中山醫學大學附設醫院

食道癌診療指引

本臨床指引參考台灣國家衛生研究院、與美國NCCN版本

食道癌多專科醫療團隊編修

2014/12/26 Version6.0
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癌症委員會主任委員	癌症委員會執行長	癌症防治中心主任	團隊負責人

修訂內容

頁數	原文	修訂/新增
第 9 頁	WORK-UP 1.History and physical exmaniation 2.Upper GI endoscopic ultrasound and biopsy 3.Chest CT scan 4.Esophagography and/or upper GI series 5.Upper abdominal sonography 6.Whole body bone scan 7.CBC and Biochemistry 8.Nutrition assessment 9.Optional：PET/CT scan 10.bronchoscopy：for cervix, upper and/or middle thorax	修訂 WORK-UP *History and physical exmaniation *Upper GI endoscopic and biopsy *Chest CT scan *.Esophagography and/or upper GI series Optional： - PET/CT scan -Endoscopic ultrasonography -Upper abdominal sonography -Whole body bone scan -bronchoscopy：for cervix, upper and/or middle third
第 10 頁	Follow-up H&P CBC, Biochemistry q3M Functional evaluation for esophageal Substitute q1Mx3, Then q3M PES/Esophagography /Dilatation prn CXRq1mx3 then q3M Chest CT q6m prn *Bone scan prn *Neck U/4 prn	修訂 H&P CBC, Biochemistry q3M Functional evaluation for esophageal Substitute q1Mx3, Then q3M PES/Esophagography CXR Chest CT q6m prn Optional：

	(*→if symptomatic)	*Bone scan prn (*→if symptomatic)
第 12 頁	Neoadjuvant chemoradiation followed by surgery for resectable cancer	刪除 Paclitaxel + Carboplatin Paclitaxel + Cisplatin
第 14 頁		修訂 Cisplatin + Capecitabine (or UFUR) 刪除 Paclitaxel + Carboplatin Paclitaxel + Cisplatin
第 15 頁		刪除 Docetaxel + Cisplatin
第 16 頁		修訂 Docetaxel (check weekly Docetaxel, 1, 8, q3w, 30-35mg/m2: 1, 8, 15, q4w; 22-25 mg/m2)
第 17 頁		刪除 Irinotecan + Cisplatin

目錄

一、前言

食道癌好發於 50-70 歲的老年人，男性多於女性，其比例約為 4：1，以喜歡吃刺激、醃製性或溫度較高的食物者，或攝取蔬菜水果或維他命 C、C 不足者、少量元素鋅的缺乏者；高粱、玉米、以及茶葉中的鞣酸（Tan-nin），也被列為與食道癌有關的物質；飲水以及食物中若含有過量的亞硝基氨（Nitrosamine），也已證實會增加食道癌發生的危險。喝酒也是食道癌的一個高危險因子，統計顯示喝酒引起食道癌是正常人的 2-4 倍，若喝酒加上抽菸，將會使罹患食道癌的危險性大為增加。慢性逆流性食道炎或 Barrett 氏食道患者：食道癌大部分發生在中、下 1/3 段的食道，此段食道特別容易受到胃液逆流影響，造成黏膜傷害使黏膜變性而容易產生食道癌的發生。有頭頸癌的病人，根據統計，頭頸癌病人所發生的繼發性癌症中，有 1/3 是在食道發生。食道弛緩不能（食道擴約肌的運動能力降低）的病人，比正常人發生食道癌的機會高出 6~14%。曾有食道腐蝕性傷害，也較易引起食道癌的產生，其位置常會在食道的中段。

二、臨床症狀

1.吞嚥困難：絕大多數的病人，第一個症狀是在吃肉，麵包及粗糙的食物（如生蔬菜）時會覺得不易下嚥，有不順暢的感覺，有些病人甚至會感到食物卡在胸骨的後方。等到腫瘤向食道內腔生長，會使得食道漸漸變狹小，先是不能吃乾飯，繼而連稀飯也難以下嚥，到了後來甚至連牛奶或水也喝不下去。

