CANCER OF THE ESOPHAGUS

INTERNAL MEDICINE GRAND ROUNDS

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Introduction

The first description of esophageal cancer comes from China over two thousand years ago. The intense fear of this deadly disease has resulted in the long-standing tradition of the worship of "god of the "throat".[1] The tremendous differences in incidence within small geographic areas and sharp changes in incidence over time, suggest a predominant role for environmental factors.[2] Although relatively uncommon in the USA, esophageal cancer is one of the most deadly Gastrointestinal tumors. It presents insidiously causing trouble swallowing and weight loss. A large group of patients have advanced disease at the time of presentation. Over the past two decades there has been a dramatic improvement in our ability to diagnose, stage, palliate and in selected patients cure this deadly tumor.

Incidence and epidemiology

Cancer in the esophagus is the sixth most common cancer in the world, but in developing countries it ranks fourth.[2,3] In some developing countries esophageal cancer is a major public health concern with an exorbitant high incidence. For example in the Gombad area of Iran the incidence of esophageal cancer is 165.5 per 100,000 population.[2]

In the USA esophageal cancer is uncommon. The overall age-adjusted incidence in 1987 was 3.9 per 100,000 population with an age-adjusted mortality of 3.4 per 100,000 population.[4] For 1995 the American Cancer Society estimated that there will be 12,100 new cases of esophageal cancer, 8,800 in men (73%) and 3,300 (27%) in women. The estimated cancer death of esophageal cancer in the USA for 1995 is 10,900 patients.[5]

In table 1 we can see the dramatic differences in incidence among different countries (figure 1). In addition, wide variation in the incidence occurs within countries. In China, the incidence of esophageal cancer is much higher in the province of Hebi (139.8 per 100,000 population) when compared to the province of Hunyuan (1.43 per 100,000) population.[1]

Race also appears to be an important factor. In the USA, the incidence of esophageal cancer is much higher in blacks than in whites. In Connecticut esophageal cancer was diagnosed in 19.5 per 100,000 population blacks while only 5.3 per 100,000 population whites.[2] In addition, geographic variation among blacks is also substantial (greater than for any other tumor). High rates of esophageal cancer in blacks have been observed in Washington,DC and South Carolina.[6] A comparison with the incidence of esophageal cancer and other races is shown in table 2.

Esophageal adenocarcinoma does not show a similar wide geographic variance as squamous esophageal cancer and appears to be mostly related to gastroesophageal reflux disease and Barrett's esophagus (see below).[7] As shown in figure 2, the incidence of esophageal adenocarcinoma has been increasing over the past 4 decades.

Predisposing conditions

Despite the exceptionally high rates of Squamous esophageal cancer in endemic regions, no single environmental factor can account or explain the formation of the tumors. Extensive comparisons of the dietary and cultural habits of people living in geographically distinct, high incidence areas have revealed little in common to suggest a similar pathogenic mechanism for squamous esophageal cancer. Thus, it seems likely that each of the high risk areas has its regional peculiarities that are of etiologic significance.
Thus, the development of esophageal cancer probably results from synergistic actions of some or many of the etiologic factors described in table 3.

Case control studies in America, Europe and South Africa have shown tobacco and alcohol as the main risk factors for esophageal cancer.[2,6] Heavy smoking has been associated with an increased risk for developing esophageal carcinoma[2,4,6,8-10] Excessive alcohol consumption appears to be a risk factor on its own, but the risk increases in a multiplicative fashion when alcohol is combined with tobacco.[2,4,6,8-10] In New York, heavy drinkers who were moderate smokers were found to have 25 times the risk of esophageal cancer than among smokers who did not drink.[11]

Tobacco can be carcinogenic when used in any form, cigarettes, cigar, snuff and chewing. The mechanism of tobacco carcinogenesis is not fully understood but smoke constituents such as 3,4-benzo[a]pyrine and various nitrosamines may play a role.

The mechanism of alcohol carcinogenesis is unknown but may be related to the aromatic hydrocarbons found in distilled liquors. Induction of the P-450 microsomal enzyme may also lead to accumulation of carcinogenic metabolites derived from food or the alcoholic beverage per se.

Nitrosamines which are carcinogen in animals, have been suggested to be associated with the risk of developing esophageal cancer.[8,12,13] In China consistent geographical correlations were found between the indices of exposure to exogenously and endogenously formed N-nitroso compounds and the development of esophageal cancer.[14]

Reduced soil levels of Molybdenum have been found in endemic regions.[1] Molybdenum is a co-factor for nitrate reductase in plants and deficiency leads to accumulation of nitrates.

In areas where esophageal cancer is endemic, grains and foodstuffs are frequently contaminated with fungi.[12] It is possible that fungi could reduce nitrates to nitrates but also could decompose proteins and increase the amount of amines in food, consequently promoting the formation of nitrosamines.

It appears that diets deficient in vitamins A,E and C, niacin, riboflavin are associated with an increased risk for esophageal cancer.[6,9,10,15,16] It is possible that low levels of these nutrients predispose to the development of esophageal cancer by increasing the susceptibility to various carcinogens.[10,12,17] However, there is no evidence that replacement or addition of vitamins will prevent the risk of esophageal cancer. In Linxian, China, 3,400 patients with severe dysplasia of the esophagus were randomized to receive a daily supplementation of a multiple

vitamin/mineral preparation versus placebo. After 6 years there was a non significant reduction in death rates due to esophageal cancer and esophagogastric junction tumors in the treatment group. There was no difference in the cumulative incidence of esophageal cancer or other tumors.[18]

Ingestion of exceptionally hot beverages has been associated with elevated risk of esophageal cancer in several studies in Asia and South America.[19]

Certain virus have the capabilities to play a role in growth regulation and under certain circumstances contribute to the oncogenic process. Human papilloma virus, Herpes, CMV and Epstein Bar virus have been implicated in the pathogenesis of a variety of human carcinomas. In addition, these virus can also infect the esophagus, thus, making them potential etiologic candidates for esophageal cancer.[12]

Achalasia is associated with an increased risk of esophageal cancer. The presumed mechanism is long standing esophagitis.[20-23] In some cases, symptoms of achalasia precede the development of cancer by a mean of 17-20 years.[20-22,24] It is of major importance to rule out secondary achalasia (pseudoachalasia) as a presentation of esophageal cancer in patients over the age of 50 or with rapid weight loss. The association of achalasia and esophageal cancer has been questioned by one prospective study.[25]
It has been well documented that patients with head and neck malignancies are at high risk for multiple synchronous or metachronous tumors. In a prospective study, second primary neoplasms in the esophagus were found in almost 2% of all patients with head and neck cancers.[26,27]

About 5% of patients with strictures due to lye ingestion develop esophageal cancer which may occur 20-40 years after ingestion. [28]

Tylosis is an autosomal dominant disease which leads to hyperkeratosis of the palms and soles as well as papillomatosis and carcinoma of the esophagus. Up to 95% of affected family members will develop esophageal cancer by the age of 65 years.[29]

In some cases, esophageal cancer has been linked to celiac sprue, a malabsorption disorder that may lead to nutritional deficiencies.[30]

Cell and Molecular biology of esophageal cancer

A malignant cell is defined as a cell with dysregulated cell division and differentiation, genomic instability, loss of normal senescence and invasion into adjacent tissues.

Genetic mutations involved in neoplastic formation involve two classes of genes. Genes that have a positive influence in cell growth are called proto-oncogenes and genes with a negative influence in cell growth are called tumor suppressor genes.

Proto-oncogenes encode proteins that regulate cell growth and proliferation. These genes act dominantly as mutation of one allele is sufficient to promote tumor formation. Potential mechanisms of activation include mutation, amplification and translocation. This family of genes also encodes for growth factors and their receptors.

Some studies have shown high levels of Epidermal growth factor receptor (EGFR) in esophageal cancer cells.[31-33] Overexpression of EGFR correlates with the degree of dysplasia and lymph node metastasis. In addition, esophageal cancer cells express several growth factors, including epidermal growth factor (EGF), transforming growth factor-alpha (TGF-alpha), and platelet-derived growth factor (PDGF).[31,32] Receptors for PDGF have been found in up to 74% of esophageal cancers.[34]

The most common proto-oncogenes in human cancers are the *ras* gene family. *ras* mutations do not appear to play a major role in the formation of squamous esophageal cancer in areas where the tumor is associated with tobacco and alcohol consumption[31,32] nor in geographical areas with a high incidence of squamous esophageal cancer.[31,32]

The hst-1 and int-2 genes are localized on chromosome 11, their products show close homology to basic and acidic fibroblast growth factors. Amplification of these genes occurs at the DNA level in esophageal cancer.[35,36] The cyclin D gene, which encodes a cell cycle regulatory protein, also is amplified in human squamous esophageal cancers.[37]

Tumor suppressor genes or anti-oncogenes This gene family inhibits oncogenes and cellular growth and proliferation. Normally, two alleles, one maternal and one paternal are inherited for a given gene. In contrast to proto-oncogenes, the loss of one of the suppressor alleles is well tolerated by the cell. The loss of the second allele deletes the gene, removing its growth suppression activity and contributing to tumor formation. The most frequently studied tumor suppressor gene is the p53 gene on chromosome 17. p53 gene abnormalities have been found in up to 55% of esophageal cancers.[31,32,38] P53 mutations have been demonstrated in both squamous and adenocarcinoma of the esophagus.[31,32] However, there is no evidence that p53 mutations or immunoreactivity in patients with squamous cell cancer can predict prognosis.[39]

Esophageal cancer also shows extensive loss of heterozygosity for other tumor suppressor genes rb (48%), APC (66%) and DCC (24%).[40]

Pathology and anatomical considerations

Squamous esophageal carcinoma most often develops in the midthoracic segment and usually invades the submucosa extensively before producing dysphagia or other symptoms. In general, 20% of squamous cell cancers arise in the upper esophagus, 50% in the middle esophagus and 30% in the distal esophagus. Most lesions are greater than 4 centimeters in linear extent before diagnosis. Malignant cells spread readily by the way of the submucosal lymphatics well beyond the macroscopic margin of the tumor. When the lesion is greater than 5 cm, about 90% of patients will have lymph node involvement.

