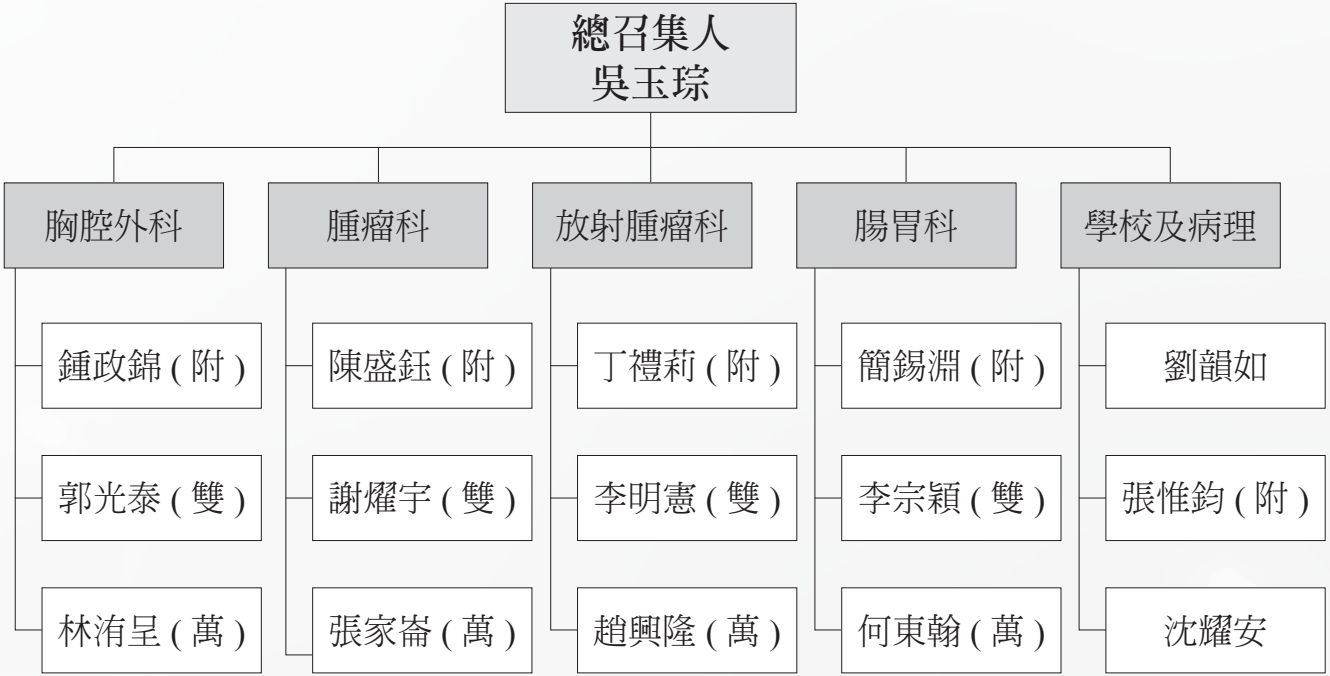
Esophageal and Esophagogastric Junction Cancer Guidelines

食道團隊成員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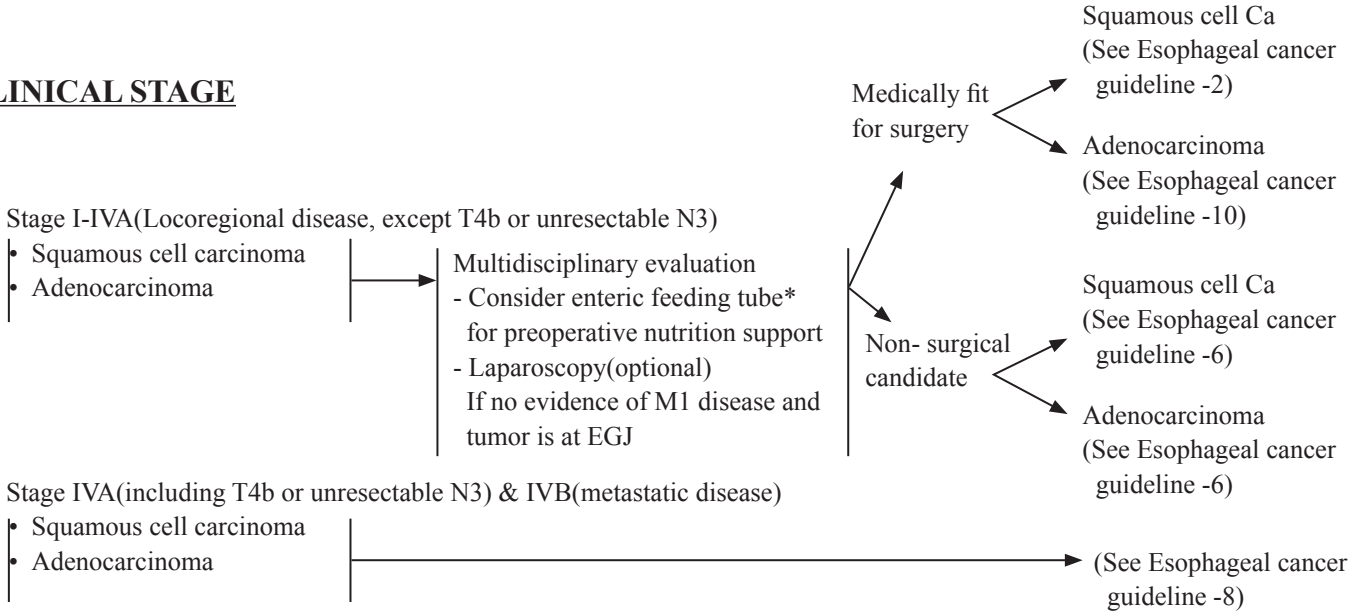
Pretreatment Workup

WORKUP

- H &P
- Upper GI endoscopy and biopsy
- Chest / abdomen CT with oral and IV contrast
- Pelvic CT with contrast as clinical indicated
- PET-CT evaluation (skull base to mid-thigh) if no evidence of M1 disease
- CBC and Chemistry profile
- Endoscopic ultrasound(EUS), if no evidence of M1 un-resectable disease
- Endoscopic resection (ER) is recommended for the accurate staging of early- stage cancers(T1a or T1b). Early-stage cancer can be best diagnosed by ER
- Biopsy of metastatic disease as clinically indicated
- Universal testing for microsatellite instability (MSI) by PCR/next-generation sequencing (NGS) or MMR by IHC is recommended in all newly diagnosed patients
- Programmed death ligand 1 (PD-L1) testing if advanced / metastatic disease is documented/suspected
- HER2-neu testing if metastatic adenocarcinoma is documented/ suspected
- Next-generation sequencing (NGS) may be considered
- Bronchoscopy, if tumor is at or above the carina with no evidence of M1 disease
- Assign Siewert category
- Nutritional assessment and counseling
- Smoking cessation advice, counseling, and pharmacotherapy as indicated
- Screen for family history