2.體重減輕：亦是常見的症狀，由於食道阻塞會造成病人進食困難，身體的營養自然不夠，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：因口腔所分泌的唾液也會聚積在腫瘤上方的食道內，有時積聚的唾液或食物會被吸入氣管而引起咳嗽，在夜晚時常會使病人無法入睡。當腫瘤繼續長大，因為局部壓力改變，以及目發性咳嗽而產生食道氣管瘻管。此時在進食時，常會將食物吸入性肺炎，及相關合併症。

5.聲音嘶啞：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，病人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，這也是食道癌常見的致命原因之一。

三、診斷方法

1.胸部 X 光：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：病人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。如果懷疑有食道氣管瘻管的併發症存在時，食道攝影不宜使用鋇劑顯影劑，而須改用水溶性顯影劑，檢查時要特別小心。

3.食道鏡檢查：食道鏡可詳細的觀察癌之表面與其侵潤的廣度，評估癌發生的位置以及食道壁內阻塞的情形。做此檢查時，喉嚨會先行局部噴霧麻醉，以減少舒服及嘔吐的感覺。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。故食道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（CT）或磁振造影（MRI）：本檢查可得知腫瘤的厚度、長度、周圍組織的侵犯程度，以及局部淋巴腺有無受到波及或是有無器官轉移的情形。

5.其他選擇性的檢查還包括：腹部超音波、正子放射斷層攝影（PET）、骨骼掃描檢查等評估食道癌是否可經轉移。

四、食道癌分期

目前有許多工具用來做食道癌的分期，最常見的就是內視鏡檢查，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，外觀等資料。電腦斷層掃描也常用來幫忙分期，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，腫瘤是否延伸穿入氣管，還是有了遠處肝臟轉移等等。在某些醫學中心，則更能安排內視鏡超音波檢查，這對局部腫瘤侵犯的深度，會有更詳細的了解。而侵犯深度常是決定 5 年存活率的重要因素，也是預測外科手術對病人是否有幫忙的重要參考資料，再分期判斷與治療選擇上，有其特有的價值。

有了足夠的資訊後，即可對腫瘤的嚴重度做出期別的判斷。目前醫學界對癌症最常用的分期系統就是 TMN 系統，對食道癌亦是如此。T 代表腫瘤（它的大小和它散佈的程度，是在食道內，或到近旁的器官。N 是代表侵犯到淋巴結的程度。 M 為轉移至其它器官的狀況。如此依不同的 TMN 分組，再區分成五期，習慣上分別以羅馬數字 0 到 IV 來表示。

第 0 期 ：這是最初期的食道癌，也就是原位食道癌，癌細胞僅侷限食道表皮層。其下面的結締組織都是正常，無任何惡性變化，也無任何淋巴結或器官的侵犯。

第 I 期：這階段食道癌的惡性細胞已侵入表皮層下的其它組織，癌細胞出現在固有層或黏膜下層，但並未侵犯至肌肉層。此時癌細胞也不會散佈淋巴結或其它器官。

第 II 期：又分成兩個亞期，IIA 和 IIB。

第 IIA 期：此時癌瘤已經侵入肌肉層，也可能侵犯到外膜層（adventitia），但尚未傳佈到淋巴結或任何其他的器官

第 IIB 期：腫瘤侵入固有層，黏膜下層肌肉層，但為影響到外膜層。然而它有吃到靠近食道的淋巴結，不過並不會散佈至其它器官。

第 III 期：這個階段癌瘤除了侵犯到外膜、靠近食道的淋巴結，並侵犯至近旁的器官，像是氣管，但是不影響到其相關淋巴結，且無遠處轉移。

第 IV 期：這時食道癌已隨血流散佈至多處器官，例如肝臟、骨頭、甚至是腦部等等。

以下是 AJCC 7th 分期資料：

Primary Tumor(T)	
TX	Primary tumor cancer be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc

