Published in final edited form as:

Ann Surg. 2019 September ; 270(3): 434–443. doi:10.1097/SLA.0000000000003466.

Trends in Treatment of T1N0 Esophageal Cancer

Tara R. Semenkovich, MD, MPHS, Jessica L. Hudson, MD, MPHS, Melanie Subramanian, MD, Daniel K. Mullady, MD, Bryan F. Meyers, MD, MPH, Varun Puri, MD, MSCI, Benjamin D. Kozower, MD, MPH

Department of Surgery, Division of Cardiothoracic Surgery, Washington University in St. Louis.

Abstract

Objective: The purpose of this study was to explore nationwide trends in treatment and outcomes of T1N0 esophageal cancer.

Background: Endoscopic treatment has become an accepted option for early-stage esophageal cancer, but nationwide utilization rates and outcomes are unknown.

Methods: T1N0 esophageal cancers were identified in the National Cancer Database from 2004 to 2014. We assessed trends in treatment; compared endoscopic therapy, esophagectomy, chemoradiation, and no treatment; and performed a subgroup analysis of T1a and T1b patients from 2010 to 2014 (AJCC 7).

Results: A total of 12,383 patients with clinical T1N0 esophageal cancer were analyzed. Over a decade, use of endoscopic therapy increased from 12.7% to 33.6%, whereas chemoradiation and esophagectomy decreased, $P < 0.01$. The rise in endoscopic treatment of T1a disease from 42.7% to 50.6% was accompanied by a decrease in esophagectomies from 21.7% to 12.8% ($P < 0.01$). For T1b disease, the rise in endoscopic treatment from 16.9% to 25.1% ($P = 0.03$) was accompanied by decreases in no treatment and chemoradiation, whereas the rate of esophagectomies remained approximately 50%. Unadjusted median survival was longer for patients undergoing resection: esophagectomy, 98.6 months; endoscopic therapy, 77.7 months; chemoradiation, 17.3 months; no treatment, 8.2 months; $P < 0.01$. Riskadjusted Cox modeling showed esophagectomy was associated with improved survival [hazard ratio (HR): 0.85], and chemoradiation (HR: 1.79) and no treatment (HR: 3.57) with decreased survival, compared to endoscopic therapy ($P < 0.01$).

Conclusions: Use of endoscopic therapy for T1 esophageal cancer has increased significantly: for T1a, as an alternative to esophagectomy; and for T1b, as an alternative to no treatment or chemoradiation. Despite upfront risks, long-term survival is highest for patients who can undergo esophagectomy.

kozowerb@wustl.edu.

The authors report no conflicts of interest.

Presentation: American Surgical Association 139th Annual Meeting in Dallas, TX on April 11th.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).

Keywords

endoscopic mucosal resection; esophageal cancer; esophagectomy

Endoscopic treatment has become an accepted option for early-stage esophageal cancer. Given the substantial morbidity of esophagectomy, combined with the ease of access to the esophagus via endoscopy and advancing technology for various types of endoscopic therapy, ¹ definitive local treatment is appealing. For high-grade dysplasia, endoscopic therapy has been shown to successfully eradicate disease,² is cost-effective,³ and has become the standard of care.⁴ For early-stage cancers, evidence showing acceptable outcomes following endoscopic resection has been predominantly demonstrated in single-institution or retrospective database studies comparing the treatment to esophagectomy.⁵

Based on the available data, endoscopic treatment for T1N0 esophageal cancer has become integrated in national guidelines as a possible option, although there is variability in the specific tumors and patients that are eligible. The Society of Thoracic Surgeons guidelines view endoscopic mucosal resection as a useful diagnostic procedure to definitively determine the depth of invasion, and as a possible therapeutic option for superficial tumors without lymphadenopathy.⁶ However, the American Society for Gastrointestinal Endoscopy guidelines recommend endoscopic eradication therapy as primary treatment for intramucosal esophageal cancer.⁵ The National Comprehensive Cancer Network (NCCN) guidelines state that endoscopic resection with or without ablation is the preferred strategy for pathologic T1a disease, an option for superficial pathologic T1b disease in surgically fit patients, and an option for all pathologic T1b disease in patients who are not surgical candidates.⁴ Tenets of treatment generally include appropriate clinical staging demonstrating node-negative localized disease, a low-grade tumor small enough to allow for complete resection with negative margins, and ablation of residual Barrett esophagus.¹

The purpose of this study was to explore nationwide trends in treatment and outcomes of T1 esophageal cancer over a decade, from 2004 to 2014. We hypothesized that the use of endoscopic therapy increased over the time period of the study and that the percentage of patients receiving an esophagectomy, chemoradiation, and no treatment decreased because of the availability of an alternative, lower-risk treatment option for patients with substantial comorbidities.

PATIENTS AND METHODS

Data Source

Patients were identified from the National Cancer Database (NCDB) Participant Use File for esophageal cancer from 2004 to 2014. The NCDB is a retrospective dataset capturing >70% of all new cancer diagnoses nationwide from >1500 facilities, sponsored by the American Cancer Society and the Commission on Cancer of the American College of Surgeons. This study was exempt from Washington University's Institutional Review Board approval because the dataset is deidentified.

Patient Population

Patients with clinically staged T1N0 esophageal cancer were included in this study. Patients were excluded if they had tumors located in the cervical esophagus or upper third, had evidence of metastatic disease, or if it was unknown whether surgery was received. Patients were categorized based on receipt of: endoscopic therapy, esophagectomy, chemotherapy and/or radiation, and no treatment. A subgroup analysis was performed for T1a (tumor invading the lamina propria or muscularis mucosa) and T1b (tumor invading the submucosa) patients that had detailed staging information from 2010 to 2014, based on the effective date of the American Joint Committee on Cancer (AJCC) 7th edition cancer staging manual.

