
Surgical Resection for Locoregional Esophageal Cancer Is Underutilized in the United States

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- BACKGROUND:** Although esophagectomy provides the highest probability of cure in patients with esophageal cancer, many candidates are never referred for surgery. We hypothesized that esophagectomy for esophageal cancer is underused, and we assessed the prevalence of resection in national, state, and local cancer data registries.
- STUDY DESIGN:** Clinical stage, surgical and nonsurgical treatments, age, and race of patients with cancer of the esophagus were identified from the Surveillance, Epidemiology and End Results (SEER) registry (1988 to 2004), the Healthcare Association of NY State registry (HANYS 2007), and a single referral center (2000 to 2007). SEER identified a total of 25,306 patients with esophageal cancer (average age 65.0 years, male-to-female ratio 3:1). HANYS identified 1,012 cases of esophageal cancer (average age 67 years, M:F ratio 3:1); stage was not available from NY State registry data. A single referral center identified 385 patients (48 per year; average age 67 years, M:F 3:1). For SEER data, logistic regression was used to examine determinants of esophageal resection; variables tested included age, race, and gender.
- RESULTS:** Surgical exploration was performed in 29% of the total and only 44.2% of potentially resectable patients. Esophageal resection was performed in 44% of estimated cancer patients in NY State. By comparison, 64% of patients at a specialized referral center underwent surgical exploration, 96% of whom had resection. SEER resection rates for esophageal cancer did not change between 1988 and 2004. Males were more likely to receive operative treatment. Nonwhites were less likely to undergo surgery than whites (odds ratio 0.45, $p < 0.001$).
- CONCLUSIONS:** Surgical therapy for locoregional esophageal cancer is likely underused. Racial variations in esophagectomy are significant. Referral to specialized centers may result in an increase in patients considered for surgical therapy. (J Am Coll Surg 2010;211:754–761. © 2010 by the American College of Surgeons)
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The incidence of esophageal carcinoma has been rising steadily during the past 3 decades, and there is no indication that this trend is slowing.¹ This is largely due to increasing numbers of adenocarcinoma cases, which are now 600% higher than in the 1970s. In fact, the absolute num-

ber of these cancers is even higher if adenocarcinoma of the cardia, often erroneously classified as arising in the stomach, is included.² Given these epidemiologic trends, providing the optimal treatment in each and every patient is a clear and desirable goal.

There is little debate that in the majority of patients with local and locoregional esophageal carcinoma, surgical resection provides the best chance for cure or prolonged survival and as such, is the mainstay of therapy. This is particularly true for adenocarcinoma, although current National Comprehensive Cancer Network (NCCN) Guidelines leave open the possibility of primary chemoradiation therapy.³ Recent evidence suggests that the use of neoadjuvant chemotherapy with or without radiation therapy may provide a small but real added survival benefit.^{4,5} Although it is commonly reported that more than half of patients with esophageal cancer initially present with systemic disease,

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Abbreviations and Acronyms

HANYS = Healthcare Association of New York State
 SEER = Surveillance, Epidemiology and End Results
 URMC = University of Rochester Medical Center

data from the American Cancer Society indicate that at least 55%, and possibly as many as 70%, have locoregional and potentially resectable disease.⁶ Historically, the success of surgical therapy has been clouded by relatively high perioperative mortality, ranging from 8% to 10%, and a morbidity ranging from 50% to 60%.⁷⁻⁹ These surgical outcomes coupled with reports of 25% or less 5-year survival may have created a therapeutic nihilism regarding the benefit of surgical resection.¹⁰ The potentially erroneous impression that a relatively low overall survival is not worth the risk of perioperative morbidity and mortality associated with esophagectomy likely persists today, despite significant advances in surgical outcomes over the last 10 years. In many centers, perioperative mortality has decreased to 0.5% to 4%, and 5-year survival has proved to be as high as 40% to 50% for resectable disease.⁷ The aim of this study was to assess esophageal resection rates in national, state, and local cancer data registries and to identify sociodemographic and clinicopathologic variables associated with the failure to pursue surgical intervention.

METHODS

Data source and selection of study population

The study population included 3 independent data sources: the national Surveillance Epidemiology and End Results (SEER) database, the Healthcare Association of New York State (HANYS) database, and the local University of Rochester Medical Center (URMC) clinical database.

