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Comparison of Transthoracic and Transhiatal Surgical Strategies for Esophageal Cancer: A Survival Analysis

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ABSTRACT

Comparison of Transthoracic and Transhiatal Surgical Strategies for Esophageal Cancer: A Survival Analysis

Felix G. Fernandez, M.D.

Introduction: The optimal surgical approach for resection of esophageal cancer, transthoracic (TT) or transhiatal (TH), remains unknown despite extensive study. The goal of this study was to compare short term mortality and long term survival based on operative approach for resection of esophageal cancer resections.

Methods: We performed a retrospective cohort analysis using Surveillance, Epidemiology, and End Results (SEER) - Medicare linked data from 2002-2009. Patient and tumor and characteristics and survival were determined with SEER data. Medicare claims data were used to determine surgical approach, medical comorbidities, administration of chemotherapy and radiation, and healthcare resource use. Logistic regression analysis was used to examine the association of operative approach with operative mortality. A Cox proportional hazards model was utilized to examine the association between operative approach and long term survival.

Results: 918 TT and 653 TH resections were identified. Patients in the TT and TH groups had the following characteristics: age (72.8 vs. 73.4 yrs., p=0.02), gender (80.1% vs. 79.2% male, p=0.66) and distribution of comorbidity scores (Charlson score of 0: 60.2% vs. 62.3%, p=0.67). There were similar proportions of adenocarcinomas (TT 71.4% vs TH 72.9%, p=0.66) located in the lower esophagus (TT 72.1% vs TH 73.5%, p<0.12). Administration of induction therapy (chemotherapy and/or radiation) was similar between groups (TT 39.3% vs. TH 37.7%, p=0.51). More lymph nodes were evaluated with TT approaches (TT 15.2 vs. TH 11.3, p<0.001). Operative mortality was no different between groups (OR for TH 1.06, 95% CI 0.73-1.53). Overall long term survival was also no different between the TT and TH groups (HR for TH 0.99, 95% CI 0.82-1.20).

Conclusions: In an adjusted analysis in Medicare patients, TT and TH approaches to esophagectomy for esophageal cancer were associated with similar operative mortality and long-term survival. Operative approach is not a predictor of survival following surgical resection of esophageal cancer. Based on these data, thoracic surgeons should select the operative approach with which they are most proficient. Future investigations should incorporate financial and patient reported outcomes to allow a true value based comparison of TT and TH surgical approaches to esophageal cancer.

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Introduction:

Esophageal cancer is a lethal malignancy. It is the seventh leading cause of cancer related mortality in the Unites States and its incidence continues to rise. [1]. The American Cancer Society's estimates for esophageal cancer in the United States for 2014 are approximately 18,170 new esophageal cancer cases diagnosed (14,660 in men and 3,510 in women) and approximately 15,450 deaths from esophageal cancer (12,450 in men and 3,000 in women) [2]. At the time of presentation and diagnosis, nearly 50% of patients have disease that has extended past the primary tumor's loco-regional confines and less than 60% of patients with tumors that are still loco-regional are able to undergo a potentially curative surgical resection [3].

The two major histopathologic forms of esophageal cancer are squamous cell carcinoma and adenocarcinoma. Worldwide, squamous cell carcinoma is the most common esophageal cancer, particularly in Central Asia, China and India. Alcohol and tobacco are major risk factors. This type of esophageal carcinoma is also more common in African American males. Conversely, adenocarcinoma is the most common type of esophageal cancer in the United States, particularly in Caucasian males [4]. Risk factors include long-standing gastro-esophageal reflux disease, obesity, and alcohol. Stage groupings in the seventh edition Tumor, Node and Metastases (TNM) classification system differ for esophageal squamous cell carcinomas and adenocarcinomas in Stages I and II [5,6]. Both types are treated preferentially with surgical therapy when localized.

Surgical resection remains the preferred modality of treatment for potentially curable esophageal cancer. Preoperative chemotherapy and/or radiation therapy, known as induction or neoadjuvant therapy, have also become a common part of multimodality therapy for locally advanced esophageal cancers in conjunction with surgery [7,8]. Unfortunately, a surgical resection of the esophagus, known as an esophagectomy, is a high risk surgical procedure. Morbidity and mortality rates following esophagectomy are considerable. Serious morbidity (complications) occurs in up to 50% of patients undergoing an esophageal resection [9,10]. In addition, operative mortality rates are substantial and reported to range from 2.7% to 13.1%, with variation dependent on the data source [11,12].

There are many potential reasons for differences in early survival rates for esophageal cancer. Because of this, esophagectomy has become the focus of surgical quality improvement efforts. There are three National Quality Forum endorsed quality metrics for esophageal cancer [13]. Additionally, the American College of Surgeons National Quality Improvement Program (ACS NSQIP) tracks comparisons for esophagectomy outcomes between hospitals [14].

The surgical approach to esophagectomy is a process of care that may contribute to variation in outcomes with esophagectomy. In addition, the surgical approach is a process that could be easily modifiable by surgeons. There is no data driven optimal surgical approach to esophagectomy. There has been, and continues to be, considerable debate as to the most appropriate surgical approach to esophagectomy: transthoracic (TT) or transhiatal (TH).

A transthoracic esophageal resection utilizes a thoracic incision (thoracotomy) to directly expose, mobilize and resect the esophageal cancer. This approach gives excellent exposure for removal of thoracic lymph nodes surrounding the esophagus. However, a thoracotomy may predispose patients to pulmonary complications such as pneumonias and respiratory failure due to restricted chest wall mechanics resulting from pain related to the thoracotomy. Pulmonary complications have been shown to be associated with longer hospital stay and worse outcomes in esophagectomy patients [15-17].

In contrast, a thoracic incision is avoided with a transhiatal esophagectomy. With this surgical approach, the esophagus is mobilized and resected through the esophageal hiatus in the diaphragm and a cervical incision. This allows access to the posterior mediastinum to remove the esophagus and allow placement of a gastric conduit for reconstruction. Avoidance of a thoracotomy incision may reduce pulmonary complication rates, and therefore, potentially morbidity and mortality rates with esophagectomy. However, because the esophageal cancer is not directly exposed with a transhiatal surgical approach, tumor clearance may be suboptimal. In particular, access to thoracic lymph nodes surrounding the esophagus is compromised. Because of this, the oncologic efficacy of a transhiatal esophagectomy has been questioned by many, and concerns have been raised that this approach may lead to fewer surgical cures of esophageal cancer compared to a transthoracic approach.

The optimal approach to surgical resection of an esophageal cancer, transthoracic versus transhiatal, remains a critical unanswered question in thoracic surgery. The objective of this study was to compare operative mortality and long-term survival between transthoracic and transhiatal approaches to esophageal cancer using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. We hypothesized that transhiatal approaches to esophagectomy for esophageal cancer are associated with lower operative mortality rates and equivalent long-term survival in comparison to transthoracic approaches.