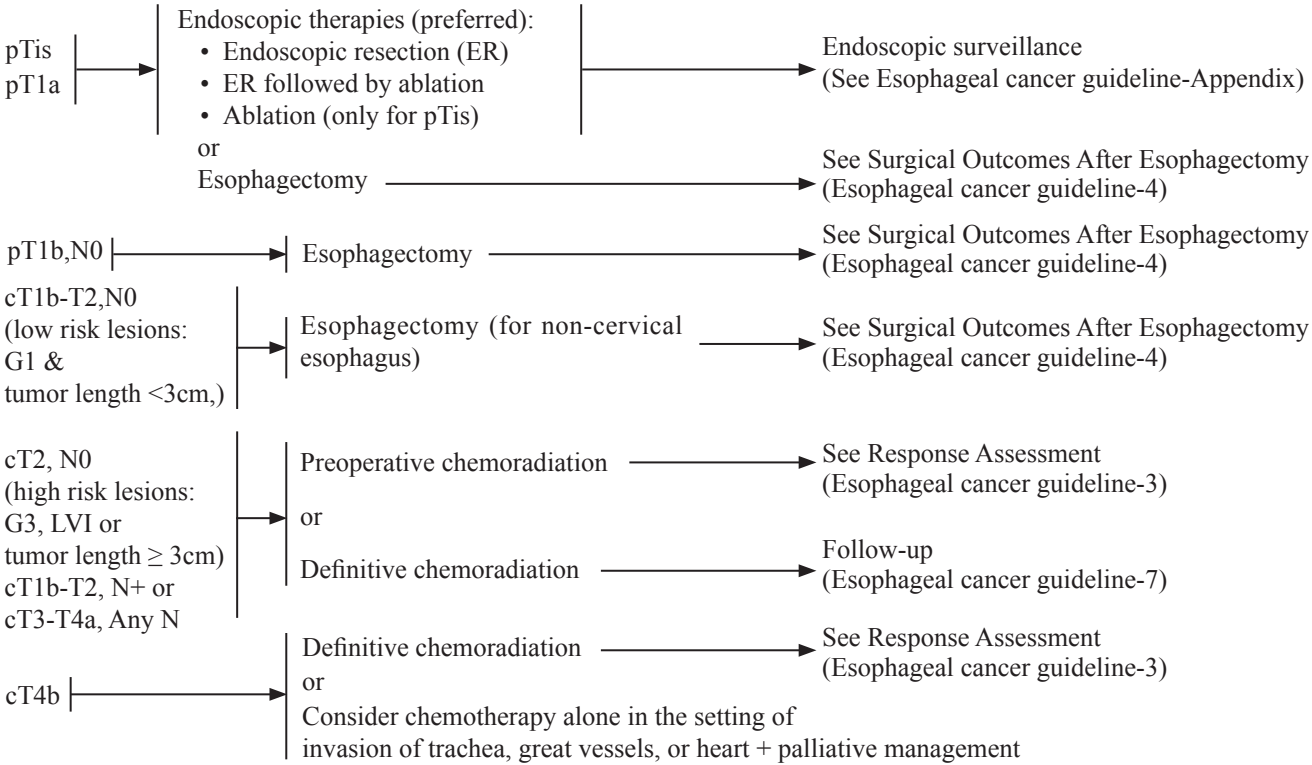
Pretreatment Workup



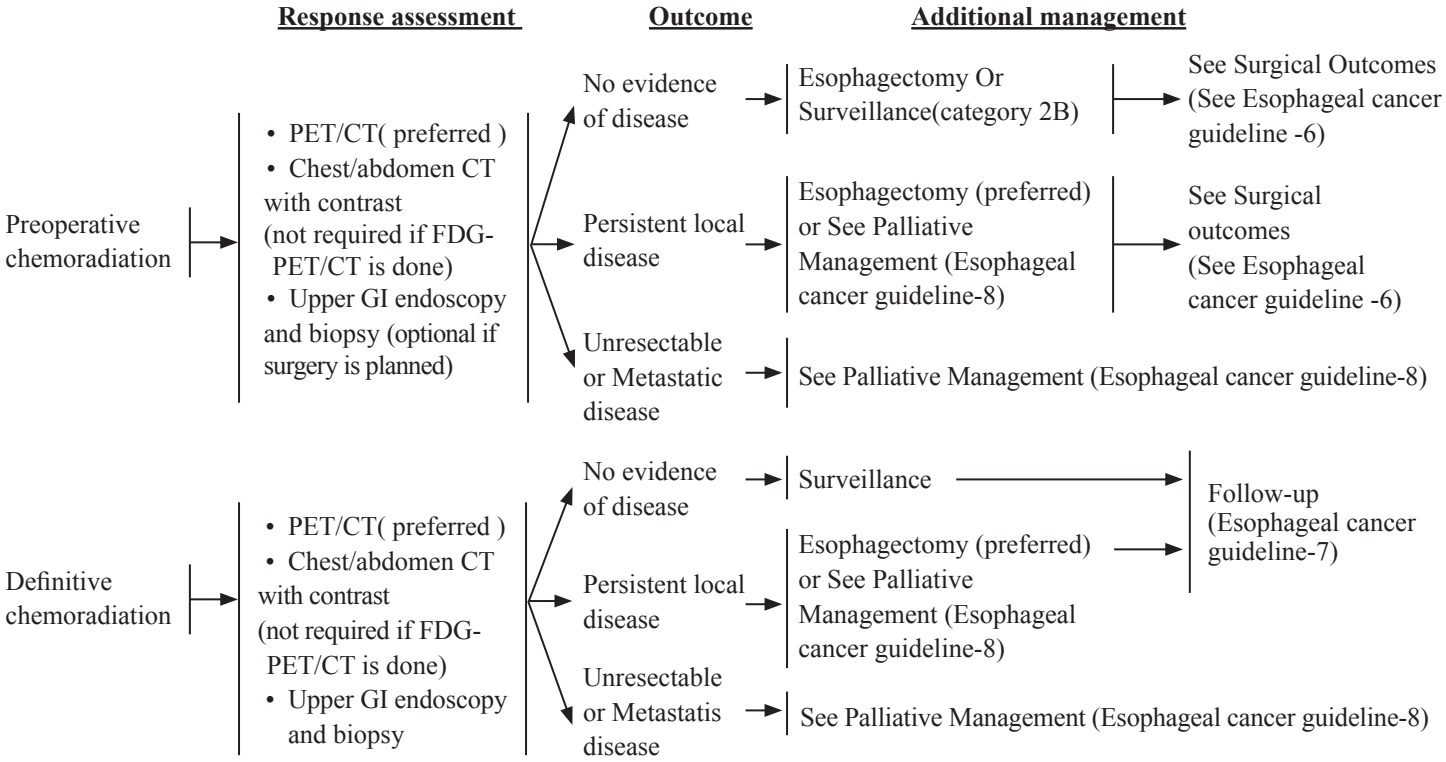
* Percutaneous gastrostomy tube (PCG) may be considered for patient with cervical esophageal tumors receiving definitive chemoradiation or for patients with marginally resectable disease.

