Esophageal and Esophagogastric Junction Cancer

Pretreatment Workup

WORKUP

- H &P
- Upper GI endoscopy and biopsy
- ChestCT with oral and IV contrast(if no contraindications)
- PET-CT evaluation
- CBC and Chemistry profile
- Endoscopic ultrasound(EUS)(M1 病人可免做)
- Endoscopic mucosal resection is essential for the accurate staging of early stage cancers(T1a or T1b)
- Biopsy of metastatic disease as clinically indicated
- MSI by PCR/MMR by IHC, and PD-L1 testing(preferred for documented/suspected metastatic disease)
- HER2-neu testing if metastatic adenocarcinoma is documented/ suspected
- If sufficient tissue is available after the above testing has been completed, 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, conseling, and pharmacotherapy as indicated
- Screen for family history(preferred)

Pretreatment Workup

CLINICAL STAGE

Stage I-IVA(Locoregional disease, except T4b or unresectable N3)

- Squamous cell carcinoma
- Adenocarcinoma

→ Multidisciplinary evaluation
- Consider enteric feeding tube* for preoperative nutrition support
- Laparoscopy(optional) If no evidence of M1 disease and tumor is at EGJ

→ Medically fit for surgery
- → Squamous cell Ca (See Esophageal cancer guideline -2)
- → Adenocarcinoma (See Esophageal cancer guideline -9)

→ Non- surgical candidate (See Esophageal cancer guideline -6)

Stage IVA(including T4b or unresectable N3) & IVB(metastatic disease)

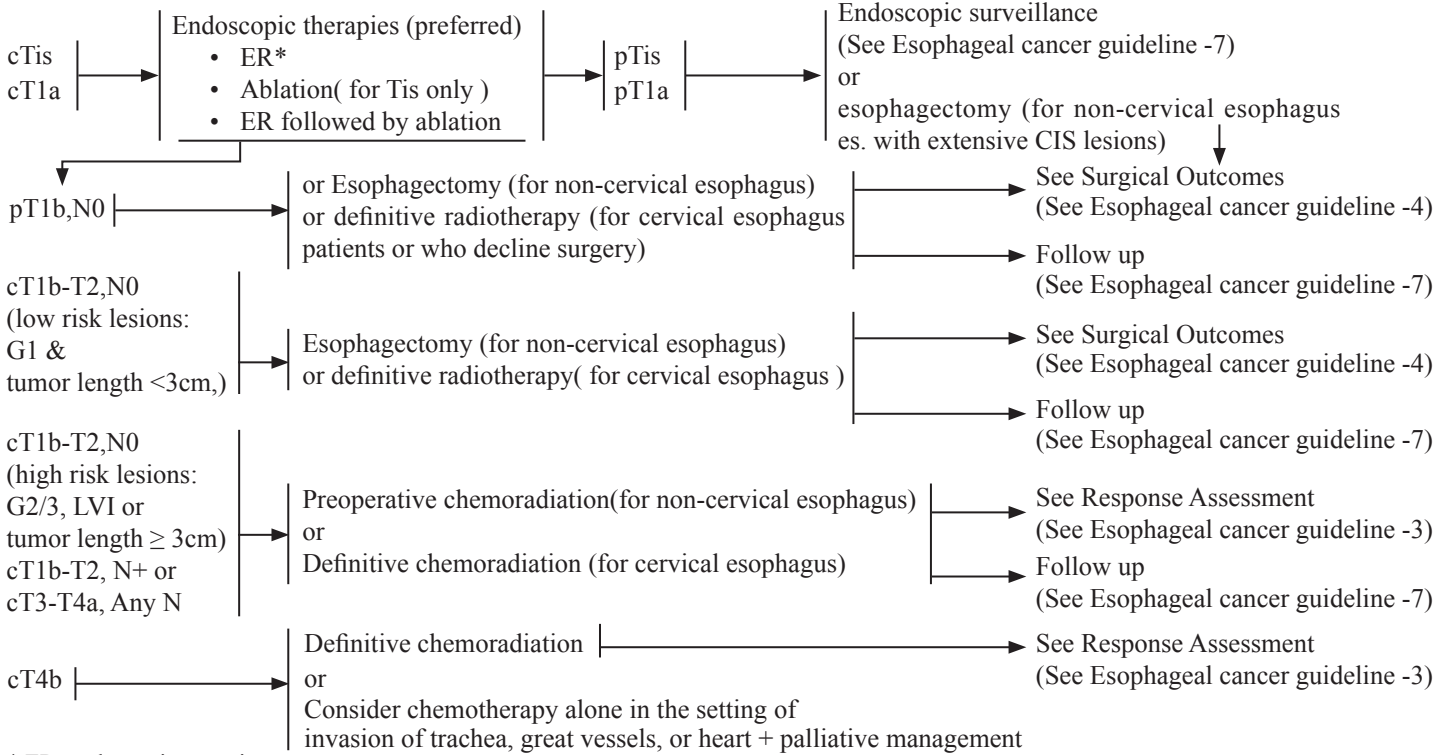
- Squamous cell carcinoma
- Adenocarcinoma

→ (See Esophageal cancer guideline -8)

