

## **Clinical guidelines for management of esophageal cancer in India**

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## **Introduction**

The esophagus is one of the common sites of malignancy in the gastro-intestinal tract. World-over, the incidence of esophageal cancer, particularly adenocarcinoma, is on the rise. In the US, the incidence has increased five fold. At the Tata Memorial hospital, between 800 and 1000 patients of cancer esophagus are registered every year. Unlike in the west, the majority of these are squamous carcinoma. The reported five year survival worldwide ranges from 5% to 30%.

## **The need for a guideline**

Esophageal cancer being a major health problem, there is a need to evolve guidelines for management of these patients which are not only evidence-based but also practical and implementable in the community. This is especially important because presently there is wide variation in the investigations and treatment of patients with esophageal cancer in India. Considering these factors, the WHO initiated the formation of practical guidelines in management of common cancers in India.

This guideline provides the best available evidence in the workup and management of patients with esophageal cancer. It also identifies basic infrastructure necessary to provide comprehensive care for patients with esophageal cancer. It is accepted that although 'optimal' facilities would be ideal, centres which have a basic 'minimum' infrastructure and expertise could also manage these patients provided they have access to an 'optimum' centre if the need arises. It is recommended that centres which lack the basic 'minimum' infrastructure necessary should not treat these patients and should refer these patients to a centre with minimum or optimum facilities.

The aims of these guidelines are to

1. Improve overall care of patients with esophageal cancer

2. Ensure uniformity of standards of care in various centres in different parts of the country.
3. Encourage early referral and diagnosis of esophageal cancer
4. Ensure that patients with esophageal cancer get the best chance of appropriate treatment – curative or palliative, regardless of their geographical location.

### **Methods used to formulate the guidelines**

Expert consensus, based on best available evidence and practical applicability in the community health care system

### **Method of guideline validation**

The guidelines were initially discussed by all the committee members and consensus reached after detailed discussion of the best available evidence and the ground realities of community health care. The guidelines were then sent back to the committee members for final comment, revisions incorporated and finalised.

### **Interventions and practices considered**

#### **Diagnosis and Staging**

1. Assessment of symptoms
2. Endoscopic biopsy
3. Computed tomography scans of the chest and abdomen
4. Endoscopic ultrasound
5. Diagnostic laparoscopy
6. PET-CT scan
7. Ultrasonography of neck

#### **Treatment**

1. Esophagectomy
2. Chemotherapy or radiotherapy (definitive, adjuvant or neoadjuvant)
3. Palliative esophageal stenting

### **Assessment of symptoms**

#### **Flexible upper gastrointestinal endoscopy**

Patients who present with any of the 'alarm' symptoms – dysphagia, vomiting, anorexia, weight loss and gastrointestinal blood loss – should undergo a flexible upper gastrointestinal (GI) endoscopy. A barium swallow\* may be performed in patients where the patient has symptoms of a tracheo esophageal fistula or mediastinal sinus, and where a tight stricture precludes a thorough endoscopy. A normal barium swallow in a patient with any of the 'alarm' symptoms does not obviate the need for an endoscopy.

(\* When a barium swallow is done, a double-contrast barium swallow should be routinely done)

#### **Flexible upper GI endoscopy is recommended as the investigation of choice in patients suspected to have esophageal cancer**

#### **Chromo endoscopy**

Chromoendoscopy is not mandatory in all patients with suspected esophageal cancer. The use of Lugol's iodine for dysplastic and malignant squamous epithelium of the esophagus and methylene blue for improved visualization of intestinal metaplasia in Barrett's epithelium may be done in specialized centres. It is recommended in areas where there is a high incidence of esophageal cancer.

#### **Biopsy**

The diagnostic accuracy is improved by increasing the number of biopsies taken during upper GI endoscopy. A minimum of four (preferably 8) biopsies have to be performed. Cytology is complementary to biopsies, especially in infiltrative, stenosing lesions. Patients with Barrett's esophagus should have a structured biopsy protocols with quadrantic biopsies every two centimeters and biopsy of

any visible lesion. Biopsies should be interpreted by pathologists with experience in gastrointestinal cancer pathology.

