
Suggestions, Opinions & Recommendations for the Diagnosis, Management, Treatment and Surveillance of Esophageal Cancer
LEGAL DISCLAIMER

HeSMO considers adherence to these guidelines to be voluntary. The ultimate determination regarding their application is to be made by the physician in light of each patient’s individual circumstances. In view of the consultory and non-binding nature, these guidelines cannot form the basis for legal action or litigation for compliance or absence of compliance in the clinical practice setting but can only be considered as general guidelines based on best available evidence for assistance in decision-making.

Any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. HESMO makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

In addition, these guidelines describe evaluations and administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that such clinical studies are designed to test innovative management strategies in a disease for which better treatment is sorely needed. However, by reviewing and synthesizing the latest literature, this practice guideline serves to identify questions for further research and the settings in which investigational therapy should be considered.
## Evidence Level and Recommendation Grade

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence from at least one large randomized control trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted RCTs without heterogeneity</td>
</tr>
<tr>
<td>II</td>
<td>Small RCTs or large RCTs with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity</td>
</tr>
<tr>
<td>III</td>
<td>Prospective cohort studies</td>
</tr>
<tr>
<td>IV</td>
<td>Retrospective cohort studies or case-control studies</td>
</tr>
<tr>
<td>V</td>
<td>Studies without control group, case reports, experts opinions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Strong evidence for efficacy with a substantial clinical benefit, strongly recommended</td>
</tr>
<tr>
<td>B</td>
<td>Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended</td>
</tr>
<tr>
<td>C</td>
<td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,..) optional</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence against efficacy or for adverse outcome, generally not recommended</td>
</tr>
<tr>
<td>E</td>
<td>Strong evidence against efficacy or for adverse outcome, never recommended</td>
</tr>
</tbody>
</table>
Table of Contents

LEGAL DISCLAIMER ........................................................................................................ 2

1. GENERAL CONSIDERATIONS .................................................................................. 6
   1.1 EPIDEMIOLOGY ..................................................................................................... 6
      1.1.1 Molecular Basis .............................................................................................. 6
      1.1.2 Genetics ......................................................................................................... 7
      1.1.3 Prognostic Factors ......................................................................................... 7
      1.1.4 Predictive Factors ......................................................................................... 8

2. DIAGNOSIS, ALARMING SYMPTOMS AND SIGNS ............................................... 9
   2.1 PRESENTATION ..................................................................................................... 9
   2.2 DIAGNOSIS ........................................................................................................... 9
      2.2.1 Endoscopic Ultrasound ............................................................................... 10
   2.3 PRINCIPLES OF ENDOSCOPIC STAGING AND THERAPY ..................................... 11

3. IMAGING, STAGING, HISTOPATHOLOGY ............................................................. 12
   3.1 CROSS SECTIONAL IMAGING MODALITIES ......................................................... 12
   3.2 POST-TREATMENT SURVEILLANCE ................................................................... 14
   3.3 HISTOPATHOLOGICAL FEATURES ...................................................................... 15

4. POTENTIALLY RESECTABLE CARCINOMA (T1-T4A, N0-N3, M0) ...................... 18
   4.1 THE ROLE OF RADIOTHERAPY WITH/WITHOUT CHEMOTHERAPY ..................... 18
      4.1.1 Neoadjuvant Radiotherapy/Chemoradiotherapy ......................................... 19
      4.1.2 Definitive Chemoradiotherapy .................................................................... 20
   4.2 NEOADJUVANT CHEMOTHERAPY ....................................................................... 21

5. LOCALIZED CARCINOMA: SURGICAL TREATMENT (T1-2, N0, M0) .............. 24
   5.1 SQUAMOUS CELL CARCINOMA (SCC) ............................................................. 24
   5.2 ADENOCARCINOMA ............................................................................................ 25

6. ADJUVANT TREATMENT ......................................................................................... 27
   6.1 POSTOPERATIVE RADIOTHERAPY/CHEMORADIOTHERAPY ................................. 27
      6.2.1 Squamous Cell Carcinoma (SCC) .................................................................... 27
      6.2.2 Adenocarcinoma ......................................................................................... 28

7. LOCALLY ADVANCED DISEASE (T3-4 N0-3 M0) ........................................... 28
   7.1 DEFINITIVE CHEMORADIOTHERAPY .................................................................. 29
   7.2 SURGICAL INTERVENTION .................................................................................. 33

8. TREATMENT OF METASTATIC DISEASE .......................................................... 35
   8.1 IMAGE STAGING AND RESTAGING ................................................................. 35
   8.2 PALLIATIVE CHEMOTHERAPY FOR METASTATIC DISEASE ............................... 37
   8.3 TARGETED AGENTS ........................................................................................... 41

Final document Page 4
8.3.1 Epidermal Growth Factor Receptor ............................................................ 41
8.3.2 Anti-HER-2 Therapies ................................................................................ 43
8.3.3 Vascular Endothelial Growth Factor (VEGF) .............................................. 45
8.4 Palliative Care ................................................................................................. 47

9 REFERENCES ....................................................................................................... 50
1. GENERAL CONSIDERATIONS

1.1 Epidemiology

Esophageal cancer is a predominantly male condition with a male/female incidence of 3.6:1, whilst it primarily affects older patients, with the peak incidence in those 65–74 years old. The incidence of esophageal cancer is trending upward in white men with a 0.4% annual percentage increase from 1992 to 2000. The 5-year survival rate is estimated to be at 15.4%, which is the fifth lowest among all cancers [Wang et al., 2005].

There are two major types of esophageal cancer: adenocarcinoma and squamous cell cancer. The primary known risk factors for esophageal adenocarcinoma are smoking, chronic gastroesophageal reflux disease, Barrett’s esophagus and obesity [Engel et al., 2003; Hvid-Jensen et al., 2011]. Known risk factors for squamous cell cancer of the esophagus include smoking, alcohol use, exposure to nitrosamines, ingestion of lye, Fanconi’s anemia, Plummer–Vinson webs, and tylosis [Engel et al., 2003].

Recommendations

➔ There is a gradual increase of annual incidence of esophageal adenocarcinoma among the white males. Prognosis of the disease is poor (LOE III; SOR A).

➔ Smoking and alcohol abuse are the main risk factors of squamous cell carcinoma, and smoking and chronic gastro-esophageal reflux with Barrett’s esophagus of adenocarcinoma of the esophagus (LOE III; SOR A). Chronic gastro-esophageal reflux disease may be incriminated even in the absence of Barrett’s esophagus (LOE IV; SOR C).

1.1.1 Molecular Basis

The above previously mentioned risk factors and possibly many others unknown so far factors are involved in the pathogenesis of esophageal and esophagogastric junction tumors by altering the function of certain oncogenes and tumor suppressor genes. Many studies have been done so far regarding the molecular basis of the development of esophageal and esophagogastric junction cancers. Data are
emerging regarding the significance of certain genes. One of these genes is Epidermal Growth Factor Receptor (EGFR) which is commonly overexpressed in early stage esophageal cancer. Another gene is the oncogene Cyclin D1, which is found to be over-expressed in squamous dysplasia and Barrett’s esophagus as well as in early esophageal cancer. Also the tumor suppressor gene p16INK4a seems to be related with Barrett’s esophagus and adenocarcinoma but not with squamous cell carcinoma. Finally other studies have shown that mutations in the tumor suppression gene p53 are expressed in 90% of esophageal adenocarcinoma and in 40 to 75% of esophageal squamous cell carcinoma [Posner et al., 2008].

1.1.2 Genetics

The vast majority of esophageal adenocarcinoma cases are sporadic. But studies have shown that approximately 7% of patients with Barrett’s esophagus or adenocarcinoma have at least one affected blood relative. In some of these cases it appears that the incidence of affected cases in the families follows a pattern of autosomal dominant mode of inheritance with incomplete penetrance or a pattern of autosomal recessive inheritance. It has been shown that germline mutations in MSR1, ASCC1 and CTHRC1 genes might be related to the inherited cases of esophageal adenocarcinoma [Orloff et al., 2011].

1.1.3 Prognostic Factors

The stage of the disease by TNM staging system in patients with esophageal cancer is an important prognostic factor as patients with higher stage of disease have worse outcome compared to patients with lower stage. The surgical staging is more accurate than clinical staging.

Another prognostic factor under consideration is the percentage of viable cancer cells in tumor specimen resected after neoadjuvant treatment. Patients with less than 50% of residual viable cells in the histology specimen have better survival compared with patients with more than 50% [Chirieac et al., 2005]
Concerning molecular markers as prognostic factors in esophageal cancer there have been many studies in the literature dealing with the specific topic. There are studies
which show that many genes and their products seem to have a prognostic role in esophageal cancer. Some of these genes or their products are HER-2, EGFR, cyclin D1, the tumor-suppressor genes p16 and p53, the family of Bcl-2, the matrix metalloproteinases, VEGF, Cox-2 and b-FGF. Probably the most important data have to do with HER-2 as treatment targeting this receptor exists. Regarding the prognostic value of the remaining genes, confirmatory studies are needed.

Another prognostic factor in esophageal cancer in patients with esophageal cancer is the level of SUV in PET-CT scan. In patients with localized disease, higher levels of SUV prior to any treatment [Sepesi et al., 2009] or after chemoradiotherapy [Sharma et al., 2011] seem to be related to worse prognosis although confirmatory studies are needed.

1.1.4 Predictive Factors

HER-2 overexpression in patients with esophagogastric junction adenocarcinoma is a predictive factor for response to the targeted agent Trastuzumab which targets the HER-2 receptor. Also the tumor suppressor genes p21 and p53 have been correlated with response to preoperative chemotherapy or chemoradiotherapy. However the few studies dealing with this topic revealed conflicting results [Vallböhmer et al., 2010].

Finally the inhibitor of apoptosis, survivin, has been shown in two studies to be related with response to preoperative treatment. High levels of survivin are related to worse outcome to neoadjuvant treatment [Vallböhmer et al., 2010]. The amount of the decrease in the FDG uptake seems to be related to pathologic complete response. However more prospective studies are needed prior reaching definitive conclusions.

Recommendations

→ HER-2 overexpression should be tested in all patients with locally advanced or metastatic adenocarcinoma of the GEJ (LOE I; SOR A) and possibly of esophagus (LOE V; SOR C) as it is a predictive factor for response to chemotherapy combined with trastuzumab.
2. DIAGNOSIS, ALARMING SYMPTOMS AND SIGNS

2.1 Presentation

Most patients with esophageal cancer present at a late stage with dysphagia as the predominant symptom [Esfandyari et al., 2002]. In particular, dysphagia that progresses rapidly within few months should heighten suspicion for esophageal cancer and prompt an endoscopic evaluation. Up to 75% of patients experience also anorexia and weight loss when seeking medical attention. Other symptoms are odynophagia, chest pain, or gastrointestinal bleeding. Cough aggravated by swallowing raises the possibility of an esophago-pulmonary fistula, a devastating complication associated with a high 30-day mortality rate [Burt, 1996].

