1) and a standardized mean cumulative count ratio of 1.22 (95% CI: 1.06 – 1.40).

5.4 Discussion

Older adults diagnosed with locally advanced esophageal cancer and their care providers face a difficult decision when choosing between definitive chemoradiation and trimodal therapy. Given the low-to-moderate rates of complete response to chemoradiation, resection may be warranted to obtain better local control of the tumor and decrease the likelihood of recurrence. On the other hand, esophagectomy is a significant surgical procedure with associated morbidity, decreased health-related quality of life, and mortality. The randomized trial evidence comparing these treatments is scant and the observational evidence contains methodologic limitations that diminish enthusiasm for extracting clinical inferences. Additionally, no large population-based studies have purposefully focused on a target population of older adults; the heightened medical complexity in this population may alter the benefit-risk profile of undergoing surgery.

Our study found that trimodal therapy is associated with decreased risks of five-year all-cause and cancer-specific mortality compared to definitive chemoradiation for both adenocarcinomas (-10.4 percentage point risk reduction for overall mortality) and squamous cell carcinomas (-9.6 percentage point risk reduction for overall mortality). The benefit was clear statistically but has moderate clinical significance. Using the risk difference of roughly -10.0

percentage points (across histologic subtype) to calculate the number needed to treat, 10 esophagectomies would have to be performed for one death (over five years) to be prevented. We also found that the risk of incident functional adverse events was higher for the trimodal therapy strategy and that the increase in days at home over a five-year period was less than six months. In fact, the trimodal therapy strategy did not surpass the definitive chemoradiation strategy in expected healthy days at home in the first year and a half.

Our estimates can aid in decision making. A discrete choice experiment in patients considering definitive chemoradiation with active surveillance or trimodal therapy found that five-year overall survival and health-related quality of life heavily influenced the decision making process: interviewed patients would accept a 16% lower 5-year survival if quality of life was at the level associated with definitive chemoradiation instead of the (lower) quality associated with resection.[237]

It is important to contextualize our findings within the current science regarding tumor response to chemoradiation. Ideally, clinical prediction models could accurately pinpoint which individuals would experience a clinical complete response from chemoradiation, and clinical response would be a perfect surrogate for pathologic response. This would facilitate improved selection of patients expected to benefit from chemoradiation and resection. Unfortunately, neither of these conditions hold in reality; it is difficult to predict who will have a clinical response to chemoradiation and clinical data alone poorly map to pathologic response. The current literature reports that 20-40% of patients who undergo trimodal therapy will achieve a pathologic complete response and that adenocarcinoma is associated with lower rates of response. Consequently, with a low chance of complete response from chemoradiation, surgical resection may be an important part of multimodal treatment, though our data suggest the benefit for older adults may be smaller than reported by prior observational studies.

Our findings improve the existing literature comparing trimodal therapy to definitive chemoradiation. The two randomized studies found better local control of tumors amongst those

who received trimodal therapy but did not find statistically significant differences in survival.[116,117] However, only 11.2% of trial participants in one study[116] had adenocarcinomas and the other[117] was exclusively composed of squamous cell carcinomas. Currently in the United States, adenocarcinomas have a higher incidence than squamous cell carcinomas.[18] The trials have also been criticized for their higher-than expected operative mortality rates, use of induction chemotherapy, split-course radiotherapy, less intensive chemotherapy, and unconventional randomization scheme in these trials.[114,238] On account of these differences in study design and target populations, it is unsurprising that our effect estimates for trimodal therapy are different.

When comparing our work to other observational studies, the dominant theme was that stronger protective effects of trimodal therapy were found in other studies. For instance, McKenzie et al. report a hazard ratio of 0.66 comparing trimodal therapy to definitive chemoradiation.[119] However, despite other strengths of this study, it contained immortal time bias because follow-up started at diagnosis but used treatment data in the future to define groups at baseline. Trimodal patients definitionally had longer survival time because they were required to survive long enough to receive resection. In practice, nearly 17% of planned trimodal therapy patients do not ultimately receive resection.[142] Immortal time bias is particularly prevalent in research of surgical interventions wherein confirmation of an individual's treatment status frequently occurs many months after follow-starts, yet this future information is used to categorize treatments at start of follow-up.[130] Our study avoided this error by using the innovative clone-censor-weight analytic approach.

Our study has numerous methodologic and clinically substantive strengths. Methodologically, we removed all potential for immortal time bias by using the clone-censor-weight analytic technique. By duplicating observations at baseline and letting individuals contribute to the risk calculations of all groups they were consistent with at each point in time, no future information was used to categorize the baseline exposure status. This represents a major reduction in bias for database-related observational studies wherein the treatment status

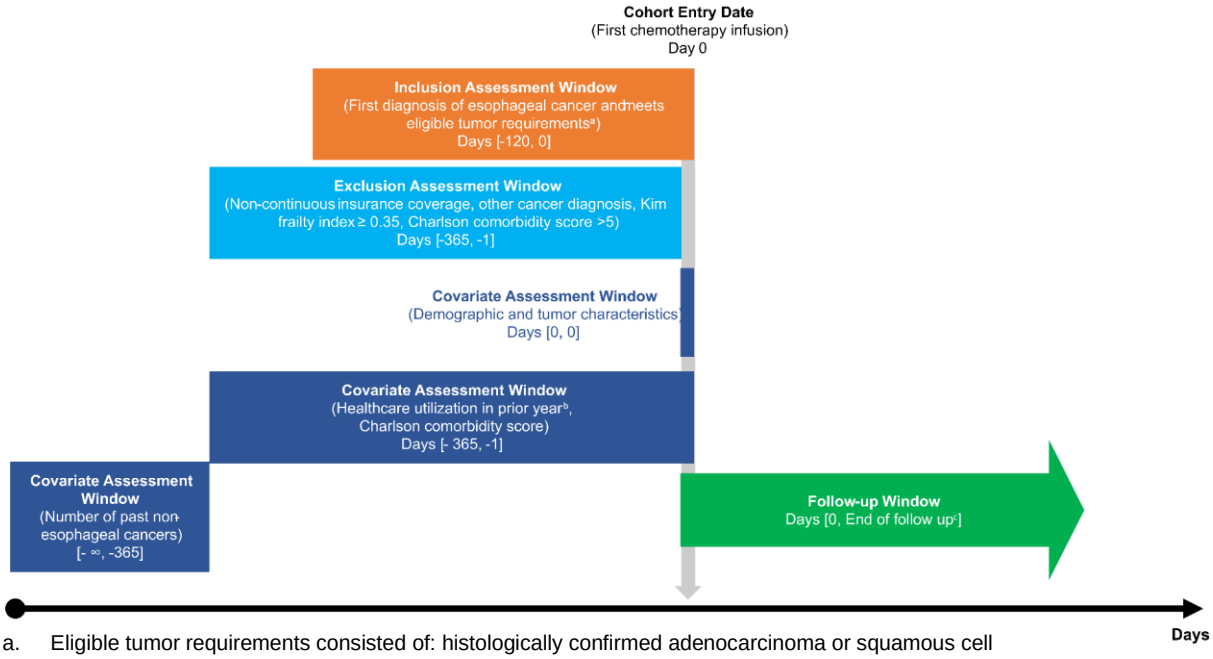
of a patient is undetermined at baseline. To date, this technique had not yet been applied to esophageal cancer research. Other strengths include the explicit consideration of competing events for all outcomes other than all-cause mortality and our reporting of risk differences and ratios, which offer greater interpretability than hazard ratios and have statistical advantages.[147,149] Additionally, our study is also the first to combine the mean cumulative count estimator created by Dong et al to the days at home outcome measure. Topically, we have generated evidence for a target population—older adults—that is frequently either excluded or underrepresented in clinical trials. We quantified proxy measurements of comorbidity and frailty using validated claims-based indices to identify a population of adults eligible for trimodal therapy and control for confounding. The SEER-Medicare linkage allowed detailed patient demographics and tumor information to be controlled for in all analyses. Lastly, we examined not only mortality, but also functional adverse events and the novel home days measure. These latter two outcomes are patient-centric and help define the benefit-risk balance of resection beyond only overall survival.

Limitations of our study center around the inability to capture more detailed clinical information in the SEER-Medicare database and the potential for misclassification of treatment group. For instance, body mass index is not contained in the database and may impact receipt of treatment and survival. Importantly, many of such unmeasured factors that would be simultaneously associated with forgoing resection and poorer prognosis could have the impact of making our protective estimates of trimodal therapy larger than they are in truth. If measured, these would likely make the relatively small risk reduction from trimodal therapy even smaller. In terms of misclassification, it is possible that definitive chemoradiation individuals who did not have an esophagectomy within 6 months of chemoradiation, but did shortly after (e.g., 6 months and a day) were thus misclassified as definitive chemoradiation because in reality they had a trimodal therapy treatment plan. However, a timepoint had to be chosen to distinguish between trimodal therapy and definitive chemoradiation with an unplanned salvage esophagectomy.

In conclusion, our study suggests that esophagectomy after chemoradiation may not be warranted for older adults with locally advanced esophageal cancer. While survival was longer for the trimodal therapy group for both adenocarcinomas and squamous cell carcinomas, the low absolute mortality risk reduction and increased risk of functional adverse events afforded by trimodal therapy compared to definitive chemoradiation merit consideration during treatment selection for older adults. Ultimately, our results can be used in tandem with clinical expertise, quality of life predictions, and patient preference to enhance shared decision making.

5.5 Tables and Figures

Figure 5.1 Study design schematic representing the use of longitudinal information from the SEER-Medicare database



a. Eligible tumor requirements consisted of: histologically confirmed adenocarcinoma or squamous cell carcinoma, malignant tumor behavior, stage IB-IIIC
b. Healthcare utilization included: number of hospitalizations and number of emergency department visits
c. Earliest of the following: outcome of interest (except for recurrent event analysis), competing event, end of outcome risk window, administrative end of the study period (December 31st 2019 for all study outcomes except cancer-specific survival which is December 31st 2017), or analytic censoring due to clone data no longer being consistent with assigned treatment strategy