Surveillance Epidemiology and End Results (SEER) database

On the national level, cases were selected from the SEER registry, a database that currently covers more than 25% of the US population and collects information on all incident cancer cases in selected areas of the US. From this database, all cases of primary esophageal and cardia tumors that were diagnosed between 1988 and 2004 were identified using tumor site codes 150.0 and 151.0. From these patients, we then narrowed the focus to cases that were not diagnosed at autopsy or from death certificate data ($n = 20,950$). We then identified all patients with SEER historic stage A in situ, local, and regional esophageal cancer; patients classified with SEER historic stage "distant" disease were excluded. The final study cohort comprised 13,771 patients with SEER historic stage A in situ, local, and regional

esophageal cancer. Information about surgical therapy, age at diagnosis, gender, race, tumor histology, and survival was obtained from SEER. Race was dichotomized into white or nonwhite.

Healthcare Association of New York database

The Healthcare Association of New York State estimates the annual incidence of esophageal cancer in New York State to be 1,012 cases (734 males, 278 females). The study population consisted of 1,519 individual admissions defined via an administrative dataset for the year 2007. Data for the state study population was obtained from the Healthcare Association of New York State (HANYS), which maintains a Statewide Planning and Research Cooperative System (SPARCS) database containing relevant information including patient characteristics, diagnosis and treatments, services provided, charges for each hospital discharge, and the number of elective or emergent hospital admissions in New York State. Established in 1979, HANYS requires all New York State hospitals to submit admission and discharge data elements in the form of diagnosis-related groups (DRG) and International Classification of Disease, Ninth revision, Clinical Modification (ICD-9-CM) codes. The study population was initially identified using ICD-9-CM (vol.1, 2) codes 150.0 (cancer of the esophagus) and 151.0 (cancer of the gastric cardia) and procedural ICD-9 codes 42.4, 42.5, 42.42, and 42.51 to 42.69. Study variables included age, gender, type of admission (elective or nonelective), and operative intervention. Admissions not associated with an operative code were classified as admissions without surgical intervention. Information about disease stage was not available from this database. The primary outcome was the rate of surgical resection of the esophagus in a single year.

University of Rochester Medical Center (URMC) esophageal cancer data

The local study population consisted of 385 patients identified from the cancer registry of the Wilmot Cancer Center at URMC, surgical departmental clinical records, and by querying billing records for patients treated at our institution for the diagnosis of carcinoma of the esophagus or cardia between January 2000 and December 2007. All patients who underwent surgical, medical, or palliative therapy for esophageal carcinoma were included; patients who underwent esophagectomy for Barrett's esophagus with high grade dysplasia were excluded from the study. Study variables included age, gender, pathologic or clinical stage, surgical procedure, tumor type, chemotherapy or radiation therapy, and time from operation to death or to the date of last follow-up. Patient ZIP codes were used to identify counties where treated patients resided. For information regarding survival, we queried our medical records and the

Social Security Death Index database (<http://ssdi.rootsweb.ancestry.com/>). Survival was calculated as the number in months from the time of the operation for esophagectomy patients, or the time from diagnosis for all others, until death or January 28, 2009. The primary outcomes measure was the rate of surgical therapy of patients with potentially resectable disease treated at the University of Rochester Medical Center URMC between January 2000 and December 2007.

All patients in the URMC cohort underwent preoperative staging including chest, abdomen, and pelvis CT. PET evaluation was added in 2004; endoscopic ultrasound was not routinely used. Patients with distant organ metastases were excluded from surgical resection, as were those with extensive nodal disease outside of the area of resection (paratracheal and or infraceliac aortic). The study received approval of the Research Subjects Review Board of URMC.

Statistics

We estimated the prevalence with 95% confidence intervals of the overall rate of surgery among patients with esophageal cancer as well as resection rates by stage at diagnosis. Univariate analysis was performed to determine the relationship between predictor variables (age, gender, race, and marital status) and primary outcome (surgical therapy). Logistic regression was used to identify significant independent predictors of the lack of surgical intervention. Rates of surgery according to the year of diagnosis were compared for temporal trends in the patterns of treatment of esophageal cancer patients. The method of Kaplan-Meier was used to assess overall survival of patients with and without surgical treatment. Survival was compared by log-rank analysis. Logistic regression was used to test the association between New York State admissions and resection rate. All analyses were conducted using SAS 9.1 (SAS Institute Inc).