Because the esophagus does not have a serosa, the tumor spreads through the muscle layers easily and invades periesophageal structures. The most common sites of involvement are trachea, bronchi, lungs, pleura, major vessels and diaphragm. Distant blood-borne metastases are less common and are late clinical problems. Esophageal adenocarcinoma arise in the distal esophagus and spreads in a similar fashion as squamous tumors.

In the USA esophageal tumors are macroscopically classified as protruding (60%) a polypoid fungating lesion that protrudes into the lumen, flat (15%), a diffuse, infiltrative form that tends to spread within the wall of the esophagus causing thickening, rigidity and narrowing of the lumen and excavated (25%) a necrotic cancerous ulceration that excavates deeply into surrounding structures.[41] In Japan, the Nishizawa classification divides esophageal tumors into Polypoid, plateau-like, flat, erosive and ulcerated.[42]

Superficial esophageal cancer is defined as a tumor limited to the submucosa regardless of lymph node status.[43,44] It is more frequently recognized in areas where there are screening programs. If superficial esophageal cancer involves only the mucosa, there appears to be little or no risk for lymph node involvement.[43-45] However, patients with submucosal extension of the tumor have lymph node involvement in 21-30% of cases and vascular invasion in up to 55.6% of cases.[43-45] This is of importance as superficial esophageal cancer with no nodal involvement has a favorable prognosis and close to a 90% 5 year survival while superficial esophageal cancer with submucosal involvement has a 5 year survival of 54.5%.[43-45]

Clinical features

Esophageal cancer is a silent killer with the early stages of the disease passing unnoticed to the patient. The most common presentation is with the sensation of food getting stuck in the throat or chest, "trouble swallowing" or dysphagia. Dysphagia occurs during the course of the disease in over 90% of patients. Unfortunately, dysphagia is an indication of advanced disease. The esophagus is an elastic and distensible organ and the patient may not recognize any problem until nearly half of the luminal diameter is compromised. Thus, the majority of patients who present with dysphagia are already inoperable for cure. Once dysphagia develops, patients usually modify their eating habits and diet subconsciously. Patients compensate by chewing their food better and "washing down the food with liquids". As the tumor progresses patients became unable to swallow solids or liquids and in advanced disease there is inability to handle secretions (about 1 liter of saliva is produced per day). Then patients complain of regurgitation of a foamy mucus. This is followed by aspiration with coughing, choking and aspiration pneumonia. Another cause for aspiration and chocking is the formation of a tracheo or bronchial esophageal fistula (TEF). This is an indication of endstage disease with about 6 weeks survival.

Weight loss is quite common by the time the patients seek medical attention. Weight loss is due to a decreased ability to eat and anorexia due to the tumor.

Pain with swallowing (odynophagia) is not as common as dysphagia. It may be associated with the passage of food through the narrowed area in the esophagus or due to tumor invasion of surrounding nerves.

Bleeding due to esophageal tumors can present as iron deficiency anemia and more rarely as an acute upper gastrointestinal bleed with hematemesis and or melena. Tumor invasion into the aorta can lead to rupture of the vessel and exsanguination.

Hoarseness is due to involvement of the recurrent laryngeal nerve.

Hiccups can occur with involvement of the mediastinum or diaphragm. A list of the signs and symptoms of esophageal cancer are summarized in table 4.

Diagnosis

Esophageal cancer is usually diagnosed by a barium swallow study or endoscopy. Barium studies usually reveal mucosal irregularities, ulceration or a mass. Peptic strictures can sometimes be difficult to distinguish from tumors. Squamous cell tumors can cause submucosal infiltration giving the appearance of esophageal varices.[46] Unfortunately, small tumors can be missed. Early cancers are usually incidental findings and appear as small polyps, nodules or plaques.

The presence of a tracheoesophageal fistula is best diagnosed with barium studies. If a fistula is suspected, the physician must notify the radiologist so that small sips of dilute barium can be given to the patient.

Endoscopy is still the gold standard for the diagnosis of esophageal cancer and allows endoscopic biopsies and brushings. Early esophageal cancer can be extremely difficult to diagnose as it can present as a flat lesion with no color change. These early tumors can be identified by staining the mucosa of the esophagus. The usual stains are 1% and 2% Lugol's solution, toluidine blue or methylene blue.[47-49] Lugol's solution stains the normal mucosa brown and is dependent of the degree of glycogen content of the epithelial cells. In one study, Lugol's solutions was very useful in the diagnosis of 32 patients with early esophageal cancer. The abnormal mucosa remained unstained and the authors characterized 3 features of the endoscopic diagnosis of early carcinoma of the esophagus, 1) a granular change of the mucosal surface with a clear margin, 2) a slight ulceration or elevation, and 3) an unstained lesion with Lugol's solution.[47] Methylene blue stains columnar epithelium blue and toluidine blue stains dysplastic or neoplastic tissue blue.

Staging

The International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) published identical recommendations for staging cancer of the esophagus in their revised staging classification in 1987 and 1988.[50,51] Both classifications are based on the TNM staging system which defines the anatomical extent of the disease. The T stage indicates the depth of invasion of the tumor which originates in the mucosa and invade progressively deeper layers. The N stage indicates the involvement of the tumor to specified regional lymph nodes and the M stage indicates distant metastases in lymph nodes or in organs. The TNM classification is summarized in tables 5, 6 and figure 3.

Although barium swallow and endoscopy can be used to stage esophageal cancer.[49,52,53] These techniques are not as accurate as computed tomography (CT) and endoscopic ultrasonography (EUS) for staging.

Computed Tomography (CT) In the USA CT is the initial radiologic test for staging esophageal cancer. Initial enthusiasm for the ability of CT to identify depth of mural involvement has waned because of the CT's inability to delineate the individual layers of the esophageal wall.[53-58] However, CT can determine mural thickness, regional lymphadenopathy and involvement of surrounding organs. The major CT criterion for diagnosis of extension beyond the wall of the esophagus is the integrity of the periesophageal fat planes. Because of the significant weight loss associated with esophageal cancer there may be little if any posterior mediastinal fat making differentiation of the T2 and T3 tumors very difficult.[53,58] Distant metastases are best seen by CT and in this category is better than endoscopic sonography. A modified CT and TNM staging of esophageal cancer is summarized in table 7.[59]

MRI There is little literature comparing the efficacy of MRI and CT for staging esophageal tumors.[53,56,57,60,61] However, there is no evidence that MRI is better than CT and because of the higher cost and more limited availability, most investigators recommend that CT remain the primary imaging test in the staging of esophageal cancer.

Endoscopic ultrasonography (EUS) The advantage of EUS for staging esophageal tumors is due to its ability to image in detail the wall of the esophagus.

EUS allows accurate characterization of the mucosa, submucosa, muscularis propria and adventitia of the esophagus.[62,63] Regional lymph nodes are easily visualized and specific criteria have been determined to differentiate between benign and malignant lymph nodes.[64] In addition, anatomic structures surrounding the esophagus can be well defined and used to locate the primary cancer and direct extension into adjacent organs.

As shown in table 8 The overall accuracy of EUS in assessing the depth of primary tumor penetration (T stage) varies from 77-92% and is better than CT.[56,62,63,65-69] Overstaging may occur due to peritumorous inflammation and understaging due to microscopic invasion. The overall accuracy of EUS in assessing regional lymph nodes metastases varies from 50-90% and is also

superior to CT (Table 9).[56,62,63,65-71] Catalano et al evaluated 100 patients with esophageal carcinoma by EUS and demonstrated that the sensitivity and specificity for EUS to determine lymph node metastases was 89.1% and 91.7% respectively. EUS features predictive of malignancy in increasing order of importance were echo poor (hypoechoic) structure, sharply demarcated borders, rounded contour and size greater than 10 mm. Collectively these features had an additive effect with respect to accuracy in prediction of malignant lymph nodes. Malignancy could be predicted with 100% accuracy when all four criteria were present.[64]

In general, the accuracy to stage tumors by EUS when compared to histopathology is over 85% for the T stage and about 80% for the N stage (table 10). EUS can also guide transesophageal biopsies of mediastinal lymph nodes and improve staging.[72,73] Unfortunately, standard EUS is not accurate enough for differentiating mucosal involvement only versus infiltration into the submucosa in early esophageal tumors. This is of major importance as has been discussed above that submucosal involvement carries a significant risk for lymph node metastases and a worse prognosis. In one study, the accuracy for determining mucosal involvement only was 67% and for submucosal involvement was 79%.[74] It is likely that the accuracy for staging early esophageal tumors will improve with the introduction of new EUS equipment with a higher sonographic frequency and better resolution.

