



# NEWS

## SWALLOWING

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### DIRECTOR'S FORUM

## ESOPHAGEAL MALIGNANCIES AND PREMALIGNANT CONDITIONS: A REMARKABLE EVOLUTION – PART I

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Esophageal cancer has been recognized for thousands of years. Over two thousand years ago in China it was referred to as Ye Ge, which literally means difficult swallowing (dysphagia) and belching.

Until the past two decades, the term esophageal cancer was synonymous with squamous cell carcinoma since this lesion was known to comprise over 90 percent of esophageal malignancies. Consequently, most of the reports on frequency in the population, cause, diagnosis and therapy for esophageal cancer published in the twentieth century refer to the squamous cell variety. However, in the twenty-first century, this imbalance favoring squamous cancer over primary adenocarcinoma of the esophagus in the United States has changed drastically. During the past two decades there has been about a ten-fold increase in adenocarcinoma of the esophagus. The dramatic increase is occurring primarily in white males in the forty to seventy year age range in association with a columnar-lined (Barrett) esophagus. In this review, the term esophageal cancer will refer to the squamous cell type and adenocarcinoma will be used specifically for this other type of malignancy arising in the esophagus. In past years many reports failed to discriminate between the two types and to exclude adenocarcinoma at the esophagogastric junction when reporting responses to therapy and survival statistics for esophageal cancer.

Malignant neoplasms other than squamous cell carcinoma and adenocarcinoma are very rare and will not be included in this review.

### CHALLENGES OF ESOPHAGEAL MALIGNANCIES

The poor prognosis for patients diagnosed with esophageal cancer has been well recognized and unchanged overall during the past century. The biological fact that symptom development (usually dysphagia) occurs late in this disease has proven to be the one constant that has thwarted all of the diagnostic and therapeutic efforts tried thus far.

The primary symptom of esophageal obstruction is dysphagia. In order for dysphagia with solid food to occur, the potential esophageal lumen diameter, normally about 2.5 cm (or 1 inch), must be narrowed either by a large tumor mass or circumferential growth through about 270° of the wall circumference. The time required for a growth to develop to this extent to produce symptoms has been variously estimated to require many months to

years. During this asymptomatic interval, the carcinoma easily spreads through the three to four millimeter thick (the thickness of 3 pennies) esophageal wall and, in the absence of the protective effect of an outer or serosal layer, readily invades the surrounding tissues and vital organs. Lymphatic invasion occurs during the asymptomatic phase with spread to regional lymph nodes as well as through lymphatic channels in the wall of the esophagus that drain in both cephalad (upward) and caudad (downward) directions.

The difficulty of curing symptomatic esophageal cancer is a continuing challenge and as a consequence, more radical, high risk therapeutic methods have been tried with improved survival in only highly selected, relatively early cases. The history of esophageal cancer is replete with surgical reports, as well as those from radiotherapists and chemotherapists, about treatment programs that initially are enthusiastic but later abandoned. The fixation on cure in earlier times slowed progress in the study on causation, early detection and the importance of palliative techniques. Knowledge of how to best cure these diseases has been limited because of the failure to recognize the need for prospective controlled studies in patients considered good candidates for curative effort. Ideally, treatment should be randomized between the best available surgical, non-surgical methods (radiation with and without chemotherapy) and combined treatment programs utilized by experts in each treatment method.

Much was learned in the twentieth century about treatment of esophageal cancer. The knowledge gained was at the cost of much unsuccessful repetition of similar treatment regimens. The study of therapeutic options must continue but history clearly demonstrates the need for a more focused effort to determine the causes and methods for identifying pre-malignant conditions. New treatment options including modern surgical techniques, combination of chemotherapy and radiation therapy plus surgery and innovative endoscopic methods are proving capable of curing true early carcinoma as evidenced by recent reports from high incidence areas. This curative potential clearly emphasizes the need to develop techniques for earlier diagnosis.

### EPIDEMIOLOGY AND PREDISPOSING FACTORS

The incidence of esophageal squamous cancer in China has been recognized for over 2,000 years and is estimated at 236/100,000 population in the highest incidence areas, and in all

## ESOPHAGEAL MALIGNANCIES AND PREMALIGNANT CONDITIONS: (continued)

areas the incidence has remained fairly constant since the report in 1924 by Davies. Reports from Northern Iran by Elgood in 1951, especially along the Caspian littoral, show an even higher peak incidence at 515/100,000 population. A high frequency has been recognized there since the twelfth century. A unique form of chronic esophagitis has been identified in Iran and China as a predisposing condition for esophageal squamous cancer. There are many high incidence areas around the world including such widely separated regions as South Africa, England and Wales, Puerto Rico, Charleston, South Carolina, France and Japan. By comparison much lower incidences in the United States are estimated at 3 to 5/100,000 population for squamous cancer and 1.3/100,000 for adenocarcinoma. The incidence of adenocarcinoma at the junction of the esophagus and stomach is 2.8/100,000.