The diagnosis of esophageal cancer is established by flexible endoscopy with biopsy. The diagnostic yield of endoscopic biopsy reaches 100% when 6 or more samples are obtained using standard forceps [Lal et al., 1992]. In patients with advanced cancers, ultrathin endoscopes (max diameter 6mm) or esophageal dilatation may be required to complete the examination and take biopsies [Mulcahy et al., 1998] but the adequacy of biopsy specimens obtained has not been formally assessed. Brush cytology could be an alternative in sampling tight malignant strictures, not easily accessed by conventional biopsy techniques [Jacobson et al., 2003; Zargar et al., 1991]. Endoscopic ultrasonography (EUS) with Fine Needle Aspiration (FNA) and/or Tru-Cut Needle Biopsy (TNB) should be considered when submucosal tumors are suspected or standard biopsies fail to confirm the diagnosis [Wittmann et al., 2006]. Oral contrast X-ray examination as an initial diagnostic test is of limited value [Esfandyari et al., 2002], however, it may be useful to confirm the presence of fistulas when clinically suspected.

2.2 Diagnosis

During an endoscopic exam, the location of the tumor relative to the teeth and the esophago-gastric junction, the length of the tumor, the extent of circumferential involvement, and degree of obstruction should be carefully recorded to assist with
treatment planning. If present, the length and circumferential extent of Barrett's esophagus should be documented in accordance with the Prague criteria (M=maximum extent of suspected columnar metaplasia, C=the most proximal extent of circumferential extent of suspected columnar metaplasia) [Sharma et al., 2006] and mucosal nodules should be carefully examined.

High-resolution endoscopic imaging and narrow-band imaging may enhance visualization during endoscopy, with improved detection of dysplastic or suspicious lesions in both Barrett's and non-Barrett's esophagus [Mannath et al., 2010]. Multiple biopsies, six to eight, using standard size endoscopy forceps should be performed to provide sufficient material for histologic interpretation. Larger forceps are recommended during surveillance endoscopy of Barrett's esophagus for the detection of dysplasia [Komanduri et al., 2009].

Endoscopic mucosal resection (EMR) of focal nodules can be performed in the setting of early stage disease (non-obstructing tumors <2cm) to provide accurate T-staging including degree of differentiation and vascular and or lymphatic invasion, with the potential of being therapeutic [Thomas et al., 2009].

2.2.1 Endoscopic Ultrasound

The staging of esophageal cancer is critical to guide further therapy. Patients with cancer confined to the mucosa or superficial submucosa can be treated using surgical resection or potentially endoscopic therapy [May et al., 2002; May et al., 2002 (a)] whilst patients who have more advanced disease will require surgical resection or chemoradiation [Stein et al., 2001; Rice et al., 2001]. Endoscopic ultrasound (EUS) performed prior to any treatment is important in the initial staging of neoplastic disease, since it provides evidence of tumor invasion (T-stage), presence of abnormal or enlarged lymph nodes likely to harbor cancer (N-stage), and occasionally signs of locally spread disease (M-stage) [Barbour et al., 2007]. Gradual loss of the layered pattern of the normal esophageal wall and hypoechoic expansion of the tumor corresponds with greater depths of tumor penetration and higher T-stages. Involvement of layers 1-3 corresponds with infiltration of the superficial and deep mucosa plus the submucosal, T1 disease. Involvement of layers 1-4 correlates
with penetration into the muscularis propria, T2 disease, and expansion beyond the smooth outer border of the muscularis propria correlates with invasion of the adventitia, T3 disease. Loss of a bright tissue plane between the area of tumor and surrounding structures such as pericardium, pleura and diaphragm (T4a), or the trachea, aorta and heart (T4b) correlates with infiltration of tumor into surrounding organs. Obstructing tumors may not allow EUS staging. Dilating the malignant stricture may be helpful but there is an increased risk of perforation. The use of wire guided EUS probes or miniprobes may permit EUS staging with a lower risk.

Mediastinal and perigastric lymph nodes are readily seen by EUS. Classically, size (short axis diameter >10mm), shape (round), echogenicity (homogeneous, echo-poor pattern) and border (well circumscribed) have been proposed to be suggestive of malignancy. The accuracy of this diagnosis is significantly increased with the combination of all features, but other data suggest that in some cases fine needle aspiration cytology is necessary to confirm malignancy [Keswani et al., 2009]. FNA of suspicious lymph nodes should be performed, without traversing an area of primary tumor, only if it will impact on treatment decisions.

2.3 Principles of Endoscopic Staging and Therapy

The goal of EMR and/or ablation is the removal of early malignancy in addition to complete eradication of all Barrett’s metaplasia. Early stage disease, Tis, also known as high grade dysplasia, needs to be evaluated for the presence of nodularity, lateral spread and multifocal disease. This is important to permit decisions on endoscopic treatment with ablative methods such as radiofrequency ablation (RFA), cryoablation, photodynamic therapy (PDT) or EMR [Shaheen et al., 2009; Shaheen et al., 2010; Overholt et al., 2007; Pech et al., 2008]. All focal nodules should be resected rather than ablated.

T1a disease, carcinoma limited to the lamina propria or muscularis mucosae, in the absence of evidence of lymph node metastases, lymphovascular invasion or poor differentiation grade can be treated with full EMR. EUS staging prior to proceeding with mucosal resection in the setting of carcinoma is recommended. Ablative therapy
of residual flat Barrett's esophagus associated with Tis or T1a disease should be performed following mucosal resection.

**Recommendations**

- **Progressive dysphagia of recent onset should prompt endoscopic investigation (LOE III; SOR A).**
- **Diagnosis of esophageal cancer is established by flexible endoscopy with biopsy. In case of large tumors, esophageal dilatation may be necessary prior to endoscopy. Presence of Barrett’s esophagus should be mentioned at the endoscopy report (LOE III; SOR A).**
- **Atypia in Barrett’s esophagus should be assessed after treatment of reflux esophagitis (LOE III; SOR A).**
- **Early Tis disease as staged by EUS is therapeutically amenable to radiofrequency ablation if lesion is not visible (LOE II; SOR A), or endoscopic mucosal resection in confined lesions (LOE II; SOR A).**
- **T1a disease as staged by EUS is therapeutically amenable to endoscopic mucosal resection (LOE II; SOR A).**

### 3. IMAGING, STAGING, HISTOPATHOLOGY

#### 3.1 Cross Sectional Imaging Modalities

Precise and optimal pretreatment staging of esophageal cancer is crucial for the initial evaluation and assessment of affected patients. The many available imaging modalities have different strengths and weaknesses with respect to each of the staging criteria.

In tumors smaller than 0.5cm, high-frequency transducers by EUS can obtain information that is not available even with highly sophisticated Computed Tomography (CT), magnetic resonance imaging (MRI), transabdominal ultrasound or positron emission tomography (PET) [Ponsaing et al., 2007].
Asymmetric thickening of the esophageal wall is a primary but nonspecific CT finding of esophageal cancer. The accuracy of CT for the assessment of T stage is lower than that of EUS [Wallace et al., 2002]. CT is unable to adequately help differentiate between T1, T2, and T3 disease. Exclusion of T4 disease, as indicated by the preservation of fat planes between the esophageal lesion and adjacent structures, is the most important role of CT in the determination of T status [Rice, 2000]. Although PET has been shown to have a higher sensitivity than CT in the detection of primary esophageal cancer, it is of limited value in assessing T stage, as it provides little information on the depth of tumor invasion [Block et al., 1997]. There are conflicting findings in the literature regarding the relationship between FDG uptake in the primary tumor and depth of tumor invasion.

Some studies have shown that surface-coil MRI of the esophagus is feasible and, when using a T2-weighted sequence, the esophageal wall layers are accurately depicted and the tumor can be identified separately from surrounding tissue. MRI has also been proven is some studies to be better than CT in the evaluation of pericardial infiltration and bone involvement by local tumor invasion [Riddell et al., 2006]. Concerning N staging, CT lacks sensitivity since even a normal-sized lymph node might contain microscopic metastatic foci that are beyond the level of detection offered by CT. In addition, the presence of benign enlarged and inflammatory lymph nodes in esophageal cancer reduces the specificity of CT for the detection of lymph node metastases.

The main drawback of PET is that intense uptake of FDG by the primary tumor commonly complicates interpretation by obscuring the adjacent regional lymph node [van Westreenen et al., 2004]. The pooled sensitivity and specificity of FDG PET for the detection of locoregional metastases are low (51% and 84%, respectively). False-positive findings due to chronic inflammation are another limitation hampering the specificity of FDG PET.

**Recommendations**

→ EUS should be used for the initial evaluation of local staging in oesophageal cancer (LOE I; SOR A).
→ **Combined use of FNA and EUS can improve the assessment of lymph node involvement and may be performed in equivocal cases (LOE II; SOR B).**

→ **CT is a good initial screening modality for determining whether the patient may undergo resection or has distant metastases (LOE II; SOR B).**

→ **MRI could be used alternatively in cases of obstructing tumors when EUS cannot be performed and CT is contraindicated (LOE III; SOR C).**

→ **PET-CT may be used whenever CT gives equivocal results for metastatic disease but is not appropriate for detecting and staging primary tumors (LOE IV; SOR C).**

### 3.2 Post-Treatment Surveillance

Assessment with endoscopy with biopsy and endoscopic ultrasound should be done 5-6 weeks after completion of preoperative therapy. Endoscopic surveillance following definitive treatment of esophageal cancer requires careful attention to detail for mucosal surface changes, and multiple biopsies of any visualized abnormalities. Although submucosal thickening at the anastomosis may be misinterpreted as a local recurrence, strictures should be biopsied to rule-out neoplastic cause. EUS performed after chemotherapy or radiation has reduced ability to accurately determine the present stage of disease [Ribeiro et al., 2006] and similarly, biopsies performed may not accurately detect the presence of residual disease [Sarkaria et al., 2009]. EUS performed in conjunction with endoscopy exams have a high sensitivity for recurrent disease [Lightdale et al., 1989]. EUS guided FNA should be performed if suspicious lymph nodes or areas of wall thickening are seen, especially when local recurrence cannot be proven by conventional endoscopy or imaging techniques.

