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Textbook of
HEPATO-GASTROENTEROLOGY



Editors
Mahmud Hasan
Sheikh Mohammad Fazle Akbar
Mamun-Al-Mahtab

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Parveen J Kumar

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CHAPTER

2

Carcinoma of Esophagus

Md Rabiul Hossain, Md Delwar Hossain

INTRODUCTION

Worldwide, esophageal cancer is the sixth leading cause of death from cancer. There were 7,966 people diagnosed with esophageal cancer in the UK in 2007, with twice as many cases occurring in men as in women. Squamous cell carcinoma (SCC) is the most common esophageal carcinoma worldwide. Adenocarcinoma is less common (<15%) esophageal cancer. Small cell carcinoma of esophagus is very rare. Approximately 15% of esophageal cancers arise in the upper one-third, 50% in the middle-third and 35% in the lower-third, and gastroesophageal junction.

EPIDEMIOLOGY

The incidence of carcinoma differs significantly by geographic regions, race, sex, and also types. The rates can vary between regions in a given country due to environmental and possibly nutritional factors. The disease predominantly affects older age groups with the peak incidence between 60 and 70 years of age. In low-risk countries, male-to-female ratio of cases is usually 3:4.1, but it is nearly equal in high-risk countries. For SCC worldwide, the highest risk populations (incidence rate >100 cases per 100,000 inhabitants/year) are found in north central China, northeastern Iran and the intervening central Asian countries sometimes collectively called "the Central Asian esophageal cancer belt". Intermediate-risk populations with incidence rates approximately 20–50 cases per 100,000 inhabitants per year are found in eastern and southern Africa, southern Brazil, Uruguay, northern Argentina, and northwest France. Most of the world is considered low risk with the incidence rates less than 10 cases per 100,000 inhabitants per year. By far, SCC is the most common esophageal cancer worldwide and adenocarcinoma accounts for less than 15% of all esophageal cancers. Over the last two decades, the incidence of adenocarcinoma has risen sharply particularly among white males, although SCC remains the predominant cell type among African Americans.

RISK FACTORS

Many factors are responsible for the development of esophageal cancer (Table 1). It varies with the types of carcinoma. Cigarette smoking and alcohol consumption are the most important predisposing factors for esophageal cancer in developed countries, particularly for SCC. The carcinogenic effects are more pronounced for SCC. The mechanism of carcinogenesis is obscure. It is postulated that many tobacco-derived chemicals, such as nitrosamines may initiate the

Table 1: Risk factors for esophageal carcinoma

Squamous cell carcinoma
• Chronic tobacco use
• Heavy alcohol consumption
• History of radiation therapy
• Chronic esophagitis (most common in Asia and Africa)
• Chronic stricture
• Tylosis
• Plummer-Vinson syndrome
• Achalasia
• Dietary deficiency of carotene, vitamins C, E and riboflavin, selenium and zinc
• Low intake of fruits and vegetables
• High intake of red meat and nitrate-containing foods
• Consumption of hot beverages
Adenocarcinoma
• Barrett's esophagus and gastroesophageal reflux disease
• Obesity
• Cigarette smoking
• Alcohol consumption
• Scleroderma
• History of colon cancer
• Medications: theophylline and β-agonists (long-term use >5 years)

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Fig. 1: Barrett's esophagus—risk for esophageal carcinoma

esophageal carcinoma or act as promotional agents. Barrett's esophagus is the most important risk factor for esophageal adenocarcinoma (Fig. 1). It is a premalignant lesion that results from gastroesophageal reflux disease (GERD) in which the squamous epithelium of the distal esophagus is replaced by intestinal type columnar epithelium. The lifetime risk of esophageal carcinoma in Barrett's esophagus is estimated to be 5%. In addition to this, GERD is an independent risk factor for esophageal adenocarcinoma.

Decreased Risk for Esophageal Carcinoma

The 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, brussel 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.

BIOLOGY AND GENETICS

The progression from basal cell hyperplasia and dysplasia to the development of invasive SCC is variable and may be of long duration. The premalignant stages may persist for 20 years or more. Alterations of oncogenes, tumor suppressor gene and deoxyribonucleic acid (DNA) mismatch repair genes play a role in the genesis of SCC of esophagus like in other cancers of the digestive tract. Cyclin D1 is overexpressed in many cancers and in up to 50% of esophageal SCC. Overexpression is associated with a poor prognosis.