## **Staging methods and techniques**

### **Computed tomography (CT) scan of the thorax and upper abdomen**

A contrast enhanced CT (CECT) scan of the thorax and upper abdomen is mandatory to stage patients with esophageal cancer being considered for definitive treatment. The CT scanner should at least be a spiral CT (preferably multi slice). CECT scan stages the primary tumor, regional lymph nodes and distant metastases. The liver has to be imaged in the portal venous phase for optimal detection of liver metastases. CECT scanning should be available in all centres treating esophageal cancer. It is not mandatory in patients with obviously advanced disease and in patients whose poor general condition preclude definitive treatment.

**Patients with esophageal cancer considered for definitive treatment should undergo CT scan of the thorax and upper abdomen with intravenous contrast and gastric distension with oral contrast or water. The liver has to be imaged in the portal venous phase.**

### **Endoscopic ultrasonography**

Endoscopic ultrasonography (EUS) has higher accuracy in staging the primary tumor (T) and the regional lymph nodes (N). It is not mandatory in patients with obviously early, resectable disease (unless endoscopic mucosal resection for very early tumors is being considered) and in patients with obviously advanced (locoregional or distant metastases) disease. Endoscopic ultrasonography should be available in an 'optimum' centre handling esophageal cancer but is not mandatory as a minimum infrastructure (or expertise). If an EUS is considered as potentially useful in a patient being treated by a centre with minimum facilities, the patient should be referred to a centre with optimum facilities including EUS.

### **Diagnostic laparoscopy**

Diagnostic laparoscopy has the potential to change treatment decisions in patients with esophageal cancer with considerable stomach involvement. It should be available in an optimal centre managing esophageal cancer. Laparoscopic ultrasound has the potential to stage disease more accurately than laparoscopy alone.

### **Bronchoscopy**

Flexible fibre optic bronchoscopy should be done in all patients with tumors abutting the tracheo bronchial tree being considered for definitive treatment. It should also be done in patients with symptoms suggestive of a tracheo esophageal fistula or a mediastinal sinus. Flexible fibre optic bronchoscopy should be available in all centres managing esophageal cancer as a minimum requirement.

### **Positron emission tomography (PET) – CT scan**

PET-CT scan has the potential to improve the overall staging of patients with esophageal cancer. It is not mandatory as a minimum requirement to treat esophageal cancer but may be done in centres where facilities are available.

### **Ultrasonography of the neck**

Neck ultrasonography has been shown to be superior to clinical examination in detecting metastatic lymph nodes in the neck. It is a low-cost investigation and with an adequately trained operator, has the potential to change treatment decisions. It should be available as a minimum investigation in centres treating esophageal cancer.

### **Treatment**

**The management of all patients diagnosed with esophageal cancer should be discussed within a multi disciplinary team.**

### **Localized disease**

Surgery is the treatment of choice in patients with localized resectable esophageal cancer provided they are fit to undergo surgery. Endoscopic mucosal resection (EMR) may be considered in patients with very early, superficial (T1a) esophageal cancer in centres with expertise and experience in EMR. Definitive chemoradiation may be given in patients with localized disease who are either unfit for surgery or who refuse surgery, provided they can tolerate chemoradiation. If patients cannot tolerate concurrent chemoradiotherapy, they may be treated with radical radiotherapy.

### **Assessment of preoperative fitness**

Patients considered for surgical resection should undergo careful assessment of preoperative fitness with special emphasis on performance score and cardiorespiratory function. Pulmonary function tests should be done as part of routine preoperative work up; echocardiography should be done only in selected cases with cardiac illness or symptoms of myocardial ischemia.

Anesthesiologists should be experienced in thoracic anesthesia, critical care and pain management.

**Surgery is the treatment of choice in patients with localized disease who are fit to undergo esophageal resection.**

### **Surgical technique**

Total esophagectomy should be done through a trans thoracic approach in patients fit to undergo thoracotomy. Transhiatal esophagectomy may be done in patients with pulmonary comorbidity, provided the disease is clearly resectable. Video assisted thoracoscopic esophagectomy may be done by experienced surgeons in specialized centres. Standard two-field lymphadenectomy should be done in patients undergoing trans thoracic esophagectomy, with clearance of abdominal (D2 clearance) and infracarinal mediastinal lymph nodes. Extended, total and three field lymphadenectomy may be performed in centres with surgical expertise. The stomach is the preferred interponat as an esophageal substitute.

The colon may be used in cases where the stomach is not available for any reason. Pyloric drainage may or may not be done depending on the operating surgeon's preference. The technique of anastomosis may be hand-sewn or stapled.