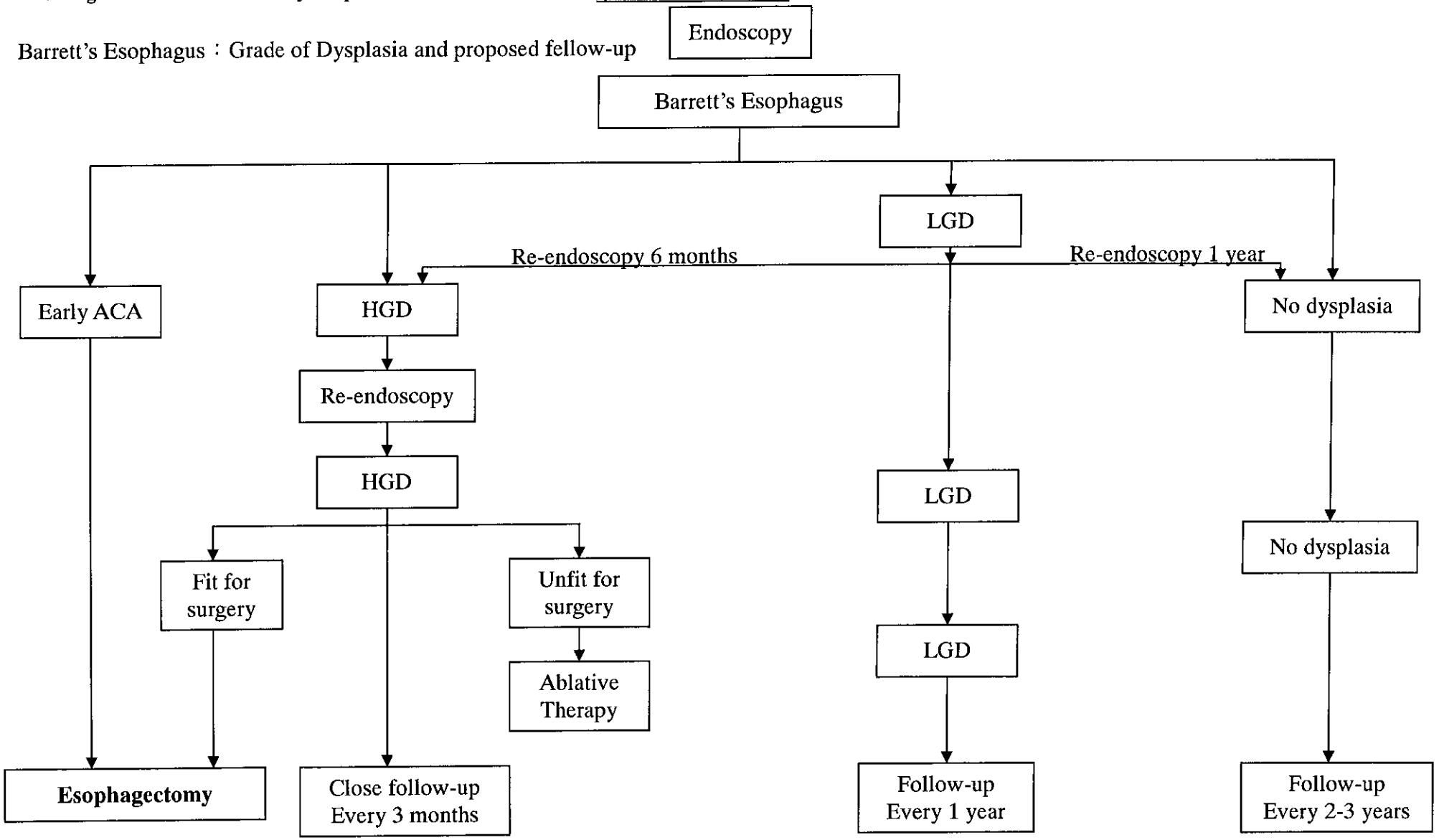
Distant Metastasis(M)	
M0	No distant metastasis
M1	Distant metastasis

Histologic Grade(G)	
GX	Grade cannot be assessed-stage grouping as G1
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated – stage grouping as G3 squamous