The p53 gene is mutated in up to 70% of esophageal cancers. Inherited germline mutations of the E-cadherin gene lead to loss of E-cadherin expression that causes increased activation of other genes, such as cyclooxygenase-2 (COX-2) and c-myc that may induce proliferation.

Abnormal variants of interleukin-1 gene are associated with an increased risk of development of cancer of gastric cardia. So, these genes may make possible screening of individuals with intestinal metaplasia of the esophagus. Furthermore, anti-inflammatory drugs, such as cyclooxygenase inhibitors may provide a means of medical intervention.

CLINICAL PRESENTATION (TABLE 2)

Dysphagia

Progressive dysphagia (90%) is the most common presentation of esophageal cancer leading to its diagnosis. A patient may not manifest dysphagia until the lumen is more than 50–60% obstructed by the tumor mass by stretching the smooth muscle due to lack of serosal layer. Initially, there is dysphagia to solid and later on for both solid and liquid.

Table 2: Signs and symptoms of esophageal carcinoma

• Dysphagia (most common)—solids then liquids
• Odynophagia
• Back pain and chest pain
• Anorexia
• Weight loss
• Regurgitation
• Hoarseness/voice change
• Aspiration/cough/recurrent pneumonia
• Anemia
• Hematemesis

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Odynophagia

Odynophagia (50%) is the second most common presenting symptom of esophageal cancer. It may be due to an ulcerated area in the tumor or mediastinal involvement. But constant pain in the mid back or mid chest is the typical presentation of mediastinal invasion.

Anorexia and Weight Loss

Up to 75% of patients have experienced anorexia and weight loss when they seek medical attention.

Gastrointestinal Bleeding and Anemia

Overt gastrointestinal bleeding as manifested by hematemesis or melena rarely occur. But anemia is more common due to subclinical bleeding. Hoarseness of voice, severe cough and recurrent pneumonia may present.

COMPLICATIONS

- Pulmonary complications: Dyspnea, chronic cough, aspiration and postobstructive pneumonia, lung abscess, esophagoairway fistula, pleural effusion, and halitosis
- Cardiovascular complications: Hemorrhage from the aorta, arrhythmias, conduction abnormalities, and pericardial effusion

PROGNOSTIC FACTORS

Radiographic Endoscopic

Tumors measuring less than 5 cm are often confined to the esophageal wall, whereas only 10% of those measuring greater than 5 cm are localized. The presence of metastases is a poor prognostic sign and is a contraindication to surgery. The presence of transmural invasion into adjacent organs, such as pericardium or trachea is associated with poor prognosis. Evidence of lymph node involvement is also associated with a poor overall 5-year survival (5%).

Pathologic

The prognosis of any malignancy depends on the histologic type and grade, and clinical stage. The vast majority of esophageal cancer are either SCC or adenocarcinoma. The overall prognosis of a poorly differentiated tumor is worse than that of a well-differentiated tumor.

Clinical Stage

The new system recognizes five major prognostic stages from stage 0 to stage IV of tumor extent and tumor stage based on local invasion, nodal involvement and presence of metastases (Table 3). The 5-year survival rates associated with the tumor invasion (T1 to T4) are approximately 80%, 45%, 25% and less than 20%, respectively.

Table 3: American Joint Committee on Cancer (AJCC) TNM staging system for esophageal cancers (1997 revision)

Primary tumor infiltration (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma *in situ*		
T1	Tumor limited to mucosa/submucosa		
T2	Tumor involving muscularis propria		
T3	Involvement of adventitia, no extraesophageal involvement		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No nodal involvement		
N1	Regional nodes involved		
Distant metastasis (M)			
MX	Distant metastases cannot be assessed		
M0	No distant metastases		
	M1 Distant metastases for tumors of the lower thoracic esophagus M1a Metastases in celiac nodes M1b Other distant metastases Tumors of the mid-thoracic esophagus M1a Not applicable M1b Nonregional lymph nodes and/or other distant metastasis Tumors of the upper thoracic esophagus M1a Metastases in cervical nodes M1b Other distant metastases		
AJCC stage groupings			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2–3	N0	M0
Stage IIB	T1–2	N1	M0
Stage III	T3	N1	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

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INVESTIGATIONS

Radiography

Chest X-ray

Posteroanterior (PA) and lateral chest radiography is indicated in patients with chronic cough and in case of abnormal chest findings on auscultation to demonstrate pulmonary metastases, pneumonia or esophagorespiratory fistula.

