

# The Changing Profile of Esophageal Cancer Presentation and Its Implication for Diagnosis

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*Context:* The incidence of esophageal adenocarcinoma is rising and has surpassed squamous cell carcinoma.

*Objective:* To determine how the increasing incidence of esophageal adenocarcinoma alters the classic clinical presentation and the implications of these changes for diagnosis.

*Design and Setting:* A five-year retrospective review (1991–1996) was made.

*Participants:* All patients were identified by a computerized registry search with a diagnosis of esophageal carcinoma.

*Main Outcome Measures:* Clinical presentation; duration of symptoms; and correlation with diagnosis, pathology, treatment and outcome.

*Results:* One-hundred-eight (35%) patients had squamous cell carcinoma and 199 (65%) had adenocarcinoma. Dysphagia and weight loss were more common among patients with squamous cell carcinoma (93% and 68%), when compared to adenocarcinoma (79% and 53%). Twenty-one percent of adenocarcinoma patients had other symptoms presentation, including gastroesophageal reflux disease. Once dysphagia was present, there was no correlation between the duration of symptoms and survival. However, cancers detected in patients who presented with reflux symptoms without dysphagia showed an improved prognosis over patients who presented with both.

*Conclusions:* Esophageal adenocarcinoma has surpassed squamous cell carcinoma. Gastroesophageal reflux was associated with an earlier stage of presentation compared to the "classic" presentation of esophageal cancer.

**Key words:** esophagus ■ cancer ■ symptoms ■ gastroesophageal reflux disease ■ survival

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## INTRODUCTION

Cure rates for esophageal cancer are low, despite advances in multimodality therapy. These facts are particularly disturbing considering the incidence of esophageal cancer in the United States is increasing at a faster rate than any other cancer.<sup>1</sup> It is estimated that in 2006, 14,550 new cases of esophageal cancer will be diagnosed.<sup>2</sup> Many patients present with advanced disease, making esophageal cancer a highly lethal disease. Five-year survival rates are only 15% in Caucasian Americans and 8% in African Americans.<sup>2</sup>

The presenting signs and symptoms of esophageal cancer tend to reflect the local extent of disease and do not typically occur until late in the course. The classic description of a patient with esophageal cancer is that of dysphagia and weight loss in patients with a history of tobacco and alcohol use. This clinical picture, however, more accurately reflects squamous cell carcinoma, which, until recently, was the most common histology of esophageal cancer. The incidence of adenocarcinoma (ADC) has risen dramatically and has surpassed squamous cell carcinoma as the most common type of esophageal cancer.<sup>1,3,4</sup>

Given the changing histological profile of esophageal cancer, it is important to re-examine our concept of the classic presentation of dysphagia and weight loss. We reviewed all patients with esophageal carcinoma treated at our institution between 1991–1996. The purpose of our study was to identify the incidence of squamous cell carcinoma and adenocarcinoma in our population. In addition, we specifically analyzed the spectrum of presenting symptoms and their duration prior to diagnosis. A correlation of these findings with the stage at presentation and prognosis was also performed.

## PATIENTS AND METHODS

All patients with the diagnosis of carcinoma of the esophagus at Roswell Park Cancer Institute (RPCI) between 1991–1996 were identified by querying our tumor registry (computerized searches of tumor registry data). A retrospective review of the charts confirmed the diagnosis of esophageal cancer in 307 patients. Patients

with cancer of the gastric cardia were excluded. Two-hundred-fifty-six patients (83%) were initially treated at RPCI, while 51 (17%) were initially treated at an outside institution and received follow-up care at RPCI.

All charts were reviewed for initial presentation, diagnostic work-up, treatment and outcome. The symptoms at presentation included all complaints that the patient stated in the initial history and physical that prompted medical attention, as well as any symptoms uncovered in the review of symptoms. The duration of symptoms was a subjective response of the patient over how long these symptoms persisted before seeking medical attention.

Statistical analysis was performed using the Fischer's exact test or Student's t test.