Covariates

We abstracted and categorized the following covariates: age, sex, race (white vs non-white), insurance status (private vs non-private), education by zip code (lowest quartile of >21% without a high school diploma vs <21%), median income by zip code (lowest quartile of <\$38,000 vs >\$38,000), population by zip code (>250,000 vs <250,000), treatment center type (academic vs nonacademic), Charlson Deyo Score (0, 1, 2), tumor size, histology (squamous cell vs adenocarcinoma), grade, and year of diagnosis.

Statistical Analyses

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Descriptive statistics to compare baseline characteristics of patients receiving various treatment modalities were performed using Wilcoxon rank sum tests or chi-square tests, as appropriate. The chi-squared test for trend was used to assess changes in use of treatment modalities over time. Univariable and multivariable analyses were performed using stepwise binary logistic regression to identify variables associated with receipt of endoscopic treatment versus esophagectomy. Variables that had a $P < 0.1$ on univariable analyses were considered for inclusion into a multivariable model, and variables that were significant with $P < 0.05$ were kept in the final model. Kaplan-Meier analysis and Cox proportional hazard modeling were performed to compare overall survival by treatment modality and assess for association with increased mortality hazard. Statistical significance was defined as $P < 0.05$.

RESULTS

Overall T1N0 Cohort Treatment Trends

From 2004 to 2014, 12,383 patients with clinical T1N0M0 esophageal cancer met criteria for analysis: 2957 (23.9%) received endoscopic therapy; 3850 (31.1%) underwent esophagectomy; 3103 (25.1%) received chemotherapy, radiation, or both; and 2473 (20.0%) received no treatment (Fig. 1). During the 11-year period, utilization of endoscopic therapy rapidly increased from 12.7% to 33.6% ($P < 0.001$), whereas the proportions receiving chemoradiation and esophagectomy decreased (Fig. 2, Supplementary Table 1, <http://links.lww.com/SLA/B697>). Of the patients receiving endoscopic therapy, the percentage of patients receiving local tumor excision increased from 61.3% to 94.0% and the percentage receiving local tumor destruction decreased from 38.7% to 6.0% during the years of the study ($P < 0.001$, Supplementary Figure 1, <http://links.lww.com/SLA/B697>).

Chemoradiation usage decreased from 39.8% to 20.6% ($P < 0.001$) and esophagectomy remained stable between 32% and 34% throughout most of the time period before decreasing to 25.1% in the last several years of the study ($P < 0.001$). The percentage of patients receiving no treatment remained stable at approximately 20% throughout the entire period of the study ($P = 0.7$). For the 2473 patients receiving no treatment, surgery, chemotherapy, and radiation were specifically documented as not recommended in 84% ($n = 2083$), 81% ($n = 1993$), and 83% ($n = 2060$), respectively. Surgery, chemotherapy, and radiation were recommended in 12% ($n = 290$), 17% ($n = 419$), and 12% ($n = 298$), respectively, and it was unknown whether or not treatments were recommended for the remainder of the patients. For those who did not receive recommended treatment, patient or family refusal was documented as the reason for 42% (123/290) for surgery, 55% (231/419) for chemotherapy, and 67% (199/298) for radiation. These results remained consistent when only the subset of patient with a Charlson Deyo Score of 0 who received no treatment was examined.

Of the patients undergoing esophagectomy with pathologic staging data available, clinical staging was accurate 70% of the time. Interestingly, staging accuracy did not improve over the years of the study ($P = 0.11$). Of the entire esophagectomy cohort, 15.1% had a higher pathologic T stage documented, 13.5% had nodal metastases, and 0.5% had metastases on pathologic examination. Looking specifically at the subgroup from 2010 to 2014 wherein detailed clinical stage information was available, 65% of the T1aN0 patients and 58% of the T1bN0 patients were staged accurately. Of the T1a patients, 20.2% had a higher pathologic T stage and 8.7% had nodal metastases. Of the T1b patients, 12.2% had a higher pathologic T stage and 14.0% had nodal metastases (Supplementary Table 2, <http://links.lww.com/SLA/B697>).

Patient Characteristics and Treatment Modalities

There were numerous differences in baseline characteristics for patients who received the 4 different treatment modalities (Table 1). Esophagectomy patients were younger (mean 64.0 years); more likely to be male, white, and have private insurance; and less likely to have a low income, low education status, and be from highly populated urban areas (all $P < 0.001$). Patients treated with either esophagectomy or endoscopy were more likely to have adenocarcinoma histology (esophagectomy: 83.5%, endoscopic treatment: 84.4%, $P < 0.001$). Patients treated endoscopically shared many of the same demographic features as esophagectomy patients, but were also much more likely to be treated at an academic center (70.1%, $P < 0.001$). On multivariable analysis, factors independently associated with receipt of endoscopic treatment versus esophagectomy included: older age, treatment at an academic center, increased comorbidity (Charlson Deyo Score of 2), later year of diagnosis, smaller tumor size, and grade 1 or X disease (all $P < 0.001$, Table 2).

Survival Analysis

Kaplan Meier analysis (Fig. 3A, entire cohort) showed unadjusted median survival was significantly longer for patients undergoing resection: esophagectomy, 98.6 months [95% confidence interval (CI), 93.5–106.8], local endoscopic therapy, 77.7 months (95% CI, 71.8–87.2), chemoradiation, 17.3 months (95% CI, 16.2–18.3), no treatment, 8.2 months (95% CI,

7.4–9.3); $P < 0.001$. Esophagectomy conferred a slightly increased upfront mortality risk compared to endoscopic treatment, but had better long-term outcome in the overall cohort with separation of the survival curves after 5 years. Perioperative mortality within 30 days was 3.2% for the esophagectomy cohort, and did not change significantly over time ($P = 0.9$). Cox proportional hazards modeling of long-term survival showed that esophagectomy had a 15% decreased risk of mortality [hazard ratio (HR) 0.85; 95% CI, 0.75–0.96] compared to endoscopic therapy, whereas chemoradiation had an 80% increased risk of mortality (HR: 1.79; 95% CI, 1.56–2.04), adjusting for age, race, insurance status, income, treatment center type, Charlson Deyo score, tumor size, histology, and grade (Table 3).