Barium Swallow Radiography

It is indicated in selected patients and details high-grade stenosis, obstruction, and fistulas (Fig. 2).

Computed Tomography

Computed tomography scanning of the chest and upper abdomen is indicated to assess the lymph nodes, and pulmonary and hepatic metastases. The primary tumor is seen as low density mass. The length and extent can be assessed as well. Magnetic resonance imaging can assess but has no advantages over CT scan (Fig. 3).

Endoscopy

Upper gastrointestinal endoscopy allows direct visualization of the esophagus as well as tissue sampling to confirm the diagnosis (Fig. 4). It allows accurate characterization of tumor's configuration, length and localization. At least six biopsy samples should be taken from a non-necrotic area to yield an accuracy approaching 100%. Brush cytology may be used as a complementary technique.

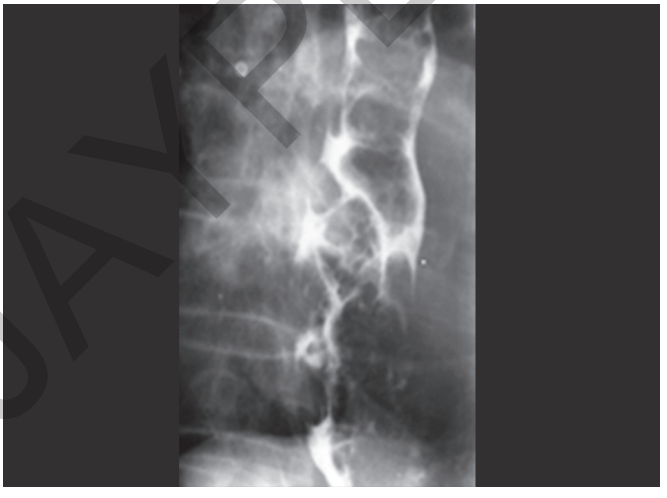


Fig. 2: Barium swallow of the esophagus showing irregular filling defects suggestive of esophageal carcinoma



