中山醫學大學附設醫院

食道癌診療指引

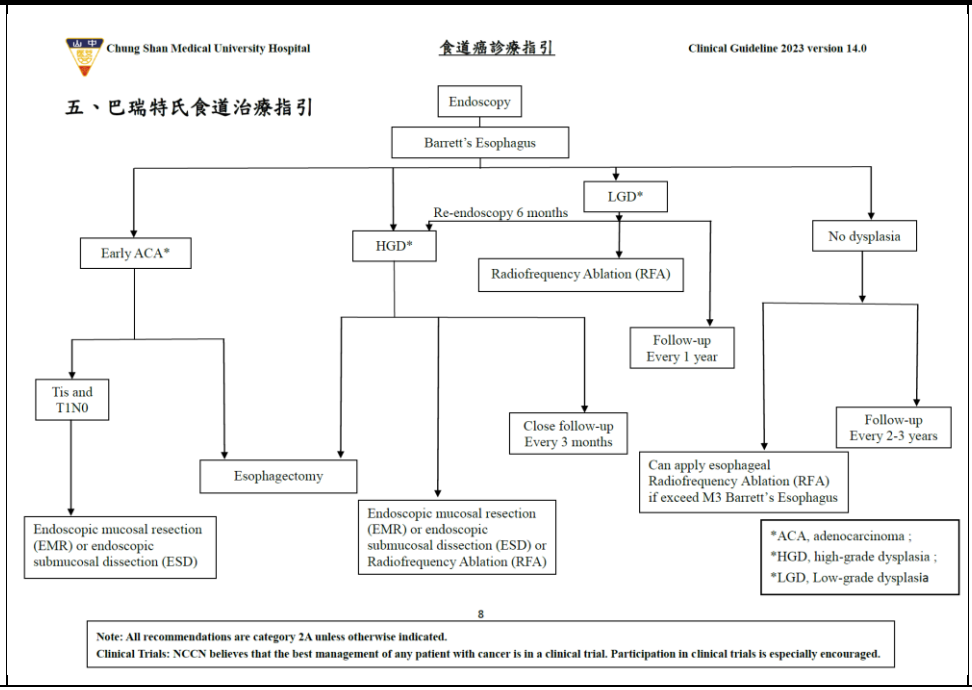
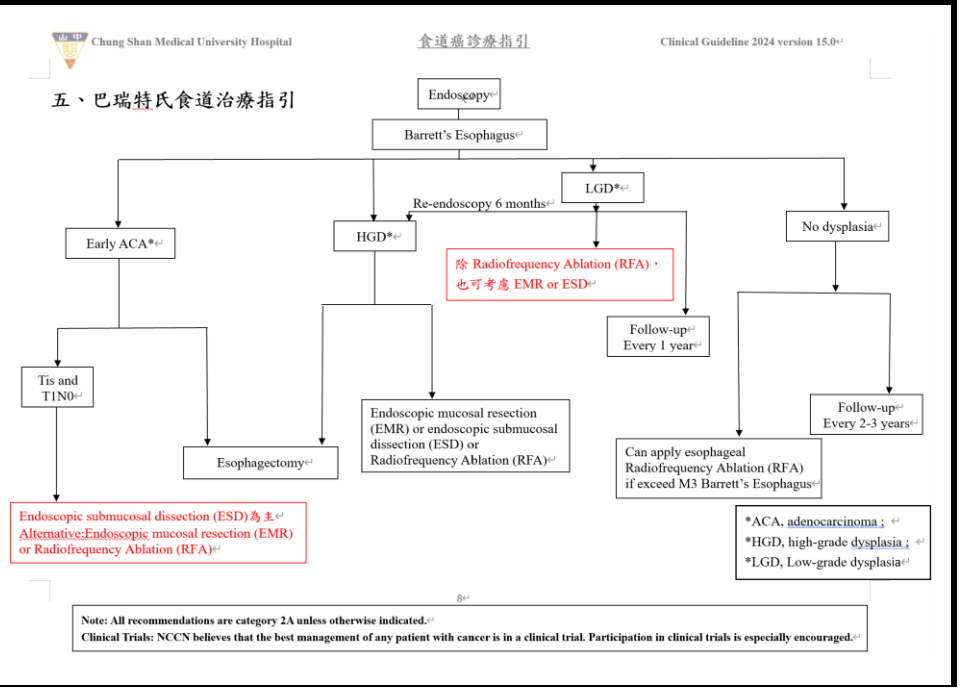
2023/12/14 Version15.0
2022/12/08 Version14.0
2021/12/09 Version13.0
2021/01/10 Version12.0
2019/12/12 Version11.0
2018/11/15 Version10.0
2017/12/21 Version9.0
2016/12/15 Version8.0
2015/12/01 Version7.0
2014/12/26 Version6.0
2013/12/27 Version5.0
2012/12/28 Version4.0
2011/12/02 Version3.0
2010/12/31 Version2.0

本臨床指引參考美國NCCN版本

食道癌多專科醫療團隊編修

癌症委員會主任委員	癌症委員會執行長	癌症中心主任	團隊負責人

修訂內容

頁數	原文	更新頁數	修訂/新增
第8頁		第8頁	

第20頁	• **Paclitaxel + Cisplatin** Cisplatin 60 mg/m² IV D1,29 Paclitaxel 50 mg/m² IV D1,8,15,and 29 Weekly for 5 weeks	第20頁	刪除此給藥方案

目錄

一、前言

根據統計，癌症為台灣十大死因首位，其中食道癌為十大癌症死因第九位。台灣地區九成食道癌屬鱗狀上皮細胞癌，其次為腺癌，好發於 50-70 歲人群，男性多於女性，致病原因和個人體質、生活習慣、飲食及環境皆有關聯。以喜歡吃刺激、醃製性或溫度較高食物者；或攝取蔬菜水果或維他命 A、C 不足者、微量元素如鋅的缺乏；此外高粱、玉米及茶葉中的鞣酸（Tan-nin），也被列為與食道癌有關的物質；飲水及食物中若含有過量的亞硝基氨（Nitrosamine），亦被證實會增加食道癌發生的風險。喝酒亦是食道癌的高危險因子，統計顯示喝酒引發食道癌是一般人的 2-4 倍，若合併菸、檳榔則罹癌風險高達 40 倍。胃食道逆流症或巴瑞特氏食道的患者，由於胃液反覆逆流到食道，長期刺激下，在食道下 1/3 段亦使黏膜受損造成食道癌，此類以腺癌占多數。曾患頭頸癌的患者，根據統計其發生的第二癌症，有 1/3 是在食道發生，兩者皆與吸菸有關。食道弛緩不能（食道擴約肌的運動能力降低）的患者，比一般人發生食道癌的機率高出 6-14%。曾有食道腐蝕性傷害，也較易引起食道癌的產生，其位置常見於食道中段。食道有豐富淋巴結及血流供應，多數患者因胃食道逆流、吞嚥困難及疼痛就診時，已是食道癌中晚期，且常併有體重減輕和營養不良等問題。