Background:

Operative mortality following esophagectomy has been a topic of extensive study, given the high risk nature of this operation. Comparisons of operative mortality based on surgical approach, TT versus TH, have yielded conflicting results. Bhayani and colleagues, using the National Surgical Quality Improvement Project (NSQIP) database found mortality to be 3.6% for TT approaches and 2.9% for TH resections out of 1,568 patients (TT 851, TH 717) [17]. A prior review of SEER-Medicare data from an earlier era, 1992-2002, demonstrated greater short-term mortality following TT (13.1%, n=643) compared to TH approaches (6.7%) [12]. Another early analysis from Veteran's Affairs (VA) medical centers NSQIP data found mortality to be approximately 10% with either approach [18]. The largest study comparing operative mortality between surgical approaches following esophagectomy comes from Conners and colleagues who examined 17,395 esophagectomies (TT 11,914, TH 5,481) performed from 1999 through 2003 in the Nationwide Inpatient Sample (NIS) database [19]. There were no differences in operative mortality between groups (TT 8.4% and TH 8.9%). This study is limited by the lack of tumor information and treatment details in the NIS database, which impairs the ability to adjust for case mix. Kutup and colleagues examined a series of 468 patients with clinical stage II or greater esophageal cancers treated in Germany and found 30 day mortality to be 6.6% for TT and 7.4% for TH [20]. Finally, a large meta-analysis by Boshier comprised of 5,905 patients (3,389 TT and 2,516 TH), did find higher short term mortality for TT (10.6%) compared to TH (7.2%) resections (OR 1.48; CI 1.20-1.83) [21]. The lowest reported operative mortality in a large series comes from the Society of Thoracic Surgeons General Thoracic Surgery Database (STS-GTSD) [11]. In this series, Wright and colleagues report an operative mortality of 2.7% in esophagectomies performed by board certified thoracic surgeons, although results are not compared by operative approach. Esophagectomy is a high risk operative intervention; however, determination of the operative approach that minimizes short term morbidity has yet to be determined.

The operative approach for esophagectomy for esophageal cancer that maximizes long term survival has also not been determined. A randomized controlled trial comparing TT (n=114) and TH (n=106) approaches for esophageal adenocarcinomas located in the distal esophagus was reported on by Hulscher and colleagues in 2002 [9]. This study found a trend towards improved survival with TT resections (5 year overall survival: TT 40%, TH 30%). A prior analysis of SEER-Medicare data, from an earlier era (1992-2002) and with a smaller sample size (n=868) has found superior long term survival for TH esophagectomies in an unadjusted analysis (5 year overall survival: TH 30.5%, TT 22.7%) [12]. However, in an adjusted analysis, operative approach was no longer associated with improved long term survival. Finally, in the systematic review by Boshier, which examined long term survival following esophagectomy from 26 studies including 3,643 patients, no operative approach was associated with improved long term survival [21]. Significant heterogeneity was noted among studies examining the impact of operative approach on long term survival following esophagectomy for esophageal cancer.

A more invasive operation (TT) may result in greater patient morbidity which may negate the benefits of the superior tumor clearance that may be gained with this approach. Which operative approach most effectively balances short term risk of mortality with long term survival from esophageal cancer, TT versus TH, is a critical knowledge gap at present in the field of thoracic oncologic surgery and thus was the focus of this study.

Specific aims and hypotheses:

Aim #1: To compare operative mortality in patients following esophagectomy for esophageal cancer based on the operative approach for resection, transthoracic or transhiatal.

Hypothesis #1: A transhiatal approach to esophagectomy for esophageal cancer results in less operative mortality compared to a transthoracic approach to resection.

Aim #2: To compare long term survival in patients undergoing esophagectomy for esophageal cancer based on the operative approach for resection, transthoracic or transhiatal.

Hypothesis #2: A transhiatal approach to esophagectomy for resection of esophageal cancer results in equivalent long term survival compared to a transhiatal approach.

Methods:

Data sources:

The study design is a retrospective cohort study using the SEER-Medicare linked database to compare operative mortality and long term survival between transthoracic and transhiatal approaches for esophagectomy in patients with esophageal cancer. Esophageal cancer patients undergoing esophagectomy in the SEER-Medicare database in the years 2002-2009 were included in the study. Medicare files linked to these patients were available through 2010. Approval for the study was obtained from the Institutional Review Board of Emory University.

The SEER database is derived from 20 tumor registries, is maintained by the National Cancer Institute (NCI), and represents approximately 28% of United States population [22]. Medicare beneficiaries within the registry have had their tumor records linked to all of their claims data. The quality, validity and generalizability of the SEER-Medicare data has been described previously [23]. We utilized the Medicare Denominator, Medicare Provider Analysis and Review (MEDPAR), Outpatient and Physician/Supplier files for this study. The Denominator file contains information on beneficiary enrollment and vital status. MEDPAR files contain claims related to inpatient hospitalizations and the Outpatient files contain claims related to outpatient visits. Lastly, the Physician/Supplier files contain claims related to physician services.

Patients:

Among all esophageal cancer patients from 2002 through 2009 in the SEER-Medicare dataset, the following sequential exclusions were made: patients less than 66 years old, patients treated with therapy other than surgery, and patients with partial fee-for-service or concurrent health maintenance organization enrollment, or both, 1 year prior to esophageal cancer surgery. Only full fee-for-service beneficiaries not enrolled in other insurance programs would have complete claims records available for analysis; therefore, all other patients were excluded. Patients who were 65 years old at the time of diagnosis were excluded because they do not have Medicare claims data in the year before esophagectomy. Missing claims data would preclude the determination of receipt of neoadjuvant chemotherapy and/or radiation, and the calculation of comorbidity scores from billing and diagnostic codes.

Patient, disease and treatment information were available through the SEER registry and Medicare database. Specifically, Current Procedural Terminology (CPT) Healthcare Common Procedure Coding System (HCPCS) and International Classification of Diseases, 9th revision (ICD-9) codes were used to determine the surgical approach to esophagectomy (transthoracic versus transhiatal), patient comorbid medical conditions, and delivery of neoadjuvant chemotherapy and radiation (see Table 1 for specific Medicare billing codes). Medicare claims within the Physician/Supplier and Outpatient files in the year before diagnosis were used to calculate a Klabunde-modified Charlson Comorbidity Index, which was then used for risk adjustment [24]. Administration of chemotherapy and/or radiation administered within 4 months of esophagectomy was considered neoadjuvant therapy, as classified in prior publications using SEER-Medicare data [25]. For analysis of patient socioeconomic status, indicators of low income or education were based on the lowest quartiles of median income and proportion with a high school education within a given zip code from Census Tract data. Tumor size, stage and histology were all based on information within four months of diagnosis in the SEER registry. All tumors were restaged to the American Joint Committee on Cancer (AJCC), 7th edition esophageal cancer staging system utilizing the available tumor (T), node (N) and metastases (M) information present in the SEER registry [26] in order to provide consistency across analyses.