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

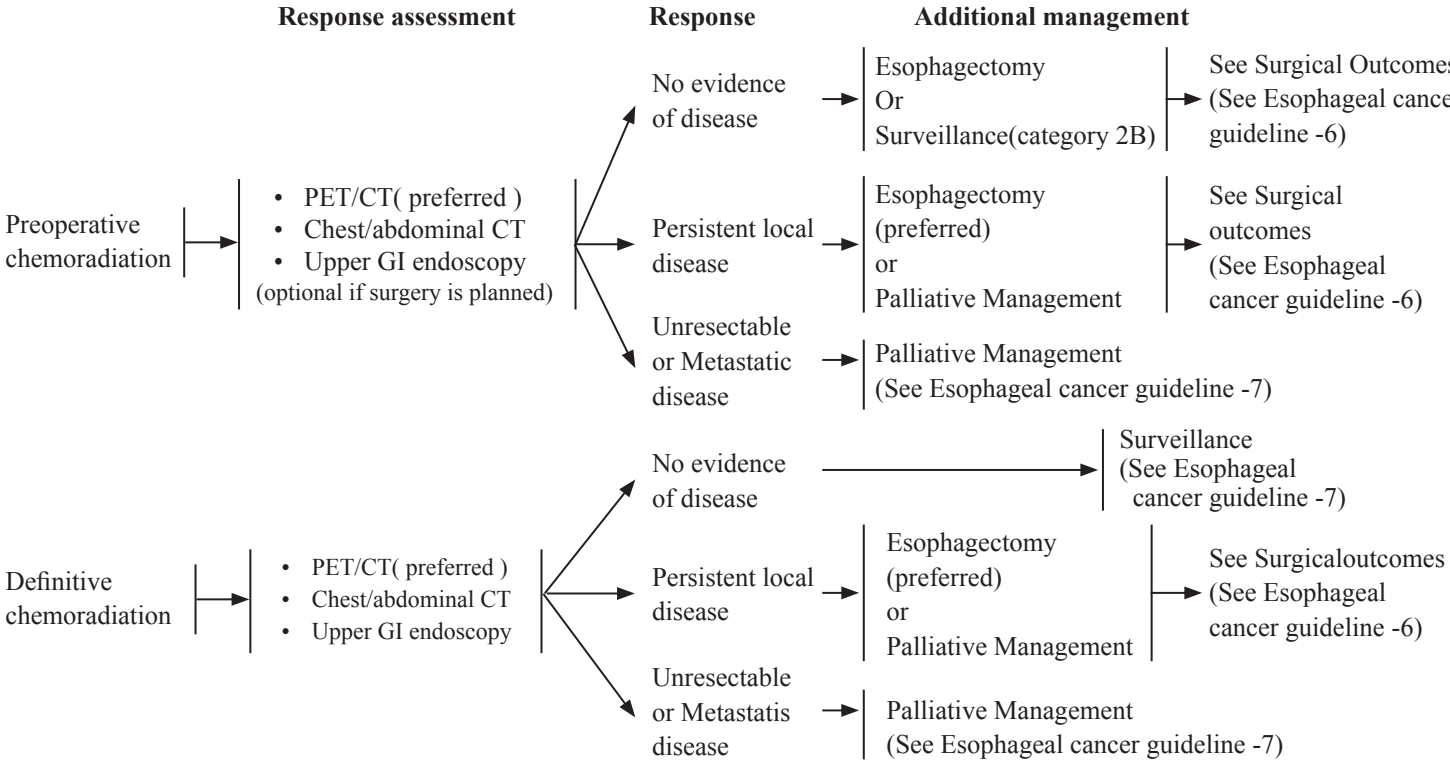
《Esophageal cancer guideline-2》

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



* ER: endoscopic resection

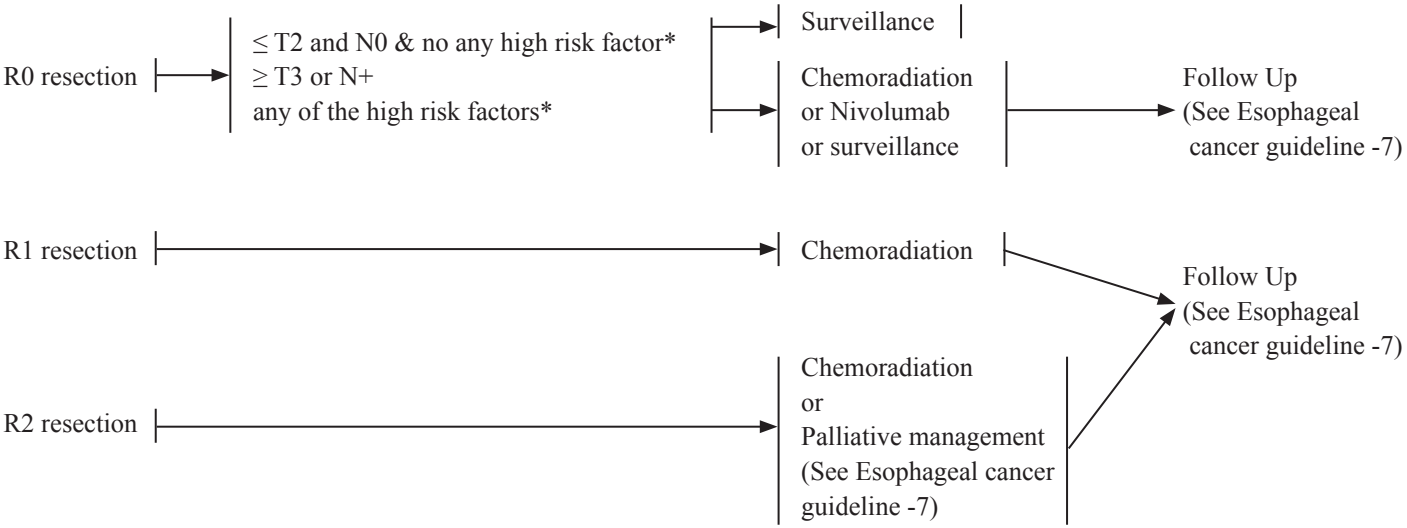
Squamous cell carcinoma: response assessment



