振興醫療財團法人振興醫院

胃癌治療準則

癌 症 委 員 會

胃癌多專科醫療團隊

注意事項：這個診療準則主要作為醫師和其他保健專家診療癌症病人參考之用。
假如你是一個癌症病人,直接引用這個研究資訊及診療準則並不恰當，
只有你的醫師才能決定給你最恰當的治療。2010 年 2 月初訂 2017 年 12 月 28 修訂

Abbreviations

1. Bx=Biopsy
2. C/T=Chemotherapy
3. C/R=Chemoradiation
4. R/T= Radiotherapy
5. Cap.=Capecitabine
6. FluoroP=Fluoropyrimidine
7. LUV=Leucovorin
8. EMR=Endoscopic Mucosal Resection =>ER
9. ESD=Endoscopic Submucosal Dissection

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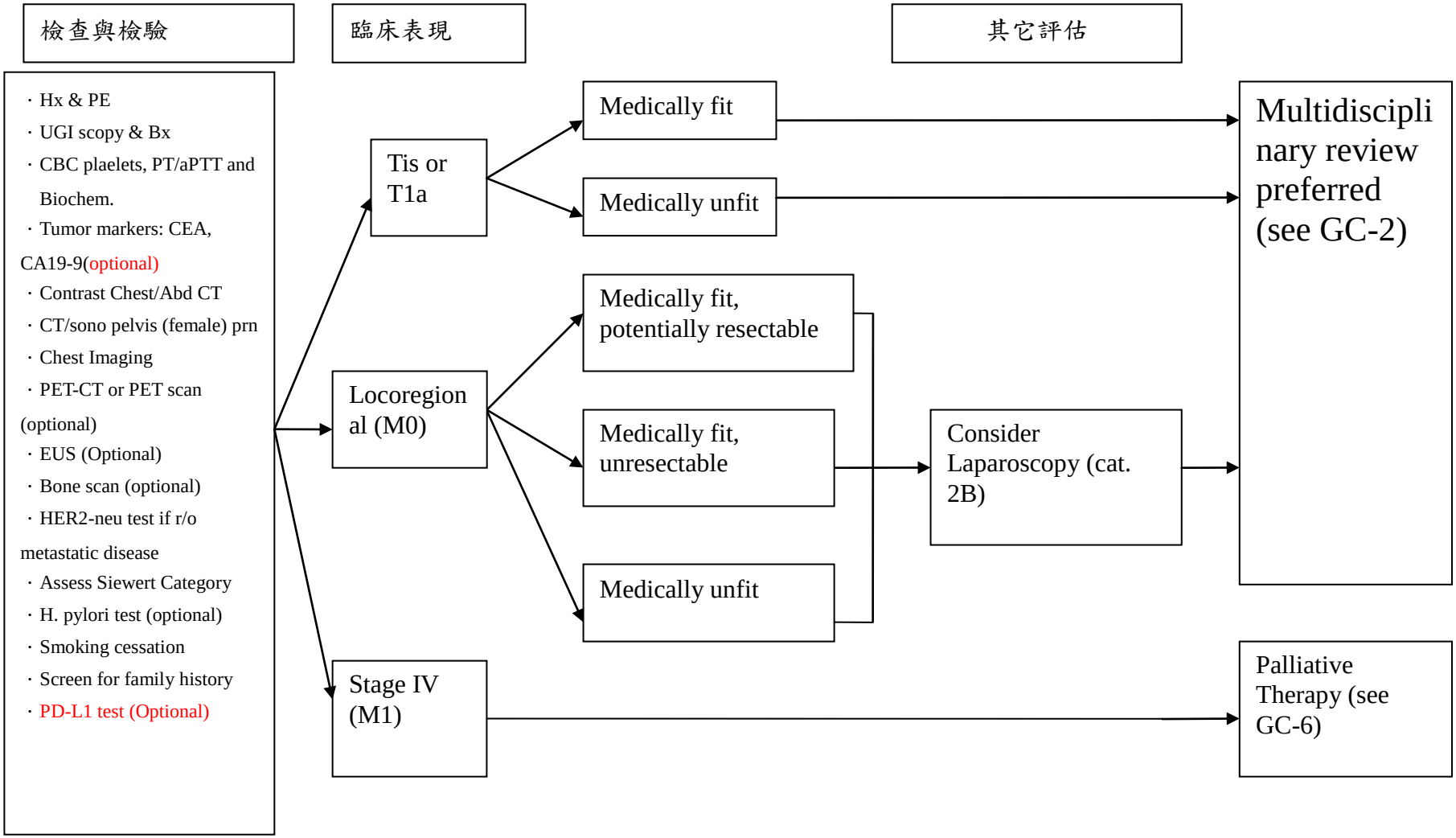