二、臨床症狀

1. 吞嚥困難：大多數患者，第一個症狀是在吃肉、麵包或粗糙的食物（如生蔬菜）時會覺得不易下嚥且不順暢的感覺，甚至會感到食物卡在胸骨的後方。隨著腫瘤生長，會使得食道漸漸變狹窄，先是不能吃乾飯，繼而連稀飯及液體也難以下嚥。
2. 體重減輕：由於食道阻塞造成患者吞嚥困難，身體的營養吸收不足，造成身體衰弱、體重減輕是必然的現象。
3. 呼吸有臭味：若食道被腫瘤完全阻塞後，食物會蓄積在腫瘤的上方，使得食物發酵而散發出惡臭。
4. 咳嗽：因唾液聚積在腫瘤上方，造成聚積的唾液或食物被吸入氣管而引起咳嗽，夜晚平躺時常會加重而使患者無法入睡。當腫瘤持續變大，可能穿出食道壁而產生食道氣管瘻管，此時進食將會引發吸入性肺炎及相關合併症。
5. 聲音嘶啞：因腫瘤壓迫到聲帶。
6. 胸痛：如果腫瘤擴展至胸腔後壁，進而侵犯到肋間神經時，患者常會有無法忍受的胸痛。
7. 大出血：若腫瘤侵犯到鄰近的大動脈時，會使大動脈破裂而產生大出血情形，是食道癌常見的致命原因之一。

三、診斷檢查

1. 胸部 X 光（Chest X-ray）：由 X 光片中了解食道以及胸腔的形狀是否有異常。
2. 食道攝影（Esophagography）：患者必須喝下鋇劑顯影劑，以觀察食物流經食道的方式，因鋇劑可附著在食道表面，透過 X 光而使病灶顯現出來。另外，本檢查可以評估食道癌所侵犯的長度範圍以及食道癌和其他相關構造的關係。若是出現食道癌，則會出現出連續不規則、模糊的連黏膜邊緣或管腔狹窄，而在阻塞處上方會有擴張的現象。但若懷疑有食道氣管瘻管，則不宜使用鋇劑顯影劑，須改用水溶性顯影劑。
3. 上消化道泛內視鏡檢查（Upper G-I panendoscopy）：可詳細的觀察癌之表面與其浸潤的廣度，評估發生的位置以及食道內阻塞的情形。做此檢查時，喉嚨會先採局部噴霧麻醉，以減少不適及嘔吐的感覺。然後醫師會以內視鏡從口腔經喉嚨進入食道，透過食道鏡取下食道腫瘤的部份組織病理切片檢查。故上消化道泛內視鏡檢查及病理切片檢查是確立診斷的最重要檢查。
4. 胸部電腦斷層攝影（Chest CT）或磁振造影（MRI）：可得知腫瘤的厚度、長度、周圍組織的侵犯程度，及局部淋巴腺有無侵犯或有無其它器官轉移的情形。

5. 其他檢查：腹部超音波、正子放射斷層攝影（PET）、全身骨骼掃描（Whole body bone scan）等評估食道癌是否可能轉移。

四、病理組織分類、食道癌分期

食道癌分為鱗狀細胞癌（Squamous cell carcinoma）和腺癌（Adenocarcinoma）。目前有許多工具可用來做食道癌的分期，最常見的就是內視鏡超音波，依據內視鏡或上消化道攝影的發現，可獲得腫瘤的大小、位置、外觀等資訊。電腦斷層掃描也常用來分期，特別是腫瘤小於 5 公分時，用處更大。它可顯現癌細胞是否擴及附近的淋巴結或肺臟，腫瘤是否穿入氣管，或是有遠處轉移等。

在本院，則安排細徑（迷你）探頭式內視鏡超音波（Miniprobe Endoscopic Ultrasound；EUS），以了解腫瘤侵犯的深度。而侵犯深度是決定五年存活的重要因素，也是預測外科手術是否能介入的關鍵。

目前根據美國癌症聯合委員會（AJCC）第八版分期法，分期如下：

Primary Tumor(T)

TX	Primary tumor can not be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined to the epithelium by the basement membrane
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Tumor invades pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Tumor invades other adjacent structures, such as aorta, vertebral body,-or airway

Regional Lymph Nodes(N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes

Distant Metastasis(M)

M0	No distant metastasis
M1	Distant metastasis

Histologic Grade(G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated, undifferentiated

Squamous Cell Carcinoma

Location	**Location Criteria**
X	Location unknown
Upper	Cervical esophagus to lower border of azygos vein
Middle	Lower border of azygos wein to lower border of inferior pulmonary vein
Lower	Lower border of inferior pulmonary vein to stomach, including gastroesophageal junction

Squamous Cell Carcinoma

Clinical Staging (cTNM)

	cT	cN	M
Stage 0	Tis	N0	M0
Stage I	T1	N0-1	M0
Stage II	T2	N0-1	M0
	T3	N0	M0
Stage III	T3	N1	M0
	T1-3	N2	M0
Stage IVA	T4	N0-2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

Pathological (pTNM)

	pT	pN	M	G	Location
Stage 0	Tis	N0	M0	N/A	Any
Stage IA	T1a	N0	M0	G1/GX	Any
Stage IB	T1a	N0	M0	G2-3	Any
	T1b	N0	M0	G1-3/GX	Any
	T2	N0	M0	G1	Any
Stage IIA	T2	N0	M0	G2-3/GX	Any
	T3	N0	M0	G1-3	lower
	T3	N0	M0	G1	upper/middle
Stage IIB	T3	N0	M0	G2-3	upper/middle
	T3	N0	M0	GX	lower/upper/middle
	T3	N0	M0	Any	Location X
	T1	N1	M0	Any	Any
Stage IIIA	T1	N2	M0	Any	Any
	T2	N1	M0	Any	Any
Stage IIIB	T2	N2	M0	Any	Any
	T3	N1-2	M0	Any	Any
	T4a	N0-1	M0	Any	Any
Stage IVA	T4a	N2	M0	Any	Any
	T4b	N0-2	M0	Any	Any
	Any T	N3	M0	Any	Any
Stage IVB	Any T	Any N	M1	Any	Any