Fig. 3: CT with contrast axial image revealing esophageal carcinoma

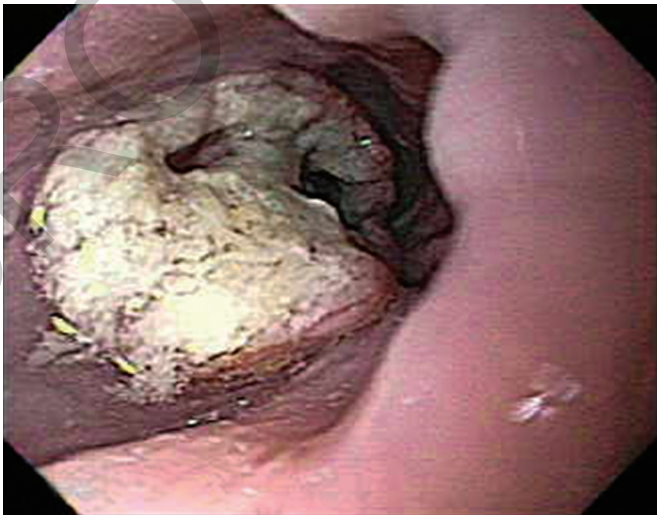


Fig. 4: Endoscopic view of esophageal carcinoma

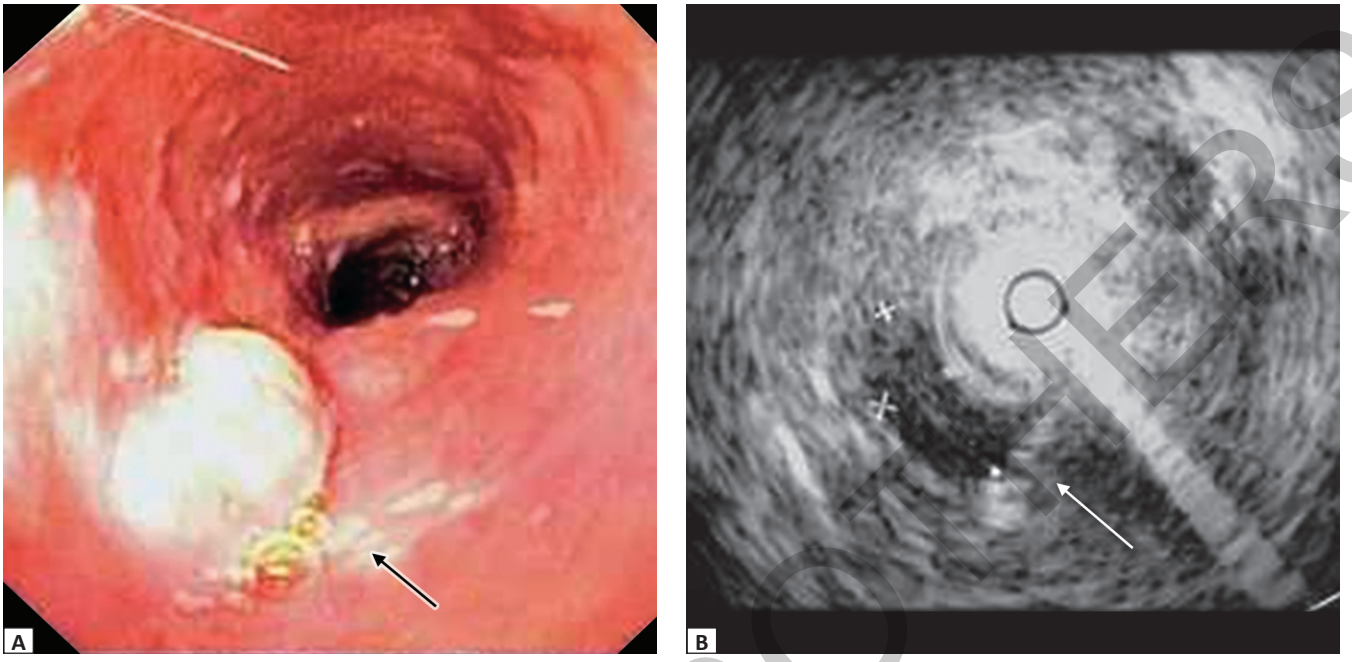
Investigations for Staging

Computed tomography and MRI are highly effective in identifying solid organ metastases when these lesions are larger than 5–10 mm (Fig. 3). For metastases detection by CT scan, the accuracy is 60–90% with overall sensitivity from 41 to 62% and specificity from 63 to 83%.

Positron Emission Tomography

Positron emission tomography (PET) is a noninvasive procedure to detect distant metastases with a sensitivity of 88%, specificity of 93%, and accuracy of 91%. In one study that compared PET with CT and endoscopic ultrasonography (EUS) for local lymph node (LN) disease, the sensitivity of PET

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Figs 5A and B: (A) Endoscopy and (B) radial ultrasound revealing submucosal esophageal tumor

was lower than that of EUS (33% vs 81%), but the specificity may have been higher (87% vs 67%).

Endoscopic Ultrasonography

It is the most accurate in identifying T3 or T4 stage. Overall EUS nodal staging is less accurate. Endoscope ultrasound-guided fine-needle aspiration has significantly improved the diagnosis of malignant adenopathy (Figs 5A and B).

TREATMENT

Esophageal carcinoma is a treatable disease, but it is rarely curable. Whether the patient is a candidate for major curative surgery is to be determined first before going to start treatment. Unfortunately, over 60% patients with esophageal carcinoma are not candidates for surgery at the time of presentation due to advanced stage of the disease or significant comorbidity.

Primary treatment modalities include:

- Surgery alone
- Chemotherapy with radiation therapy
- Combined modality therapy (chemotherapy + surgery, chemotherapy and radiation therapy + surgery) is under clinical evaluation
- Endoscopic mucosal resection (EMR) and or photodynamic therapy in selected patients with superficial carcinoma is also under evaluation.