Table 5.1 Features of the target trial versus the observational emulation

Feature	Target Trial	Observational Emulation using SEER-Medicare data
Overall design	Parallel-arm pragmatic randomized clinical trial	Retrospective cohort study comparing two treatment options head-to-head using real world data
Eligibility criteria	Adults 65 years of age and older. Diagnosed (in the past 120 days) with an incident, histologically-confirmed, non-cervical stage IB-IIIC esophageal adenocarcinoma (AC) or squamous cell carcinoma (SCC). Karnofsky Performance Score (KPS) > 70. A geriatric assessment would be performed to identify patients with functional status that would permit esophagectomy.	Adults 66-79 years of age. Histologically confirmed diagnosis (in the past 120 days) of non-cervical stage IB-IIIC esophageal AC or SCC. One-year continuous insurance enrollment prior to diagnosis is required, making the youngest eligible age 66. KPS and geriatric assessment not available in the data, so claims-based comorbidity and frailty indices used to exclude those a Charlson comorbidity score ≥5 or with a Kim frailty index ≥0.35.
Treatment strategies	Trimodal therapy: Initiate concurrent chemoradiation (chemotherapy and radiation on *same day*) and receive esophagectomy 6-8 weeks after completing chemoradiation. Chemoradiation could be any infusion-delivered chemotherapeutic agent paired with external beam radiation. Definitive chemoradiation: Initiate concurrent chemoradiation (chemotherapy and radiation on *same day*) and do not receive esophagectomy with curative intent. Chemoradiation could be any infusion-delivered chemotherapeutic agent paired with external beam radiation.	Trimodal therapy strategy: Start chemotherapy, receive radiation within 7 days of starting chemotherapy, and receive esophagectomy within 6 months of starting chemotherapy Definitive chemoradiation strategy: Start chemotherapy, receive radiation within 7 days of starting chemotherapy, and do not receive esophagectomy within 6 months of starting chemotherapy
Assignment procedures	Patients randomized at baseline in unblinded fashion. Confounders balanced across treatment arms in expectation.	Patients self-selected into treatments. Thus, the assumption is that such selection is adequately captured by the following measured confounders: age, sex, race and ethnicity, year of diagnosis, histologic subtype, tumor grade, cancer stage, tumor location, Charlson comorbidity score, Kim frailty index, health care utilization in the prior year, geographic region, and a census-level measure of poverty. This amounts to an assumption of conditional randomization.
Follow-up	Study population individuals followed until the occurrence of the outcome, loss of fee-for-service insurance coverage, all-cause death, endpoint evaluation horizon (depending on outcome, e.g., 5 years for survival endpoints), or administrative end of study (12/31/2019).	Study population individuals followed until the occurrence of the outcome, analytic censoring, loss of fee-for-service insurance coverage, death, endpoint evaluation horizon (depending on outcome, e.g., 5 years for survival endpoints), or administrative end of study (12/31/2017 for cancer-specific mortality outcome, 12/31/2019 for all other outcomes).
Outcomes	5-year overall mortality, 5-year cancer-specific mortality, 1-year risk of functional adverse events, 5-year cumulative count of days at home. Follow-up surveys administered to ascertain patient-reported occurrence of functional adverse events and healthy days at home.	Same as the target trial, though functional adverse events and healthy days at home ascertained through claims data instead of survey data.
Causal contrasts	Risk difference, risk ratio, mean cumulative count difference, mean cumulative count ratio	Same as target trial.
Estimands	Intent to treat and per-protocol effects	Per-protocol effect
Analysis plan	Intent-to-treat effect estimated via following groups up from baseline randomization regardless of compliance with assigned strategy. Per-protocol-effect estimated within those who competed all elements of the intervention to which they were randomized.	Clone-censor-weight analysis to estimate the per-protocol effect.

Table 5.2 Study population descriptive statistics, amongst a population of Medicare-enrolled older adults diagnosed with non-cervical locally advanced esophageal or gastroesophageal cancer in SEER registry regions between 2004-2017

	Adenocarcinomas (N= 1,240)	Squamous cell carcinomas (N= 661)
Age, median (IQR)	72 (68 – 75)	72 (69 – 75)
Sex		
Male	1,090 (87.9)	366 (55.3)
Female	150 (12.1)	295 (44.6)
Race		
White Non-Hispanic	1,166 (94.0)	474 (71.7)
White Hispanic	37 (3.0)	37 (5.6)
Black	19 (1.5)	98 (14.8)
Other race and ethnicity	18 (1.5)	52 (7.9)
Year of diagnosis		
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		
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		
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		
Upper and middle esophagus	73 (5.9)	414 (62.6)
Lower esophagus	1,092 (88.1)	188 (28.4)
Overlapping lesion or NOS	75 (6.0)	59 (8.9)
Stage group		
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		
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		
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 cancer diagnosis		
No	1,019 (82.2)	526 (79.6)
Yes	221 (17.8)	135 (20.4)
Hospitalizations in past year, n (%)		
0	823 (66.4)	400 (60.5)
1	304 (24.5)	185 (28.0)
≥2	113 (9.1)	76 (11.5)
ED visits in past year, n (%)		
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, n (%)		
0% - <5%	345 (27.8)	154 (23.3)
5%-<10%	373 (30.1)	189 (28.6)
10% - <20%	343 (27.7)	180 (27.2)
20% - 100%	179 (14.4)	138 (20.9)

Abbreviations: IQR, interquartile range; NOS, not otherwise specified
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

Table 5.3 Select demographic and tumor characteristics before and after attrition from eligible cohort due to missing stage data

	Adenocarcinomas		Squamous cell carcinomas	
	Before attrition N=14,326	After attrition N=6,095	Before attrition N=7,661	After attrition N=3,118
Age, median (IQR)	76 (70 - 82)	75 (70 - 81)	76 (71 - 82)	75 (70 - 81)
Sex, n (%)				
Male	11,806 (82.4)	5,164 (84.7)	4,466 (58.3)	1,815 (58.2)
Female	2,520 (17.6)	931 (15.3)	3,295 (41.7)	1,303 (41.8)
Grade, n (%)				
Well differentiated	721 (5.0)	365 (6.0)	349 (4.6)	155 (5.0)
Moderately differentiated	4,772 (33.3)	2,167 (35.6)	2,913 (38.0)	1,275 (40.9)
Poorly differentiated	6,038 (42.2)	2,353 (38.6)	2,852 (37.2)	1,080 (31.5)
Undifferentiated	166 (1.2)	80 (1.3)	72 (0.9)	27 (25.2)
Not determined	2,629 (18.4)	1,130 (18.5)	1,475 (35.9)	581 (34.0)
Tumor site				
Thoracic esophagus	237 (1.7)	109 (1.8)	420 (5.5)	182 (5.8)
Abdominal esophagus	110 (0.8)	62 (1.0)	34 (0.4)	15 (0.5)
Upper third of esophagus	162 (1.1)	59 (1.0)	1,192 (15.6)	488 (15.6)
Middle third of esophagus	964 (6.7)	394 (6.5)	2,763 (36.1)	1,192 (38.2)
Lower third of esophagus	11,108 (77.5)	4,872 (79.9)	2,078 (27.1)	852 (27.3)
Overlapping lesion	528 (3.7)	169 (2.8)	384 (5.9)	143 (4.6)
Not otherwise specified	1,217 (8.5)	430 (7.1)	790 (10.3)	246 (7.9)

Figure 5.2 Flowchart depicting selection of study population through application of eligibility criteria

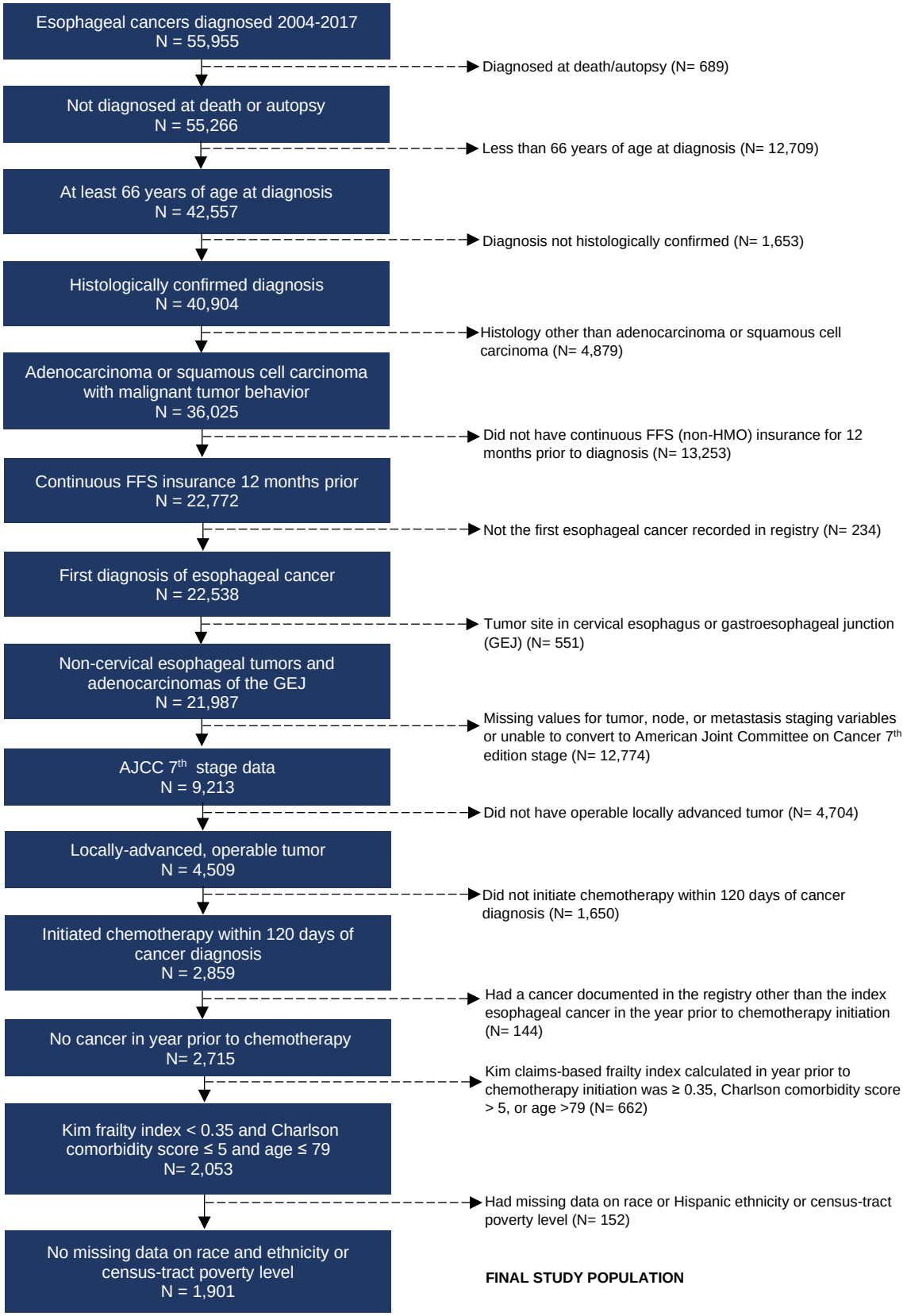


Figure 5.3 Standardized mean differences of confounding variables at 183 days before and after implementing inverse probability of censoring weights, adenocarcinomas