Endoscopic surveillance after ablative therapy or EMR of early esophageal malignancy should continue after completion of treatment. Patients with Tis or T1a who undergo EMR should have endoscopic surveillance every 3 months for one year, then annually. Endoscopic surveillance should also include a search for the presence of Barrett's esophagus, and four-quadrant biopsies should be taken to detect residual or recurrent dysplasia. Biopsies of the neo-squamous mucosa should be taken even
in the absence of mucosal abnormalities as dysplasia may occasionally be present beneath the squamous mucosa. The ablation of residual or recurrent high-grade and low-grade dysplasia should be considered. Ablation of non-dysplastic Barrett's esophagus is not recommended.

**Recommendations**

- **Endoscopic surveillance with biopsies is recommended after ablative treatment of Barrett's esophagus or EMR of Tis lesions, on regular 3-month intervals (LOE III; SOR B).**
- **Endoscopy with biopsy is recommended for local assessment after neoadjuvant treatment (LOE III; SOR B).**
- **Endoscopy combined with EUS could accurately detect local post-operative recurrence. FNA should be performed especially if local recurrence cannot be proven by other means of investigation (LOE IV; SOR B).**

### 3.3. Histopathological Features

A histopathological examination should offer information concerning the optimum therapeutic regime and the prognosis. The pathology report should include the following data:

**Specimen Preparation**

The surgical specimen is preferably to be sent to the pathology department immediately after removal from the patient. Length of the esophagus shortens after removal by at least a quarter. Also, esophagectomy specimen loses again a small part of the original length if fixed without pinning. Outer surface of the esophagus should be painted before opening.

**Gross Description**: a) length of surgical specimen (length of esophagus and length of stomach), b) site of tumor, c) distance of tumor from proximal and distal resection margins, d) depth of invasion, e) other lesions no related to the tumor and f) number of lymph nodes [Burroughs et al., 1999; Mapstone et al., 2007].
In addition, gross description should include status of the periesophageal tissue and macroscopic appearance of the tumor (ulcerated, plaque-like, polypoid, flat), although the macroscopic appearance of the tumor per se has little contribution to the prognosis, with the exception of a polypoid tumor [Mapstone et al., 2007; Stanley et al., 2000].

Depending on its location, esophageal tumors are classified in three types: type 1 those arising 1-5cm above the gastro-esophageal junction, type 2 those arising at the gastro-esophageal junction and type 3 those arising 2-5 cm below the gastro-esophageal junction. Type 1 is considered as esophageal carcinoma and type 2 and type 3 are considered as gastric carcinomas. There is some argument on whether adenocarcinomas arising at the gastroesophageal junction must be considered as esophageal or gastric carcinoma. The recent International Union Against Cancer (UICC) guidance on the issue contradictory. At a certain point of this publication, it is stated that adenocarcinomas of the gastro-esophageal junction (GOJ) should be classified according to the gastric TNM system. At other point in the same text, tumors of the gastro-esophageal junction should be considered as esophageal if more than 50% of the tumor involves the esophagus and as gastric if less than 50% of the tumor mass involves the esophagus. More confusingly, it is proposed that tumors of the junction should be classified according to their histological type: squamous cell carcinomas, small cell carcinomas and undifferentiated carcinomas should be considered as oesophageal carcinomas and adenocarcinomas as gastric carcinomas [Mapstone et al., 2007; Siewert et al., 1998; Wittekind et al., 2003].

**Microscopic Description:** a) histological type, b) histological grade, c) depth of invasion, d) status of serosa, e) status of distal and proximal resection margins, f) status of circumferential resection margin, g) presence of vascular and perineural invasion, h) number of involved lymph nodes, and i) presence of Barrett metaplasia and/or dysplasia.

**Histological Classification**

The majority of esophageal tumors are squamous carcinomas and adenocarcinomas. The WHO _histological classification_ is the most widely in use, and classifies esophageal tumors as squamous cell carcinoma, verrucous carcinoma, basaloid...
squamous cell carcinoma, adenocarcinomas, adenoid cystic carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, undifferentiated carcinoma, small cell carcinoma and other [Burroughs et al., 1999; Mapstone et al., 2007; Stanley et al., 2000].

*Differentiation* of the tumor is classified as well, moderate and poorly differentiated carcinomas. The prognostic significance of the differentiation is contradictory [Mapstone et al., 2007; Lieberman et al., 1995].

According to TNM system, *depth of invasion* (T stage) is classified as:

- Tis: although Tis is used for in situ carcinoma, most authors propose the term high grade dysplasia
- T1a: limited to lamina propria (intamucosal carcinoma)
- T1b: tumor invading submucosa
- T2: tumor invading muscularis propria
- T3: tumor invading adventitia
- T4: tumor invading adjacent structures [Fujita et al., 2011; Mapstone et al., 2007; Stanley et al., 2000]

Following neoadjuvant *treatment tumor regression grading* is recommended [Chang et al., 2008; Mapstone et al., 2007].

Status of *circumferential resection margin* (CRM) represents a possible prognostic factor, according to some authors. Involvement of CRM is a poor prognostic factor [Mapstone et al., 2007].

*Lymphatic invasion* and *intra-extramural vascular invasion* are additional tumor characteristics that should be recorded, as are status *distal and proximal margins* (with or without neoplastic invasion) [Mapstone et al., 2007; Stanley et al., 2000; Haggitt et al., 2000; Allum et al., 2002].

In case of *Barrett’s esophagus*, proximal margin at squamous-Barrett mucosa junction and presence or not of dysplasia should be reported. If the proximal margin demonstrated presence of gastric mucosa, any helicobacter-associated gastritis or atrophy should be mentioned [Burroughs et al., 1999; Haggitt et al., 2000; Mapstone et al., 2007].
Finally, all lymph nodes excised should be thoroughly examined, and the number of the involved over the total number of lymph nodes is reported [Allum et al., 2002; Burroughs et al., 1999; Chang et al., 2008; Mapstone et al., 2007; Stanley et al., 2000].

**Recommendations**

Necessary elements of a histological report on esophageal cancer specimens are (LOE III; SOR A):

- **Maximum tumor diameter**
- **Site of tumor**
- **Macroscopic appearance of the tumor**
- **Maximum depth of invasion (anatomical layer)**
- **Histological type**
- **Histological grade**
- **Serosal involvement (gastric, pleural or pericardial)**
- **Resection margins (proximal, distal and circumferential)**
- **Vascular, perineural invasion**
- **Lymph node status**

4. POTENTIALLY RESECTABLE CARCINOMA (T1-T4a, N0-N3, M0)

4.1 The Role of Radiotherapy With/Without Chemotherapy

The management of local-regional esophageal and gastroesophageal junction (GEJ) cancer has undergone a major evolution over the past 15 years. The majority of patients now undergo some form of combined modality therapy rather than local therapy alone which is associated with poor oncological outcomes. However, the optimal management of these patients remains controversial. The main factors for
selecting primary treatment are tumor stage and location, histological type and the medical condition as well as the requests of the patients.

4.1.1 Neoadjuvant Radiotherapy/Chemoradiotherapy

Neoadjuvant radiotherapy alone has little to offer either in local control of the disease or overall survival as shown by five CRTs and a meta-analysis using individual patients data [Arnott et al., 1998]. A preliminary report of at least one randomized trial comparing preoperative chemotherapy to preoperative chemoradiotherapy in patients with gastroesophageal junction (GEJ) adenocarcinoma suggests that the likelihood of a complete pathologic response (pCR) is higher (2% versus 15.6%) with chemoradiotherapy and that survival might also be superior (27% versus 47%) [Stahl et al., 2009] although surgery did not involve complete lymph node dissection in either arm. Whether these results can be extrapolated to the setting of distal esophageal adenocarcinomas or SCCs is uncertain. Furthermore, local failure rates may be lower in patients treated with chemoradiotherapy followed by surgery compared to those receiving either chemotherapy followed by surgery or surgery alone. Most of the contemporary series suggest that a concurrent trimodality approach, concomitant chemoradiotherapy (using mainly cisplatin/5-FU or capecitabine or carboplatin/paclitaxel or oxaliplatin/irinotecan) followed by surgery provides a survival benefit compared to surgery alone. This conclusion is supported by several randomized studies [Urba et al., 2001; Tepper et al., 2008; Gaast et al., 2010] and at least three meta-analyses [Urschel and Vasan, 2003; Gebski et al., 2007; Sjoquist et al., 2011]. The meta-analysis by Gebski et al. of 10 CRTs involving 1209 patients showed a significant survival benefit (13% absolute benefit in 2-year survival) for preoperative chemoradiotherapy for both SCC and adenocarcinoma [Gebski et al., 2007]. The recently published update of this meta-analysis including 12 RCTs and 1854 patients also provided strong evidence for a survival benefit of neoadjuvant chemoradiotherapy over surgery alone. The HR for all-cause mortality was 0.78 (95% CI 0.70-0.88, P<0.0001); the HR for SCC was 0.80 (0.68-0.93, p=0.004) and for adenocarcinoma was 0.75 (0.59-0.95, p=0.02) [Sjoquist et al., 2011].
4.1.2 Definitive Chemoradiotherapy

Definitive chemoradiotherapy has been mainly studied in patients unable or unwilling to undergo surgery and also in those with cancer in the cervical esophagus. The RTOG 85-01 trial, which randomized medically unfit patients with T1-3N0-1M0 either adenocarcinoma or SCC to radiotherapy alone or chemoradiotherapy, showed a significantly lower incidence of local failure and also improved median and overall survival with combined modality treatment [Cooper et al., 1999]. The INT 0123 trial was the follow-up trial to the RTOG 85-01, comparing two different RT doses used with the same chemotherapy regimen [Minsky et al., 2002]. No significant difference was seen in median survival, 2-year survival and loco-regional failure between the high-dose and the standard-dose regimens. Based on these studies, definitive chemoradiotherapy with cisplatin and 5-fluorouracil and radiotherapy 50.4Gy in 1.8Gy per fraction was established as the standard regimen. It should be mentioned that definitive chemoradiation is the standard treatment of the upper esophageal SCC. Recent studies report on the efficacy of definitive chemoradiation with newer agents such as cisplatin / docetaxel, carboplatin / docetaxel and FOLFOX. Although response rates and survival figures appear significantly higher compared to cisplatin/5-FU, so far no randomized studies have been performed.