T1a and T1b Treatment Trends and Characteristics

From 2010 to 2014, 3595 patients had detailed data on tumor stage: 2449 (68.1%) were T1a and 1146 (31.9%) were T1b. Over 5 years, the use of endoscopic treatment for T1a disease rose significantly from 42.7% to 50.6% ($P = 0.002$), whereas esophagectomies decreased from 21.7% to 12.8%, ($P < 0.001$). No significant changes occurred in the use of chemoradiation or no treatment (both $P = 0.6$). For T1b disease, the rise in endoscopic treatment from 16.9% to 25.1% ($P = 0.03$) was accompanied by nonstatistically significant decreases in no treatment (12.3%–9.2%, $P = 0.3$) and chemoradiation (19.2%–15.9%, $P = 0.3$), the esophagectomies whereas rate of remained around 50% ($P = 0.7$, Table 4).

In the T1a subgroup, 1123 (45.9%) patients received endoscopic treatment, 428 (17.5%) underwent esophagectomy, 365 (14.9%) received chemoradiation, and 533 (21.8%) had no treatment. Variables independently associated with T1a patients receiving endoscopic treatment versus esophagectomy included: increasing age, Charlson Deyo Score 2, later year of diagnosis, smaller tumor size, and grade (all $P < 0.001$, Supplementary Table 3, <http://links.lww.com/SLA/B697>). In the T1b subgroup, 259 (22.6%) patients received endoscopic treatment, 588 (51.3%) underwent esophagectomy, 193 (16.8%) received chemoradiation, and 106 (9.3%) received no treatment. Variables independently associated with T1b patients receiving endoscopic treatment versus esophagectomy included: increasing age, smaller tumor size, and grade (all $P < 0.001$, Supplementary Table 3, <http://links.lww.com/SLA/B697>).

For T1a patients, Kaplan-Meier analysis showed no significant difference in survival between patients receiving endoscopic treatment versus esophagectomy ($P = 0.8$, Fig. 3B, T1a Subgroup), whereas both endoscopic treatment and esophagectomy conferred significantly better survival than both chemoradiation and no treatment ($P < 0.001$). Cox proportional hazards modeling showed that esophagectomy had a comparable mortality risk to endoscopic therapy (HR: 0.95; 95% CI, 0.66–1.39), adjusting for age, Charlson Deyo Score, tumor size, and grade. Chemoradiation (HR: 2.60; 95% CI, 1.81–3.75) and no treatment (HR: 5.63; 95% CI, 4.02–7.88) conferred a substantially higher risk of mortality than endoscopic therapy (Supplementary Table 4, <http://links.lww.com/SLA/B697>).

For T1b patients, Kaplan-Meier analysis showed there was a trend toward better survival for patients receiving esophagectomy that did not reach statistical significance ($P = 0.07$, Fig. 3C, T1b Subgroup), whereas both endoscopic treatment and esophagectomy again conferred significantly better survival than both chemoradiation and no treatment ($P < 0.001$). For T1b

disease, esophagectomy patients had a more favorable mortality risk (HR: 0.76; 95% CI, 0.52–1.11) compared to those receiving endoscopic therapy, and no treatment (HR: 3.27; 95% CI, 1.94–5.50) patients fared worse, adjusting for age, insurance status, tumor size, and grade (Supplementary Table 4, <http://links.lww.com/SLA/B697>).

DISCUSSION

Previous research by Taylor et al⁷ has shown increasing use of endoscopic therapy for high-grade dysplasia and early-stage esophageal cancer. In this study, we evaluated nationwide trends in treatment of clinical T1N0 esophageal cancer over a decade, focused on differences by tumor stage. We demonstrated rapidly increasing utilization of endoscopic therapy, with trends of the treatment options and corresponding outcomes differing by subgroup. In the overall T1N0 cohort, endoscopic treatment was used in 33.6% of cancers by 2014 and replaced chemoradiation and esophagectomy. Over time, the percentage of endoscopic local tumor excision versus destruction dramatically increased to 94.0%. This represents an important improvement in the quality of endoscopic care provided, as local excision allows for both accurate pathologic tumor staging and therapeutic management.¹ Esophagectomy, which has historically been the standard of care for early stage resectable esophageal cancer,⁶ was associated with better long-term survival on Kaplan-Meier analysis and Cox proportional hazards modeling. This benefit was seen despite a greater upfront risk of mortality, which in this series remained stable at approximately 3.2% and was consistent with previous reports.⁸ Although we adjusted for comorbid conditions and other important clinical variables, the observed long-term survival benefit in our study may be because of overall healthier patients being treated with esophagectomy, or may be because of the impact of 13.5% occult nodal disease and improved long-term locoregional cancer control particularly for the T1bN0 patients with deeper invasion. This finding reveals the importance of appropriate risk assessment for operative patients. It also underscores the value of understanding the inaccuracies of esophageal cancer staging—a study by Bartel et al found that up to 11% of patients after pathologic examination were not treated with the optimal modality based on clinical endoscopic ultrasound staging,⁹ and demonstrates the significance of our subgroup analysis.