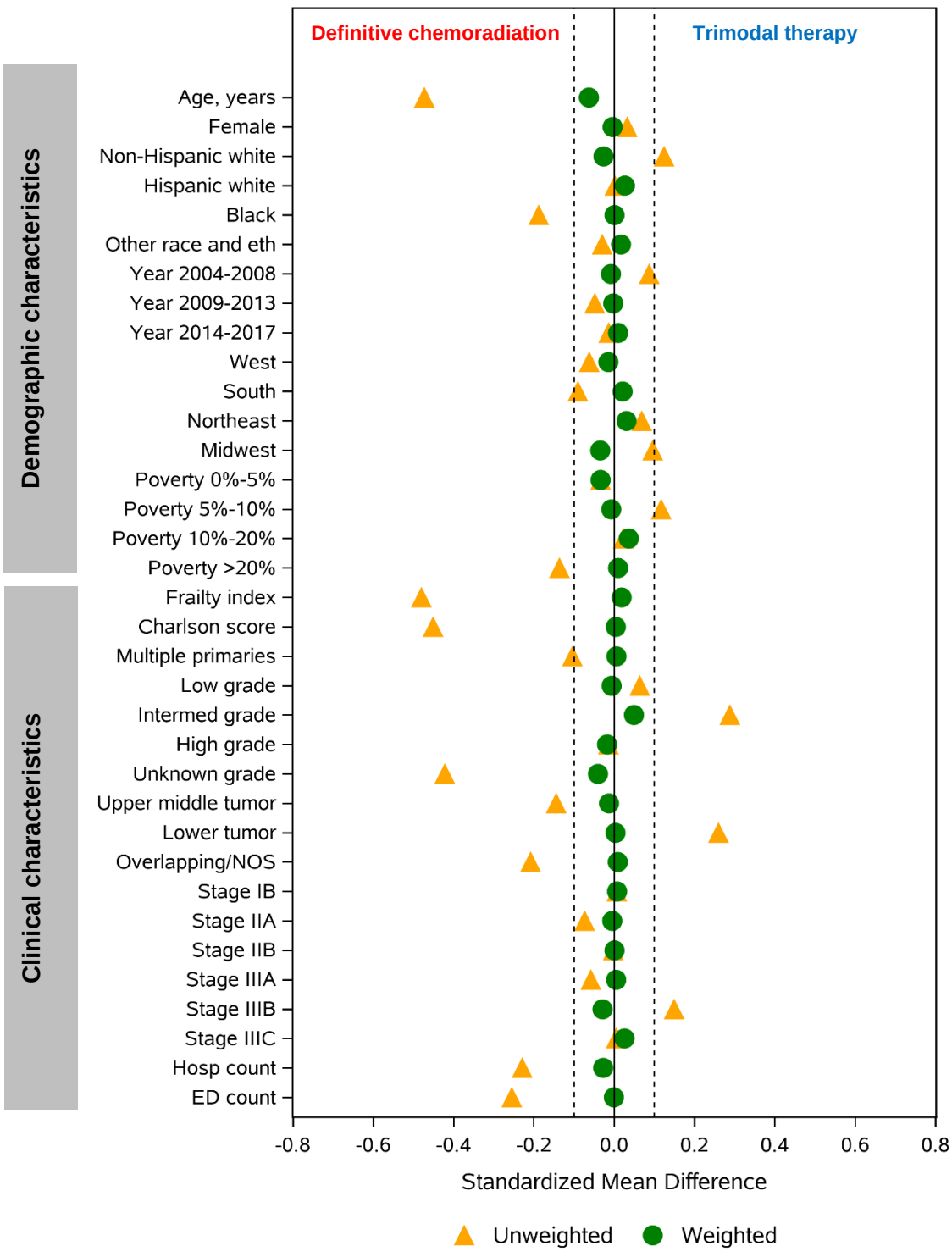


Figure 5.4 Standardized mean differences of confounding variables at 183 days before and after implementing inverse probability of censoring weights, squamous cell carcinomas

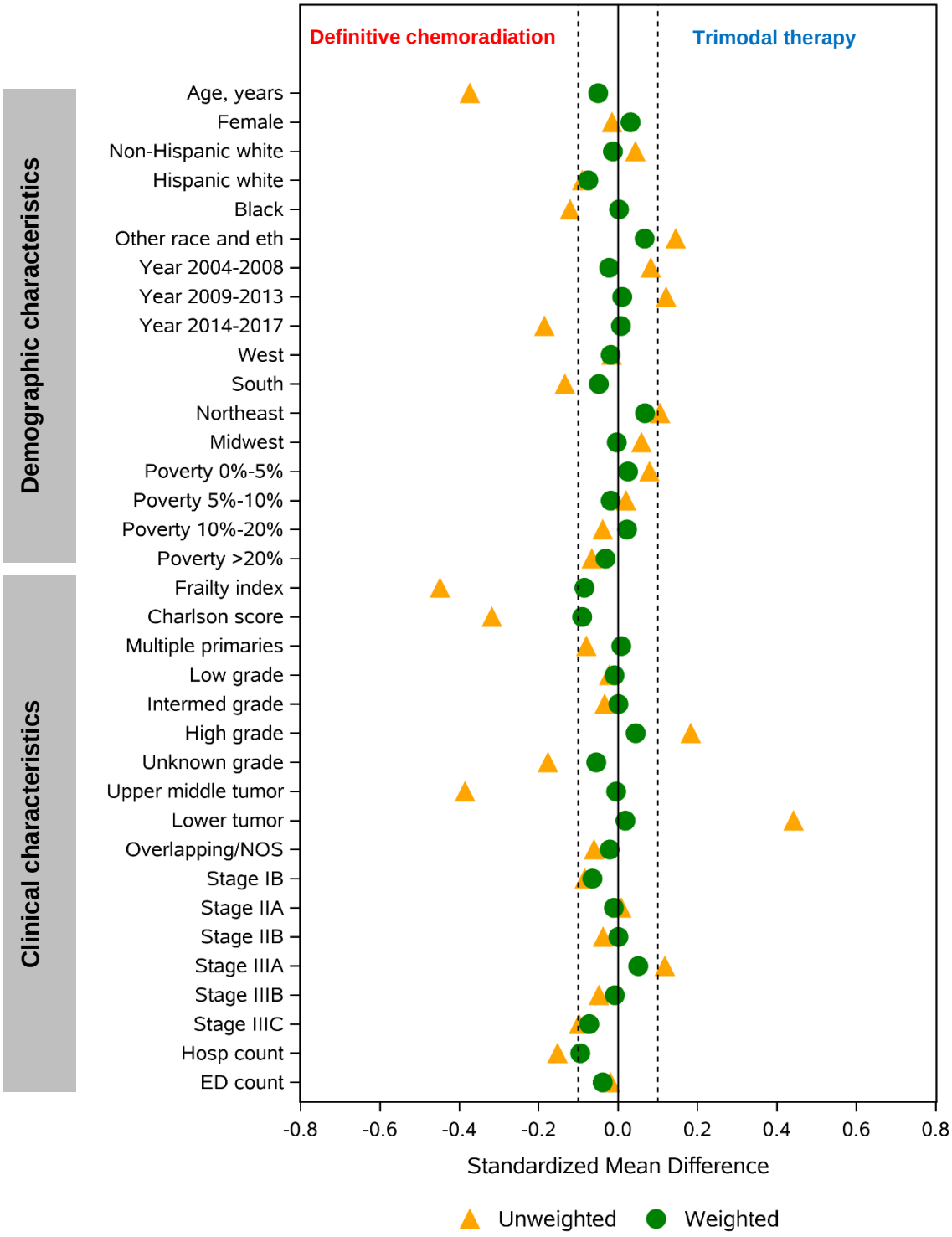


Figure 5.5 Five-year standardized cumulative incidence of overall mortality in adenocarcinomas (panel A) and squamous cell carcinomas (panel B), according to treatment strategy

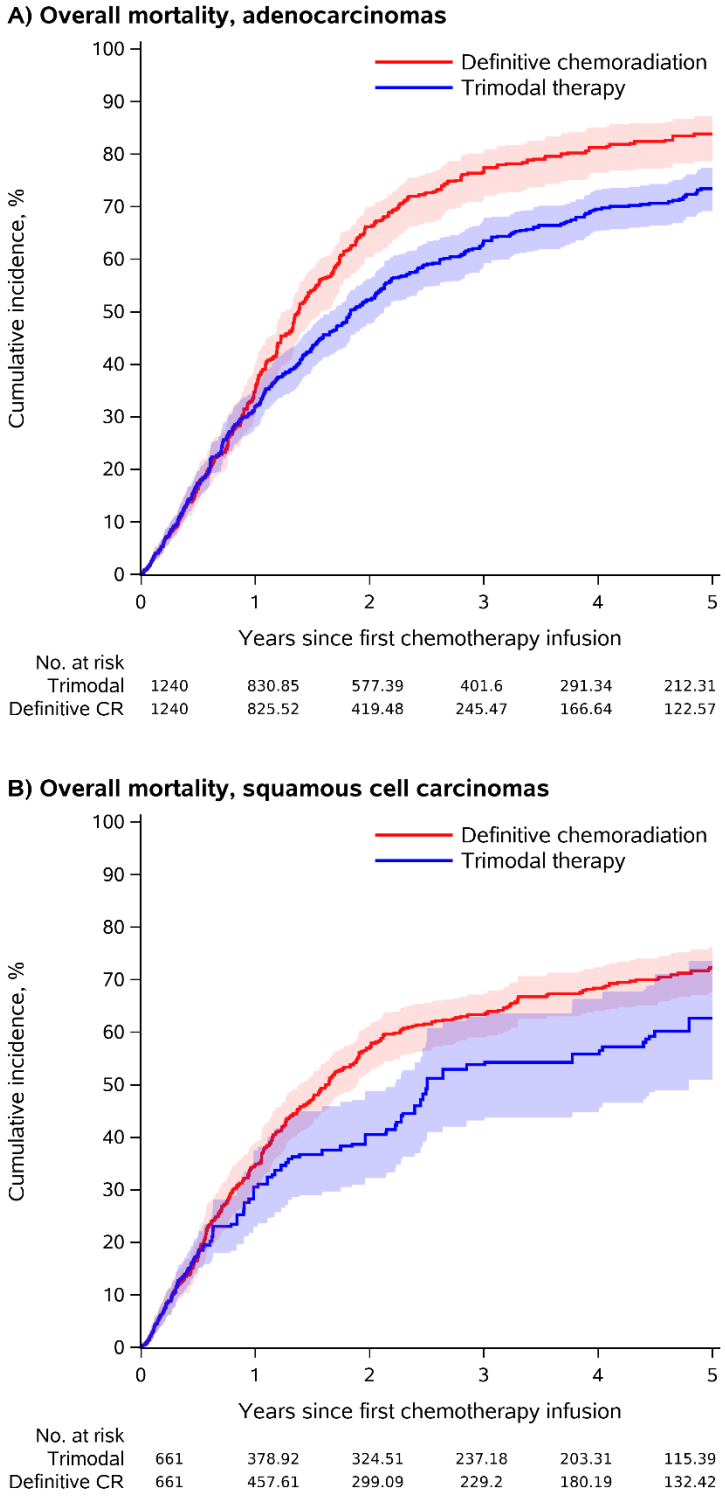


Figure 5.6 Five-year standardized cumulative incidence of esophageal cancer-specific mortality in adenocarcinomas (panel A) and squamous cell carcinomas (panel B), according to treatment strategy

