ESOPHAGEAL CANCER

Causes

Increased risk

- Age – most patients are over 60, and the median in US patients is 67.
- Sex – the disease is more common in men.
- Heredity – it is more likely in people who have close relatives with cancer.
- Tobacco smoking and heavy alcohol use increase the risk, and together appear to increase the risk more than either individually. Tobacco and alcohol account for approximately 90% of all esophageal squamous cell carcinomas. Tobacco smoking is also linked to esophageal adenocarcinoma though no scientific evidence has been found between alcohol and esophageal adenocarcinoma.
- Gastroesophageal reflux disease (GERD) and its resultant Barrett's esophagus increase esophageal cancer risk due to the chronic irritation of the mucosal lining. Adenocarcinoma is more common in this condition. A consequence of GERD is increased exposure of the esophagus to bile acids; and bile acids have been implicated as causal agents in esophageal adenocarcinoma (reviewed by Bernstein et al.)
- Human papillomavirus (HPV)
- Corrosive injury to the esophagus by swallowing strong alkalines (lye) or acids
- Particular dietary substances, such as nitrosamines
- A medical history of other head and neck cancers increases the chance of developing a second cancer in the head and neck area, including esophageal cancer.
- Plummer–Vinson syndrome (anemia and esophageal webbing)
- Tylosis and Howel–Evans syndrome (hereditary thickening of the skin of the palms and soles)
- Radiation therapy for other conditions in the mediastinum
- Coeliac disease predisposes towards squamous cell carcinoma.
- Obesity increases the risk of adenocarcinoma fourfold. It is suspected that increased risk of reflux may be behind this association.
- Thermal injury as a result of drinking hot beverages
- Alcohol consumption in individuals predisposed to alcohol flush reaction
- Achalasia

Decreased risk

- Risk appears to be less in patients using aspirin or related drugs (NSAIDs).
- The role of *Helicobacter pylori* in progression to esophageal adenocarcinoma is still uncertain, but, on the basis of population data, it may carry a protective effect. It is postulated that *H. pylori* induces chronic gastritis, which is a risk factor for reflux, which in turn is a risk factor for esophageal adenocarcinoma.
- According to the National Cancer Institute, "diets high in cruciferous (cabbage, broccoli/broccolini, cauliflower, Brussels sprouts) and green and yellow vegetables and fruits are associated with a decreased risk of esophageal cancer.
- Moderate coffee consumption is associated with a decreased risk.
- According to one Italian study of "diet surveys completed by 5,500 Italians"—a study which has raised debates questioning its claims among cancer researchers cited in news reports about it—eating pizza more than once a week appears "to be a favorable indicator of risk for digestive tract neoplasms in this population."

Diagnosis

Although an occlusive tumor may be suspected on a barium swallow or barium meal, the diagnosis is best made with esophagogastroduodenoscopy (EGD, endoscopy); this involves the passing of a flexible tube down the esophagus and examining the wall. Biopsies taken of suspicious lesions are then examined histologically for signs of malignancy.

Additional testing is usually performed to estimate the tumor stage. Computed tomography (CT) of the chest, abdomen and pelvis can evaluate whether the cancer has spread to adjacent tissues or distant organs (especially liver and lymph nodes). The sensitivity of a CT scan is limited by its ability to detect masses (e.g. enlarged lymph nodes or involved organs) generally larger than 1 cm. Positron emission tomography is also used to estimate the extent of the disease and is regarded more precise than CT alone. Esophagealendoscopic ultrasound can provide staging information regarding the level of tumor invasion, and possible spread to regional lymph nodes.

The location of the tumor is generally measured by the distance from the teeth. The esophagus (25 cm or 10 inches long) is commonly divided into three parts for purposes of determining the location. Adenocarcinomas tend to occur distally and squamous cell carcinomas proximally, but the converse may also be the case.