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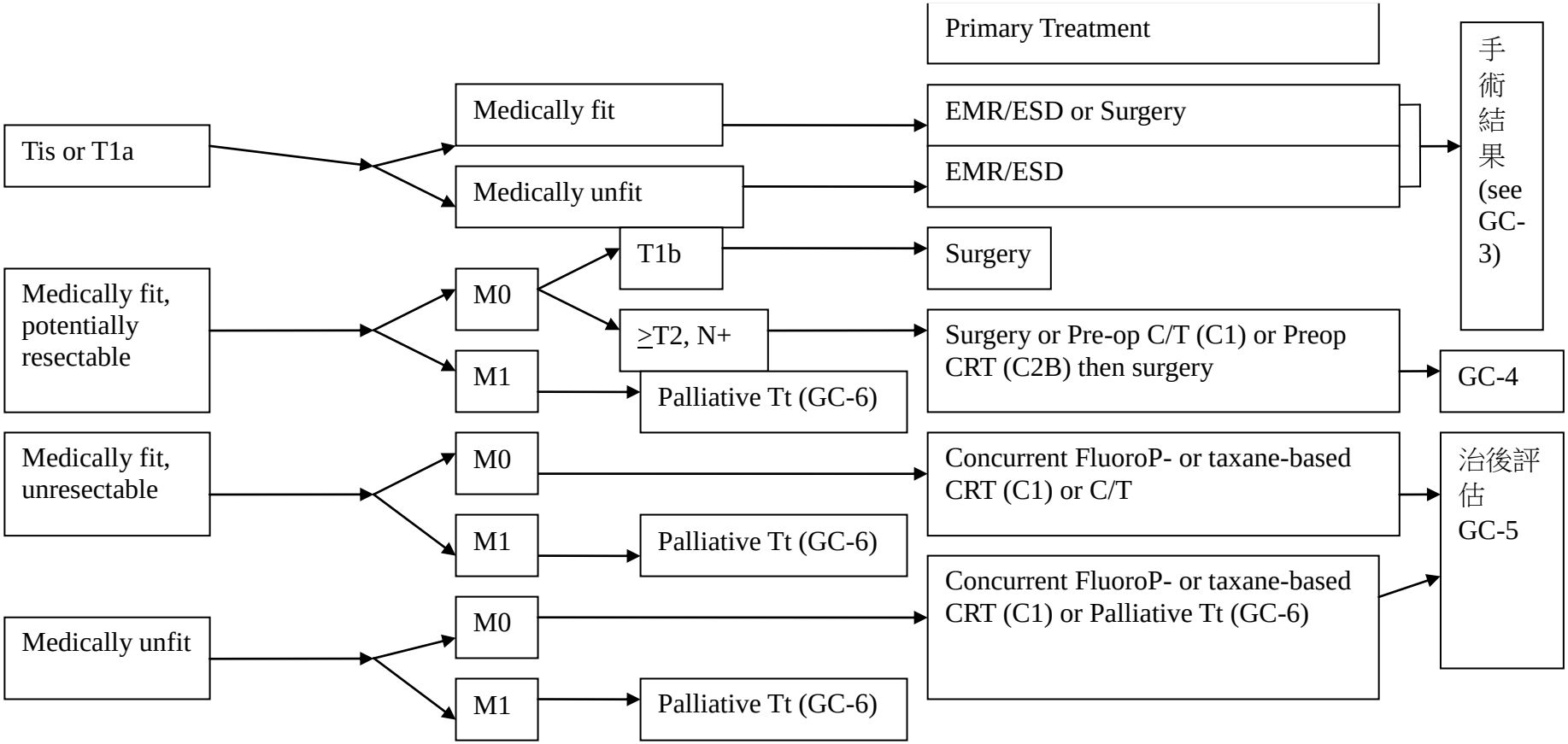