Postneoadjuvant Therapy (ypTNM)

	ypT	ypN	M
Stage I	T0-2	N0	M0
Stage II	T3	N0	M0
Stage IIIA	T0-2	N1	M0
Stage IIIB	T3	N1	M0
	T0-3	N2	M0
	T4a	N0	M0
Stage IVA	T4a	N1-2/NX	M0
	T4b	N0-2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

Adenocarcinoma

Clinical Staging (cTNM)

	cT	cN	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N0	M0
Stage III	T2	N1	M0
	T3	N0-1	M0
	T4a	N0-1	M0
Stage IVA	T1-4a	N2	M0
	T4b	N0-2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

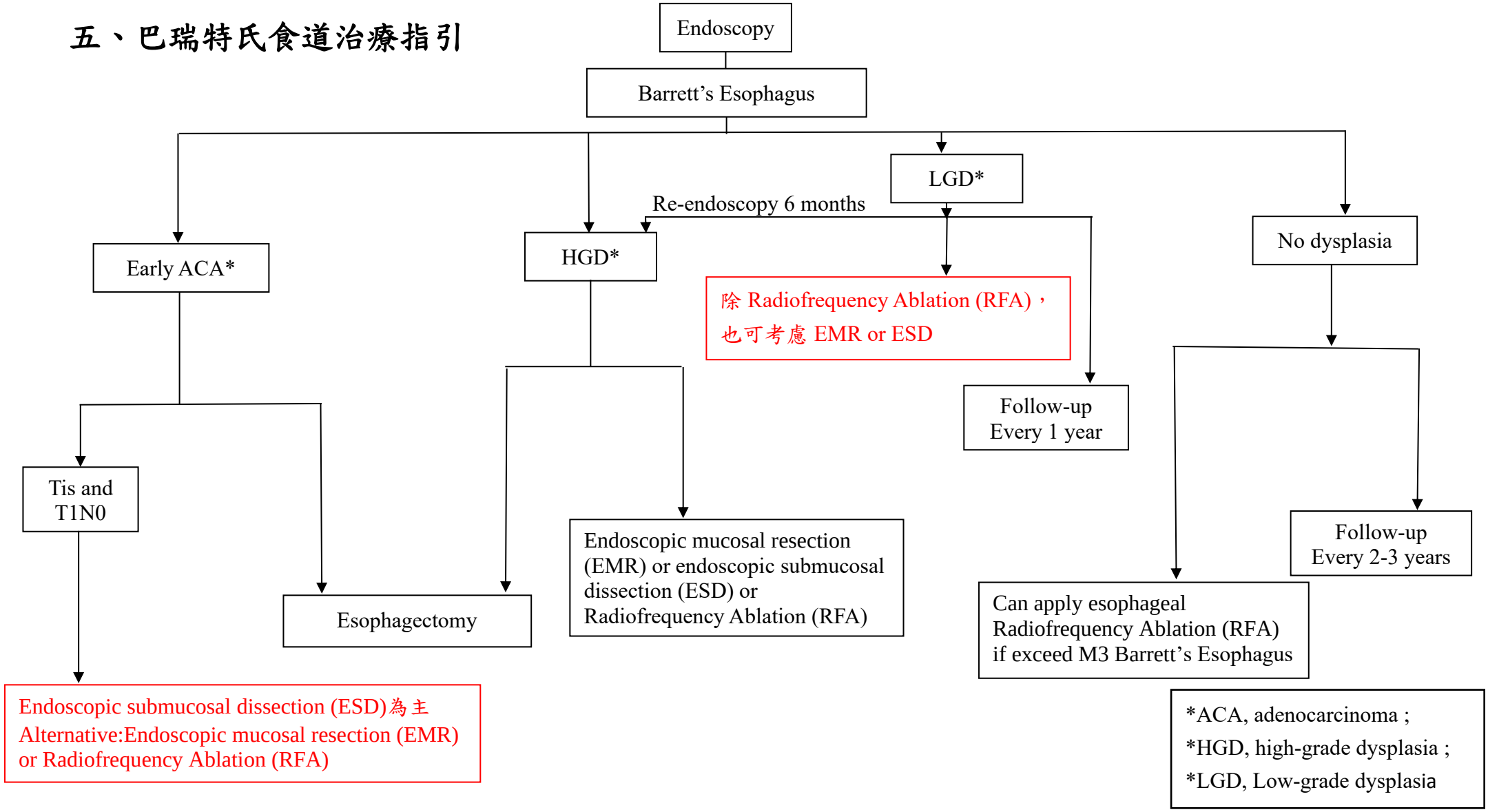
Postneoadjuvant Therapy (ypTNM)

	pT	pN	M	G
Stage 0	Tis	N0	M0	N/A
Stage IA	T1a	N0	M0	G1
	T1a	N0	M0	GX
Stage IB	T1a	N0	M0	G2
	T1b	N0	M0	G1-2
	T1b	N0	M0	GX
Stage IC	T2	N0	M0	G3
	T2	N0	M0	G1-2
Stage IIA	T2	N0	M0	G3
	T2	N0	M0	GX
Stage IIB	T1	N1	M0	Any
	T3	N0	M0	Any
Stage IIIA	T1	N2	M0	Any
	T2	N1	M0	Any
Stage IIIB	T2	N2	M0	Any
	T3	N1-2	M0	Any
	T4a	N0-1	M0	Any
Stage IVA	T4a	N2	M0	Any
	T4b	N0-2	M0	Any
	Any T	N3	M0	Any
Stage IVB	Any T	Any N	M1	Any

Postneoadjuvant Therapy (ypTNM)