## RESULTS

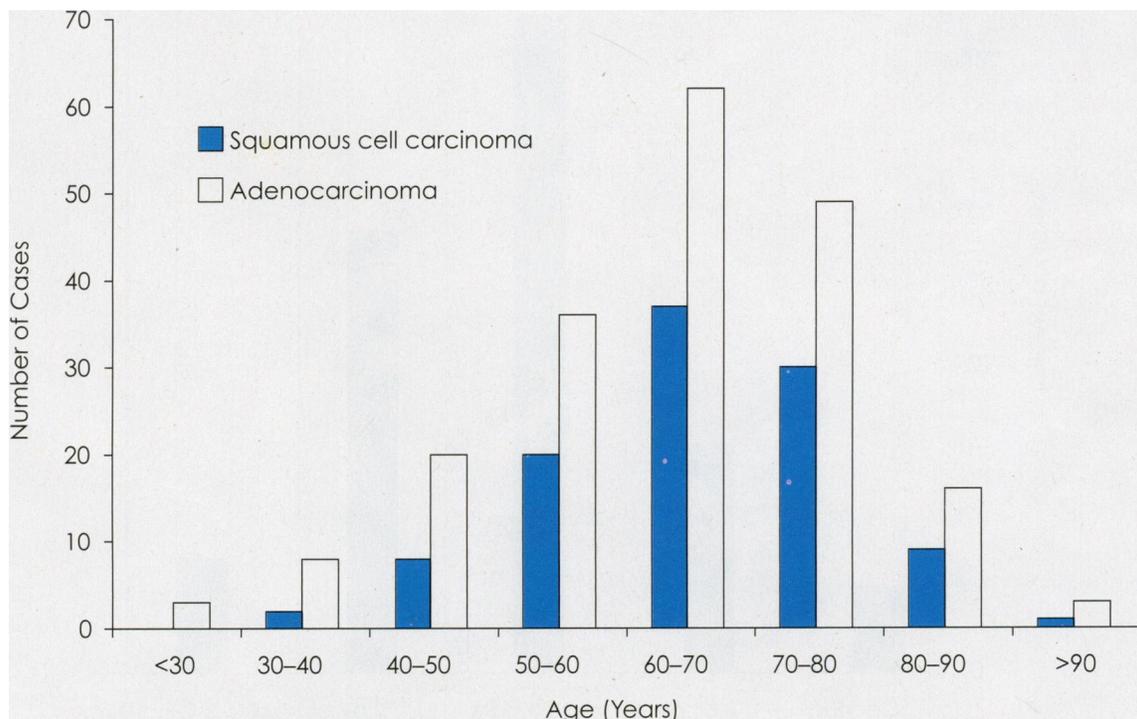
### Patient Characteristics

Among the 307 evaluable patients, 277 (90.3%) were Caucasian, 26 (8.4%) African American and four (1.3%) Asian. Two-hundred-thirty-six (76%) of the patients were male and 71 (24%) were female, resulting in a 3:1 M:F (male:female) ratio. Of the 307 patients reviewed, 108 (35%) presented with squamous cell carcinoma, whereas 199 (65%) had adenocarcinoma. Twenty-five African-American patients had squamous cell carcinoma. The male:female ratio was 4.4:1 for adenocarcinoma; for squamous cell carcinoma, it was approximately 2.3:1. The age distribution for both histologies was similar (Figure 1), with the majority of patients presenting in the seventh decade and an average age of 63 for both patients

**Table 1. AJCC staging (6th ed) for 307 esophageal cancer cases were similar between both the squamous cell carcinoma and adenocarcinoma groups**

Stage	Squamous Cell Carcinoma	Adenocarcinoma
0	0 (0%)	3 (2%)
1	3 (3%)	6 (3%)
2A	9 (8%)	21 (11%)
2B	14 (13%)	20 (10%)
3	26 (24%)	52 (26%)
4	33 (30%)	60 (30%)
Not staged	23 (21%)	37 (19%)

**Figure 1. The age distribution for 307 cases of esophageal cancer was similar between squamous cell carcinoma and adenocarcinoma the majority of patients presented in the seventh decade of life (average age 63 years)**



with adenocarcinoma and squamous cell carcinoma.

Alcohol use was more prevalent among patients with squamous cell carcinoma. Almost three-quarters of these patients reported heavy or moderate use of alcohol. Of pa-

tients with adenocarcinoma, the trend was opposite, with 60% reporting that they either rarely or never used alcohol. Smoking was more common in squamous cell carcinoma than adenocarcinoma patients (90% vs. 75%).