Laparoscopy In a recent prospective study in patients with tumors of the esophagogastric junction (EGJ), 24% of patients had peritoneal or liver metastases. The sensitivity of laparoscopy was 92% while the combination of CT and EUS was 44%. Thus, in patients with distal esophagus or EGJ tumors laparoscopy may prevent unnecessary surgery.[75]

In summary, esophageal cancer staging should include an endoscopic examination with biopsies. Then EUS should be done to determine local staging. An abdomen and chest CT is mandatory to evaluate distant metastases. CT and EUS are complimentary modalities (figure 4) to allow accurate staging of esophageal cancer and are needed to prevent unnecessary surgical interventions. A proposed work up for staging esophageal cancer is shown in figure 5.

Treatment

Because of the insidious presentation, a large number of patients with esophageal cancer seek medical attention at a time when extensive tumor is present with lymph node or distant metastases.

Surgery is the only "curative" option for the fortunate patients with local resectable disease.

There is no simple, straightforward algorithm that can be followed to select the proper palliative treatment of an individual patient with esophageal cancer. This is in large part because there are several therapeutic options but without a single modality showing a tremendous or clear-cut advantage over others.

Surgery Although surgery is the only curative therapy for esophageal cancer, the majority of patients are unresectable for cure at the time of presentation.

Most studies from the Western world suggest that about 25-45% of patients may be suitable for curative surgery.[76-79] However, in the eastern world and in some reports of the western world resectability rates are over 80%.[80-82]

In the past, resection of esophageal tumors was associated with high morbidity and mortality (29%).[78,83] Current operative mortality should be 5% or less in experienced centers.[80-82,84-87]

The two principal factor that affect resectability and long term survival are tumor penetration through the wall of the esophagus and the presence or absence of regional lymph nodes.[85] Unfortunately, even patients with apparently resectable tumors have lymph node micrometastases.[88]

For resectable tumors there are three approaches.[83,89-91] The most common approach is the right thoracic approach or Ivor-Lewis operation which includes a right thoracotomy to resect the esophagus and a laparotomy to mobilize the stomach for replacement.[83,91] A second approach is the transhiatal esophagectomy. Using this technique the surgeon inserts its hand through the esophageal hiatus and bluntly dissects the esophagus. Transhiatal esophagectomy works best for esophageal tumors located in the upper and lower thirds of the esophagus. The advantage of this method is the avoidance of a thoracotomy and its inherent complications. The drawbacks are the inability to perform en-bloc resection and the risk of damage to the trachea or major vessels, especially in patients with bulky tumors in the thoracic esophagus.

In some trials there was no difference in the morbidity or mortality between transhiatal esophagectomy or esophagectomy through a right thoracotomy approach.[89,92,93]

Lymph node dissection is usually a two field dissection including the abdominal and lower mediastinal lymph node groups. However, there are many investigators who recommend three field lymph node resection which includes bilateral removal of the lower cervical groups of nodes, the superior, middle and inferior mediastinal lymph nodes and the abdominal groups. Three field lymph node dissection improves 5-year survival and does not increase

mortality.[94] However, this technique has not been studied in a randomized trial properly.

In patients with early tumors stage I (T1 N0 M0) treatment varies from a radical operation with en-bloc resection and systematic dissection of lymph nodes to subtotal esophagectomy and lymphadenectomy.[83] For stage I tumors Huang et al reported a 5-year survival of 89.9% and a 10-year survival of 60%.[95]

After resection, the stomach is the most common organ used for replacement. Alternatives to the stomach for reconstruction include the colon and jejunum. However, both colonic and jejunal replacement are associated with a higher failure rate and should be used when the stomach can not be used for reconstruction.[81,83,89,91] The most common surgical complications associated with mortality are shown in table 11. In general pulmonary complications are the most common cause of death in the 30-day postoperative period.[96,97]

Perioperative adjuvant therapy It is controversial if preoperative radiotherapy improves resectability or survival.[98-100] Table 12 summarizes the results of preoperative radiotherapy in 4 randomized trials. The routine use of preoperative XRT as a single modality is not warranted at this point.[98,99]

Although a large number of studies using postoperative radiotherapy claim an improvement in survival, in two randomized trials there was only a trend but not a statistically significant improvement in 5-year survival.[100]

Because of the limited success with XRT alone in the pre or post operative period, some studies have used preoperative chemotherapy (chemo) in an attempt to improve resectability and improve survival. Overall, preoperative chemotherapy with cisplatin-based combination achieves a response in 17-66% of patients with pathologic complete responses in 3-10% of patients. However, the survival of these patients has been disappointing.[98] Preoperative chemo alone does not seem to be better than preoperative radiotherapy alone. In a randomized trial from Memorial Sloan-Kettering comparing preoperative chemo versus preoperative XRT there was no difference in resectability or median survival.[101]

In an effort to improve adjuvant therapy investigators have used combination therapy XRT and chemo. The most common chemotherapeutic agents include cisplatin or mitomycin-C with 5-FU. In general combination therapy shows good tumor response in 40-60% of patients.[4,98,100,102-107] Orringer reported improved 2-year survival in patients receiving pre-operative radiotherapy and chemotherapy (Cisplastin, Vinblastine and 5-FU) when compared to historical controls only treated with surgery (60% versus 32%, respectively).[90] In a study by the Therapy Oncology Group (RTOG) combination therapy 5-FU, cisplatin and XRT (5000 cGY) was compared to XRT alone (6400 cGy). Combination therapy showed a significant improvement in 2-year survival (38% versus 10%) (figure 6).[107] However, this was at the expense of a high incidence of severe side effects (44%) and 20% of life threatening complications.[107]

Combination therapy can initially improve dysphagia in up to 90% of patients.[108] However, subsequent local recurrence and or stricture formation may diminish function in up to 50% of patients.[103]

The most common complications of combination therapy are related to the effect on the esophagus (esophagitis), oropharynx (stomatitis) and hematologic depression. The incidence of severe toxicity with combination therapy can be as high as 64%.[98,103,107]

Palliation

To quote Steiger "the multimodality treatment of esophageal cancer brings creativity and imagination to a field of medicine plagued with failure.[109]

Surgical palliation either a bypass or resection for dysphagia in unresectable tumors is associated with poor median survival time (4-6 months) and with high operative mortality.[83,110-112] There is no firm evidence that surgical palliation is better than endoscopic palliation for patients with tumors in stage III or IV.[113] This is why endoscopic palliation is preferred to palliative surgery.

Endoscopic esophageal dilation Peroral endoscopic dilation of esophageal tumors is simple and widely available at a relative low cost. In retrospective studies, dilation can relieve dysphagia in up to 90% of patients.[114-116] However, the effect of dilation is usually short lived and multiple procedures are required to maintain luminal patency. As tumor growth progresses, dilation become less effective. Dilation therapy is almost always required before insertion of an esophageal endoprosthesis and may be required before laser or BICAP therapy can be performed. Dilation can also be used as adjuvant therapy to radiotherapy and or chemotherapy. Perforation is the most feared complication of dilation and in average occurs in 4 per 1000 treatments.[116]

Endoscopic injection therapy Injection therapy of tumors is similar to endoscopic sclerotherapy. A needle catheter is introduced through the working channel of the endoscope and a caustic solution is injected into the tumoral tissue. This technique is appealing because of its simplicity, low cost and ease of delivery.

In preliminary studies using alcohol or other sclerosant agents, patients with inoperable esophageal cancer had good control of dysphagia.[117-120] However, its efficacy is yet to be proven in large randomized controlled trials. In a prospective randomized study with 34 patients with inoperable esophageal cancer and dysphagia. Treatment with local injection (3% of polidocanol) was compared to YAG laser therapy. Relief of dysphagia was 81.2% in the injection and 88.8% in the laser group. Both techniques had statistically the same effectiveness for length of treatment, number of sessions, relief of dysphagia and possibility of treatment on an outpatient basis.[121]

In a recent study, injectable gels of methotrexate and cisplatin was used to palliate 5 patients with esophageal cancer with good results and low toxicity.[122] This report requires confirmation in a large randomized study.

Endoscopic resection Endo reported his experience with endoscopic resection of 8 esophageal tumors less than 3 cm in diameter and affecting only the mucosa (Tis). No postoperative complication occurred and follow-up to two years and 9 months did not show recurrences.[123] Other report from Japan have found good results with endoscopy resection in 37 patients with mucosal tumors. The 5-year survival rate was 92.5% and only one perforation.[124]

Snare resection is also useful in debulking large polypoid tumors and can be used as a preliminary to laser or BICAP therapy.

BICAP tumor probe The BICP tumor probe consists of metal olives of different diameters (6-15mm) that attach to a semiflexible shaft that can be passed over a guidewire. When current is applied, the tissue in contact with the olive is heated and coagulated to a depth of 2-4 mm. The benefits of BICAP therapy are low equipment cost, the equipment is portable, increased speed, increased efficacy of tumor ablation, and good results in tumors with a significant submucosal component. BICAP is not recommended for treatment of non circumferential, tortuous and exophytic tumors.[125-127]

In a prospective non randomized study with 28 patients with esophageal cancer. 14 patients were treated with BICAP and 14 with YAG laser. Treatment results were similar during the median follow-up and survival of 16 weeks.126 About 86% of patients could eat a soft or solid meal diet after treatment compared with only the intake of fluids before the treatment.[126] It was concluded that both techniques are complimentary.