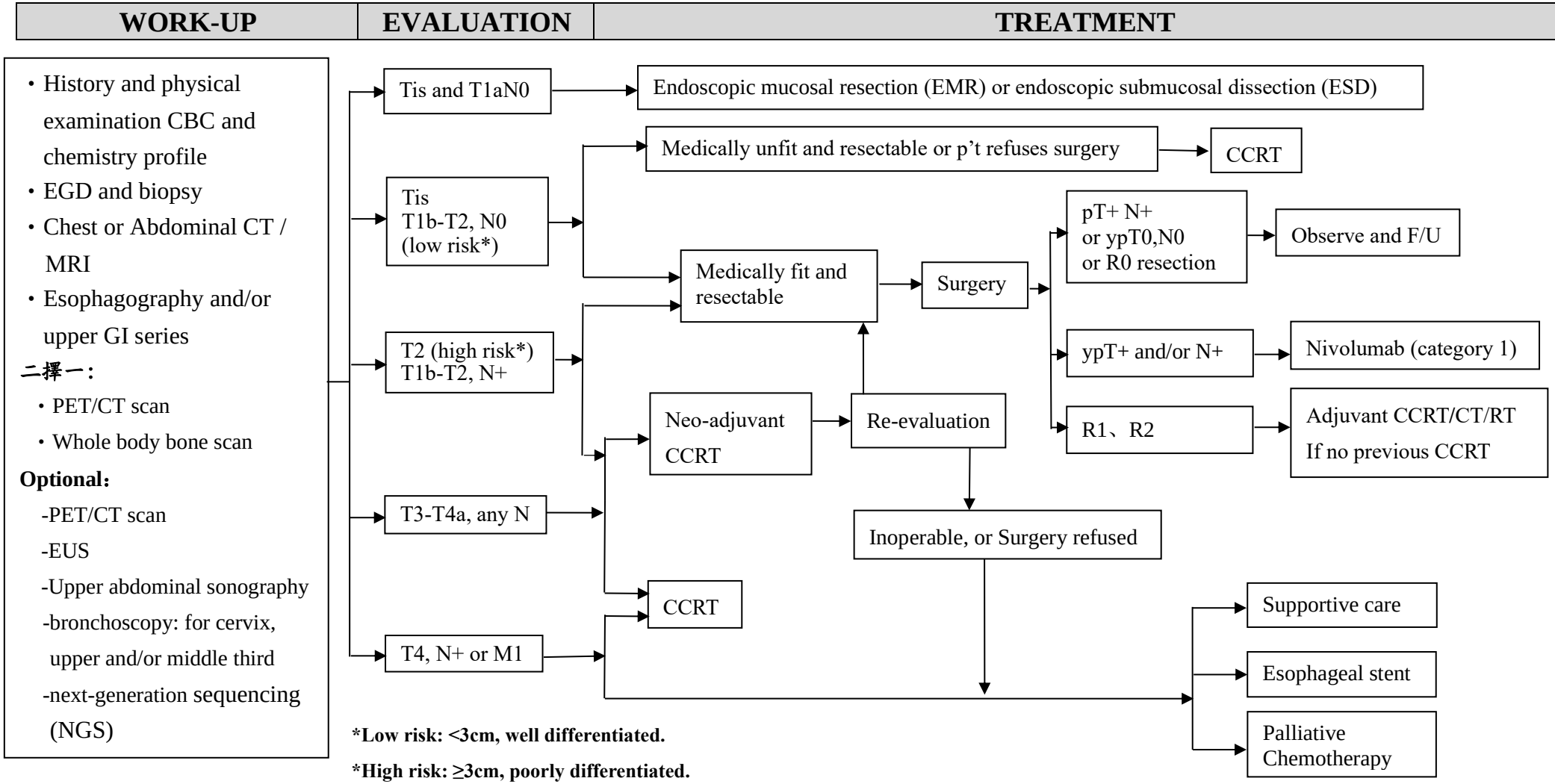
	ypT	ypN	M
Stage I	T0-2	N0	M0
Stage II	T3	N0	M0
Stage IIIA	T0-2	N1	M0
Stage IIIB	T3	N1	M0
	T0-3	N2	M0
	T4a	N0	M0
Stage IVA	T4a	N1-2	M0
	T4a	NX	M0
	T4b	N0-2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

五、巴瑞特氏食道治療指引



Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

六、食道癌治療指引 (Squamous Cell Carcinoma)



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食道癌治療指引 (Adenocarcinom)

