Endoscopic Ultrasound and Impact on Survival in Rectal Cancer Patients: a SEER-Medicare study

By

Steven McNamara

A Thesis Presented to
The Department of Public Health and Preventative Medicine
at the Oregon Health & Science University
School of Medicine in partial fulfillment of the requirement for the degree
of Master of Public Health
October 29, 2010

Department of Public Health and Preventive Medicine

School of Medicine

Oregon Health & Science University

CERTIFICATE OF APPROVAL

This is to certify that the Master's thesis of

Steven McNamara

has been approved

Thesis Chair – Atif Zaman, MD, MPH

Thesis Advisor – Tomi Mori, PhD

Thesis Advisor – Sarah Rodriguez, MD

Table of Contents

List of Tables

List of Figures

Acknowledgments

There are so many people to thank for making this project become reality. I would like to thank my thesis committee members, Dr. Atif Zaman, Dr. Tomi Mori, and Dr. Sarah Rodriguez for all their support, guidance, and time on this project.
Dr. Zaman's willingness to chair my committee despite his busy schedule exemplifies his student-orientated qualities that students seek in professors. Dr. Sarah Rodriguez always was there to provide expert help, answer questions, and offer suggestions for research variables. She has been both a friend and a great mentor. And, I would like to thank Dr. Tomi Mori. She was always open to me stopping by her office for statistical help and support.

Finally, I would like to extend my greatest accolades to Dr. Domi Le. It was over a year ago, Domi pitched an idea, which culminated in this thesis, to me over coffee. Throughout all the false starts and frustrations, she has toiled with me over every step and setback. Since she was unable to be a part of the committee, I wanted her to know that I am grateful to her for bringing me into this project.
Everyone, thank you for all your support.

Abstract

Background: Endoscopic ultrasound (EUS) is the most accurate imaging modality used in the staging of rectal cancer, but its impact on clinical outcomes of patients with rectal cancer remains unclear. The aim of this study was to evaluate the receipt of EUS and its association with overall survival in a cohort of patients with rectal cancer.

Methods: All patients over the age of 65 who were diagnosed with rectal cancer between January 1997 and December 2003 in the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database were identified, with follow-up data through 2006, and demographic, cancer-specific, and EUS procedural information were extracted. The primary goal of this analysis was to examine whether patients who received EUS evaluations experienced differences in survival rates than patients who did not receive EUS. Additionally, adjusted Hazard Ratios (HR) were estimated using Cox proportional hazards regression, to examine rectal cancer specific survival among EUS and non-EUS groups. A secondary analysis was performed to examine the factors that influenced receipt of EUS. A multivariate logistic regression model was fit to examine the association, adjusting for demographic and clinical characteristics.

Results: A Total of 6,294 patients with adenocarcinoma of the rectum were identified from the SEER-Medicare linked database that fulfilled the inclusion and exclusion criteria. Their median age was 76 years (IQR 71-82 years), 3121 (49.6%) were men, and 5598 (88.9%) were white. The stages of rectal cancer diagnoses were local (58.2%) and regional (41.8%).

Overall, 801 of 6,294 (12.7%) patients underwent EUS for evaluation and staging of rectal cancer. Patients without comorbidities were no more likely than patients with

comorbidity scores ≥ 1 to receive EUS (13.6% vs. 11.9% p=0.05). Curative surgery, chemotherapy and radiation therapy were also performed more frequently in the patients who underwent EUS. Receipt of EUS was associated with a reduced risk of death (adjusted relative ratio, 0.68; 95% CI, 0.59-0.77; $p < 0.001$). Additionally, in the multivariate model, age older than 75 years, late tumor stage, and a comorbidity score > 0 were significant predictors of poor survival.

Conclusions: After adjusting for patient factors and clinical characteristics, receipt of EUS is associated with improved survival in rectal cancer patients compared to non-receipt of EUS. The improved benefit is likely a marker of access to stage-appropriate management such as neo-adjuvant therapy and surgical resection.

Research Question and Specific Aims

Title: Endoscopic Ultrasound and Impact on Survival in Rectal Cancer Patients: a SEER-Medicare study

Research question: For patients who have been diagnosed with rectal adenocarcinoma, does the use of endoscopic ultrasound vary among patients and does its use impact overall survival?

Study Aims: Using the 2007 release of Surveillance, Epidemiology, and End Results (SEER) - Medicare database, we accomplished the following study objectives:

1. Examine the data and restrict the original sample based upon predetermined exclusion criteria, and weight comorbid conditions using the Charlson-Deyo-Romano MACRO provided by SEER.
2. Using the Kaplan-Meier estimates, and a multivariate Cox proportional hazards model, assess rectal cancer survival benefit between those who did receive EUS and those who did not, controlling for:
    a) Total weighted comorbid index.
    b) Surgery, chemotherapy, and radiotherapy.
    c) Other socio-demographic factors such as race, gender, and stage of cancer.
3. Use multiple logistic regression to build a predictive model of factors influencing a patients receipt of EUS, controlling for:
    a) Total weighted comorbid index.
    b) Regional differences and income.
    c) Other socio-demographic factors such as race, gender, and stage of cancer.

Background

The Burden of Rectal Cancer

Rectal cancer is a form of colorectal cancer (CRC) among men and women, affecting an estimated 40,000 Americans per year.[1] Colorectal cancer is the second most common cause of cancer death in the United States and one third of all colorectal cancers occur in the rectum. An estimated 39,670 new cases of rectal cancer will be diagnosed in 2010.[2]

Briefly, rectal cancer occurs when cancerous cells develop in the tissue of the rectum (anatomically: the rectum is the last portion of the large intestine and leads to the anus). Though rectal cancer occurs less frequently than colon cancer, it seems to share a similar geographic distribution.[3] Overall the lifetime risk of developing CRC is about 1 in 19 (5.2%), with the risk being slightly higher for men than women.[2] Approximately 95% of colorectal cancers are found as adenocarcinomas.[1] These types of cancers start in cells that line the gastrointestinal (GI) tract and make mucus to lubricate the inside of the colon and rectum. The tumors are usually small and are mainly discovered incidentally during routine sigmoidoscopy. The majority of rectal tumors are localized at diagnosis (75-85%), with distant metastases at diagnosis being uncommon.[4]

Rectal cancer is considered to be an under-diagnosed condition because it often lacks early symptoms. This delay can alter the prognosis of a treatable condition if it is identified early. Though the exact causes of rectal cancer are unknown, certain risk factors have been identified that may increase a person's lifetime risk of developing the disease (these include age, bowel disease, diet and exercise, smoking, alcohol consumption, genetic factors, and certain ethnic backgrounds). Current treatment for

rectal cancer includes surgery, radiation therapy, chemotherapy, or a combination of these modalities.

Standard treatment for rectal cancer consists of surgery for resectable lesions; in addition, pre-operative chemo-radiation has been shown to reduce local recurrence rates in patients with advanced loco-regional disease. Improved survival has been described among patients with resectable rectal cancer who received high-dose pre-operative radiotherapy.[5,6] Current guidelines recommend neo-adjuvant chemo-radiation for patients with advanced loco-regional rectal cancer (T3, T4 N0, or Tx N1 N2).[7] Tumor stage of rectal cancer at time of clinical presentation ultimately guides management and prognosis.

Five-year Survival by Stage

As previously mentioned, the management of treatment modalities are dictated by tumor stage and response to therapy.[8] The observed 5-year survival rate for patients with rectal cancer by stage is shown in Table 1.

Table 1 – Cancer Survival by Stage

Stage at Diagnosis	5-year survival (percent) for patients diagnosed between 1999-2006[a].
Localized	88
Regional	67.1
Distant	12.3
Unstaged	47.1

[a] Based on the SEER 17 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana and New Jersey). California excluding SF/SJM/LA, Kentucky, Louisiana, and New Jersey contribute cases for diagnosis years 2000-2006. The remaining 13 SEER Areas contribute cases for the entire period 1999-2006. Based on follow-up of patients into 2007.