Laser therapy Laser is an acronym for "light amplification by stimulated emission of radiation". The majority of esophageal tumors are treated with Nd:YAG (Neodymium:yttrium-aluminum-garnet) laser. Photodynamic therapy (PDT) is another modality for tumor ablation.

YAG laser Using endoscopic YAG laser therapy, luminal patency can be obtained in the majority of patients.[125,128-130] However, functional is probably around 70%.[125,130-133] Because of anatomical reasons, cervical tumors are the most difficult to treat with laser and have the poorest outcome.[125,131] YAG laser can be given with contact or non contact probes but there appears to be similar results with both methods of delivery of the laser.[134]

YAG laser therapy has been compared to other endoscopic therapeutic modalities. As mentioned above, BICAP tumor probe and laser seem to be equally effective with equal risks. The success rate of laser therapy is also similar to endoscopic placement of plastic esophageal prosthesis. However, laser is associated with a lower morbidity (3.6% for laser and 13.8% for prosthesis) and lower mortality (0% for laser and 4.3% for prosthesis).[125]

The newly introduced metal esophageal endoprosthesis may have better long term results and lower complication rates. In the cases in which there is tumor overgrowth within an endoprosthesis, laser therapy can be used to recanalize the stent.[135]

The most feared complication of laser therapy is perforation which can occur in 2-10% of cases.[125,129,130,132,133] Hemorrhage is uncommon and it is difficult to determine if the formation of tracheoesophageal fistula is increased as a result of laser therapy or is a reflection of the natural course of the disease.

Laser therapy has also been used in combination with radiotherapy or chemotherapy. It appears that combination therapy (laser and radiotherapy) may improve results but there are no large randomized controlled trials to show any significant benefit.[136]

Photodynamic therapy (PDT) Photodynamic laser therapy is based on the selective retention by malignant cells of a photosensitizer that can be activated by exposure to light. When the photosensitizer is activated by penetrating light, cytotoxic singlet oxygen and other oxygen-derived free radicals lead to cell death.[125,137]

Theoretically, PDT may potentially cure tumors involving the mucosa without lymph node metastases.[137-140] In a recent study, Sibille et al [138] reported the use of PDT in 123 patients with early esophageal cancer (both squamous and adenocarcinoma) and showed a 87% complete response. Local recurrence occurred in 36% patients within 18 months and the majority of patients had again good response to retreatment with PDT.138 The overall 5-year survival for this group of patients was 25% with a disease-specific survival of 74%. Indicating that the poor overall 5-year survival rate reflected the poor clinical status of the population treated.

PDT is also used for palliation in patients with previous treatment failures and advanced disease.[132,133,141] PDT resulted in short-term improvement of lumen size and dysphagia. The improvement in lumen size facilitated the placement of endoprosthesis.[142,143] PDT has also been used to ablate tumor ingrowth into metal endoprosthesis.[144,145]

The complications associated with PDT include cutaneous photosensitization, stenosis which seems directly related to tumor destruction or fibrosis and formation of fistula.

Esophageal prosthesis Esophageal prosthesis are indicated in patients with tracheoesophageal fistulas (TEF) and in patients in whom repeated endoscopic therapy should be avoided (table 13).[116,146]

The major advantage of prosthesis is long lasting relief of dysphagia without the need for further procedures. The classical prosthesis are made of plastic and extensive experience has shown good relief of dysphagia.[116,146] However, prosthesis insertion is associated with significant risks and mortality from 2.2 to 10.2%.[116,146,147] The most common complications associated with esophageal endoprosthesis are summarized in table 14.

One of the most dreaded complications of esophageal cancer is the development of a tracheoesophageal fistula (TEF). These patients have an extremely poor quality of life, with chronic aspiration, sensation of drowning, incessant cough and severe malnutrition. A modified cuffed esophageal endoprosthesis is particularly helpful in patients with TEF. The cuffed esophageal prosthesis has been developed in an attempt to "seal" the fistula and give symptomatic relief to this group of desperate patients.[148,149]

Another approach to treat TEF is placement of airway (tracheal or bronchial) prosthesis. This interesting approach is still investigational.[150]

The recently introduced self expandable metal stents have advantages when compared to the standard plastic stents. First, their delivery system is smaller, which allows for easier insertion and possibly a reduced risk of perforation. Second, the stents expand to a larger internal diameter, allowing for greater relief of dysphagia and potentially longer patency.[151]

In a randomized trial comparing expandable metal stents to conventional plastic stents, metal stents were more cost effective and associated with fewer complications and mortality.[152] The drawbacks of metal stents are its high cost, insertion is technically intricate and misplacement is difficult or impossible to correct and tumor overgrowth through the metal mesh. In order to fix this problem coated stents are now available and are useful for treating TEF.[153-155]

In summary, multiple endoscopic palliative procedures are available and are complimentary. In a study with 836 patients using a combination of these modalities, recanalization of lumen was accomplished in the majority of patients (96%), with low complication rates (8%) and a median survival of 6 months.[156]

External beam radiation (XRT) Most of the patients undergoing XRT as the single therapy have unresectable advanced tumors (stages III and IV) and are not amenable to other therapy due to poor overall medical health. Therefore, the results of XRT alone may indicate the poor medical status of this group of patients. Overall the 5-year survival in these patients is 10% or less.[99,100]

Although XRT does not appear to improve survival it can provide palliation of dysphagia in 60-85% of patients.[99]

Brachytherapy (intracavitary radiation) The dose of external beam radiation that can be safely delivered is limited by the tolerance limits of normal tissue and surrounding vital structures. Thus, brachytherapy has been used to increase the biologically effective dose of radiation to the primary tumor.[99] In some studies with patients with inoperable esophageal cancer, brachytherapy has been shown to relief dysphagia. It appears that brachytherapy in combination with external beam radiation may be of benefit. However, brachytherapy is associated with esophagitis (23%), fistula formation (9%) and bleeding (9%).[157]

Chemotherapy and radiotherapy In patients with unresectable disease chemo may provide transient relief of dysphagia. A recent study with carboplatin and 5-FU showed durable relief of dysphagia in 57% of patients.[84] However, survival was only 6 months,84 similar to the poor survival in earlier studies.[103]

Survival

The crude survival rate of all patients with esophageal cancer at 5 years is about 10%.[158] The survival rates for squamous and adenocarcinoma are similar.[6] Survival after esophagectomy is considered as the reference point and in most studies the 5-year survival rate after transthoracic or transhiatal esophagectomy is 20-27%.[77,84,158,159] Node-negative tumors have much better prognosis than node-positive tumors (47.4% and 10.3% respectively).[77] The curative benefit of surgery concerns only to the small group of T1 N0 M0 patients.[158] The 5-year survival of intramucosal tumor is nearly 100% but only 40-65% if the tumor involves the submucosa.[44] Table 15 summarizes the median survival of a large group of patients with esophageal cancer operated in Hong Kong.[87]

Barrett's esophagus and esophageal cancer

Barrett's esophagus (BE) is defined as a circumferential columnar epithelium lining as far as 3 cm above the esophagogastric junction.[7,160-162] BE seems to be associated with chronic damage to the squamous epithelia of the distal esophagus by gastric acid reflux (GERD).[7,160,162-165] There are few reports of familial clustering and a family with autosomal dominant inheritance pattern.[166] There is also suggestion that chemotherapeutic agents may induce the formation of BE.[167]

The true prevalence of BE is unknown. In the Mayo Clinic a population based study comparing clinically diagnosed cases in patients who had undergone endoscopy and clinical autopsy material, revealed that the prevalence of BE in the clinical group was 22.6/100,000 and 376/100,000 in the autopsy group. Indicating that the majority of cases go unrecognized.[168]

Histology There are three different cell types that are usually randomly arrayed throughout the epithelium. The gastric fundus-type, the junctional epithelium which resembles the cells from the gastroesophageal junction and gastric cardia, and the intestinal-like which is the most common type and the one most likely associated with malignant transformation.[7,161,162,169]

Dysplasia It is classified into low grade and high grade (similar to the criteria established for inflammatory bowel disease). The features that define dysplasia include: pleomorphism, hyperchromatism, nuclear enlargement, stratification, abnormal mitosis and loss of nuclear polarity. Unfortunately, there is significant interobserver variation in classifying dysplasia.[7,161,170] This is very important to the clinician because the histologic changes of high grade dysplasia are similar to adenocarcinoma and the differentiation between tumor in situ and high grade dysplasia is based on the presence or absence of invasion of the basement membrane.[161]

The natural history of dysplasia in patients with BE is poorly understood.[7] It is estimated that 5-10% of all patients with BE will develop low grade dysplasia and the majority will not progress to high grade dysplasia. High grade dysplasia occurs in only 1-2% of patients with BE.[161]

Although the progression of high grade dysplasia to adenocarcinoma is well established [171,172] it is not an universal phenomena.[161,165] It is estimated that about 5% of patients with BE without dysplasia will progress to high-grade dysplasia or adenocarcinoma, whereas 25% of patients with indefinite or low grade dysplasia progress.[165] High grade dysplasia appears to be an indicator of a coexisting adenocarcinoma. In some studies up to 45% of patients undergoing resection because of high grade dysplasia already had unsuspected invasive adenocarcinoma.[7,161,165,172-174]

Cytogenetic markers Because most patients with BE will not develop cancer it is not cost efficient to screen all patients. Thus, subgrouping of patients based on their likelihood for developing cancer may improve cost efficiency. Currently, dysplasia is the gold standard indication of cancer risk but as mentioned above, there is interobserver variation and the disappearance of dysplasia may represent sampling error during endoscopic biopsies. Thus, numerous investigators have tried to find specific cytogenetic markers predictive of malignant degeneration.