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

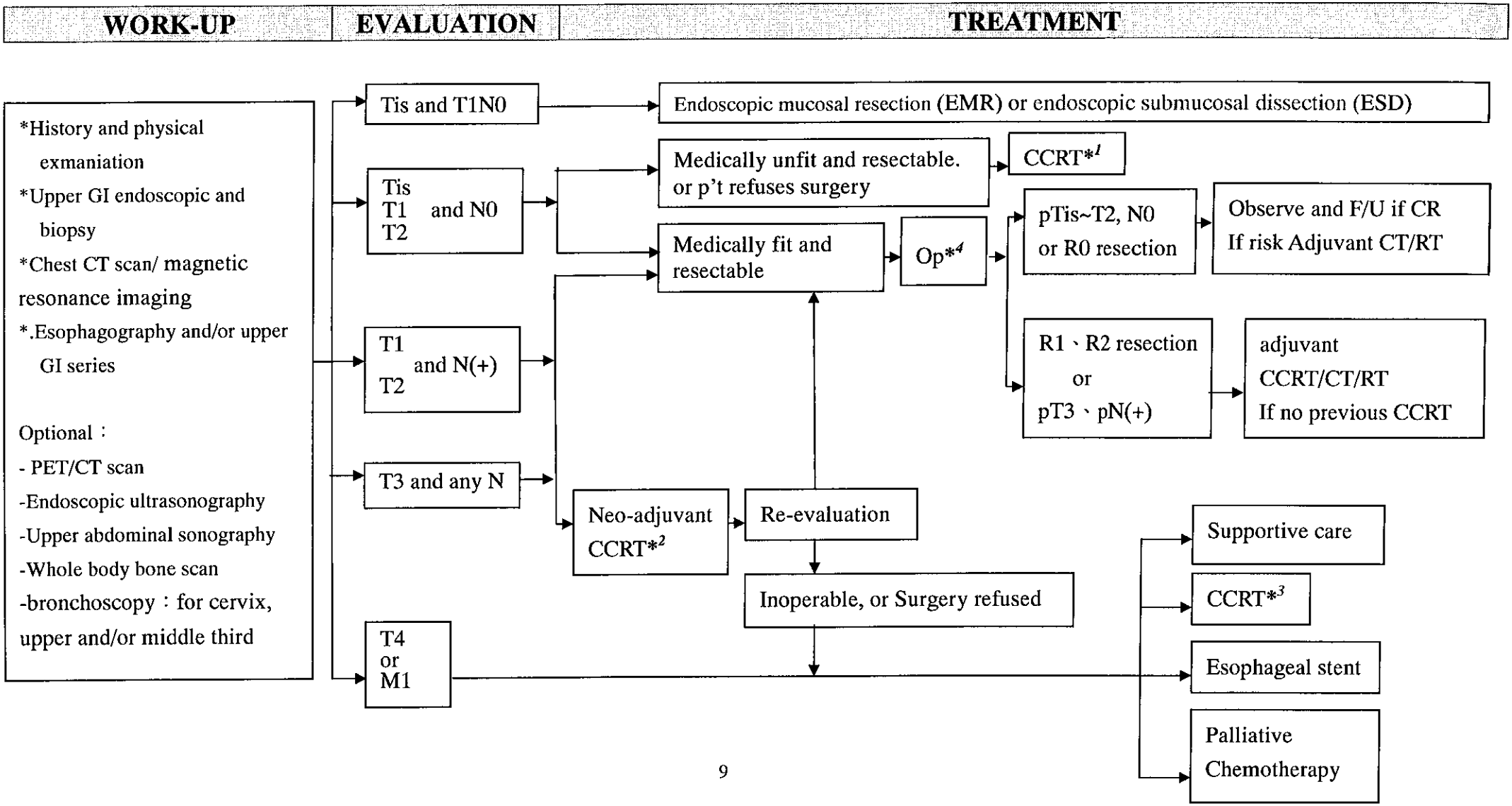
T-N-M Stage Grouping										
Squamous Cell Carcinoma						**Adenocarcinoma**				
Stage	T	N	M	Grade	Tumor Location	Stage	T	N	M	Grade
0	Tis(HGD)	N0	M0	1,X	Any	0	Tis(HGD)	N0	M0	1,X
I A	T1	N0	M0	1,X	Any	I A	T1	N0	M0	1,X
I B	T1	N0	M0	2-3	Any	I B	T1	N0	M0	3
	T2-3	N0	M0	1,X	Lower,X		T2	N0	M0	1-2,X
II A	T2-3	N0	M0	1,X	Upper,middle	II A	T2	N0	M0	3
	T2-3	N0	M0	2-3	Lower,X					
II B	T2-3	N0	M0	2-3	Upper,middle	II B	T3	N0	M0	Any
	T1-2	N1	M0	Any	Any		T1-2	N1	M0	Any
III A	T1-2	N2	M0	Any	Any	III A	T1-2	N2	M0	Any
	T3	N1	M0	Any	Any		T3	N1	M0	Any
	T4a	N0	M0	Any	Any		T4a	N0	M0	Any
III B	T3	N2	M0	Any	Any	III B	T3	N2	M0	Any
III C	T4a	N1-2	M0	Any	Any	III C	T4a	N1-2	M0	Any
	T4b	Any	M0	Any	Any		T4b	Any	M0	Any
	Any	N3	M0	Any	Any		Any	N3	M0	Any
IV	Any	Any	M1	Any	Any	IV	Any	Any	M1	Any