《Esophageal cancer guideline-4》

Squamous cell carcinoma: surgical outcomes

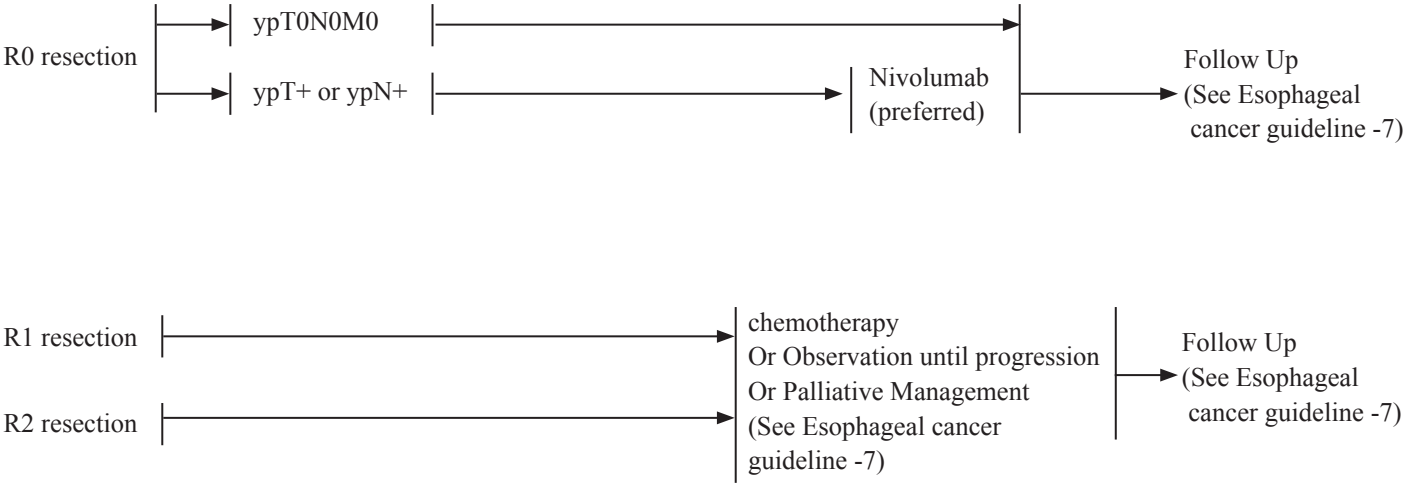
Patients **Have Not** Reveived Preoperative Chemoradiation



*High risk factors: close circumferential/surgical margin, LVI, perineural invasion, extracapsular nodal extension

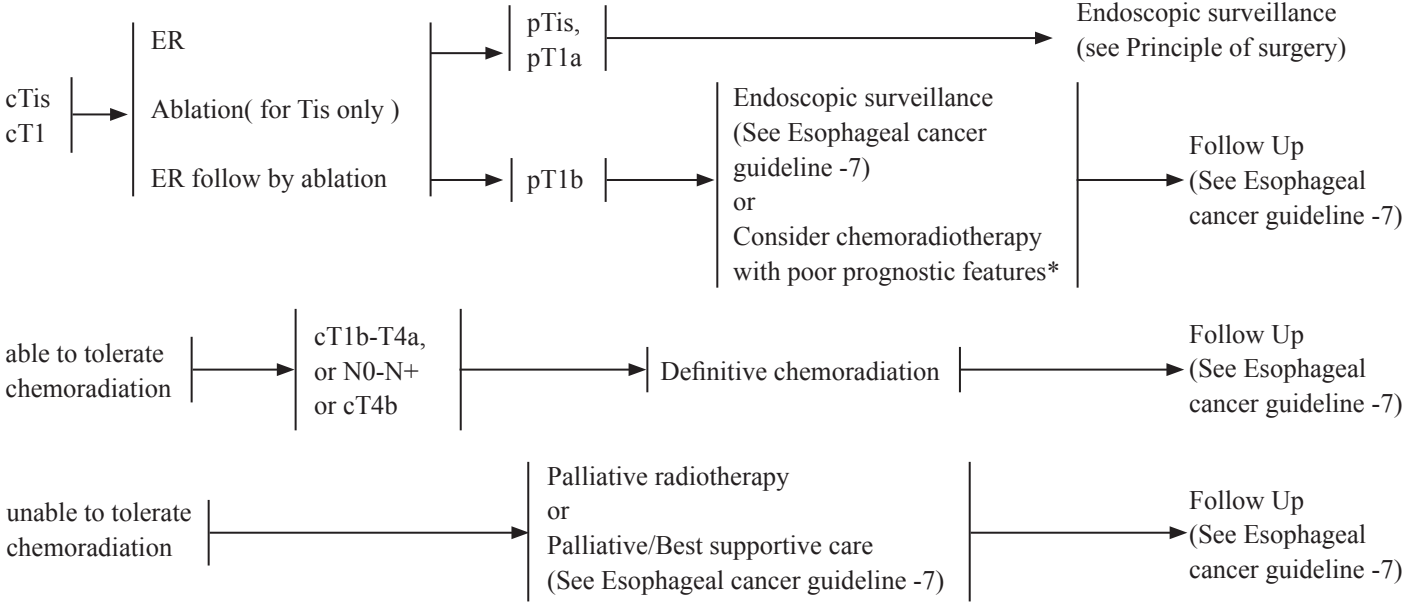
Squamous cell carcinoma: surgical outcomes