Flow cytometry is an analysis of cell DNA content that quantitates the number of cells in different phases of division. Normal cells have two chromosomes and therefore are diploid. For the time the cells duplicate their DNA until they divide the cell is tetraploid. Cells with abnormal number of chromosome (aneuploid) are common in tumors.

The results of flow cytometry are controversial. Although some studies did find a correlation between dysplasia in BE and flow cytometry DNA aneuploidy and increased G2/tetraploid populations,[175,176] other studies did not find a correlation.[177,178] At this point flow cytometry does not seem to provide sufficient additional information to justify its routine application in clinical practice.[179]

P53 gene mutations The wild-type TP53 gene is located in the short arm of chromosome 17 (allele 17p) and acts as a tumor suppressor gene. However, some forms of mutated TP53 act as an oncogene and is the most common genetic alteration in human cancer.[180]

Ramel et al reported that the incidence of p53 protein overexpression was found in 5% of patients with BE without dysplasia, 15% in patients with BE and low grade dysplasia, 45% of patients with BE and high grade dysplasia, and 53% of patients with BE and adenocarcinoma.[181] In a recent study, Hamelin et al demonstrated a high incidence (94%) of TP53 gene mutation and or p53 protein nuclear immunoreactivity in patients with BE and adenocarcinoma.[182] By studying gene mutations and protein overexpression in Barrett's epithelium adjacent to the adenocarcinoma. The authors found that the TP53 gene mutation is absent in the non dysplastic mucosa but present in the dysplasia-carcinoma sequence before the actual malignant transformation and therefore conclude that analysis of the TP53 mutation may have importance in surveillance programs.[182]

Clinical features BE is usually a disease of white men in their mid 50s. For unknown reasons, BE is uncommon in blacks which have in contrast a predilection for developing squamous cell cancer of the esophagus.[7,160-162] Although BE seems to be associated with GERD, in the majority of cases GERD symptoms are not severe and recent data suggest that up to 90% of patients with BE do not seek medical attention for esophageal symptoms. Thus, most cases of BE go unrecognized.[168] While some patients with BE present with GERD symptoms, other patients present with complications of GERD such as esophageal ulceration, stricture, and bleeding.

In patients with significant GERD symptoms the prevalence of BE varies from 8-20%.[162]

The diagnosis of BE is based on endoscopic biopsies.[165] The endoscopic appearance of BE is a velvety, salmon-pink esophageal lining which usually extends in irregular, finger-like projections or circumferential sheet. However, in a large study endoscopic appearance was able to diagnose BE in only 69.2% of patients.[183]

As mentioned above, endoscopic ultrasound (EUS) provides detailed images of the esophageal wall. In a preliminary study, increasing esophageal wall thickening within the Barrett's epithelium was associated with carcinoma.[184] Thus, EUS may play a role in evaluating patients with dysplasia in BE.

Treatment Asymptomatic patients with low grade dysplasia do not require treatment. Although controversial, there is no firm evidence that antireflux procedures or antisecretory treatment (histamine 2 receptor antagonists or proton pump inhibitors) reverse the dysplastic process or prevent the formation of adenocarcinoma.[7,161,165,185,186] Medical or surgical treatment should be reserved for patients with reflux symptoms. BE patients with reflux symptoms should be monitored to ensure adequate acid control. In a recent study, BE patients with reflux symptoms were treated with omeprazole (20-60 mg) to eliminate symptoms. Despite symptomatic improvement, Ph monitoring revealed significant reflux.[187]

Laser therapy with Nd:YAG or PDT lasers has been used to ablate columnar epithelium followed by antisecretory treatment in an attempt to allow reepithelization with squamous epithelium and "cure" BE.[140,188-190] More randomized studies are required to define the clinical role of this modality of treatment.[191]

High grade dysplasia is considered by many investigators to be an indication for surgical resection.[161,165,172-174]

Adenocarcinoma of the esophagus and Barret's esophagus BE is the single most important factor for esophageal adenocarcinoma.[7,161,192] For unclear reasons, there is a significant increase in the incidence of adenocarcinoma associated with BE (Figure 2).[7,160,192,193]

The cancer risk in patients with BE is about 60-100 times the control population.[161] The annual incidence of adenocarcinoma associated with BE is estimated at 800/100,000. This number is quite striking when we know that the incidence of lung cancer in men over age 65 is 500/100,000.[7]

Adenocarcinoma associated with BE has a predilection for white men age 50-60 years. The association between this tumor and tobacco and or alcohol history is not as striking as in the case of squamous cell cancer of the esophagus.[161]

Surveillance BE is a definite premalignant condition. As mentioned above the most important independent predictor for survival in esophageal cancer is the pathologic state of the disease. Endoscopic surveillance has been recommended primarily to seek high grade dysplasia, with the rationale that early resection of this epithelium may prevent the progression to invasive adenocarcinoma.[7] Streitz et al reported a statistically significant increase in the postoperative survival in patients who underwent endoscopic surveillance when compared to patients not under surveillance (62.% versus 20% 5-year survival). This results was due to the earlier recognition and lower staging of tumors in the surveillance group (Figures 7 and 8).[174]

The recommended biopsy protocol is obtaining yearly four quadrant biopsies specimens at 2-cm intervals throughout the columnar-lined epithelium using "jumbo" biopsy forceps.[161,165] Some studies have suggested that brush cytology may be helpful for the diagnosis of BE and dysplasia but appears to be a complement rather than a replacement for biopsies.[7,161,165,194,195]

There is no agreement in the proper interval of surveillance endoscopy in BE. However, most investigators agree that in patients with no dysplasia follow up endoscopy should be done in 1-2 years and patients with high grade dysplasia should consider resection if they are good surgical candidates. The problem is what to do if there is low grade or indefinite dysplasia (table 16).[161,165] In the United Kingdom, the cost effectiveness of endoscopic surveillance in BE compares well with the cost of other cancer screening programs.[196] However, the cost effectiveness of a surveillance program in the USA has been challenged.[197] It is estimated that the cost of quality adjusted life year gained is $118,000.[197] In a decision analysis study, it was estimated that in the USA endoscopy surveillance every 2-3 years will provide the greatest quality-adjusted life expectancy. But when costs are considered endoscopy surveillance every 5 years increases life expectancy and has an incremental cost-effectiveness ratio similar to common medical practices.[198]

Table 1

World age standardized incidence rates (ASIR) of esophageal cancer per 100,000 males [2]

Asian belt		**Other Asia**	
Iran-Gombad	165.5	Hong Kong	18.1
China-Linxian	161.0	Japan, Miyagi	14.1
Turkmeninstan-west	115.0	India, Nagpur	12.6
Uzbekistan	28.8	N. Zealand	7.0
Tadjikistan	18.7	Kuwait	3.7

Africa		**Europe**	
Zimbabwe	63.8	France	26.1
South Africa	40.9	Spain	10.3
Mozambique	4.4	UK	9.4
Algeria-Setif	1.4	Italy	7.6
Gambia	0.9	Norway	2.6

America	
Brazil	27.0
Bermuda (black)	24.9
Paraguay	11.2
Puerto Rico	9.8
Uruguay	9.6
Canada	4.2
Costa Rica	3.8
Peru	1.0

Table 2

Reported esophageal cancer deaths for blacks, American indian, Chinese and Hispanics in the USA for 1991 [5]

Blacks	1987
American Indian	20
Chinese	25
Hispanic	233

Table 3

Risk factors for squamous cell carcinoma of the esophagus

Environmental

Geographic location
Low soil molybdenum level
Soil salinity
Thermal (hot tea ingestion in Iran)
Vulcanization process exposure in factory
Water pollution by petroleum
Asbestos exposure
Dietary
Bush tea
Fungi (Fusarium, Alternaria)
Mate drinking
Retinol-containing food
Maize (corn) consumption
Nutritional deficiencies: Vit A, E and C, riboflavin, niacin, Zn
Nitrosamines
Chronic irritation
Achalasia
Injection sclerotherapy
Reflux esophagitis
Lye ingestion

Habits

Alcohol consumption
Smoking

Cultural

Low socioeconomic status
Race

Miscellaneous

Hiatal hernia
Ionizing radiation
Papillomavirus
Pharyngoesophageal diverticulum
Plummer-Vinson syndrome
Sprue
Tylosis
ENT cancers

Table 4

Signs and symptoms of esophageal cancer

Dysphagia	Weight loss
Odynophagia	Vomiting
Hoarseness	Cough
Regurgitation	Hematemesis or melena
Iron deficiency anemia	Pain
Pharyngeal discomfort	Hiccups
Horner's syndrome	Superior vena cava syndrome
Malignant ascites	Malignant pleural effusion
Bone pain	Palpable supraclavicular/cervical lymphadenopathy
Hypercalcemia	Exsanguination due to invasion of the aorta

Table 5

TNM staging classification

Primary tumor (T)

TX Minimum requirements to assess the primary tumor cannot be seen.
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor invades into but not beyond the submucosa
T2 Tumor invades into but not beyond the muscularis propria
T3 Tumor invades into the adventitia
T4 Tumor invades into contiguous structures (pleura, heart, trachea, etc.)