Endoscopic Ultrasound

Endoscopic Ultrasound (EUS) is an imaging modality that was first reported 30 years ago by DiMagno *et al*.[9] EUS is a procedure performed by gastroenterologists in which an endoscope fitted with an ultrasound-capable tip is passed into the gastrointestinal tract. The ultrasound is then used to assess various problems in the esophagus, stomach, small intestine, or rectum. Lesions can originate in the lining of the GI tract (for example, gastric cancer) or may originate outside of the GI tract (e.g., large lymph nodes or liver lesions). EUS is used for a variety of indications including assessment and diagnosis of submucosal tumors (tumors underneath the gastrointestinal lining), diagnosis of malignancy in patients with suspected cancer but in whom cross-sectional imaging such as CT scan is negative, biliary indications such as assessment of common bile duct stones, and for therapeutic indications such as drainage of pancreatic pseudocysts or celiac plexus block for pain control. EUS can be performed with blind, rigid, or flexible endoscopes. Endo-rectal imaging is primarily performed using flexible endoscopes. Though rigid scopes are less expensive than flexible echoendoscopes, they do not have the spectrum of capabilities (i.e. imaging of the upper intestinal tract). Typically, in EUS staging, overstaging (more advanced tumor at the time of diagnosis) occurs more frequently than under-staging. This problem is primarily due to the inability of EUS to differentiate inflammation surrounding the malignancy from the tumor itself.[10,11] The accuracy of N-staging by EUS has been found to range between 73-83% when compared to pathological findings.[12,13,14]

The literature establishes the superiority of EUS in pre-operative accurate staging to that using CT and MRI, both are methods traditionally used to stage rectal tumors.

Compared to computed tomography (CT), EUS has been found to be equal or superior for T and N staging.[15,16] Magnetic Resonance imaging (MRI) using endorectal surface coils shows similar findings, but does not surpass EUS in accuracy.[17,18] Additionally, MRI is more expensive than EUS and lacks wide availability. It should be noted, that the accuracy of both tumor staging and nodal staging is dependent on the experience of the endosonographer.[8]

Prior studies also support EUS's staging accuracy and cost-effectiveness in the management of rectal cancer.[19] A 2004 study of 60 consecutive patients with rectal cancer found EUS had more accuracy than CT scanning for staging local tumors, and EUS changed management of 38% of patients.[20] It is currently hypothesized the ability of function of EUS is to identify patients who would benefit most from neo-adjuvant therapy may impart a positive, though indirect, impact on survival. One study has reported a recurrence-free survival advantage of EUS use in patients at a single tertiary care center.[21] However, to date, no large study has evaluated whether more accurate staging offered by EUS actually leads to improved overall survival in patients with rectal cancer. There is also scant data on the impact of EUS on survival in cancer patients in general. One study attempted to address this question in esophageal cancer patients utilizing the SEER-Medicare database and found that only 10.7% of patients had an EUS. Those who did, were more likely to undergo esophageal resection and more likely to have received other modalities of therapy such as chemotherapy. Additionally, receipt of EUS was associated with reduced risk of death, with a hazard ratio of 0.59 (95% CI: 0.52-0.68).[22]

A recent meta-analysis found EUS is accurate for staging rectal cancers, with EUS sensitivity being higher for advanced disease than for early disease. These findings lead the authors to recommend EUS be considered as the preferred test for providing tumor staging in rectal cancer patients.[23] Although EUS, as a diagnostic procedure, cannot directly improve survival, it may still have an impact on survival through other mechanisms such as improved local staging of tumors leading to more patients receiving preoperative chemoradiotherapy. It may also simply be a marker of access to more specialized care, or care in a more specialized center which might then be linked to improved surgical outcomes.

Our hypothesis is that the receipt of EUS is associated with improved survival in rectal cancer patients, likely related to accurate pre-operative staging, and thereby facilitating stage-appropriate treatment. This study assessed the association of receiving EUS and overall survival in a large cohort of patients with rectal cancer from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database.

Methods

IRB Approval

Our study was approved by the Oregon Health & Science University Institutional Review Board. Patient data was already de-identified prior to receipt from the National Cancer Institute and the requirement for consent was waived.

Overview of the SEER-Medicare database

For our population-based observational study, we used the existing large database named SEER-Medicare. The Surveillance, Epidemiology and End Results Program (SEER) database compiles data on cancer diagnoses, outcomes, and cancer characteristics from population-based registries.[1] During 1994-1999, the SEER areas comprised the metropolitan areas of San Francisco/Oakland, Detroit, Atlanta, Seattle, Los Angeles, Rural Georgia, San Jose-Monterey, Connecticut, Iowa, New Mexico, Utah, and Hawaii. In 2000, the States of Kentucky, Louisiana, New Jersey, and Greater California were added to the registry. The database collects patient level information about cancer site, stage, histology, treatment information, and survival. Importantly, SEER data has been validated for its accuracy and coverage of cancer patients in the registry.[28] The SEER-Medicare database links SEER data with Medicare files from the same patients. Ninety-three percent of persons age 65 and older were matched to the Medicare enrollment file. This linking allows investigators to have additional information such as comorbidity, health services utilization, and procedures.

SEER data that is released as part of the SEER-Medicare project is in a customized file known as the Patient Entitlement and Diagnosis Summary File (PEDSF).

The PEDSF contains one record per individual in the SEER database with matching records in the Medicare files. Medicare is a federally funded social insurance program that provides health insurance to nearly 97% of individuals in the United States 65 years and older. Nearly all of Medicare participants have Part A, which covers inpatient hospital stays, skilled nursing facility services, and some home-stay nursing. To receive payment, hospitals submit medical claims coding up to ten diagnoses and ten procedures using the International Classification of Diseases 9th Revision, Clinical Modifications (ICD-9-CM) classification. A majority (96%) of participants enrolled in Part A choose to pay for additional coverage in Part B, which covers inpatient and outpatient services. SEER-Medicare claims are recorded in two sources: (1) the Outpatient Standard Analytic file (SAF), which documents outpatient hospital procedures, and (2) the National Claims History (NCH) files, which document physician and supplier procedure claims. Medicare documents date of death based on information provided by the Social Security Administration.

The linked database is jointly owned by the National Cancer Institute (SEER) and Centers for Medicare and Medicaid Services (Medicare component of SEER-Medicare) and is managed by the programming contractor Information Management Services, Inc. The data in this proposal included patients from SEER through 2003 and their Medicare claims through 2004. SEER follow-up was until December 31, 2006.

Cohort Eligibility Criteria

We used the following inclusion/exclusion criteria to identify our study cohort:

1) Patients with the SEER registry rectal cancer site recode ICD-O-3 (26) as their first reported cancer and no subsequent tumors were included;
2) Patients diagnosed between 1997 and 2003 were included;
3) Patients 65 years and older at the time of diagnosis were included;
4) Patients with local or regional stage disease were included;
5) Subjects with missing demographic information (sex, age, race, stage, and grade) were excluded;
6) Patients who Medicare eligible by End-Stage Renal Disease or disability were excluded;
7) Patients whom were not enrolled in Medicare Part B, or those enrolled in a Health Maintenance Organization, were excluded because they may have received cancer directed therapy not documented by Medicare.
8) Patients who received a cancer diagnoses on the date of death or by autopsy were excluded.
9) Patients with histologically diagnosed adenocarcinoma (Histology codes: 8050,8140-8147, 8160-8162,8180-8221, 8250-8507,8520-8551,8560, 8570-8574,8576,8940-8941) were included;
10) Patients that lacked comorbidity information were excluded;

Study Variables

Endoscopic Ultrasound

Claims for the Outpatient Standard Analytic Files (SAF) and NCH files one month before and three months after diagnosis were reviewed, and patient claims with procedure codes for EUS (Endo-Anal ultrasound [CPT-4 76872] or EUS-radiological interpretation [CPT-4 76975]) were identified in the Medicare NCH Carrier and Outpatient files.

Pelvic MRI

The use of magnetic-resonance imaging (MRI) is another method used to stage cancers of the rectum. We hypothesized those patients who did not receive EUS might have received a Pelvic MRI instead. Receipt of Pelvic MRI with and without contrast agent [CPT-4 72195, 72196, 72197] was also identified.