In T1a patients, endoscopic treatment was increasingly used as an alternative to esophagectomy and was utilized in 50.6% of cases by 2014. This represents an appropriate transition to a less morbid but similarly effective form of curative resection for patients with small, low-risk tumors. A previous propensity-matched study of T1a cancers by Marino et al showed that survival was similar after esophagectomy or endoscopic resection, but the endoscopically treated patients experienced less short-term mortality, shorter hospital stays, and fewer readmissions. The esophagectomy patients had greater longevity, but this benefit was tempered by the upfront risk.¹⁰ Another population-based study by Wani et al demonstrated that esophageal cancer-related mortality was similar between patients receiving endoscopic resection and esophagectomy at 2 and 5 years. However, patients receiving endoscopic resection had higher mortality from alternate causes, suggesting the modality is used preferentially in sicker patients.¹¹ Our study confirms this finding of favorable outcomes with endoscopic resection, but demonstrates stable rates of chemoradiation and no treatment for T1a patients with markedly worse survival. Although

some of these patients may not be candidates for endoscopic resection procedures because of comorbidities, functional status, tumor size, or patient preference, a subset may benefit substantially from improved access to endoscopic therapies, which we demonstrate is currently more likely at academic centers. It is also worth noting that although endoscopic ultrasound examination is the most commonly used clinical staging modality, it can be inaccurate, and may affect treatment choice or outcomes. These inaccuracies appear both in the assessed depth of invasion as well as lymph node assessment. Even within the clinical T1a patients, there were 20.2% of patients with deeper invasion seen after esophagectomy and 8.7% of patients that had occult lymph node metastases that were missed on endoscopic ultrasound examination. If these patients are understaged with endoscopic ultrasound and treated with endoscopic mucosal resection, post-procedure surveillance is important to detect recurrent locoregional disease that may be treatable with esophagectomy. Within this dataset, the frequency of recurrent resectable disease is unknown; however, this represents an important area where additional research is needed to inform evidence-based surveillance recommendations.

In T1b disease, endoscopic treatment was used as an alternative to chemoradiation and no treatment, and accounted for 25.1% of cases by 2014. The use of esophagectomy remained stable at approximately 50%, suggesting that patients who were found to have this level of invasion were appropriately referred for surgery if they were deemed acceptable operative candidates. Our study demonstrated a trend toward improved survival with esophagectomy, possibly because of a higher risk of occult positive lymph nodes in T1b disease and improved locoregional control or appropriate adjuvant therapy administration in the surgery group. Previous research has shown the risk of occult lymph nodes can be as high as 7% in T1a tumors and 20% in T1b tumors.^{12,13} In the setting of low perioperative mortality and better longevity, referral for esophagectomy in low and moderate risk patients is likely to yield the best outcomes. Additionally, we demonstrated significantly improved survival with endoscopic resection compared to both chemoradiation and no treatment in T1b disease. This suggests patients who are not operative candidates may benefit from the local control provided by endoscopic resection, even without a pathologic examination of lymph nodes. As techniques improve and endoscopic submucosal dissection becomes more widely prevalent, endoscopic treatment may become even more efficacious for these patients. For high-risk operative candidates, a nuanced, patient-focused discussion of risks and benefits of esophagectomy versus endoscopic resection with intensive surveillance may be warranted. Resection with either modality is associated with better survival than chemoradiation alone. With increasing use of endoscopic treatment for T1b disease, there is also a role for investigating the benefit of adjunctive therapies in patients with possible occult regional disease.

Another important finding of this analysis is that there are a substantial number of patients receiving no treatment, and this percentage remained stable at 20% throughout the years of the study. This is despite the apparent increasing availability and utilization of endoscopic resection, which can be quite effective for early-stage esophageal cancer and is comparatively low-risk in patients with substantial comorbidities. In the majority of patients who received no treatment, none was recommended by their providers. Of the patients for whom treatment was recommended, patient refusal was documented as the reason in only

roughly half of cases. Certainly, in patients with competing risks to life, no treatment may be appropriate. However, the untreated group encompassed a large number of individuals with a Charlson Deyo Score of 0, and it is unknown why these patients were not deemed candidates for therapy. Perhaps there was a barrier to access of surgery, or there was not adequate consideration of endoscopic resection as a less morbid option. Understanding why a number of potentially curable esophageal cancers go untreated is an important area for further study, and whether improved provider education or wider availability of endoscopic therapy could reduce these numbers merits further investigation.

This study has a few limitations that should be acknowledged. First, because the NCDB is a retrospective database, there is likely treatment selection bias present. Although we can adjust for several important variables when examining treatment outcomes including baseline patient demographics as well as tumor size, grade, and histology, additional relevant information that could affect treatment choice is missing. For example, patient comorbidities are summarized in the Charlson Deyo Score, but detailed data on specific comorbidities and overall functional status are unavailable. Additionally, granular data regarding staging modalities are not available within the NCDB. The available clinical stage is based on what is recorded by a physician or registrar from documents within a patient's record, and does not specify the technique utilized. We therefore cannot assess what percentage of patients was staged with endoscopic ultrasound alone, or had endoscopic resection before esophagectomy. Endoscopic resection is clearly captured when it is the definitive surgical procedure, but not when used diagnostically. Third, endoscopic therapy is provided much more frequently at academic or tertiary centers, and practical availability of skilled endoscopic providers to an individual patient through referrals and travel is unknown. Finally, the recommended treatment for T1N0 cancers differs by depth of invasion—T1a and T1b tumors are different populations with regards to criterion standard treatment options, risks, and benefits. Because AJCC 7 was adopted in 2010, there is a smaller sample size available for this important subgroup analysis.

These limitations are balanced by several major strengths. The NCDB is a large database that captures patients across demographics and practice settings, and tracks the majority of esophageal cancer diagnoses nationally. The broad patient population and years of data captured allow for a useful analysis of trends in national practice patterns. The data and results are generalizable to the real-world care being provided in the United States. In this study, this is especially important because we found that there are a substantial number of patients receiving no treatment. Given the variety of treatment options available for T1N0 disease, this a notable area to improve appropriate provision of care and patient outcomes for potentially curable esophageal cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by the Barnes Jewish Hospital Foundation (TRS), National Institutes of Health (NIH) Grant Numbers 2T32HL7776 (TRS, MS) and 5T32CA009621 (JLH), and the Division of Cardiothoracic Surgery at Washington University in St. Louis.