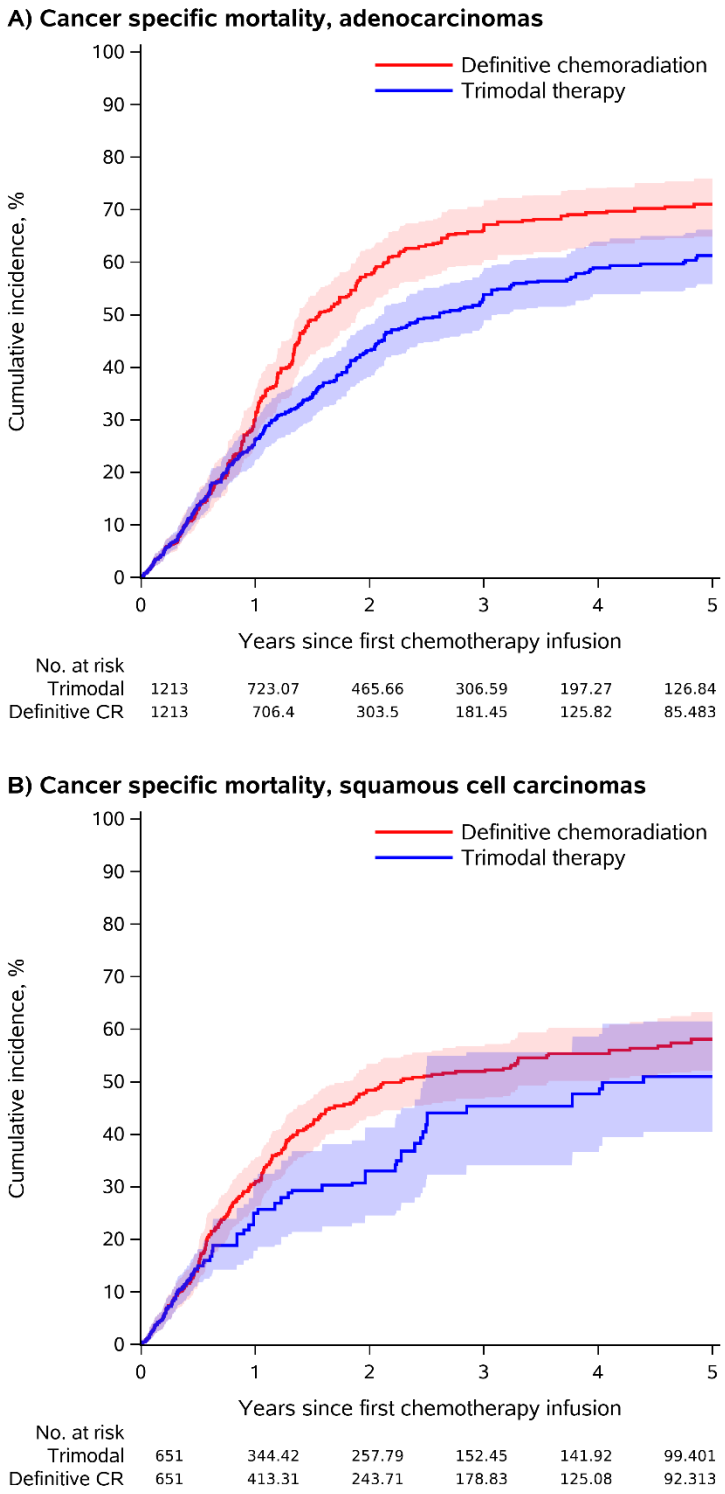
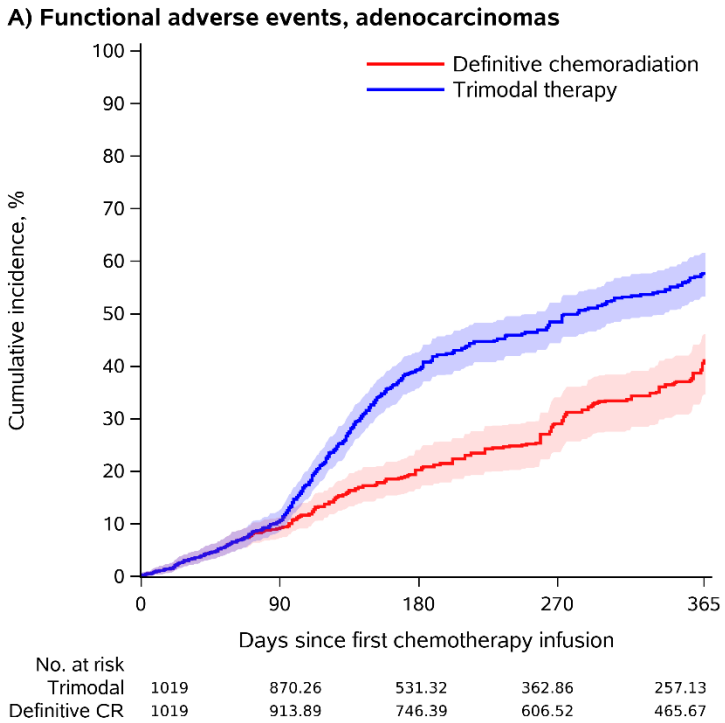


Figure 5.7 One-year standardized cumulative incidence of functional adverse events in adenocarcinomas (panel A) and squamous cell carcinomas (panel B), according to treatment strategy



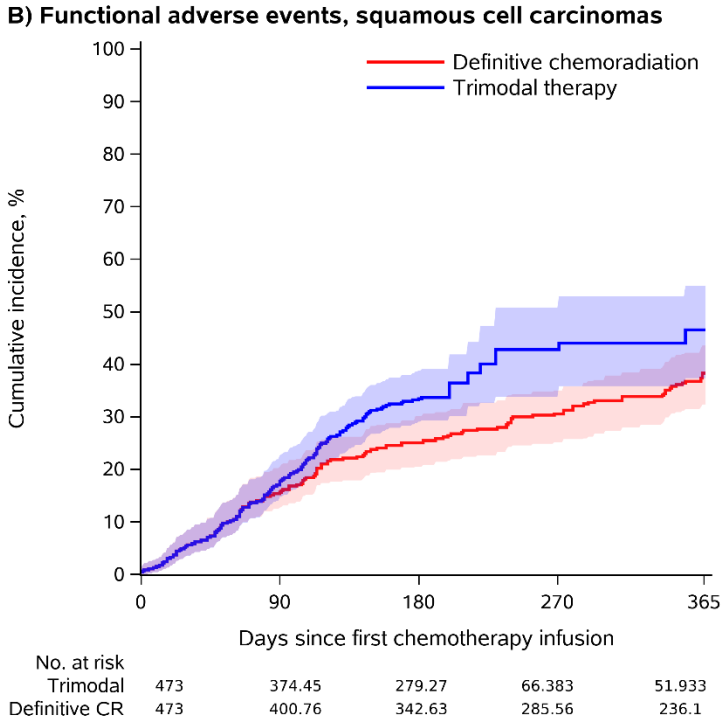
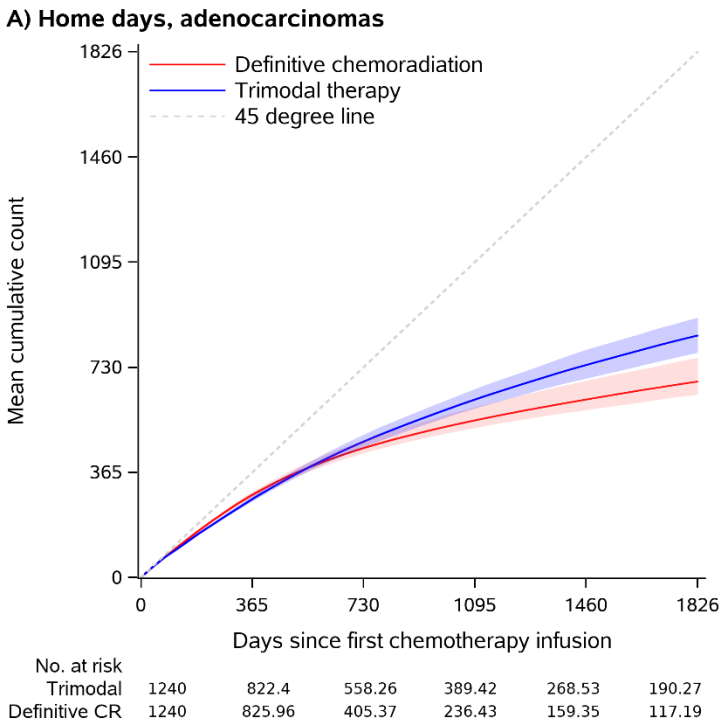


Figure 5.8 Five-year standardized mean cumulative count of days at home in adenocarcinomas (panel A) and squamous cell carcinomas (panel B), according to treatment strategy



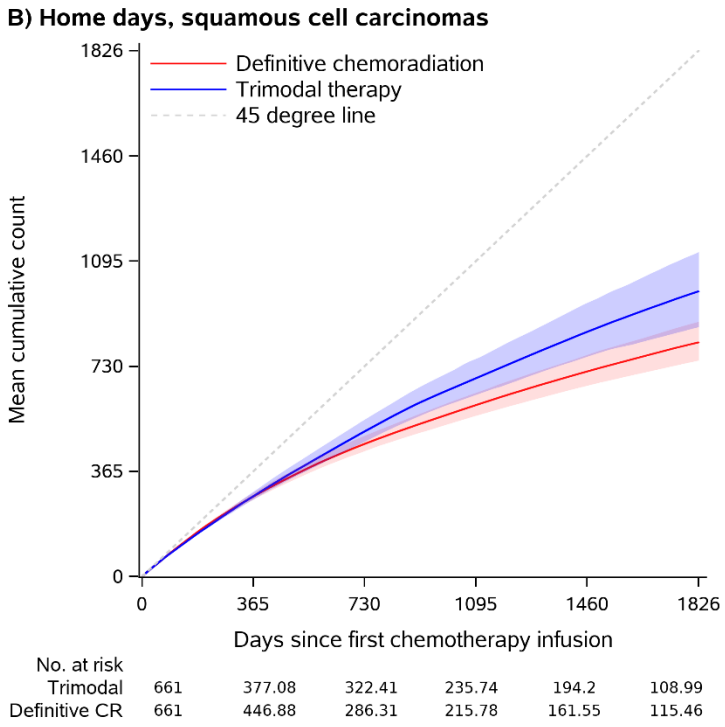


Table 5.4 Measures of cumulative risk and burden with corresponding contrasts between treatment groups for the primary study outcomes amongst a cohort of locally advanced esophageal cancer cases identified in SEER-Medicare, 2004-2017

Overall mortality			
	5-year Risk (95% CI)	Risk Difference (95% CI)	Risk Ratio (95% CI)
Adenocarcinomas			
Definitive chemoradiation	83.8 (78.6 – 87.2)	REF	REF
Trimodal therapy	73.4 (69.1 – 77.4)	-10.4 (-15.6 – -3.9)	0.88 (0.82 – 0.95)
Squamous cell carcinomas			
Definitive chemoradiation	72.3 (67.6 – 76.3)	REF	REF
Trimodal therapy	62.6 (50.9 – 73.5)	-9.6 (-21.6 – 0.8)	0.87 (0.70 – 1.01)
Esophageal cancer-specific mortality			
	5-year Risk (95% CI)	Risk Difference (95% CI)	Risk Ratio (95% CI)
Adenocarcinomas			
Definitive chemoradiation	71.0 (64.9 – 75.9)	REF	REF
Trimodal therapy	61.2 (55.8 – 66.2)	-9.8 (-17.2 – -1.5)	0.86 (0.77 – 0.98)
Squamous cell carcinomas			
Definitive chemoradiation	58.1 (52.1 – 63.2)	REF	REF
Trimodal therapy	51.0 (40.5 – 61.5)	-7.1 (-18.9 – 4.4)	0.88 (0.68 – 1.07)
Functional adverse events			
	1-year Risk (95% CI)	Risk Difference (95% CI)	Risk Ratio (95% CI)
Adenocarcinomas			
Definitive chemoradiation	41.3 (34.6 – 46.1)	REF	REF
Trimodal therapy	57.9 (53.3 – 61.6)	16.5 (9.8 – 23.3)	1.40 (1.22 – 1.65)
Squamous cell carcinomas			
Definitive chemoradiation	38.5 (32.3 – 43.6)	REF	REF
Trimodal therapy	46.8 (37.4 – 54.9)	8.2 (0.0 – 17.5)	1.21 (1.00 – 1.49)
Days at home			
	5-year MCC (95% CI)	MCC Difference (95% CI)	MCC Ratio (95% CI)
Adenocarcinomas			
Definitive chemoradiation	680.3 (634.8 – 762.0)	REF	REF
Trimodal therapy	840.1 (779.9 – 901.6)	159.8 (67.3 – 229.2)	1.23 (1.09 – 1.36)
Squamous cell carcinomas			
Definitive chemoradiation	813.0 (749.5 – 883.9)	REF	REF
Trimodal therapy	990.3 (865.7 – 1,125.8)	177.3 (50.8 – 313.1)	1.22 (1.06 – 1.40)