While definitive chemoradiotherapy is a potentially curative option for SCC, there remains a high rate of locally persistent/recurrent disease after chemoradiotherapy alone and a lack of data for nonsurgical management of patients with adenocarcinoma. Thus, inclusion of surgery is preferred for clinically resectable esophageal cancer. The effect of adding surgery to chemoradiation has been evaluated in two randomized trials. Both trials suffer from suboptimal design and low numbers of patients. The first one showed better 2-year progression-free survival in the surgery group but no difference in overall survival, while the second one showed no difference either in median or in overall survival. In both studies treatment-related mortality and quality of life were worse in the surgery arm [Stahl et al., 2005; Bedenne et al., 2007]. Both trials showed that tumor response to induction chemoradiation was the most important prognostic factor with responders having similar outcome regardless of surgery. It appears therefore, that induction chemoradiotherapy might
allow for selecting patients who will not have a survival benefit from additional surgery. In a very recently published meta-analysis of 6 RCT comparing definitive chemoradiation with either surgery alone or induction chemoradiation followed by surgery in potentially resectable mainly SCCs, there was a higher risk of locoregional progression (HR 1.54) but a similar survival (HR 0.98) between definitive chemoradiation and surgery [Pottgen and Stusche 2011]. Definitive chemoradiotherapy is indicated in cervical esophageal SCC, and unfit and unwilling patients. For the rest of the indications a multidisciplinary tumor border should decide.

In the recent trials, radiotherapy was delivered with the 3D conformal technique following appropriate patient immobilization and CT simulation. In an attempt to improve tumor coverage and limit normal tissue toxicities, IMRT has been evaluated for treatment of esophageal carcinoma; however, most data has been limited to dosimetric analyses. Retrospective planning studies comparing 3D conformal versus IMRT treatment plans have generally shown superior dose conformity and homogeneity within the target volume and reduction of radiation dose to the lungs and heart [Chandra et al., 2005]. However, there have been no randomized studies so far comparing 3D conformal and IMRT techniques with regards to response rates and local control.

The use of brachytherapy as a single modality is palliative, however, the rationale for the addition of HDR brachytherapy to external beam radiotherapy is the increase in total dose delivered aiming to improve local control. The RTOG 9907 study investigated the role of intraluminal brachytherapy after concurrent chemoradiotherapy to 50Gy and showed a local failure rate of 27% but significantly increased acute and late grade 3, 04 and 5 toxicity [Gaspar et al., 2000]. Therefore brachytherapy is not routinely recommended due to high toxicity.

### 4.2 Neoadjuvant Chemotherapy

Neoadjuvant or preoperative chemotherapy alone has been employed in patients with potentially resectable disease in order to increase the rate of R0 resections and improve local control. Long term results of the RTOG 8911 trial which randomized patients with potentially resectable squamous and adenocarcinoma to either
preoperative chemotherapy (cisplatin plus 5-fluorouracil) or surgery alone showed that the rate of R0 resection was 63% with preoperative chemotherapy compared to 59% with surgery alone (Kelsen et al., 2007). Although the rate of R1 resection was decreased (4% compared with 15% in the surgery only group), no improvement was seen in overall survival between the two groups.

The Medical Research Council trial (MRC OEO2) randomized 802 patients with potentially resectable esophageal cancer to 2 cycles of preoperative continuous infusion 5-fluorouracil and cisplatin followed by surgery, or surgery alone. At a short median follow-up time of 2 years, the group treated with preoperative chemotherapy had a 3.5 month survival time advantage (16.8 vs 13.3 months). Long term follow-up confirmed a modest but enduring survival benefit from neoadjuvant chemotherapy with 5 year survival of 23% compared to 17% with surgery. Results were consistent in patients with adenocarcinoma and SCC (Allum et al., 2009).

The British Medical Research Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial for (Cunningham et al., 2006) evaluated the effect of perioperative ECF chemotherapy (epirubicin, cisplatin and 5-fluorouracil) regimen given before and after surgery in resectable gastroesophageal adenocarcinoma. Most (74%) patients had stomach cancer, whereas a small group of patients had adenocarcinoma of the lower esophagus (14%) and EGJ (11%). The perioperative chemotherapy group had a greater proportion of pathologic T1 and T2 tumors (51.7%) than the surgery group (36.8%). Five-year survival rates were 36% among those who received perioperative chemotherapy and 23% in the surgery group.

The recently published up-dated meta-analysis (Sjoquist et al., 2011) of ten studies (2062 patients) provided evidence for a survival benefit of neoadjuvant platinum-based chemotherapy over surgery alone. The pooled HR was 0.87 (0.79–0.96; p=0.005) corresponding to an absolute survival benefit of 5.1% at 2 years. In subgroup analysis, this benefit was statistical significant in patients with adenocarcinoma histology (HR of 0.83 (0.71–0.95; p=0.01).

**Recommendations**
Combined modality therapy using preoperative chemoradiotherapy followed by surgery rather than either surgery alone or definitive radiotherapy is recommended for patients with stages IB, IIA, IIB, and III esophageal SCC (excluding cervical lesions) or adenocarcinoma of the esophagus (LOE II; SOR B).

Induction chemoradiotherapy instead of chemotherapy alone followed by surgery are also recommended in the same groups (LOE II; SOR B).

Definitive chemoradiotherapy is a reasonable approach for patients who are not surgical candidates (LOE I; SOR B).

The benefit of preoperative chemoradiotherapy for patients with T1N0 esophageal or GEJ adenocarcinoma or SCC is less clear and therefore surgery alone is recommended in these patients (LOE I; SOR B).

Definitive chemoradiotherapy is a reasonable approach for the same subset of patients who are not surgical candidates.

Although the optimal type, dose, combination, and schedule of drugs are not clear, multi-agent chemotherapy rather than single agent cisplatin is recommended. The concurrent treatment involves two courses of cisplatin and 5-FU plus radiation therapy (50 Gy). An alternative option is the low-dose weekly carboplatin plus paclitaxel regimen (LOE II; SOR C).

The optimal dose-fractionation RT schedule for concurrent chemoradiotherapy regimens remains to be determined. However, CT simulation and 3-D conformal techniques should be used for modern treatment planning with efforts to minimize toxicities to adjacent vital organs. A standard dose of radiation for patients treated with concurrent 5-FU and cisplatin is 50.4 Gy in 1.8-2.0 Gy per fraction (LOE I; SOR A).

IMRT may be appropriate for selected patients (LOE V; SOR C).

The additional benefit of adding intraluminal brachytherapy to external beam radiotherapy or combined modality treatment, although reasonable, remains unclear. (LOE II; SOR D).

Management of carcinoma arising in the cervical esophagus is more closely related to SCC of the head and neck than for malignancies involving the
more distal esophagus. Definitive chemoradiation is the standard treatment (LOE IV; SOR B).

- Perioperative chemotherapy with cisplatin and 5-FU should be considered standard in locally advanced adenocarcinomas (LOE Ia; SOR A).
- Preoperative chemoradiation is preferred over preoperative chemotherapy for selected patients with adenocarcinoma of the distal esophagus or EGJ (LOE I; SOR B).

5. LOCALIZED CARCINOMA: SURGICAL TREATMENT (T1-2, N0, M0)

5.1 Squamous Cell Carcinoma (SCC)

In 65% of the cases, squamous cell carcinoma (SCC) develops at the region above the tracheal bifurcation and therefore it is in extremely close contact with the tracheal bronchial tree [Siewert et al., 2006]. For this reason a R0 resection of the tumor via surgery alone, may be difficult in most of the cases. In addition, it is known that early SCC has a higher prevalence of associated lymphatic vessel invasion, specifically in tumors invading the submucosa as compared to adenocarcinoma (36% vs 20%). Mucosa invading SCC shows a rate of lymph node involvement of 10% [Stein et al., 2005]. In carefully selected patients, where tumor invasion does not outreach the mucosa layers, the application of endoscopic mucosal resection (EMR) or ablation, depending on available expertise, could be a definitive treatment of choice with long-term disease free intervals [Fujita et al., 2001; Soetikno et al., 2005; Conio et al., 2005; Ell et al., 2000]. Esophagectomy for Tis or T1a tumors, via transhiatal approach, should be reserved for unsuccessful EMR.

High frequency of distant lymph nodes metastases (>40% not in anatomic proximity to the primary tumor) [Stein et al., 2005] makes the use of preoperative chemoradiation an integral part of the treatment algorithm, particularly in cases where the submucosa is involved [Iyer et al., 2004; Urschel et al., 2003; Fiorica et al., 2004]. As mentioned above, there is an important role for chemoradiation as the sole
treatment in patients unfit or unwilling for surgery, and also as the definitive treatment in cases with cervical SCC of this stage [Li et al., 2010; Ruppert et al., 2010; Gwynne et al., 2011; Conroy et al., 2010; Meerten et al., 2010].

Intrathoracic SCC cases of stage T1b and higher should be offered a transthoracic esophagectomy with two-field lymph node dissection (abdominal and mediastinal (level of evidence: III, recommendation grade: B) [Stahl et al., 2010]. For Tis lesions, the extent of lymphadenectomy is not defined, but for T1N0M0 tumors at least 12 lymph nodes in SCC and at least 10 in adenocarcinomas should be excised along with specimen [Rizk et al., 2010].

5.2 Adenocarcinoma

Cancer associated with Barrett’s esophagus is nearly always located (94%) below the tracheal bifurcation [Siewert et al., 2006]. Lymph node metastasis (LNM) and operability are the main determinants of the algorithm treatment [Vieth M. et al., 2005]. Superficial cancer lesions (Tis-T1a), less than 15-20mm in diameter are treated with EMR. If histology shows high risk features or submucosal invasion, a more definite treatment is necessary. EMR is associated with higher recurrence rates, if applied to larger lesions and of higher stage (piecemeal resection) [Esaki et al., 2007].

Lesions invading the muscularis mucosae, without evidence of LNM are treated with transhiatal esophagectomy. In these cases EMR/Ablation is not recommended because invasion of muscularis mucosae is associated with LNM in 10% of the cases [Abraham et al., 2007]. For lesions invading the submucosa (T1b-T2N0M0) surgical resection with lymphadenectomy of two fields should be performed [Hulscher et al., 2002] as the risk for LNM is as high as 25 % [Ancona et al., 2008]. In some cases of this stage, it might be difficult to demonstrate submucosal invasion on preoperative staging (EUS). Furthermore, patients with early esophageal adenocarcinoma frequently have multicentric neoplasia within the underlying Barrett mucosa that could be missed without a complete esophagectomy [Stein et al., 2005].

The advantage of radical surgery is removal of potentially involved regional lymph nodes, and is achieved by transthoracic esophagectomy with a two-field
lymphadenectomy. It has been shown that in patients with 1-8 involved lymph nodes, extended two–field lymphadenectomy significantly improves 5-year survival by 45%, over one-field lymphadenectomy [Hulscher et al., 2002]. In high risk patients, transhiatal esophagectomy could be alternatively offered. For pT1N0M0 lesions optimum lymphadenectomy should include at least 10 resected lymph nodes. This figure rises to 15 in cases with pT2N0M0 lesions [Rizk et al., 2010].