**Table 2. Presenting symptoms of patients with esophageal carcinoma**

Symptoms	Number Pts (%)
Dysphagia	259 (83)
Weight loss	179 (58)
Abdominal pain	27 (9)
Chest pain	21 (7)
GI bleed	20 (6.5)
GERD	17 (5.5)
Nausea/vomiting	16 (5)
Hoarseness	6 (2)
Fatigue	5 (1)
Back pain	4 (1)
Neck pain or mass	3 (1)
Early satiety	2 (<1)
Hiccups	2 (<1)
Hemoptysis	1 (<1)
Barrett's surveillance	1 (1)

The classic combination of dysphagia and weight loss was significantly different between patients with squamous cell carcinoma (65%) and adenocarcinoma (47%).

### Site and Extent of Disease

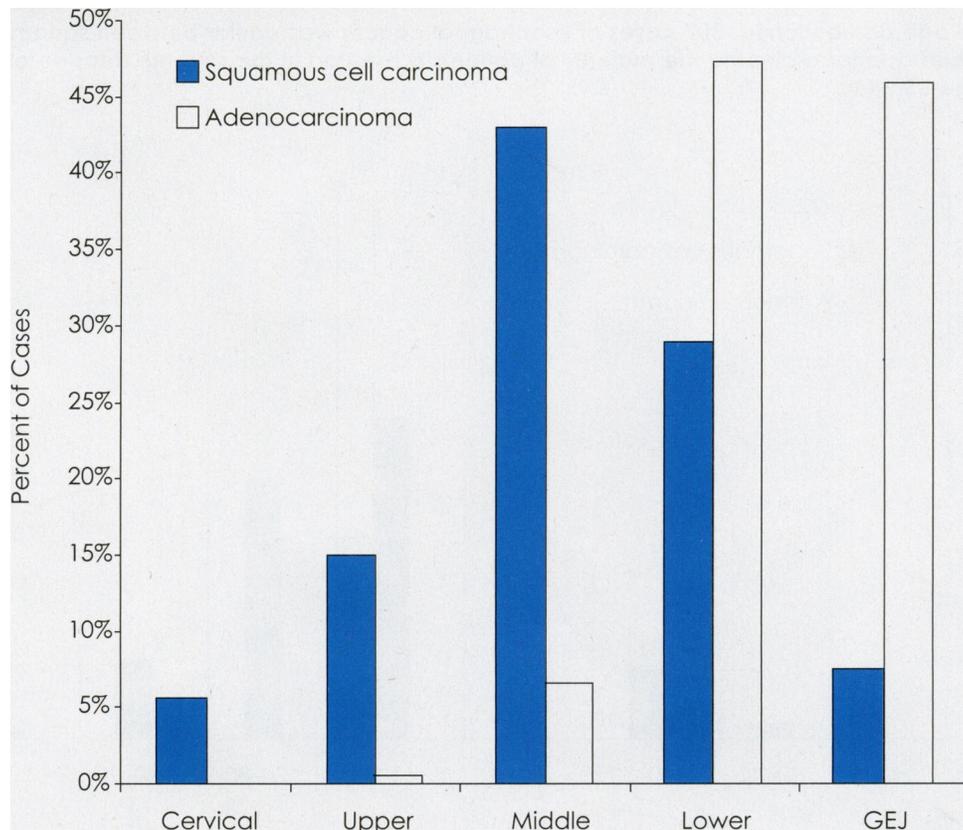
The tumor location is shown in Figure 2. Squamous cell carcinoma was distributed throughout the length of the esophagus, with the greatest number (43%) being in the middle third of the esophagus. Greater than 90% of adenocarcinomas were limited to the lower third or the gastroesophageal junction. Figure 3 depicts the transition from predominantly squamous cell carcinoma to adenocarcinoma in the study time interval (for each year 1991–1996).

The extent of disease at the time of diagnosis was relatively equal for both squamous cell carcinoma and adenocarcinoma. Only one-fifth of patients presented with disease confined to the esophagus, 19% of squamous cell carcinoma and 23% of adenocarcinoma. Table 1 shows the stage at presentation for the 307 patients, segregated by histology.