Abbreviations: MCC, mean cumulative count; REF, reference group

CHAPTER 6 – DISCUSSION

Esophageal cancer is a rare but highly fatal malignancy. Four out of five patients diagnosed with this poor prognosis cancer will die within five years of diagnosis. Trimodal therapy and definitive chemoradiation are two treatment strategies with curative intent endorsed by the NCCN and ASCO treatment guidelines for non-metastatic locally advanced esophageal cancer.[3,4] Trimodal therapy occupies its position as the standard of care mostly on account of trials that have demonstrated its superiority over surgical resection alone.[5,6] However, this comparator is of less relevance to the older adult population. Compared to their younger counterparts, older esophageal cancer patients have a heightened comorbidity burden, increased frailty, and decreased life expectancy.[88,239] These characteristics may meaningfully attenuate the beneficial effect of trimodal therapy and inflate adverse events, viable concerns which may influence the treatment decisions of older adults. Thus, the decision for many in this population is between trimodal therapy and definitive chemoradiation—whether or not to include surgical resection in the multimodal treatment plan.

Practice patterns within the older adult population have not been described using contemporary data. Specifically, treatment trends over time and the distribution of treatment received by patient characteristics have not been well-characterized in the decade after the CROSS trial. A SEER-Medicare study using data from older adults diagnosed prior (1992-2002) to CROSS found that definitive chemoradiation was the dominant treatment strategy (39%) and very few individuals received trimodal therapy (7%); patients that did receive trimodal therapy were younger, had adenocarcinomas, and a lower Charlson score.[94] CROSS was a landmark trial, the results of which (24 months extended survival in trimodal therapy vs. surgery alone) may have influenced care patterns for trimodal-eligible older adults more broadly than merely

supplanting surgery alone with trimodal therapy. Within the older adult population, it is uncertain if there has been any channeling away from definitive chemoradiation and how patient characteristics such as frailty correspond to treatment receipt. Broader studies that examined all-age esophageal cancer populations have found an increase in trimodal therapy use over time but also substantial variation in care according to age, race, region, stage of disease, and comorbidity burden.[16,35,45,240]

To date, only two randomized clinical trials have compared trimodal therapy and definitive chemoradiation and they have major limitations that hinder drawing inferences for older adults in modern practice.[116,117] The Fédération Francophone de Cancérologie Digestive-9102 (FFCD-9102) randomized 259 patients who initially responded to chemoradiation to further chemoradiation or surgery and found no benefit of surgery; the point estimate even suggested longer survival (19.3 vs. 17.9 months) in the chemoradiation arm compared to trimodal therapy.[116] The second trial, conducted in a German population diagnosed with squamous cell carcinoma, also found no improvement in survival from trimodal therapy, but significantly higher treatment-related mortality amongst those receiving surgery (12.8% versus 3.5%).[117] The limitations of these studies include underrepresentation of older adults (maximum eligible age of 70 in German trial), small sample sizes, focus on squamous cell carcinomas, randomization of only those who responded to initial chemoradiation (FFCD-9102), higher than expected surgical mortality rates, and use of split-course radiotherapy. These limitations preclude drawing any conclusions for a modern older adult cohort in the US composed largely of adenocarcinomas.

When turning to the observational evidence comparing trimodal therapy to definitive chemoradiation (Appendix 1), many of the existing studies exhibit methodological problems and do not focus on older adult populations. Immortal time bias and selection bias were pervasive in the literature, with numerous studies defining exposure status at baseline based on information that emerged during follow-up.[21–23,33,34,119,122] The result was that no trimodal therapy patient could be classified as such unless they lived long enough to receive resection after

chemoradiation. In contrast, the definitive chemoradiation group in such studies did not have these survival requirements, conferring an artificially higher survival (low mortality risk) in the trimodal therapy group. The studies with immortal time bias produced exaggerated protective effects from trimodal therapy. The bias was visible graphically in extreme Kaplan-Meier curves that departed immediately and significantly between groups, likely before resection had even occurred for many of the trimodal therapy patients. A few of the studies did not contain enough information on how follow-up was handled statistically and two implemented strategies to properly handle immortal time bias with time-dependent Cox proportional hazards models and landmark analysis.[27,231] However, even in studies that remove immortal time bias through correct allocation of person-time during follow up, selection bias can remain present from studying the subset of individuals who experienced all elements of trimodal therapy. In reality, some trimodal therapy patients will die prior to planned esophagectomy and this possibility is an unfortunate part of the trimodal therapy treatment strategy in practice.

Beyond the potential for immortal time bias to overstate the benefits of trimodal therapy, there are clinical reasons why the addition of surgery may have a smaller beneficial, or even harmful, effect in older adults. Several retrospective cohort studies have demonstrated that a higher comorbidity burden at the time of resection portends a shorter survival time after surgery.[44,230] Though this pattern is unsurprising, the implication is that the poorer health status, on average, compared to younger adults places a ceiling on an absolute risk reduction from esophagectomy. Older age and comorbidity burden also decrease the likelihood of a successful surgery. A successful esophagectomy will fully remove the tumor and leave negative surgical margins on the pathology report. A recent NCDB study found that older age and greater comorbidity burden are associated with an increased risk of positive surgical margins.[241] Esophagectomy is major surgical procedure for a patient of any age and can cause anastomotic leaks, pneumonia, ongoing dysphagia, and decreases in health-related quality of life.[59,61,74,242,243]

Risks from the surgery itself, including immediate complications, downstream sequalae, and operative mortality increase with advancing age.[66]

Despite the reasons that adding resection to chemoradiation may not be warranted, there remains a compelling counter argument that resection should be a cornerstone of multimodal treatment of locally advanced esophageal cancer. It is estimated that only 20-40% of trimodal therapy patients demonstrate a pathologic complete response. Confronted with a low probability of complete response to chemoradiation, surgical removal of the tumor may logically delay recurrence and extend survival. The probability of complete response to chemoradiation is particularly low for adenocarcinomas, reinforcing the need for surgery in patients with these tumors. In the CROSS trial, only 23% of trimodal therapy patients with adenocarcinomas experienced pathologic complete response compared to 49% of squamous cell carcinomas. The two trials that compared trimodal therapy to definitive chemoradiation both found better local tumor control amongst individuals who received trimodal therapy. The fact that survival was not improved may be an artefact of the small sample sizes, near universal restriction to squamous cell carcinomas, and the aforementioned limitations in study design. The degree of benefit from adding surgery to chemoradiation in older adults with adenocarcinomas is particularly unsettled. Esophagectomy has become a safer surgical procedure over time with the development of minimally invasive surgery and new protocols for perioperative care.[244]

To address the uncertainty surrounding the use and effectiveness of these treatments for locally advanced esophageal cancer in older adults, we conducted two retrospective cohort studies using SEER-Medicare data of cases diagnosed from 2004 to 2017.

6.1 Summary of Findings

In our first study, we performed a retrospective cohort study examining practice patterns amongst older adults newly diagnosed with locally advanced esophageal cancer in the SEER-Medicare database between 2004 and 2017. We sought to examine temporal trends in use of

treatments, describe the distribution of treatment across patient demographic and clinical characteristics, and ascertain whether the use of specific chemotherapeutic agents has changed amongst the sub-population treated with definitive chemoradiation or trimodal therapy.

Treatment for locally advanced tumors changed during the study period, as seen in shifting age-standardized percentage of patients receiving each treatment category. We found that the age-standardized use of trimodal therapy increased from 2004 to 2017 for adenocarcinomas (16.7% to 26.1%) but was statistically stable for squamous cell carcinomas (7.3% to 9.1%). During this time the use of definitive chemoradiation also increased and is currently the dominant treatment paradigm for older adults with locally advanced esophageal adenocarcinoma (49.8% in 2017) and squamous cell carcinoma (59.5% in 2017).

We described the distribution of treatment received according to individual-level demographic and clinical characteristics and found substantial variation according to these factors. Amongst adenocarcinomas, 35.2% (95% CI: 32.5% – 38.0%) of individuals aged 66-72 received trimodal therapy compared to only 6.1% (95% CI: 4.4% – 7.8%) of adults 80 years of age and older. We quantified comorbidity burden and frailty using claims-based indices and found that the use of trimodal therapy drops precipitously as the degree of comorbidity and frailty increases. This pattern was observed across both histologic subtypes. Our descriptive estimates identify which populations which may not be receiving standard of care. For instance, only 56.3% of black patients with squamous cell carcinomas received definitive chemoradiation or trimodal therapy, compared to 61.7% of white non-Hispanic patients. Our descriptive findings additionally had ramifications for our comparative effectiveness study of trimodal therapy versus definitive chemoradiation by identifying which factors may be acting as confounders, simultaneously impacting treatment decisions and prognosis.

The last finding of the first study was that the specific chemotherapeutic agents used for treating locally advanced esophageal cancers have changed. Amongst individuals who received either definitive chemoradiation or trimodal therapy, the use of cisplatin-based regimens was

largely replaced with carboplatin-based regimens for both adenocarcinomas and squamous cell carcinomas. In 2004, carboplatin-based regimens were used for 47.0% (95% CI: 33.2- 60.8%) of adenocarcinomas and 37.3% (95% CI: 16.3 – 58.3) of squamous cell carcinomas. By 2017, carboplatin-based regimens were used in 85.3% (95% CI: 80.1 – 90.3) and 78.3% (95% CI: 69.5% – 87.2%) of adenocarcinomas and squamous cell carcinomas, respectively.

In the second study, we estimated the effect of receiving trimodal therapy compared to definitive chemoradiation on all-cause mortality, esophageal cancer-specific mortality, functional adverse events, and days at home. For adenocarcinomas, we found that trimodal therapy decreases the risks of all-cause (RR = 0.88; 95% CI: 0.82, 0.95) and cancer-specific mortality (RR = 0.86; 95% CI: 0.77, 0.98) compared to definitive chemoradiation. However, these decreases were smaller than suggested by the prior literature. Importantly, the standardized cumulative incidence between treatment groups tracked closely at the beginning of follow-up, when patients in both arms are receiving chemoradiation but not surgery. Similar protective effects were found for squamous cell carcinomas (Overall mortality RR = 0.87, 95% CI: 0.70, 1.01; cancer-specific mortality RR = 0.88, 95% CI: 0.68 – 1.07), though findings were less precise. We additionally found that the trimodal therapy strategy was associated with a substantially greater one-year risk of functional adverse events for both histologic subtypes. When we estimated the effect of trimodal therapy on the mean cumulative count of days at home, we found an interesting pattern: trimodal therapy was actually associated with the same or fewer days at home in the first two years and then eventually surpassed definitive chemoradiation in the expected count, though differences in the final five-year count of days at home was modest for both adenocarcinomas and squamous cell carcinomas.