Outcome measures:

The primary outcome measure for the first aim of this study was operative mortality, defined as death during the hospitalization for the index esophagectomy, in the transhiatal and transthoracic esophagectomy groups. This was determined by vital status listed in the CMS MEDPAR file corresponding to the hospitalization for esophagectomy. Secondary outcome measure included length of hospital stay (LOS) in the hospital following esophagectomy and hospital readmission following discharge to home. The denominator for analysis of hospital readmission was all patients discharged to home following esophageal resection for cancer. Hospital readmissions at 30 and 90 days following discharge were measured. Patients discharged to an intermediate care facility (ICF) were not considered in the readmission analysis, as it is difficult to determine what constitutes a discharge and hospital readmission in a patient being transferred from one inpatient care facility to another.

The primary outcome measure for the second aim of the analysis was overall long-term survival in the transthoracic and transhiatal esophagectomy groups. Long term survival data were determined from the SEER database, not from CMS data, as vital status in SEER data is a validated data field. Because of this, long-term survival data were not available for patients having undergone esophagectomy in the year 2009. A secondary outcome measure was cancer specific survival, or cause specific survival

(CSS). This measure represents esophageal cancer survival in the absence of other causes of death.

Statistical analysis:

SAS Version 9.3 (Cary, NC) was used to perform all statistical analyses. Descriptive statistics are presented as counts with percentages, means with standard deviation, and/or median with interquartile range. The transthoracic and transhiatal esophagectomy groups were compared with two-sample t-tests for continuous data and Chi-square test for categorical data. All statistical tests were two-sided and used an $\alpha = 0.05$ level of significance.

Under the first study aim, the association between the exposure, operative approach (transthoracic versus transhiatal) and the primary outcome measure, operative mortality, was examined with a logistic regression model. Covariates for inclusion in the model were selected *a priori* based on what was thought to be risk factors for operative mortality based on experience and expert opinion. The associations between operative approach and hospital length of stay and 30 day hospital readmissions were examined with linear and logistic regression models, respectively.

In aim two, Kaplan-Meier (KM) survival curves were generated using the product limit approach to provide unadjusted overall survival estimates for patients undergoing transthoracic and transhiatal esophageal resection. Differences between the strata were examined with the log rank test. Unadjusted cancer specific survival was also compared according to surgical approach, also using the Kaplan-Meier method. Next, a Cox proportional hazards model was used to examine the association between the exposure, operative approach (transthoracic versus transhiatal) and the instantaneous risk of death.

Covariates again were selected *a priori* for inclusion in the model. The proportional hazards assumption was tested for each covariate with log-log survival curves. Finally, a Cox proportional hazards model was used to examine the association between operative exposure and the instantaneous risk of cancer specific mortality.

Power analysis:

Power calculations were generated for the analyses of operative mortality and long-term overall survival. Operative mortality for a transthoracic esophagectomy was estimated to be 0.09 based on prior literature on esophagectomies using Medicare data. [19] The power to detect a difference in operative mortality with rates for transhiatal esophagectomy ranging from 0.05 to 0.14 with a two-tailed t-test? (α=0.05) is shown in Table 2. Five year overall survival following a transhiatal esophagectomy is estimated to be 0.23, based on prior estimates using SEER-Medicare data. [12]. The power to detect a difference in five year survival with rates for transhiatal esophagectomy ranging from 0.13 to 0.33 is shown in Table 3.

Results:

Patient characteristics:

1,571 patients in the SEER-Medicare dataset underwent esophageal resection for esophageal cancer between the years 2002 and 2009 and met inclusion criteria. The demographics and clinical details of patients at the time of hospital admission for esophagectomy are summarized in Table 4. These patients were predominantly elderly Caucasian males. More than half the patients had a modified Charlson comorbidity score of zero. The most common presentation of esophageal cancer was a distal esophageal adenocarcinoma. Nearly 40% of patients in each treatment approach group received neoadjuvant chemotherapy and/or radiation. A transthoracic approach to esophagectomy was more common than transhiatal (56.8% vs. 41.2%).

Perioperative outcomes:

Perioperative outcomes in patients following esophagectomy for esophageal cancer are detailed in Table 5. The extent of lymph node evaluation with surgery, as measured by the number of lymph nodes sampled, was superior for transthoracic compared to transhiatal esophagectomies. Operative (in-hospital) mortality rates associated with esophagectomies were substantial at 9.0% in each group. No statistical differences were found in hospital length of stay, intensive care unit stay, or patient discharge to home between groups. Out of 1,027 patients discharged to home following esophagectomy, there were no differences noted in 30 or 90 day hospital readmission rates between the transthoracic and transhiatal esophagectomy patients.

A multivariable logistic regression model was developed to examine the association between the exposure of interest, operative approach, and the outcome of operative mortality. Results of the logistic regression model are shown in Table 6. No statistically significant association was noted between surgical approach and operative mortality. Covariates found to be associated with operative mortality included: increasing age (years), comorbidity score of 2, urgent admission type, and urban area of residence.

The association between the operative approach, transthoracic versus transhiatal, and hospital length of stay was examined with a multivariable linear regression model. The results of this linear regression model are shown in Table 7. No significant association was observed between operative approach and length of stay. Covariates noted to be significantly associated with hospital length of stay included: non Caucasian or African American race, not married, and comorbidity score of 3+.

In table 8, the results of a logistic regression model examining the association between operative approach and 30 days hospital readmission are shown. Again, there was no significant association noted between the operative approach and hospital readmission and 30 days in patients who were discharged to home. Covariates found to be significantly associated with hospital readmission included: African American race, comorbidity score of 3+, urgent admission type, and urban or rural area of residence.

Long-term survival:

Long-term overall survival was compared between patients undergoing a transthoracic or transhiatal esophagectomy for esophageal cancer using the Kaplan-Meier method. Unadjusted survival curves are shown in Figure 1. In this unadjusted analysis, long-term survival was superior in the transhiatal esophagectomy group. Survival in patients undergoing a transthoracic esophagectomy was 63% at one year, 47% at two years, 39% at three years, 35% at four years, and 30% at five years following surgery. In comparison, survival in patients undergoing a transhiatal esophagectomy was 66% at one year, 55% at two years, 46% at three years, 40% at four years, and 36% at five years following surgery.