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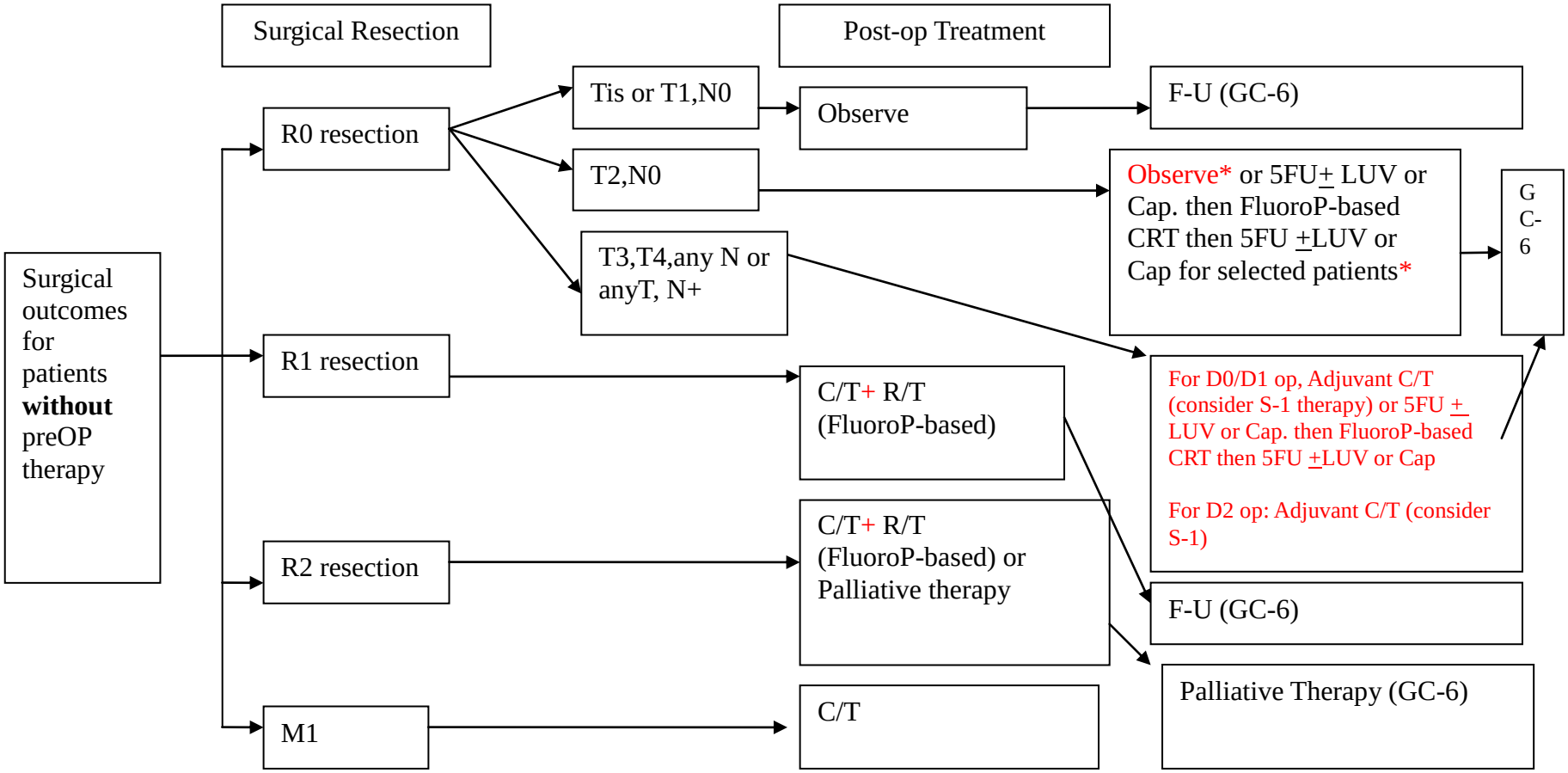