The frequency among white men and women has not changed appreciably, but there has been a 30 percent increase among the black population over the last 30 years. King and Locke have reported that persons who were born in China or Japan and moved to the United States have a two to three times higher incidence for esophageal cancer than those of the same racial background born in this country.

Various combinations of possible predisposing factors for esophageal squamous cancer have included dietary deficiencies, dietary carcinogens, race, heredity, tobacco, alcohol and other chemical injury, stagnation of esophageal contents, and intestinal metaplasia (Barrett Esophagus) with dysplasia following prolonged gastroesophageal acid reflux disease.

### Upper Aerodigestive Carcinoma

Squamous cell carcinoma of the esophagus has been reported to have a remarkably high associated incidence (10 to 16.4%) of similar carcinomas in the mouth, tongue and throat (oropharynx) and larynx. Surveillance endoscopy is reasonable to utilize for screening patients with a history of cancer in these locations, although no precise interval for such examination has yet been established. Early esophageal squamous cancer in the United States is most likely to be found in this high-risk group with a history of cancer of the head and neck areas.

### Columnar-Lined Esophagus (BE)

In 1950, Barrett reported peptic ulceration in a tubular segment in the chest lined by columnar epithelium that he incorrectly believed was the stomach attached to a congenitally short esophagus. Three years later, Allison and Johnstone correctly pointed out that the segment lined by columnar epithelium was in all other respects located within the esophagus. Although the squamocolumnar mucosal junction (squamous in the esophagus and columnar in the stomach) was displaced proximally in the tubular esophagus, they recognized that the columnar epithelium extended above the lower esophageal sphincter, that the muscular layers surrounding this segment was typically esophageal and that esophageal glands were located beneath the columnar epithelium. They also correctly proposed that this condition was acquired as a consequence of gastroesophageal acid reflux and that it may be a precursor of esophageal adenocarcinoma.

There is some evidence for an inheritable basis for the columnar-lined esophagus related to a predisposition of the esophagus to develop the disorder or the tendency to severe gastroesophageal reflux. There are reports of multiple cases of GERD or acid reflux disease and columnar-lined (Barrett) esophagus in the same family. This predisposition in some families seems definitely

inherited and is more often associated with an early age of onset.

### Correlation Between Columnar-Lined Esophagus and Adenocarcinoma

Between 1952 and 1971 there were eleven cases of adenocarcinoma reported with BE. Haw et al. added five more cases in 1973 and emphasized BE as a premalignant condition that was increasing in frequency. In 1975, Naef et al. reported that 8.5 percent of their 140 patients with BE had developed adenocarcinoma. The histologic evolution of carcinoma in BE was clarified by the proposal of Haggitt et al. that this malignancy probably evolves through a sequence of dysplasia and carcinoma-in-situ (non-invasive superficial cancer) that is detectable by endoscopic biopsy. There has been no convincing evidence to date that prevention of gastroesophageal reflux will lead to alteration of the intestinal metaplasia of BE or reduce the predisposition to dysplasia (pre-cancer) and carcinoma.

### Increasing Prevalence of Adenocarcinoma

Esophageal adenocarcinoma is increasing at an alarming rate. Between 1926 and 1976 several reports indicated that adenocarcinoma accounted for 1.7 to 7.3 percent of esophageal cancers. A report from Boston University tumor registries in 1989 revealed 31 percent of esophageal cancers were adenocarcinomas with 84 percent located in the lower third of the esophagus. They compared this report with an 8 percent frequency for adenocarcinoma among esophageal malignancies reported in the National Cancer Survey for the years 1969 to 1971. At this time clinicians must recognize BE as the most reliable indicator for risk of adenocarcinoma of the esophagus. In a 1986 report by Wang et al., of thirty-five esophageal cancers, adenocarcinoma accounted for 34 percent of all cancers and 60 percent of those occurring in the lower third of the esophagus. All adenocarcinomas were in males and all but one was associated with BE.