REFERENCES

1. di Pietro M, Canto MI, Fitzgerald RC. Endoscopic management of early adenocarcinoma and squamous cell carcinoma of the esophagus: screening, diagnosis, and therapy. *Gastroenterology*. 2018;154:421–436. [PubMed: 28778650]
2. Shaheen NJ, Sharma P, Overholt BF, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med*. 2009;360:2277–2288. [PubMed: 19474425]
3. Hu Y, Puri V, Shami VM, et al. Comparative effectiveness of esophagectomy versus endoscopic treatment for esophageal high-grade dysplasia. *Ann Surg*. 2016;263:719–726. [PubMed: 26672723]
4. Farjah F, Gerdes H, Gibson M, et al. NCCN Guidelines Version 2.2018 Esophageal and Esophagogastric Junction Cancers NCCN Evidence Blocks™. Available at: https://www.nccn.org/professionals/physician_gls/pdf/esophageal_blocks.pdf. 2018 Accessed October 17, 2018.
5. Wani S, Qumseya B, Sultan S, et al. Endoscopic eradication therapy for patients with Barrett's esophagus-associated dysplasia and intramucosal cancer. *Gastrointest Endosc*. 2018;87 907–931.e9. [PubMed: 29397943]
6. Varghese TK Jr, Hofstetter WL, Rizk NP, et al. The society of thoracic surgeons guidelines on the diagnosis and staging of patients with esophageal cancer staging of esophageal cancer. *Ann Thorac Surg*. 2013;96:346–356. [PubMed: 23752201]
7. Taylor LJ, Greenberg CC, Lidor AO, et al. Utilization of surgical treatment for local and locoregional esophageal cancer: analysis of the National Cancer Data Base. *Cancer*. 2017;123:410–419. [PubMed: 27680893]
8. Chang AC, Kosinski AS, Raymond DP, et al. The society of thoracic surgeons composite score for evaluating esophagectomy for esophageal cancer. *Ann Thorac Surg*. 2017;103:1661–1667. [PubMed: 28385375]
9. Bartel MJ, Wallace TM, Gomez-Esquivel RD, et al. Role of EUS in patients with suspected Barrett's esophagus with high-grade dysplasia or early esophageal adenocarcinoma: impact on endoscopic therapy. *Gastrointest Endosc*. 2017;86:292–298. [PubMed: 27889544]
10. Marino KA, Sullivan JL, Weksler B. Esophagectomy versus endoscopic resection for patients with early-stage esophageal adenocarcinoma: a National Cancer Database propensity-matched study. *J Thorac Cardiovasc Surg*. 2018;155 2211–2218.e1. [PubMed: 29455958]
11. Wani S, Drahos J, Cook MB, et al. Comparison of endoscopic therapies and surgical resection in patients with early esophageal cancer: a population-based study. *Gastrointest Endosc*. 2014;79 224–232. e1. [PubMed: 24060519]
12. Gamboa AM, Kim S, Force SD, et al. Treatment allocation in patients with early-stage esophageal adenocarcinoma: prevalence and predictors of lymph node involvement. *Cancer*. 2016;122:2150–2157. [PubMed: 27142247]
13. Dubecz A, Kern M, Solymosi N, et al. Predictors of lymph node metastasis in surgically resected T1 esophageal cancer. *Ann Thorac Surg*. 2015;99:1879–1885. discussion 1886. [PubMed: 25929888]

DISCUSSANTS

G. Darling (Toronto, QB):

This is clearly an important contribution to our knowledge of the treatment of early-stage esophageal cancer, and I think the key points you have made are that, first of all, the increasing use of endoscopic resection for T1N0 and particularly for the T1a subgroup and the decreasing use of esophagectomy for that group. You also pointed out that survival with endoscopic resection for T1aN0 is similar to that with esophagectomy but lower in the T1b group. I was astonished to find that 20% of patients received no treatment, and I think that's another important contribution of your study.

Lastly, I think again you have pointed out the inaccuracy of clinical staging in esophageal cancer, particularly the use of endoscopic ultrasound.

For the T1b patients, a lot of patients are now being offered endoscopic treatment as an alternative to esophagectomy because it is viewed as a lower risk procedure, and yet the survival is inferior with endoscopic resection, and you have shown that the rate of esophagectomy is similar over the years despite increasing use of endoscopic resection.

In patients who receive no treatment, do you know if they have the opportunity to discuss treatment options? Does the database provide for that kind of information? Have they had an opportunity to have a consultation with a surgeon or gastroenterologist who performs endoscopic resection?

Response From T.R. Semenkovich (St. Louis, MO):

We don't know specifically who the patients met with. What we do have within the National Cancer Database is whether the different treatment modalities were recommended for the patient. So we can look at 'was surgery part of the treatment plan?' 'was chemotherapy?' and 'was radiation part of the treatment plan?' – each of those 3. And what is documented is for about 80% to 85% of the patients who received no treatment, all 3 modalities were not part of the treatment plan, but we don't necessarily know the reasons for that.

For the remaining 12% to 15% of patients where we know that some treatment was recommended, patient refusal is documented as the reason for no treatment in about half of those patients, but what we don't know is whether patients had access to gastroenterologists or a surgeon who would perform their resection for complete assessment as to whether or not they were candidates for resection.

G.E. Darling (Toronto, QB):

It seems to me that esophageal cancer is a devastating disease, and you don't die silently or asymptotically, and that there should be improved access to a less invasive therapy or discussion, and I think that's something that we as clinicians should pursue.

The other question I had is related to the endoscopic ultrasound. All our guidelines recommend that we use endoscopic ultrasound for staging esophageal cancer, and yet it seems to be relatively inaccurate, and in particular in this group of patients where they

could have curative treatment, I think that that we should be recommending endoscopic resection as a staging modality, not just a diagnostic modality. Can you comment on that?

Response From T.R. Semenkovich:

I think that's a really important point. We are not able to look at the specifics of how patients were staged within the National Cancer Database. The clinical staging information comes from documents within the patient records that are recorded either by a physician or a registrar, but it does not specify the modality used. So likely many of these patients were staged with endoscopic ultrasound, and endoscopic mucosal resection is captured clearly when it is used as a definitive therapy—it is captured as the surgery that the patients had—but it's not clearly captured if it is used diagnostically before an esophagectomy to determine depth of invasion, but that certainly would be a way to improve accuracy of determining depth of invasion and making sure that patient got appropriate therapy.