6.2 Strengths and Limitations

Our work has numerous strengths. We delivered tailored evidence on the use and effectiveness of treatments for locally advanced esophageal cancer specific to the older adult

population, a group frequently excluded or underrepresented in clinical trials. With increased medical complexity (e.g., multiple chronic conditions), the benefit-risk profile of trimodal therapy over definitive chemoradiation was unlikely to be similar to that of younger individuals diagnosed with esophageal cancer. Yet, prior to our work, there was scant evidence comparing these treatment modalities for older adults. In addition to our findings on mortality, we reported on two outcomes highly germane to older adults trying to incorporate quality of life into their decision-making process: the risk of functional adverse events and the expected number of non-medicalized days at home. These outcomes provide crucial context around the mortality findings; our results indicated that although trimodal therapy decreases the risk of mortality, it also increases the risk of functional adverse events and modestly increases expected days at home.

Using the SEER-Medicare linked database, we were able to control for many of the strongest confounders in our analysis including tumor characteristics and individual-level demographic and clinical variables. Assessing the medical claims one year prior to the index date, we constructed comorbidity and frailty measurements for each individual in the study population. Empirical comparisons of SEER-Medicare and NCDB measurements of comorbidity burden demonstrate that longitudinal assessment via claims in SEER-Medicare provides more complete measurement, reducing the amount of residual confounding in effect estimates.[146] We also incorporated measurement of a novel frailty index into our confounding control strategy.[162] Frailty is critical to account for when conducting comparative effectiveness research in older adult populations because increased levels of frailty can strongly channel patients away from aggressive therapies while also impacting prognosis.[245] Studies that fail to aptly account for frailty via study design or analysis often possess strong bias. The confounding effect of frailty has been demonstrated to be above and beyond comorbidity burden. We also used restriction to control for confounding. Though using the AJCC 7th edition staging manual may have caused a decrease in sample size (some AJCC 6th edition tumors could not be converted), it provided

us the powerful advantage of only including tumors that were amenable to resection: the unresectable T4b tumors were excluded from analysis.

Methodologically, we used the innovative clone-censor-weight technique to remove the possibility of immortal time bias from our findings. This was perhaps the greatest strength of our work, as past studies had been afflicted by this bias and therefore estimated implausibly fast and strong protective effects of trimodal therapy. This provided more realistic estimates of the effect of trimodal therapy, as outcome occurrence prior to receiving resection could occur and is a part of rolling out trimodal therapy in practice. Our use of this analytic tool represents a major reduction in bias for database-related observational studies wherein the treatment status of a patient is sequential. To date, this technique had not yet been applied to esophageal cancer research.

Further strengthening our comparative effectiveness study was our use of the target trial emulation framework. This framework facilitates the comparison of well-defined interventions and the alignment of eligibility, treatment assignment, and follow-up.[188] The alignment of these three features permitted the use of inverse-probability weighted non-parametric estimators, producing interpretable step-functions commonplace in the randomized trial setting. One such tool was the weighted Dong-Yasui estimator, which we used in a novel application to estimate the mean cumulative count of home days, a new patient-centric outcome measure.

Compared to claims-only or registry-only studies, the linked SEER-Medicare database allowed for a greater depth of confounder control. Our control of measured confounding was strengthened by availability of SEER data on tumor characteristics, such as stage and grade, which have strong prognostic effects. The Medicare claims data facilitated calculation of comorbidity burden, frailty indices, and prior healthcare utilization. We were able to diagnostically assess balance in all of our confounders at the end of the 6-month grace period using standardized mean differences before and after implementing weights. This provided reassurance that our weights (truncated at the 99th percentile) produced adequate balance.

Throughout our work we retained a focus on using appropriate statistical methods that would yield interpretable findings. For instance, we reported risk differences and risk ratios instead of hazard ratios. Hazard ratios are difficult to communicate and have multiple troublesome statistical properties. Presenting risk differences and ratios involved a more labor-intensive process to obtain confidence intervals (bootstrapping), but ultimately provided numbers that are easier to communicate to patients and aid in decision making. Another analytic decision made with interpretability in mind was the use of competing events analysis. Instead of censoring patients when a competing event occurred, we used statistical estimators that explicitly handle the risk-terminating qualities of competing events. As a result, our findings are not constrained to an unrealistic world where competing events are assumed not to occur, an assumption required with common strategies that censor individuals at the occurrence of a competing event.

Our studies contain important limitations. Though our work offers a major advance in comparative effectiveness research for older adults with esophageal cancer, the findings are only generalizable to the Medicare fee-for-service population. The Medicare Advantage population is known to be composed of healthier patients,[228] which would likely alter treatment selection and the expected effect of trimodal therapy in this population. Participation in Medicare Advantage has grown nationally, from 13% in 2004 to 33% in 2017.[246] The clone-censor-weight method is an effective tool for eliminating immortal time bias but is not infallible in its task of appropriately classifying person-time. In our application, we are trading immortal time bias for early misclassification of treatment groups when clones are assigned to both treatment strategies. The SEER-Medicare linked database allows for control of tumor characteristics, with access to data on tumor stage, grade, histology, and location. These characteristics are strong confounders that would be unavailable in claims data alone. However, compared to electronic medical records or a prospectively maintained database, the level of clinical detail in SEER-Medicare is of lower resolution. For instance, it would have been valuable to have a

measurement on body mass index, as this could have a strong effect on eligibility for surgery while also impacting outcomes. Additionally, access to data on radiation dose and clinical response to chemoradiation would have been inordinately useful at creating a more specific treatment definition for trimodal therapy, such as “receive surgery after delivery of chemotherapy and 41.4 Gy radiation unless there is a clinical complete response”. Lastly our requirement that cancers be staged using the 7th edition of the AJCC staging manual led to a substantial number of individuals being excluded from analysis, potentially biasing our final sampling frame in ways that are difficult to understand.

6.3 Public Health Significance

Our work has strong implications for public health. Esophageal cancer has a poor prognosis and, despite being a rare cancer, is the sixth leading cause of cancer-related mortality globally.[229] The incidence of esophageal cancer, like most malignancies, increases with advancing age. On account of an aging population, the burden of esophageal cancer will grow considerably with nearly 19,000 predicted US cases in 2030.[52] With a median age at diagnosis of 68, the majority of cases are diagnosed in older adults. However, prior to our work, rigorous estimates of the effect of trimodal therapy versus definitive chemoradiation did not exist for this highly impacted population.

Specifically, our studies deliver crucial information that patients seek when making decisions. A prospective cohort study that conducted a discrete choice experiment in patients considering definitive chemoradiation with active surveillance or trimodal therapy found that five-year overall survival and health-related quality of life heavily influenced the decision making process. In the discrete choice experiment, interviewed patients would accept a 16% lower 5-year survival to retain the (higher) quality of life associated with definitive chemoradiation instead of the (lower) quality associated with resection.[237] Our effect estimates are critical for treatment-related decision making as patients, families, and providers try to match treatment

selection with goals and preferences. As the discrete-choice experiment demonstrated, context is critical when making treatment-related decisions. The decision may swing on the magnitude of benefit, not just a simple yes-no statement that trimodal therapy is superior. Our results (mortality, cancer-specific death, functional adverse events, and home days) can deliver this information on benefit and risk magnitude to help inform discussions between patients and their providers.

6.4 Future Research

The possibility for heterogenous treatment effects within the older adult population should be explored in additional studies. Our work focused on estimating the average treatment effect in a population of older adults. Analyses were performed in a cohort of adults 66-79 years of age to provide more relevant effect estimates to the typical older adult than existing studies. Past studies, in addition to methodologic concerns, frequently underrepresented older adults or focused on all-age cohorts. The conventional interpretation of the average treatment effect is the difference in expected outcome if everybody in the study population had been treated versus if everybody had been untreated (or given an alternative treatment).[215] Thus, the average treatment effect from prior all-age cohort studies is weighted towards a younger population. By studying a cohort of patients 66-79 years of age, our “local” average presents a closer estimate of anticipated effect for older adults. However, even within the older adult population there is likely a distribution of anticipated benefit and harm from trimodal therapy. Heterogenous treatment effects occur when patients within a population do not uniformly have the same effect of treatment due to patient characteristics (e.g., age, sex, stage of cancer, comorbidity burden, etc.) that either impact baseline outcome risk or directly modify the relative treatment effect.[247] Future work exploring heterogeneity could begin by reporting sub-group effects across strata of age, comorbidity scores, frailty indices, and tumor stage. These preliminary sub-group analyses could help inform more useful multivariable approaches to modelling heterogenous treatment

effects, including estimation of individualized treatment effects.[248–252] Ultimately, if successful, this work could have a profound impact by helping personalize estimates of anticipated effect to the individual considering treatment instead of relying on the applicability of single study-wide average.[253]

Secondly, given our observation that most older adults are treated with chemoradiation either definitively or with added surgical resection, future work should examine the comparative effectiveness of particular chemoradiation regimens. This is already a rich area of ongoing research with multiple studies comparing the effectiveness of carboplatin and paclitaxel versus cisplatin and fluorouracil.[227,254–261] Interestingly, these comparative studies have had mixed findings when considering overall survival. Carboplatin and paclitaxel are known to have improved tolerability and few adverse effects compared to cisplatin and fluorouracil, but oncologic efficiency may be greater with cisplatin. On the other hand, findings that cisplatin is associated with longer survival compared to carboplatin may be on account of unmeasured confounding. Our finding of extreme channeling away from cisplatin-based regimens and towards carboplatin-based regimens suggests that instrumental variable analysis (with calendar time as an instrument) may be a highly fruitful avenue for estimating the comparative effectiveness of these strategies. Theoretically, this approach would handle both measured and unmeasured confounders, making it a powerful tool in the armamentarium for causal effect estimation using observational data.[262]

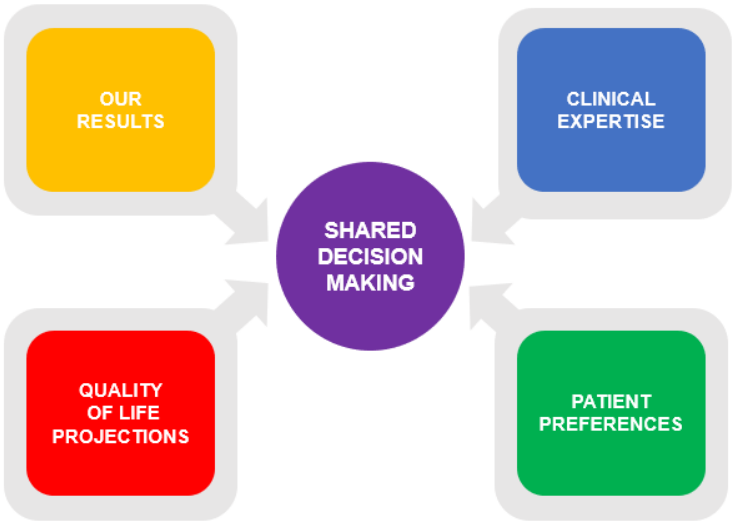
6.5 Conclusions

Esophageal cancer is a deadly malignancy, with four out of five patients dying within five years of diagnosis. As cancer is strongly associated with aging, older adults bear the brunt of the disease burden. However, older adults are often underrepresented in oncology clinical trials, leaving an evidentiary void for clinicians and patients attempting to determine the best course of treatment. Our work demonstrated that most older adults with locally advanced esophageal

cancer are treated with definitive chemoradiation and that, while trimodal therapy is associated with longer survival, the beneficial effect is smaller than prior observational studies have reported. Taken together, these findings suggest that trimodal therapy should be selectively delivered to older adults and the observed high use of definitive chemoradiation may be appropriate when considering anticipated benefit and risks. Our results can be used in tandem with clinical expertise, quality of life projections, and patient preferences to inform shared decision making. It is our hope that our findings will function as a complimentary piece (Figure 6.1), helping clinicians and patients shift from a landscape of uncertainty to one where decisions are based on less biased results and wider consideration of outcomes relevant to older adults.