### **Perioperative mortality and volume of work**

Esophageal resectional surgery should be carried out in high-volume specialist units by surgeons with a high operative case-load. Centres performing esophageal surgery should have well-equipped operating rooms, intensive care unit or high dependency unit and experience with major surgeries. Operating surgeons should have a case volume of at least 12 surgeries per year.

### **Role of perioperative nutrition**

Patients with dysphagia grade III or above should have preoperative nasogastric feeding till the time of surgery, though surgery should not be postponed purely for the sake of nutritional build-up. There is no role of perioperative total parenteral nutrition (TPN). Immuno nutrition may be useful in reducing the postoperative morbidity but has no impact on mortality.

### **Neoadjuvant treatment**

There is no role for neoadjuvant treatment in clearly resectable esophageal cancer. Neoadjuvant chemotherapy or chemoradiotherapy may be considered in patients with bulky disease with borderline operability, where the chances of an R0 resection are less likely. Platinum-based chemotherapy or chemoradiotherapy should be offered to fit patients with borderline resectable disease. When chemotherapy alone is considered, two to three cycles of platinum-based chemotherapy should be administered and response assessed to look for operability. When chemoradiotherapy is used, platinum-based chemotherapy should be administered concurrent with 4000 to 4500 cGy radiation. There is no role for preoperative radiation therapy alone.

**Neoadjuvant platinum-based chemotherapy or concurrent chemoradiotherapy should be administered to patients with borderline resectable esophageal cancer.**

### **Adjuvant treatment**

There is no role for adjuvant treatment in completely resected esophageal squamous cell carcinoma. Adjuvant radiotherapy may be considered in patients with residual disease after surgery or patients with positive resection margins. Perioperative (pre+post operative) chemotherapy may be considered in patients with adenocarcinomas of the lower esophagus and gastro esophageal (GE) junction (as per the MAGIC trial protocol). Postoperative chemoradiotherapy may be considered in patients with completely resected adenocarcinomas of the GE junction (MacDonald regime) but the toxicity is high. It should be considered only in very fit patients with an uneventful postoperative recovery.

### **Pathological staging of resected specimens**

Pathology reports should include a minimum dataset (as per appendix 1) with detailed information on the resected specimen. Ideally, the operating surgeon should individually dissect the different lymph node groups and label them separately. The final histopathology report should give the pathological pTNM staging and resection status.

### **Non surgical treatment for localized esophageal cancer**

Patients with localized esophageal cancer should be considered for non surgical treatment only if patients are unfit or refuse surgery. In these patients, concurrent chemoradiotherapy should be given to patients who are medically fit and considered to be able to tolerate treatment. Patients who are unfit for concurrent chemoradiotherapy should be treated with radical radiotherapy. Patients who are unfit for radical radiotherapy should be considered for palliative radiotherapy, intraluminal radiotherapy (ILRT) or palliative esophageal stenting.

Concurrent chemoradiotherapy may consist of external beam radiotherapy delivered to a dose of 59.4 – 63 Gy/ 33 - 35 fractions over 6-7 weeks using a shrinking field technique.

Patients who are candidates for concomitant chemoradiotherapy should be simulated for the radiotherapy. Localization of the lesion centre maybe done upfront to be able to appropriately boost the involved segment to higher doses.

Phase 1: The first phase of radiotherapy includes the gross disease with involved nodes, with 5cm longitudinal, proximal and distal margins and 2 cm margins laterally. The beam arrangement is a pair of parallel opposed (AP/PA) template to deliver a dose of 39.6Gy/ 22 fr/ 4.2 weeks

Phase 2: Boost to the lesion with 2- 3 cm margins, to achieve a total dose of 63Gy/ 35 fr/ 7 weeks. The portal arrangement depends upon the location of the lesion and usually is a combination of two or three fields. Care should be taken to shield the spinal cord and to see that dose to the spinal cord does not exceed 45Gy/ 25 fr/ 5 weeks. After a total dose of 50.4Gy/ 28 fr/ 5.3 weeks, the field maybe further reduced depending on the response.

The chemotherapy may consist of Inj. Cisplatin, 30-35mg/m<sup>2</sup>, once every week for the duration of the radiotherapy. When using a concurrent chemo-radiotherapy regimen, avoid incorporation of brachytherapy.