### Symptoms at Presentation

Dysphagia and weight loss were the most common symptoms overall among patients with esophageal cancer (Table 2), although they were more common in pa-

**Figure 2. Location of squamous cell carcinoma was distributed throughout the length of the esophagus with the greatest number in the middle third. In contrast, the majority of adenocarcinoma involved the distal esophagus and gastroesophageal junction.**



tients with squamous cell carcinoma of the esophagus. Almost all squamous cell carcinoma patients (93%) presented with dysphagia (Figure 4), while only 79% of the adenocarcinoma presented with dysphagia. Weight loss was the second most common symptom, occurring in 68% of the patients with squamous cell carcinoma and 53% of patients with adenocarcinoma. The “classic” combination of these two symptoms was significantly different between patients with squamous cell carcinoma (65%) and adenocarcinoma (47%) (Fischer’s exact test,  $p=0.002$ ).

The 50 patients who presented without dysphagia are summarized in Table 3. Forty-two (84%) had adenocarcinoma. These patients had their cancers diagnosed after undergoing esophagogastroduodenoscopy (EGD) for abdominal pain (28%), gastroesophageal reflux disease (GERD) (22%) or gastrointestinal bleed (26%). Two patients had EGD as part of a cancer work-up for metastases

with an unknown primary, and one early-stage cancer was discovered during surveillance for Barrett’s esophagus.

### Correlation of Symptoms with Prognosis

While there was no correlation between dysphagia and prognosis, a correlation did exist between weight loss and prognosis. When weight loss was not present as one of the symptoms at presentation, there was a lower incidence of metastatic disease (24% vs. 43%) (Fischer’s exact test,  $p=0.001$ ). This translated into an improved survival for patients who did not present with weight loss (20 months vs. 13 months) (Student’s t test,  $p<0.001$ ).

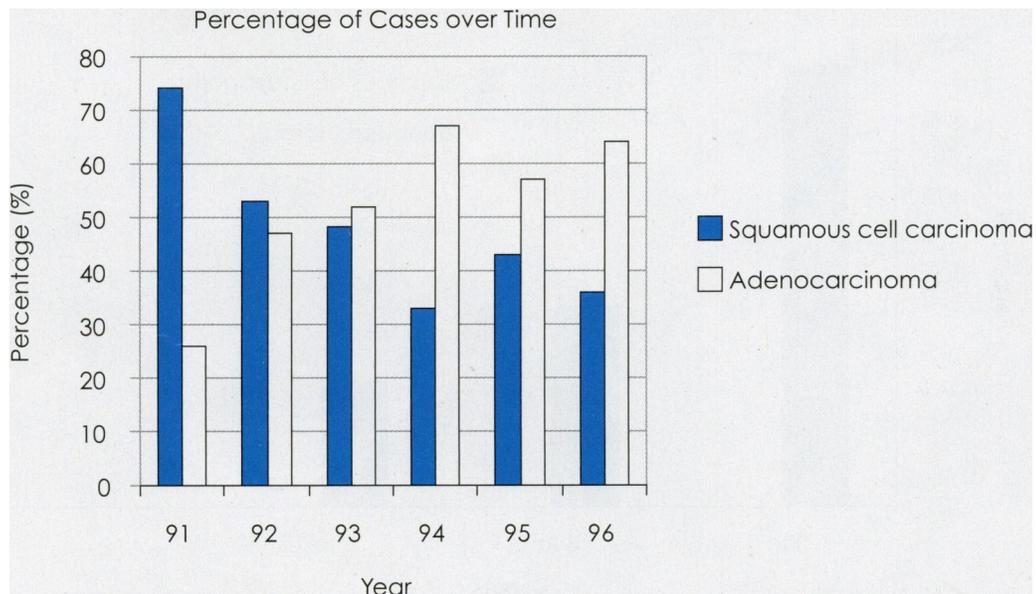
Despite the small number of patients who presented with GERD, there was a correlation between GERD, disease stage and prognosis. All patients with adenocarcinoma who presented with GERD alone were stage 2a or lower, including three carcinomas in situ. On the oth-

**Table 3. Symptoms that prompted investigation in 50 esophageal cancer**

Presenting Symptoms	Number of Patients	Percent
Abdominal pain	15	5
GI Bleed	12	5
GERD	10	3
Nausea/vomiting	3	1
Incidental	3	1
Unexplained weight loss	2	<1
Chest pain	2	<1
Back pain	1	<1
Hoarseness	1	<1
Barrett’s surveillance	1	<1

Patients who did not present with dysphagia, 84% of these patients had adenocarcinoma of the esophagus.