《 Esophageal cancer guideline-2》

Squamous cell carcinoma: primary treatment options for medically fit surgery patients



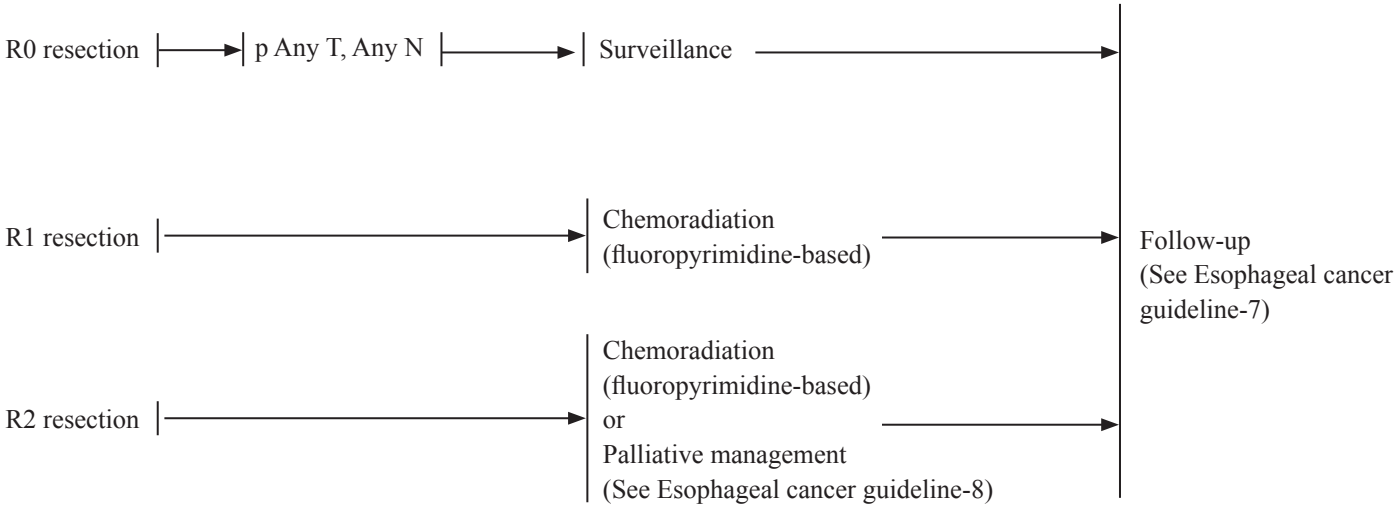
Squamous cell carcinoma: response assessment



《 Esophageal cancer guideline-4》

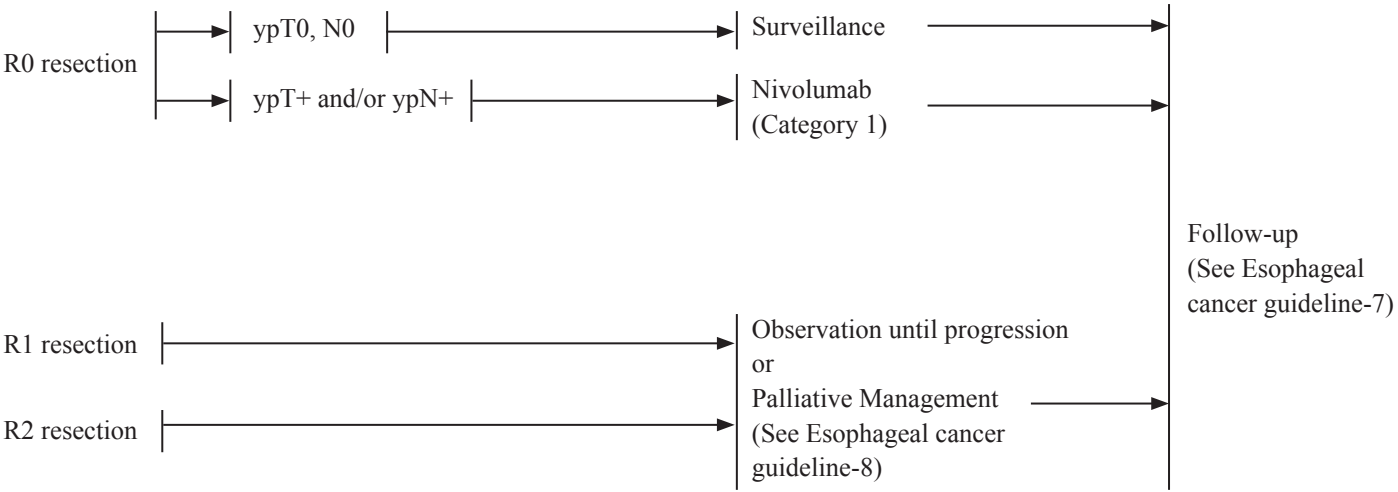
Squamous cell carcinoma: surgical outcomes

Patients **Have Not** Reveived Preoperative Chemoradiation



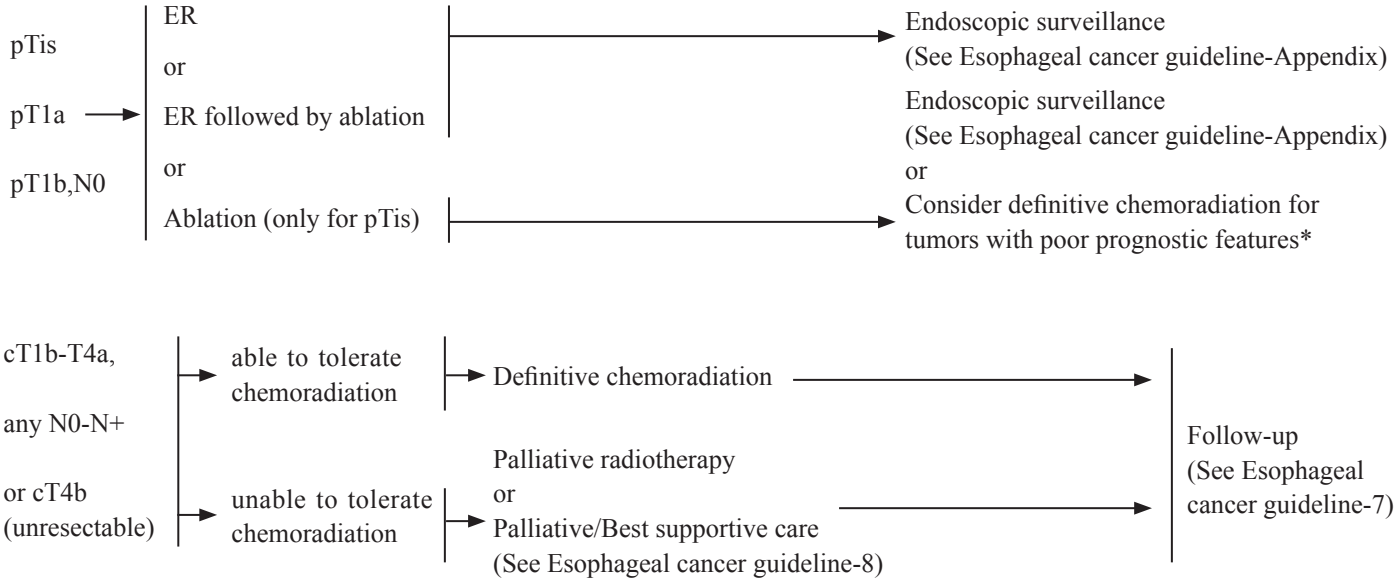
Squamous cell carcinoma: surgical outcomes