For patients who are suitable for radical radiotherapy alone, the above guidelines can be followed, however, if the patient is suitable for a brachytherapy boost, this should be considered after 50.4 Gy/ 28 fr/ 5.3 weeks. The brachytherapy insertion can be performed about 7 -10 days after completion of the external beam radiotherapy.

A dose of 6 Gy X 2fr, HDR, weekly or an equivalent LDR dose as a single insertion maybe delivered. The dose is prescribed at 1 cm. off axis, unoptimised.

### **Palliation of grossly unresectable or metastatic disease**

Patients with gross infiltration of mediastinal structures, patients unfit for definitive treatment and patients with distant metastases should be evaluated for palliation

of dysphagia. Palliative radiotherapy (external or intra luminal) or stenting are the preferred methods of palliation.

Such a patient maybe considered for palliative radiotherapy if there is no tracheo-oesophageal fistula. If the patient is suitable for Intraluminal brachytherapy (ILRT), as determined by Barium swallow or on Endoscopic evaluation, palliative ILRT maybe performed. The schedule consists of two applications, a week apart, delivering a dose of 8Gy/ fraction, at 1 cm, off axis, unoptimised. If the response to ILRT is favorable, further external radiotherapy (EBRT) boost maybe considered.

In patients not suitable for ILRT, palliative external beam radiotherapy can be considered to doses of 20-30 Gy/ 5 – 10 fractions/ 1-2 weeks. The response may be assessed after 2 weeks and if favorable, a further boost with EBRT or ILRT maybe considered.

For palliative ILRT the lesion is treated with 2 cm. proximal and distal margins, while in external beam radiotherapy 3 cm. margins are applied.

Palliative radiotherapy may also be considered in patients with tumor overgrowth in a stent.

### **Follow up**

Patients should be ideally followed up 3-4 monthly for the first two years, six monthly for the next three years and annually after five years. Patients who live far away may be followed up six monthly for the first five years and annually thereafter. Work up of patients at follow up should be symptom-directed.

### **Treatment of recurrent disease**

Patients with recurrent disease should be evaluated to distinguish isolated loco regional recurrence from distant metastases. Patients with isolated loco regional recurrence should be evaluated for disease control using surgery, chemotherapy, radiotherapy or a combination of the above. Patients with disease not suitable or unfit for definitive treatment and patients with distant metastases should be treated symptomatically.

## Appendix 1: Minimum dataset for pathology reporting

Name	Reg No
Pathologist	

Maximum length of specimen:	mm	Type of tumour:	Squamous
Length of oesophagus:	mm		Adenocarcinoma
Length of stomach (maximum):	mm		Other (specify)
Width of tumour:	mm	Differentiation by predominant area:	Well
Length of tumour:	mm		Moderate
Tumour edge to nearest distal margin:	mm		Poor
Tumour edge to nearest proximal margin:	mm	Depth of invasion:	Tis high grade dysplasia
Macroscopic type of tumour:	Polypoid		Tx No tumor identified
	Ulcerative		T1 invasion of lamina propria/submucosa
	Infiltrative		T2 invasion of muscularis propria
	Ulceroinfiltrative		T3 invasion beyond muscularis propria
	Other (specify)	T4 invasion of adjacent structures	

Circumferential margin:	Involvement : Free    Close(<1mm)    Involved
	Distance of carcinoma to nearest circumferential margin ____mm
Proximal margin:	Normal                  Barrett's                  Dysplasia                  Carcinoma
Distal margin:	Normal                  Dysplasia                  Carcinoma

### Pathology Staging

Complete resection at all margins	Yes	No
pT		
pN		
pM		

Lymph node group	Metastatic nodes	Total nodes
Left cervical para esophageal (101)		
Left supraclavicular (104)		
Right cervical para esophageal Right 101		
Right supraclavicular 104		
Right recurrent (106)		
Right tracheo bronchial (106 Tb)		
Upper paraesophageal (105)		
Pretracheal (106 pre)		
Left recurrent (106)		
Left tracheo bronchial (106 Tb)		
A-P window nodes		
Subcarinal (107)		
Left bronchial (L 109)		
Right bronchial (R 109)		
Middle para esophageal (108)		
Lower para esophageal (110)		
Supra diaphragmatic (111)		
Posterior mediastinal (112)		
Left CO junction (1)		
Right CO junction (2)		
Lesser curve (3)		
Greater curve (4)		
Left gastric (7)		
Hepatic (8)		
Celiac (9)		
Splenic (11)		
Total lymph nodes		