Tumor Grade

Microscopically determined cell differentiation at diagnosis is described as grade 1 (well-differentiated), grade 2 (moderately well-differentiated), grade 3 (poorly differentiated), and grade 4 (undifferentiated or anaplastic tumors). Tumor grade was categorized into Well-/Moderately differentiated and Poorly-/Undifferentiated. This information was obtained from the SEER PEDSF.

Staging of Rectal Cancer

Cancer staging was computed from the SEER historic stage variable in the PEDSF file. This variable is assigned by SEER after all clinical and pathologic documentation of the extent of disease (EOD) is examined. SEER historic staging is determined from information on the size of tumor, the extent of tumor invasion, and lymph node involvement according to the American Joint Committee on Cancer and the International Union Against Cancer, 6^{th} edition. SEER has defined localized stage as an invasive neoplasm confined entirely to the rectum. Regional stage is defined as a neoplasm that has extended either beyond the rectum or into regional lymph nodes. Distal stage is defined as a neoplasm that had spread to parts of the body remote from the primary tumor. Cancers that have been unstaged lack sufficient information (these cases were excluded from our study population).

Curative Surgery

The SEER database provides information on cancer directed surgery received by patients. This variable originally had nine categories: surgery performed, surgery not recommended, surgery not recommended due to other conditions, surgery not performed because patient died prior to surgery, surgery was recommended but not performed due to unknown reasons, surgery recommended but patient refused surgery, and an unknown category (this included death certificate of autopsy information as the source of the information). This analysis eliminated patients with unknown information and patients were partitioned into two categories: subject received curative surgery or they did not receive surgery.

Patient socio-demographic variables

Patient socio-demographic variables included age, gender, race, median household income at the census tract based on the 2000 census (if the value was missing, it was imputed from the corresponding zip code median household income), metropolitan county residence status (yes versus no), SEER region residence location, and marital status at the time of cancer diagnosis (married versus unmarried). Race was reclassified into White (Race Recode 1 or 11) or Other. This information was obtained from the SEER PEDSF file.

Comorbidity Identification

Since the SEER database does not contain information on comorbid conditions that may affect treatment and therapy decisions, we searched the Medicare claims for conditions that may have such effects. The Charlson comorbidity index with modifications that reflect the Deyo and Romano adaptations was used to calculate a comorbidity score for each patient. Claims were searched for International Classification of Diseases-ninth revision-Clinical Modification (ICD-9-CM) comorbidity codes for the 12 months preceding the month before diagnosis and assigned patients the maximal comorbidity observed: Myocardial infarction (ICD-9-CM 410-410.9, 412), Congestive heart failure (ICD-9-CM 428-428.9), peripheral vascular disease (ICD-9 441-441.9), COPD (ICD-9-CM 490-496, 500-505, 506.4), cerebrovascular disease (ICD-9-CM 430-437.9), dementia (ICD-9-CM 290-290.9), paralysis (ICD-9-CM 342-342.9), Diabetes (ICD-9-CM 250-250.3, 250.7), diabetes with squelae (ICD-9-CM 250.4-250.6, 250.8-

250.9), chronic renal failure (ICD-9-CM 582-582.9, 583-583.9, 588-588.9), various cirrhodites (ICD-9-CM 571.2, 571.4x, 571.5, 571.6), moderate-severe liver disease (ICD-9-CM 572.2-572.8, 456.0-456.1, 456.2-456.21), ulcers (ICD-9-CM 531.0-531.7, 532.0-532.7, 533.0-533.7, 534.0-534.7, 531, 531.9, 532, 532.9, 533, 533.9, 534, 534.9), rheumatoid (ICD-9-CM 714.82, 725, 710.0, 710.1, 710.4, 714.0-714.2), AIDS (ICD-9-CM 042-044.9)

The weighted comorbid conditions are listed in table 2; subjects with conditions not in the list were given a comorbidity score of 0. This measures the effect of weighted comorbid conditions on receipt of EUS and survival.

Table 2 – Weighted Index of Comorbidity

Assigned weights for diseases	Conditions
1	Myocardial Infarct Congestive Heart Failure Peripheral Vascular disease Cerebrovascular disease Chronic Pulmonary Disease Dementia Diabetes Various Cirrhodites Ulcers Rheum
2	Paralysis Diabetes with Sequelae Chronic Renal Failure
3	Moderate-Severe Liver Disease
6	AIDS

*Adapted from SEER-Medicare SAS MACRO

Chemotherapy and Radiation

Chemotherapy and Radiation treatment was identified from Medicare procedure and revenue center claims up to 12 months post-diagnosis. Inpatients or Outpatient claims (ICD-9-CM 99.25), CPT-4 (96400-96549), physician or outpatient claim codes (J9000-J9999, Q0083-Q0085), revenue center codes (0331 (chemo injected), 0332 (oral chemo), 0335 (chemo IV), and follow-up after chemo (ICD-9-CM V58.0, V66.2, V67.2). Radiation treatment was identified using ICD-9 codes V58.0, V66.1, V67.1; ICD-9 procedure codes 92.21-92.29; revenue center codes 0330, 0333; HCPCS/CPT-4 codes (77401-77499, 77520, 77523, 77750-77799, G0256, G0261).

Survival period

Survival time was measured in days after primary diagnosis of rectal cancer to death or the SEER follow-up period. Survival time from the date of diagnosis was calculated from the SEER database using date of death or last follow-up. For those who are known to be alive at the end of the follow-up period, the date of December 31, 2006 was used as the date to last contact to calculate their survival time. Since SEER calculates survival times by months so survival specific survival rates could be determined.

Table 3 – Summary of Study Variables

Variable	Variable Type	Description
Endoscopic Ultrasound	Outcome/Covariate	0 = Did not receive EUS 1= Received EUS
Gender	Covariate/Potential confounder	
Marital Status	Covariate/Potential confounder	Married = 1 Unmarried (Single, Divorced, Separated, Widowed) = 0
Race	Covariate/Potential confounder	White =1 Other (African-American, Asian, Native American, Hispanic) = 0
Income	Covariate/Potential confounder	< 30000 ($) 30001-60000 ($) >60001 ($)
Comorbidity Score	Covariate/Potential confounder	Numerical value based on score dictated by SEER-Medicare Macro
Cancer Stage	Covariate/Potential confounder	Described previously in methods: 1 = Local 2= Regional 3= Distal
Survival time after diagnosis	Covariate/Potential confounder	Survival time in days
Patient Residence	Covariate/Potential confounder	Metropolitan > 250,000 Non-Metropolitan < 249,000
SEER region	Covariate/Potential confounder	Described previously in the methods. Geographic location condensed into respective
Curative Surgery	Covariate/Potential confounder	1 = Surgery received 0= Surgery not received
Chemotherapy	Covariate/Potential confounder	1 = Chemotherapy received 0= Chemotherapy not received
Radiotherapy	Covariate/Potential confounder	1 = Radiotherapy receive 0= Radiotherapy not received

Statistical Analysis

Analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC) statistical software.

Descriptive Analysis

Frequencies for each categorical variable of interest were calculated. Differences between the proportions were determined using the χ^2 statistic.

Univariate Regression

Logistic regression was used to analyze factors associated with EUS utilization. The Wald F statistics and their associated p values were used to determine statistical significance. All variables with a p-value of 0.10 or lower were considered a variable of interest for model building. Variables that were possible confounders such as patient location or race were also considered during the model building phase, regardless of their significance level.

Multiple Regression

After assessing the univariate logistic regression results, multiple regression analysis was performed to evaluate associations. Using a backward-stepwise approach, all variables were first entered into the model. The independent variables were removed singularly removed until all remaining variables were significant ($p < 0.05$). After the stepwise process was completed, confounding variables were added back into the model. If coefficients changed by more than 10% after the addition of the variable, then the

variable was considered a confounder. The Homer and Lemeshow goodness-of-fit statistic was used to assess the fit of the final models.