6.6 Tables and Figures

Figure 6.1 Complimentary pieces that contribute to shared decision making



APPENDIX 1. OBSERVATIONAL STUDIES COMPARING TRIMODAL THERAPY AND DEFINITIVE CHEMORADIATION

Author (Year)	Population	N	Treatment groups compared	Key Results	Strengths and Limitations
McKenzie (2011)	Los Angeles County Cancer Surveillance Program, 1988-2006 Local and regional esophageal cancers (American Joint Committee on Cancer stage I-III)	2,233	Trimodal therapy (n= 286) Definitive chemoradiation (n= 645)	<u>Overall survival (trimodal vs. definitive chemoradiation)</u> • Adjusted HR = 0.66, 95% CI: 0.56, 0.77 • Median unadjusted survival 25.2 months in trimodal group • Median unadjusted survival 12.3 months in definitive chemoradiation group <u>Unadjusted median survival (trimodal vs. definitive chemoradiation)</u> • Slightly longer survival gain from trimodal therapy for adenocarcinomas than squamous cell carcinomas • Squamous cell carcinomas (24.2 vs. 12.8 months; 5-year survival 30% vs. 14%) • Adenocarcinomas (25.9 vs. 10.6 months; 5-year survival 30% vs. 5%)	Strengths: • Included older adults: 36% of trimodal and 59% of definitive chemoradiation arms were 65 and older • Included both histologic subtypes • Conducted sensitivity analysis stratifying by histologic subtype to explore heterogeneity in treatment effect Limitations: • Immortal time bias: follow-up started at diagnosis, but categorized exposure based on future information; seen in immediate departure of survival curves • Selection bias: only those healthy enough to complete trimodal therapy made it into that exposure group • 22% of the trimodal therapy arm had adjuvant chemoradiation as opposed to neoadjuvant chemoradiation: not a well-defined intervention • Reported hazard ratio instead of more interpretable risk ratio or risk difference • Used univariate model to determine which variables should be in multivariable model

Author (Year)	Population	N	Treatment groups compared	Key Results	Strengths and Limitations
Hategan (2015)	Single center study in the United Kingdom of all esophageal cancers treated with definitive chemoradiation or trimodal therapy	102	Trimodal therapy (n=55) Definitive chemoradiation (n=47)	2-year overall survival • 57.3% (median overall survival 39.7 months) for the definitive chemoradiation group • 77.8% (median survival did not occur during follow up) for the trimodal therapy group 5-year overall survival • 38% for the definitive chemoradiation group • 58% for the trimodal group Pathologic complete response • Pathologic complete response was observed in 23.6% of trimodal patients	Strengths: • Broad inclusion criteria: both histologic subtypes included, patients of any age Limitations: • Analysis was unadjusted, Cox proportional hazards model only included the treatment group • Not a clear target population: tumors of all stages were included • Immortal time bias: follow-up starts at diagnosis, groups determined at start using during information from future follow-up
Shao (2016)	National Cancer Database 2004-2011 Esophageal squamous cell carcinomas and adenocarcinomas treated with definitive chemoradiation or trimodal therapy	8,064	Trimodal therapy (n=3,619) Definitive chemoradiation (n= 4,445)	Median survival in propensity-matched cohort • 35.2 months in trimodal group • 16.9 months in definitive chemoradiation group 3-year overall survival in propensity-matched cohort • 49.1% in trimodal group • 26.0% in definitive chemoradiation group Heterogeneity in treatment effect: • Benefit of trimodal therapy over definitive chemoradiation was consistent between both histologic subtypes; slightly stronger effect in squamous cell carcinomas which is different from other studies	Strengths: • Included cancers of both histologic subtypes and a wide range of patient age • Implemented propensity score matching to control measured confounding Limitations: • Patients excluded if they survived less than 3 months • Selection bias from only following trimodal therapy patients who were able to complete therapy • Immortal time bias: follow-up starts at diagnosis, groups determined at start using during information from future follow-up • The NCDB has limited data on patient comorbidities and does not contain measures of frailty • Did not report a contrast measure of effect

Author (Year)	Population	N	Treatment groups compared	Key Results	Strengths and Limitations
De Heer (2017)	Single-center study of locally advanced esophageal cancer cases from 2005-2015 in the Netherlands	152	Trimodal therapy (n=72) Definitive chemoradiation (n=80)	Overall survival • Unadjusted Kaplan-Meier curves were different (p=0.01 via logrank test) • Adjusted Cox proportional hazards model showed differences that were not statistically significant (p=0.45)	Strengths: • Explicitly focused on a cohort of older adults receiving trimodal therapy who did not meet the age eligibility criteria of the CROSS trial; generalizability enhanced Limitations: • Definitive chemoradiation comparator group contained some patients who would not have been eligible for trimodal therapy because of inoperable tumors • Only reports p-values and not effect sizes for the contrast of the two groups • Limitation above is likely on account of fact that this treatment comparison was an ancillary analysis; the primary analysis was a cohort of only trimodal patients with a comparison of those who met and did not meet age-based eligibility criteria of the CROSS trial
Naik (2017)	National Cancer Database 2003-2011 Patients with clinical stage II, III non-cervical esophagus cancers 18-90 years of age	11,122	Trimodal therapy (n=3,031) Definitive chemoradiation (n= 8,091)	<u>Overall survival (trimodal vs. definitive chemoradiation)</u> • Adjusted HR = 0.66, 95% CI: 0.45, 0.97 • Unadjusted median survival 25.2 months in trimodal, 12.3 months in definitive chemoradiation <u>PS matched median survival</u> • Trimodal: 32.5 months, 95% CI: 29.6, 34.8 • Definitive chemoradiation: 14.2 months, 95% CI:13.4, 15.5 The adjusted <u>5-year adjusted survival</u> • Trimodal: 35.9%, 95% CI: 33.3%, 38.5% • Definitive chemoradiation: 15.2%, 95% CI:13.3%, 17.2%	Strengths: • Handled immortal-time bias through use of a time-dependent Cox model • Propensity-score matching to handle measured confounders • Included both histologic subtypes Limitations: • Though immortal time bias is handled through time-dependent Cox, there is still selection bias patients surviving long enough to complete surgery • Selection bias: only those healthy enough to complete trimodal therapy made it into that exposure group • Reported HR instead of more interpretable RR or RD • Control of comorbidities in NCDB is limited to Charlson score at presentation

Author (Year)	Population	N	Treatment groups compared	Key Results	Strengths and Limitations
Yen (2017)	Taiwan Cancer Registry database, 2006-2014 Esophageal squamous cell carcinomas, age>20, AJCC stage IA-IIIC	2,962	Trimodal therapy (n= 869) Definitive chemoradiation (n= 2,093)	<u>Overall mortality (trimodal group vs. definitive chemoradiation):</u> Stage IIA: HR= 0.62 (0.41, 0.93) Stage IIB: HR= 0.61 (0.41, 0.91) Stage IIIA: HR= 0.47 (0.38, 0.55) Stage IIIB: HR= 0.47 (0.38, 0.55) Stage IIIC: HR= 0.46 (0.37, 0.57)	Strengths: • Registry contained data on smoking and alcohol use, potentially important confounders unmeasured in other databases • Stratified results by clinical stage of disease, demonstrating important treatment effect heterogeneity Limitations: • Short look-back time for comorbidity assessment (6 months) • Not generalizable to adenocarcinomas • Immortal time bias: follow-up was the date of diagnosis, while treatment categorization depended on future exposure information • Selection bias: only those healthy enough to complete trimodal therapy made it into that exposure group
Vlacich (2017)	National Cancer Database 1998-2012 Patients ≥70 years old with clinical stage II, III esophageal cancer	1,910	Trimodal therapy (n= 955) Definitive chemoradiation (n= 955)	<u>Median survival in propensity-matched cohort</u> • 27.6 months (95% CI: 24.7, 30.4) in trimodal group • 15.6 months (95% CI: 14.3, 16.9) in definitive chemoradiation group	Strengths: • Explicitly focused on population of older adults (≥ 70 years old) with locally advanced esophageal cancer • Implemented greedy propensity score matching technique with small caliper to handle measured confounders • Examined factors related to receipt of trimodal therapy versus definitive chemoradiation, as well as temporal trends in use of trimodal therapy (increase over time) Limitations: • Immortal time bias and selection bias from the exposure definition limitation of the NCDB • Control of comorbidities in NCDB is limited to Charlson score at presentation • Did not report a contrast measure of effect

Author (Year)	Population	N	Treatment groups compared	Key Results	Strengths and Limitations
Haefner (2018)	Single-center retrospective study of patients with locally advanced esophageal cancer between 2000 and 2012 in Germany Karnofsky performance status (KPS) ≥70,	130	Trimodal therapy (n= 37) Definitive chemoradiation (n=93)	<u>3-year local recurrence rate</u> • 10.8% in trimodal group • 21.5% in definitive chemoradiation group <u>Median progression free survival</u> • 15.6 months in trimodal group • 14.9 months in definitive chemoradiation group <u>Median overall survival</u> • 20.6 months in trimodal group • 25.9 months in definitive chemoradiation group	Strengths: • In addition to overall survival, also considered local recurrence rate and progression free survival as study endpoints • Able to characterize performance status and radiation technique, which are often missing from the large secondary database analyses Limitations: • Very sample size from single center • Did not perform any multivariable analysis because their univariate analysis did not reveal any statistically significant associations between predictors and outcomes • About 85% of cancers were squamous cell carcinomas, hampering generalizability to populations with greater proportion of adenocarcinoma tumors
Barbetta (2018)	Institutional study of esophageal squamous cell carcinomas diagnosed between 2000-2016 at Memorial Sloan Kettering Cancer Center Cervical or upper esophagus cancers excluded	232	Trimodal therapy (n= 56) Definitive chemoradiation (n= 56) 112 patients in total after propensity score matching	<u>Overall survival in propensity score matched cohort</u> • HR = 0.57 (95% CI: 0.34, 0.97) comparing trimodal group to definitive chemoradiation group <u>Disease free survival in propensity score matched cohort</u> • HR = 0.51 (95% CI: 0.32, 0.83) comparing trimodal group to definitive chemoradiation group <u>Median overall survival</u> • 3.1 years in trimodal group • 2.3 years in definitive chemoradiation group <u>Median disease-free survival</u> • 1.8 years in trimodal group • 1.0 years in definitive chemoradiation group	Strengths: • Handled immortal-time bias through use of a time-dependent Cox model • Propensity-score matching to handle measured confounders • Detailed clinical information from institutional database allowed for better confounding control Limitations: • Small sample size • Though immortal time bias is handled through time-dependent Cox, there is still selection bias patients surviving long enough to complete surgery • Selection bias: only those healthy enough to complete trimodal therapy made it into that exposure group • Reported HR instead of more interpretable RR or RD