RESULTS

Prevalence of resection in national, state, and local populations

Patient characteristics in each population and the prevalence of surgical treatment are shown in Tables 1 and 2. There were 20,950 patients with esophageal cancer who were entered into SEER data between 1988 and 2004. Of these, 13,771 (65.7%) were classified as having locoregional esophageal cancer that was considered potentially resectable. Surgical exploration was performed in 35.8% of the total (7,496 of 20,950) and 44% of those with locoregional disease (6,093 of 13,771). New York statewide resection rates were estimated by dividing the 2007 incidence of esophageal cancer in NY State (1,012) by the number of

Table 1. Patient Characteristics in National, State, and Local Population

Characteristics	SEER	HANYS	URMC
n	20,950	1,012	385
Locoregional disease, n	13,771	n/a	277
Age	67	68	66
Male:female ratio	3.08	2.7	3.09
White, %	80	70	n/a
Adenocarcinoma, %	49	n/a	75.5
Age >80 y, %	13.3	15	9

HANYS, Healthcare Association of New York State; SEER, Surveillance, Epidemiology and End Results; URMC, University of Rochester Medical Center.

hospital admissions with the diagnosis of cancer of the esophagus (1,005) or cardia (514) in which either esophagectomy (288), total, or partial gastrectomy (140) was performed. This analysis resulted in an overall surgical resection rate of 42% (428 of 1,012), remarkably similar to that in the SEER data, despite the potential for comorbidity and stage discrepancies between the groups. The relative numbers of admissions to resection for each of the 100 highest volume NY state hospitals is shown in Figure 1. As can be seen, hospitals with more than 32 admissions had the highest resection rates. Twenty hospitals admitted more than 50% of all patients. Five percent (9 of 167) of all hospitals performed 13 resections or more. Thirty-one percent (52 of 167) of all NYS hospitals did not perform a single esophageal resection in 2007. Thirty-three percent of patients with surgically resected esophageal cancer were operated on in hospitals performing less than 13 resections per year.

For comparison with national and state statistics, the treatment of all 385 patients with esophageal or cardia cancer seen at the URMC between January 2000 and December 2007 (Fig. 2) was reviewed. Patients with the diagnosis of Barrett's esophagus with high-grade dysplasia were excluded. Of these, 72% (277) had locoregional disease. Although the populations may not be strictly comparable, surgical therapy was performed on 64% of the total (246 of 385) and 88% of those with preoperative locoregional disease (246 of 277), both nearly twice the rate reported in national and state data. Nine (3.7%) of the 246 patients treated surgically had unresectable disease at the time of surgical exploration. Table 3 shows the rate of surgical therapy relative to the extent of disease in national and local populations. Analysis of the prevalence of surgical treatment by histology revealed that patients with adenocarcinoma were more likely (56% SEER, 94% URMC) than those with squamous cell cancer (32% SEER, 76% URMC) to undergo surgical intervention.

Table 2. Estimated Prevalence of Surgical Resection in National, State, and Local Populations

Variable	National (SEER)	State (SPARCS)	Local (URMC)
n	20,950	1,012	385
Local or locoregional disease, n	13,771	n/a	277
Surgical intervention, n	6,093 (explorations)	428 (resections)	246 (resections)
% of surgical intervention	44	42	88

SEER, Surveillance, Epidemiology, and End Results; SPARCS, Statewide Planning and Research Cooperative System; URMC, University of Rochester Medical Center

Patients with locoregional disease not undergoing surgery

Characteristics of patients classified as having local or regional disease who did not undergo resection were assessed in both the SEER and URMC data. Table 4 shows the results of univariate logistic regression of the factors associated with no surgery in the SEER patients with locoregional disease. Patients older than 65 years, particularly those greater than 80 years, women, and nonwhite race were associated with decreased odds for operative therapy. Table 5 compares the reasons patients did not undergo surgical therapy as recorded in the dataset. The majority of the SEER patients (38%) were classified as “not recommended,” 4% as contraindicated, and 2% due to patient refusal. Of the URMC patients, 11% (31 of 277) patients with locoregional disease did not undergo surgical therapy due to comorbidities in 17, and/or refusal of surgical resection in 8 (for 6 it was unknown). Twenty-eight percent (108 of 385) of patients were judged to have advanced disease, 54% (n = 58) underwent chemotherapy, radiation therapy or both; and 46% (n = 50) received best supportive care (Fig. 2).