Long-term cancer specific survival was also compared between patients undergoing a transthoracic or transhiatal esophagectomy for esophageal cancer using the Kaplan-Meier method. Unadjusted survival curves are shown in Figure 2. In this unadjusted analysis, there were no significant differences in cancer specific survival between transthoracic and transhiatal esophagectomy patients. Cancer specific survival in patients undergoing a transthoracic esophagectomy was 72% at one year, 58% at two years, 50% at three years, 48% at four years, and 4% at five years following surgery. In comparison, cancer specific survival in patients undergoing a transhiatal esophagectomy was 73% at one year, 64% at two years, 58% at three years, 53% at four years, and 51% at five years following surgery.

In order to control for potential known confounding variables, a Cox proportional hazards model was created to examine the association between the exposure, operative approach, and the instantaneous risk of mortality. Results of this model are presented in Table 9. No significant association was observed between operative approach and the hazard of mortality. Covariates associated with a significant hazard of death included: increasing age, comorbidity score of 3+, non squamous cell or adenocarcinoma tumor histology, poor or undifferentiated tumor grade, increasing tumor stage, and less urban area of residence.

Finally, a Cox proportional hazards model was created to examine the association between the exposure, operative approach, and the instantaneous risk of cancer specific mortality. Results of this model are presented in Table 10. No significant association was observed between operative approach and the hazard of cancer specific mortality. Covariates associated with a significant hazard of cancer specific death included: poor or undifferentiated tumor grade and increasing tumor stage.

Discussion:

In this retrospective cohort study utilizing the SEER-Medicare linked database, no significant differences in outcomes were identified between transthoracic and transhiatal surgical approaches for resection of esophageal cancer. Operative mortality, a short-term outcome, was equivalent between the two surgical approaches. In addition, hospital length of stay and readmission to the hospital with 30 days of discharge, surrogates of post-operative complications following surgery, were no different between the two groups. Transthoracic approaches to esophagectomy were found to be associated with greater numbers of lymph nodes removed at the time of surgery compared to transhiatal resections. Despite this, when controlling for potential known confounding factors, long-term overall and cancer specific survival rates were no different between the two approaches as well.

Prior studies have not conclusively demonstrated that one operative approach to esophagectomy is safer or results in less patient mortality [12,17-21]. Our study supports the existing literature with a larger sample size and rather contemporary cohort. One may hypothesize that the optimal approach to surgical resection depends on unique patient and tumor characteristics. For example, it may be that the optimal approach is a TT resection in a younger patient in good health with a locally advanced esophageal cancer. Conversely, in an elderly individual in poor health with an early stage esophageal cancer, a TH approach may be more favorable. More clinical detail and a large study sample are necessary to perform such subgroup analysis. In our study, age, comorbidity score, urgent admission type and urban area of residence were associated with operative mortality. Other studies have found age and various comorbidities to be associated with higher operative mortality following esophagectomy [11,27,28]. TT and TH approaches to esophagectomy appear to be associated with similar risks of operative mortality; however, operative mortality following esophagectomy remains unacceptably high.

Hospital postoperative length of stay (LOS) is frequently used a surrogate of perioperative complications and a measure of surgical quality. We did not observe a significant difference in LOS between TT and TH approaches (18.7 vs. 17.2 days, p=0.08). Connors and colleagues reported similar results, with LOS of 18.3 days for TH and 18.0 days for TT [19]. Prior SEER-Medicare data from Chang et al. found LOS to be 20.7 days with TT and 21.4 days with TT approaches [12]. Postoperative LOS is reported as an average of 14 days in the STS-GTSD, although comparison of TT and TH is not provided [11]. In separate analyses of NSQIP data, both Papenfuss and Bhayani also found no differences in LOS between TT and TT esophagectomies [17,28]. Again, however, the large meta-analysis report by Boshier does find an advantage for TH, with hospital LOS on average 4 days less than TT [21]. The factors associated with LOS in our study are African American race, not married, and increasing comorbidity. No study has previously examined factors with hospital LOS following esophagectomy. Again, a conclusive significant difference in hospital LOS between TT and TH esophagectomies cannot be demonstrated.

Rehospitalization after discharge to home was found to occur frequently in our study cohort. The 30 day readmission rates for patients discharged to home were 18.5% and 19.2% in the TT and TH groups, respectively. These rates increased to 31% in each group at 90 days following discharge. Factors associated with rehospitalization included African American race, comorbidity score of 3 or greater, an urgent admission status for the initial hospitalization, and residence in an urban or rural area. With the recent passage of the Patient Protection and Affordable Care Act, the Centers for Medicare and Medicaid Services (CMS) have placed an emphasis on reducing hospital readmission rates in order to improve the quality of health care in the United States [29]. Hospital readmissions following an esophagectomy for esophageal cancer have previously been shown to be a common occurrence, ranging from 5-25% [30-32]. No prior studies have compared readmission to the hospital based on surgical approach to esophagectomy. However, given the importance of readmissions as a quality of care metric, readmission rates should be considered in conjunction with other outcomes when selecting the treatment strategy for esophageal cancer.

The number of lymph nodes examined with surgical resection was significantly greater with a TT approach compared to TH (15.2 vs 11.3, $p<0.001$) in our study. This finding is not surprising, given that a thoracotomy provides more direct access for removal of thoracic lymph nodes compared to a transhiatal exposure. Four prior reports have examined lymph node yield with esophagectomy based on the operative approach [9,33-35]. The meta-analysis by Boshier pools the 461 patients in these 4 studies, reporting that on average 8 more lymph nodes are excised with TT versus TH approaches ($p=0.02$, CI 1-14) [21]. This finding is important, as greater extent of lymphadenectomy has been previously associated with survival following esophagectomy for esophageal cancer [36-39]. Our study is the largest to date comparing lymph node yield between TT and TH approaches and confirms the advantage of increased access to thoracic lymph nodes with a TT esophagectomy.

In this study, unadjusted long term survival was found to be superior for TH compared to TT esophagectomies. However, in an adjusted analysis, there was no difference in operative approaches with respect to long term survival. One may speculate that the differences in survival in the unadjusted analysis are due to tumor biology, as there were more early stage tumors in the TH group. More advanced cancers may be more likely to be treated with a more invasive approach (TT) due to the extent of disease. At the same time, more advanced tumors will be associated with lesser chance of cure and inferior long term survival for patients. In our study, patient characteristics, such as age and comorbidity score, as well as tumor stage, were associated with survival, whereas operative approach was not. This result is in agreement with the existing literature on surgical therapy for esophageal cancer, which does not strongly support one operative approach over the other as being associated with improved long term survival [7,12,21]. Therefore, the available data do not support one operative approach, TT or TH, for resection of esophageal cancer to be preferred in order to maximize long term survival.