**Figure 3. The transition between the predominant squamous cell carcinoma compared to adenocarcinoma of the esophageal during the study interval is seen in 1993**

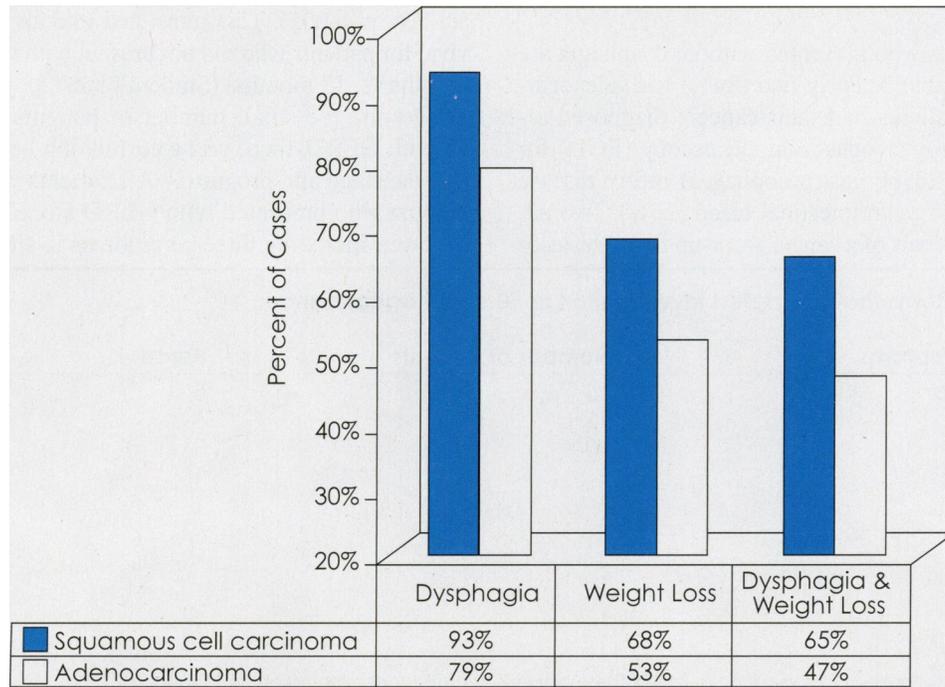


er hand, when patients had both dysphagia and GERD, all patients were stage 2b or higher (one was not staged). This was reflected in the average survival. Patients who had GERD alone had an average survival of 29.8 months, as compared to 19.6 months for patients with both GERD and dysphagia.

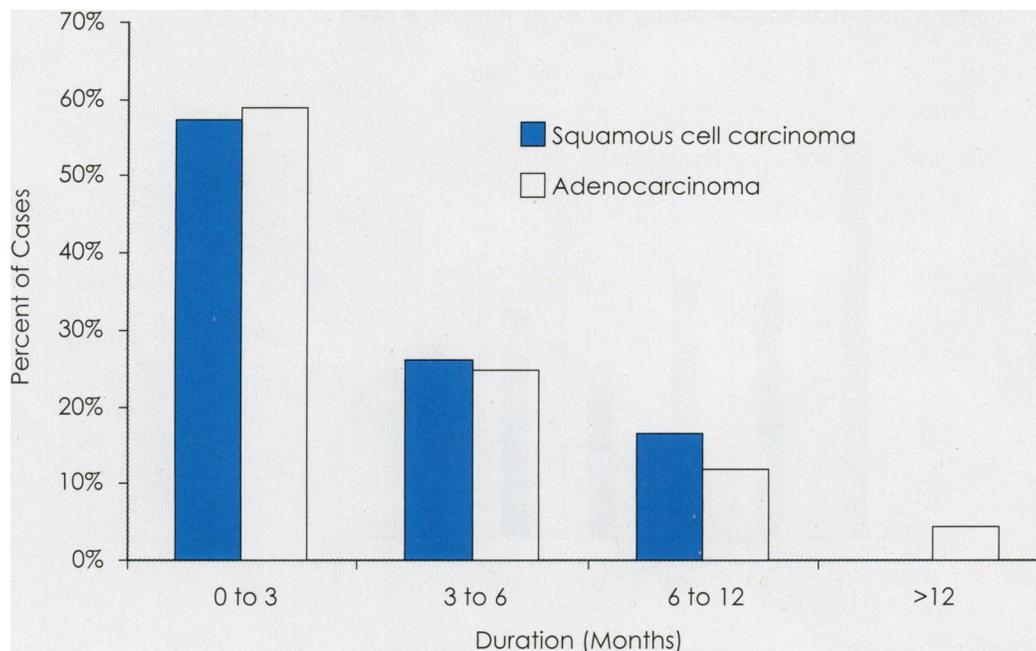
### Correlation between Symptom Duration and Prognosis