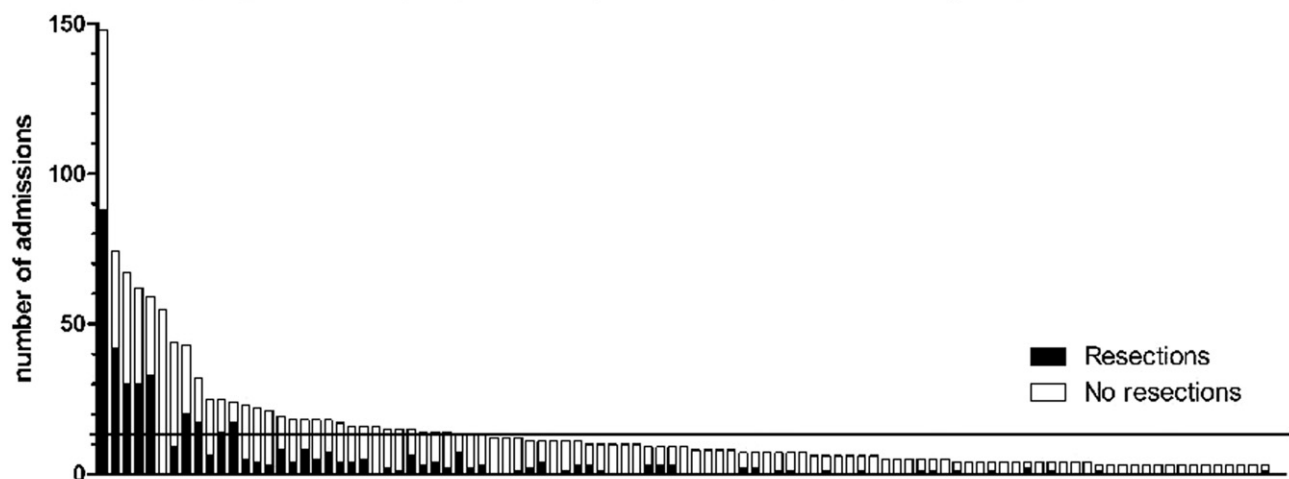
Survival

SEER patients with locoregional disease who received surgical therapy had significantly longer median and 5-year survivals than those receiving no operative treatment for locoregional disease (Fig. 3). Figure 4 compares overall survival of patients with preoperative locoregional disease between SEER and URMC populations. Figure 5 shows survival of all URMC patients who underwent resection; perioperative 30-day mortality in this group was 3%. Predicted 5-year overall survival for URMC patients was 39% in esophagectomy patients and 25% in all patients with esophageal or cardia cancer. Median survival was 30 months in surgically resected patients and 16.7 months for all patients.

DISCUSSION

These data suggest that despite the available evidence and National Cancer Center Network guidelines, surgical treatment of esophageal cancer is underused in the United States and in the state of New York. According to the SEER dataset, more than half of patients with resectable esopha-

Number of admissions and ratio of resections in NYS hospitals*



*Patients were admitted in 167 hospitals, top 100 is displayed

Figure 1. Histogram of esophageal cancer admissions and resections in hospitals in New York State (NYS). Line annotates 13 admissions/year. Patients were admitted in 167 hospitals; top 100 are displayed.