Survival Analysis

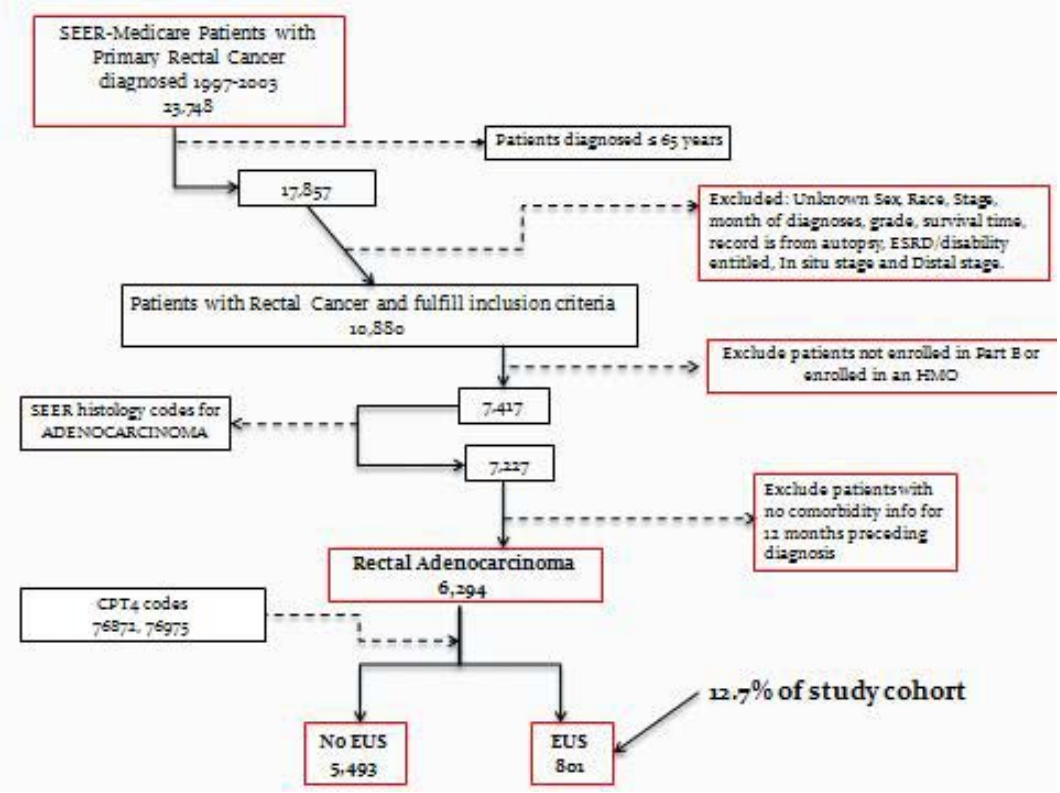
Survival time was measured in months after cancer diagnosis to the date of death or end of the SEER follow-up period. Univariate survival analysis was calculated using the Kaplan-Meier method to estimate mean survival time, and the log-rank test was used to test differences in overall survival between two groups (e.g., EUS vs. no EUS).

We also performed a multivariate analysis using Cox proportional hazards regression to study the association of EUS receipt and survival, adjusting for known confounders of age, race, gender, tumor stage, and comorbidity index. The Cox regression is a semi-parametric method for time-to-event outcomes that can evaluate the independent effects of chosen variables while controlling for potential confounders.[24] Independent variables considered for the multivariate model were assessed using the backwards stepwise approach described previously.

Results

Initially, 23,748 subjects were provided by SEER in the Medicare linked data that had a primary rectal cancer diagnosis from 1997-2003. Figure 1 shows the application of the restriction criteria and the number of subjects eliminated from the original sample. Individuals that were below the age of 65 were excluded (N = 5,891). We excluded 7,307 subjects with missing socio-demographic information, had cancer in situ/distal diagnosis, or had information abstracted from an autopsy or death certificate. Next, subjects who were not enrolled in Medicare Part B were excluded (N = 3,133). Subjects who did not receive a histologic diagnosis of adenocarcinoma (N = 190) were excluded. Finally, patients that lacked comorbidity information were excluded (N = 933). The number of subjects excluded from the initial sample was 17,454 which left a total of 6,294 subjects for analysis.

Figure 1 – Description of dataset inclusion/exclusion procedure



Demographic Characteristics

The demographic and clinical characteristics of the study population are summarized in table 4. A total of 6,294 patients with adenocarcinoma cancer of the rectum were identified from the SEER-Medicare linked database that fulfilled the inclusion and exclusion criteria. The distribution of stages was: Local (58.2%) and Regional (41.8%). Overall, 801 (12.7%) underwent EUS for evaluation and tumor staging.

The median age was 76 years (IQR, 71-82 years); 3121 (49.6%) were men; 5598 (88.9%) were white; 3376 (53.6%) were married at the time of diagnosis. The majority of patients lived in a metropolitan area (89.3%); with 60.7% residing in residence areas with a median income between $30001-60000 (USD). The majority of subjects resided

in SEER regions in the western portions of the US (42.7%); with 19.2% living in the Midwest, 22.7% in the Northeast, and 15.4% living in the South. This is to be expected with the way the SEER catchment areas are designed. A majority of subjects had a comorbidity score of zero (47.4%) or only one (27.4%). Those with scores of 2 (14.0%) were more common than subjects with scores of 3+ (11.2%). Interestingly, subjects were more likely to receive curative surgery (92.4%) than radiation (43.8%) and chemotherapy (40.0%). Additionally, the percentage of the cohort diagnosed each year with rectal cancer increased from 1997 (8.5%) to 2003 (17.8%). This increase reflects the expansion in SEER coverage area that took effect 2001 which added additional geographic areas where EUS is more likely to be available.

Table 4 – Descriptive statistics of study cohort			
Variable	**Category**	**Number of Patients (N = 6,294)**	**Percentage (%)**
SEER Stage	Local	3664	58.2
	Regional	2630	41.8
Tumor Grade	Well-/Moderately differentiated	5342	84.9
	Poorly/Undifferentiated	952	15.1
Comorbidity Index Score	0	2984	47.4
	1	1724	27.4
	2	878	14.0
	3+	708	11.2
Sex	Male	3121	49.6
	Female	3173	50.4
Race	White	5598	88.9
	Other	696	11.1
Marital Status	Married	3376	53.6
	Not Married	2918	46.4
Year of Diagnosis	1997	538	8.5
	1998	574	9.1
	1999	560	8.9
	2000	1171	18.6
	2001	1170	18.5
	2002	1156	18.4
	2003	1125	17.8
Chemotherapy	Received	2518	40.0
	Not Received	3776	60.0
Radiation	Received	2756	43.8
	Not Received	3583	56.2
Combination therapy	Received	2150	34.2
	Not Received	4144	65.8
Surgery	Received	5813	92.4
	Not Received	481	7.6
Income Category	< 30000	854	13.6
	30001-60000	3821	60.7
	> 60001	1619	25.7
Pelvic MRI	Received	98	1.6
	Not Received	6196	98.4
Metro vs. Non-Metro	Metropolitan	5620	89.3
	Non-Metropolitan	674	10.7
SEER region	West	2685	42.7
	Midwest	1647	19.2
	South	970	15.4
	Northeast	1428	22.7

Endoscopic Ultrasound

Demographic and Clinical characteristics are of subjects based on receiving EUS or not receiving EUS are shown in table 5. Due to the large sample size, almost all variables showed a significant difference between subjects who did or did not receive EUS. Median age among subjects who underwent EUS was similar to non-EUS subject (75.2 vs. 76.9 years), but this was statistically significant ($p < 0.001$). Only 801 of 6294 (12.7%) patients had undergone EUS during their initial diagnosis. There was slightly more early stage disease in the EUS group than in the non-EUS group. There were differences in the proportion of patients treated with EUS (group I) and non-EUS (group II) who were treated with chemotherapy (51.1% vs. 38.4%, $p < 0.001$), radiotherapy (61.4% vs. 41.2%; $p < .001$), but no difference between the groups for cancer-directed surgery (92.3% vs. 92.4%; $p = 0.91$)

There were significant variations in use of EUS among SEER registry areas. Patients in both groups were similar in metropolitan residence ($p=0.88$) and in tumor grade ($p=0.98$). The total comorbidity score was similar among groups and patients with a comorbidity score of 0 were no more likely than patients with a score > 0 to undergo EUS (13.6% vs. 11.9%, $p = 0.05$).