Primary Therapy

Surgery

General considerations: Patients in the subgroup with limited local spread (T1–T2) and no regional lymph node involvement are potentially curable by surgery. Resectable tumors are characterized by the absence of extension into mediastinal structures and the absence of nodal or organ metastases. Prior to surgery, the patient should have sufficient cardiopulmonary reserve. Forced expiratory volume (FEV1) should be 2 L or more. Resting ejection fraction of less than 40% is an ominous finding.

Surgical approach: The surgical options available for esophageal tumor resection include:

- Transhiatal: It is currently the preferred surgical approach.
- Combined right thoracic and abdominal (Ivor Lewis)
- Left thoracoabdominal
- En bloc, either two field- or three field-resection remains the definitive surgical cure for esophageal cancer (field one—celiac and splenic nodes, field two—infracarinal posterior mediastinal nodes, field three—upper mediastinal and cervical nodes).

Combination Therapy

It is alternative to surgery. Definitive radiation therapy in combination with chemotherapy (fluorouracil and mytomycin) is used for treatment.

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Treatment of Superficial Esophageal Cancer Endoscopically

- EMR
- Laser therapy
- Argon plasma coagulation (APC)
- Photodynamic therapy.

Palliation Therapy

Palliative therapy remains the mainstay of treatment options for incurable esophageal carcinoma with what the majority of patients present. The following palliative therapy options are available.

Radiation Therapy

External beam radiation therapy alone provides reasonable palliation for esophageal cancer. Radiotherapy achieves palliation of dysphagia in 70–90% of patients. Combination of external beam radiation with intraluminal irradiation using cobalt-60, cesium-137 or iridium-192 is possible to increase the dose of radiation to the tumor, and it is promising both in median and 5-year survival.

Contraindication to radiotherapy:

- Tracheal or bronchial involvement
- Cervical esophageal location of the tumor
- Stenosis.

Chemotherapy

Single agents: The clinical response rates (5–10%) and duration response (2–4 months) of any single agent of any class of chemotherapy are poor.

Combination chemotherapy: It is superior to single agent chemotherapy in the management of esophageal cancer. In general, the cisplatin-based combination chemotherapy (commonly used) has yielded a response rate of 25–35%. To date, there is no role of single agent or combination chemotherapy as an adjuvant to surgery.

Endoscopic Therapy

Dilation: Esophageal dilation is commonly done by expandable balloons through-the-scope or wire-guided polyvinyl bougies under fluoroscopy.

Ablation: The available options for tumor ablation are as follows:

- Chemical sclerosant injection: Absolute alcohol is the most widely used sclerosant chemical agent
- Photodynamic therapy (PDT): It has been successful in reducing tumor bulk and in opening the lumen in patients with complete obstruction. It also acts as a salvage therapy in patient with stents failure due to tumor ingrowth or overgrowth. It is done by intravenous injection of a photosensitive chemical, porfimer sodium (Photofrin), at a dose of 2 mg/kg body weight followed by exposure of red light at a wave length of 630 nm to tumor resulting in necrosis of the tumor
- Monopolar and bipolar electrocautery: It is rarely used now a days
- Argon plasma coagulation: It uses ionized argon gas to convey electrical energy to achieve thermal desiccation of the tumor tissue. But it is less effective in relieving dysphagia in advanced esophageal cancer
- Neodymium:yttrium-aluminium-garnet (Nd:YAG): Nd:YAG laser relieves dysphagia by coagulating and vaporizing the malignant tissue under endoscopic control. Multiple laser sessions are required to improve dysphagia. The requirement for the laser therapy are as follows:
  - Growth should be exophytic or polypoid
  - Preferably, it will be located in the straight segment of esophagus
  - Mass shorter than 5 cm.

Endoscopic mucosal resection: EMR or mucosectomy is used to treat superficial flat and polypoid neoplasm of the mucosa of gastrointestinal tract. Long-term studies show that EMR outcomes are similar to those of surgery to the treatment, particularly in early gastrointestinal cancers. Different EMR techniques are as follows:

- Injection and snare cautery
- Injection with precut
- EMR with cap
- EMR with band ligation.

It is indicated:

- When the lesion is superficial lesion
- No evidence of lymph node metastasis

Bleeding, perforation and necrosis are the major complications.

The commonly employed modalities of EMR include strip biopsy, double-snare polypectomy, resection with combined use of highly concentrated saline and epinephrine, and resection using a cap.