Patients **Have** Reveived Preoperative Chemoradiation



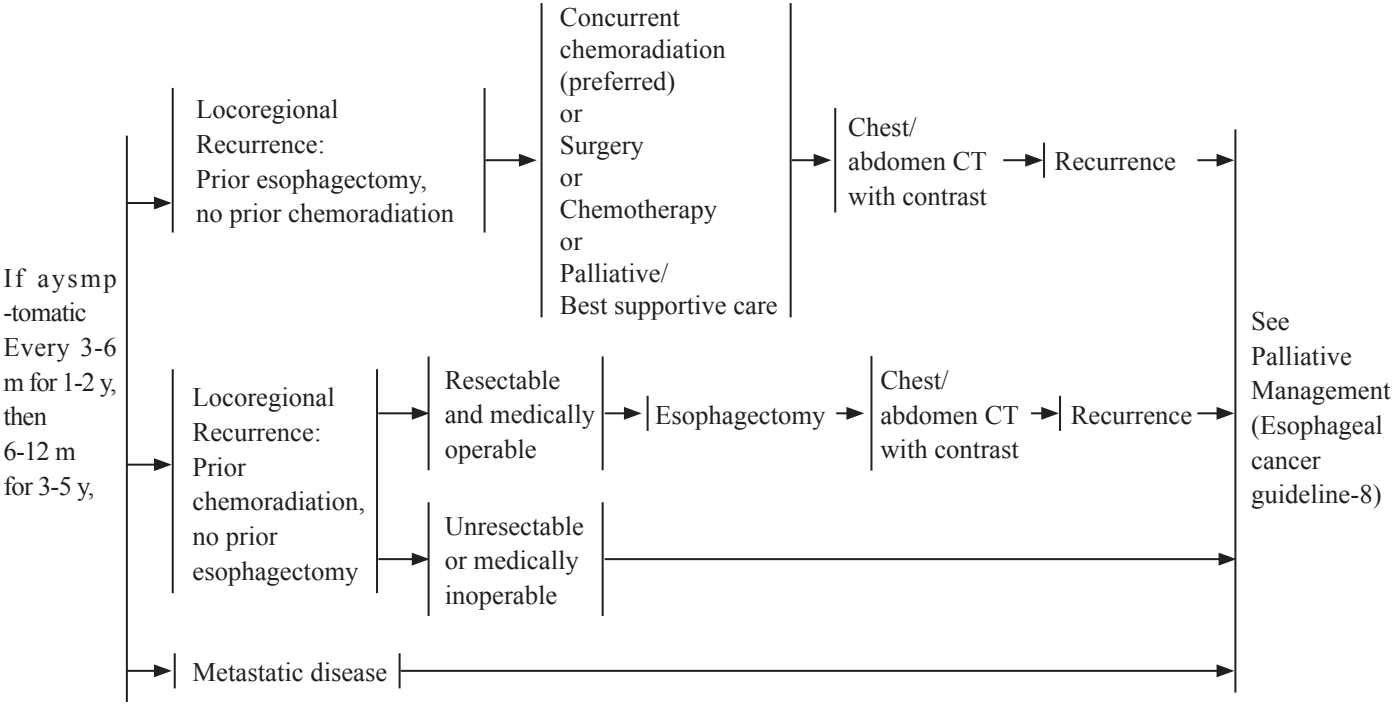
《 Esophageal cancer guideline-6》

Squamous cell carcinoma &adenocarcinoma : non-surgical candidate



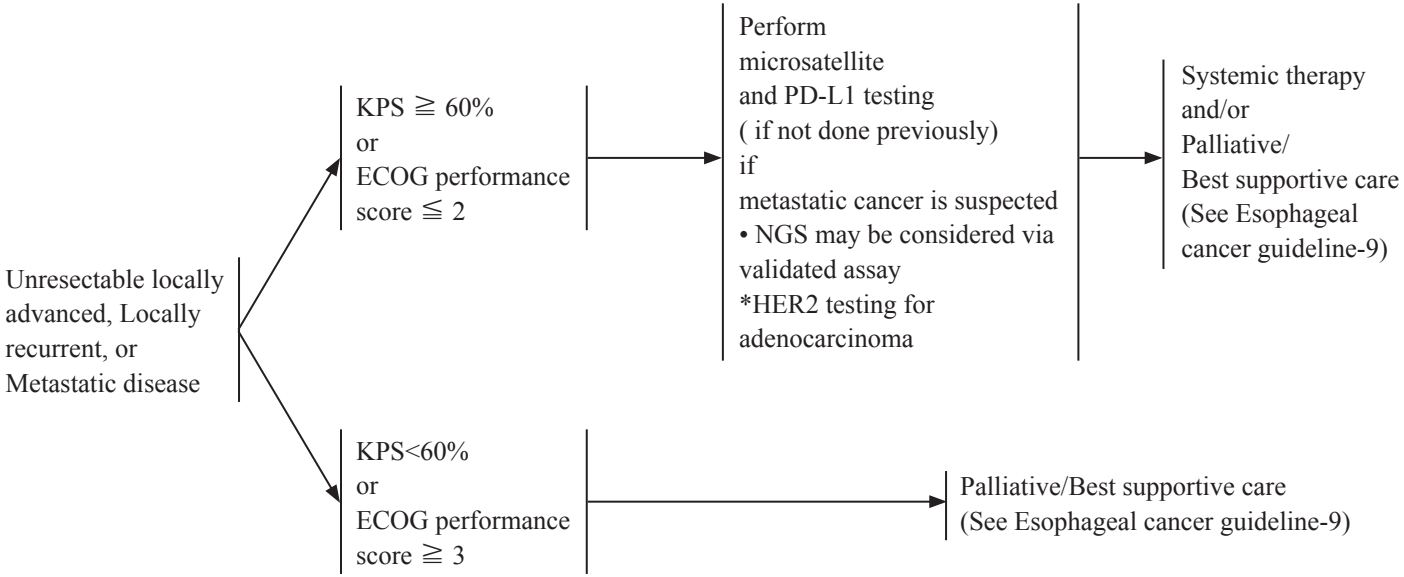
* Poor prognostic features: positive margin(s), max. tumor diameter > 2cm, G2/3, LVI or more

Squamous cell carcinoma & adenocarcinoma follow up – recurrence – palliative management



《 Esophageal cancer guideline-8》

Squamous cell carcinoma & adenocarcinoma : unresectable locally advancer, locally recurrent, or metastatic disease