Patients **Have** Reveived Preoperative Chemoradiation



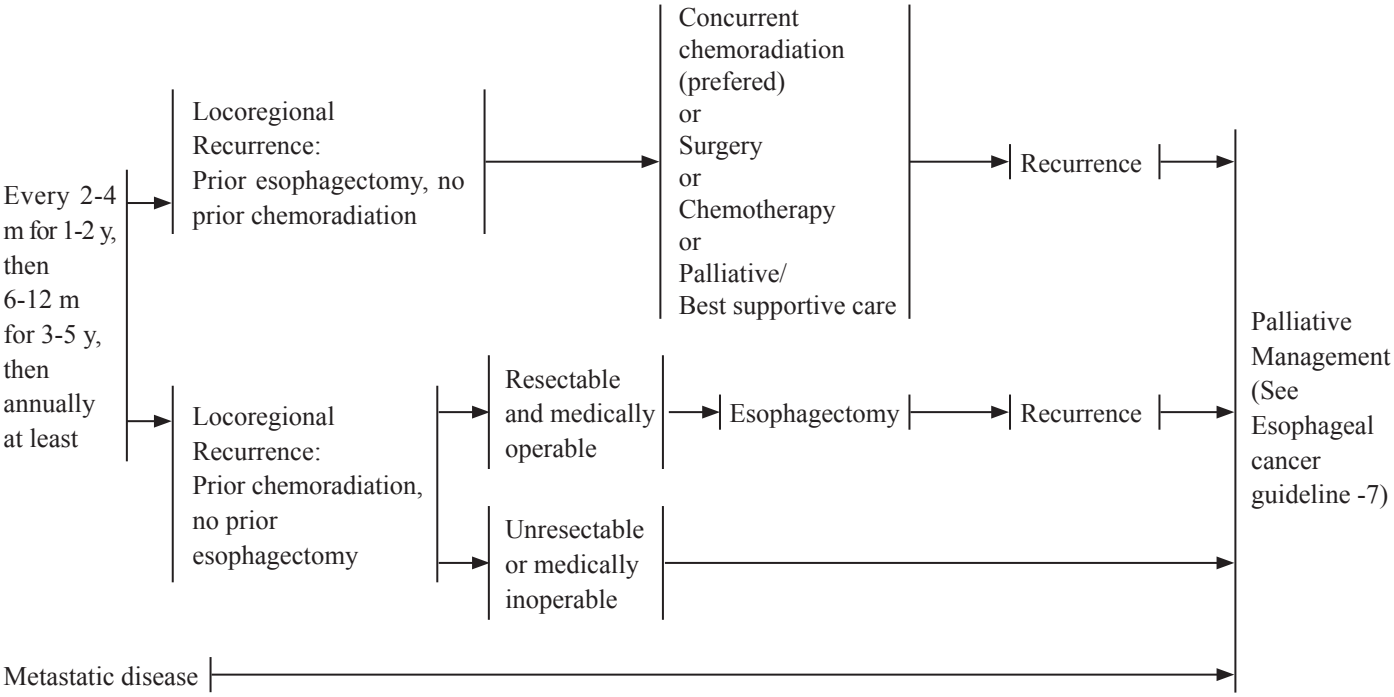
《Esophageal cancer guideline-6》

Squamous cell carcinoma & adenocarcinoma : Non- surgical candidate



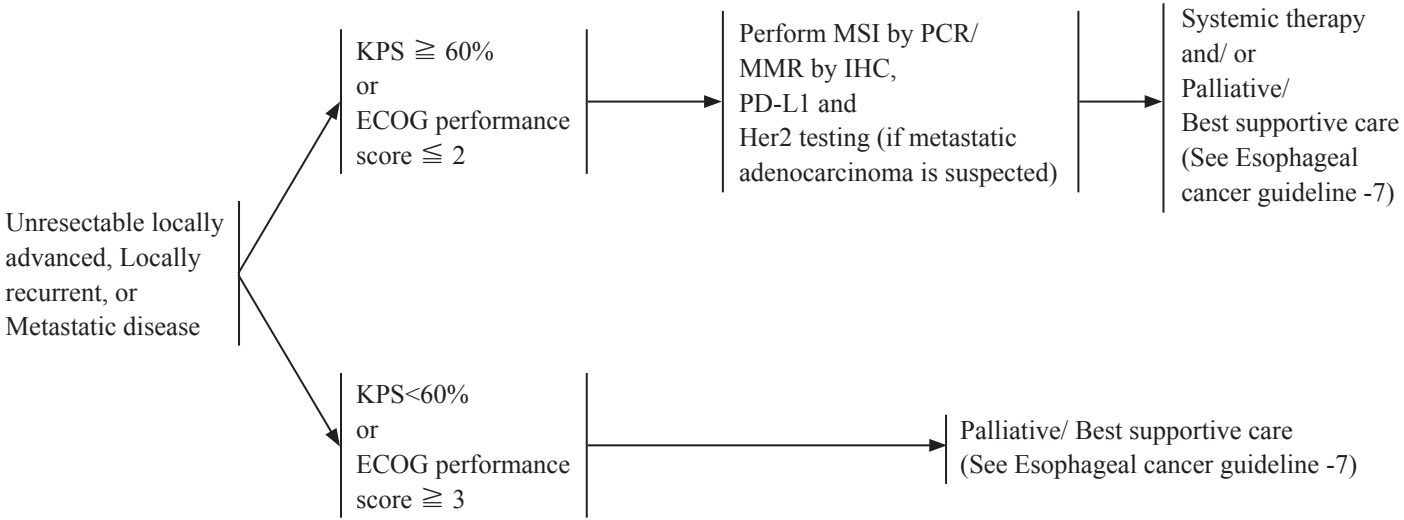
* Poor prognostic features: positive margin(s), max. tumor diameter > 2cm, G2/3, LVI or more