Treatment

The treatment is determined by the cellular type of cancer (adenocarcinoma or squamous cell carcinoma *vs* other types), the stage of the disease, the general condition of the patient and other diseases present. On the whole, adequate nutrition needs to be assured, and adequate dental care is vital.

If the patient cannot swallow at all, an esophageal stent may be inserted to keep the esophagus patent; stents may also assist in occluding fistulas. A nasogastric tube may be necessary to continue feeding while treatment for the tumor is given, and some patients require a gastrostomy (feeding hole in the skin that gives direct access to the stomach). The latter two are especially important if the patient tends to aspirate food or saliva into the airways, predisposing for aspiration pneumonia.

Esophagectomy is the removal of a segment of the esophagus; as this shortens the length of the remaining esophagus, some other segment of the digestive tract (typically the stomach or part of the colon or jejunum) is pulled up to the chest cavity and interposed. If the tumor is unresectable or the patient is not fit for surgery, palliative esophageal stenting can allow the patient to tolerate soft diet.

Types of esophagectomy

The thoracoabdominal approach opens the abdominal and thoracic cavities together.
The two-stage Ivor Lewis (also called Lewis–Tanner) approach involves an initial laparotomy and construction of a gastric tube, followed by a right thoracotomy to excise the tumor and create an esophagogastric anastomosis. The three-stage McKeown approach adds a third incision in the neck to complete the cervical anastomosis.

Data are accumulating to indicate endoscopic therapy is a safe, less invasive, and effective therapy for very early esophageal cancer. The candidates for endoscopic therapy are Stage 1 patients with tumors invading into the lamina propria (T1 mucosal) or submucosa (T1 submucosal) that do not have regional or distant metastasis.

Patients with carcinoma *in situ* or high-grade dysplasia can also be treated with endoscopic therapy. Submucosal cancers with increased risk of nodal metastases may not be as amenable to curative therapy. Forms of endoscopic therapy have been used for Stage 0 and I disease: endoscopic mucosal resection (EMR) and mucosal ablation using radiofrequency ablation, photodynamic therapy, Nd-YAG laser, or argon plasma coagulation.

EMR has been advocated for early cancers (that is, those that are superficial and confined to the mucosa only) and has been shown to be a less invasive, safe, and highly effective nonsurgical therapy for early squamous cell esophageal cancer. It has also been shown to have been safe and effective for early adenocarcinoma arising in Barrett's esophagus. The prognosis after treatment with EMR is comparable to surgical resection. This technique can be attempted in patients, without evidence of nodal or distant metastases, with differentiated tumors that are slightly raised and less than 2 cm in diameter, or in differentiated tumors that are ulcerated and less than 1 cm in diameter. The most commonly employed modalities of EMR include strip biopsy, double-snare polypectomy, and resection with combined use of highly concentrated saline and epinephrine, and resection using a cap.

The strip biopsy method for endoscopic mucosal resection of esophageal cancer is performed with a double-channel endoscope equipped with grasping forceps and snare. After marking the lesion border with an electric coagulator, saline is injected into the submucosa below the lesion to separate the lesion from the muscle layer and to force its protrusion. The grasping forceps are passed through the snare loop. The mucosa surrounding the lesion is grasped, lifted, and strangulated and resected by electrocautery. The endoscopic double-snare polypectomy method is indicated for protruding lesions. Using a double-channel scope, the lesion is grasped and lifted by the first snare and strangulated with the second snare for complete resection.

Endoscopic resection with injection of concentrated saline and epinephrine is carried out using a double-channel scope. The lesion borders are marked with a coagulator. Highly concentrated saline and epinephrine are injected (15–20 ml) into the submucosal layer to swell the area containing the lesion and elucidate the markings. The mucosa outside the demarcated border is excised using a high-frequency scalpel to the depth of the submucosal layer. The resected mucosa is lifted and grasped with forceps, trapping and strangulating the lesion with a snare, and then resected by electrocautery.