V. Velanovich (Tampa, FL):

My question has to do with clinical decision-making. When you see those survival curves, it's striking that it goes from the most invasive to the least invasive. And were the choices over their survival course more to do with the patient's other comorbidities, and that's why they were chosen rather than the actual treatments, because it seems to me if you are not going to survive an esophagectomy, you are more likely going to die sooner whether you had this larger tumor smaller tumor.

Response From T.R. Semenkovich:

I agree, and that's definitely a limitation of the database. There is likely treatment selection bias, and the Kaplan-Meier curve shows unadjusted survival, so that's going to represent a lot of those factors that you are talking about, that make somebody who got the chemoradiation probably a less fit overall person who is less likely to survive compared to somebody who is getting an esophagectomy. However, there are also higher risks, like tumor features that make it a little more likely for a patient to get an esophagectomy. And we adjusted for those things on our Cox proportional hazards modeling and found for the overall cohort that there was a reduction in mortality hazard with the most invasive therapy. So I think we can say that there are certainly limitations in the selection.

V. Velanovich (Tampa, FL)

Basically you have to decide whether it's cancer-related death or comorbidity-related death.

S. Demeester (Portland, OR)

I think it is important that we recognize that in 2019, we cannot lump all T1 tumors together. As you pointed out, and the literature confirms, there are big differences between T1a and T1b. The risk of lymph node metastases is very much related to depth of invasion and the presence of risk factors like lymphovascular invasion and so forth, so we really need to hone in on T1a versus T1b. And that brings up the question, in the past, we were not paying that much attention to depth of invasion, mucosa versus submucosa,

T1 was T1. So how carefully do you think the pathologist looked at these to confirm they were actually T1a lesions? You had a surprisingly high rate of lymph node metastases for T1a tumors. Most of us believe this should be <2%. In addition, the only patients that had lymph nodes dissected had an esophagectomy, so why did they have an esophagectomy? How accurate was the pathology to really show that this was a T1a tumor back 15, 20 years ago when nobody cared that much about mucosal versus submucosal disease? In other words, how reliable are these data?

Response From T.R. Semenkovich:

That's definitely a limitation of the database as well, that we do not have that granular data. But one of the purposes of our study was not necessarily to make specific recommendations. There are guidelines that specify what should be done based on depth of invasion, and those have been evolving, but we wanted to look at what is actually being done for patients and how are they doing based on the treatment that's received, and I think that your question also highlights the value of the subgroup analysis for 5 years of data to look at the difference between T1a and T1b tumors.

L.E. Ferri (Montreal):

What you have shown with the National Cancer Database with all of its flaws and lack of granularity, what is being done? You mentioned a little earlier what is more important to us is what should be done in these scenarios.

So really comparing chemo rad patients with endoscopic therapy, we know those are 2 different areas. People can barely tolerate a haircut, let alone an endoscopic resection. So what should be done is really based on some data that might be in the database. I am not sure. And I would personally like to see this mentioned a little bit more about histologic features of the tumor and cells. What are the grades? What are the histology and the subtype, the depth of vascular invasion? Those are things that help us determine whether or not the patient should undergo laparoscopic resection.

My first question is whether or not you looked at those particular pathological features.

My second question is looking particularly at the endoscopic therapies. Endoscopic therapies are sort of like a catch phrase, ESD, BMR, and even have ablative therapies, T1a and some T1b lesions. So could you tell me what endoscopic therapies were used?

Finally, can you tell me the number of endoscopic therapies that failed and not going on to resection? That should be in the database. If you are able to capture those endoscopic therapies on their own, you should be able to find endoscopic therapies and a procedure afterwards.

Response From T.R. Semenkovich:

To first answer your question about the endoscopic therapies that were used, we basically were able to categorize them as either destructive, so ablative therapies, or some type of resection. There was not specific detail as to whether it was endoscopic mucosal resection or whether there was a submucosal dissection procedure performed. That data are not in the database yet in terms of how the endoscopic therapies are categorized. So really we can just say was it resection with pathologic examination or was the tumor

destroyed? So that were the data that we had presented, but remains a limitation especially as more advanced therapies become available and the utilization of them increases.

L. Ferri (Montreal, QC):

Do you have data on the pathological features such as vascular invasion, grade, and depth of invasion, FN1 and FN2, and the subtype squamous adenoma?

And finally, the last question, whether or not you can look at failure of endoscopic therapies that preceded esophagectomy.

Response From T.R. Semenkovich:

We did examine a number of the features. We looked at pathology, grade, and we looked at tumor size. We did not include lymphovascular invasion. It is missing for a very large number of patients within the database.

L. Ferri (Montreal):

That is what most of us in the room would determine is whether we do endoscopic resection or do esophagectomy without the LVI because that is probably the biggest predictor. The article that Gail and I did demonstrate it is probably the biggest predictor of lymph node metastases.

Response From T.R. Semenkovich:

I think that is an important point but not information that we were able to include reliably in this study. Then the database captures endoscopic therapy if it is performed as a definitive surgery but not if it is used as either staging or diagnostic procedure wherein the patient was then referred to esophagectomy or as a failed therapy that there has been a subsequent operation for. Basically, the database captures what was the definitive surgical treatment for the patient, and so I think those are very important points and, also, kind of highlight the value of this as a hypothesis generating study of looking at additional areas of care for these patients. Further study might improve both the processes that they go through as well as the outcomes that they experience.

D.E. Wood (Seattle, WA):

I have 2 brief questions. The first is, in your subset analysis of just the last 4 years of this study, do you think there is adequate power to detect the expected differences between esophagectomy and endoscopic therapy?

Response From T.R. Semenkovich:

For the patients that were in the subgroup analysis, there are much smaller groups of patients than in the overall cohort. It was 12,000 patients versus roughly 2000 that were T1a and a thousand or so that were T1b and then there was follow-up information that was missing for a subset for the T1b patients as well.