Principles of Palliative/Best Supportive Care

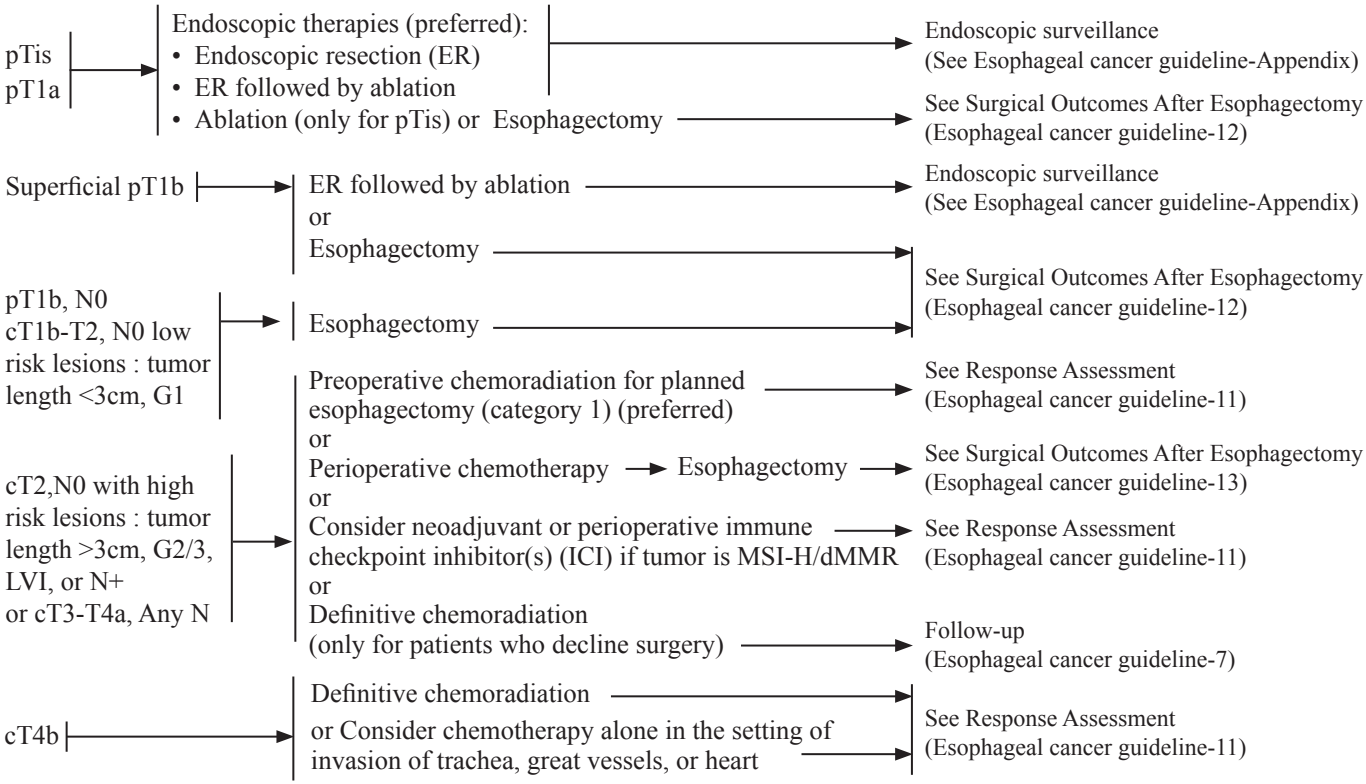
The goal of best supportive care is to prevent and relieve suffering and to support the best possible quality of life for patients and their families, regardless of the stage of the disease or the need for other therapies. For esophageal cancer, interventions undertaken to relieve major symptoms may result in significant prolongation of life. This appears to be particularly true when a multimodality interdisciplinary approach is pursued and, therefore, a multimodality interdisciplinary approach to palliative care of the esophageal cancer patient is encouraged.

Dysphagia

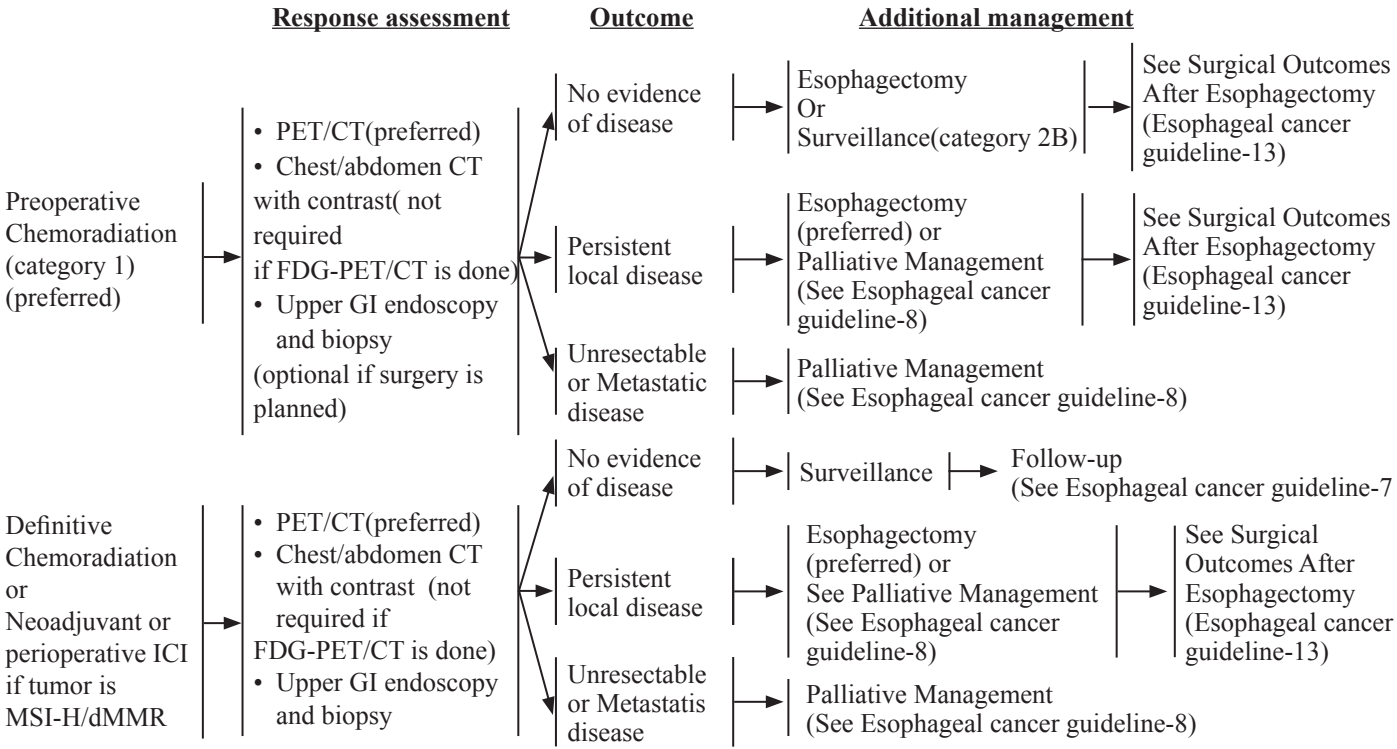
- Assess the extent of disease and the functional degree of swallowing impairment, preferably through a standardized scoring scale and confirm the etiology of dysphagia
- Dysphagia grading scale
  - Grade 0: Able to eat solid food without special attention to bite size or chewing
  - Grade 1: Able to swallow solid food cut into pieces less than 18 mm in diameter and thoroughly chewed
  - Grade 2: Able to swallow semisolid food (consistency of baby food)
  - Grade 3: Able to swallow liquids only
  - Grade 4: Unable to swallow liquids or saliva
- Dysphagia arising from esophageal cancer most often is due to obstruction, but on occasion may be primarily due to tumor-related dysmotility.
- Patients with dysphagia who are not candidates for curative surgery should be considered for palliation of their dysphagia symptoms, based on symptom severity. This can be achieved through multiple modalities, although placement of an esophageal stent is most commonly utilized. In contrast, stent placement is generally not advised in patients who may undergo curative surgery in the future due to concerns that stent-related adverse events may preclude curative surgery in the future.