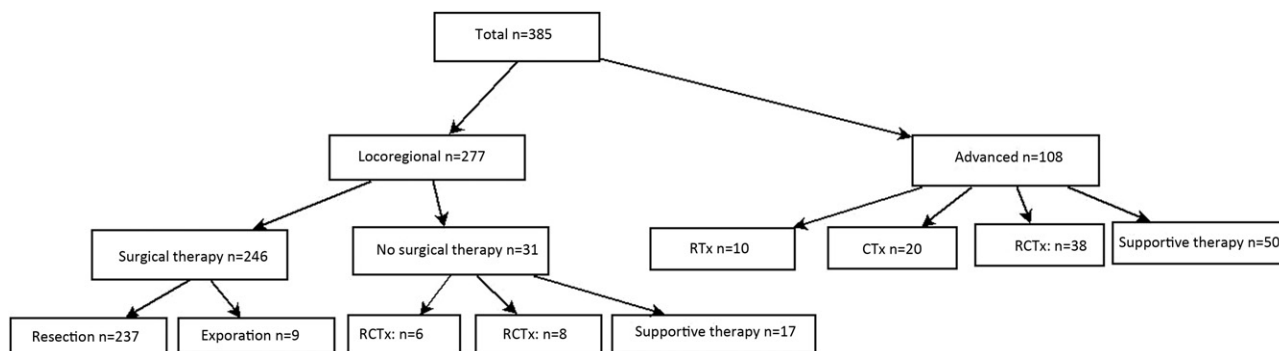


Figure 2. Flowchart of treatment of esophageal cancer patients 2000 to 2007 at the University of Rochester Medical Center. CTx, chemotherapy; RCTx, radiation and chemotherapy; RTx, radiation therapy.

geal cancer did not undergo surgical therapy between 1988 and 2004. Further, the rate of resection did not change over time. Data limited to New York State support this finding of underuse, with an estimated 42% of patients with esophageal or cardia cancer undergoing surgical resection in 2007. (This rate, however, maybe overestimated because we do not know whether ICD-9 code 151, cancer of the cardia, is administratively included with cancer of the stomach or the esophagus). In contrast to the state and national data, 68% of patients seen at our tertiary referral center underwent surgical intervention, with approximately 10% of these judged to have unresectable disease at the time of operation. The aim of the analysis was to consider those surgically resectable as a group, so we did not separate local from regional disease. It seems unlikely that the large differences noted are due to disproportionate stage prevalence, particularly given the large numbers of patients. When taken as a whole, the prevalence of locoregional (oncologically operable) disease was indeed similar (65.7% vs 71.9%).

With continued improvements in surgical therapy and postoperative care, as well as adjuvant chemotherapy and radiation, we anticipate that an even larger number of patients may meet criteria for resection, emphasizing the importance of multidisciplinary care regardless of the extent of disease. The centralization of complex surgical procedures is well established in selected European centers. Reported resection rates at these centers is compatible with

Table 3. Prevalence of Surgical Intervention by Extent of Disease; URM (n = 277) and SEER data (n = 13,771)

Extent of disease	SEER, % of total	URMC, % of total
In situ	67.7	87.9
Localized	40.0	88.7
Regional	47.0	89.3
Total	44.0	88.0

SEER, Surveillance, Epidemiology and End Results; URM, University of Rochester Medical Center.

those seen at our local tertiary referral center.¹¹⁻¹⁴ Although the nearly 2-fold difference between local versus national and state surgical intervention rates could arguably be due to a marked referral bias, it seems unlikely for several reasons. First, the difference is large. Second, analysis of the estimated annual incidence of esophageal cancer in the 7 counties surrounding URM (57 cases per year) reveals that the vast majority (72%, n = 330) of this population sought their care at our institution during the 8-year period (2000 to 2007). This would suggest that the majority of patients are being captured in an unbiased fashion. Also important may be the fact that 90% of the patients treated at URM for esophageal cancer within the last 8 years received consultation from a surgeon specializing in the treatment of esophageal cancer. Treatment algorithms in the URM cohort included surgical resection in all patients in whom an R0 resection was feasible; ie, those without prohibitive preoperative surgical risk and the absence of distant organ metastases or paratracheal or infraceliac nodal metastases on PET/CT. Neoadjuvant chemotherapy

Table 4. Multivariate Analysis of Factors Associated with Not Undergoing Surgery in SEER Patients with Locoregional Disease

Variable	p Value	Odds ratio	95% CI
Age, y			
<65		1	
65-80	0.0049	0.75	0.335-3.433
>80	0.0006	0.44	0.121-2.43
Gender			
Male		1	
Female	0.0040	0.74	0.185-2.732
Race			
White		1	
Nonwhite	0.0003	0.45	0.121-2.43
Marital status			
Married		1	
Nonmarried	0.8760	0.90	

Table 5. Reasons for No Surgical Treatment in SEER (n = 7,678) and URM (n = 31) Populations with Potentially Resectable Esophageal Cancer

Reason	SEER		URM	
	n	%	n	%
Not recommended	5,255	83.1	0	0
Contraindicated	544	3.9	17	6.1
Unknown	1,545	11.2	6	2.0
Patient refused	334	2.4	8	2.9

SEER, Surveillance, Epidemiology, and End Results; URM, University of Rochester Medical Center.

consisting of epirubicin, cisplatin, and 5FU/Xeloda (Roche) and/or chemoradiotherapy (5FU, cisplatin/ 42 to 45Gy) was used with increasing frequency beginning in 2004 and would be the current standard in the absence of prohibitive comorbidity.