WORK-UP	EVALUATION	TREATMENT

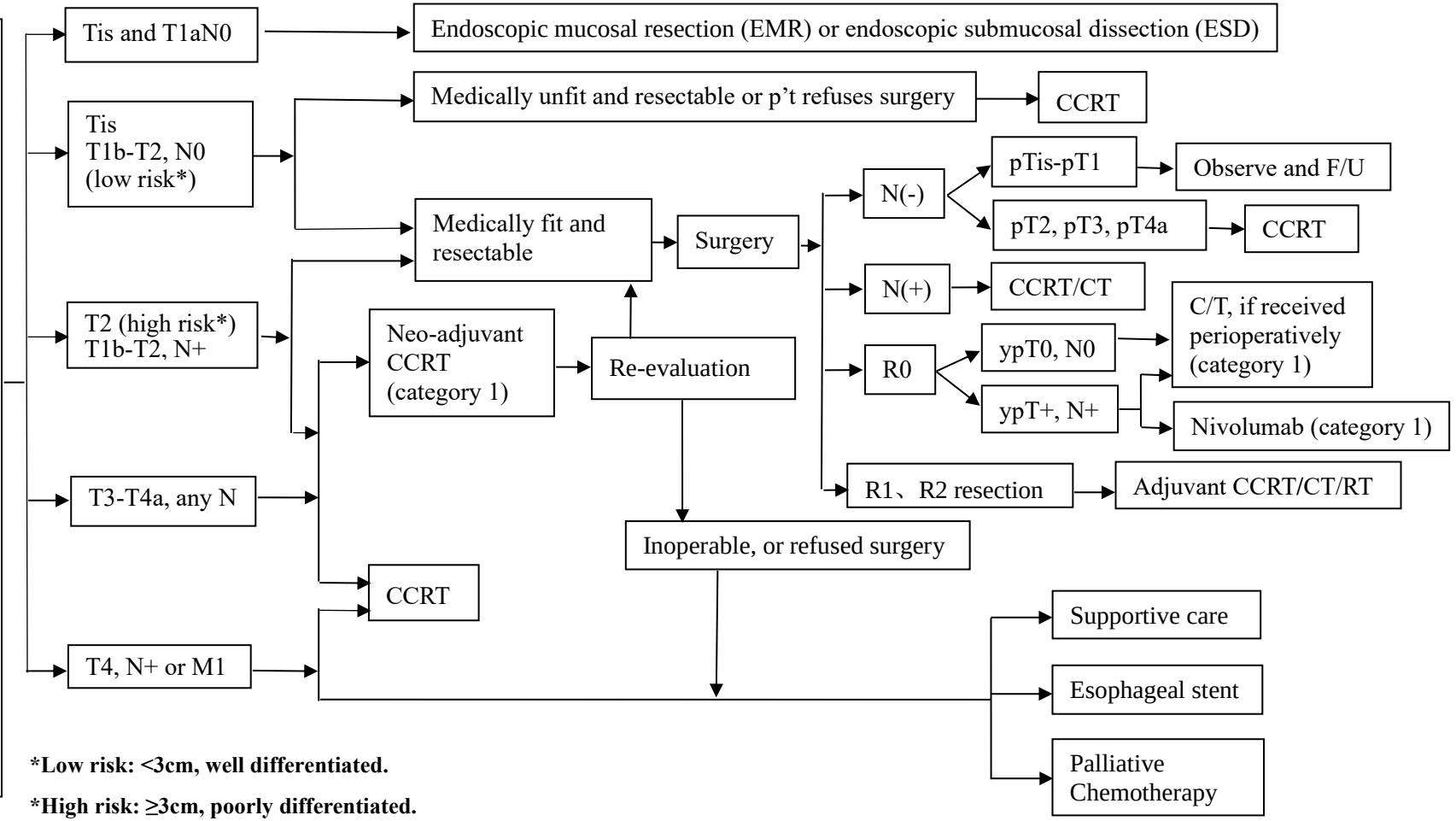
- History and physical examination CBC and chemistry profile
- EGD and biopsy
- Chest or Abdominal CT / MRI
- Esophagography and/or upper GI series

二擇一:

- PET/CT scan
- Whole body bone scan

Optional:

-PET/CT scan
-EUS
-Upper abdominal sonography
-bronchoscopy: for cervix, upper and/or middle third
-next-generation sequencing (NGS)



***Low risk: <3cm, well differentiated.**

***High risk: ≥3cm, poorly differentiated.**

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FOLLOW-UP	RECURRENCE	PALLIATIVE THERAPY

- History and physical examination
- CBC, Biochemistry Q3-6M
- Chest CT Q6M prn

二擇一：

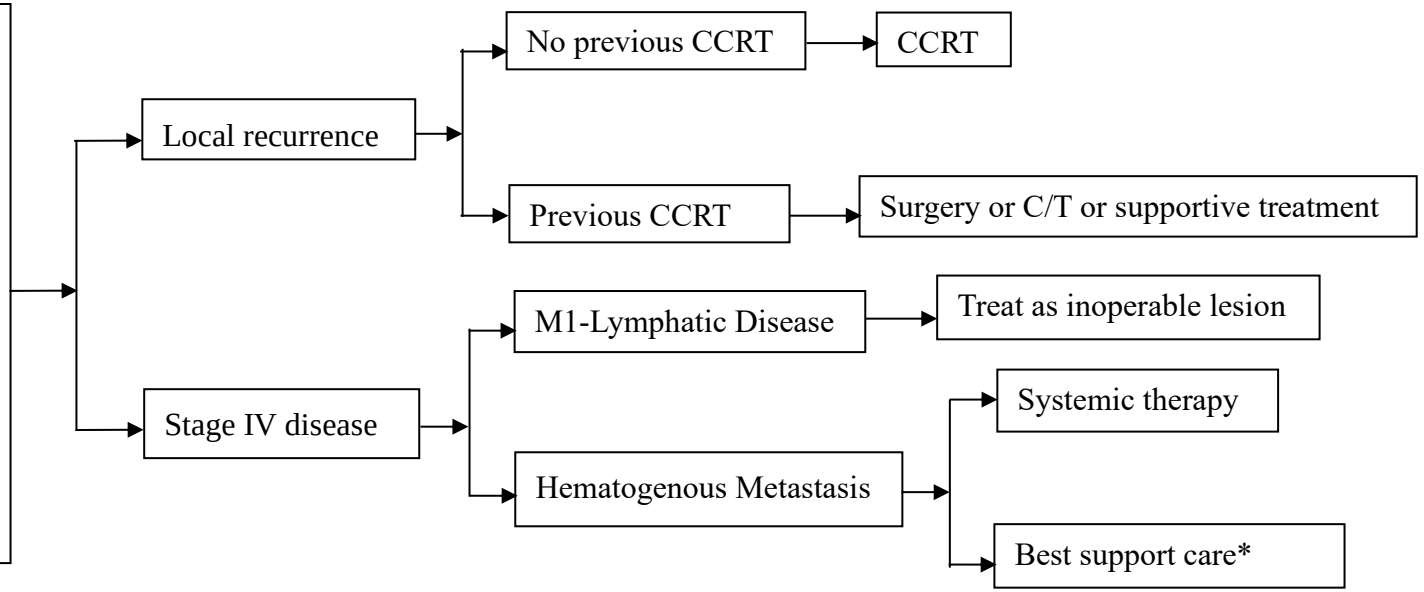
- PET/CT scan
- Whole body bone scan

Optional:

★CXR

★PES/ Esophagography

(★→ If symptomatic)



*Best supportive care：

- Obstruction: Stent, RT
- Nutrition: J-tube (for potential surgical candidate), PEG, G-tube
- Pain control: RT or medications

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七、化學治療原則

(一) PRINCIPLES OF SYSTEMIC THERAPY

- 根據患者體能狀態、合併症和毒性反應選擇，對於晚期食道癌患者以三種藥物合併使用前，應確定患者的體能狀況良好（ECOG PS 0~1），並須定期進行毒性評估。
- 若有證據支持毒性更低且療效不受影響時，則優先選擇第 1 類（category 1）方案或使用第 2A、2B 類。
- 任何方案的劑量和用藥方案若不是來自第 1 類證據，則只能作為建議，應根據具體情況進行適當修改。
- 靜脈滴注 5-FU 和口服 capecitabine 可互換使用。與口服 capecitabine 相比，應優選靜脈持續滴注 5-FU。
- 完成化療後，應該評估療效和晚期併發症。