Limitations:

There are several limitations to consider when interpreting the results of this study. Foremost, this is a retrospective cohort study analyzing data from a national cancer registry linked to a large administrative dataset (CMS) and, therefore, subject to misclassification of data. This concern is particularly true for CMS data, which are collected for billing and not clinical purposes, and often lack accuracy on clinical diagnosis. Also, because this is a Medicare population, the study is restricted to individuals aged 65 or older. Our study may not be representative of a younger cohort of patients, those with private insurance, or those treated exclusively by board certified thoracic surgeons. In addition, specific clinical detail with regard to patient comorbid medical conditions and post-operative complications was not available in the analyzed datasets. Clinical data registries, such as the STS-GTSD, contain richer clinical detail allowing for more robust risk adjustment. In addition, the SEER registry contains only the pathologic (true or post treatment) stage of the tumor and not the clinical (pretreatment) stage. This is a limitation because treatment decisions, such as whether to operate and operative approach, must be based on the preoperative, clinical stage of the tumor. Finally, data regarding hospital and surgeon volume were not examined, as these factors could not accurately be analyzed with our dataset.

Strengths:

This study also has several strengths that must be acknowledged. The patient population with esophageal cancer that is examined is a nationally representative cohort of older patients taken from the SEER-Medicare data. Data from the SEER registry provides detailed tumor information on the esophageal cancers, not available in most clinical registries. Administrative data from CMS allows for accurate determination of resource utilization endpoints, including: length of hospital stay, discharge to an intermediate care facility, or readmission to the hospital. Given the large sample size, excellent power is available for all analyses performed. This is the largest series of which we are aware examining esophagectomy for esophageal cancer that considers operative mortality, resource utilization and long term survival. Predictors of survival in our study were patient age, comorbidity, and tumor characteristics.

Future directions:

Future studies will build on the findings of this analysis. Linkage of the STS-GTSD to CMS data will allow for better risk adjustment when comparing patients treated with competing operative approaches (TT vs. TH). Use of GTSD data will also allow determination of the clinical stage of the esophageal cancer. In addition, CMS data will be used to compare Medicare cost between operative approaches to esophagectomy for esophageal cancer. Costs will be examined based on episode of care costs over a 90 day time period and consider inpatient hospital, outpatient, and physician services costs. We will further examine postoperative complications between TT and TH approaches to esophagectomy. This will be determined two ways: first utilizing the Guller classification system for inpatient surgical complications using administrative data and, second, from the clinical outcomes data found in the STS-GTSD [40]. The final piece in a comparative effectiveness analysis of operative approaches for esophageal cancer is the patient experience. To achieve this goal, future studies will need to collect pre- and post operative patient reported outcomes to examine patient's symptoms and quality of life following surgery for esophageal cancer. This will allow the integration of the patient experience with hard clinical outcomes, such as complications and survival, and economic outcomes, such as resource use and costs, in order to fully evaluate the value of surgical approaches for esophageal cancer.

In conclusion, transthoracic and transhiatal approaches to esophagectomy for esophageal cancer are associated with similar operative mortality and long term patient survival. Based on clinical outcomes, there is no compelling evidence to recommend one operative approach over the other in clinical practice guidelines. It is advised that thoracic surgeons employ the operative approach with which they have the greatest comfort and proficiency. Potential trade-offs, invasiveness of approach versus extent of lymphadenectomy, should be discussed with patients as part of the decision making process. Measurement of costs and patient reported outcomes are likely to further inform the selection of operative approach for esophageal cancer in the future.

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TABLES

Table 1: Medicare billing codes used to define type of esophagectomy and the administration of chemotherapy and radiation therapy.

Surgical approach	Billing codes
Transhiatal esophagectomy	
ICD-9*	42.40 – 42.42
HCPCS**	43107
Transthoracic esophagectomy	
ICD-9	42.52, 42.5
HCPCS	43112, 43117, 43121, 43122

Radiation therapy	Billing codes
ICD-9	V58.0 V66.1 V67.1 92.20 92.21 92.22 92.23 92.24 92.26 92.27 9.28
HCPCS	31643 77300 77301 77305 77310 77315 77321 77326 77327 77328 77331 77332 77333 77334 77336 77370 77380 77381 77399 77401 77402 77403 77404 77406 77407 77408 77409 77411 77412 77413 77414 77416 77417 77418 77419 77420 77425 77427 77430 77431 77432 77470 77499 77520 77522 77523 77525 77750 77761 77762 77763 77781 77782 77783 77784 77799 C1716 C1717 C1718 C1719 C1720 C1790 C1791 C1792 C1793 C1794 C1795 C1796 C1797 C1798 C1799 C1800 C1801 C1802 C1803 C1804 C1805 C1806 C2616 G0126 G0173

Chemotherapy	Billing codes
ICD-9	V58.1 V66.2 V67.2 99.25
HCPCS	95549 96400 96404 96406 96410 96412 96414 96420 96420 96422 96423 96425 96440 96445 96450 96542 96545 C9017 J0182 J8510 J8530 J8560 J8610 J899 J9000 J9001 J9010 J9045 J9060 J9062 J9070 J9080 J9090 J9091 J9092 J9093 J9094 J9095 J9096 J9097 J9170 J9180 J9181 J9182 J9190 J9201 J9206 J9208 J9230 J9250 J9260 J9265 J9280 J9290 J9291 J9350 J9360 J9370 J9375 J9380 J9390 J9999 Q0083 Q0084 Q0085 Q0125 Q0127 Q0128 Q0129 S0178 S0182 S9329 S9330 S9331

* ICD-9: International Classification of Diseases, 9th revision (ICD-9)
** HCPCS: Healthcare Common Procedure Coding System

Table 2: Power calculation for operative mortality
Assumes a sample size of 1,571, 918 transthoracic esophagectomies (TT) and 653 transhiatal esophagectomies (TH). Two-tailed α=0.05 for power estimations.

Assumed operative mortality for TT	Operative mortality for TH	Power (%)
	0.04	97.8%
	0.05	87%
	0.06	61.5%
	0.07	31%
	0.08	10%
0.09	0.09	2.5%
	0.10	9.6%
	0.11	24.5%
	0.12	47.3%
	0.13	69.3%
	0.14	86.3%

Table 3: Power calculation for overall survival
Assumes a sample size of 1,524, 887 transthoracic esophagectomies (TT) and 637 transhiatal esophagectomies (TH). Two-tailed α=0.05 for power estimations.