Esophageal prostheses: The prostheses (stents) are inserted endoscopically under fluoroscopic guidance and provide relief of dysphagia effectively. At present, self-expanding metallic stents (SEMS) covered/uncovered are widely used

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Fig. 6: Self-expanding metallic stents used for the palliation of esophageal carcinoma

(Fig. 6). Covering the stent with a polymer sheet effectively reduces tumor ingrowth and provides for treatment of tracheoesophageal fistulas. Commercially available SEMS are as follows:

- The Wallstent II (Microvasive, Boston Scientific, Inc, Natick, Mass)
- The Flamingo, Wallstent
- The Ultraflex stent (Microvasive, Boston Scientific, Inc, Natick, Mass)
- The "Z" stent (Cook medical, Inc, Winston-Salem, NC).

Other than the SEMS, the Polyflex (Boston Scientific, Inc, Natick, Mass) is a completely covered self-expanding non-metallic (plastic) stent recently introduced. It is approved by the Food and Drug Administration (FDA) for palliation of malignant dysphagia.

Major complications of SEMS placement include tumor ingrowth or tumor overgrowth (5–20%), which can be treated effectively with laser or thermal contact therapy, stent migration (10%) and chest pain. Other complications are food impaction, bleeding, and reflux esophagitis.

Enteral Nutrition

Enteral nutrition support may be indicated in an attempt to improve functional status before and after surgery, during chemotherapy and as an adjunct to other palliative measures. Enteral access is achieved surgically (gastrojejunostomy), endoscopically [percutaneous endoscopic gastrostomy (PEG), direct percutaneous jejunostomy or PEG with a jejunal feeding tube extension] or radiologically.

PROGNOSIS

Despite the widespread use of different modalities of treatment, the reported overall 5-year survival rates are at best 10–15%. Delayed presentation, rapid intramural invasion and distant metastases are responsible for poor prognosis. The patients with early stage of disease carry better prognosis. The 5-year survival rate is greater than 40% in a patient with T1 or T2 disease without nodal involvement, but it is less than 25% for patients with T3 or T4 lesion.

Stage 0, I, and III tumors are resectable for cure and 5-year survival is greater than 85%, 50% and 40%, respectively. On the other hand, stage IV tumors are considered incurable and nonresectable. Nodal involvement has prognostic impact and it is independent of the T classification. The 5-year survival is over 70% for N0 disease, but for N1 disease it is near to 40%.

BIBLIOGRAPHY

1. Bollschweiler E, Wolfgarten E, Gutschow C, et al. Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. Cancer. 2001;92(3):549-55.
2. Cancer research UK. Oesophageal cancer incidence statistics. [online]. Available from http://www.cancerresearchuk.org/cancer-info/cancerstats/types/oesophagus/incidence/uk-oesophageal-cancer-incidence-statistics. [Accessed January, 2013].
3. Corley DA, Kerlikowske K, Verma R, et al. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. Gastroenterology. 2003;124:47-56.
4. Ell C, May A, Gossner L, et al. Endoscopic mucosal resection of early cancer and high-grade dysplasia in Barrett's oesophagus. Gastroenterogy. 2000;118:670-7.
5. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med. 2003;349:2241-52.
6. Heath EI, Limburg PJ, Hawk ET, et al. Adenocarcinoma of the esophagus: risk factors and prevention. Oncology (Williston Park). 2000;14(4):507-14.
7. Koshy M, Esiashvilli N, Landry JC, et al. Multiple management modalities in esophageal cancer: epidemiology, presentation and progression, work-up and surgical approaches. Oncologist. 2004;9(2):137-46.
8. Ku GY, Ilson DH. Preoperative therapy for esophageal cancer. Gastroenterol Clin North Am. 2009;38(1):135-52.