PRINCIPLES OF SYSTEMIC THERAPY

Preoperative chemoradiation (Infusional Fluorouracil[b] can be replaced with Ufur on Capecitabine)
Preferred Regimens • Paclitaxel and Carboplatin (category 1)[1] • Fluorouracil[b] and Oxaliplatin (category 1)[2,3](for Adenocarcinoma)
Perioperative Chemotherapy (Only for adenocarcinoma of the thoracic esophagus or EGJ)
Preferred Regimens • Fluorouracil,[b] Leucovorin, Oxaliplatin, and Docetaxel (FLOT)[8] (category 1)[c] • Fluoropyrimidine and Oxaliplatin[b,d] Other Recommended Regimens • Fluorouracil and Cisplatin (category 1)[9]
Preoperative Chemotherapy (Only for adenocarcinoma of the thoracic esophagus or EGJ)
• Fluorouraci and Oxaliplatin • Fluorouracil and Cisplatin (category 2B)[10]
Definitive Chemoradiation (Infusional fluorouracil can be with capecitabine)
Preferred Regimens • Fluorouracil and Cisplatin (category 1)[11] • Paclitaxel and Carboplatin[1] • Fluorouracil[b] and Oxaliplatin (category 1)[2,3] (for Adenocarcinoma) Other Recommended Regimens • Cisplatin with Docetaxel or Paclitaxel[12-14]

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Postoperative Therapy
Preferred Regimens • Nivolumab only after preoperative chemoradiation with R0 resection and residual disease (category 1)[e,15] Other Recommended Regimens • Fluorouracil[b] and Cisplatin or oxaliplatin • Ufur • Capecitabine and oxaliplatin[16]
Postoperative Chemoradiation
• Fluoropyrimidine (infusional Fluorouracil[b] or Capecitabine) +/- Platinum

[b]Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without Leucovorin. For important information regarding the Leucovorin shortage, please see the Discussion.

[c]Due to toxicity, three-drug regimens are recommended only in select patients who are medically fit.

[d]The use of this regimen and dosing schedules is based on extrapolations from published literature and clinical practice.

[e]See NCCN Guidelines for Management of Immunotherapy-Related Toxicities**.**

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, nutritional status, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

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PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

First-Line Therapy

- **Oxaliplatin is generally preferred over Cisplatin due to lower toxicity. 但健保僅給付於腺癌。**

Preferred Regimens

- HER2 overexpression positive adenocarcinoma[g]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,18]
- HER2 overexpression negative[g]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab for adenocarcinoma (category 1 for PD-L1 CPS ≥ 5; category 2B for PD-L1 CPS <5)[e,h,19]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab for squamous cell carcinoma[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and nivolumab for squamous cell carcinoma[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (category 2A for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[e,h,21]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[e,h,21]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin[22-24]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[22,25-27]
  - Nivolumab and ipilimumab for squamous cell carcinoma[e,h,20]

Other Recommended Regimens (Trastuzumab[a] should be added to first-line chemotherapy for HER2 overexpression positive adenocarcinoma)

- HER2 overexpression positive adenocarcinoma[g]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab[a] and pembrolizumab[e,h,28]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a] and pembrolizumab[e,h,28]
- Paclitaxel with or without cisplatin or carboplatin[j,30-34]
- Docetaxel with or without cisplatin[j,35-38]
- Fluoropyrimidine[j,26,39,40] (fluorouracil[b] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b,j,41,42]
- Docetaxel, carboplatin, and fluorouracil (category 2B)[j,43]

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

Second-Line or Subsequent Therapy
- **Dependent on prior therapy and PS**

Preferred Regimens
- Nivolumab for esophageal squamous cell carcinoma (category 1)[e,h,44]
- Pembrolizumab[e,h]
  For second-line therapy for esophageal squamous cell carcinoma with PD-L1 expression levels by CPS of ≥10 (category 1)[45]
- Ramucirumab and paclitaxel for adenocarcinoma(category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[46]
- Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma[47]
- Docetaxel (category 1)[37,38]
- Paclitaxel (category 1)[33,34,48]
- Trifluridine and tipiracil for third-line or subsequent therapy for EGJ adenocarcinoma (category 1)[54]

Other Recommended Regimens
- Ramucirumab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[55]

Useful in Certain Circumstances
- Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors[60,61]
- Pembrolizumab[e,h] for MSI-H or dMMR tumors[62-64]
- Pembrolizumab[e,h] for TMB high (≥10 mutations/megabase) tumors[65]

[a] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see the Discussion.
[e] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[g] See Principles of Pathologic Review and Biomarker Testing (ESOPH-B).
[h] If no prior tumor progression while on therapy with a checkpoint inhibitor.
[j] Trastuzumab should be added to first-line chemotherapy for HER2 overexpression positive adenocarcinoma. An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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(二) REGIMEN

NEOADJUVANT CHEMORADIATION

(followed by surgery for resectable cancer)

- **Paclitaxel + Carboplatin**

Paclitaxel	50 mg/m^2	IV	D1
Carboplatin	AUC 2	IV	D1
Weekly for 5 weeks			

van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-2084.

- **Fluorouracil (5-FU) + Oxaliplatin (For ECJ adenocarcinoma)**

Oxaliplatin	65 mg/m^2	IV	D1
(Leucovorin 400 mg/m^2 on Day1; Fluorouracil 400 mg/m^2 IV Push on Day 1)			
Fluorouracil (5-FU)	600 mg/m^2	IV	D1,29
IV continuous infusion over 24 hours daily on Days 1–2 Cycled every 14 days for 3 cycles with radiation.			

1. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-2084.
2. Conroy T, Galais MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ ACCORD17): final results of a randomised, phase 2/3 trial. Lancet Oncol 2014;15:305-314.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

• **PF**

Cisplatin	60 - 80 mg/m^2	IV		D1
Fluorouracil (5-FU)	600 - 800 mg/m^2	civi		D1-4
Q4w x 2 cycles				

Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 2008;26:1086-1092.