We might be lacking statistical power to detect a true difference. There certainly was a trend toward the benefit of esophagectomy versus endoscopic therapy. I think that is reflected in a lot of the guidelines for patients that have deeper invasion. Surgical

treatment is preferred if patients are operative candidates. Again, the purpose of our study was not to tell people what to do or to make those guidelines, but rather to look at the subgroups of patients, what is happening to them and how are they doing, kind of confirming the treatment that is recommended.

D.E. Wood (Seattle, WA):

You anticipated my second question; I am going to put you now on the NCCN Esophageal Gastric Guideline Panel. Given your study, would you change anything in the guidelines in terms of recommendations about optimal therapy?

Response From T.R. Semenkovich:

For the NCCN guidelines, I think they are fairly comprehensive in terms of representing the options that are available to patients, and specifying for the T1a and T1b subgroups, which is appropriately preferred. For the T1a subgroup, what's recommended is endoscopic mucosal resection, or esophagectomy as an alternative for larger tumors to ensure complete resection may be achieved.

For the T1b subgroup, the recommendation is to treat patients with esophagectomy if they are candidates, or chemoradiation if they are not, or endoscopic mucosal resection for patients that have a more superficial T1b tumor and are high-risk surgical candidates. For patients with deeper invasion who are not surgical candidates, endoscopic mucosal resection is an option versus chemoradiation which is often palliative.

D.E. Wood (Seattle, WA):

So nothing would change?

Response From T.R. Semenkovich:

I think looking at how patients have done, those recommendations are reasonable. The goal would be to improve the number of patients that actually got a valid treatment modality.

FIGURE 1.
Patient selection diagram.

FIGURE 2.

Trends in treatment modality usage for clinical T1N0 esophageal cancer.

FIGURE 3.

Overall survival of clinical T1N0 esophageal cancer patients by treatment group. (A) Entire cohort, (B) T1a subgroup, (C) T1b subgroup.

TABLE 1.

Patient and Tumor Characteristics by Treatment Group

	No Treatment N = 2473 (20.0%)	Chemotherapy and/or Radiation 3103 (25.1%)	Endoscopic Treatment 2957 (23.9%)	Esophagectomy 3850 (31.3%)	P
Demographics					
Age, y (mean $\pm$ SD)	72.7 $\pm$ 12.2	71.8 $\pm$ 11.2	69.7 $\pm$ 10.7	64.0 $\pm$ 9.8	<0.001
Sex (% male)	1773 (71.7%)	2240 (72.2%)	2386 (80.7%)	3123 (81.1%)	<0.001
Race (% White)	2113 (85.4%)	2549 (82.2%)	2743 (92.8%)	3584 (93.1%)	<0.001
Insurance Status (% private)	529 (21.4%)	600 (19.3%)	852 (28.8%)	1634 (42.4%)	<0.001
Education (% lowest quartile)	441 (17.8%)	577 (18.6%)	310 (10.5%)	501 (13.0%)	<0.001
Income (% <\$38,000)	464 (19.1%)	677 (22.5%)	390 (13.4%)	568 (15.0%)	<0.001
Population (% >250,000)	1779 (75.0%)	2151 (72.8%)	2056 (72.1%)	2587 (70.2%)	<0.001
Treatment center type (% academic)	815 (33.0%)	898 (28.9%)	2074 (70.1%)	2251 (58.5%)	<0.001
Charlson Deyo Score: 0	1671 (67.6%)	2208 (71.2%)	2224 (75.2%)	2704 (70.2%)	<0.001
1	516 (20.9%)	606 (19.5%)	534 (18.1%)	919 (23.9%)	
2	286 (11.6%)	289 (9.3%)	199 (6.7%)	227 (5.9%)	
Year: 2004–2009	1171 (47.4%)	1745 (56.2%)	1025 (34.7%)	1926 (50.0%)	<0.001
2010–2014	1302 (52.7%)	1358 (43.8%)	1932 (65.3%)	1924 (50.0%)	
Tumor Characteristics					
Tumor size: <1 cm	127 (5.1%)	82 (2.6%)	641 (21.7%)	721 (18.7%)	<0.001
1–<2cm	141 (5.7%)	203 (6.5%)	456 (15.4%)	785 (20.4%)	
2–<3 cm	155 (6.3%)	242 (7.8%)	182 (6.2%)	590 (15.3%)	
3–<4 cm	135 (5.5%)	278 (9.0%)	86 (2.9%)	371 (9.6%)	
4– <5 cm	103 (4.2%)	232 (7.5%)	32 (1.1%)	201 (5.2%)	
5 cm	288 (11.7%)	484 (15.6%)	53 (1.8%)	290 (7.5%)	
Missing	1524 (61.6%)	1582 (51.0%)	1507 (51.0%)	892 (23.2%)	
Histology: Squamous	872 (35.9%)	1432 (46.8%)	459 (15.6%)	632 (16.5%)	<0.001
Adenocarcinoma	1555 (64.1%)	1620 (53.2%)	2476 (84.4%)	3192 (83.5%)	
Grade: 1	191 (7.7%)	172 (5.5%)	382 (12.9%)	537 (14.0%)	<0.001
2	707 (28.6%)	1112 (35.8%)	842 (28.5%)	1574 (40.9%)	
3	709 (29.7%)	976 (31.5%)	394 (13.3%)	1075 (27.9%)	

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

	No Treatment	Chemotherapy and/or Radiation	Endoscopic Treatment	Esophagectomy	P
	N = 2473 (20.0%)	3103 (25.1%)	2957 (23.9%)	3850 (31.3%)	
4	14 (0.6%)	23 (0.7%)	18 (0.6%)	46 (1.2%)	
X	852 (34.5%)	820 (26.4%)	1321 (44.7%)	618 (16.1%)	

TABLE 2.
Univariable and Multivariable Analyses of Variables Associated With Endoscopic Treatment vs Esophagectomy—Overall Cohort

