Esophageal Cancer

The Increasing Face of Adenocarcinoma

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March 29, 2001
Medicine Grand Rounds

This is to acknowledge that Steven Burdick, M.D. has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Burdick will be discussing "off –label" uses in his presentation.

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Rank
Assistant Professor of Medicine
Appointment UTSW September 16, 1996

Administrative Responsibilities

Director of Endoscopy and GI Parkland

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Human Service Award Delivered by Mother Teresa 1995
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American Gastroenterology Association Young Investigator Award 1997
American Digestive Health Foundation Wilson Cook Endoscopic Research Scholar 1998
Physician of the Year Award at Parkland Health and Hospital System 1999
American Gastroenterology Association, AGA Distinguished Presentation Award 2000

Current Research Funding Sources

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Research Areas

Pancreatic and Biliary Diseases
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10 2nd and 3rd Place finishes at State Finals

Esophageal cancer has a frequency of 3.3 per 100,000 population from squamous cell and adenocarcinoma subtypes combined.1 While the incidence of squamous cell cancer has declined over the past 20 years, adenocarcinoma of the esophagus and esophageal-gastric junction has risen 5-6 fold in the United States and Europe, a rate exceeding any other cancer. 1,2 Squamous cell cancer had been the predominate cancer type representing the vast majority of esophageal cancers. In four series ranging from 1926-1976, the proportion of adenocarcinoma was 0.8%, 2.4%, 3.1%, and 3.7% of esophageal cancers. 3,4,5,6 However, multiple reports have identified a trend begin in the 1970's of a rising incidence of adenocarcinoma of the esophagus. 1,7,8,9,10 Adenocarcinoma has surpassed squamous cell carcinoma as the predominate cell type of esophageal cancer.1,2 (See Figure 1). Esophageal adenocarcinoma is predominately a disease of white men with an age-adjusted incidence of 2.5 per 100,000, a white-black ratio of 4:1 and a male to female ratio of 7:1 in whites. 9,11,12,13 Although the risk of adenocarcinoma is greatest among white males, the incidence has risen two or three times in black men and women.13

The American Cancer Society estimated that 12,300 persons in the United States would develop esophageal cancer in 1996. 13-14 This can be compared to incidence of colon cancer which afflicts 6% of the United States population or 133,500 individuals in 1996. 15 Esophageal cancer thus has an incidence of only one tenth of colon cancer yet the mortality is high at 90% at 5 years. 16 SEER (Surveillance Epidemiology and End Results) data from 1989-1995 lists the 5 year survival at 13.3%, thus ranking esophageal cancer as the third most lethal cancer behind only liver and pancreatic malignancies in the United States. 1 A finding which may account for poor survival, is early dissemination of disease. Micrometastasis in resected rib of patients during esophagectomy were detected in 88% of patient. 17 Micrometastasis were independent of histology type, nodal status, or neoadjuvant therapy. Metastatic lesions may not be optimally recognized by routine histologic analysis.18 In a study of 68 patients believed without lymph nodes involvement, an immunochemical analysis identified tumor in 62% of patients (42/68). The presence for Ber-EP4, a monoclonal anti-epithelial cell antibody, was predictive of survival, relapse and relapse free survival. Of note, micrometastasis in bone marrow positive for Ber-EP4 had no prognostic significance.18

The prognosis of esophageal cancer is dependent upon the stage of tumor, histology, and patient age. 19,20 Five year survival rates for tumor stage 1 lesions range between 50-85% for resected tumors. 21-26 Overall actuarial 10 year and 15 year survival were 76.6% and 53.6% for tumor stage 1 and 2. 26 Unfortunately, esophagectomy is not without significant risk to the patient with both acute and chronic impacts. Traditionally the emphasis has been upon survival, but a better understanding of the quality of life and functional outcome assist in the choice therapeutic options. A review in 1994 noted only 44 of 7,569 publications dealt with the quality of life in esophageal carcinoma. 27 Surgical complications appear to be linked to the volume of procedures performed. Low volume centers in one paper had 78% excessive deaths from esophageal cancer surgery. 28 A meta-analysis noted an average mortality of 8% of 76,911 patients of whom 21% were treated with esophagectomy. 29 Arguably, immediate surgical outcomes are improved in early disease. Thus a comparison to early tumors of the esophagus is a

useful comparison. A meta-analysis of esophagectomy outcomes for high grade dysplasia noted an average mortality of 2.6%. 30 The same paper described in more detail other perioperative outcomes regarding esophagectomy for high grade dysplasia at the University of Chicago and Saint Louis University. The complication rate was 70%, anastomotic leak rate of 36%, and a mean length of hospitalization of 18.5 days. 30 Chronic symptoms of reflux 60%, dumping 50%, dysphagia for solids 25%, and significant decrements in health perception and energy /fatigue scores have been noted in long-term survivors of esophagectomy for early esophageal cancer. 26 However, despite advances in surgical techniques and perioperative mortality, minimal improvements in 5 year survival rates have occurred over the past 10 years. 16 Esophageal cancer 5-year survival rates were 11% in the early 1990's as compared to below 10% in the early 1980's. The recognition of micro-metastasis and the minimal impact on the disease outcome with surgery alone has lead to the use of multimodal therapy including radiation and chemotherapy prior to surgery.17,18 However, comparisons among multimodal clinical trials is limited by the lack of a common standard for staging.