**Recommendations**

→ *Tis and T1a esophageal cancers can be treated by EMR in centers of excellence (LOE III; SOR B). Alternatively, esophagectomy without lymph node dissection can be done in centers with low morbidity and mortality (LOE III; SOR B).*

→ *T1b esophageal cancers should be treated with esophagectomy and two-field lymphadenectomy (LOE II; SOR B).*

**TABLE 1. Treatment of Localized Esophageal Cancer According to Histological Type and Stage**

<table>
<thead>
<tr>
<th>Histological Type</th>
<th>Tis – T1a</th>
<th>T1b – T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC</td>
<td>EMR/ablation OR transhiatal esophagectomy</td>
<td>surgery (optional chemoradiation + definitive chemoradiation)</td>
</tr>
<tr>
<td>Adeno:</td>
<td>EMR OR transhiatal esophagectomy</td>
<td>transthoracic esophagectomy + lymphadenectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR transhiatal esophagectomy (multimorbid patients)</td>
</tr>
</tbody>
</table>

[1], [2]
6. ADJUVANT TREATMENT

Postoperative therapy may allow better patient selection based on defined pathological findings. However, due to a generally reduced performance status after esophagectomy, only a minority of eligible patients tolerate an intensive postoperative treatment protocol, which is accompanied by a potentially increased toxicity of the treatment with subsequent poor compliance. Furthermore, adjuvant therapy is often initiated after a long delay due to postoperative complications.

6.1 Postoperative Radiotherapy/Chemoradiotherapy

6.2.1. Squamous Cell Carcinoma (SCC)

The results of two randomized control trials have failed to show any benefit for postoperative adjuvant chemotherapy, although in one study there was a disease-free survival improvement for node-positive patients [Iizuka et al., 1998; Ando et al., 2003]. In two retrospective analyses the addition of postoperative chemoradiation in patients with locoregionally advanced esophageal cancer has been associated with survival benefit, compared to historical outcomes with surgery alone [Bedard et al., 2001; Rice et al., 2003]. A multicenter randomized trial from France showed that the addition of radiotherapy to radical surgery in patients with SCC of the middle and lower third did not confer a survival benefit. However, the rates of locoregional recurrence were lower in patients receiving postoperative radiotherapy versus surgery alone [Teniere, 1991]. The largest randomized trial [Xiao et al., 2003] comparing surgery to surgery plus postoperative radiotherapy in patients with SCC showed decreased locoregional recurrence rates in those with positive nodes or positive resection margins but no survival benefit for the entire group. Subgroup analysis showed significantly improved 5-year overall survival for patients with stage III disease (13% versus 35%). An analysis of the SEER database evaluating the role of adjuvant radiation reported a significant improvement in median, 3 year overall survival and cause specific survival in both SCC and adenocarcinoma stage III patients [Schreiber, 2010].
Recommendations

- For patients with no residual disease (R0 resection) and negative lymph nodes (N0), no further treatment is necessary (LOE II; SOR D).
- Adjuvant chemoradiation is recommended for patients with microscopic (R1 resection) or macroscopic residual disease at surgical margins (R2 resection) [LOE II; SOR C].
- Adjuvant chemoradiotherapy could be considered for patients who underwent R0 resections but have regional nodal metastases (LOE III; SOR C).

6.2.2. Adenocarcinoma

Perioperative (pre- and post-operative) chemotherapy significantly improve progression-free and overall survival in patients with operable gastric and lower esophageal adenocarcinomas, as have been shown in MAGIC trial [Cunningham et al., 2006]. In addition the adjuvant chemoradiation study published by MacDonald et al. showed both a survival and local control benefit [MacDonald, 2001]. In this study approximately 20% of patients had adenocarcinoma of the esophagogastric junction or lower esophagus and were treated with 5-FU based radiotherapy to 45Gy. A 10% absolute benefit in overall survival (41% versus 50%) and also reduced local recurrence (29% versus 19%) were reported. These results must be interpreted with caution and not extrapolated to all esophageal adenocarcinomas.

Recommendations

- Perioperative chemotherapy may be offered to fit patients with T2-T4, Nany disease (LOE II; SOR C).
- Patients with microscopic (R1 resection) or macroscopic residual disease at surgical margins (R2 resection) could be treated with fluoropyrimidine-based chemoradiation (LOE III; SOR B).

7. LOCALLY ADVANCED DISEASE (T3-4 N0-3 M0)
7.1 Definitive Chemoradiotherapy

Concomitant chemoradiation therapy versus RT was studied in the randomized trial RTOG 85-01 [Cooper et al., 1999]. Patients with SCC or adenocarcinoma received 4 cycles of 5-fluorouracil and cisplatin. RT dose of 50.4 Gy at 2 Gy/d was given concurrently. Patients received the combined modality therapy showed a significant improvement in 5-year overall survival (27% vs none). In the INT 0123 trial [Minsky et al., 2002], compared 2 different RT doses used the same chemotherapy regimen (5-FU and cisplatin), no significant difference was observed in median survival and local/regional failure, between the high and standard dose RT arms. After the results of these trials definitive chemoradiation therapy was established as the standard of care for patients with locally advanced disease esophageal cancer. The treatment consists of Cisplatin /5FU ×2 cycles concurrent with radiation followed by 2 more cycles of chemotherapy. Cisplatin 75mg/m2 D1 or 25mg/m2 D1-3, 5FU 1000 mg/m2 D1-4 (2 cycles week 1+5 with RT, 2 more cycles 3 weekly to start 3 weeks after radiation). Capecitabine can be substituted for 5FU. Radiation doses range from 45 - 50.4 Gy/25-28 fractions. Higher radiation dose can be considered for squamous cell cancer (SCC) of cervical esophagus. Definite chemoradiation therapy can be considered in medically unfit patients for surgery, in patients with squamous cell carcinoma of cervical esophagus or if patient declines surgery.

Definitive chemoradiation therapy with newer agents: Docetaxel and cisplatin in SCC was associated with high overall response rates [Li QQ et al., 2010]. Carboplatin and paclitaxel was also resulting in superior overall survival and disease-specific survival [Rupert et al., 2010]. FOLFOX-4 (randomized phase II trial) was associated with better median time to progression and median overall survival [Conroy et al., 2010].

Recommendations

➔ Multimodality therapy is preferred for good performance status patients with T3-4, N0/N+, M0 esophageal cancer (LOE I; SOR A).
➔ Preoperative chemoradiation for surgically fitted SCC, followed by postoperative CT and/or RT for R1-2 patients (LOE I; SOR A).
➔ Definitive chemoradiation is indicated for surgically unfit SCC (LOE I; SOR A).
Preoperative chemoradiation or perioperative CT for surgically fit adenocarcinomas, followed by postoperative CT (LOE I; SOR A)

Palliative CT and/or RT for surgically unfit adenocarcinomas.

Treatment options for poor performance status patients with T3-T4, N0/N+, M0 esophageal cancer include Palliative radiotherapy (40Gy/16#, 36Gy/12#, 30Gy/10#, 20Gy/5#, 8Gy/1#), Palliative chemotherapy, Best supportive care, Palliative stenting for relief of dysphagia, Intra-luminal brachytherapy (LOE III; SOR C).

Chemotherapy schedules

1. Adenocarcinoma of the distal esophagus and GE (Level of Evidence I).
   Perioperative therapy

   - ECF: Epirubicin 50mg/m2, Cisplatin 60mg/m2, 5FU 200 mg/m2 continuous infusion (CI) every 21 Days, up to 6 cycles.

   - ECF modifications:
     A. Epirubicin 50mg/m2 iv day 1, Cisplatin 60mg/m2 iv day 1, Capecitabine 625mg/m2 p.os twice daily every 21 Days, up to 6 cycles.
     B. Epirubicin 50mg/m2 iv day 1, Oxaliplatin 130 mg/m2 iv day 1, 5FU 200mg/m2 continuous infusion 24 hours daily days 1-21
     C. Epirubicin 50mg/m2 iv day 1, Oxaliplatin 130 mg/m2 iv day 1, Capecitabine 625mg/m2 p.os. twice daily every 21 Days, up to 6 cycles.

2. Squamous carcinoma or centrally located tumors

   - Neoadjuvant Chemoradiotherapy in good PS patients, 2 cycles week 1+5 with cisplatin 75mg/m2 d1 or 25mg/m2 d1-3 and 5FU 1000mg d1-4 and radiotherapy 45-50.4 Gy in 25– 28 fractions
   - Carboplatin AUC2/paclitaxel 50mg/m2 Weekly for five weeks and radiotherapy 41.4 Gy in 23 fractions followed by surgery in 4-6 weeks
   - 2 cycles with Cisplatin 80mg/m2 d1 and 5FU 1000mg/m2 d1-4 followed by surgery 4-6 εβδομάδες.

3. For locally advanced HER-2 positive GE tumors, Cisplatin 80 mg/m2 D1, 5FU 800mg/m2 D1-5 CI, Herceptin 8mg/kg LD followed by Herceptin 6mg/kg MD
every 21 Days, up to 6 cycles. Herceptin can be continued after 6 cycles if no progression. Capecitabine can be substituted for 5FU.