Regional lymph nodes (N)

NX Lymph nodes can not be assessed
N0 No demonstrable involvement into regional lymph nodes
N1 Involvement of regional lymph nodes

For tumors in the upper esophagus, the cervical nodes (including the supraclavicular nodes) are considered regional.
For tumors in the thoracic esophagus, the mediastinal and perigastric lymph nodes (excluding celiac nodes) are considered regional.

Distant metastases (M)

MX Distant metastases cannot be assessed
M0 No evidence of distant metastases
M1 Distant metastases present

Table 6

TNM group staging of esophageal cancer

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2	N0	M0
	T3	N0	M0
IIB	T1	N1	M0
	T2	N1	M0
III	T3	N1	M0
	T4	Any N	M0
IV	Any T	Any N	M1

Tis = Tumor in situ

Table 7

Modified CT and TNM staging of esophageal carcinoma

CT T-1 Wall thickness 5-10 mm without evidence of mediastinal involvement

CT T-2 Wall thickness > 10 mm with evidence of mediastinal involvement but without evidence of invasion into adjacent structures.

CT T-3 Evidence of invasion into adjacent structures, contact > 90 degrees with the aortic circumference.

Table 8

Reported accuracy of EUS compared to CT in T staging of esophageal carcinoma Modified from [63]

Author	N patients	T stage By CT	T stage by EUS
Tio	74	59%	89%
Botet	50	60%	92%
Grimm	49	62%	89%

Table 9

Reported accuracy of EUS compared to CT in N staging of esophageal carcinoma Modified from [63]

Author	N patients	N stage by CT	N stage by EUS
Tio	74	51%	80%
Vilgrain	51	48%	50%
Botet	50	74%	88%

Table 10
Accuracy of EUS compared to histopathology in determining the T and N stage of esophageal cancer. Modified from [63]

Author	N patients	T stage	N stage
Murata	173	88%	88%
Tio	102	89%	81%
Dittler	97	85%	75%

Table 11
Primary causes of mortality after resection in 26 out of 528 patients (5%)

Pulmonary complications	38.4%
Cardiac complications	26.8%
Anastomotic leakage	7.7%
Nonanastomotic leakage	3.8%
Other forms of sepsis	11.4%
Miscellaneous	11.9%

Table 12
Randomized trials of preoperative XRT

Author	Resectable (%)		5-year survival (%)	
	Surgery	XRT	Surgery	XRT
Lanouis	70	76	10	10
Huang	90	92	25	46
Mei	85	93	30	35
Gignoux	58	47	8	10

Table 13
Indications for esophageal endoprosthesis for palliation of esophageal cancer

Evidence of unresectability
- TEF
- Aortic involvement
- Distant metastases

Iatrogenic perforation

Patients unfit for major surgery
- Age
- Severe malnutrition
- Advanced coexisting diseases (COPD, CAD)

Table 14

Complications of esophageal endoprosthesis

Fistula formation
Migration
Obstruction (food bolus, tumor ingrowth or prolapse of mucosa)
Hemorrhage
Perforation
Reflux
Aspiration
Halitosis
Airway obstruction
Tube degradation (plastic)

Table 15

Survival by stage of tumor in patients with esophageal cancer

Stage	Median survival in months
I	83.5
IIA	24.3
IIB	37.8
III	8.6
IV	5.0

Table 16

Recommendations for endoscopic surveillance of Barrett's esophagus modified from [165]

1. Surveillance should only be considered in patients who are surgical candidates
2. No dysplasia: continue surveillance at 1-2 year interval.
3. Low grade/indefinite dysplasia: omeprazole for 8-12 weeks followed by EGD and rebiopsies at 3 months.
   a) If low grade/indefinite dysplasia persists: continue surveillance at 3-6 month interval.
   b) If low grade/indefinite dysplasia regresses: continue surveillance at 3-6 month interval until two consecutive sets of biopsy results are negative.
4. High grade dysplasia
   a) Confirm diagnosis by experienced pathologist.
   b) Repeat biopsies plus cytology within a month and look for unsuspected carcinoma.
   c) If high grade dysplasia or adenocarcinoma is confirmed surgery should be considered.

Esophageal cancer

Age standardized rates in males per 100,000

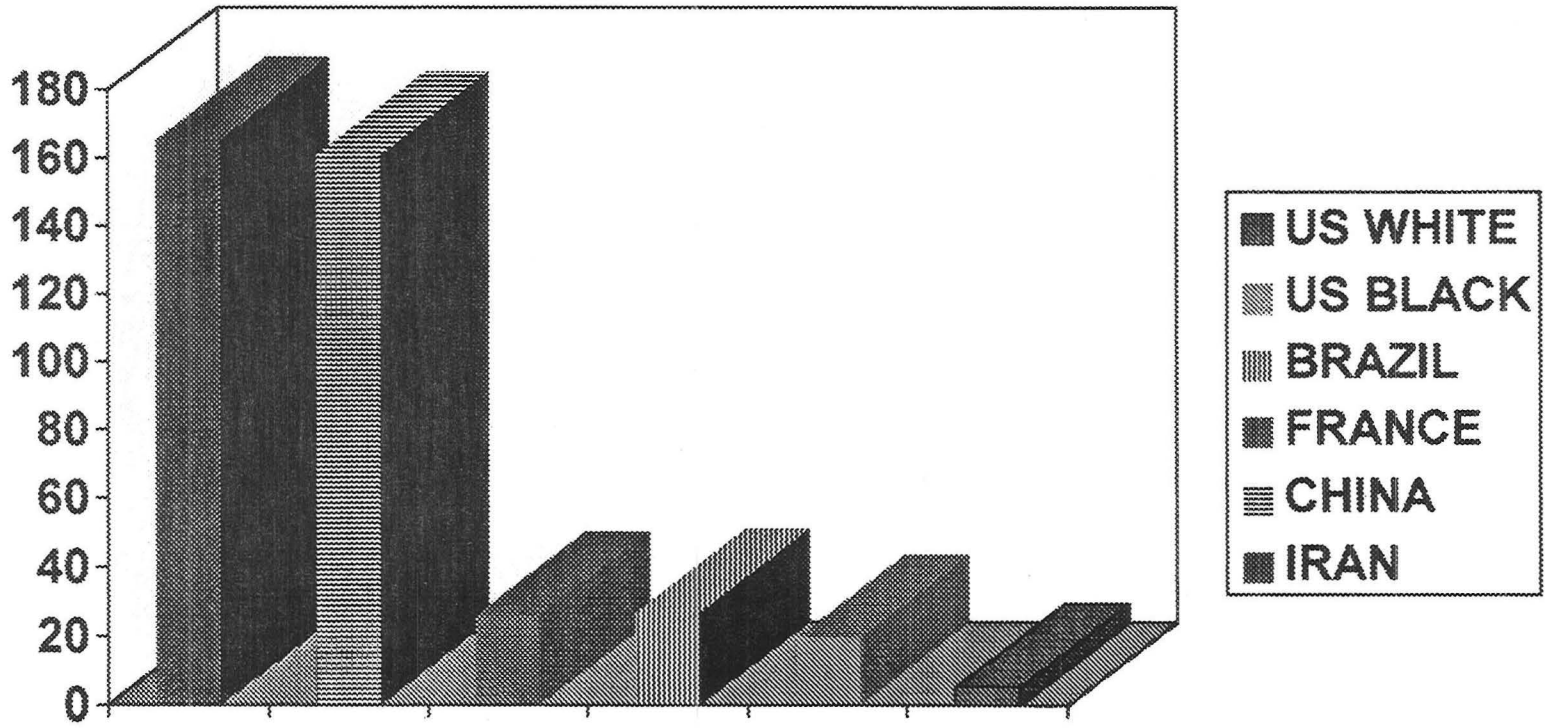

Figure 1
Age standarized rates of esophageal cancer in men per 100,000 in different countries