* **High risk features**: poorly differentiation or higher grade, lymphovascular invasion, neural invaision or < 50 y/o or patients who did not undergo D2 LN dissection.

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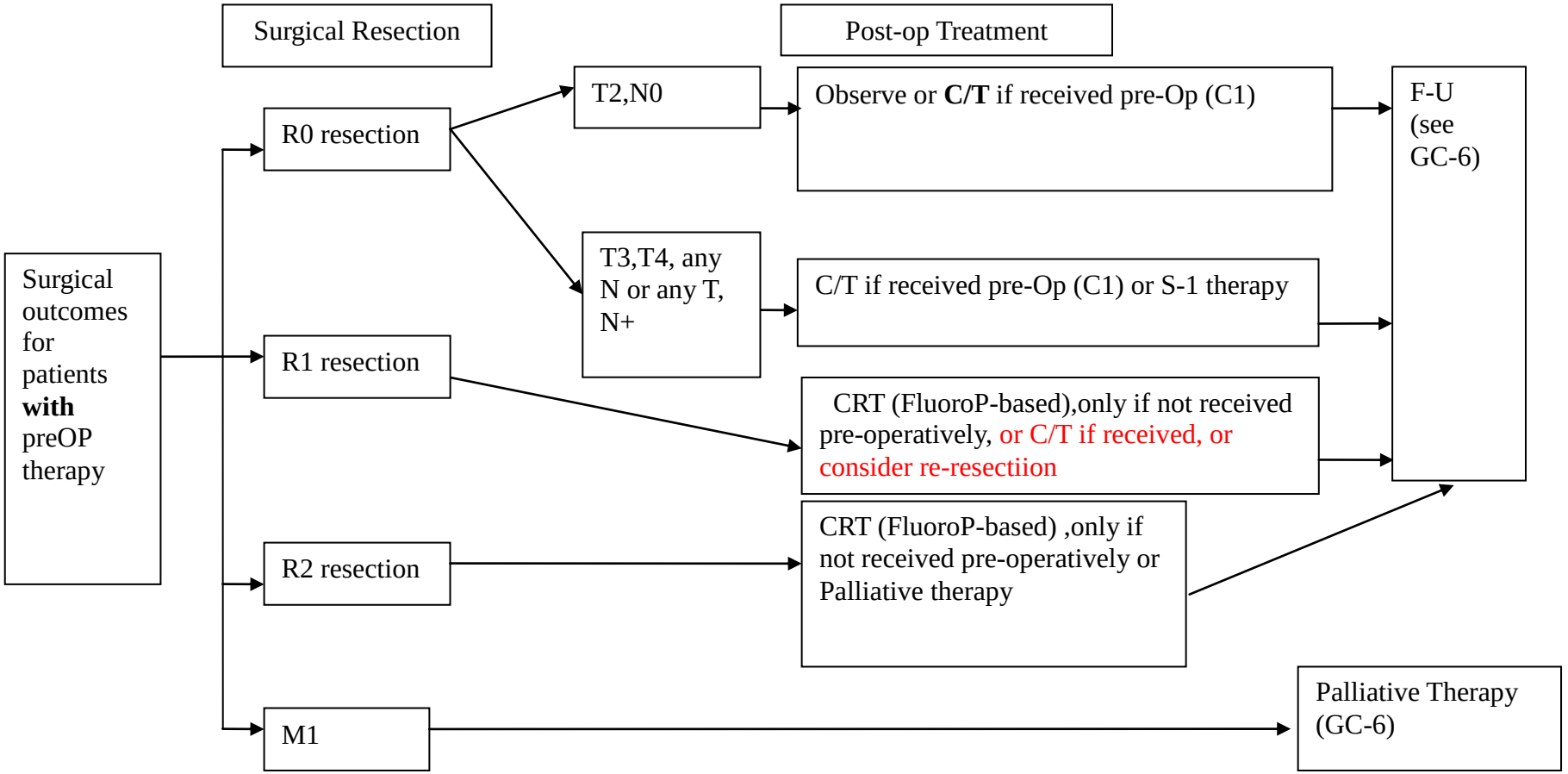