4. For Poor PS or reduced creatinine clearance, consider Carboplatin instead of Cisplatin.

Appendix – Treatment Algorithms

Figure 1: Treatment algorithm for locally advanced esophageal cancer

Localy advanced disease

T3-4 N0-3 M0

SCC

Fit

Preoperative Chemoradiation (45-50 Gy)

Surgery

R0

No further treatment

R1-2

SFU based postoperative CT-RT for selected patients

Unfit

Definitive Chemoradiation (>60 Gy)

AdenoCa

Fit

Preoperative CRT or Perioperative CT

CF(+E) x 3 + Surgery + CF(+E) x 3

Palliative therapy

Unfit

Definitive Chemoradiation (>60 Gy)

Chemotherapy +/- Radiotherapy Local palliation

Figure 2: Primary treatment options algorithm for locally advanced esophageal cancer

Postoperative treatment (patients who have received preoperative therapy)

R0 resection

Node negative

SCC

Observe

AdenoCa

T2, N0 Observe or ECF category 1

T3, N0 Observe or Chemoradiation or ECF category 1

Node positive

SCC

AdenoCa proximal-mid esophagus

Observe

Observe or Chemoradiation Fluoropyrimidine

AdenoCa distal Esophagus or EGJ

Chemoradiation Fluoropyrimidine or ECF category 1
Figure 3: Postoperative treatment for pts who have received preoperative CT

Postoperative treatment (patients who have received preoperative therapy)

Node negative

- SCC
  - Observe
  - T2, N0 Observe or ECF category 1
  - T3, N0 Observe or Chemoradiation or ECF category 1

- AdenoCa
  - Observe or Chemoradiation or ECF category 1

Node positive

- SCC
  - Observe or Chemoradiation Fluoropyrimidine

- AdenoCa proximal-mid esophagus
  - Observe or Chemoradiation Fluoropyrimidine or ECF category 1

- AdenoCa distal Esophagus or EGJ

R0 resection

Figure 4: Postoperative treatment for pts who have not received preoperative CT

Postoperative treatment (patients who have not received preoperative therapy)

Node negative

- SCC
  - Observe
  - T2, N0 Observe
  - T3, N0 Observe or Chemoradiation (fluoropyrimidine)

- AdenoCa
  - Observe

Node positive

- SCC
  - Observe
  - T2, N0 Observe
  - T3, N0 Observe or Chemoradiation (fluoropyrimidine)

- AdenoCa proximal-mid esophagus
  - Observe

- AdenoCa distal esophagus or EGJ
  - Chemoradiation (fluoropyrimidine)
7.2 Surgical Intervention

Squamous Cell Carcinoma (SCC)

Surgery alone is not the standard treatment in locally advanced disease, since even in M0 cases complete tumor resection is not feasible in 30% (pT3) to 50% (pT4) of the cases. Furthermore, even after complete tumor resection, long-term survival rarely exceeds 20%. Two meta-analyses highlight a benefit from preoperative chemoradiation by increasing the rates of complete tumor resection, improving local tumor control and survival rates [Gebski, 2007; Sjoquist, 2011]. For tumors of the upper third of esophagus in particular, chemoradiation may be considered as the definitive treatment in selected cases. However, close follow-up is required and salvage surgery may be indicated for local tumor progression. This remains also, the treatment of choice for patients unfit or unwilling to undergo surgery. Although overall survival rates are similar according to studies comparing patients after radiation alone with those treated via chemoradiation, whether tumors were resected or not, local control rate is lower if the tumor is not resected [Stahl et al., 2010].

Taking into consideration that optimal lymphadenectomy means 42 resected lymph nodes in T3/4N0M0 lesions and at least 50 when 3-6 nodes are involved [Rizk et al., 2010], the surgical procedure recommended is the transthoracic approach with lymphadenectomy of two fields.

Adenocarcinoma

In esophageal adenocarcinomas, multimodal neoadjuvant therapy should be used liberally in patients with bulky disease in an attempt to downsize-downstage the tumor, sterilize the field from micrometastasis and increase the curative resection rate [Pennathur et al., 2008]. For patients with locally advanced disease, in whom chemotherapy is not contraindicated, neoadjuvant chemotherapy followed by surgery [Omloo et al., 2007] is the standard of care [Allum et al., 2009].

In the MRC OEO2 trial, 66% of tumors were adenocarcinomas mainly of the lower third and over 50% were locally advanced. Long term analysis showed a significant benefit in 5 year survival (23% with preoperative chemotherapy compared to 17%
with surgery only), the treatment effect being consisted for both adenocarcinomas and SCCs [Allum et al., 2009].

Patients who did not receive neoadjuvant chemotherapy and shown to have lymph node involvement as well as those with R1/R2 resections could benefit from the adjuvant use of chemotherapy or chemoradiotherapy. However, some studies show a benefit from the use of adjuvant multimodal therapy [Rice et al., 2003; Adelstein et al., 2009] although others show no effect [Ando, 2003]. Moreover, there is limited data on the direct comparison of neoadjuvant therapy plus surgery vs. surgery plus adjuvant therapy, especially if surgery involves two field lymph node dissection and the issue is not elucidated at present.

While randomised trials have not consistently shown a benefit from neoadjuvant chemo-radiotherapy over surgery, several meta-analyses have concluded that neoadjuvant CRX is superior to surgery alone for adenocarcinoma (HR .75) revealing a significant survival benefit especially in high risk patients [Gebski, 2007]. Most recently, the German POET trial demonstrated modest, clinically relevant but not statistically significant benefits of neoadjuvant chemotherapy plus chemoradiotherapy versus induction chemotherapy alone in patients with EGJ adenocarcinoma [Stahl, 2009].

**Table 2. Treatment of Locally Advanced Esophageal Cancer According to Histological Type and Stage (T3-T4, N0-3, MO)**

<table>
<thead>
<tr>
<th>SCC:</th>
<th>Chemoradiation (pre- Op) + Surgery (transthoracic or transhiatal if patient unfit) [1], [2]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adeno:</td>
<td>Perioperative Chemotherapy + Transthoracic Surgery (if patient fit) OR Optional preoperative chemoradiotherapy + Transthoracic Surgery OR Transthoracic Surgery (fit patient) + Adjuvant Chemotherapy</td>
</tr>
</tbody>
</table>
Recommendations

→ Patients with T2-T4a, N0- N2 SCC and adenocarcinoma should be treated with two field lymph node dissection, if they are fit for surgery (LOE I; SOR B).

→ Preoperative chemoradiation is strongly recommended for SCC of the same stage (LOE I; SOR A).

→ Perioperative chemotherapy is recommended for adenocarcinoma of the same stage (LOE I; SOR B).

→ Preoperative chemoradiotherapy could be also considered for adenocarcinoma (LOE I; SOR B).

8. TREATMENT OF METASTATIC DISEASE

8.1 Image Staging and Restaging

Early detection of metastatic disease prior to the initiation of therapy is very important for the determination of resectability and planning of the appropriate treatment. Contrast-enhanced CT remains the mainstay for imaging patients with esophageal cancer to rule out distant metastasis, because it allows assessment of the most common sites of distant metastases. CT has an established role in the detection of liver metastases while it is also very sensitive in the detection of pulmonary nodules [Kim et al., 2009]. MRI has an additional role only in the assessment of indeterminate liver lesions. Endoscopic US has limited value in the assessment of distant metastases, except for celiac lymph node deposits. Therefore, CT or FDG PET is the first-line study for the detection of distant metastases.

Analysis of different studies evaluating the staging performance of PET scans in esophageal cancer show that FDG-PET has a moderate level of accuracy (sensitivity 51%, specificity 84%) for the detection of lymph nodes and reasonably better accuracy for the detection of more distant spread (sensitivity 67%, specificity 97%) [Steyerberg et al., 2007].

The primary role of FDG PET in esophageal cancer appears to be the detection of distant metastases. Because M stage is a major determinant of case management, the potential contribution of FDG PET to M staging should carry more weight than its
role in T or N staging when one is deciding whether to include FDG PET in the
standard preoperative work-up of patients with esophageal cancer. Several
comparative studies have demonstrated that FDG PET is more accurate than CT in
detecting distant metastases [Luketich et al., 1999]. FDG PET may be cost effective
in the prevention of non-curative surgery by helping detect metastases not identified
with other imaging modalities. However, the diagnostic yield of FDG PET in the
detection of unsuspected metastatic disease in early-stage esophageal cancer is very
low. Therefore, routine use of FDG PET in patients with early-stage disease is not
recommended [Flamen et al., 2000].

Concerning imaging assessment of therapeutic response to radiation or
chemotherapy, CT is not accurate. According to recent systematic reviews, the
accuracy of EUS in the assessment of therapeutic response is higher than that of CT
but inferior to that of FDG PET specifically after radiotherapy [Westerterp et al., 2005].
Overstaging is the most common error, since at EUS fibrosis and inflammation
associated with radiation-based therapy are indistinguishable from residual tumor.
Understaging is also possible and may be related to microscopic foci of viable tumor
within the esophageal wall, which is detectable only at histopathologic analysis of the
surgically resected specimen.

FDG PET currently seems to be the best imaging modality for the assessment of
response to neoadjuvant therapy in patients with esophageal cancer. Recent studies
suggest that the quantitative decrease in FDG uptake seen after neoadjuvant therapy
correlates closely with patient survival and with pathologic response to therapy
[Swisher et al., 2004]. In addition, FDG PET has an important post-therapeutic role in
detecting interval distant metastases, which have been reported in 8%–17% of cases
[Cerfolio et al., 2005; Bruzzi et al., 2007]. Several recent studies have demonstrated
the usefulness of FDG PET in differentiating “responders” from “non-responders”
early in the course of chemotherapy–radiation therapy [Wieder et al., 2004].

**Recommendations**

> **CT is the first line imaging modality for the detection of distant metastases (LOE II; SOR B).**
MRI is indicated only for the differential diagnosis of equivocal liver lesions (LOE III; SOR B).

Routine use of FDG PET in patients with early-stage disease is not recommended (LOE II; SOR B).

FDG PET could be used in locally advanced disease and in equivocal cases of possible metastatic disease in order to prevent unnecessary surgery specifically in patients at high risk (LOE II; SOR B).

FDG PET currently seems to be the best imaging modality for the assessment of response to neoadjuvant therapy (LOE I; SOR A).

There are no currently available guidelines for the optimal timing of FDG PET in the assessment of therapeutic response.

8.2 Palliative Chemotherapy for Metastatic Disease

The majority of the trials testing chemotherapy drugs for esophageal cancer was performed at a time when SCC was the predominant histology (1970s and 1980s) and the drugs used were those initially developed for SCC of the head and neck [Grunberger, 2007]. The followed changes in histologic and anatomic distribution has led to the convergence of the treatments of advanced gastric and esophageal cancers and the majority of clinical trials conducted since the mid 1990s included patients with gastric, esophageal or GEJ cancer, regardless of histology [Webb, 1997; Ross, 2002]. Although SCCs now represent a small minority of patients enrolled on most clinical trials, histologic subtype does not seem to play a major role in response rate or survival duration in patients treated with a variety of regimens [Chau, 2000; Ilson, 2007; Muro, 2004; Einzig, 1996; Petrasch, 1998]. As a consequence in general, chemotherapy regimens recommended for advanced esophageal/esophagogastric adenocarcinoma, squamous cell carcinoma of the esophagus and gastric adenocarcinoma may be used interchangeably (NCCN guidelines 2011).

A number of controlled trials and a meta-analysis provide evidence for the beneficial effect of palliative systemic chemotherapy as compared to supportive care alone for
patients with advanced gastric cancer [Murad, 1993; Pyrhonen, 1995; Glimelius, 1997; Wagner, 2006]. This was not proven in two older studies regarding exclusively esophageal cancer [Levard, 1998; Nicolaou 1982].