The rate of esophageal adenocarcinoma is increasing in the western world but not in Asia or Eastern Europe. 1,2 Esophageal cancer is associated with a poor prognosis secondary to presentations with advanced disease. Detection of esophageal cancer in early stages results in the best therapeutic results. Thus screening programs or chemoprevention, which target high-risk individuals, may offer the potential for increased life span. A review of risk factors and mechanism for esophageal cancer may be helpful in selection of at risk populations. An influence of the outcomes in advanced disease will likely require a new therapy, which influences the disseminated disease into lymphatic and bone marrow.

Risk Factors for Esophageal Cancer

Body Mass Index

The body-mass index is associated with mortality with a direct influence of obesity and cancer deaths. In one report, a 40-80 percent increase of death from cancer occurred in a prospective study involving 1,184,657 individuals. 31 A correlation to this work in animals studies where dietary restrictions noted a reduction in tumor incidence and growth via effects on apoptosis, cellular proliferation and tumor progression. 32 Insulin resistance, compensatory hyperinsulinemia, and increased production of insulin-growth factors accompany obesity. Insulin and its precursors stimulate mitogenesis and carcinogenesis. The prevalence of obesity is significant in the United States and is increasing. Obesity prevalence, as defined by a body mass index of $30kg/m^2$, increased from 12.0% in 1991 to 17.9% in 1998. 33 NHANES III estimated 22.3% of adults the United States meet the criteria for grade 2 and grade 3 obesity by the World Health Organization definition of a body mass index of 30.0 or higher. 34 An additional 32.6% of adults meet the World Health organization's definition of grade 1 disease with a body-mass index between 25.0-29.9. The link between obesity and adenocarcinoma of the esophagus or cardia was further implicated in a Scandinavian population. 35 In this study, obesity as defined by a body mass index (BMI) of $30kg/m^2$ was compared to lean

body mass mean 22kg/m^2. The odds ratios for esophageal adenocarcinoma and cardia adenocarcinoma were 16.2 and 4.3 respectively for the obese group. In contrast, squamous cell cancer was not associated with BMI. Factors including age, sex, tobacco smoking, ethanol use, socioeconomic status, intake of fruits and vegetables, and physical activity did not alter the BMI correlations in this study. Five case control studies concerning obesity concur with this finding noting an increased risk 1.5-6.0 of both esophageal and cardia adenocarcinoma. 36-40 Two other case controlled studies did not observe a link between obesity and esophageal cancer. 41,42 Critics of the negative studies note a failure to differentiate esophageal cancer from cardia adenocarcinoma. The selection of esophageal adenocarcinoma would allow a stronger association to be noted. Second, the exposure estimates in positive findings were obtained via personal interviews not from surrogates. Third estimates of body weight were obtained not more recently than 20 years prior to the interview in which a positive association was found. Recent weight comparisons may have been influenced by tumor effects in some studies. In contrast to the obesity link to adenocarcinoma, squamous cell cancer development appears highest in the lean body mass group. The risk appears highest in the first quartile lean body mass while the risk of adenocarcinoma progressively increases with increasing body mass. The lack of an influence of reflux over obesity is remarkable when noting the prior publication having an odds ratio from 7.7 (5.3-11.4) to 43.5 (18.3-103.5) associated with reflux which was uncontrolled for BMI. 35,43

Table 1. Relative Risks* of Esophageal Cancer, By Cell Type, Associated With Obesity

BMI Quartile	Squamous Cell	Adenocarcinoma
I (low)	1.0	1.0
II	0.5 (0.3-0.9)	1.3 (0.8-2.2)
III	0.8 (0.5-1.3)	2.0 (1.3-3.3)
IV	0.6 (0.3-1.0)	2.9 (1.8-4.7)

Abbreviation: BMI, body mass index.
*Relative risks adjusted for age, gender, race, and smoking.
Data from Chow et al.

Table 2. Body Mass Index 20 Years prior to Interview and risk of Esophageal Adenocarcinoma with regard to reflux symptoms

REFLUX	BMI Q I	BMI Q II	BMI Q III	BMI Q IV
NO	1.0	2.0 (0.7-6.1)	4.4 (1.6-12.4)	7.6 (2.8-20.5)
YES	1.0	2.0 (0.7-6.3)	3.3 (1.2-9.1)	8.8 (3.2-24.2)

Data from Annals of Internal Medicine 1999;130:883-890

Smoking and Ethanol

Influences of smoking and ethanol use have been evaluated for contributing to esophageal cancer. 36,42,43,44,45,46 Smoking and ethanol abuse appear more commonly with squamous cell cancer. 36,42,44,45 (See Table 3 and 4) The cancer risk appears greater with an increased consumption of alcohol. Significant risk has been noted in nonsmokers who drink. However, smoking in combination with ethanol results in a multiplication effect. In one French study, heavy ethanol and smoking resulted in excess of 100 fold-increased risk.47 Variations in ethanol source may increase the risk of cancer. Spirits consumption association appears stronger than other ethanol sources and clusters of areas with a high incidence esophageal cancer are linked with local ethanol beverages. 48,49 These include apple brandies in northern France, maize beer in South African Transkei, sugar distilled beverages in Puerto Rico and South America, and moonshine whiskey in South Carolina. Conversely, adenocarcinoma developing from intestinal metaplasia, appears limited or not related to ethanol use. A few small studies have suggested a weak increase in adenocarcinoma but the effect is always less than the effect noted with squamous cell cancer. 48