• **Bi-weekly PF**

Cisplatin	30 - 40 mg/m^2	IV		D1
Fluorouracil (5-FU)	1200 -1600 mg/m^2/day	civi	46-48 hours	D1
Q2w x 3 cycles				

• **Cisplatin +/- Capecitabine (UFUR)**

Cisplatin	25 - 30 mg/m^2	IV		D1
Capecitabine	800 mg/m^2	PO	BID	D1-5
UFUR	200-250 mg/m^2/day	PO	BID	D1-5
Qw x 12 cycles				

Lee SS, Kim SB, Park SI, et al. Capecitabine and cisplatin chemotherapy (XP) alone or sequentially combined chemoradiotherapy containing XP regimen in patients with three different settings of stage IV esophageal cancer. Jpn J Clin Oncol 2007;37:829-835.

• **Capecitabine + Oxaliplatin**

Oxaliplatin	65 mg/m^2	IV		D1, 15, and 29 for 3 doses
Capecitabine	625 mg	PO	BID	D1–5 weekly for 5 weeks

Javle MM, Yang G, Nwogu CE, et al. Capecitabine, oxaliplatin and radiotherapy: a phase IB neoadjuvant study for esophageal cancer with gene expression analysis. Cancer Invest 2009;27:193-200.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

• **Capecitabine + Cisplatin**

Cisplatin	30 mg/m^2	IV		D1
Capecitabine	625 mg	PO	BID	D1–5 weekly for 5 weeks

Lee SS, Kim SB, Park SI, et al. Capecitabine and cisplatin chemotherapy (XP) alone or sequentially combined chemoradiotherapy containing XP regimen in patients with three different settings of stage IV esophageal cancer. Jpn J Clin Oncol 2007;37:829-835.

PERIOPERATIVE CHEMOTHERAPY

(Only for adenocarcinoma of the thoracic esophagus or EGJ)

• FLOT

Fluorouracil (5-FU)	2600 mg/m^2	civi	46-48 hours	D1
Leucovorin	200 mg/m^2	IV		D1
Oxaliplatin	85 mg/m^2	IV		D1
Docetaxel	50 mg/m^2	IV		D1
Q2w (4 cycles preoperative and 4 cycles postoperative)				

Al-Batran S-E, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastrooesophageal junction adenocarcinoma (FLOG4): a randomised, phase 2/3 trial. Lancet 2019;393:1948-1957.

• FOLFOX

Oxaliplatin	85 mg/m^2	IV		D1
Leucovorin	200 mg/m^2	IV		D1
Fluorouracil (5-FU)	2600 mg/m^2	civi	46-48 hours	D1
Q2w(4 cycles preoperative and 4 cycles postoperative)				

Al-Batran S-E, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008;26:1435-1442.

• Cisplatin + Fluorouracil (5-FU)

Cisplatin	60 - 80 mg/m^2	IV		D1
Fluorouracil (5-FU)	800 - 1000 mg/m^2	civi	46-48 hours	D1-4
Q4w total 6 cycles (2-3 cycles before operation)				

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PREOPERATIVE CHEMOTHERAPY

(Only for adenocarcinoma of the thoracic esophagus or EGJ)

- **PF**

Cisplatin	60 - 80 mg/m^2	IV	D1
Fluorouracil (5-FU)	800 - 1000 mg/m^2	civi	D1-4
Q4w x 2 cycles			

Alderson D, Cunningham D, Nankivell M, et al. Neoadjuvant cisplatin and fluorouracil versus epirubicin, cisplatin, and capecitabine followed by resection in patients with oesophageal adenocarcinoma (UK MRC OE05): an open-label, randomised phase 3 trial. Lancet Oncol 2017;18:1249-1260.

DEFINITIVE CHEMORADIATION
(for locally advanced cancer)

• PF

Cisplatin	60 - 80 mg/m^2	IV		D1
Fluorouracil (5-FU)	800 - 1000 mg/m^2	civi		D1-4
Q4w x 2 cycles with radiation followed by 2 cycles without radiation				

Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combinedmodality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002;20:1167-1174.

• PFL

Cisplatin	40 - 50 mg/m^2	IV		D1
Leucovorin	200mg/m^2	civi	46-48 hours	D1
Fluorouracil (5-FU)	1200 - 1600 mg/m^2/day	civi	46-48 hours	D1
Qw x 12 cycles				

• Bi-weekly PF

Cisplatin	40 - 50 mg/m^2	IV		D1
Fluorouracil (5-FU)	1200 - 1600 mg/m^2/day	civi	46-48 hours	D1
Qw x 12 cycles				

• Cisplatin +/- Capecitabine (UFUR)

Cisplatin	25 - 30 mg/m^2	IV		D1
Capecitabine	800 mg/m^2	PO	BID	D1-5
UFUR	200 - 250mg/m^2/day	PO	BID	D1-5
Qw x 12 cycles				

Lee SS, Kim SB, Park SI, et al. Capecitabine and cisplatin chemotherapy (XP) alone or sequentially combined chemoradiotherapy containing XP regimen in patients with three different settings of stage IV esophageal cancer. Jpn J Clin Oncol 2007;37:829-835.

• Paclitaxel + Carboplatin

Paclitaxel	50 mg/m^2	IV		D1
Carboplatin	AUC 2	IV		D1
Weekly for 5 weeks				

van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-2084.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Chemotherapy for stage IV cancer

• Cisplatin + Fluorouracil (5-FU)

Cisplatin	60 - 80 mg/m^2	IV		D1
Fluorouracil (5-FU)	800 - 1000 mg/m^2	civi	46-48 hours	D1-4
Q4w total 3-6 cycles				

Lorenzen S, Schuster T, Porschen R, et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 2009;20:1667-1673.

• PFL

Cisplatin	40 - 50 mg/m^2	IV		D1
Leucovorin	200 mg/m^2	civi	46-48 hours	D1
Fluorouracil (5-FU)	1200 - 1600 mg/m^2/day	civi	46-48 hours	D1
Qw x 12 cycles				

• P-HDFL

Cisplatin	25 - 30 mg/m^2	IV		D1, 8, 15
Leucovorin	200 mg/m^2	civi	46-48 hours	D1, 8, 15
Fluorouracil (5-FU)	2000 - 2600 mg/m^2/day	civi	46-48 hours	D1, 8, 15
Q4w x 3-6 cycles				

Hung TC et al. Weekly 24-hour infusional 5-fluorouracil as initial treatment for advanced gastric cancer with acute disseminated intravascular coagulation. Anticancer Res 2008;28:1293.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

• **Docetaxel**

Docetaxel	30 - 35 mg/m^2	IV	D1, 8	Q3w
OR				
Docetaxel	22 - 25 mg/m^2	IV	D1, 8, 15	Q4w

Albertsson M et al. Phase II studies on docetaxel alone every third week, or weekly in combination with gemcitabine in patients with primary locally advanced, metastatic, or recurrent esophageal cancer. Med Oncol 2007;24:407.