《Esophageal cancer guideline-10》

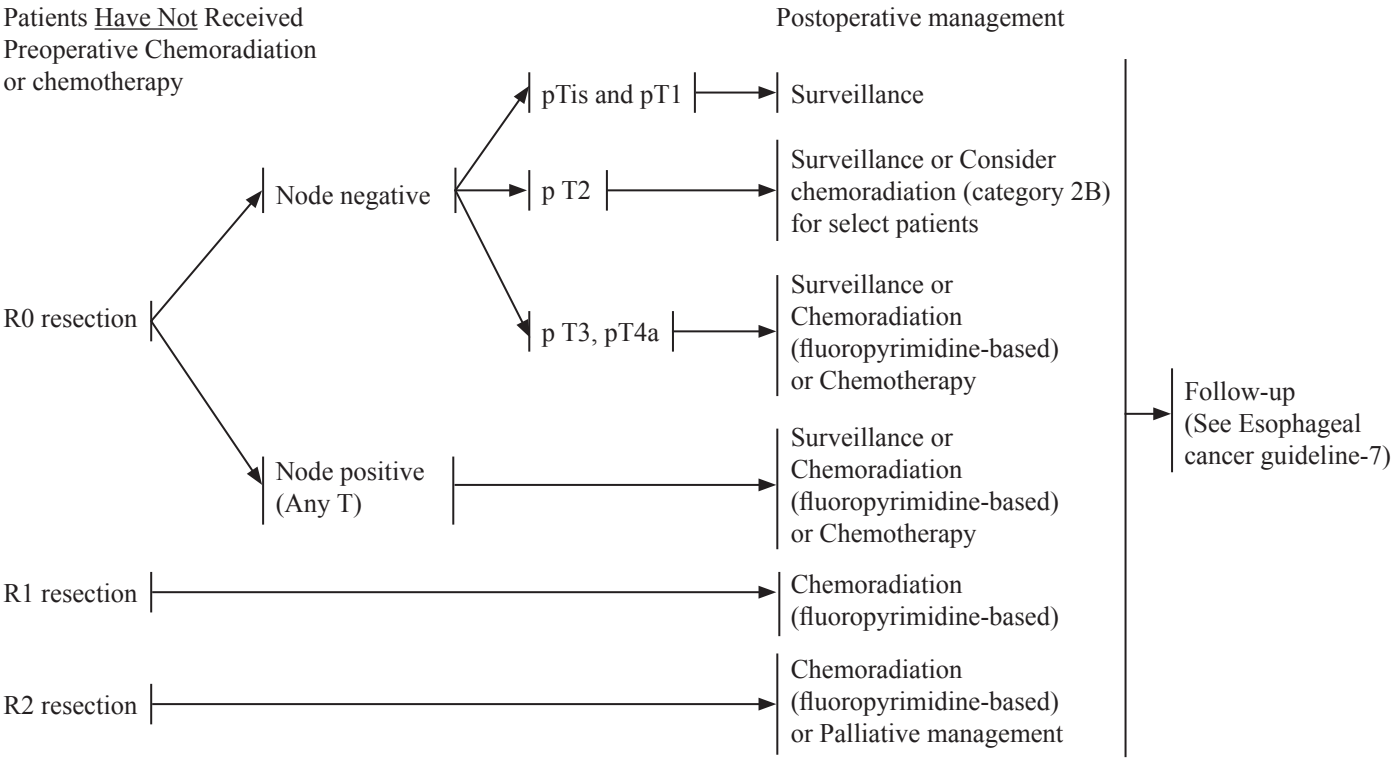
Adenocarcinoma: primary treatment for medically fit surgery patients



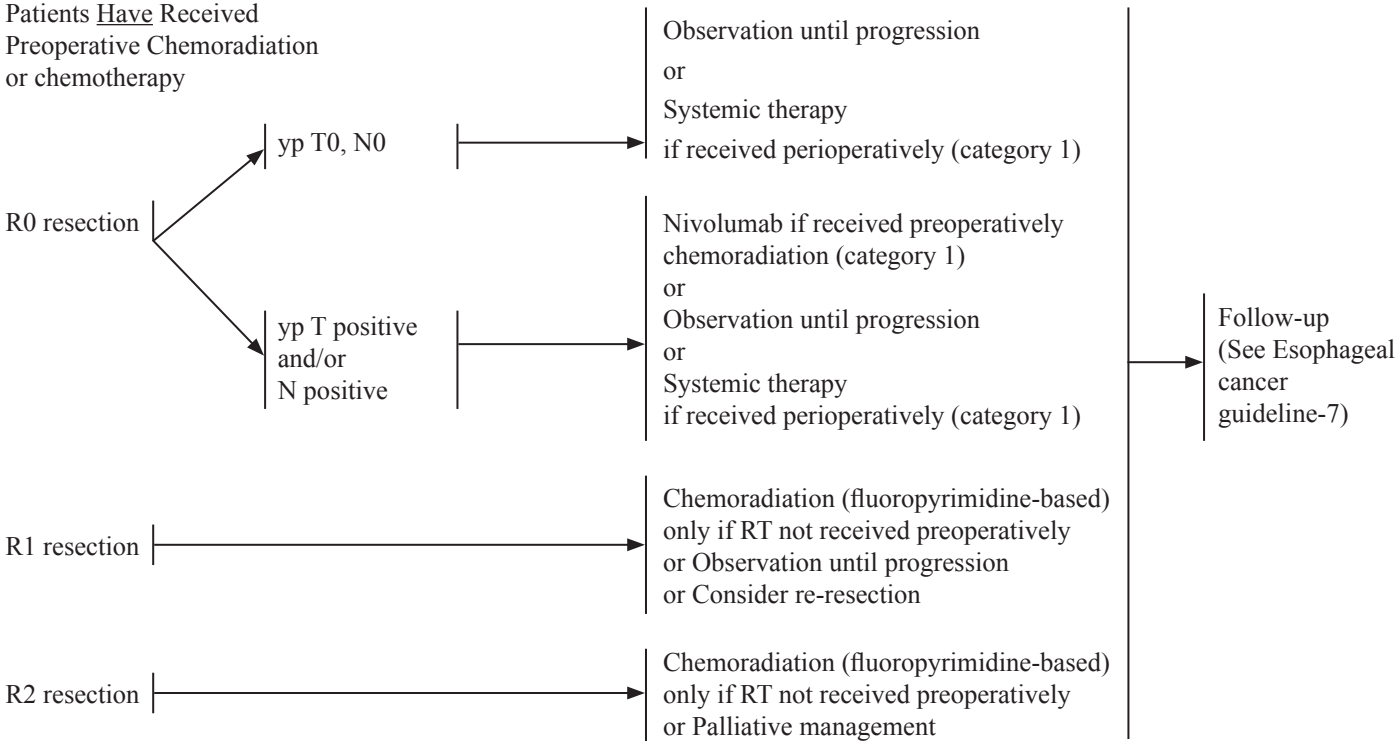
Adenocarcinoma: response assessment



Adenocarcinoma: surgical outcomes



Adenocarcinoma: surgical outcomes



Principles of Endoscopic Staging and Therapy

Treatment of Symptoms

- Esophageal dilation can be performed with the use of dilating balloons or bougies to temporarily relieve obstruction from tumors, or treatment-related strictures. Caution should be exercised to avoid overdilation, to minimize the risk of perforation.
- Long-term palliation of dysphagia can be achieved with endoscopic tumor ablation by Nd:YAG laser, PDT and cryoablation, or endoscopic and radiographic-assisted insertion of expandable metal or plastic stents.
- Long-term palliation of anorexia, dysphagia, or malnutrition may be achieved with endoscopic or radiographic-assisted placement of feeding gastrostomy or jejunostomy. The placement of a gastrostomy in the preoperative setting may compromise the gastric vasculature, thereby interfering with the creation of the gastric conduit in the reconstruction during esophagectomy and should be avoided.