Smoking is also a cause of esophageal adenocarcinoma. 36, 41,42,44,45 Data from three areas of the United States connote a 2 fold increased risk of adenocarcinoma among smokers versus nonsmokers. 44 The relative risk of smoking is however consistently higher for squamous cell than adenocarcinoma. The risk of smoking in adenocarcinoma persists up to 30 years after smoking cessation.44 However, the risks of squamous cell cancer decrease within a decade of smoking cessation.

Table 3. Relative Risks* of Esophageal Cancer, by Cell Type, Among Cigarette Smokers

Smoking Status	Squamous Cell	Adenocarcinoma
Nonsmokers	1.0**	1.0 **
Former	2.8 (1.5-4.9)***	2.0 (1.4-2.9)***
Current	5.1 (2.8-9.2)	2.2 (1.4-2.3)

* Relative risks adjusted for age, gender, race, income, and alcohol.
** Reference category.
*** 95% confidence interval
Data from Gammon et al.

Table 4. Relative Risks* of Esophageal Cancer, by Cell Type, According to Alcoholic Beverage Intake		
Alcohol Intake (Drinks/wk)	Squamous Cell	Adenocarcinoma
None	1.0**	1.0**
<5	0.8(0.4-1.6)***	0.7 (0.4-1.0)***
5-11	1.8 (0.9-3.5)	0.6 (0.4-0.9)
12-30	2.9 (1.5-5.4)	0.7 (0.4-1.1)
>30	7.4 (4.0-13.7)	0.9 (0.5-1.4)
* Relative risks adjusted for age, gender, race, income, and smoking. ** Reference Category. *** 95% confidence interval Data from Gammon et al.		

Dietary and Nutritional Factors

Dietary factors play a role in the development or suppression of esophageal cancer. Nutrition deficiencies are seen in both Plummer-Vinson syndrome, a condition characterized by iron deficiency, and celiac disease, a malabsorption disorder of the small intestines. These two disorders were linked to esophageal cancer and initially suggested an impact of nutrition and esophageal cancer. 50,51 Case-control results from throughout the world have linked dietary factors to adenocarcinoma and squamous cell cancer of the esophagus. 37,41,52 After adjusting for smoking and alcohol, there is an approximately two-fold increase risk with a diet low in intake of fruits and vegetables. Trials investigating the influence of specific minerals and vitamins have been performed with respect to their influence on esophageal cancer. 53-56 In one series, evaluations were performed in an area with a high incidence of esophageal cancer Linxian, China. 53-55 In this area, 20% of individuals have esophageal dysplasia. The area is afflicted with both squamous cell cancer and adenocarcinomas at rates 100 times
the average for American Caucasians. The adenocarcinoma of the esophageal-gastric junction frequently involves the gastric cardia and was termed stomach cancer in regard to this study. In one study, 3,318 individuals with esophageal dysplasia were randomized to receive either a multiple vitamin or placebo. 53 Follow-up was performed at 30 and 72 months with one-four and one-eighth of patients completing follow-up at the respective intervals. The predominate cause of death was cancer in 54% of all deaths. Cytologic abnormalities of squamous or columnar cells were grouped into abnormal classifications. A reversion to non-dysplastic cytology was noted with an odd ratio of 1.23 times higher than the placebo group. The cumulative risk of developing esophageal cancer was 8% lower a non-significant difference. In a second study, mortality and cancer deaths were assessed in 29,584 adults age 40-69 over 5 years. 54 Subjects were randomized in a 2^4 pattern to assess the four combinations A) Retinol/Zinc B) Riboflavin/niacin C) vitamin

C/Molybdenum and D) Beta-Carotene, Vitamin E, and Selenium. Cancer was the leading cause of death with 32% of all deaths secondary to esophageal or gastric cardia cancer. A significant reduction in mortality occurred in group D($P=0.03$). The reduction was mainly related to lower cancer rates and was most pronounced from stomach etiology. In the United States conflicting results regarding an association with selenium and cancer lead to a multi-centered trial in the United States. 56 Seven dermatology clinics in low-selenium area investigated the influence of selenium on the development of basal and squamous cell skin cancers with a secondary endpoint of all cause mortality. A significant reduction in cancer deaths ($P<0.01$) occurred with the use of selenium. The reduction was significant in lung, prostate and colorectal cancers. Esophageal cancer occurred in 2 patients within the selenium group compared to six in the control group and did not reach significance. The influence of these dietary factors suggests a role in diets low in these nutrients. Whether a reduction in the cancer could be seen in the well nourished United States population has not been demonstrated.