From 1975 to 2001, the incidence of esophageal adenocarcinoma rose approximately 6 fold in the United States (from 4 to 23 cases per million), a relative increase greater than that of melanoma, breast, or prostate cancer (Pohl, H. 2005). The evolution of adenocarcinoma toward predominance among esophageal malignancies was further confirmed by the 1991 report of Blot et al. They reported a review of cases of esophageal carcinoma collected between 1976 and 1987 by the nine population-based cancer registries that constitute the National Cancer Institute's surveillance, epidemiology and end-results program. This registry accounts for 10 percent of the U.S. population. In this review of 9,405 cases of esophageal cancer, adenocarcinoma accounted for 17 percent. Rates for squamous cell cancer remained relatively constant, but the average annual rates of increase of adenocarcinoma were 9.4 percent among white males, 9.8 percent for black males, and 4.5 percent among white females. Between 1984 and 1987, adenocarcinomas accounted for 34 percent of esophageal cancers in white men. The rate of increase of this cancer in the 1970's and 1980's was higher than any other malignancy. From 1976 to 1987, the rates for squamous cell carcinoma were relatively stable, but rates increased more than 100 percent for adenocarcinoma and actually exceeded rates of squamous cell cancer among white men below age 55. At the time of my arrival in Tampa in 1975, less than 10 percent of cases of esophageal cancer were adenocarcinomas. Today over 60 percent of esophageal malignancies seen in our Swallowing Center are adenocarcinomas.

*Part II of this article will be continued in the next issue.*

## DYSPHAGIA AFTER ANTI-REFLUX SURGERY – Part II

Milton C. Johnson, M.D.

### Therapy

The majority of studies reported in the literature on post-fundoplication dysphagia pertain to re-operation. A review of the literature reveals minimal data pertaining to the success and safety of endoscopic dilation for the treatment of dysphagia after fundoplication. Waring describes his group's experience in the management of dysphagia following anti-reflux surgery. Upper endoscopy and standard dilation was performed as primary treatment in all patients. A non-wire-guided or wire-guided technique was employed for dilation. Fluoroscopy (x-ray guidance) was used for all wire-guided dilations. Dilator sizes ranged from 13 mm to 19 mm. Dilations were performed as early as six weeks after fundoplication. An average of two dilation sessions was required for each patient. Standard dilation was repeated if dysphagia persisted. Pneumatic dilation using a 30 mm balloon dilator and fluoroscopy guidance was offered to individuals with persistent dysphagia despite multiple standard dilations. Pneumatic 30 mm balloon dilation was performed in four of the thirty-five (11%) patients. No complications (e.g., perforation, fundoplication disruption, or new onset gastroesophageal reflux symptoms) were observed after standard dilation or pneumatic (30 mm) dilation therapy.

### Outcomes

Waring discovered several key points when his group evaluated the outcome of their study group. They reported that dysphagia resolved after standard dilation in sixteen out of the thirty-five (46%) patients studied. Dilation is safe in the early postoperative period if the standard gastroscope passes through the area of the fundoplication without overt resistance. Standard dilation was significantly less successful in individuals with a slipped or displaced fundoplication (27%) as compared to individuals with an intact fundoplication (67%). Standard dilation therapy more than four months after fundoplication resulted in

post-fundoplication dysphagia relief in only one out of twelve (8.3%) individuals. In addition, dilation therapy was effective in only one out of six (17%) patients that had undergone multiple fundoplications. The four patients who underwent pneumatic 30 mm balloon dilation had previously undergone more than one fundoplication. These four patients did not demonstrate improvement of their dysphagia following pneumatic 30 mm balloon dilation. Eleven of thirty-five patients (31%) underwent a surgical revision of their fundoplication and eight of thirty-five (23%) decided to undergo repeat dilations over the course of a one year period prior to deciding to undergo re-operation.

### Therapy Summary

The ideal therapy for severe post-fundoplication dysphagia has yet to be determined. Since 1982, four case series report the use of pneumatic 30 mm balloon dilation for the management of dysphagia following fundoplication. The findings reveal only that pneumatic 30 mm balloon dilation can be performed safely. Only the 1990 case series published by the collaborative efforts of Castell and Richter describe the effectiveness of pneumatic 30 mm balloon dilation therapy in the management of dysphagia after fundoplication. They report that "pneumatic 30 mm balloon dilation is safe and effective in those cases in which achalasia patients have undergone fundoplication."

Dysphagia following fundoplication is transient in the majority of individuals. Spontaneous resolution occurs in the majority of patients. Persistent dysphagia is uncommon after anti-reflux operations; but requires an evaluation to determine which patients will respond to standard dilation therapy. Severe dysphagia that persists despite Maloney, Savary or pneumatic (30 mm) balloon dilation that is not discovered to be related to a primary motor disorder of the esophagus (e.g., achalasia) should be considered for surgical revision of the fundoplication.