Chemotherapy as a single modality has largely been used for palliation in patients with advanced esophageal cancer and several agents, “older” (bleomycin, mitomycin-C, methotrexate, 5-fluorouracil, cisplatin, doxorubicin) and “newer” (taxanes, irinotecan, vinorelbine, oral fluoropyrimidines) have shown activity in this setting [Grunberger, 2007]. The cumulative response rate for any one drug is low, in the order of 15% to 35%, the duration of response short, and there is no indication of survival benefit.

Higher response rates are reported in phase II trials evaluating combination therapy in patients with advanced esophageal and gastric cancer. However response rates have been lower in randomized trials and this was translated into only modestly longer durations of disease control and survival that are measured in weeks to a few months.

In patients with HER-2 positive metastatic tumors, the addition of herceptin to chemotherapy confers a survival benefit (see Targeted agents).

For the patients with tumors non overexpressing HER-2:

- The ECF combination (epirubicin, cisplatin, continuous infusion 5-FU) remains a reference regimen, although the survival benefit in comparison to FAMTX (methotrexate, doxorubicin, 5-FU) was modest (8.9 versus 5.7 months) [Webb, 1997]. The study accrued 256 patients with adenocarcinoma, with 51 and 57 having an esophageal and gastroesophageal junction tumor respectively. The data from the REAL-2 trial [Cunningham, 2008] show comparable outcomes when capecitabine (X) was substituted for infusional 5-FU and oxaliplatin (O) for cisplatin. Even more when the four groups (ECF, ECX, EOF, EOX) were considered separately median survival in patients treated with EOX was modestly longer when compared to ECF (median 11.2 versus 9.9 months, HR 0.80, 95%CI 0.66 to 0.97). From the 964 patients
included in the REAL-2 study, the 1/3 had esophageal and 1/4 gastroesophageal cancer. 90% of the tumors were adenocarcinomas while 10% squamous cell carcinomas. All tests for heterogeneity with regard to treatment effect, overall survival, and prognostic factors, including the primary site and the results of histologic analysis, for two-by-two comparisons did not reveal any significant heterogeneity (p>0.05 in all cases).

- The combination of docetaxel-cisplatin-5-FU (DCF) has been established as another reference regimen following the comparison with the 5-FU/cisplatin combination in the V-325 study [Van Cutsem, 2006]. The results were in favor of DCF in terms of response rate, time to tumor progression and median survival (10.2 versus 8.5 months, p=0.006) at the cost of a higher incidence of grade 3/4 diarrhea (20% vs 8%) and neutropenia (30% vs 14%). DCF also showed significant improvement in measures of clinical benefit. In the V-325 study 445 patients with adenocarcinoma were included and 22% of them had gastroesophageal junction tumor. Similar results are reported using docetaxel and infusional 5-FU or capecitabine [Thuss-Patience, 2005; Giordano, 2006]. A modified schedule for DCF is associated with preserved efficacy and improved tolerability (Shah, 2010).

- The combination of cisplatin plus 5-FU in different regimens [Bleiberg, 1997; Warner, 1999; Mitry, 2004] is one of the most commonly used. Capecitabine may substitute for 5-FU in combination with cisplatin [Kang, 2009]. A meta-analysis of two randomized trials concluded that, compared to 5-FU combinations, capecitabine combinations were associated with higher response rates and better overall survival [Okines, 2009].

- A meta-analysis of the REAL-2 trial and two other randomized trials (Al-Batran, 2008; Popov, 2008) showed that oxaliplatin-based (EOX, FOLFOX, FLO) compared to cisplatin-based regimens were associated
with significant improvement in PFS and overall survival (HR for death 0.88, 95%CI 0.78 to 0.99) and less neutropenia, anemia and thromboembolic events, but more neurotoxicity and diarrhea (Montagnani, 2011).

- The FOLFIRI regimen was proved superior over 5-FU/leucovorin with or without cisplatin in a French randomized phase II trial (Bouche 2004). Irinotecan has been also combined with cisplatin, docetaxel and oral fluoropyrimidines (Boku 2009, Burtness 2009, Moehler 2010, Narahara 2011). There are no phase III trials comparing an irinotecan-based combination with a cisplatin-based triplet regimen.

**Recommendations**

- **Cytotoxic chemotherapy in selected patients with advanced esophageal cancer can provide symptom palliation, improve quality of life and prolong survival (LOE III; SOR B).** Regimens should be chosen in the context of performance status, medical co-morbidities, toxicity profile and HER-2 status (for adenocarcinomas only).

- In randomized trials, the ECF and DCF combinations have emerged as standard regimens for first-line treatment (LOE I; SOR A). The use of three-drug regimens should be reserved for patients who are medically fit, with a good performance status (ECOG 0 or 1) and with access to frequent toxicity assessment.

- If the classical three-drug combination is not preferred, alternative regimens include modified DCF (LOE II; SOR A), cisplatin and fluoropyrimidine combination (LOE I; SOR B), FOLFOX (LOE II; SOR B), FOLFIRI (LOE II; SOR B).

- Infusional 5-FU and capecitabine may be used interchangeably.

- Cisplatin and oxaliplatin may be used interchangeably.

- Elderly patients or those with a poor performance status may be treated with leucovorin/5-FU alone or capecitabine or alternatively single agent irinotecan or low dose weekly taxanes.
No standard approach for second-line therapy exists. For patients who retain an adequate performance status, utilization of other active agents (docetaxel, irinotecan) not used in the first line regimen is reasonable.

8.3 Targeted Agents

In the metastatic setting of gastroesophageal cancer, chemotherapy is the mainstay of palliative therapy and results in objective response rates (ORRs) of only 20–40% and median overall survivals (OS) of 8–10 months (Enzinger, 2003). Given the poor overall survival in the metastatic setting with standard chemotherapy, the potential for making significant progress lies in understanding and exploiting the molecular biology of these tumors. The overexpression of epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF) and HER-2/neu is associated with poor prognosis. Targeted treatments against these factors have been evaluated in clinical trials of patients with advanced esophageal cancer and EGJ adenocarcinomas.

8.3.1 Epidermal Growth Factor Receptor

EGFR or erbB1 is a member of the erbB tyrosine kinase family. Binding of ligand to the receptor causes dimerization either with itself or another member of the erbB family. Overexpression by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) in EGCs has been seen in 30–90% of tumors, and correlates with increased invasion, poorly differentiated histology, and worse prognosis. Anti-EGFR therapies which have been evaluated in metastatic EGCs include the moAbs (cetuximab, panitumumab, and matuzumab) and oral, small molecule TKIs (erlotinib and gefitinib).

In metastatic disease, multiple studies have evaluated the safety and efficacy of adding cetuximab to first-line chemotherapy regimens, including FOLFIRI, FUFIRI, FOLFOX, 5FU/cisplatin, cisplatin/docetaxel, and others. These studies suggest that this approach is safe and in some cases, objective response rates are over 50 percent and median survival ≤10 months. Whether these results are better than can be achieved with chemotherapy alone is unclear. In a randomized phase II German trial of 66 previously untreated patients with metastatic squamous cell cancer (SCC)
of the esophagus the benefit of adding cetuximab to cisplatin plus 5-FU was evaluated (Lorenzen, 2009). The objective response rate was only slightly higher (19 versus 13 percent), and there was a trend toward longer median PFS (5.7 versus 3.6 months) and overall survival (9.5 versus 5.5 months) when cetuximab was added to the CF backbone. Although these differences were not statistically significant (the trial was not powered to detect such differences), these results suggest that the addition of cetuximab to chemotherapy may be beneficial, at least in esophageal SCC.

In a randomized phase II trial from the CALGB that aimed to determine the best chemotherapy backbone for further study, cetuximab was combined with either ECF (epirubicin, cisplatin, and infusional 5-FU), cisplatin/irinotecan, or FOLFOX for the treatment of metastatic esophageal or GE junction cancers (Enzinger, 2010). Cetuximab plus ECF or FOLFOX had response rates greater than 40% and met the criteria for further development.

The utility of adding an anti-EGFR MoAb to first line chemotherapy for advanced EGC must await the results of randomized phase III studies. Ongoing phase III studies include the EXPAND trial, an international phase III evaluation of cisplatin/capecitabine +/- cetuximab and the REAL3 trial in the United Kingdom, which is randomizing patients with advanced EGCs to the EOX (epirubicin/oxaliplatin/capecitabine) regimen +/- panitumumab while MATRIX EG, an European phase II randomized trial of the ECX regimen +/- matuzumab, has completed accrual.

In the second line setting, monotherapy with cetuximab has been evaluated. In a phase II study, 55 patients with metastatic esophageal adenocarcinoma who failed one prior chemotherapy regimen received cetuximab as second line therapy (Gold, 2010). The 6-month overall survival rate (primary end-point) was 36% (95% confidence interval [CI]: 24-50%) failed to meet the primary survival objective. The median overall survival was 4.0 months (95% CI: 3.2-5.9) and the median progression-free survival was 1.8 months (95% CI: 1.7-1.9).

Another way of interfering with EGFR signaling is through the use of orally active tyrosine kinase inhibitors (TKIs), gefitinib or erlotinib. Both TKIs have been evaluated in advanced EGCs, with very modest results.
In a phase II evaluation of first-line erlotinib in advanced gastric and GE junction adenocarcinoma performed by SWOG, 70 patients with unresectable or metastatic adenocarcinoma originating in the GEJ or stomach received first line treatment with erlotinib (Dragovich, 2006). Six patients had an objective response rate (9 percent, one complete), all of whom had GEJ tumors. There were no responses in the patients with gastric primaries.

In a phase II study trial investigating the addition of erlotinib to modified FOLFOX6 chemotherapy in 38 patients with gastroesophageal junction tumors only, the response rate was 50% with an overall survival of 11 months (Wainberg, 2010).

In another phase II study of erlotinib in 30 patients with previously treated squamous cell and adenocarcinoma of the esophagus, Responses were limited to patients who had squamous cell carcinoma (2 of 13 patients; 15%; response duration, 5.5-7 months) (Ilson, 2010).

Gefitinib as a single agent for treatment of EGC has also only produced modest results. Gefitinib was studied in a phase II evaluation as second-line treatment for 28 patients. One patient had a 3-month partial response, and 10 patients had stable disease (Janmaat, 2006). In another study that evaluated gefitinib as either first or second-line therapy for esophageal and GE junction adenocarcinoma, the overall response rate was 11%, but overall survival was 4.5 months (Ferry, 2007).