Another method of EMR employs the use of a clear cap and prelooped snare inside the cap. After insertion, the cap is placed on the lesion and the mucosa containing the lesion is drawn up inside the cap by aspiration. The mucosa is caught by the snare and strangulated, and finally resected by electrocautery. This is called the "band and snare" or "suck and cut" technique. The resected specimen is retrieved and submitted for microscopic examination for determination of tumor invasion depth, resection margin, and possible vascular involvement. The resulting "ulcer" heals within three weeks.

EMR can also be used to debulk or completely treat polypoid dysplastic or malignant lesions in Barrett's esophagus, the known precursor lesion to esophageal adenocarcinoma. In a preliminary report from Germany, EMR was performed as primary treatment or adjunctive therapy following photodynamic therapy for early adenocarcinomas in Barrett's esophagus. The "suck and cut" technique (with and without prior saline injection) was used, as well as the "band and cut" technique. Although all tumors were resected without difficulty, 12.5% developed bleeding (which was managed successfully by endoscopic therapy). Eighty-one percent of the lesions were completely resected. The other lesions were also treated with other endoscopic techniques.

The major complications of endoscopic mucosal resection include postoperative bleeding, perforation and stricture formation. During the procedure, an injection of 100,000 times diluted epinephrine into the muscular wall, along with high-frequency coagulation or clipping can be applied to the bleeding point for hemostasis.

It is important to administer acid-reducing medications to prevent postoperative hemorrhage. Perforation may be prevented with sufficient saline injection to raise the mucosa containing the lesion.

The "non-lifting sign" and complaints of pain when the snare strangulates the lesion are contrainidications of EMR. When perforation is recognized immediately after a procedure, the perforation should be closed by clips. Surgery should be considered in cases of endoscopic closure failure. The incidence of complications ranges from 0–50% and squamous cell recurrence rates range from 0–8%.

Laser therapy is the use of high-intensity light to destroy tumor cells; it affects only the treated area. This is typically done if the cancer cannot be removed by surgery. The relief of a blockage can help to reduce dysphagia and pain. Photodynamic therapy, a type of laser therapy, involves the use of drugs that are absorbed by cancer cells; when exposed to a special light, the drugs become active and destroy the cancer cells.

Chemotherapy depends on the tumor type, but tends to be cisplatin-based (or carboplatin or oxaliplatin) every three weeks with fluorouracil (5-FU) either continuously or every three weeks. In more recent studies, addition of epirubicin was better than other comparable regimens in advanced nonresectable cancer.

Chemotherapy may be given after surgery (adjuvant, i.e. to reduce risk of recurrence), before surgery (neoadjuvant) or if surgery is not possible; in this case, cisplatin and 5-FU are used. Ongoing trials compare various combinations of chemotherapy; the phase II/III REAL-2 trial – for example – compares four regimens containing epirubicin and either cisplatin or oxaliplatin, and either continuously infused fluorouracil or capecitabine.

Radiotherapy is given before, during or after chemotherapy or surgery, and sometimes on its own to control symptoms. In patients with localised disease but contraindications to surgery, "radical radiotherapy" may be used with curative intent.

Radiofrequency ablation is a new treatment modality for the treatment of Barrett's esophagus and dysplasia, and has been the subject of numerous published clinical trials. The findings demonstrate radiofrequency ablation has an efficacy of 80–90% or greater with respect to complete clearance of Barrett's esophagus and dysplasia with durability up to 5 years and a favorable safety profile.

Recent clinical trials have shown that endoscopic resection of esophageal mucosal irregularities and nodules which contain dysplasia or carcinoma combined with subsequent radiofrequency ablation of the remaining flat Barrett's esophagus and dysplasia can effectively and safely eradicate the disease.

Further, a recent multicenter randomized control trial found that in patients with Barrett's esophagus containing nodules or mucosal irregularities which contained high grade dysplasia or cancer, subsequent radiofrequency ablation resulted not only in eradication of Barrett's esophagus and dysplasia, but had significantly less esophageal stricture versus patients who had circumferential endoscopic mucosal resection for their disease.