Esophageal cancer
Incidence of adenocarcinoma

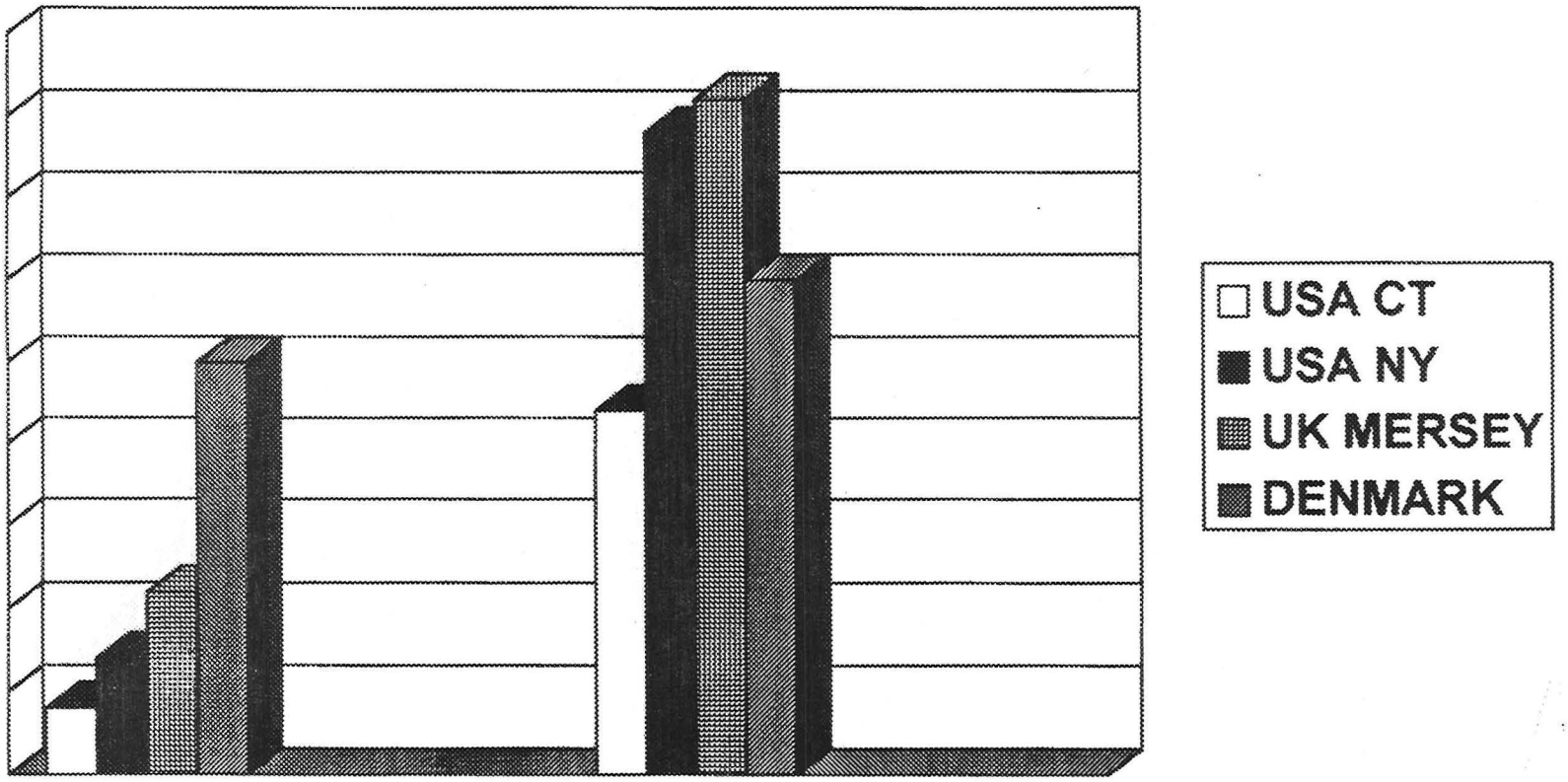

Figure 2
Incidence of esophageal adenocarcinoma
This graph shows the increased incidence of esophageal adenocarcinoma over the past few decades.

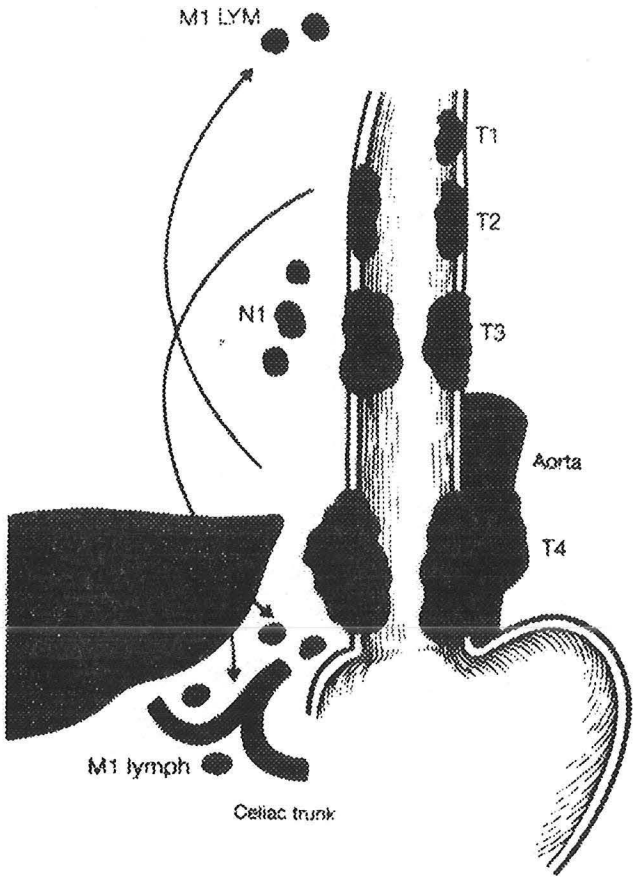

Figure 3
Staging of esophageal cancer

Esophageal cancer
Comparison CT vs EUS staging

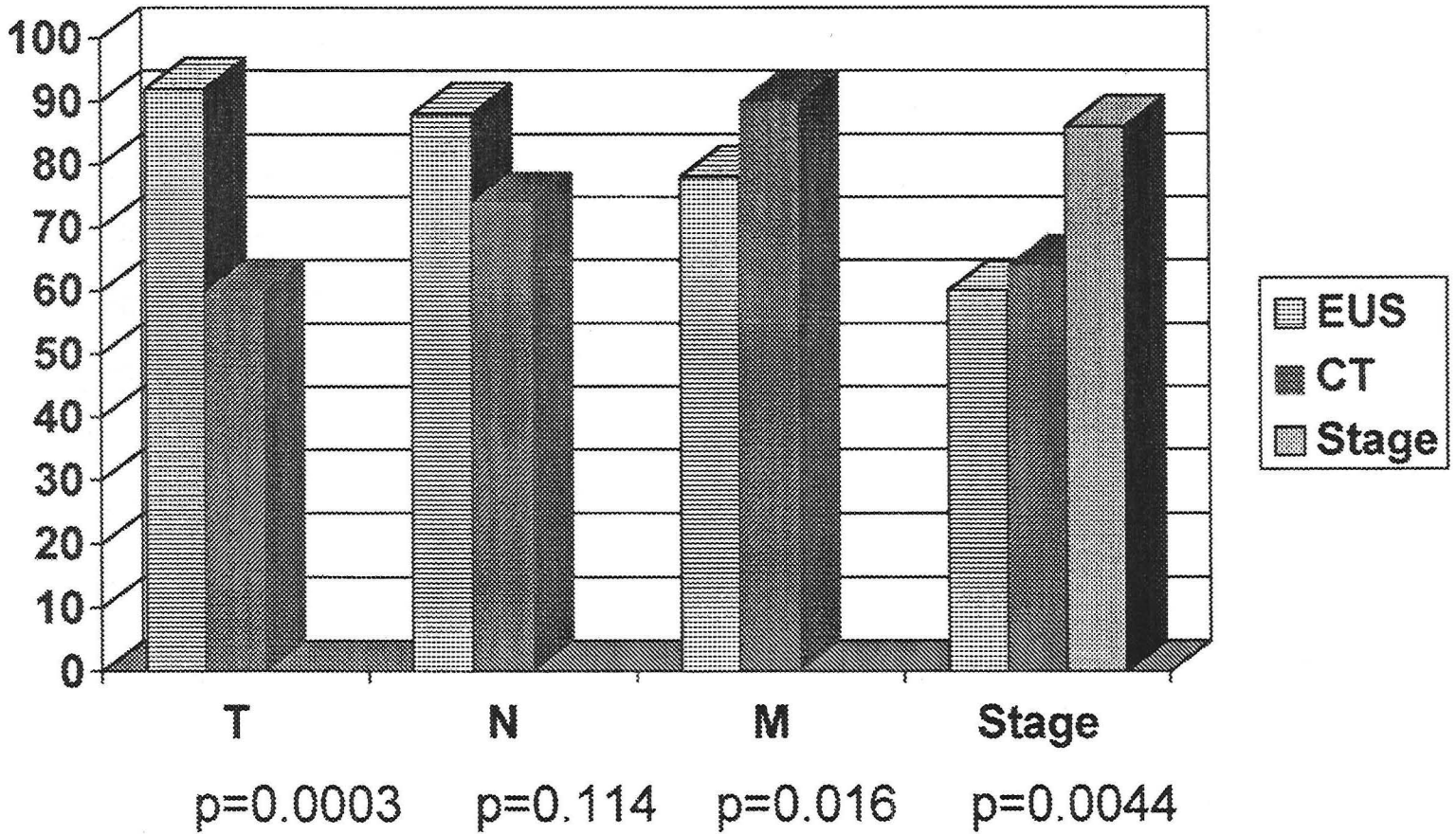

Figure 4
Use of EUS and CT in staging esophageal cancer
This graph shows that EUS and CT are complimentary modalities and have additive effect on the accuracy for staging esophageal cancer.

