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Research Article

Does Pre-Operative EUS Staging Have Influence on the 5 Year Survival Rate of Esophageal Cancer?

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Introduction

Esophageal cancers have long been a source of morbidity and mortality throughout the world. Patients with this disease typically present with dysphagia (74%), weight loss (57%) and odynophagia (17%) [1]. Squamous cell carcinoma has historically been the most common subset of esophageal cancer, but with the rise of obesity and the "Western diet" over the past 40 years, adenocarcinoma is now being seen much more often. With an incidence increase from 4 to 23 people per million since 1975, esophageal adenocarcinoma is the fastest growing cancer in the United States [2].

Numerous risk factors contribute to the development of esophageal cancer. From an epidemiological standpoint, the incidence of adenocarcinoma has increased significantly compared to its cohort, squamous cell carcinoma [3]. The distribution of ages for those affected tends to peak at 50 to 60 years of age, and the ratio of males to female patients ranges from 2:1 to 12:1 [4] The relationship of esophageal carcinoma and Barrett's esophagus has been well studied and established throughout the literature. Factors such as elevated body mass index (BMI), regardless of the presence of reflux symptoms [5], and low consumption of fruits and vegetables in early adulthood have been shown to be significant risk factors for developing esophageal cancer. The type of obesity also seems to play a significant role, with the "male pattern distribution" of abdominal obesity (central and retroperitoneal) associated with a higher rate of malignant transformation [6]. Data also exists to hypothesize a protective effect of breast feeding on the development of the disease as well [7].

Genetic predisposition is another area in which the progression of the cancer can be modulated. Analysis of biopsy samples from Barrett's esophagus has shown p53 expression to be predictive of disease progression [8] Non-steroidal drugs (NSAIDs) and aspirin are promising modulators of esophageal cancer through their inhibition of the cyclo-oxygenase 2 (COX-2) enzyme. The Aspirin Esomeprazole Chemoprevention Trial (AspECT) is currently underway to evaluate if such a therapy may have a protective effect [9].

The staging of esophageal cancer follows the well-known Tumor-Node-Metastasis system (TNM Staging) developed by the American Joint Committee on Cancer. Common modalities for staging often involve the use of CT scanning of the chest, abdomen, and pelvis, endoscopic ultrasound (EUS), and positron emissions tomography (PET) to determine the appropriate stage and thus appropriate treatment modality [3].

EUS is regarded as an essential step in the staging of esophageal carcinoma given its ability to image not only the esophageal wall layers, but also the majority of mediastinal, perigastric, and celiac nodes as well as the left lobe of the liver [10]. There are also reported cases where EUS identified celiac node involvement as well as metastases to the liver that were initially missed on CT scanning, thus resulting in an upstaging of the disease, with a major impact on therapeutic management [11,12]. While preoperative EUS is routinely used for staging esophageal cancer in major cities in the USA, such procedures are not always available in relatively smaller communities and patients have to travel hundreds of miles to have this study performed. Regionalization of care has been strongly advocated by many experts, but is not

always practical and feasible for the patients. This study looks whether there is any benefit of performing preoperative EUS staging in the management of esophageal cancer patients.

Methods

Retrospective chart review was performed to collect the clinical data for patients diagnosed with esophageal cancer from 2000 to 2013 at a community teaching hospital. For survival analysis, those who were diagnosed before 2009 were included. Data variables included demographics, comorbidities, imaging (CT, PET, EGD, EUS), staging, insurance status, and survival duration. Early stages included stage IA to IIB; late stages included stage III and IV. Correlation, cross tabulation, linear regression, and T-TEST analysis were performed using SPSS software.

In the non-EUS group, patients who were non-symptomatic were assumed to have early stage disease and were treated with initial esophagectomy, while symptomatic individuals were assumed to have advanced disease and received neoadjuvant chemotherapy and radiation before surgical resection.

Results

55 patients were included in this study. Of these, 80% (43) were white, 6% (3) black, 11% (6) Hispanic, 4% (2) other. Sex distribution was 74% male, 26% female. 29 (54%) had preoperative EUS workup, while 25 (46%) did not. Overall mean survival was measured at 20 months. The mean survival duration was 21 and 19 months in EUS and non-EUS groups respectively with no statistical significance ($p = 0.08$). 19 patients were in the early stage of the cancer, 34 patients in the late stages. When controlled for stage of the cancer, there was no observed difference in survival between the EUS and non-EUS groups. There was also no statistical difference in the survival duration between those diagnosed with squamous cell carcinoma versus those with adenocarcinoma ($p = 0.5$). There was a positive correlation between the albumin level, BMI, and the 5-year survival ($p = 0.01$) and negative correlation between the existence of comorbities and the 5-year survival with no difference between the EUS and non-EUS groups.