Similar findings were reported by Paulson and colleagues¹⁰ using the SEER-Medicare linked database (patients older than 65 years). They reported that 34.1% of patients with locoregional esophageal cancer underwent surgical intervention between 1997 and 2002. Linking SEER data with Medicare files has the advantage of providing detailed information about comorbidities and other oncologic treatments, but it is limited to patients older than 65 years.

These data raise the question of why surgical treatment may be underused. There are likely several driving forces, including misinformation of ideal treatment options, physician bias in patients with advanced age or comorbidities, lack of specialty expertise in those caring for the patient, hospital and physician volume, and legitimate treatment

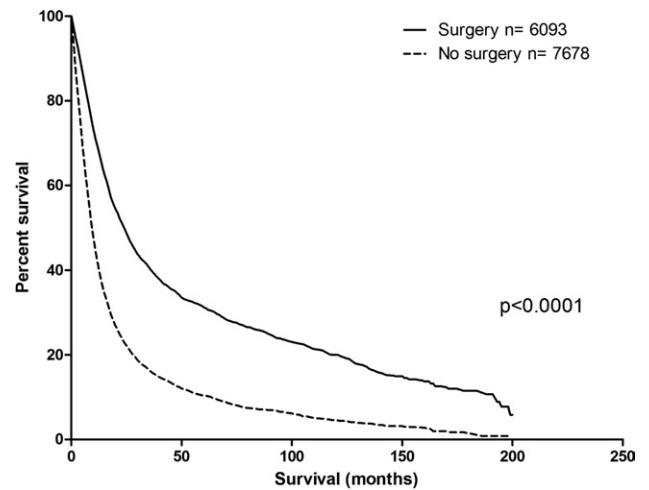


Figure 3. Comparison of survival of Surveillance, Epidemiology and End Results (SEER) patients with locoregional disease with and without surgical therapy.

controversies.¹⁵ Although controversy exists regarding the indication of esophagectomy in patients with advanced age (older than 80 years), most recent studies report morbidity and mortality comparable to that in younger patients.¹⁶⁻¹⁸ SEER data suggest that acceptable 30-day and long-term mortality can be achieved. Hospital and physician volume have been reported to be associated with morbidity, mortality, long-term survival, and indeed, treatment decisions. Numerous studies suggest that patients with esophageal cancer should be referred to regional high-volume centers with a dedicated multidisciplinary team that includes well-trained surgeons, oncologists, anesthesiologists, intensivists, and others familiar with complex therapy. Although not universally accepted,¹⁹ volume-based referral initiatives for complex surgical procedures such as esophagectomy

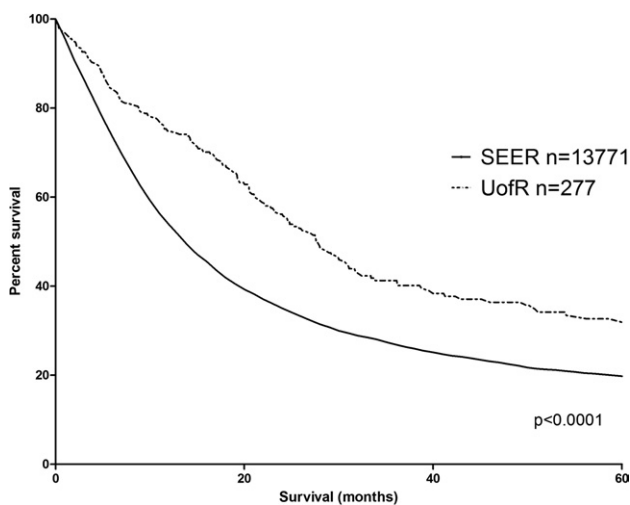


Figure 4. Comparison of the survival curves of Surveillance, Epidemiology and End Results (SEER) and University of Rochester Medical Center (U of R) population with locoregional cancer.