Author (Year)	Population	N	Treatment groups compared	Key Results	Strengths and Limitations
Schlottmann (2018)	Surveillance, Epidemiology, and End Results Program registry data, 2004-2014 Adenocarcinomas with clinical stage III tumors		Trimodal therapy (n= 1,518) Definitive chemoradiation (n= 1,115)	<u>Five year overall survival:</u> • 27% in trimodal group • 13% in definitive chemoradiation group • Adjusted HR = 0.56 (95% CI 0.50, 0.63) comparing trimodal therapy to definitive chemoradiation	Strengths: • Large sample size • Handled immortal-time bias through use of a five-month landmark • Multivariable model controlled for many demographic and clinical confounders Limitations: • SEER data alone does not offer optimal measurement of comorbidity burden • Though immortal time bias was handled, selection bias is present in only following trimodal patients healthy enough to have received treatment in full; results only apply to those who lived at least 5 months after diagnosis
Verma (2019)	National Cancer Database 2004-2014 Patients ≥76 years old with T1N1M0 or T2-3N0-1M0 tumors	4,099	Trimodal therapy (n= 594) Definitive chemoradiation (n= 3,011)	<u>Propensity score matched median survival</u> • 26.7 months in trimodal group • 18.2 months in definitive chemoradiation group • Logrank p<0.001	Strengths: • Used data on radiation dosage to identify ranges that would be plausible for exposure groups of interest • Explicitly focused on an older adult population that was excluded from the CROSS trial • Included both histologic subtypes • Propensity score matching implemented to account for measured confounders Limitations: • Immortal time bias: follow-up at diagnosis, groups determined during follow-up • Control of comorbidities in NCDB is limited to Charlson score at presentation • Selection bias from those who could survive long enough to complete chemoradiation and surgery • Problematic covariate selection process: screened for variables that were significant upon univariate analysis • No effect estimate contrasting survival with 95% CI reported, just a statistical test of difference in survival

Author (Year)	Population	N	Treatment groups compared	Key Results	Strengths and Limitations
Munch (2019)	Single-center retrospective study of squamous cell carcinoma patients treated with trimodal therapy or definitive chemoradiation between 2011-2017 in Germany	95	Trimodal therapy (n= 40) Definitive chemoradiation (n=55)	<u>3-year overall survival</u> • 57.2% in trimodal group • 38.6% in definitive chemoradiation group • Adjusted HR = 1.45 (95% CI: 0.69, 3.07) <u>Median unadjusted survival</u> • 43.3 months in trimodal group • 23.2 months in definitive chemoradiation group <u>Median unadjusted progression-free survival</u> • 18.3 months in trimodal group • 12.7 months in definitive chemoradiation group • p = 0.108	Strengths: • Contemporary cohort with radiation treatment consisting of modern techniques • Rich clinical details from institutional data Limitations: • Small single-center study with limited precision • Only included squamous cell carcinoma tumors, results may not generalize to patients with adenocarcinomas • Selection bias from not including anybody who did not complete their course of therapy • Potential for immortal time bias, all trimodal patients had longer therapy duration they were required to have completed in order to be categorized as trimodal
Wang (2019)	Taiwan Cancer Registry, stage II and III ESCCs diagnosed 2008-2014	3,322	Trimodal therapy (n= 1,661) Definitive chemoradiation (n=1,661)	<u>3-year overall survival in propensity score matched cohort</u> • 41.1% in trimodal group • 17.9% in definitive chemoradiation group • Adjusted HR = 0.45 (95% CI: 0.40, 0.51)	Strengths: • Controlled for measured confounding using propensity score matching • Largest study of a contemporary cohort Limitations: • Only included squamous cell carcinomas, unlikely to generalize to adenocarcinomas • Residual confounding is possible from inadequate comorbidity characterization and also the lack of data on patient performance status or frailty • Did not report any metrics of covariate balance after propensity score matching • Selection bias from excluding anybody who did not complete their course of therapy • Immortal time bias, even though follow-up started at treatment because all trimodal patients had longer therapy they were required to have completed to be included in study • Reported HR instead of more interpretable RR or RD

APPENDIX 2. CODES USED TO IDENTIFY ELIGIBLE STUDY COHORT AND TREATMENTS RECEIVED

Construct	Type of code	Code
Esophageal cancer (non-cervical)	ICD-O-3 site codes	C15.1-C15.9
Adenocarcinomas and squamous cell carcinomas	ICD-O-3 histology codes	Squamous cell carcinomas: 8050, 8051, 8052, 8070, 8071, 8072, 8073, 8074, 8075, 8076, 8082, 8083 Adenocarcinomas: 8140, 8142, 8144, 8145, 8200, 8210, 8211, 8240, 8244, 8246, 8255, 8260, 8261, 8263, 8310, 8323
Esophagectomy (and related gastrectomy)	ICD-9 procedure codes	4240, 4241, 4242, 435, 4399
Esophagectomy (and related gastrectomy)	ICD-10 procedure codes	0DB10ZZ, 0DB13ZZ, 0DB17ZZ, 0DB20ZZ, 0DB23ZZ, 0DB27ZZ, 0DB30ZZ, 0DB33ZZ, 0DB37ZZ, 0DB40ZZ, 0DB43ZZ, 0DB44ZZ, 0DB47ZZ, 0DB50ZZ, 0DB53ZZ, 0DB57ZZ, 0DT10ZZ, 0DT14ZZ, 0DT17ZZ, 0DT18ZZ, 0DT20ZZ, 0DT24ZZ, 0DT27ZZ, 0DT28ZZ, 0DT30ZZ, 0DT34ZZ, 0DT37ZZ, 0DT38ZZ, 0DT40ZZ, 0DT44ZZ, 0DT47ZZ, 0DT48ZZ, 0DT50ZZ, 0DT54ZZ, 0DT57ZZ, 0DT58ZZ, 0DT60ZZ, 0DT64ZZ, 0DT67ZZ, 0DT68ZZ
Esophagectomy (and related gastrectomy)	CPT codes	43100, 43101, 43107, 43108, 43112, 43113, 43117, 43118, 43121, 43122, 43123, 43124
Chemotherapy	HCPCs codes	J9045, C9127, C9431, J9264, J9265, J9267, J9060, J9062, C9418, J9190, C9205, J9263, C9474, J9206, J9170, J9171, J9178, J9180, J8520 , J8521, J0594, J0894, J8510, J8530, J8560, J8565, J8600, J8610, J8700, J8705, J8999, J9000, J9001, J9010, J9015, J9017, J9020, J9025, J9027, J9031, J9033, J9035, J9040, J9041, J9043, J9050, J9055, J9065, J9070, J9080, J9090, J9091, J9092, J9093, J9094, J9095, J9096, J9097, J9098, J9100, J9110, J9120, J9130, J9140, J9150, J9151, J9155, J9160, J9165, J9175, J9179, J9181, J9182, J9185, J9200, J9201, J9202, J9207, J9208, J9209, J9211, J9212, J9213, J9214, J9215, J9216, J9217, J9218, J9219, J9225, J9226, J9228, J9230, J9245, J9250, J9260, J9261, J9266, J9268, J9270, J9280, J9290, J9291, J9293, J9300, J9302, J9303, J9305, J9307, J9310, J9315, J9320, J9328, J9330, J9340, J9350, J9351, J9355, J9357, J9360, J9370, J9375, J9380, J9390, J9395, J9999, Q2017, Q2024, Q0083, Q0084, Q0085, C9432, C9433, C1178, C9207, C9213, C9214, C9215, C9217, C9218, C9235, C9257, C9262, C9414, C9415, C9417, C9419, C9420, C9421, C9422, C9423, C9424, C9425, C9426, C9427, C9429, C9437, C9440, S0088, S0115, S0116, S0172, S0176, S0178, S0182
Delivery of external beam radiation	CPT codes	77401, 77402, 77403, 77404, 77406, 77407, 77408, 77409, 77411, 77412, 77413, 77414, 77416, G6003, G6004, G6005, G6006, G6007, G6008, G6009, G6010, G6011, G6012, G6013, G6014, 4165F, 0073T, 77385, 77386, G6015, G6016, 77417, 77418, G0174, 77422, 77423, 77520, 77522, 77523, 77525

APPENDIX 3. EQUATIONS USED TO ESTIMATE RISK, CUMULATIVE INCIDENCE, AND THE MEAN CUMULATIVE COUNT

Risk

$$\hat{F}(t) = 1 - \prod_{k:R_k \le t} \left[1 - \frac{Y_k^{w(t)}}{N_k^{w(t)}} \right]$$

Notes: k indexes the list of ordered unique event times, R_1, R_2, …, R_c. $Y_k^{w(t)}$ is the weighted number of events at the k[th] event time and $N_k^{w(t)}$ is the weighted number of individuals at-risk going into the k[th] event time.

Cumulative incidence

$$\hat{F}(t,j) = \sum_{k:R_k \le t} \left[\frac{d_{jk}^{w(t)}}{n_k^{w(t)}} \times \prod_{h<k} \left\{ 1 - \frac{d_h^{w(t)}}{n_h^{w(t)}} \right\} \right]$$

Notes: The type of event is denoted by j (e.g., j=1 for events of interest and j=2 for competing events). k indexes the list of ordered unique type j event times, R_1, R_2, …, R_c. h indexes the list of ordered overall event times (any event type). $d_{jk}^{w(t)}$ is the weighted number of type j events at the k[th] type j event time and $n_k^{w(t)}$ is the number of weighted individuals at-risk going into the k[th] type j event time. $d_h^{w(t)}$ is the weighted number of overall events (any j) at the h[th] event time. $n_h^{w(t)}$ is the weighted number of at-risk individuals going into the h[th] event time.

Mean cumulative count

$$\hat{F}(t,j) = \sum_{k:R_k \le t} \left[\frac{e_{jk}^{w(t)}}{n_k^{w(t)}} \times \prod_{h<k} \left\{ 1 - \frac{p_h^{w(t)}}{n_h^{w(t)}} \right\} \right]$$

Notes: The type of event is denoted by j (e.g., j=1 for events of interest and j=2 for competing events). k indexes the list of ordered unique type j event times, R_1, R_2, …, R_c. Unlike analysis of time to first event, this ordering also includes times of recurrent events. Here, h indexes the list of ordered competing event times. $e_{jk}^{w(t)}$ is the weighted number of type j events at the k[th] type j event time and $n_k^{w(t)}$ is the number of weighted individuals at-risk going into the k[th] type j event time. $p_h^{w(t)}$ is the weighted number of competing at the h[th] event time. $n_h^{w(t)}$ is the weighted number of at-risk individuals going into the h[th] competing event time.

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