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



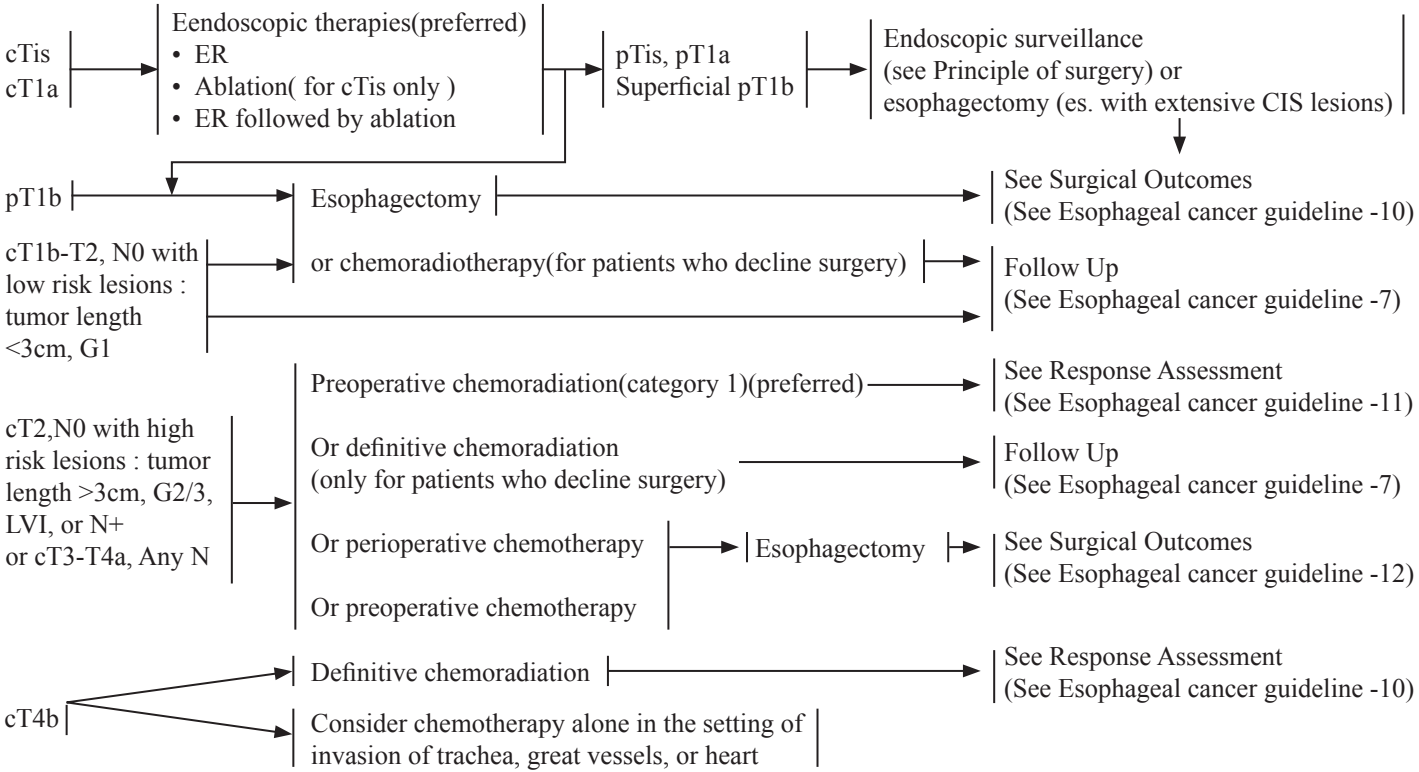
《 Esophageal cancer guideline-8》

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



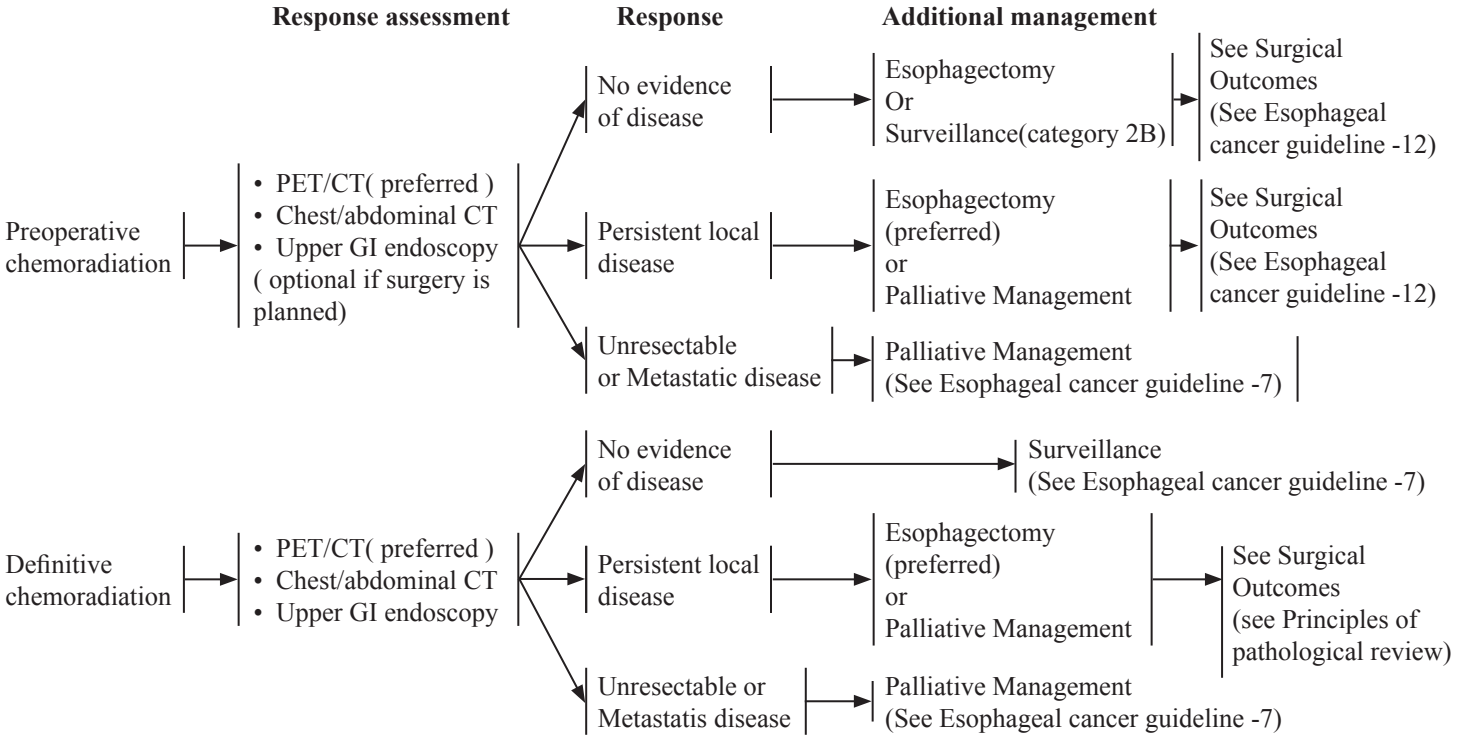
《 Esophageal cancer guideline-9》

Adenocarcinoma: primary treatment for medically fit for surgery patients

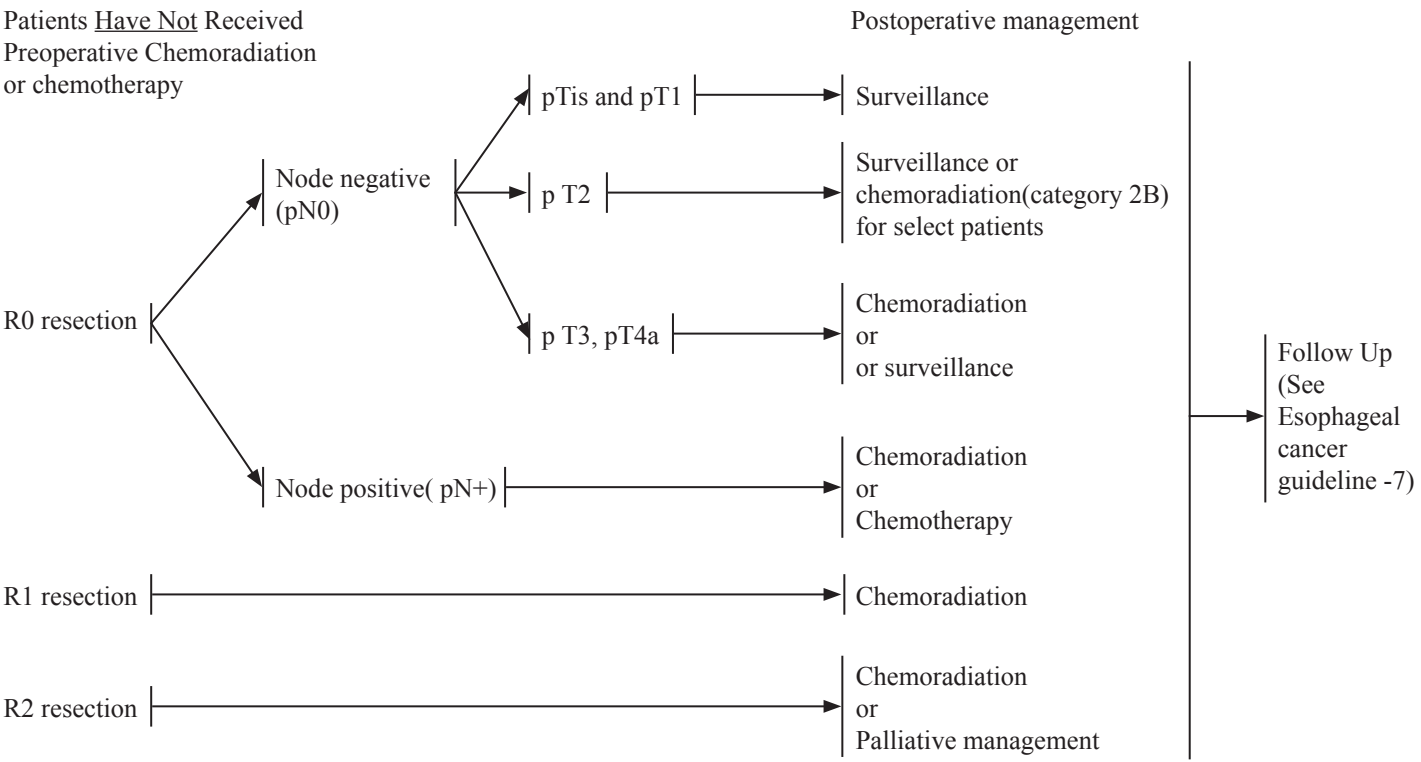


《Esophageal cancer guideline-10》

Adenocarcinoma: response assessment

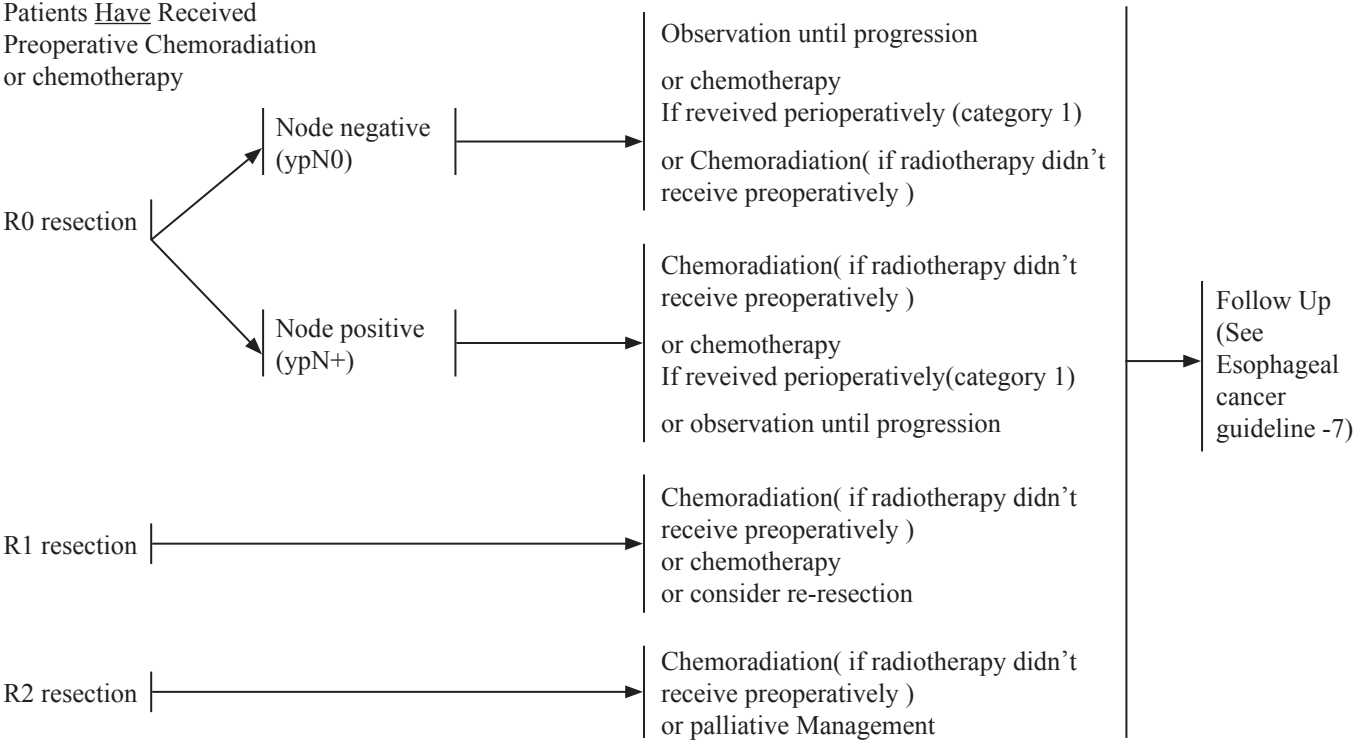


Adenocarcinoma: surgical outcomes



《Esophageal cancer guideline-12》

Adenocarcinoma: surgical outcomes



Principles of pathological review

- Pathology review 的目的包括：
  - Classification of tumor
  - Determine the extent of invasion
  - Establish status of cancer involvement of surgical margins
- 所有手術病理報告都應該依照食道癌 WHO 分類
- 所有手術病理報告都應該依 AJCC/UICC TNM 8th edition 分期
- 手術病理報告應包括下列項目
  - Histologic type
  - Histologic grade (G1: well differentiated; G2: moderately differentiated; G3: poorly differentiated)
  - Microscopic tumor extension
  - Margin status

Principles of pathological review