Gastroesophageal Reflux Disease (GERD) and Intestinal Metaplasia

The link between adenocarcinoma and reflux disease is thought to be due to reflux induced intestinal metaplasia with progression through dysplasia into cancer. 57 Reflux of acid and duodenal-gastric contents cause an increased proliferation and loss of cellular differentiation. 58,59 These changes can be improved with acid suppression and avoidance of duodenal-gastric reflux. 58 Correspondingly the symptoms of reflux or regurgitation have been linked with the risk of adenocarcinoma. The development of Intestinal metaplasia above the esophago-gastric junction is found in 10-15 % of patients suffering from gastro-esophageal reflux disease. 60,61 The finding of intestinal metaplasia of greater than 3 centimeters in length is clearly recognized as Barrett's disease. This finding has an approximate annual incidence of 0.8% conversion to adenocarcinoma in prospective trials (range 0.5-1.9) or when compared to controls, a 30-60 fold higher risk than that of the general population. 43,62 Barrett's esophagus appears more common in white men with chronic reflux symptoms. 2,43 Short (less than 3 centimeter) segments of intestinal metaplasia and intestinal metaplasia without displacement of the squamo-columnar junction appear to have a significantly lower risk of developing adenocarcinoma than intestinal metaplasia of >3 centimeters.63,64 However, the contribution of short segment Barrett's may
partially explain the observation that Barrett's esophagus can not be consistently associated with all cases of adenocarcinoma.63,65 In one study only 46% of patients with esophageal adenocarcinoma had detectable Barrett's mucosa.65 The progression from intestinal metaplasia through dysplasia to adenocarcinoma has been proposed. 66 Dysplasia is neoplastic cells confined within the basement membrane of the gland from which it arose. Dysplasia is classified as indeterminate, low grade or high grade.

Barrett's esophagus has malignant potential and we need to ask who do we screen, what techniques to utilize, and question the effectiveness of surveillance. The American College of Gastroenterology practice guidelines recommend endoscopy for patients with long standing GERD symptoms or age greater than 50 years of age. 64 Additional data suggests higher yields and greater cost efficiency could be obtained with concentration on

the higher risk groups of Caucasian males. Surveillance with biopsies should be obtained every 2 centimeters in four-quadrant fashion. The use of a large channel endoscope, jumbo forceps, and turn/suction technique will optimize tissue sampling. Areas of dysplasia should be screened more intensively. 67 The interval recommendations are 2 years for intestinal metaplasia without dysplasia, 6 months for low grade or indeterminate dysplasia, and 3 months or resection for high-grade dysplasia. 64 Surveillance for Barrett's has been debated as to the ability to diagnose early cancer and the cost-effectiveness of this practice.

There are no randomized controlled trials demonstrating the effectiveness of interval surveillance of intestinal metaplasia. Further calls for such a trial would require thousands of patients over a long period of time. However, series of outcomes with the use or nonuse of screening provide insight into their respective outcomes. One study elected not to perform surveillance for 155 patients with intestinal metaplasia. 68 Follow-up at eight years noted 79 had died, five had developed esophageal cancer, and two had died from esophageal cancer. Thus, death from other co-morbidities is frequent. Three studies that adopted screening techniques found a significantly higher frequency of early esophageal cancer than a control group of unscreened patients who presented de novo.69,70, 71 Further, survival was influenced. In one study two-year survival was improved at 85.9% for surveyed patients versus 43.3% in non-surveyed patients with Barrett's carcinomas. 69 In this report only 1 of 16 surveyed patient was diagnosed with nodal disease versus 34 of 54 in the non-surveyed patients. To emphasize the importance of detection prior to symptoms 63% of the surveillance group was asymptomatic versus 0% in the non-surveillance group. In another report 5 year survival was 62% versus 20% in a cohort of unscreened Barrett's esophagus patients.70 In a third report survival was not assessed but early disease with lymph node negative was seen in 83% verus 48% in the unscreened group. 71 In a fourth report a group from Marseilles France noted an increasing prevalence of early tumors. 72 Patients referred from endoscopic surveillance programs were associated with improved survival.

The use of screening of intestinal metaplasia should be compared on a cost-effectiveness basis to other common accepted screening measures. The cost of detecting cancer was calculated at 14,868 pounds for men (one cancer per every 59 patient years) and 42,084 pounds for women (one cancer per every 167 years). 71 In comparison the cost per year of life saved for breast cancer with mammography was 1,000,000 pounds.71 An American study compared the cost of cancer detection in screening Barrett's mucosa versus mammography to detect breast cancer. 73 They utilized surveillance results from 1980 to 1995 for Barrett's and 1994 mammography results in Duluth, Minnesota. The cost to detect a case of adenocarcinoma was 37,928 dollars and was comparable with mammography costs of 54,513 dollars per occult breast cancer diagnosis. The cost per year of life saved was 4,151 dollars for adenocarcinoma in Barrett's versus 57,926 dollars for breast cancer. A third cost-utility analysis estimated endoscopic surveillance every 5 years was comparable to other health care costs. 74 This study elected to use a 0.4% yearly incidence of intestinal metaplasia conversion to adenocarcinoma. Thus despite the use of low estimate of cancer risk in Barrett's screening, the cost appeared at 39% of the cost of cervical screening per quality adjusted life year gained. The reader should

appreciate the impact of targeting population at risk, as the prevalence of disease directly impacts upon with the costs of surveillance. However, screening of intestinal metaplasia appears more cost effective than the accepted practices of mammography or cervical (PAP) smears.