Table 5 - Baseline Characteristics of Group I (EUS) and group II (no EUS)			
Variable	Group I (n=801)	Group II (n=5493)	P-Value
Median Age at diagnosis (SE), y	75.2 (0.26)	76.9 (0.09)	<0.001
Cancer Stage by SEER Stage			
Local	499 (62.3%)	3165 (57.6%)	0.01
Regional	302 (37.7%)	1987 (42.4%)	
Tumor Grade:			
Well -/ Moderately differentiated	680 (85.0%)	4662 (84.9%)	0.98
Poorly/Undifferentiated	121 (15.0%)	1068 (15.1%)	
Comorbidity index score:			
0	406 (50.7%)	2578 (46.9%)	0.04
1	220 (27.5%)	1504 (27.4%)	
2	106 (13.2%)	772 (14.1%)	
3+	69 (8.6%)	639 (11.6%)	
Sex: Male	441 (55.1%)	2680 (48.8%)	<0.001
Race: White	728 (90.9%)	4870 (88.7%)	0.06
Marital Status: Married	503 (62.8%)	2873 (52.3%)	<0.001
Cancer-directed Surgery performed	739 (92.3%)	5074 (92.4%)	0.91
Chemotherapy received	409 (51.1%)	2109 (38.4%)	<0.001
Radiotherapy received	492 (61.4%)	2262 (41.2%)	<0.001
Combination Therapy	383 (47.8%)	1767 (32.2%)	<0.001
SEER region			
West	306 (38.2%)	2379 (43.3%)	<0.001
Midwest	162 (20.2%)	1049 (19.1%)	
South	89 (11.1%)	881 (16.0%)	
Northeast	244 (30.5%)	1184 (21.5%)	
Income ($)			
<30000	81 (10.1%)	773 (14.1%)	<0.001
30001-60000	433 (54.1%)	3388 (61.7%)	
>60001	287 (35.8%)	1332 (24.2%)	
MRI performed	22 (2.7%)	76 (1.4%)	0.003
Metropolitan Residence	714 (89.1%)	4906 (89.3%)	0.88

We further stratified the groups by tumor stage (table 6). Patients who received EUS were more likely to receive chemotherapy and radiotherapy than non-EUS patients for both local and regional stages.

Table 6 - Baseline Characteristics of Group I (EUS) and group II (no EUS) by SEER stage			
Variable	**Group I**	**Group II**	**P-Value**
Local Stage	499	3165	
Curative surgery performed	468 (93.7%)	2890 (91.3%)	0.06
Chemotherapy received	181 (36.3%)	745 (23.5%)	<0.001
Radiation received	242 (48.5%)	924 (29.2%)	<0.001
Comorbidity Score = 0	252 (50.5%)	1423 (44.9%)	0.02
Regional Stage	302	2328	
Curative surgery performed	271 (89.7%)	2184 (93.8%)	0.007
Chemotherapy received	228 (75.5%)	1364 (58.6%)	<0.001
Radiation received	250 (82.8%)	1340 (57.6%)	<0.001
Comorbidity Score = 0	154 (51.0%)	1155 (49.6%)	0.65

Logistic Regression

Univariate Regression analysis regarding the receipt of EUS

All independent variables except for metropolitan residence, race, and comorbidity score were significantly associated with receiving EUS ($p < 0.05$). The unadjusted relative odds ratios and p-values are found in table 7. Gender was significantly associated with EUS. Women were less likely to receive EUS than men (OR = 0.78, 95% CI: 0.67-0.90). Additionally, as cancer stage increased the probability of receiving EUS decreased. The opposite was true with incomes. As incomes increased, the probability of receiving EUS increased compared to the referent (< $30,000). Although, not statistically significant, patients with a comorbidity score > 0 had a lower probability of receiving EUS compared to patients with a score of zero (OR=0.86, 95% CI: 0.74-1.00).

Table 7- Unadjusted Odds ratios on the probability of receiving an EUS evaluation			
Variable	OR	95% CI	P-value
SEER stage (Local vs. Regional*)	1.21	1.04-1.41	0.01
Age at Diagnosis (y), ≤75 vs. > 75*	1.47	1.27-1.70	<0.001
Sex (Female vs. Male*)	0.78	0.67-0.90	<0.001
Marital Status (married vs. unmarried*)	1.53	1.32-1.79	<0.001
Income ($) (vs. < 30000*) 30001-60000 >60001	 1.22 2.05	 0.95-1.56 1.58-2.67	<0.001
Race (White vs. Other*)	1.27	0.98-1.64	0.06
Comorbidity index (score =0* vs. score ≥1)	0.86	0.74-1.00	0.05
SEER region (vs. West*) Midwest South Northeast	 1.20 0.78 1.60	 0.97-1.47 0.61-1.00 1.33-1.92	 <0.001
Metropolitan vs. non-Metro	1.02	0.80-1.29	0.88

*Reference category

Multivariate Regression analysis regarding the receipt of EUS

All previously significant variables were considered for the multivariate model. We generated a logistic-regression model to evaluate the effect of stage, age at diagnosis, sex, marital status, income level, race, and Charlson comorbidity score with EUS receipt after controlling for other covariates. Table 8 summarizes the multivariate model. After adjusting for covariates, sex was no longer a significant predictor of receiving EUS (p = 0.18). However, after adjustment, patients who were married at the time of diagnosis were 35% more likely to undergo EUS evaluation than unmarried patients (OR = 1.35, 95% CI: 1.14-1.60). Though income did not become less significant after adjustment, only patients that earned more than $60,001 were more likely to receive EUS compared to the lowest income bracket (OR = 1.62, 95% CI: 1.22-2.15). Patient location was a significant predictor of receiving EUS, though only patients in the Midwest and Northeast were more likely to receive EUS than patients from Western SEER registry

areas (OR = 1.27, 95% CI: 1.03-1.57 and OR = 1.51, 95% CI: 1.25-1.83, respectively). The Hosmer and Lemeshow goodness-of-fit test gives a $\chi^2 = 2.63$ (p = 0.95), which indicates there is no lack of fit to the model.

In summary, the multivariate model determined younger age, being married, earlier staging, high incomes, and residing in the Northeast were significant predictors of undergoing EUS.

Table 8 - Predictors of undergoing EUS evaluations: Multivariate logistic regression model

Variables	Adjusted Odds Ratio	95% CI	P-value
SEER stage (Local vs. Regional*)	1.20	1.03-1.40	0.01
Age at Diagnosis (y), ≤75 vs. > 75*	1.40	1.20-1.64	<0.001
Sex (Female vs. Male*)	0.89	0.76-1.05	0.18
Marital Status (married vs. unmarried*)	1.35	1.14-1.60	<0.001
Income ($) (vs. < 30000*)			
30001-60000	1.04	0.80-1.36	<0.001
>60001	1.62	1.22-2.15	
Race (White vs. Other*)	1.13	0.87-1.47	0.35
Comorbidity index (score =0* vs. score ≥1)	0.89	0.77-1.05	0.16
SEER region (vs. West*)			
Midwest	1.27	1.03-1.57	
South	0.85	0.66-1.10	<0.001
Northeast	1.51	1.25-1.83	

*Reference category

Survival Analysis

Kaplan-Meier

The survival of subjects was assessed. The graph of the log(-log(survival)) versus log of survival graph showed parallel lines (Figure 2), indicating the proportional hazards assumption was satisfied for EUS. The patient specific survival difference among diagnostic groups (Figure 3) was significant (Log-Rank Test, $P < 0.001$). We further sub-divided the survival times to diagnostic groups among the different cancer stages (Appendix A) and all survival differences were significant (Log-Rank Test, $p < 0.05$). The average survival time decreased with increasing cancer stage. Mean survival times among categories are summarized in tables 9 and 10.