The duration of symptoms ranged for 1 week to 24 months, with more than half of patients having <3 months of symptoms prior to seeking medical attention (Figure 5). There was no significant correlation between the duration of symptoms and prognosis. Survival did to appear

**Figure 4. Presence of dysphagia and/or weight loss at initial presentation for patients with esophageal cancer**



**Figure 5. Duration of symptoms prior to seeking medical attention for patients with esophageal cancer**



to worsen significantly as the time between the onset of symptoms and diagnosis lengthened. The mean survival for patients with symptoms of <3 months (n=168) was 15 months. This was approximately the same for patients with symptoms from 3–6 months (n=74, 14 months) and 6–12 months (n=40, 17.2 months).

## DISCUSSION

Adenocarcinoma accounted for <15% of cases of esophageal cancer 30 years ago. Since the 1970s, there has been about 350% increase in incidence of adenocarcinoma, and it has surpassed squamous cell carcinoma as the most common type of esophageal cancer.<sup>1,3</sup> In the present study, approximately twice as many patients presented with adenocarcinoma compared to squamous cell carcinoma. Epidemiological studies of the pathogenesis of adenocarcinoma have identified several risk factors, including obesity, tobacco, persistent reflux, anticholinergic medications, bacterial nitrosation, hiatal hernia, family history and dietary insufficiency.<sup>5</sup>

A nationwide case-control study reported that people with long-standing severe reflux symptoms were 43 times more likely to develop adenocarcinoma of the esophagus compared to asymptomatic individuals.<sup>6</sup> The presence of intestinal metaplasia or Barrett's esophagus is the major risk factor. In one study, subjects with Barrett's were found to have 30 times<sup>7</sup> increased risk of adenocarcinoma, whereas those with reflux but without Barrett's had only a modestly increased risk (3.1 times) compared with the general population.<sup>7</sup> Although it is unlikely that the prevalence of reflux disease in the population has changed dramatically over the last 30 years, it is interesting that during this time period there has been a dramatic increase in the availability and potency of pharmacological gastric acid-suppressing agents. Whether there is an association between pharmacologic manipulation of gastric acidity and increased risk of adenocarcinoma remains to be determined.

Several studies have correlated rising obesity in the population with increasing incidence of adenocarcinoma and decrease in squamous cell carcinoma.<sup>8,9</sup> Increasing body mass index promotes gastroesophageal reflux and formation of Barrett's esophagus, which is a precursor of adenocarcinoma. In addition, a decrease in *H. pylori* infection in the United States has led to parallel rise in acid reflux and Barrett's esophagus, which are independent risk factors for esophageal adenocarcinoma.<sup>10</sup> Infection by cag-A-positive strain of *H. pylori* is protective against esophageal adenocarcinoma as it promotes achlorhydria. Decrease in gastric acid production as a result has increased the risk of gastric carcinoma, but the associated reduction in acid reflux decreases the risk of adenocarcinoma.<sup>11</sup>

Dysphagia is the classically described and the most common symptom of esophageal cancer, present in 86% of patients in this study. Certainly, any patient complain-

ing of dysphagia should be considered to have cancer until proven otherwise. While dysphagia can occur with minimal luminal encroachment (secondary to dysmotility caused by the tumor), it usually requires >60% of the circumference to be invaded by tumor before patients experience severe dysphagia and seek medical attention.<sup>12</sup> Unfortunately, the cancer is often advanced at that point. In this study, the majority of the patients presented both with dysphagia and had advanced disease. Only one-fifth of patients presented with disease localized to the esophagus, a point at which a chance for cure still exists.