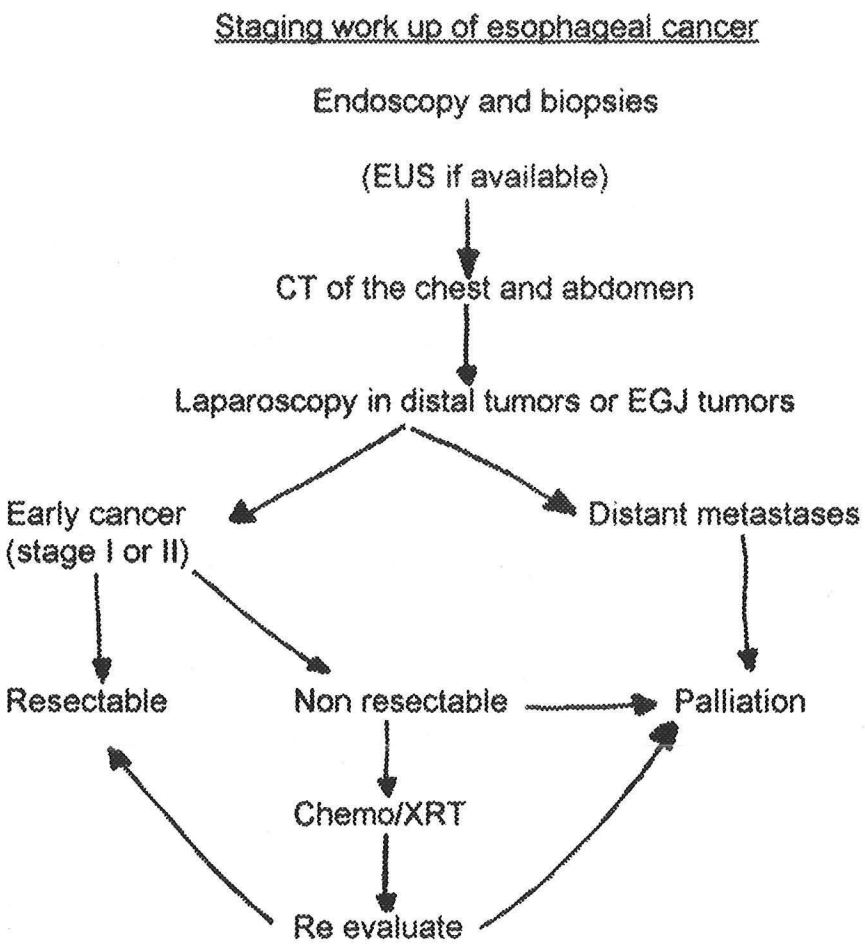

Figure 5
Staging work up of esophageal cancer

Esophageal cancer
Comparison of XRT and combined therapy on 2-year survival

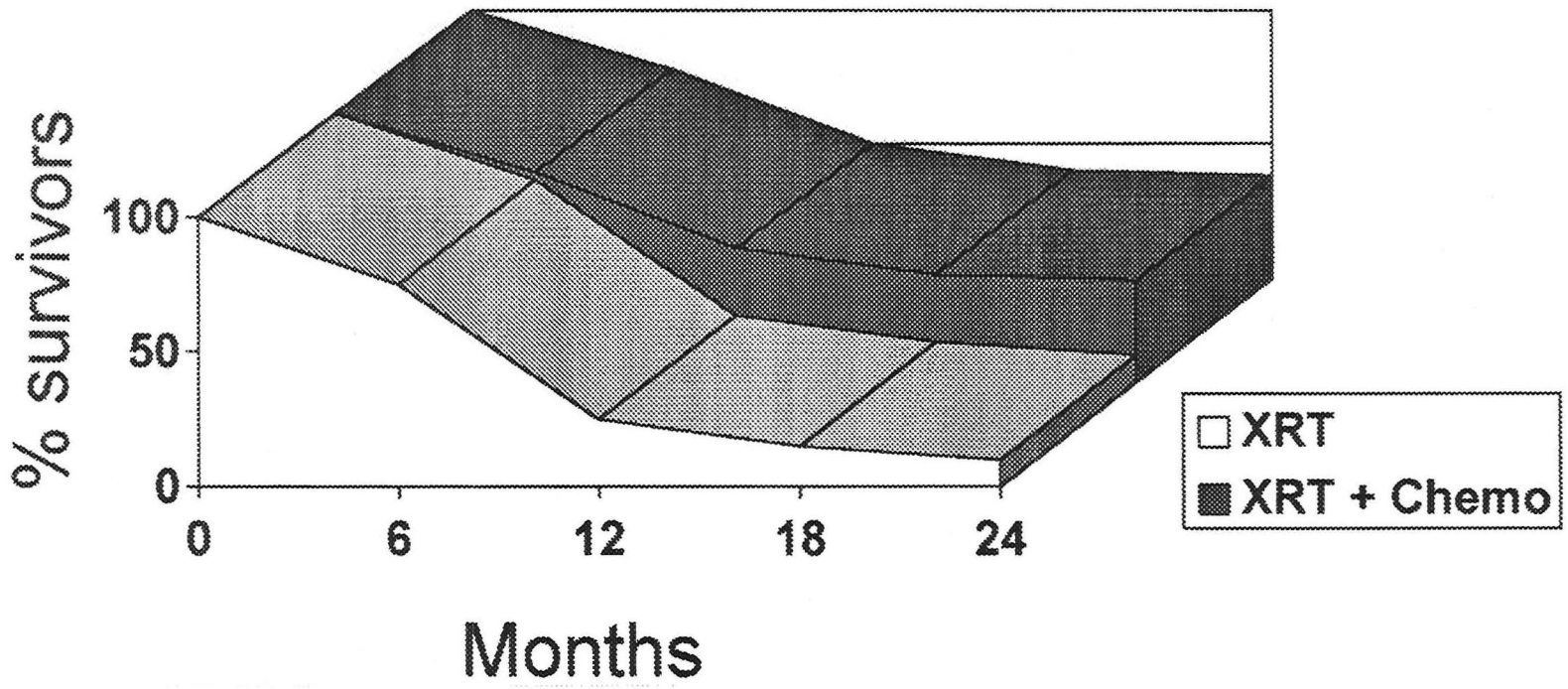

Figure 6
Comparison of XRT versus combined therapy (Chemo and XRT) on survival
Combination therapy had a significant improvement in two year survival in patients with esophageal cancer.

Barrett's esophagus
Effect of surveillance on survival

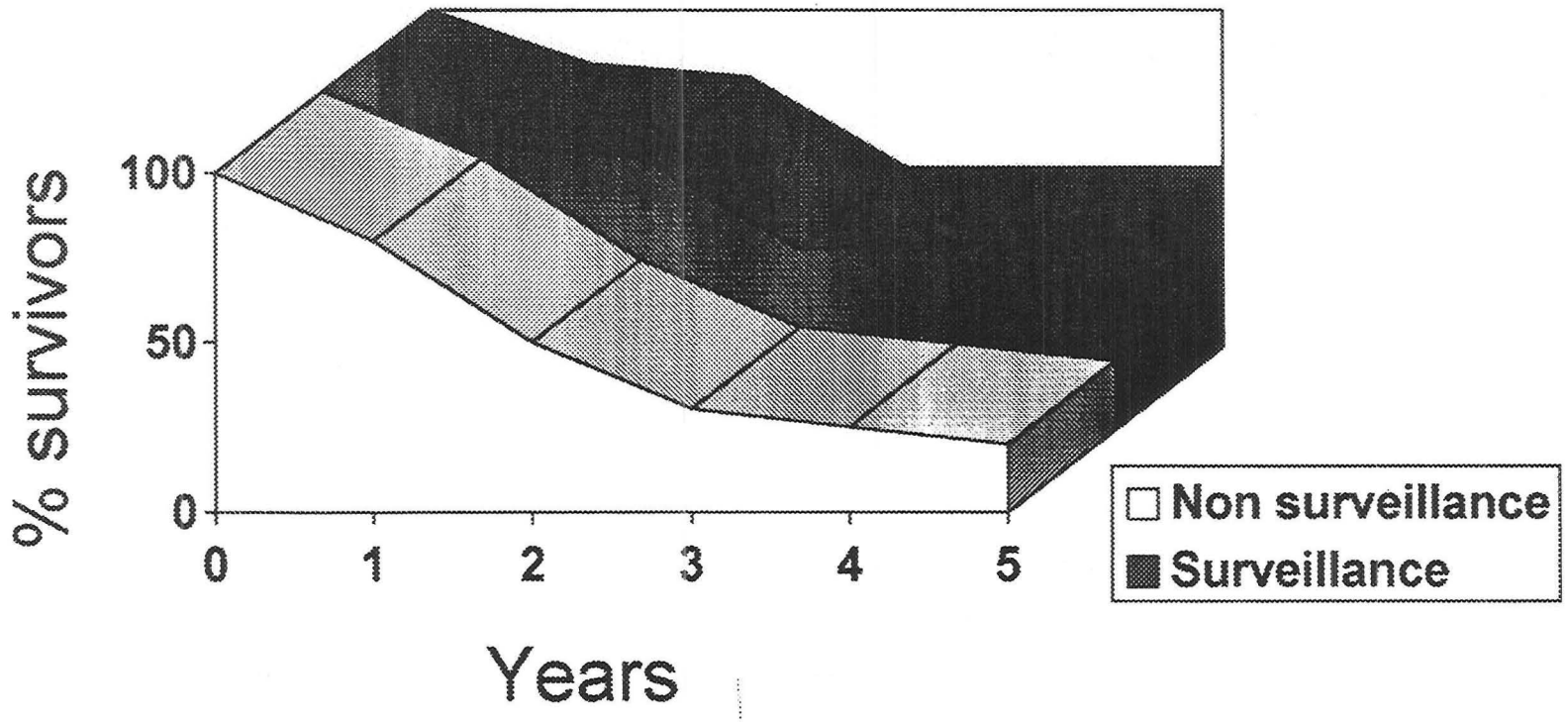

Figure 7
Effect of surveillance on survival of patients with Barrett's esophagus
Surveillance had a significant improvement in survival.

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