Assumed 5 year survival for TT	5 year survival for TH	Power (%)
0.23	0.13	99%
	0.16	92%
	0.18	66%
	0.23	2.5%
	0.28	60%
	0.30	86%
	0.33	99%

Table 4: Clinical characteristics of patients undergoing esophagectomy for esophageal cancer

	Transthoracic N=918 Mean(SD)/ N(%)	Transhiatal N=653 Mean(SD)/ N(%)	p-value
Age	72.8 (5.3)	73.4 (5.3)	0.02
Male	735 (80.1)	517 (79.2)	0.66
Race			0.001
Caucasian	837 (91.2)	625 (95.7)	
African American	56 (6.1)	15 (2.3)	
Other	25 (2.7)	13 (2.0)	
Residence			0.68
Big Metropolitan	486 (52.9)	364 (55.7)	
Metropolitan	275 (30.0)	192 (29.4)	
Urban	62 (6.7)	35 (5.4)	
Less Urban	75 (8.2)	47 (7.2)	
Rural	20 (2.2)	15 (2.3)	
Education:			<0.0001
<25% high school graduates	238 (25.9)	109 (16.7)	
Poverty:			0.01
>25% below poverty level	81 (8.8)	35 (5.4)	
Married	660 (71.9)	446 (71.4)	0.82
Comorbidity Score			0.67
0	551 (60.0)	407 (62.3)	
1	244 (26.6)	159 (24.4)	
2	69 (7.5)	53 (8.1)	
3+	54 (5.9)	34 (5.2)	
Type of Admission			0.10
Elective	802 (87.3)	591 (90.5)	

Emergency	41 (4.5)	27 (4.1)	
Urgent	74 (8.1)	35 (5.4)	
Unknown	1 (0.1)	0 (0.0)	
Induction therapy			
Any induction therapy	361 (39.3)	246 (37.7)	0.51
Both chemotherapy and radiation	239 (26.0)	178 (27.3)	0.59
Chemotherapy only	54 (5.9)	16 (2.5)	0.001
Radiation only	68 (7.4)	52 (8.0)	0.68
Stage			0.01
I	293 (31.9)	257 (39.4)	
II	307 (33.5)	207 (31.7)	
III	278 (30.2)	164 (25.1)	
IV	25 (2.7)	9 (1.4)	
Unknown	15 (1.6)	16 (2.5)	
Location of tumor in esophagus			0.12
Lower	662 (72.1)	480 (73.5)	
Middle	156 (17.0)	90 (13.8)	
Upper	24 (2.6)	28 (4.3)	
Other	76 (8.3)	55 (8.4)	
Histology			0.66
Adenocarcinoma	655 (71.4)	476 (72.9)	
Squamous	231 (25.2)	150 (23.0)	
Other	20 (2.2)	15 (2.3)	
Unknown	12 (1.3)	12 (1.8)	
Grade			0.004
Poor or undifferentiated	425 (46.3)	279 (42.7)	
Well to moderate	395 (43.0)	267 (40.9)	
Unknown	98 (10.7)	107 (16.4)	

Table 5: Perioperative clinical outcomes of patients undergoing esophagectomy for esophageal cancer

	Transthoracic N=918 Mean(SD)/ N(%)	Transhiatal N=653 Mean(SD)/ N(%)	p-value
Number of lymph nodes examined	15.2 (20.2)	11.3 (14.8)	<0.001
Length of hospital stay (days)	18.7 (16.1)	17.2 (16.5)	0.08
Intensive care unit stay (days)	11.3 (14.1)	9.9 (15.4)	0.07
Hospital Death	83 (9.0)	59 (9.0)	0.99
Discharge to home	604 (65.8)	423 (64.8)	0.68
Hospital readmission at 30 days after discharge*	112 (18.5)	81 (19.2)	0.81
Hospital readmission at 90 days after discharge*	189 (31.3)	132 (31.3)	0.98

* Out of patients discharged to home.

Table 6: Logistic regression model examining the association between the exposure, surgical approach, and outcome, operative mortality.

Odds Ratio Estimates

Effect	**Point Estimate**	**95% Wald Confidence Limits**	**p-value**
Surgical approach			
Transthoracic	1 (Ref)		
Transhiatal	1.06	0.73-1.53	0.77
Induction therapy			
No	1 (Ref)		
Yes	0.75	0.50-1.13	0.17
Gender			
Male	1 (Ref)		
Female	0.67	0.41-1.11	0.12
Age at Diagnosis	1.05	1.02-1.09	0.00
Race			
Caucasian	1 (Ref)		
African American	0.53	0.21-1.32	0.17
Other	0.46	0.11-2.03	0.31
Marital status			
Married	1 (Ref)		
Unmarried	1.36	0.91-2.04	0.13
Education			
Lowest 25%	1.34	0.84-2.14	0.22
Other	1 (Ref)		
Poverty Level			
Lowest 25%	1.68	0.85-3.32	0.14
Other	1 (Ref)		
Comorbidity Score			
0	1 (Ref)		
1	1.05	0.68-1.63	0.83
2	2.05	1.16-3.62	0.01
3+	1.58	0.81-3.09	0.18
Admission Type			
Elective	1 (Ref)		
Emergency	1.70	0.82-3.51	0.15
Urgent	2.45	1.39-4.31	0.00
Location of tumor is esophagus			
Lower	1 (Ref)		
Middle	1.31	0.77-2.23	0.32
Upper	0.91	0.30-2.76	0.86
Other	1.50	0.81-2.75	0.20

Histology			
Adenocarcinoma	1 (Ref)		
Squamous cell	1.55	0.94-2.57	0.09
Other / unknown	0.78	0.27-2.26	0.65
Grade			
Well to moderate	1 (Ref)		
Poor to undifferentiated	1.25	0.84-1.88	0.27
Unknown	1.26	0.69-2.33	0.45
Stage			
1	1 (Ref)		
2	0.93	0.57-1.50	0.76
3	1.29	0.81-2.05	0.28
4	<0.001	<0.001->999.999	0.98
Unknown	0.69	0.15-3.24	0.63
Residence			
Metropolitan	1 (Ref)		
Urban	0.53	0.28-1.01	0.05
Rural	1.56	0.57-4.28	0.39

Table 7: Linear regression model examining the association between the exposure, surgical approach, and the outcome, hospital length of stay.