Post-Treatment Surveillance

- Consider deferring assessment endoscopy with biopsy to 6 weeks or later after completion of preoperative therapy in patients whom avoidance of surgery is being considered.
- EUS exams performed after chemotherapy or radiation therapy have a reduced ability to accurately determine the present stage of disease. Similarly, biopsies performed after chemotherapy or radiation therapy may not accurately diagnose the presence of residual disease.
- Endoscopic surveillance following definitive treatment of esophageal cancer requires careful attention to detail for mucosal surface changes, and multiple biopsies of any visualized abnormalities. Strictures should be biopsied to rule out neoplastic cause. EUS-guided FNA should be performed if suspicious lymph nodes or areas of wall thickening are seen on cross-sectional imaging.
- Endoscopic surveillance after ablative therapy or ER of early-stage esophageal cancer should continue after completion of treatment. Biopsies should be taken of the neosquamous mucosa even in the absence of mucosal abnormalities as dysplasia may occasionally be present beneath the squamous mucosa.
- Endoscopic surveillance should also include a search for the presence of Barrett esophagus and four-quadrant biopsies to detect residual or recurrent dysplasia. The ablation of residual or recurrent high-grade and low-grade dysplasia using RFA or cryoablation should be considered.
- Patients who have received therapeutic ER should have endoscopic surveillance.

Principles of Pathologic Review

- The purposes of Pathologic review include ：
  - Classification of tumor
  - Determine the extent of invasion
  - Establish status of cancer involvement of surgical margins
- All surgical pathology reports should be in accordance with the WHO classification of esophageal cancer
- All surgical pathology reports should be in accordance with the WHO classification of esophageal cancer
- The surgical pathology report should include the following items
  - Histologic type
  - Histologic grade (G1: well differentiated; G2: moderately differentiated; G3: poorly differentiated)
  - Microscopic tumor extension
  - Margin status

Principles of Pathologic Review

The pathology report should include the following items depending on the specimen:

- Biopsy: invasion, if present; high-grade dysplasia in Barrett esophagus; histologic type; Grade; Presence or absence of Barrett esophagus; Universal testing for MSI by PCR/NGS or MMR by IHC is recommended in all newly diagnosed patients
- Endoscopic resection (ER): include all elements as for biopsy specimen plus the depth of tumor invasion; lymphovascular invasion (LVI), and the status of mucosal and deep margins; Universal testing for MSI by PCR/NGS or MMR by IHC is recommended in all newly diagnosed patients
- Esophagectomy, without prior chemoradiation: include all elements as for ER specimen plus the location of the tumor midpoint in relation to the EGJ, whether the tumor crosses EGJ, lymph node status, and the number of lymph nodes recovered; Universal testing for MSI by PCR/NGS or MMR by IHC is recommended in all newly diagnosed patients, if not previously performed
- Esophagectomy, with prior chemoradiation :
  - the tumor sites should be thoroughly sampled, with submission of entire EGJ or ulcer/tumor bed for specimens without grossly obvious residual tumor
  - For pathology report, include all elements as for esophagectomy without prior chemoradiation, plus assessment of the treatment effect
  - Assessment treatment effect: The modified Ryan scheme in the CAP Cancer Protocol for Esophageal Carcinoma

Description	Tumor Regression Score
No viable cancer cells (complete response)	0
Single cells or rare small groups of cancer cells (near complete response)	1
Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response)	2
Extensive residual cancer with no evident tumor regression (poor or no response)	3

Principles of Biomarker Testing

- Molecular testing of HER2 status, microsatellite instability (MSI) status, programmed death ligand 1 (PD-L1) expression, and NTRK gene fusion detection are used to predict locally advanced, unresectable, or metastatic esophageal and EGJ cancers clinical treatment drug selection.
- Assessment of overexpression or amplification of Her2 in Esophageal and EGJ Cancer
  - For patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of esophagus or EGJ for whom trastuzumab therapy is being considered
  - Immunohistochemical criteria for scoring HER2/neu expression

	Surgical Specimen Expression Pattern, Immunohistochemistry	Biopsy Specimen Expression Pattern, Immunohistochemistry	HER2 Overexpression Assessment
0	No reactivity or membranous reactivity in <10% of cancer cells	No reactivity or no membranous reactivity in any cancer cell	Negative
1+	Faint or barely perceptible membranous reactivity in ≥10% of cancer cells; cells are reactive only in part of their membrane	Cluster of five or more cancer cells with a faint or barely perceptible membranous reactivity irrespective of percentage of cancer cells positive	Negative
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in ≥10% of cancer cells	Cluster of five or more cancer cells with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Equivocal
3+	Strong complete, basolateral, or lateral membranous reactivity in ≥10% of cancer cells	Cluster of five or more cancer cells with a strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Positive

  - HER2 IHC is performed first, followed by FISH methods in cases showing 2+ (equivocal) expressions by IHC. Cases with HER2: CEP17 ratio >=2 or an average HER2 copy number >=6.0 signals/cell are considered positive by FISH.

Principles of Biomarker Testing

◆ *Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing:*

- Universal testing for MSI by polymerase chain reaction (PCR), NGS, or MMR by IHC should be performed for all newly diagnosed esophageal and EGJ cancers. The testing is performed on formalin-fixed paraffin-embedded (FFPE) tissue and results are interpreted as MSI-high (MSI-H) or mismatch repair-deficient (dMMR) in accordance with CAP DNA Mismatch Repair Biomarker Reporting Guidelines. Testing should be performed only in Clinical Laboratory Improvement Amendments (CLIA)-approved laboratories. Patients with MSI-H or dMMR tumors should be referred to a genetics counselor for further assessment in the appropriate clinical context.
- MMR Interpretation
  - ◊ No loss of nuclear expression of MMR proteins: No evidence of dMMR (low probability of MSI-H)
  - ◊ Loss of nuclear expression of one or more MMR proteins: dMMR
- MSI Interpretation
  - ◊ MSI-stable (MSS)
  - ◊ MSI-low (MSI-L)
  - – 1%–29% of the markers exhibit instability
  - – 1 of the 5 National Cancer Institute (NCI) or mononucleotide markers exhibits instability
  - ◊ MSI-H
  - – ≥ 30% of the markers exhibit instability
  - – 2 or more of the 5 NCI or mononucleotide markers exhibit instability

◆ *PD-L1 Testing:*

- PD-L1 IHC testing may be considered on locally advanced, recurrent, or metastatic esophageal and EGJ cancer in patents who are candidate for treatment with PD-1 inhibitors
- Assessment of PD-L1 Protein Expression
  - Pembrolizumab as a second-line treatment option for esophageal SCC with PD-L1 expression levels by combined positive score (CPS) of >=10, and as a third-or subsequent-line treatment option for EGJ adenocarcinoma with PD-L1 expression levels by CPS >=1, as determined by an FDA-approved companion diagnosed test
  - CPS is determined by

$$\text{CPS} = \frac{\text{\# of PD-L1-positive cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# of tumor cells}} \times 100$$

Principles of Biomarker Testing

◆ *Next-Generation Sequencing (NGS):*

- At present, several targeted therapeutic agents, trastuzumab,i pembrolizumab/nivolumab,m and entrectinib/larotrectinib, selpercatinib, and dabrafenib/trametinib, have been approved by the FDA for use in esophageal and EGJ cancers. Trastuzumab is based on testing for HER2 overexpression. Use of select immune checkpoint inhibitors is based on testing for MSI by PCR or NGS/MMR by IHC, PD-L1 immunohistochemical expression, or high tumor mutational burden (TMB) by NGS. The FDA granted approval for the use of select TRK inhibitors for NTRK gene fusion-positive solid tumors, and selpercatinib for RET gene fusion-positive tumors. Dabrafenib/trametinib has been approved for tumors with BRAF V600E mutations. When limited tissue is available for testing, or the patient is unable to undergo a traditional biopsy, sequential testing of single biomarkers or use of limited molecular diagnostic panels may quickly exhaust the sample. In these scenarios, comprehensive genomic profiling via a validated NGS assay performed in a CLIA-approved laboratory may be used for the identification of HER2 amplification, MSI status, MMR deficiency, TMB, NTRK gene fusions, RET gene fusions, and BRAF V600E mutations. The use of IHC/ISH/targeted PCR should be considered first followed by NGS testing as appropriate.