The esophageal gastric junction is generally recognized at the proximal margin of the gastric fold, but recognition of the characteristic salmon pink mucosa above the esophageal-gastric junction can be difficult. Histology remains the standard for the diagnosis of metaplasia or cancer. Intensive histologic sampling has been advocated as the area of dysplasia can be small and patchy. 64,67 In clinical practice, this intensive method of sampling may not be adhered to as it is time intensive and tedious. Thus alternative methods to enhance detection may be useful. Chromoendoscopy is a cheap and readily available method, which every endoscopist can use. A dye is sprayed onto the targeted mucosa and washed. Methylene blue chromoendoscopy has been used to enhance identification of areas of intestinal metaplasia but the technique can be tedious, prolong procedure time, and has not consistently demonstrated enhanced recognition of Barrett's esophagus. 64,75,76,77. Advocates of the technique note areas of heterogenous staining in area of dysplasia and staining of and intestinal metaplasia allowing one to distinguish areas of gastric metaplasia. In a prospective trial comparing endoscopy with biopsy every two centimeters to methylene blue directed biopsies methylene blue directed biopsy was significantly superior in the ability to diagnosis either dysplasia or cancer in more patients than endoscopy directed biopsies (P=0.03. 77). The costs to diagnosis either cancer or dysplasia were significantly lower (P=0.0001). This advantage was significant in only the segments of intestinal metaplasia /Barrett's greater than three centimeters. Alternative methods to optically sampled tissue or direct biopsies in Barrett's have been evaluated with spectroscopy. 78,79 In these methods, a light is placed upon the area in question and the light which is absorbed for fluorescence or scattered have been correlated with dysplasia. Other potential areas under evaluation include optical coherent tomography and electrical impedance biopsies. 81

When high-grade dysplasia is present and esophagectomy has been performed 33-48% of patients have been found to have adenocarcinoma.30,81,82 The failure to diagnose adenocarcinoma in high-grade dysplasia by endoscopic surveillance may be related to the number and size of biopsies taken.67 An extensive biopsy surveillance program utilizing jumbo biopsy technique has provided a natural history of high-grade dysplasia in 58 patients. 83 In this series 26% progressed to cancer, 27% had improvement in dysplasia score, and 47% of patients remained stable. The median follow-up for patients was 23.7 months in this study. The progression from intestinal metaplasia through adenocarcinoma correlates with changes in tumor suppressor genes, tumor oncogenes, and cellular proliferation.

Helicobacter

The rising incidence of esophageal adenocarcinoma has been observed to coincidence with an opposing decline in peptic ulcer disease and Helicobacter organism prevalence. 84,85 The potential for a protective effect of Helicobacter is noted to correlate with a

decrease in the bacteria's presence in patients with gastroesophageal reflux disease, Barrett's, and adenocarcinoma. 86,87,88 Cag-A positivity may be an important virulence factor, as it appears associated with a reduced risk of cancer. The higher incidence of Helicobacter in black and Asian races may explain the low frequency of adenocarcinoma in these ethnic groups.89 However,the disparity in sex differences can not be explained by this model. Proton Pump use was not significantly associated with intestinal metaplasia, dysplasia or esophageal adenocarinoma. 88

Mechanisms of Proliferation and Differentiation Leading to Cancer Sequence

The P 53 tumor suppressor gene is located on the short arm of chromosome 17 (17P).90 Wild type P 53 protein has an inhibitory effect of cellular proliferation, related to its ability to arrest cells in G1 phase of cell cycle. P 53 thus is involved in cell cycle regulation, DNA repair, and programmed cell death (apoptosis). P 53 alterations become progressively increased through the sequence from intestinal metaplasia to adenocarcinoma.91 P53 alterations were found in 5% of patients with intestinal metaplasia, 15% with indefinite or low-grade dysplasia, 45% with high-grade dysplasia, and 53% with adenocarcinoma. P 53 expression may thus be a marker for progression to esophageal cancer. P 53 mutations additionally correlate with outcomes including advanced TNM stage, residual disease after surgery, and shorter survival. 92,93

Mutations involving epidermal growth factor receptor (EGFR) or the putative oncogene (ERB-B-2), have been noted in adenocarcinoma and squamous cell cancer of the esophagus. 94,95 EGF and its ligand transforming growth factor alpha act by autocrine or paracrine mechanism to promote cell cycle progression. Epidermal growth factor mutations can work with k-ras dependent pathways to accelerate G1. 96 However, k-ras mutations are very rare in esophageal cancer. 97 Malignant transformation from intestinal metaplasia to adenocarcinoma is suggested by epidermal growth factor alterations in Barrett's esophagus. 94 Inhibition of EGF through receptor blockade is currently being investigated in the therapy of esophageal cancer and additionally may offer the potential for prevention of Barrett's progression to cancer.