Parameter Estimates

Variable	**DF**	**Parameter Estimate**	**Standard Error**	**t Value**	**p-value**
Surgical approach					
Transthoracic	(Ref)				
Transhiatal	1	-1.47	0.84	-1.75	0.08
Induction therapy					
No	(Ref)				
Yes	1	-0.63	0.89	-0.71	0.48
Gender					
Male	(Ref)				
Female	1	-0.04	1.13	-0.04	0.97
Age at Diagnosis	1	0.15	0.08	1.91	0.06
Race					
Caucasian	(Ref)				
African American	1	1.67	2.25	0.74	0.46
Other	1	5.69	2.69	2.11	0.03
Marital status					
Married	(Ref)				
Unmarried	1	2.15	0.97	2.21	0.03
Education					
Lowest 25%	1	-0.08	1.12	-0.07	0.94
Other	(Ref)				
Poverty Level					
Lowest 25%	1	1.21	1.84	0.66	0.51
Other	(Ref)				
Comorbidity Score					
0	(Ref)				
1	1	0.14	0.97	0.14	0.89
2	1	2.01	1.56	1.28	0.20
3+	1	6.71	1.82	3.68	0.00
Admission Type					
Elective	(Ref)				
Emergency	1	-0.76	2.04	-0.37	0.71
Urgent	1	2.06	1.62	1.27	0.20
Location of tumor in esophagus					
Lower	(Ref)				
Middle	1	1.28	1.33	0.96	0.34
Upper	1	3.34	2.41	1.39	0.17

Other	1	1.39	1.52	0.91	0.36
Histology					
Adenocarcinoma	(Ref)				
Squamous cell	1	1.11	1.23	0.90	0.37
Other / unknown	1	-0.82	2.19	-0.37	0.71
Grade					
Well to moderate	(Ref)				
Poor to undifferentiated	1	-0.77	0.91	-0.84	0.40
Unknown	1	-1.29	1.39	-0.93	0.35
Stage					
1	(Ref)				
2	1	-1.62	1.07	-1.52	0.13
3	1	-1.63	1.09	-1.49	0.14
4	1	-4.20	2.90	-1.45	0.15
Unknown	1	-1.54	3.17	-0.49	0.63
Residence					
Metropolitan	(Ref)				
Urban	1	-0.91	1.21	-0.76	0.45
Rural	1	-0.63	2.78	-0.23	0.82

Table 8: Logistic regression model examining the association between the exposure, surgical approach, and the outcome, hospital readmission 30 days after discharge. Only the 1,027 patients discharged to home are included in this analysis (transthoracic – 604; transhiatal – 423).

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	p-value
Surgical approach			
Transthoracic	1 (Ref)		
Transhiatal	1.08	0.78-1.51	0.64
Induction Therapy			
No	1 (Ref)		
Yes	1.25	0.88-1.76	0.21
Gender			
Male	1 (Ref)		
Female	1.16	0.73-1.84	0.53
Age at Diagnosis	1.00	0.97-1.04	0.90
Race			
Caucasian	1 (Ref)		
African American	2.31	1.02-5.26	0.05
Other	0.71	0.20-2.52	0.59
Marital status			
Married	1 (Ref)		
Unmarried	1.07	0.72-1.59	0.74
Education			
Lowest 25%	1.12	0.73-1.72	0.60
Other	1 (Ref)		
Poverty Level			
Lowest 25%	0.76	0.36-1.58	0.46
Other	1 (Ref)		
Comorbidity Score			
0	1 (Ref)		
1	1.03	0.70-1.52	0.87
2	1.30	0.69-2.47	0.42
3+	2.21	0.99-4.91	0.05
Admission Type			
Elective	1 (Ref)		
Emergency	1.48	0.66-3.33	0.35
Urgent	1.89	1.04-3.45	0.04
Location of tumor in esophagus			

Lower	1 (Ref)		
Middle	1.01	0.58-1.75	0.98
Upper	1.52	0.63-3.69	0.35
Other	1.14	0.64-2.06	0.65
Histology			
Adenocarcinoma	1 (Ref)		
Squamous cell	0.92	0.56-1.51	0.73
Other / unknown	0.94	0.39-2.30	0.90
Grade			
Well to moderate	1 (Ref)		
Poor to undifferentiated	1.18	0.82-1.68	0.37
Unknown	1.28	0.74-2.23	0.37
Stage			
1	1 (Ref)		
2	1.25	0.82-1.89	0.30
3	0.90	0.58-1.40	0.64
4	0.71	0.19-2.62	0.60
Unknown	1.27	0.41-3.98	0.68
Residence			
Metropolitan	1 (Ref)		
Urban	1.59	1.04-2.42	0.03
Rural	2.86	1.11-7.33	0.03

Table 9: Cox proportional hazards model examining the association between the exposure, surgical approach, and the outcome, instantaneous risk of mortality. Includes 1,524 esophagectomy patients with long-term survival data available (887 transthoracic and 637 transhiatal esophagectomies).

	Hazard Ratio	95% Confidence Limits	p-value
Surgical approach			
TT	1 (Ref)		
TH	0.99	0.82-1.20	0.93
Induction therapy			
No	1 (Ref)		
Yes	1.21	0.99-1.48	0.07
Gender			
Male	1 (Ref)		
Female	0.87	0.67-1.13	0.31
Age at Diagnosis	1.03	1.01-1.05	0.01
Race			
Caucasian	1 (Ref)		
African American	0.92	0.54-1.55	0.74
Other	0.88	0.43-1.79	0.71
Marital status			
Married	1 (Ref)		
Unmarried	0.95	0.74-1.21	0.68
Education			
Lowest 25%	1.25	0.98-1.60	0.08
Other	1 (Ref)		
Poverty Level			
Lowest 25%	1.12	0.73-1.72	0.60
Other	1 (Ref)		
Comorbidity Score			
0	1 (Ref)		
1	1.00	0.81-1.25	0.99
2	1.32	0.91-1.91	0.15
3+	1.71	1.06-2.75	0.03
Admission Type			
Elective	1 (Ref)		
Emergency	1.29	0.80-2.07	0.29
Urgent`	1.33	0.91-1.93	0.14
Location of tumor in esophagus			
Lower	1 (Ref)		
Middle	1.26	0.93-1.69	0.13

Upper	1.42	0.84-2.39	0.19
Other	1.09	0.76-1.57	0.63
Histology			
Adenocarcinoma	1 (Ref)		
Squamous cell	0.98	0.74-1.30	0.89
Other / unknown	1.81	1.13-2.90	0.01
Grade			
Well to moderate	1 (Ref)		
Poor to undifferentiated	1.23	1.01-1.50	0.04
Unknown	0.70	0.49-1.02	0.06
Stage			
1	1 (Ref)		
2	1.80	1.37-2.36	<.0001
3	4.00	3.08-5.18	<.0001
4	4.21	2.47-7.17	<.0001
Unknown	0.87	0.33-2.27	0.78
Residence			
Big Metropolitan	1 (Ref)		
Metropolitan	0.94	0.76-1.17	0.59
Urban	1.04	0.72-1.51	0.83
Less Urban	1.38	1.01-1.90	0.05
Rural	0.90	0.46-1.78	0.77

Table 10: Cox proportional hazards model examining the association between the exposure, surgical approach, and the outcome, instantaneous risk of cancer specific mortality. Includes 1,524 esophagectomy patients with long-term survival data available (887 transthoracic and 637 transhiatal esophagectomies).