## CONTINUING MEDICAL EDUCATION

The Center for Swallowing Disorders has continued active participation in graduate medical education by lectures at regional, national and international meetings and by contributions to the medical literature.

### Lecture Presentations by CSD Staff

October 18, 2004: Visiting Professor, University of Michigan Medical School: Esophageal Stricture Classification as a Guide to Therapy. Ann Arbor, MI (Boyce)

November 17-18, 2004: Visiting Professor, Rochester University Medical Center: Medical Therapy of Achalasia. Rochester, NY (Boyce)

December 2-4, 2004: University of South Florida Center for Swallowing Disorders Postgraduate Course: Disorders of the Esophagus and Stomach: 1) Endoscopic Anatomy of the Esophagus, 2) Achalasia – Indications and Technique for BOTOX Therapy, 3) Biopsy Diagnosis of Barrett Esophagus – When, Where and How?, and 4) Complex Strictures: Reflux, Rare and Resistant. Lake Buena Vista, FL (Boyce)

December 2-4, 2004: University of South Florida Center for Swallowing Disorders Postgraduate Course: Disorders of the Esophagus and Stomach: 1) Esophageal and Zenker Diverticula; 2)

Endosonography of Esophagus and Stomach – How Does it Improve Patient Management? and 3) Post fundoplication Dysphagia – Case Studies, Therapy and Outcomes. Lake Buena Vista, FL (Johnson)

March 11, 2005: Walter Reed Army Medical Center Postgraduate Course: Eosinophilic Esophagitis. Washington, DC (Boyce)

May 16-17, 2005: Digestive Disease Week: 1) AGA Clinical Symposium – Transfer Dysphagia and Zenker Diverticulum and 2) ASGE Clinical Symposium – Approach to the Patient with Dysphagia and Management of the Complex Stricture. Chicago, IL (Boyce)

June 15, 2005: University of Minnesota Postgraduate Course: Advances in Gastrointestinal and GI Laparoscopic Surgery: 1) Management of Complex Strictures and 2) Current Techniques for Treatment of Malignant Esophageal Obstruction. Minneapolis, MN (Boyce)

### Contributions to Medical Literature

Boyce HW: The Experts Corner: Dilation of Difficult Benign Esophageal Strictures. Am J Gastroenterol, (Accepted for publication 9/04).

(Continued on page 4)

**Contributions to Medical Literature (continued)**

Choudhry U, Boyce HW. Treatment of Esophageal Disorders Caused by Medications, Caustic Ingestion, Foreign Bodies and Trauma. In: Wolfe MM, ed. Therapy of Digestive Disorders, 2nd Edition. W.B. Saunders, Philadelphia, Pennsylvania, 2005.

Kochman ML, McClave S, Boyce HW. The Refractory and the Recurrent Esophageal Stricture: A Definition. (Accepted Gastrointestinal Endoscopy 5-05).

**THINGS TO REMEMBER**

1. **OFFICE HOURS:** 8:00 a.m. 'til 5:00 p.m. Monday through Friday. Telephone hours: 8:00 a.m. 'til 5:00 p.m. Also, our emergency telephone number for after hours is (813) 974-2201

2. **BILLING:** Payment for services rendered is due at the time of your visit. Please be prepared to pay any co-payments due at the time of your visit to the Center.

Patients who have problems with their physician or facility fee bills should contact Gayle Stephens, Financial Specialist, at the University of South Florida Medical Clinics at (813) 974-3575 between the hours of 9:00 a.m. and 4:00 p.m. Monday through Thursday.

For those patients who are from out-of-town, a new toll-free number has been added for you to call with billing questions. The number is 1-888-873-3627. This number is for calls originating in Florida and is only for billing questions and help with insurance authorizations.

3. **HAS YOUR INSURANCE COMPANY OR PRIMARY CARE PHYSICIAN CHANGED?** With an ever changing medical insurance market (shopping for the best contract, companies merging, others closing their doors, etc), you may have changed insurance company. If you changed your insurance company you may have a new primary care physician. Maybe you have moved and had to choose a new doctor closer to your home. Regardless of the circumstances we would very much appreciate your contacting our office to let us know, (813) 974-3374. This will not only insure we can obtain the necessary authorizations/pre-certifications and that your medical bills go to the right insurance company but it will help us make sure your medical records are forwarded to the right doctor. Thank you for helping us keep the records straight.

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