Increased cellular proliferation with a decrease in cell differentiation, cell cycling, and alterations in DNA content are seen with the progression from intestinal metaplasia to cancer. 91,97 The magnitude of cellular proliferation directly correlates with the severity of dysplasia. 97 In normal squamous cell tissue, the majority of cells remain in the G 0 (quiescent) phase. In contrast, in Barrett's metaplasia, 1/3 of biopsy specimens are in the G1 phase of cell cycling and high-grade dysplasia has an increase in G2 fraction. 91 DNA content or ploidy of the cell undergoes changes with neoplastic proliferation. With the exception of germline cells, all cells of the body are normally diploid. Aneuploidy is seen in 4% of intestinal metaplasia, 6% of low-grade dysplasia, and 63% of high-grade dysplasia. The combined significance of proliferative changes as measured by either aneuploidy or G2 in patients with high grade dysplasia or adenocarcinoma, is striking. Aneuploidy or increased G2 cycle was seen in 9/13 with high-grade dysplasia/adenocarcinoma. In comparison these proliferative changes did not occur in a group of patients without high grade dysplasia or adenocarcinoma. These collective

changes indicate abnormal cellular proliferation is a fundamental change that underlies progression from intestinal metaplasia to adenocarcinoma. The proliferative changes and decrease in cell differentiation can be improved with acid suppression and, in theory, control of acid secretion may offer a potential means to reverse dysplasia. 58 However, these proliferative changes may not be solely attributed to acid reflux as bile and pancreatic reflux can induce similar proliferative changes in animal models. 58,59 Additionally, patients with Barrett's esophagus may be acid insensitive, and therefore, resolution of symptoms is a poor marker for elimination of acid reflux. Recent trials in patients with Barrett's disease have found significant reflux occurring despite resolution of symptoms with proton pump therapy. 98 The adequacy of acid suppression has rarely been documented in clinical trials for dysplasia and thus the influence of acid suppression as measured by 24-hour intraesophageal Ph remains an attractive theory needing evaluation. Cell proliferation may also be decreased with inhibition of the enzyme polyamine synthesis. Difluoromethylornithine (DFMO) is a polyamine synthesis inhibitor currently in investigation. 99 Proliferating cells additionally, interact with environmental procarcinogens to convert to carcinogens through the cytochrome p 450 system.100 Therefore inhibitors of cytochrome P 450 may have chemopreventive activity.

Prostaglandin synthesis (PGE2) correlates with multiple gastrointestinal tumors including colon, gastric, and esophagus origins. 101,102Therefore the suppression of PGE 2 synthesis with either a selective COX 2 inhibitors or nonselective COX 1 and 2 inhibitor (NSAID), may offer therapy for esophageal cancer. Prostaglandin E2 is increased from esophageal mucosa in chronic esophagitis. 103Additionally, prostaglandin E 2 may contribute to dysmotility and duodenogastric reflux.104 Epidemiologic studies have yielded conflicting results with one study noting no protection, while two found a reduction of cancer ranging from 40-90% with regular aspirin use.105,106 Selective COX-2 inhibitors have recently become available and will offer less adverse side effects than non-selective inhibitors. In one study, COX 2 was seen in 78% of esophageal cancers and 91% of squamous cell carcinomas but did not appear to be expressed in Barrett's metaplasia. 107 Another study confirmed COX-2 expression in esophageal cancer and additionally noted expression in 80% of Barrett's. 108

Other proposed chemopreventive strategies include induction of protective mechanisms and induction of apoptosis.63, 100 Heat shock proteins and glutathione are protective to cells during inflammation.109,110 Barrrett's esophagus has reduced levels of heat shock proteins and glutathione, thus increasing either may confer protection from inflammation and dysplasia. Additionally, intestinal metaplasia is less responsive to apoptotic stimuli. 99 The impaired removal of damaged or neoplastic cells may increase the risk of cancer.

Therapy

The survival for esophageal cancer is correlated with tumor stage. The TNM staging system has been recommended by the American Joint Committee on Cancer (AJCC) and the International Union against Cancer (UICC). 111,112 T stage is the depth of invasion, N is nodal status, and M is Metastasis classification. T1 invade the lamina propria or submucosa, T2 lesions invade the muscularis propria, T3 lesions invade the adventitia,

and T4 lesions invade adjacent structures. Comparing clinical trials without a standard means of staging to evaluate the influences of therapy makes the comparison dubious. Surgical resection has been the traditional approach for esophageal cancer. Yet, this approach has resulted in an overall survival of 16-18.6 months despite complete resections. 113,114 The limited survival is related to the development of metastatic disease. When rib resected during esophagectomy for esophageal cancer is analyzed for occult metastasis, micrometastasis had occurred in 88% of patients. 17 Micrometastasis were independent of histologic subtypes, t stage, or nodal involvement. In early stage disease (T1 or T2) micrometastasis were seen in 10/11 adenocarcinomas and 3/3 squamous cell cancers. Additionally, neoadjuvant pre-surgical therapy appears to have little influence on the prevalence of micrometastasis in rib marrow. 87% of patients who received neoadjuvant therapy had micrometastasis versus 89% in-patients who underwent surgery. This data suggests an incomplete or non-response with neoadjuvant chemotherapy or chemo-radiation therapy. Further, macroscopic tumor was evident in all patients who received either adjuvantive therapy or radiotherapy. In a separate study of histologically tumor free lymph nodes, immuno-histochemical stains identified metastatic disease is 50% of the patients. 18 Ber-EP4 cells in lymph nodes were independently predictive of significantly reduced relapse free survival and overall survival. 12 of 67 patients had lymph nodes free of tumor and survived without recurrence at median follow up of 21 months. The incidence of BER-EP 4 cells appeared to increase with T stage of disease was 14/30 for T2 disease, 24/35of T3 and 3/3 of T4. These findings may account for the overall poor prognosis of therapy and raise questions whether less invasive therapies may produce similar outcomes to the traditional surgical therapies.