Gender	**Female**		**Male**		
	14		40		
Race	White	Hispanic	African American	Mixed/Other	
	43	6	3	2	
Diagnosis	Squamous	10	Adenocarcinoma	41	
Stage	0 - IIB	III	IV		
	19	13	21		
Preoperative EUS	YES		NO		
	29		25		
Gender	Male	Female	Male	Female	
	17	12	23	2	
Race	White	20	White	23	
	Hispanic	4	Hispanic	2	
	African American	3	African American	0	
	Other	2	Other	0	
Diagnosis	Squamous Cell Carcinoma	9	Squamous Cell Carcinoma	1	
	Adenocarcinoma	18	Adenocarcinoma	28	
Mean Survival	**21 months**		**18 months**		**P = 0.08**

Discussion

Our study suggests that the role of preoperative EUS for the staging workup of esophageal cancer may be limited. We specifically found that there is no statistical significance in the 5-year survival between groups who had EUS as a staging workup and those who did not have EUS.

Known Limitations of EUS

Much literature has established the use of EUS as the best tool for locoregional staging of esophageal cancers [13]. Yet surprisingly the EUS accuracy dropped when evaluating superficial lesions (T1), with an accuracy of only 67% [14]. Additionally, esophageal stenosis from progressed cancers also significantly limit the evaluation that can be performed by EUS. The risks and benefits of dilation have been a source of controversy, as is the use of miniature EUS probes that have a limited depth of penetration due to the frequency at which they operate [15]. EUS has also been used to restage cancers following neoadjuvant therapy, but Misra., *et al*. showed that EUS staging after neoadjuvant chemotherapy is less accurate than initial staging for patients with locally advanced esophageal cancers, frequently overstaging the T stage of the tumor [16].

Early stages of esophageal cancer often present with minimal symptoms, and may remain undetected for a significant amount of time. Up to 70% of patients with early stage tumors present with only mild dyspepsia without any associated findings such as anemia, dysphagia, or weight loss [4]. Allum., *et al*. goes so far as to recommend that all patients with the afore mentioned symptoms be considered high risk and undergo EUS even though the overall detection rate is low at 1 - 3% [4].

If discovered early, stage I cancers can be successfully treated by a combination of endoscopic mucosal resection (EMR) and photodynamic therapy (PDT) with much lower levels of morbidity and mortality when compared to surgical esophagectomy, but patients undergoing EMR/PDT had a higher incidence of non-response to therapy [17].

According to the SEER database, however, at the time of diagnosis only 20% of cases were localized, i.e. stage 1 cancers. 31% were "regional" cases (spread to regional lymph nodes (N1), stage IIB to III) and another 38% were "distant" cases (cancer metastases (M1), stage IV) [18]. Overall 5-year survival rate is low at 18.4%. Breakdown based on SEER categories list survival rates at 40% for localized cases, 22.8% for regional cases, and 4.5% for distant cases. Other studies cite the incidence of metastatic disease as high as 50% [19]. Schrager., *et al*. demonstrated the greatest difference in survival was with surgical versus nonoperative management, independent of whether preoperative staging was performed with EUS or with CT alone [19].

In many rural communities, the population often adopts a mantra of hard-working self-sustenance, and will often delay medical care due to the inconvenience it would cause in their work lives and daily routines. These types of individuals present much later in the natural progression of the disease, often already with a significant tumor burden and the afore mentioned "typical" symptoms of dysphagia, fatigue, weight loss, and melena. Once the tumor progresses to these later stages, surgical esophagectomy is often pursued in an attempt to either achieve an oncologically thorough resection or provide palliation for the patient. T stage as determined by EUS would therefore be irrelevant in this subset of patients. The benefit of EUS in assessing T and N stages is minimal as the tumor would have already progressed beyond the therapeutic role of nonsurgical treatment such as endoscopic mucosal resection.

Limitations of Study

For the purposes of this study, recruited patients were divided into EUS and non-EUS arms. For those in the non-EUS arms, patients who presented with minimal symptoms were assumed to be at an early stage, and diagnoses was made by esophagogastroduodenoscopy (EGD). These patients proceeded directly to surgery without neoadjuvant therapy. Clinically symptomatic patients, on the other hand, were assumed to have advanced stages of disease, with cancer progression beyond the mucosal and submucosal layers, making their staging at least T2 or T3. These patients were treated with neoadjuvant chemotherapy and radiation first, with subsequent surgical resection, regardless of the N stage of their disease.

Conclusion

In summary, the primary focus of treatment for esophageal cancer, as with all other cancers, should be prevention and minimizing risk factors for its development. Proper monitoring and recognition of those at risk, and a low threshold for suspicion on the part of the primary care physician, may help reduce cases of the cancer and improve incidence rates, reducing morbidity and mortality.

For those who unfortunately are found to have esophageal cancer, EUS has long been accepted as standard of care in the workup and treatment of the condition. Known limitations of the imaging modality, such as inability to pass through tumor strictures (up to 33% of cases) may limit its ability to fully and accurately stage the cancer's progression. Additionally, the characteristics of rural populations, such as less frequent visits to health care providers, as well as postponing medical treatment for what they may perceive as minor inconveniences (heartburn, etc) may result in later presentation of the tumor, long after it can be managed with less morbidity with EMR/PDT. At this point, the only resection option remains surgical esophagectomy.

In communities with lack of access to healthcare resources, clinical judgement may substitute advanced imaging modalities without significantly impacting good patient care.

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