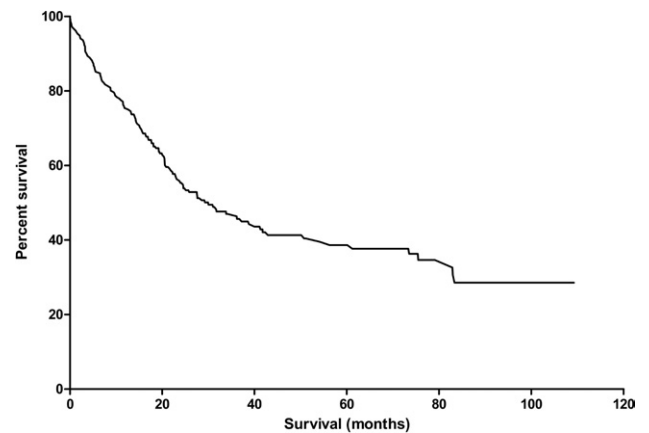


Figure 5. Survival of esophagectomy patients (all stages excluding high-grade dysplasia) at the University of Rochester Medical Center, 2000 to 2007.

have been advocated by health care organizations such as the Leapfrog group. The revised Leapfrog criteria in 2003 recommended that esophagectomy be performed at centers with at least 13 cases annually.²⁰ Other possible reasons for underuse of surgical resection include nihilism on the part of physicians or patients, physician biases based on outdated surgical data, and differences in access to care. In our study, a significant number of patients refused surgery, which could be partly due to physician bias. At URM, 2% refused surgical therapy.

Previous population-based studies report resection rates between 21% and 40%,²¹⁻²³ with single institutions between 55% and 80%.^{7,24,25} Interestingly, the resection rates for locoregional squamous cell carcinoma of the esophagus were lower in both SEER and URM data. This correlates with previously published single institutional experiences from the US and Germany.^{25,26}

Our study has several limitations. First, there is the possibility of misclassification of tumor stage when using administrative data. Second, SEER has sparse information detailing true contraindications, including comorbidities, which may distort the findings, given that high risk patients with resectable disease but limited operability do not contribute to underuse. SEER data report that 4% of potentially resectable patients had a contraindication to esophageal surgery. The previously mentioned study by Paulson and colleagues¹⁰ analyzing a significantly older SEER-Medicare population, showed that less than 15% of all patients not having surgery had serious comorbidities. In the cohort of patients treated at our medical center, 6.5% of patients had severe comorbidities that precluded them from surgical resection. On the other hand, SEER data have been well validated for studying cancer surgery outcomes and have been used in numerous such studies.^{27,28} We selected the datasets to be as comprehensive as possible and recognize that the time periods chosen may inadvertently bias the findings. Comparison of national, state, and institutional databases including various time periods has obvious limitations, as stated above, but the difference between the use of surgical therapy in the respective databases is unlikely to be explained by the difference in histology over time alone. Given our study criteria, the data may not include some patients who underwent partial or total gastrectomy as treatment for cancer of the gastroesophageal junction. Although the SEER database can be queried for the type of operative treatment, we believed that including gastrectomy as the primary resection criteria would add more bias than it resolved.

The institutional setting (academic vs nonacademic), volume (high vs low), and process such as the use of tumor boards may also affect the prevalence of resection. URM

data reflect that of a high volume academic institution with multidisciplinary discussion and treatment. New York State data are estimates. The Statewide Planning and Research Cooperative System (SPARCS) database is limited to hospital admissions. Although it is safe to assume that every esophagectomy patient has to be hospitalized, we do not know how many patients who did not have esophagectomy were admitted to NY State hospitals, or how many were treated in an outpatient setting. Moreover, some NY State patients may have sought their care outside of NY State and others from out of state may have been treated in NY State hospitals.

In conclusion, surgical therapy is likely underused in the treatment of resectable esophageal cancer in the United States. Patients and their physicians should be aware of current outcomes data when discussing treatment options, and efforts should be made to identify the primary reasons why ideal treatment may not be advocated. The ultimate goal of the best possible treatment for each patient should be vigorously pursued.

Author Contributions

Study conception and design: Dubecz, Sepesi, Peters, Wisnivesky, Salvador

Acquisition of data: Sepesi, Dubecz, Wisnivesky, Litle, Polomsky

Analysis and interpretation of data: Peters, Dubecz, Wisnivesky, Sepesi, Watson

Drafting of manuscript: Dubecz, Peters, Raymond, Litle, Jones, Watson, Sepesi

Critical revision: Peters, Raymond, Litle, Jones, Watson, Polomsky

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