A worrisome finding of this study is the lack of association between the duration of symptoms and prognosis. While waiting >3 months increased the likelihood of having a higher T-staged tumor, larger tumor or increased invasion of the cancer into local structures, it did not alter the chances of having nodal or metastatic disease. Other studies have suggested a correlation between delay in diagnosis and stage; however, this correlation did not demonstrate statistical significance<sup>13</sup> or was based on an extremely small sample size.<sup>14</sup> Regardless, no study, ours included, has been able to demonstrate a correlation between a short duration of symptoms and survival. While it makes sense that prompt referral to a physician may help improve the stage at presentation, for esophageal cancer this improvement may be slight and most likely have little effect on survival. Decreasing the time that it takes patients to seek medical attention, even by a month or two may not significantly alter the outcome.

Weight loss, the second most common symptom, is an even more ominous sign. In this study, a significantly higher percentage of patients with weight loss had evidence of metastatic disease at presentation and, therefore, had an expectedly lower survival. The cause of weight loss in esophageal cancer patients is multifactorial, stemming from both dietary modifications to avoid the dysphagia as well as cachexia from tumor burden.<sup>15</sup> The duration of the dysphagia in this study was equal in both groups, arguing towards cachexia from metastatic disease as an explanation for the differences seen. Therefore, any patient with esophageal cancer who presents with weight loss should undergo an aggressive search for metastatic disease prior to the initiation of therapy.

In this study, the transition to a predominant presentation of adenocarcinoma compared to squamous cell carcinoma occurred in 1993, a trend reflected throughout the country. The most significant finding in this study is the changing presentation of esophageal cancer, specifically the increasing number of patients with adenocarcinoma who present with symptoms other than dysphagia. The standard teaching has been that dysphagia and weight loss are the presenting symptoms in well over 90% of cases. However, squamous cell carcinoma has represented the majority of those cancers. Fewer than half the patients with adenocarcinoma presented with the "classic" picture

of dysphagia and weight loss, which is significantly less than patients with squamous cell carcinoma.

As adenocarcinoma continues to make up a larger percentage of the cases seen in the United States, fewer patients will have the classic presentation associated with esophageal cancer, and it is important to detect these patients before grave symptoms such as weight loss occur. GERD was a relatively uncommon presenting complaint among patients diagnosed with esophageal cancer. Only 17 (6%) of the patients in our study mentioned symptoms of heartburn or reflux at the time of presentation. The apparent discrepancy between the increased incidence of adenocarcinoma and lack of a history of GERD in this study can only be attributed to lack of awareness of the symptom complex difference with squamous cell carcinoma during the study years. Interestingly, 42 patients with adenocarcinoma (21%) did not come to their physician with complaints of dysphagia but rather with abdominal pain, GI bleed or symptoms of reflux disease. In those patients who presented with GERD, there was a correlation with earlier stage at presentation and improved survival.

There is a strong association between symptoms of GERD and the risk of esophageal adenocarcinoma.<sup>6</sup> This study highlights that the one group of patients who presented at a significantly better stage were those patients who presented with reflux symptoms in the absence of dysphagia. Waiting until dysphagia was present significantly worsened their prognosis. Early endoscopy in patients with GERD appears to be one of the few approaches available to identify that subset of patients with early-stage adenocarcinoma. More importantly, it may identify patients with Barrett's esophagus, the only known precursor to adenocarcinoma, which is found in approximately 10–15% of patients who undergo endoscopy for evaluation of symptoms suggestive of GERD.<sup>16</sup> Barrett's esophagus is an initiating step in the development of adenocarcinoma, with a risk of adenocarcinoma in patients with Barrett's esophagus being about 500 cancers per 100,000 patients per year.<sup>17</sup> A relatively high number of esophageal adenocarcinomas can be detected early with endoscopic surveillance for Barrett's.<sup>18,19</sup> Given the advantage in survival associated with early diagnosis,<sup>20,21</sup> this approach is justified.

In conclusion, esophageal carcinoma continues to carry with it an extremely dismal prognosis, which is a worrisome fact considering that the incidence is increasing. With an increasing proportion of adenocarcinoma, the clinical presentation of these patients is changing. Maintaining a high index of suspicion for esophageal cancer is critical to identifying them prior to the onset of dysphagia, especially patients with severe GERD symptoms. Early use of EGD in these patients may represent a true

opportunity to identify early-stage cancer, dysplasia or high-risk Barrett's esophagus patients. As the incidence of adenocarcinoma continues to rise, this approach will be more important if we are to make an impact in the rising number of deaths due to esophageal cancer.

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