Table 9– Rectal cancer survival statistics

Variables		Mean Survival (Months)	Log-Rank Test p-value
EUS	Yes No	71.7 64.2	<0.001

Figure 2 – Proportionality test for EUS

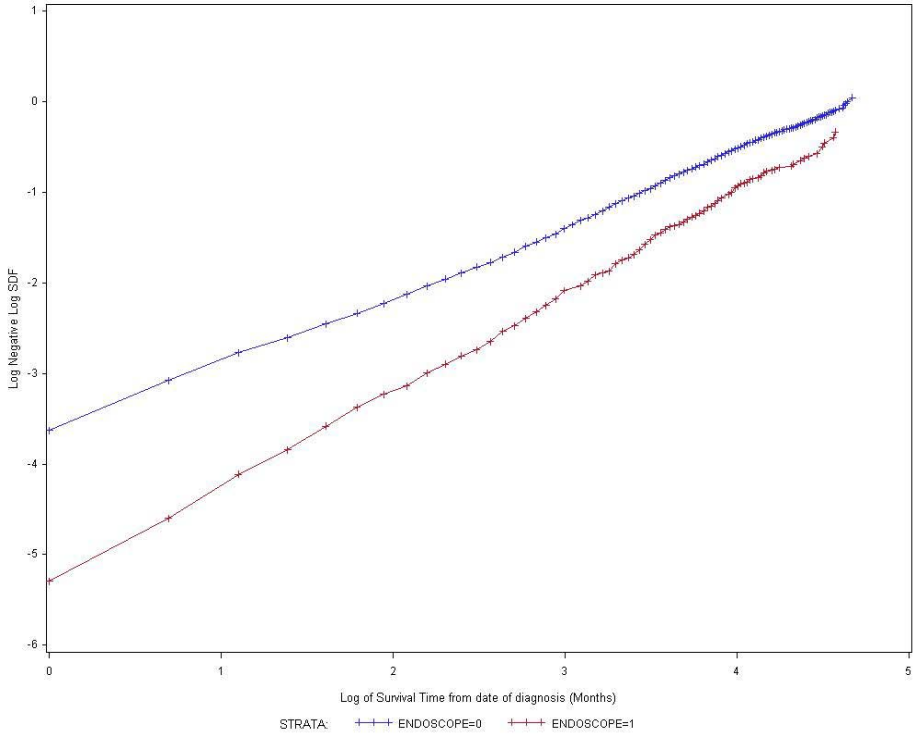


Figure 3 – Rectal cancer survival time among group I and group II

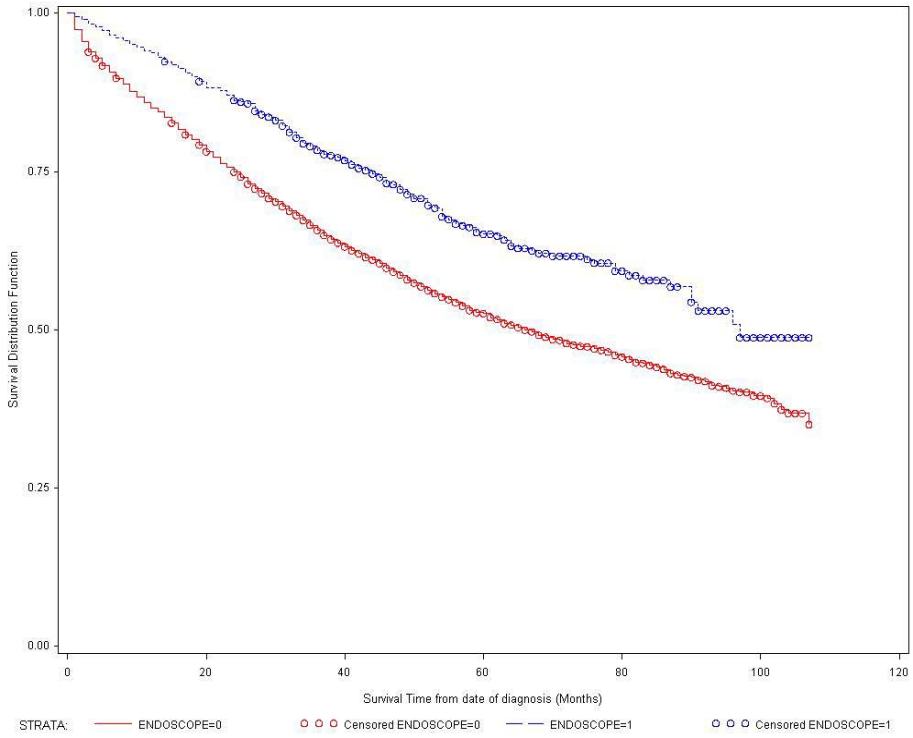


Table 10 – Rectal Cancer survival statistics among stages stratified by SEER Stage				
SEER Stage	**EUS**	Mean Survival (Months)	Percent Censored	Log-Rank Test p-value
Local	Yes No	77.7 71.1	75.2 62.8	<0.001
Regional	Yes No	61.1 54.1	56.9 44.7	< 0.001

Cox-Regression Analysis

In our univariate analysis, both clinical and demographic characteristics (except for race and sex) were associated with survival ($p < 0.001$). Though gender and sex were not significant at the .05 level, they were entered into the multivariate model due to their clinical significance. The univariate survival statistics can be reviewed in table 11.

Older age, high comorbidity scores, and increasing cancer stage at diagnosis were associated with poor survival. Patients who received curative surgery were 75% more likely to experience improved survival compared to patients who did not undergo surgery. A similar benefit was observed for patients who received chemotherapy and radiotherapy as part of their post-diagnosis treatment. Finally, patients who received EUS were 38% less likely to experience mortality than patients who did not receive EUS during their diagnosis period (HR = 0.62, 95% CI: 0.54-0.71).

Table 11- Unadjusted relative hazards and 95% CI of variables in Cox regression model			
Variables	Hazard Ratio	95% CI	p-value
Receipt of EUS, Group I (EUS performed) vs. Group II (no EUS)*	0.62	0.54-0.71	<0.001
SEER stage of rectal cancer Local vs. Regional*	0.56	0.51-0.60	<0.001
Age at Diagnosis (y), ≤ 75 vs. > 75*	0.40	0.37-0.43	<0.001
Chemotherapy (received vs. not received*)	0.82	0.77-0.90	<0.001
Radiation (received vs. not received*)	0.93	0.86-1.00	0.07
Cancer-directed surgery (performed vs. not performed*)	0.31	0.27-0.35	<0.001
Race (White vs. Other*)	0.99	0.88-1.11	0.90
Sex (Female vs. Male*)	0.99	0.92-1.07	0.84
Comorbidity Score (score =0* vs. score ≥1)	1.60	1.18-1.73	<0.001

* Reference Category for Cox regression model

In a multivariate Cox proportional hazards model that adjusted for age at diagnosis, gender, race, chemotherapy, radiotherapy, cancer-direct surgery, comorbidity score, and tumor stage, the association of undergoing EUS and survival was assessed (table 12). Receipt of EUS was associated with a reduced risk of death (relative hazard, 0.68; 95% CI, 0.59-0.77; $p < 0.001$). Additionally, in the multivariate model, age older than 75 years, increasing tumor stage, and a comorbidity score > 0 were significant predictors of poor survival.

Interestingly, women had a slightly better survival compared to men (HR 0.88, 95% CI: 0.82-0.95). And, whites appeared to have better survival than other races in the multivariate model (HR = 0.89, 95% CI: 0.79-1.01), though this was not statistically significant ($p = 0.08$).