The above data raise questions regarding the rationale for multimodal therapy (radiation, chemotherapy, and surgery). However, outcome data in a randomized prospective multi-centered trial favors the use of multimodal therapy for adenocarcinoma. 113 Chemoradiation therapy with surgery versus surgery alone in adenocarcinoma, noted a survival advantage and downstaged nodal disease, with a 3% incidence of life threatening side effects associated with multimodal therapy. The results in squamous cell cancer were less favorable. 114 Chemoradiation preoperatively did not improve survival, but was associated with longer disease free survival and longer interval of disease free local disease, at the expense of a statistically significant increase in post-operative deaths. Neoadjuvant chemotherapy versus surgery alone has been studied for squamous cell cancer and adenocarcinoma.115 The addition of cisplatin and fluorouracil did not improve overall survival and did not influence the rate of local or regional disease. While the therapy did little good, it also appeared to have few adverse influences on outcomes as the addition of chemotherapy did not increase the morbidity or mortality associated with surgery.

The pattern of esophageal cancer appears to be changing in select centers with early disease, T1 or T2 noted more commonly. 72 This improvement in patient selection appears to be linked to a risk reduction of esophagectomy. Survival was statistically improved when referred from endoscopic surveillance programs. Five year survival for early disease treated with surgery is 62-82%. 26,30 Complications are high at 40-73% and the risk of death has ranged from 2.6-10%.26,30, 116 Centers with higher volumes

have better outcomes. 117,118,119 Accompanying esophagectomy were strictures in 70%, anastomotic leaks in 25%, and hospital stays of greater than 2 weeks. 30 Long term follow-up in cured patients note symptoms of reflux in 60%, dumping in 50%, and dysphagia in 46%. 26 Quality of life after curative esophagectomy has been compared to a normal population with SF-36 form. Decreased physical function and energy occurred after esophagectomy. 26 Anastomotic leaks adversely affected physical functioning on long term evaluation. However, 16% of patients were asymptomatic and mental health was increased. A cervical anastomosis resulted in a statistically significant reduction of reflux symptoms. Minimally invasive esophagectomy has been successfully performed in significant numbers and may replace larger incisions associated with conventional surgery. In this minimally invasive surgery, the lower esophagus is approached via laparoscopically and the upper surgical margin is accessed with either mini-thoracotomy or thoracoscopy. In one series of 77 patients, no mortalities occurred in relationship to surgery.120 Four patients required conversion to open procedures and the major complication rates was 27%. The most common major complication was anastomotic leaks in 7/77. Median length of stay was 7 days. Patients with esophageal cancer or high-grade dysplasia may be at increased risk of complications secondary to age, co-morbid disease, or find the reduced quality of life associated with surgery unattractive. Therapy thus needs to be a tailored to each individual patient with consideration of the natural history of disease and alternative therapies including photodynamic therapy, radiation therapy, or endoscopic ablation.

Photodynamic therapy involves the administration of a photosensitiziting agent followed by photoactivation with an energy source. Photodynamic therapy requires an aerobic environment and tissue photoactivation with an energy source. Photodynamic therapy requires an aerobic environment and tissue destruction can not occur without oxygen. It is important to appreciate that each photosensitizing agent will have different properties which will influence the treatment depth. For example, 5 ALA has a superficial action of 1-2 mm whereas Sodium porfimer is activated with 630nm wavelength of light and can have effects to 10 mm depth. 121,122 Sodium porfimer has been evaluated in 123 patients with early esophageal cancer who were not considered operative candidates secondary to co-morbid disease. 123 One hundred and four patients had squamous cell cancer and 19 had adenocarcinoma. The five year disease specific survival was 75% and compares to the 62-82% survival with surgical series of early esophageal cancer. 26,30,123 Combination therapy with radiation and chemotherapy therapy has been advocated to reduce the stage of disease and decrease the incidence of metastasis. All 19 adenocarcinoma and 37 squamous cell cancer patients were treated without other modalities secondary to co-morbidities limiting therapy. Although not randomly studied in this trial, multi-modal therapy did not appear to improve outcomes. Adverse effects with photodynamic therapy included stenosis 35%, photosensitive reactions 13%, and local recurrence 35% at 18 months. Photodynamic therapy alone or in combination with other ablation techniques has been used to treat Barrett's dysplasia and early adenocarcinoma of the esophagus. The results are better with lower dysplasia scores.116,121,122 The results of the largest series are reported below in Table 1.122 However, strictures, photosensitivity, and a high incidence of residual Barrett's are disadvantages of this investigational technique.