◆ *Liquid Biopsy*:

- The genomic alterations of solid cancers may be identified by evaluating circulating tumor DNA (ctDNA) in the blood, hence a form of "liquid biopsy." Liquid biopsy is being used more frequently in patients with advanced disease, particularly those who are unable to have a clinical biopsy for disease surveillance and management. The detection of mutations/alterations in DNA shed from esophageal and EGJ carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. Therefore, for patients who have metastatic or advanced esophageal/esophagogastric cancers who may be unable to undergo a traditional biopsy or for disease progression monitoring, testing using a validated NGS-based comprehensive genomic profiling assay performed in a CLIA-approved laboratory may be considered. A negative result should be interpreted with caution, as this does not exclude the presence of tumor mutations or amplifications.

Principles of Biomarker Testing

- Assessment of *NTRK* gene fusions:
  - The FDA granted approval for the use of select TRK inhibitors for *NTRK* gene fusion-positive solid tumors
  - A two-step approach is used, which includes IHC first and confirmation of any positivity detected with IHC by Next generation sequencing (NGS)
  - TRK IHC as a screening tool:
    - IHC negative: No TRK expression
    - IHC positive: Detection of TRK expression, confirmation by NGS

- If there are only a small amount of tissue (biopsy specimen) available for testing different types of biomarkers, it is recommended that clinicians specify on the pathology application form when ordering the test. In addition to H&E stain, tissue blanks should be reserved for the same pathological tissue section to avoid wax staining. Blocks are processed multiple times, causing tumor cell consumption.

Principles of Endoscopic Staging and Therapy

1. Patients with esophageal squamous cell carcinoma must undergo an upper gastrointestinal tract examination by an endoscopist who specializes in image enhancement technology IEE when initially diagnosed. Endoscopy is performed to confirm whether there are other cancers and precancerous lesions originating from the mucosa. (workup)
2. All patients with esophageal cancer should consult a gastroenterologist to discuss whether to perform endoscopic or surgical gastroenterostomy before undergoing surgery or CCRT to take into account the patient's nutritional status before and after treatment .(Principles of surgery)
3. Before receiving treatment for esophageal cancer, EUS diagnosis should be performed except for patients who have been clearly confirmed to be M1 (such as CT scan, PET scan) (workup)
4. Regarding early esophageal cancer,the absolute indications for endoscopic resection are that the tumor depth is limited to the m1 and m2 layers, and LN(-); the relative indications are that the tumor depth is limited to the m3 and sm1 layers, and LN(-); unable If the situation is clear, diagnostic ESD may be considered .
5. If sufficient tissue is available after the above tests are completed, a second test using NGS may be considered.
6. If LN(+) is found on EUS in patients with esophageal cancer, FNA/FNB can be optionally performed.
7. After CCRT for esophageal cancer, EUS can be optionally added for re-staging (optional).
8. Palliative endoscopic treatment (such as metal stent expansion, argon plasma coagulation, local ablation, etc.) should be discussed in the esophageal cancer multidisciplinary team meeting and then implemented.

Principles of Surgery

◆ Acceptable surgical procedures for resection of esophageal and gastric junction tumors

- Ivor Lewis esophagogastrectomy
- McKeown esohagogastrectomy
- Minimally invasive Ivor Lewis esophagogastrectomy
- Minimally invasive McKeown esophagogastrectomy
- Transhiatal esophagogastrectomy
- Robotic minimally invasive esophagogastrectomy
- Left transthoracic or thoracoabdominal approaches with anastomosis in chest or neck

◆ Acceptable substitutes for esophageal reconstruction

- Stomach (preferred)
- the large intestine
- Jejunum

◆ Acceptable lymphadenectomy methods

- Standard way
- Expansion mode (overall En-bloc mode)

◆ At least 15 or more lymph nodes need to be removed or evaluated to achieve appropriate lymphatic staging. If you have received radiochemotherapy before surgery, although the appropriate number of lymph nodes that need to be removed or evaluated is still unknown, it is still recommended to remove or evaluate more than 15 lymph nodes. of lymph nodes

◆ After definitive chemoradiation , if the patient still has resectable local tumors without distant metastasis, esophageal resection can be considered

◆ Esophagectomy, endoscopic esophageal mucosal resection, and other cautery procedures should be performed by experienced surgeons or endoscopists in a high-volume esophageal treatment center

Reference for principles of surgery

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9. Wang BY, Goan YG, Hsu PK, Hsu WH, Wu YC. Tumor length as a prognostic factor in esophageal squamous cell carcinoma. Ann Thorac Surg. 2011;91:887-93. (SCI)

Follow-up

- **History and Physical examination**
  - Every 3 to 6 months for 1 to 2 years.
  - Every 6 to 12 months for 3 to 5 years.

- **Clinical examination**
  - Chemistry profile and CBC, as clinically indicated.
  - Imaging studies as clinically indicated.
  - Upper GI endoscopy and biopsy as clinically indicated.
  - Dilatation for anastomotic stenosis.
  - Nutritional assessment and counseling.

Radiotherapy guideline for esophargeal cancer

一、Treated area

1. Esophageal tumor
2. Regional lymphadenopathy
3. High risk lymphatic region

二、Total dose / fractions

▲ Post-operative adjuvant therapy

1. Total dose

(a) Residual tumor / Primary tumor bed：50 Gy (50~50.4 Gy) *

(b) High risk area：48 Gy (45~50.4 Gy)

(c) Irradiated fractions：27 fx (25~30 fx)

▲ Definitive radiotherapy

1. Total dose

(a) Tumor：50 Gy (50~50.4 Gy) *

(b) High risk area：48 Gy (45~50.4 Gy)

(c) Irradiated fractions：27 fx (25~30 fx)

*Cervical esophageal cancer may increased dose up to 60~66 Gy；middle to lower esophageal cancer may increased dose up to 60 Gy。

▲ Pre-operative neoadjuvant radiotherapy

1. Total dose

(a) Tumor：48 Gy (45~50.4 Gy)

(b) High risk area：48 Gy (45~50.4 Gy)

(c) Irradiated fractions：27 fx (25~30 fx)

or

2. Total dose

(a) Tumor：41.4 Gy

(b) High risk area：41.4 Gy

(c) Irradiated fraction：23 fx

三、Irradiation technique :

Using intensity modulated radiotherapy, volumetric modulated arc therapy, tomotherapy or proton therapy and cooperation with image guide radiotherapy. High dose area may be treated concomitantly or sequentially.

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