### 8.3.2 Anti-HER-2 Therapies

HER-2/neu (ERBB2) is another member of the ERBB TK receptor family. Reported rates of HER-2 overexpression in gastroesophageal cancer vary widely (2–45%) due to small sample sizes, differences in patient populations and methodological and scoring differences between studies (Moelans, 2010). The data on HER-2 overexpression in esophageal cancer are variable, with most studies showing HER-2 overexpression in 9%–60% of cases, whereas other reports failed to observe HER-2 expression. The relationship between HER-2 expression and the prognosis of patients with esophageal cancer is not clear. It has been demonstrated that HER-2 overexpression correlates with tumor invasion and lymph node metastasis, and thus indicates a poor prognosis (Moelans, 2010).
Anti-HER-2/neu therapies that have been evaluated in EGCs are the moAb, trastuzumab and the TKI, lapatinib.

### 8.3.2.1 Anti-HER-2 moAb

Trastuzumab is a humanized IgG1 moAb against the HER-2 receptor and is approved for the treatment of HER-2 positive breast cancer. The benefit of trastuzumab in advanced HER-2 positive adenocarcinoma of the stomach or gastroesophageal junction (GEJ) was addressed in the phase III ToGA trial, which compared standard chemotherapy (six courses of infusional 5-FU or capecitabine plus cisplatin) with and without trastuzumab (8 mg/kg loading dose, then 6 mg/kg every three weeks until disease progression) (Bang, 2010). Of tumors from 3807 patients, 22.1% were found to be HER-2/neu-positive (either fluorescence FISH-positive or by IHC; 47 percent 3+, 30 percent 2+, and 22 percent 0 or 1+). Five hundred and ninety-four patients were randomized. One hundred and six patients had tumor of the gastroesophageal junction. There was a statistically significant increase in overall response rate (47.3% vs 34.5%), median progression free survival (6.7 vs 5.5 months) and median overall survival (13.8 vs 11.1 months) in favor of the trastuzumab containing arm. In prespecified group analysis, the hazard ratio for overall survival in the patients with GEJ tumors was 0.67 (CI 0.42-1.08). There was no unexpected toxicity in the trastuzumab arm, but as expected there was an increased incidence of asymptomatic decrease in the left ventricular ejection fraction. Based upon these data, trastuzumab was approved, in combination with cisplatin and a fluoropyrimidine, for the treatment of patients with metastatic HER-2-overexpressing gastric or GEJ adenocarcinomas who have not received prior treatment for metastatic disease.

### 8.3.2.2 Lapatinib

Lapatinib is an oral TKI that has activity against EGFR and HER-2/neu. In phase II studies, monotherapy with lapatinib has shown modest results. In a study of 47 patients with advanced gastric cancer, lapatinib as first-line treatment showed a documented partial response rate of 7% median time-to-treatment failure of 2 months, and median overall survival was 5 months (Iqbal, 2007). In a second study, 25
patients with adenocarcinoma of the esophagus or gastroesophageal junction (GEJ) who had received multiple prior therapies were selected on the basis of EGFR positivity by IHC and/or HER-2/neu positivity by IHC or FISH. While the ORR was 0% in 21 evaluable patients, 2 patients had SD for 5 and 9 months, respectively (Hecht, 2008). Despite the limited activity of lapatinib, two phase III studies are currently evaluating the role of lapatinib in combination with chemotherapy for the treatment of advanced EGC. The LOGIC trial is evaluating the combination of capecitabine/oxaliplatin ± lapatinib as first-line therapy for HER-2 overexpressing EGCs. The TYTAN trial is an Asian study evaluating lapatinib in combination with paclitaxel as second-line therapy in gastric cancer. Both studies are still in progress, and final results are pending.

8.3.3 Vascular Endothelial Growth Factor (VEGF)

In esophageal cancer, VEGF is over-expressed in 30–60% of patients. Several studies have demonstrated a correlation between high levels of VEGF expression, advanced stage and poor survival (Reddy, 2011). In SCCs the expression of VEGF in tumors correlates with more advanced tumor stage, the presence of nodal and distant metastases and a poorer survival outcome. Additionally in esophageal adenocarcinoma, increasing expression of VEGF correlates with the transition from Barrett’s esophagus to high-grade dysplasia and with the transition from microinvasive to locally advanced cancer (Ku, 2010).

These data, in conjunction with the demonstrated benefit of adding the anti-VEGF monoclonal antibody bevacizumab to chemotherapy in metastatic colorectal cancer, non-small cell lung cancer, and breast cancer provide the rationale to study antiangiogenic therapies in advanced upper GI cancer. Anti-VEGF therapies that have been evaluated include the moAb, bevacizumab, as well as the multi-target TKIs, sunitinib and sorafenib.
8.3.3.1 Bevacizumab

Promising results were reported in phase II studies of bevacizumab in combination with cisplatin plus irinotecan or docetaxel as a single agent. The phase III AVAGAST study was launched to evaluate first-line fluoropyrimidine (5-FU or capecitabine) and cisplatin plus bevacizumab or placebo in patients with advanced adenocarcinoma of the stomach or gastroesophageal junction (Ohtsu, 2011). There were 774 patients enrolled in this trial, and approximately 95% had metastatic disease. Most of the patients had gastric cancer, although 103 patients had advanced cancer of the GEJ. There was no statistically significant difference in median overall survival (10.1 months with chemotherapy vs 12.1 months with chemotherapy plus bevacizumab, HR=0.87, P=0.1002), which was the primary end-point of the trial. Both median progression-free survival (6.7 v 5.3 months; hazard ratio, 0.80; 95% CI, 0.68 to 0.93; P=0.0037) and overall response rate (46.0% v 37.4%; P=0.0315) were significantly improved with bevacizumab versus placebo. Furthermore, in a subset analysis of geographical regions, increased benefit in the European and Pan-American regions was noted.

Recommendations

→ For patients with unresectable locally advanced, recurrent, or metastatic adenocarcinoma of the esophagus or EGJ assessment for tumor HER-2/neu overexpression should be performed using immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH), following the scoring system used in the ToGA trial (LOE II; SOR A).

→ Trastuzumab with chemotherapy for patients who are HER-2/neu-positive, as determined by a standardized method
  - Combination with cisplatin and fluoropyrimidine (LOE I; SOR A)
  - Combination with other chemotherapy agents (LOE II; SOR B)
8.4 Palliative Care

In patients with unresectable or locally advanced cancer, palliative interventions provide relief of symptoms and may prolong life, improve the nutritional status and overall quality of life. Dysphagia is one the most common symptoms in patients with esophageal cancer. Palliative methods for dysphagia include endoscopic therapies, radiation therapy, brachytherapy, chemotherapy or surgery. Endoscopic palliation includes dilation, laser ablation therapy, endoscopic injection therapies, endoscopic mucosal resection, photodynamic therapy, and prosthetic stenting of the obstructing tumor. The optimal management is not clear and is debated. The choice of the individual palliative method should be based upon anatomical features of the lesion, patient status and preference, and expertise availability.

In one study, single dose brachytherapy was associated with fewer complications and better long-term relief of dysphagia compared with metal stenting of the tumor (Homs, 2004). Placement of self-expanding metal stents is the preferred treatment for patients with tracheoesophageal fistula and those who are not candidates for chemoradiation or those who fail to achieve adequate palliation with such therapy (Ross et al., 2007). Treatment options for the management of dysphagia should be individualized and multimodality interdisciplinary approach is encouraged.

For patients with complete esophageal obstruction, endoscopic lumen restoration, external beam RT, chemotherapy or surgery is recommended. Surgically or radiologically constructed jejunostomy or gastrostomy may be necessary to provide adequate hydration and nutrition.

Bleeding can occur in patients with esophageal cancer and occasionally could be secondary to tumor related aorto-esophageal fistulization. Surgery or external beam RT and/or endoscopic therapy may be indicated in patients with brisk bleeding from the cancer. Bleeding that occurs primarily from the tumor surface may be controlled with endoscopic electrocoagulation techniques such as bipolar electrocoagulation or argon plasma coagulation.

Nausea and vomiting can be palliated with pharmacological methods, and if associated with obstruction, endoscopic evaluation is indicated and appropriate therapies should be applied.
Surgery

Current evidence is not enough to support resection of liver or lung metastasis from esophageal adenocarcinoma or squamous cells carcinoma [Gee et al., 2007]. The only surgical–endoscopic approach indicated is endotherapy, by means of stenting obstructing logo-regional metastasis and strictures, for palliation [Lampert, 2003]. In patients with metastatic disease to distant organs, stenting or balloon dilation of the primary esophageal lesion, chemotherapy, radiation therapy with external beam or brachytherapy, or a combination of these modalities are all options for symptomatic relief.

Recommendations

→ Chemo-radiation is the treatment of choice for esophageal cancer not amenable to surgical resection (LOE II; SOR B).
→ Palliative intervention is recommended to relieve symptoms and improve quality of life (LOE III; C).
→ Resection of metastatic disease is not indicated (LOE III; SOR D).

POSITION STATEMENT

According to current evidence and practice, patients with “esophageal cancer” and “gastric cancer” should be referred for care to highly specialized centers with adequate case volume, as this ensures better outcomes in terms of morbidity, mortality, local recurrence and survival. At those centers, a multidisciplinary team of surgeons, oncologists, pathologists, radiotherapists and radiologists should be on charge, caring for the patients at any stage of the treatment, from the initial evaluation to the follow-up, according to the recommendations listed above.

Audit and quality control of therapeutic services require compulsory patient's full data collection and registration according to regional or national programs. Registered data should include all preoperative characteristics, intraoperative outcomes and quality of surgery parameters, postoperative morbidity and mortality, follow-up details and oncological outcomes, as also defined above. A case-mixed adjusted feedback is crucial in the whole process of the “quality assurance” concept. If suboptimal
performance is encountered, the responsible treating team should be instructed to improve results by further and more intensive training or to cease treating such cases.
9. REFERENCES


Hecht J, Urba S, Koehler M, et al., Lapatinib monotherapy in recurrent upper


Mapstone N The Royal College of Pathologists. Dataset for the histopathological reporting of oesophageal carcinoma (2nd edition). February 2007 publications @rcpath.org


NCCN clinical practice guidelines in Oncology, 2011.


Shah MA, Shibata S, Stoller RG, et al. Random assignment multicenter phase II study of modified docetaxel, cisplatin, fluorouracil (mDCF) versus DCF with growth


Wainberg ZA, Lin L, DiCarlo B et al. Final results of a phase II study of modified FOLFOX6 (mFOLFOX6) and erlotinib (E) in patients with metastatic adenocarcinoma of the esophagus (Eso) and gastroesophageal junction (GEJ). J Clin Oncol 2010, 28:15s (suppl; abstract 4050)