Table 12- Adjusted relative hazards and 95% CI of variables in Cox regression model

Variables	Hazard Ratio	95% CI	p-value
Receipt of EUS, Group I (EUS performed) vs. Group II (no EUS)*	0.68	0.59-0.77	<0.001
SEER stage of rectal cancer Local vs. Regional*	0.47	0.43-0.51	<0.001
Age at Diagnosis (y), ≤ 75 vs. > 75*	0.46	0.42-0.50	<0.001
Chemotherapy (received vs. not received*)	0.72	0.65-0.80	<0.001
Radiation (received vs. not received*)	0.97	0.87-1.08	0.61
Cancer-directed surgery (performed vs. not performed*)	0.31	0.27-0.34	<0.001
Race (White vs. Other*)	0.89	0.79-1.01	0.08
Sex (Female vs. Male*)	0.88	0.82-0.95	0.002
Comorbidity Score (score =0* vs. score ≥1)	1.51	1.40-1.64	<0.001

* Reference Category for Cox regression model

Discussion

The literature has established EUS as a superior staging modality over CT and MRI in the evaluation of gastrointestinal malignancies. EUS remains a diagnostic modality, not a therapeutic one, and by itself is unable to confer a direct survival benefit. However, recent studies have attempted to assess patient outcomes related to EUS. The common hypothesis lies in the assumption that better staging through EUS may be able to impart a survival advantage. Shami *et al* studied 60 patients with rectal cancer and found EUS to be more accurate for local staging compared to CT scan; undergoing EUS had changed management in 38% of patients.[20] In a retrospective study of patients with pancreatic cancer, Erickson *et al.* observed that patients whose cancers were diagnosed by EUS had a longer short-term survival than those diagnosed by CT scan although this may be partly explained by a lead-time bias given that EUS can detect tumors at an earlier stage.[25] From the National Cancer Database, multimodality therapy (surgery, radiation therapy, chemotherapy) has been shown to increase over time for localized pancreatic cancers and that this has had a positive impact on survival. More recently, Ngamruengphong *et al* found that EUS was independently associated with improved outcomes in patients with loco-regional pancreatic cancer from the SEER-Medicare database.[26] Das *et al* came to similar conclusions studying patients with esophageal cancer; they also observed that patients undergoing EUS were more likely to undergo esophageal resection and more likely to have received other therapeutic modalities such as chemotherapy.[22] These studies suggest that EUS may have an indirect positive impact on survival since it can detect malignancy at an earlier, potentially resectable stage.

The hypothesis that EUS would confer an indirect survival benefit has not been widely studied in rectal cancer and outcomes of patients with rectal cancer who receive EUS remain unclear. Randomized control trials are not feasible since it is thought EUS has become standard of care in the staging of rectal cancer. However, our findings indicate EUS utilization is low among patients with rectal cancer and may not be widely available. Harewood assessed the clinical outcome of 141 patients with non-metastatic rectal cancer before and after the introduction of EUS at their institution and reported recurrence-free survival advantage in patients who underwent EUS.[21] However, this experience took place at a single tertiary center and is limited by small numbers.

Our current study used the national SEER-Medicare database to examine a large cohort of patients with rectal cancer. A multivariate analysis, controlling for demographic and clinical variables, revealed that receipt of EUS was associated with reduced mortality. Undergoing EUS was also significantly associated with increased use of neoadjuvant chemotherapy and surgical resection. In our multivariate model, age over 75 years, late tumor stage, and a high comorbidity score were significant predictors of poor survival.

The reduced mortality associated with EUS is most likely multi-factorial and stems mainly from the stage-appropriate administration of neo-adjuvant therapy and surgical resection in rectal cancer patients. Among gastrointestinal malignancies, rectal cancer is one where stage dictates management, not only prognosis. With its more accurate pre-operative staging abilities, EUS indirectly improves survival by better identifying patients with advanced loco-regional disease in whom neo-adjuvant therapy offers the most benefit. The majority of EUS is performed at academic tertiary care

centers. Arguably, the improved outcomes in rectal cancer patients at these institutions may be linked to better access to more specialized multidisciplinary care and EUS is a marker of access to improved care.

Selection bias in EUS utilization may not only derive from its use at tertiary care institutions, but also from its preferential use in patients who are healthier, have a better performance status, and presumptively carry a better prognosis. We attempted to address this issue by including comorbid conditions in our multivariate analysis. The Deyo-Romano adaptation of the Charlson index has been commonly used in studies from the SEER-Medicare database. Although limitations of comorbidity measures from a claims database are known and somewhat unavoidable,[27] we used both inpatient and outpatient claims to assess comorbidity and examined data from 13 months to 1 month before date of diagnosis. Despite finding that patients with no comorbidities were more likely to undergo EUS than patients with comorbidities, there was no significant difference in severity of comorbid conditions among those who received EUS and those who did not. Still, one may contend that patients who present early with clinical suspicion of disease are more likely to undergo EUS which would lead to reduced mortality among patients who underwent EUS. Our study, found a similar proportion of early stage cancer among both groups.

An overall strength of the SEER-Medicare database in that it contains population-based data. This makes it less exposed to bias present in a hospital-based study. Through standardized case-finding procedures, data collection, and quality control, the database is highly accurate.[28]

Limitations

Important limitations exist in this study. First, though accuracy of procedural claims in the Medicare database and accuracy of tumor staging in the SEER registry have been established,[29] the reliability of diagnostic and procedural coding related to endoscopic procedures is not well known. The SEER database is limited in its capacity for variable selection, making adjustment for specific known confounders unattainable, though this was attempted through our use of inpatient and outpatient claims. SEER does not collect information on disease reoccurrence and cause of death information is not always reliable, making analysis of end points and disease-free survival problematic. Additionally, survival data collected over a period of time may not accurately reflect current oncology practices as these may change during the study period of interest.

Second, despite the relative accuracy of claims of neo-adjuvant chemotherapy and radiation, the temporal relationship between these procedures to cancer-directed surgical resection could not be extracted.

Third, comorbidity data was evaluated 13 months to 1 month before date of diagnosis and comorbidity data before the age of 65 was not available. We tried to reduce these effects by using both inpatient and outpatient claims data for assessing comorbidity.

Fourth, due to the patient population above age 65 in this linked SEER-Medicare database, our conclusions may only be applicable to an elderly population and may not be generalized to a broader population. However, it has been previously pointed out that a majority of patients with rectal cancer are older.[30]

Socioeconomic status and access to healthcare traditionally have been important factors that are known to be associated with race and regions, and are known to have an impact on post-cancer survival.[31,32] These variables are not available through our SEER-Medicare dataset. Additionally, factors such as referrals to tertiary treatment centers, and economic status of geographic areas surrounding the SEER reporting areas are potential confounders that were we unable to account for due to the nature of the SEER-Medicare reporting system. We attempted to address these variables by including median household income and proximity to a metropolitan area.

Fifth, due to lack of a CPT-4 code for EUS-FNA, this component of EUS was not evaluated in our study. EUS FNA, in its improved pre-operative accurate staging, has been shown to be associated with reduced tumor recurrence in rectal cancer.[21] Incorporating EUS FNA may have added to the mortality benefit imparted by EUS in our patients. Lastly, our study interval included an early era of EUS utilization given that CPT4 codes for endoscopic ultrasound related to the evaluation of rectal cancer were first introduced in 1999. Given EUS' technological advancement and increased utilization over the past decade, EUS' potential impact on rectal cancer may be underestimated.

Finally, because we used an observational study design, we could not establish any casual relationship between EUS use and survival for rectal cancer. Nonetheless, our study provides evidence that EUS might play an important role in the treatment decision processes.

Study Importance

We have found EUS evaluation results in improved survival among patients diagnosed with rectal cancer. This study reflects other published literature and confirms the feasibility of studying EUS in an analysis of a large database such as the SEER-Medicare linked database.[22]

Public Health Importance

Overall, despite the limitations of our current study, endoscopic ultrasound is associated with improved survival in patients with rectal cancer, most likely from more accurate staging and better selection of patients in whom neo-adjuvant therapy would be most beneficial. Change in management imparted by superior staging of EUS can lead to reduced mortality thus supporting its use in the evaluation of rectal cancer.

Future Directions

Further research is still needed to help explain why patients who receive EUS experience improved survival. A possible prospective research study that uses physician interviews could help researchers understand why the decision for EUS evaluation was made. Additionally, further analyses should be conducted to evaluate the impact of EUS among patients that did or did not receive other forms of cancer treatment (i.e. chemotherapy or radiation). We must reiterate that EUS is a diagnostic tool and cannot impart any direct therapeutic benefit to a patient. EUS technology has become widely available to patients throughout the country, but patient access to this technology is poorly understood. The SEER-Medicare database is continually being updated with new information, giving researchers a valuable tool to monitor trends in EUS availability to patients.

References

1. Surveillance, Epidemiology, and End Results. Bethesda, Md: National Cancer Institute. Available at http://www.seer.gov/about. Accessed on May 12, 2010.

2. American Cancer Society Cancer Statistics, Rectal Cancer. 2010

3. Parkin DM, Pisani P, Ferlay J (1999) Global cancer statistics. *CA Cancer J Clin.* 49:33–64.

4. Modlin IM, Lye KD, Kidd M: A five-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003; 97:934–959.

5. Swedish Rectal Cancer Trial. Improved survival with pre-operative radiotherapy in resectable rectal cancer. *N Engl J Med.* 1997; 336 (14): 980-7.