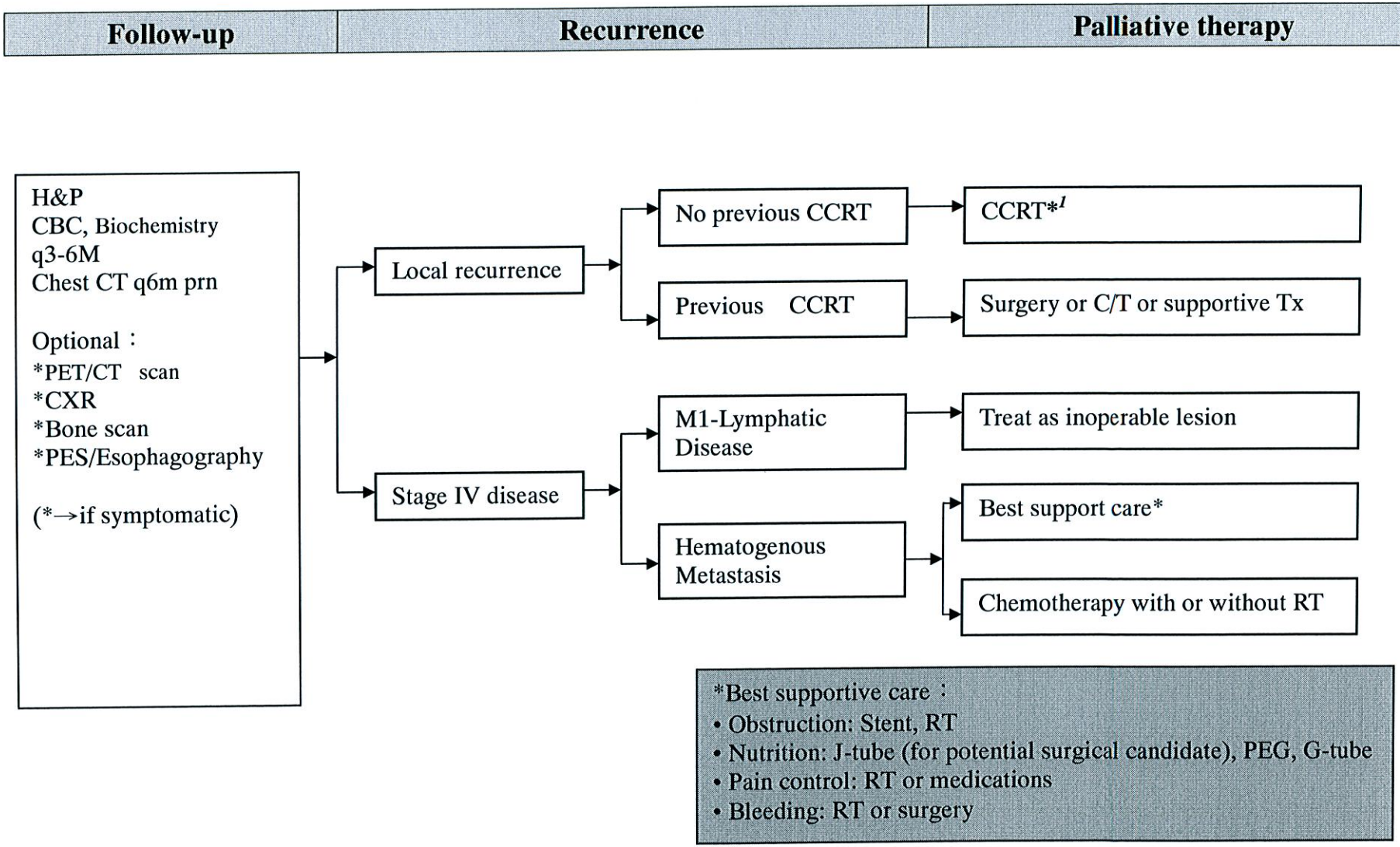
Barrett's Esophagus：Grade of Dysplasia and proposed fellow-up