	Hazard Ratio	95% Confidence Limits	p-value
Surgical Appraoch			
Transthoracic	1 (Ref)		
Transhiatal	1.08	0.86-1.35	0.52
Induction Therapy			
No	1 (Ref)		
Yes	1.20	0.95-1.52	0.14
Gender			
Male	1 (Ref)		
Female	0.90	0.66-1.22	0.48
Age at Diagnosis	1.02	1.00-1.05	0.07
Race			
Caucasian	1 (Ref)		
African American	0.89	0.47-1.70	0.73
Other	0.99	0.43-2.27	0.99
Marital status			
Married	1 (Ref)		
Unmarried	0.87	0.65-1.18	0.38
Education			
Lowest 25%	1.10	0.82-1.48	0.52
Other	1 (Ref)		
Poverty Level			
Lowest 25%	0.99	0.58-1.70	0.98
Other	1 (Ref)		
Comorbidity Score			
0	1 (Ref)		
1	0.95	0.73-1.23	0.69
2	1.44	0.94-2.22	0.10
3+	1.43	0.78-2.62	0.25
Admission Type			
Elective	1 (Ref)		
Emergency	1.26	0.70-2.28	0.44
Urgent	1.24	0.79-1.95	0.34
Location			
Lower	1 (Ref)		

Middle	1.35	0.95-1.91	0.10
Upper	0.91	0.43-1.90	0.80
Other	1.23	0.82-1.85	0.33
Histology			
Adenocarcinoma	1 (Ref)		
Squamous cell	1.01	0.73-1.40	0.94
Other / unknown	1.27	0.68-2.38	0.46
Grade			
Well to moderate	1 (Ref)		
Poor to undifferentiated	1.33	1.05-1.68	0.02
Unknown	0.64	0.40-1.00	0.05
Stage			
1	1 (Ref)		
2	1.90	1.37-2.65	0.001
3	4.85	3.54-6.65	<.0001
4	6.03	3.40-10.70	<.0001
Unknown	0.62	0.14-2.68	0.52
Residence			
Big Metropolitan	1 (Ref)		
Metropolitan	0.97	0.76-1.25	0.84
Urban	0.95	0.61-1.50	0.83
Less Urban	1.33	0.91-1.93	0.14
Rural	0.58	0.21-1.58	0.29

FIGURES

Figure 1: Unadjusted Kaplan-Meier overall survival, transthoracic versus transhiatal esophagectomy. Number of patients at risk, transthoracic (TT) and transhiatal (TH), shown.

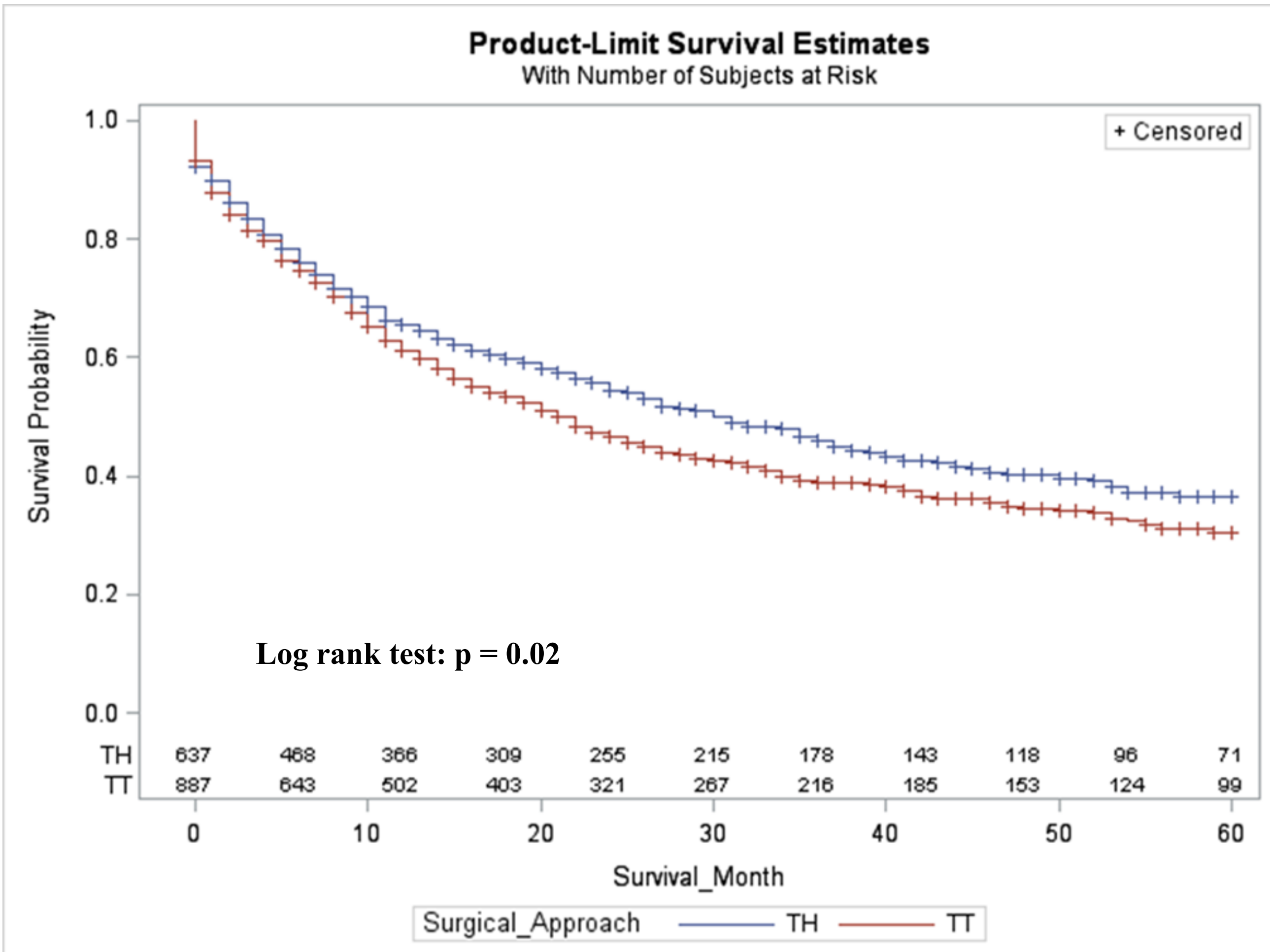

Figure 2: Unadjusted Kaplan-Meier cancer specific survival, transthoracic versus transhiatal esophagectomy. Number of patients at risk, transthoracic (TT) and transhiatal (TH), shown.