• **Paclitaxel**

Paclitaxel	60 - 80 mg/m^2	IV	D1, 8, 15
Q4w total 3-6 cycles			

Ilson DH et al. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. Ann Oncol 2007;18:898.

• **Modified Paclitaxel + Cisplatin**

Paclitaxel	60 - 80 mg/m^2	IV	D1, 8, 15
Cisplatin	70 - 80 mg/m^2	IV	D1
Q4w x 3 -6 cycles			

1. Kornek, GV et al. Effective combination chemotherapy with paclitaxel and cisplatin with or without human granulocyte colony-stimulating factor and/or erythropoietin in patients with advanced gastric cancer. Br J Cancer 2002; 86:1858.
2. Ilson DH et al. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. Ann Oncol 2007;18:898.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

• **S-1 (TS-1)**

Tegafur/potassium oxonate/gimeracil	BSA < 1.25	40 mg	BID
	BSA 1.25 - 1.5	50 mg	BID
	BSA ≧1.5	60 mg	BID
4 weeks on, 2 weeks off (or 2 weeks on, 1 weeks off), 1 year			

Sakuramoto S, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med. 2007;357:1810. S-1 Monotherapy as Second- or Third-Line Chemotherapy for Unresectable and Recurrent Esophageal Squamous Cell Carcinoma Akutsu Y. · Kono T. · Uesato M. · Hoshino I. · Narushima K. · Hanaoka T. · Tochigi T. · Semba Y. · Qin W. · Matsubara H. Department of Frontier Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan

• **Pembrolizumab**

(for second-line therapy for esophageal squamous cell carcinoma, esophageal adenocarcinoma, and EGJ adenocarcinoma with PD-L1 expression levels by CPS of ≥10 or for third-line or subsequent therapy for esophageal and EGJ adenocarcinoma with PD-L1 expression levels by CPS of ≥1)

Pembrolizumab	200 mg	IV	D1
Cycled every 21 days			

1. Kojima T, Muro K, Francois E, et al. Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: phase III KEYNOTE-181 study. J Clin Oncol 2019;37:2.
2. Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. JAMA Oncol 2018;4:e180013.

• **Nivolumab+ipilimumab (for squamous cell carcinoma)**[e,i]

Nivolumab	3 mg/kg	IV	every 2 weeks
Ipilimumab	1 mg/kg	IV	every 6 weeks
per study, maximum of 2 years			

Doki Y, Ajani JA, Kato K, et al. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma.N Engl J Med 2022;386:449-462.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

POSTOPERATIVE THERAPY

- **Nivolumab**

Nivolumab	240 mg	IV		every 14 days for 16 weeks
followed by Nivolumab 480 mg every 28 days				
Maximum treatment duration of 1 year				
自費 3mg/kg IV				

Kelly R, Ajani J, Kuzdzal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiation therapy: first results of the CheckMate 577 study. [abstract]. Presented at the Oral Presentation presented at the ESMO 2020 Annual Meeting; September 19-21, 2020; Virtual Meeting.

- **Oxaliplatin + Leucovorin + Fluorouracil (5-FU)**

Oxaliplatin	65-85 mg/m^2	IV		D1
Leucovorin	200 mg/m^2	IV		D1
Fluorouracil (5-FU)	2600 mg/m^2	civi	46-48 hours	D1
Q2w				

Al-Batran S-E, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008;26:1435-1442.

八、放射治療原則

Treatment Regimen
CCRT： Definitive RT：Favor IMRT dose of 4500-6600 cGy. Neoadjuvant / Adjuvant RT：Favor IMRT dose of 4140-5400 cGy.

Chun, S. G., Skinner, H. D., & Minsky, B. D. (2017). Radiation therapy for locally advanced esophageal cancer. Surgical Oncology Clinics, 26(2), 257-276.

九、支持性治療(Supportive treatment)原則

- 避免因可控制的急性毒性而中斷治療或減少劑量。積極的監測及支持治療比中斷治療更好。
- 在放射治療過程中，至少每週檢查一次患者的狀態，記錄生命徵象、體重和全血球計數。
- 應在適當的時機以預防為基礎給予止吐藥。評估患者狀況後對症下藥，例如 :開立制酸劑或止瀉藥。
- 熱量攝入<1500 kcal/天，應考慮腸內或靜脈輸液營養。視患者狀況，放置空腸造廔或鼻胃管讓足夠的熱量攝入。
- 在整個放化療和恢復過程中，充分的腸內或靜脈輸液是必要的。

十、安寧緩和照護原則

若預期疾病難以治癒時，病人存活期小於6個月便適合安寧療護（Pomeranz & Brustman, 2005；Waldrop & Rinfrette, 2009）。若藉由症狀、檢驗數據、及確切的腫瘤診斷，證實臨床上該惡性腫瘤已經廣泛侵犯、或進展快速；功能分數（Palliative Performance Scale）低於70%；拒絕進一步腫瘤治癒性治療，或在治療之下仍持續惡化者，即可轉介緩和醫療團隊（彭等，2006）。

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十二、食道癌完治定義

癌別	期別		治療方式	完治定義
食道癌	治療期	0 期 1 期	OP	EMR/ESD or OP：Margin free
		2 期	OP or Neo-adjuvant CCRT+OP or Definitive CCRT	1.術後 Margin free 2.Margin (+) → Adjuvant CCRT 結束日 3.Definitive CCRT 結束日
		3 期	Neo-adjuvant CCRT+OP or Definitive CCRT	1.術後 Margin free 2.Margin (+) → Adjuvant CCRT 結束日 3.Definitive CCRT 結束日
		4 期	Definitive CCRT	1.Definitive CCRT 結束日 2.Palliative C/T 達三個月(含口服化療 Ufur) 3.Palliative C/T 未達三個月，評估病患治療反應不佳，改二線藥持續治療，第一次治療就可算完治 4.治療中轉安寧