Grade of dysplasia and proposed follow-up algorithm for the treatment of Barrett's esophagus.
ACA, adenocarcinoma ; HGD, high-grade dysplasia ; LGD, LOW-grade dysplasia

五、食道癌治療指引


WORK-UP
EVALUATION
TREATMENT
*History and physical exmaniation
*Upper GI endoscopic and biopsy
*Chest CT scan/ magnetic resonance imaging
*.Esophagography and/or upper GI series
Optional：
- PET/CT scan
-Endoscopic ultrasonography
-Upper abdominal sonography
-Whole body bone scan
-bronchoscopy：for cervix, upper and/or middle third
Tis and T1N0
Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD)
Tis T1 T2 and N0
Medically unfit and resectable. or p't refuses surgery
CCRT*1
Medically fit and resectable
Op*4
pTis~T2, N0 or R0 resection
Observe and F/U if CR
If risk Adjuvant CT/RT
R1、R2 resection or pT3、pN(+)
adjuvant CCRT/CT/RT
If no previous CCRT
T1 T2 and N(+)
T3 and any N
Neo-adjuvant CCRT*2
Re-evaluation
Inoperable, or Surgery refused
Supportive care
CCRT*3
Esophageal stent
Palliative Chemotherapy
T4 or M1


Follow-up
Recurrence
Palliative therapy
H&P
CBC, Biochemistry
q3-6M
Chest CT q6m prn
Optional：
*PET/CT scan
*CXR
*Bone scan
*PES/Esophagography
(*→if symptomatic)
Local recurrence
Stage IV disease
No previous CCRT
Previous CCRT
M1-Lymphatic Disease
Hematogenous Metastasis
CCRT*1
Surgery or C/T or supportive Tx
Treat as inoperable lesion
Best support care*
Chemotherapy with or without RT
*Best supportive care：
• Obstruction: Stent, RT
• Nutrition: J-tube (for potential surgical candidate), PEG, G-tube
• Pain control: RT or medications
• Bleeding: RT or surgery

六、化學治療原則

(一) PRINCIPLES OF SYSTEMIC THERAPY

- 化療方案應該根據病患體力狀態、合併症、毒性反應選擇，對晚期腫瘤患者應用三種藥物聯合處方前，應確定患者的身體狀況良好（ECOG PS 0~1），並能夠經常進行毒性評估。
- 如果有證據支持毒性更低並且療效不受影響時可以優先選定（如有指示）1 類方案的改良方案或使用 2A、2B 類方案。
- 任何方案的劑量和用藥方案若不是來自 1 類證據，則只作為一種建議，應根據具體情況進行適當修改。
- 允許基於是否能獲得的藥物、臨床指引中的喜好和禁忌證據改變細胞毒藥物的組合及用藥方案。
- 靜脈滴注 5-FU 和口服 capecitabine 可互換使用（除非明確標示）。與 5-FU 注射相比，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。

(二) Regimen

Neoadjuvant chemoradiation followed by surgery for resectable cancer

Cisplatin + 5-FU

5-FU	600 - 1000 mg/m2/d civi	d1-4
Cisplatin	70 – 80 mg/m2 iv	d1
q3-4w x 2 cycles		

1.Bedenne L et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 2007; 25:1160.

2.Herskovic A et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Eng J Med 1992; 326:1593.

Cisplatin +/- Capecitabine (UFUR) (Cisplatin alone ?)

Cisplatin	25-30 mg/m2 iv	d1
Capecitabine	800 mg/m2 po bid	d1-5
Qw x 12 cycles		

Lee SS 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.