6. Sauer R, Becker H. Hohenberger W, et al. Pre-operative versus postoperative chemoradiotherapy in rectal cancer. *N Engl J Med*. 2004; 351: 1731-1740.

7. National Comprehensive Cancer Network Guidelines, Version 1.2011. Rectal Cancer 2010.

8. Ahmad NA, Kochman ML, Ginsberg GG. Endoscopic ultrasound and endoscopic mucosal resection for rectal cancers and villous adenomas. *Hematol Onco Clin N Am*. 2002; 16(4):897-906.

9. DiMango EP, Buxton JL, Regan PT, Hattery RR, Wilson DA, Saurez JR, Green PS. Ultrasonic endoscope. *Lancet*. 198; I: 629-31.

10. Boyce GA, Sivak MV, Jr., Lavery IC, Fazio VW, Church JM, Milsom J, *et al*. Endoscopic ultrasound in the preoperative staging of rectal carcinoma. *Gastrointest Endosc.* 1992;38:468-71.

11. Gualdi GF, Casciani E, Guadalaxara A *et al*. Local staging of rectal cancer with transrectal ultrasound and endorectal magnetic resonance imaging: comparison with histologic findings. *Dis Colon Rectum* 2000; 43: 338-45.

12. Marone P, Petrulio F, de Bellis M. *et al*. Role of endoscopic ultrasonography in the staging of rectal cancer: a retrospective study of 63 patients. *J Clin Gastroenterol* 2000; 30: 420-4.

13. Spinelli P, Schiavo M, Meroni E, *et al*: Results of EUS in detecting perirectal lymph node metastases of rectal cancer: The pathologist makes the difference. *Gastrointest Endosc* 1999; 49: 754-8.

14. Herzog U, von Flue M, Tondelli P *et al*. How accurate is endorectal ultrasound in the preoperative staging of rectal cancer? *Dis Colon Rectum* 1993; 36: 127-134.

15. Pappalardo G, Reggio D, Frattaroli FM, *et al*. The value of endoluminal ultrasonography and computed tomography in the staging of rectal cancer: A preliminary study. *J Surg Oncol.* 1990; 43: 219-22.

16. Thaler W, Watzka S, Martin F, *et al*. Preoperative staging of rectal cancer by endoluminal ultrasound vs. magnetic resonance imaging: Preliminary results of a prospective, comparative study. *Dis Colon Rectum* 1994; 37: 1189-93.

17. Schaefer H, Gossmann A, Heindel W, *et al*. Comparison of endorectal MR imaging and transrectal ultrasound with pathology in rectal tumors. Endoscopy 1996; 28: S9.

18. Meyenberger C, Huch Boni RA, Bertschinger P, *et al*. Endoscopic ultrasound and endorectal magnetic resonance imaging: a prospective, comparative study for preoperative staging and follow-up of rectal cancer. *Endoscopy* 1995; 27: 469-79.

19. Harewood, GC, Wiersema, MJ. Cost-effectiveness of endoscopic ultrasonography in the evaluation of proximal rectal cancer. *Am J. Gastroenterol* 2002;97:874-882.

20. Shami V, Parmar K, Waxman I. Clinical impact of endoscopic ultrasound and endoscopic ultrasound-guided fine-needle aspiration in the management of rectal carcinoma. *Dis Colon Rectum* 2004; 47:59-65.

21. Harewood, GC. Assessment of clinical impact of Endoscopic ultrasound on rectal cancer. *Am J Gastro.* 2004 Apr 99(4):623-7.

22. Das, A, Chak, A., Sivak, M., Payes, J, Cooper, G. Endoscopic ultrasounography and prognosis of esophageal cancer. *Clin Gastro and Hepa.* 2006; 4;695-700.

23. Puli SR, Reddy JB, Bechtold ML, *et al*. Accuracy of endoscopic ultrasound to diagnose nodal invasion by rectal cancers: A meta-analysis and systematic review. *Ann Surg Oncol*. 2009;16(5):1255-1265.

24. Zang, MJ. Cox proportional hazards regression models for survival data in cancer research. *Cancer Treat Res*. 2002; 113:59-70.

25. Erickson, RA, Garza, A. Impact of endoscopic ultrasound on the management and outcome of pancreatic carcinoma. *Am J. Gastroentero.l* 2000; 95(9); 2248-54.

26. Ngamruengphong,S, Li,F, Zhou, Y, Chak, A, Cooper, GS, Das, A. EUS and Survival in patienst with pancreatic cancer: a population-based study. *Gastrointestinal Endoscope* 2010 Jul: 72(1): 78-83.

27. Klabunde, C.N., Warren, J.L., Legler, J.M. Assessing comorbidity using claims data. *Med Care* 2002; 40(Suppl):26-35.

28. Warren, JL, Klabunde CN, Schrag D, *et al*. Overview of the SEER-Medicare data: content research applications, and generalizability to the United States elderly population. *Med Care* 2002; 40(suppl):3-18.

29. Cooper, GS, Yuan, Z, Stange, KC, et al. Agreement of Medicare claims and tumor registry data for assessment of cancer related treatment. *Med Care* 2000; 38: 411-421.

30. Enzinger PC, Mayer RJ. Gastrointestinal cancer in older patients. *Semin Oncol*. 2004; 21:206-219.

31. Byer, TE et al. The impact of socioeconomic status on survival after cacner in the United States: findings from the Nation Program of Cancer Registires Patterns of Care Study. *Cancer* 2008;113(3):582-91.

32. Kagawa-Singer, M, dadia, AV et al. Cancer, culture and health disparities: time to chart a new course? *CA Cancer J Clin*. 2010 Jan-Feb;60 (1):12-39.

Appendix A

Figure 4 – Rectal Cancer survival time among patients with local SEER stage

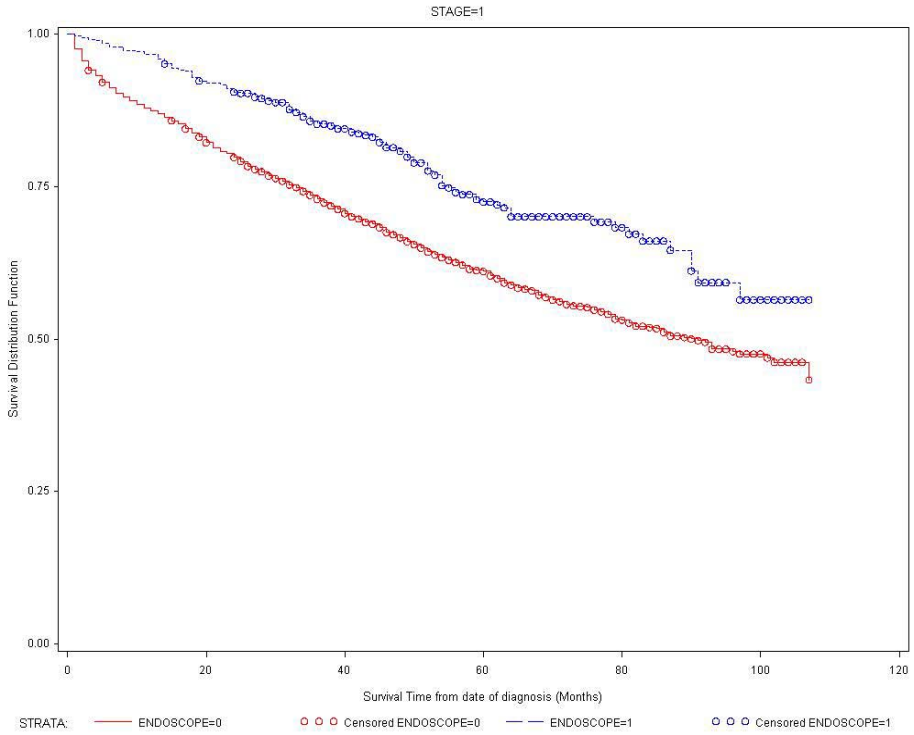


Figure 5 – Rectal cancer survival time among patients with regional SEER stage