	Univariable		Multivariable	
	OR (95% CI)	P	OR (95% CI)	P
Age, y (mean ± SD)	1.06 (1.05–1.06)	<0.001	1.06 (1.05–1.07)	<0.001
Sex: female vs male	1.03 (0.91–1.16)	0.7		
Race: non-white vs white	1.05 (0.87–1.27)	0.6		
Insurance status: private vs non-private	0.55 (0.50–0.61)	<0.001		
Education: lowest quartile vs remainder	0.78 (0.67–0.91)	0.001		
Income: <\$38k vs >\$38k	0.87 (0.76–1.00)	0.05		
Population: <250k vs >250k	0.91 (0.82–1.02)	0.09		
Treatment center type: academic vs nonacademic	1.67 (1.51–1.85)	<0.001	1.54 (1.32–1.80)	<0.001
Charlson Deyo Score:		<0.001		<0.001
1 vs 0	0.71 (0.63–0.80)		0.69 (0.58–0.83)	
2 vs 0	1.07 (0.87–1.30)		1.09 (0.81–1.45)	
Year of diagnosis:		<0.001		<0.001
	(Reference)		(Reference)	
2005	0.96 (0.69–1.33)		1.09 (0.58–2.07)	
2006	0.89 (0.64–1.25)		1.16 (0.62–2.16)	
2007	1.16 (0.85–1.57)		1.68 (0.94–3.00)	
2008	1.29 (0.96–1.72)		2.31 (1.34–3.99)	
2009	1.42 (1.07–1.88)		2.91 (1.71–4.96)	
2010	1.72 (1.30–2.28)		3.35 (1.97–5.68)	
2011	1.89 (1.42–2.51)		3.50 (2.06–5.95)	
2012	2.20 (1.66–2.93)		4.50 (2.66–7.63)	
2013	2.56 (1.93–3.39)		6.30 (3.74–10.63)	
2014	2.94 (2.21–3.92)		8.19 (4.83–13.87)	
Tumor size:		<0.001		<0.001
<1 cm	(Reference)		(Reference)	
1–<2 cm	0.65 (0.56–0.76)		0.74 (0.62–0.89)	
2–<3 cm	0.35 (0.29–0.42)		0.41 (0.33–0.51)	

	Univariable			Multivariable		
	OR (95% CI)	P		OR (95% CI)	P	
Grade: Histology: squamous vs adenocarcinoma	3–<4 cm	0.26 (0.20–0.34)		0.31 (0.23–0.41)		
	4 cm to <5 cm	0.18 (0.12–0.26)		0.24 (0.16–0.36)		
	5 cm	0.21 (0.15–0.28)		0.25 (0.18–0.35)		
	2 vs 1	0.94 (0.82–1.07)	0.3	0.78 (0.63–0.96)		<0.001
	3 vs 1	0.75 (0.64–0.88)		0.52 (0.41–0.66)		
	4 vs 1	0.52 (0.43–0.61)		0.75 (0.37–1.49)		
	X vs 1	0.55 (0.31–0.96)		3.37 (2.65–4.28)		
		3.01 (2.56–3.53)				

OR indicates odds ratio.

TABLE 3.

Cox Proportional Hazards Model for T1N0 Cohort

Variable	HR (95% CI)	P
Treatment:		<0.001
Endoscopic therapy	(Reference)	
None	3.57 (3.11–4.09)	
Chemoradiation	1.79 (1.56–2.04)	
Esophagectomy	0.85 (0.75–0.96)	
Age, per year	1.02 (1.02–1.03)	<0.001
Race: non-white vs white	0.85 (0.75–0.96)	0.007
Insurance status: nonprivate vs private	1.18 (1.07–1.30)	<0.001
Income: <\$38k vs >\$38k	1.17 (1.06–1.28)	0.005
Treatment center type: academic vs nonacademic	0.83 (0.77–0.89)	<0.001
Charlson Deyo Score:		<0.001
1 vs 0	1.24 (1.14–1.35)	
2 vs 0	1.47 (1.30–1.67)	
Tumor size:		<0.001
< 1 cm	(Reference)	
1–<2cm	1.37 (1.20–1.57)	
2–<3 cm	1.65 (1.44–1.90)	
3–<4cm	2.17 (1.89–2.51)	
4–<5 cm	2.34 (2.00–2.74)	
5 cm	2.57 (2.24–2.94)	
Histology: squamous cell vs adenocarcinoma	1.18 (1.08–1.28)	<0.001
Grade:		<0.001
1	(Reference)	
2	1.25 (1.09–1.44)	
3	1.71 (1.48–1.97)	
4	1.26 (0.81–1.97)	
X	1.15 (0.99–1.33)	

TABLE 4.

Trends in Treatment Modality by Year for T1a and T1b Disease

Year	No Treatment	Chemoradiation	Endoscopic Treatment	Esophagectomy
T1a				
2010	102 (21.9%)	64 (13.7%)	199 (42.7%)	101 (21.7%)
2011	97 (21.1%)	74 (16.1%)	197 (42.8%)	92 (20.0%)
2012	104 (20.5%)	91 (17.9%)	223 (43.9%)	90 (17.7%)
2013	119 (22.8%)	66 (12.7%)	254 (48.8%)	82 (15.7%)
2014	111 (22.5%)	70 (14.2%)	250 (50.6%)	63 (12.8%)
<i>P</i>	0.6	0.6	0.002	<0.001
T1b				
2010	27 (12.3%)	42 (19.2%)	37 (16.9%)	113 (51.6%)
2011	19 (8.3%)	39 (17.0%)	50 (21.7%)	122 (53.0%)
2012	22 (9.7%)	39 (17.1%)	54 (23.7%)	113 (49.6%)
2013	16 (7.0%)	35 (15.2%)	58 (25.2%)	121 (52.6%)
2014	22 (9.2%)	38 (15.9%)	60 (25.1%)	119 (49.8%)
<i>P</i>	0.3	0.3	0.03	0.7