Perioperative chemotherapy for resectable adenocarcinoma

Cisplatin + 5-FU check **Full paper**

Cisplatin	70- 100 mg/m2 iv	d1
5-FU	750 -1000 mg/m2/d civi	d1-4
Q3-4w total 6 cycles (2-3 cycles before operation)		

Boige V et al. Final results of a randomized trial comparing preoperative 5-fluorouracil (F) / cisplatin (P) to surgery alone in adenocarcinoma of stomach and lower esophagus (ASLE): FNLCC ACCORD07-FFCD 9703 trial. 2007 ASCO annual meeting. Abstract 4510.

Concurrent chemoradiation for locally advanced cancer

Cisplatin + 5-FU

5-FU	600 - 1000 mg/m2/d civi	d1-4
Cisplatin	70 – 80 mg/m2 iv	d1
q3-4w x 4 cycles		

Herskovic A et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Eng J Med 1992; 326:1593.

Cisplatin + Capecitabine (or UFUR)

Cisplatin	25-30 mg/m2 iv	d1
Capecitabine	800 mg/m2 po bid	d1-5
Qw		

Cisplatin + UFUR

Lee SS 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.

Chemotherapy for stage IV cancer

Cisplatin + 5-FU

Cisplatin	75- 100 mg/m2 iv	d1
5-FU	750 -1000 mg/m2/d civi	d1-4
Q4w x 3 - 6 cycles		

Lorenzen S 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 Arbeitsgemeninschaft internistische Onkologie. Ann Oncol 2009;20:1667.

PFL

Cisplatin	50 mg/m2 iv	d1
5-FU	2400 - 3000 mg/m2/d civi 46-48 hours	d1
Leucovorin	200 mg/m2/d civi 46-48 hours	d1
Q2w x 6 - 12 cycles		

Bouche O et al. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study--FFCD98.3. J Clin Oncol 2004;22:4319.

P-HDFL

Cisplatin	25-30 mg/m2 iv	d1, 8, 15
5-FU	2000 - 2600 mg/m2/d civi	d1, 8, 15
Leucovorin	200 mg/m2/d civi	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.

Docetaxel (check weekly Docetaxel, 1, 8, q3w, 30-35mg/m2: 1, 8, 15, q4w; 22-25 mg/m2)

Docetaxel	60-75 mg/m2 iv	d1
Q3w x 4 - 6 cycles		

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/m2 iv	d1, 8, 15
Q4w x 3 -6 cycles		

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

Paclitaxel + Cisplatin

Paclitaxel	90 mg/m2 iv	d1
Cisplatin	50 mg/m2 iv	d1
Q2w		

Modified Paclitaxel + Cisplatin

Paclitaxel	60 - 80 mg/m2 iv	d1, 8, 15
Cisplatin	70-80 mg/m2	d1
Q4w x 3 -6 cycles		

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.

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

S-1 Check TS-1

Tegafur/potassium oxonate/gimeracil	BSA < 1.25	40mg bid
	BSA 1.25 - 1.5	50mg bid
	BSA ≧1.5	60mg 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

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七、放射治療原則

Treatment Regimen	Reference
CCRT： CCRT*[1]：Favor 3D CRT or IMRT with definitive dose of 60~70Gy CCRT*[2]：Favor 3D CRT or IMRT with neoadjuvant/adjuvant dose of 45~52Gy CCRT*[3]：Complete definitive CCRT dose Chemotherapy（Recommed regimen）： ①weekly cisplatin：25-30mg/m^2 ②PF：cisplatin 75-80mg/m2 D1；5-Fu 600-800 mg/m2 /day D1-4, q3-4wk ③weekly PFL：cisplatin 25mg/ m^2、5-Fu 2000mg/ m^2、LV 250mg/ m^2	Minsky BD, Pajak T, Ginsberg RJ, et al. INT 0123(RTOG 94-05) Phase III trial of combined modality therapy for esophageal cancer: high dose (64.8Gy) vs. standard dose (50.4 Gy) radiation therapy. J Clin Oncol 2004:22:45-52. Al-Sarraf M, Martz K, Herskovic A, et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol.1997; 15(1):277-284.

八、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，或者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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