- 病理報告根據標本的不同應包括下列項目：
- Biopsy: invasion, if present; high-grade dysplasia in Barrett esophagus; histologic type; Grade; Presence or absence of Barrett esophagus
- 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
- 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
- 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: 術前治療反應與預後相關。目前採用 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

- HER2 狀態，微衛星不穩定性（MSI）狀態的分子測試，程序性死亡配體 1（PD-L1）表達和 NTRK 基因融合檢測被用於預測局部晚期，不可切除或轉移性食道癌和 EGJ 癌的臨床治療用藥選擇
- 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

- Mismatch Repair (MMR) Testing:
  - MMR by IHC should be considered on locally advanced, recurrent, or metastatic esophageal and EGJ cancer in patents who are candidate for treatment with PD-1 inhibitors
  - MMR status is assessed by IHC staining performed on formalin-fixed , paraffin-embedded (FFPE) tissue to measure levels of proteins involved in DNA mismatch repair including MLH1, MSH2, MSH6, and PMS2
  - MMR IHC interpretation
    - No loss of nuclear expression of MMR proteins: No evidence of deficient mismatch repair (low probability of MSI-H)
    - Loss of nuclear expression of one or more MMR proteins: deficient mismatch repair
- 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

- 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

- 若只有少量組織 (biopsy specimen) 可供檢測不同種類的 biomarker， 建議臨床醫師開立檢測請在病理申請單註明，同一次病理組織切片除了 HE，應預留組織空白片，以避免因蠟塊多次處理，造成腫瘤細胞消耗

Principles of Endoscopic staging and therapy

1. 食道鱗狀細胞癌病患，在初步確診時，必須由專精影像強化技術 IEE 的內視鏡醫師進行一次上消化道內視鏡精查，以確認是否同時存在其他源於黏膜的癌症及癌前病變。(work up)
2. 所有食道癌等病患，在進行手術或 CCRT 前，應會診胃腸科醫師討論是否施行內視鏡或外科性胃腸造口，以顧全病患治療前後的營養狀態。(principle of surgery)
3. 食道癌在接受治療前，除了已明確證實爲 M1 的病人外（如 CT scan、PET scan），應進行 EUS 診斷。(work up)
4. 關於早期食道癌：適用內視鏡切除的絕對適應症爲腫瘤深度侷限在 m1、m2 層，且 LN(-)；相對適應症爲腫瘤深度侷限在 m3、sm1 層，且 LN(-)；無法辨明情況下，可考慮行 diagnostic ESD。
5. 如果在上述測試完成後有足夠的組織可用，可以考慮用 NGS 做第二次檢測。
6. 食道癌病患若 EUS 發現 LN(+)，可選擇性加做 FNA/FNB。
7. 食道癌 CCRT 之後，可選擇性加做 EUS 做 re-staging。(optional)
8. 姑息性的內視鏡治療（例如：金屬支架擴張術、氬氣電漿凝固術局部消融…等），應於食道癌多科團隊會議中提出討論後執行。

註一：執行上消化道內視鏡精查時，應備有擴大型內視鏡、魯格爾試液（Lugol’s solution）、稀釋醋酸、影像強化光源（例如 NBI、BLI 等），由具早期癌判斷能力的內視鏡醫師執行並撰寫報告。