Dysplasia Type	Dysplastic Ablation	Barrett's Ablation
LGD	13(92.9%)	7(50%)
HGD	56(76.7%)	32(43.8%)
Cancer T_1 or T_2	9(69.2%)	4(30.8%)

Photodynamic therapy with 5-Aminolevulinic acid (5-ALA) has been used in Barrett's with dysplasia. 121,124 HGD or intra mucosal cancer was eliminated in 10/10 patients and 17/22 (77%) respectively at mean follow-up of 9.9 months. 121 In a second prospective randomized trial, 5-ALA was compared to placebo in 36 patients with low grade dysplasia. 124 All dysplasia was ablated with intervention although Barrett's mucosa persisted in every patient. 5-ALA has a lower depth of penetration than hematoporphyrin derivatives and thus has a very low stricture rate. Additionally, the photosensitive period is much shorter with 5-ALA (36-48 hours) than hematoporphyrins (30 days). Photodynamic theory with hematoporphyrin derivatives has been compared to other palliative means to improve dysphagia. 218 patients were randomized to therapy with Nd:YAG laser or sodium porfimer. 125 Perforations occurred less frequently with PDT 1% versus 7% ND:YAG ($P<0.05$). Termination of laser was less frequent with PDT 3% versus 19% but photosensitive reactions occurred in 19% of patients. The time to palliation failure was 34 days for PDT and 42 days for ND:YAG. Survival was limited to 4-5 months in both groups. The addition of radiation therapy to endoscopic therapy has resulted in improved ECOG performance index, dysphagia score, and survival when compared to endoscopic procedures of dilation and plastic stenting alone. 126

Endoscopic thermal ablation techniques is another area of research of alternative therapies for Barrett's disease or dysplasia.116,127 One difficulty with these techniques is the need to have a depth of 1-2 mm through out the targeted area. A superficial therapy risks residual disease while deeper injuries may result in strictures or perforations. Attempting to "paint" or cover the area is more difficult with longer segments. One could compare this to a French impressionist painting in which multiple small dots were used to create an image. Argon plasma coagulation technique appears the most promising of the thermal approaches.128 Endoscopic mucosal resections have been performed to treat esophageal dysplasia and adenocarcinoma of the esophagus safely and effectively. 129 However, the application has been limited to select centers and concern for multifocal disease or cancers arising from other sites of dysplasia in Barrett's is not addressed with this therapy.

Palliation of dysphagia can be achieved by several endoscopic techniques including dilation, injection ,and stenting. 130-132 Esophageal stenting has evolved from placement of plastic sleeves to the deployment of expandable metal stents into the affected area. Stenting is associated with life threatening complications including bleeding, perforation, or compression of the adjacent airway. 130 Radiation and chemotherapy may increase the risk of complications
but other investigators have not confirmed these results and emphasize stent design may influence the migration and complication rates. 133,134 Other concerns are tumor locations, which require stenting adjacent to the trachea or intragastric with respective

concerns for airway compression, regurgitation and aspiration, or mechanical injury with bleeding. 135 After stenting, patients are at risk to reflux gastric contents and additionally require a soft diet. Despite these disadvantages, stenting is the best treatment option for esophageal-bronchial fistula disease. Additionally, stenting results in sustained relief of dysphagia with one treatment. The ability to provide dysphagia relief in one session and the less frequent need for subsequent dysphagia therapy are advantages over other endoscopic therapies. Despite the high initial stent costs the need ability to avoid multiple endoscopic therapies may contribute to a favorable cost-benefit for stenting in the palliative care of patients. 136

Radiation therapy has provided long-term survival in 23%-71% of cases. 137 A review of 1,382 patients found persistence or recurrence of the primary site in 56-85% of patients. 137 Local regional failure was more common than distal disease despite combination with chemotherapy. Combined chemo-radiation therapy versus radiotherapy alone trials have included both adenocarcinoma and squamous cell carcinoma. The results favor combined therapy at the expense of an increased risk of life threatening adverse effects. One trial was stopped when the results demonstrated a survival advantage for combination therapy. 138 Median survival was 8.9 months with radiotherapy alone versus 12.5 months for combination therapy. Combination therapy had fewer local and distant recurrences, but life threatening side effects were noted in 20 percent of patients as compared to 3% when treated by radiation alone. Local recurrence was 26% in combination therapy and 37% in medication therapy alone. 139 A second trial of local disease noted 5-year survival of 26% in combination therapy and 30% in radiation therapy alone. Life-threatening side effects were 10% with combination versus 2% with radiotherapy. Palliative radiation therapy improves dysphagia in 60-85%.137,140,141. Dysphagia relief will last 5-10 months. The success of radiation therapy decreases with increased tumor length, and strictures occur in 50-67%. 25-50% of these strictures will be benign and amenable to dilation.

Summary

Esophageal cancer outcomes are best when the disease is recognized early, preferably in the asymptomatic stage. Adenocarcinoma arising from intestinal metaplasia is rapidly increasing and insights into the metaplasia, dysplasia, carcinoma sequence have yielded several valuable areas, which offer the potential for chemoprevention, prognosis, and therapy. Alterative therapies for esophageal dysplasia and early esophageal cancer are being investigated, but surgery is the traditional therapy. Endoscopic screening, which identified early lesions, has increased the prevalence of early disease at select centers. Advanced disease, T3 or T4, has poor outcomes, and therapy is primarily palliative. Novel therapies which influence the biology of advanced esophageal cancer will likely be need to influence the survival of advanced disease.

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