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9. Lagergren J, Bergström R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999;340(11):825-31.
10. Lepage C, Rachet B, Jooste V, et al. Continuing rapid increase in esophageal adenocarcinoma in England and Wales. Am J Gastroenterol. 2008;103(11):2694-9.
11. Narahara H, Lishi H, Tatsuta M, et al. Effectiveness of endoscopic mucosal resection with submucosal saline injection technique for superficial squamous carcinomas of the esophagus. Gastrointest Endosc. 2000;52:730-4.
12. NICE Interventional Procedural Guideline. (2007). Palliative photodynamic therapy for advanced oesophageal cancer. [online]. Available from http://guidance.nice.org.uk/IPG206 [Accessed January, 2013].
13. Pisani P, Parkin DM, Bray F, et al. Estimates of the worldwide mortality from 25 cancers in 1990. Int J Cancer. 1999;83: 18-29.
14. Radu A, Wagnières G, van den Bergh H, et al. Phtodynamic therapy of early squamous cell cancers of the esophagus. Gastrointest Endosc Clin N Am. 2000;10(3):439-60.
15. Systemic review of the staging performance of 18F-fluorod-eoxyglucose position emission tomography in esophageal cancer. J Clin Oncol. 2004;22:3805-12.

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Mahmud Hasan did his MBBS in 1970 securing the first place in all parts of the MBBS examination with honor marks in several subjects. He stood first in the FCPS examination in medicine in 1975 and was awarded the prestigious Ashab Gold Medal for his outstanding performance. He got trainning in gastrointestinal, liver and pancreatic diseases in Edinburgh for five years and also obtained PhD of the Edinburgh University for original research in 1982. He has conducted research work on peptic ulcer disease, chronic viral hepatitis and irritable bowel syndrome and has been credited with more than 200 publications in national and international journals. Professor Hasan had been the editor of the *Journal of Bangladesh Medical Association* and the *Journal of the Bangladesh College of Physicians and Surgeons (BCPS).* He has worked as the Honorary Secretary, Treasurer and the Vice President and President of the BCPS. He was the elected President of the Association of Physicians of Bangladesh in the past. He has been the Secretary General of the Bangladesh Gastroenterology Society and is currently the President of the Bangladesh Gastroenterology Society. He is also the President of the Bangladesh Medical Association (BMA) (elected for the second term), and the Chairman of Bangladesh Medical Research Council. He is also the President of Bangladesh Gastro-Liver Foundation.



Sheikh Mohammad Fazle Akbar graduated in Medicine from Rajshahi University, Bangladesh in 1980 and worked in the field of infectious disease control program under Ministry of Health and Family Welfare until 1987 when he moved to Japan for research in Medicine with a Japanese Government scholarship. He was awarded the degree of PhD in Medical science from Ehime University, Japan in 1993. He became a full faculty member of Ehime University Graduate School of Medicine in 1996 and was attached to the Department of Gastroenterology and Metabology until 2008, when he moved to Toshiba General Hospital, Tokyo, Japan as Principal Investigator. He has published more than 110 peer-reviewed articles in international journals. He also authored a book entitled *Dendritic Cell in Clinics*. He is the Executive Editor of *Euroasian Journal of Hepato-Gastroenterology*. He is a member of American Association for the Study of Liver Diseases (AASLD), European American Association for the Study of the Liver (EASL), Asian Pacific Association for the Study of Liver (APASL), and Japan Society of Hepatology (JSH), as well as several other immunological associations.



Mamun-Al-Mehtab is currently an Associate Professor at the Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. He is graduated in medicine from Dhaka University, Bangladesh in 1995. He did his MSc. in gastroenterology from University of London, UK in 1998 and, subsequently, did MD in hepatology from Bangabandhu Sheikh Mujib Medical University in 2006. He is a Fellow of the American College of Gastroenterology. He has conducted several clinical trials for developing immunetherapy for chronic HBV infection and hepatocellular carcinoma. He has compiled three books, namely *Liver: A Complete Book on Hepato-Pancreato-Biliary Diseases*, published by Elsevier; *Comprehensive Text Book on Hepatitis B*, published by M/s Jaypee Brothers; and *Fatty Liver Disease,* published by McMillan. He is the Deputy Editor-in-Chief-cum-Managing Editor of *Euroasian Journal of Hepato-Gastroenterology* and is also serving in the Editorial Boards of several other peer-reviewed international journals in the fields of hepatology and gastroenterology. He has received many awards for his scientific works from various international organizations. He has more than 100 international publications and over 70 conference talks to his credit. He is the Secretary General of Association for Study of the Liver, Dhaka, Bangladesh (ASLDB) and Executive Council Member of South Asian Association for Study of the Liver (SAASL). He is also a life member of APASL and member of European Association for the Study of the Liver (EASL).

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