註二：巴瑞特氏食道病患，須例行接受上消化道內視鏡精查，以確認是否發生癌變，精查應由專精影像強化技術 IEE 的內視鏡醫師執行。（有 dysplasia 者至少每年一次，無 dysplasia 者至少每三年一次。）

註三：應由食道癌共識會議向三院相關癌症多科團隊提出診療建議「所有口腔癌（含舌癌）、頭頸癌、下咽癌、喉癌等病患，在初步確診時及術後至少每年，必須由專精影像強化技術 IEE 的內視鏡醫師進行一次上消化道內視鏡精查，以確認是否同時存有食道癌及癌前病變。」

Principle of surgery

- 手術前之臨床分期應使用胸腹部電腦斷層， 正子電腦斷層掃描 (PET-CT）及內視鏡超音波，以評估可否切除
- 治療前所有病患皆需諮詢胸腔外科醫師，接受是否可以耐受食道切除之生理評估
- 所有生理狀態適合食道切除，且爲局部可切除之胸腔 (超過環咽部 5 公分以下) 及腹腔食道癌患者，皆應考慮手術切除
- 食道交接處 (EGJ) 腺癌之病患皆應有 Siewert 分類
  - Siewert Type I: adenocarcinoma of the lower esophagus with the epicenter location located within 1cm to 5 cm above the anatomic EGJ
  - Siewert Type II: true carcinoma of the cardia with the tumor epicenter within 1 cm above and 2 cm below the EGJ
  - Siewert Type III: subcardial carcinoma with the tumor epicenter between 2 cm and 5 cm below the EGJ, which infiltrates the EGJ and lower esophagus from below
- Siewert type I 及 II 腫瘤應遵從食道癌及胃食道交接癌治療準則。 Siewert type III 則視爲胃癌，應遵從胃癌治療準則，然某些狀況下需增加部分食道切除，以獲取適當的之切除距離
- 腹腔內視鏡可以偵測放射線影像檢查無法找到之潛伏轉移病灶（Occult metastatic disease) 尤其是 Seiwert type II 及 III 腫瘤
- 腹膜積液細胞學檢查陽性與不良預後相關，應視爲 M1 疾患。患者若爲進展期之腫瘤，臨床分期 T3 或 N+ 疾患，應考慮接受腹腔內視鏡腹膜沖洗分期檢查 (laparoscopic staging with peritoneal washings)。
- 頸部食道癌或不超過環咽部 (cricopharygeal) 5 公分以上之食道癌應該以決定性放射化療 (definitive chemoradiation) 治療

Principle of surgery

- 可切除的食道癌 Stage I-IVA(Locoregional disease, except T4b or unresectable N3) :
  - Tis or T1a 腫瘤 (可考慮 EMR+Ablation 或手術)
  - T1b 腫瘤
  - T1-T3 腫瘤，即使局部淋巴腺已經轉移，多區域 (multi-station) 淋巴腺或巨大 (bulky) 淋巴腺轉移爲手術切除之 relative contraindication ，可否切除尚應考慮，如年齡、體能狀態、或治療反應等其他因素
  - T4a 腫瘤，侵犯至肋膜、心包膜或橫隔膜

- 不可切除的食道癌 Stage IVA(including T4b or unresectable N3) & IVB(metastatic disease)
  - cT4b 腫瘤 : 侵犯心臟、大血管、氣管、或鄰近器官包括肝、胰、肺及脾臟
  - 多區域 (multi-station) 淋巴腺或巨大 (bulky) 淋巴腺侵犯，大多數應視爲不可切除，然而淋巴侵犯可否切除尚應考慮，如年齡、體能狀態、或治療反應等其他因素
  - EJG 腫瘤患者合併鎖骨上淋巴轉移應視爲不可切除
  - 轉移第 IV 期之食道癌 (包括非區域淋巴腺 non-regional lymph node 轉移）

- 食道切除方式之選擇取決於腫瘤位置、可選擇重建之器官，手術者之經驗及喜好，以及病患之喜好
- 病患在術前引導期間無法經口進食以維持營養者可考慮食道擴張或空腸造瘻 (J-tube)，優於胃造瘻術 (會妨礙往後胃重建手術時胃管之健全

Principle of surgery

- 可接受之食道及胃交接腫瘤切除術式
  - Ivor Lewis esophagogastrectomy (開腹及右側開胸）
  - McKeown esohagogastrectomy (右側開胸、開腹及頸部吻合)
  - Minimally invasive Ivor Lewis esophagogastrectomy (腹腔鏡及微創右側開胸)
  - Minimally invasive McKeown esophagogastrectomy (胸腔鏡、微創開腹 / 腹腔鏡及頸部吻合)
  - Transhiatal esophagogastrectomy (開腹不經胸腔及頸部吻合)
  - Robotic minimally invasive esophagogastrectomy (機器手臂輔助微創術式)
  - Left transthoracic or thoracoabdominal approaches with anastomosis in chest or neck(左側開胸或胸腹聯合術式、胸腔或頸部吻合)
- 可接受之食道重建取代物
  胃（優先選擇）
  大腸
  空腸
- 可接受之淋巴擴清方式
  標準方式
  擴展方式（整體 En-bloc 方式)
- 至少需移除或評估 15 個以上之淋巴結以達到適當的淋巴分期，然而若術前接受過放射化學治療，則適切的需移除或評估之淋巴結數量則仍然未知
- 患者經過決定性放射及化學治療後，如果沒有遠端轉移而發現可切除之局部復發，可以考慮姑息性的食道切除 (palliative esophagectomy)
- 食道切除，內視鏡食道黏膜切除，及其他燒灼術式，應在高容量之食道治療中心由有經驗的外科醫師或內視鏡醫師執行

Reference for principle of surgery

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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, then annually.

- Clinical examination

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