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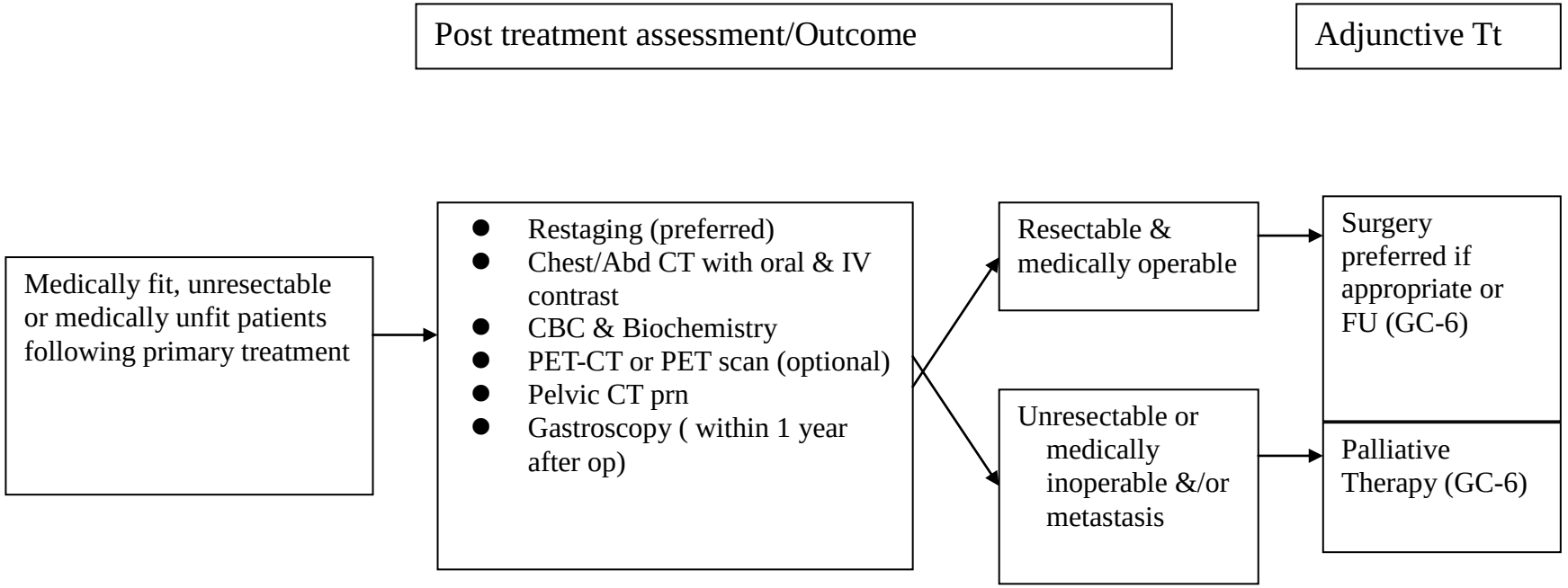

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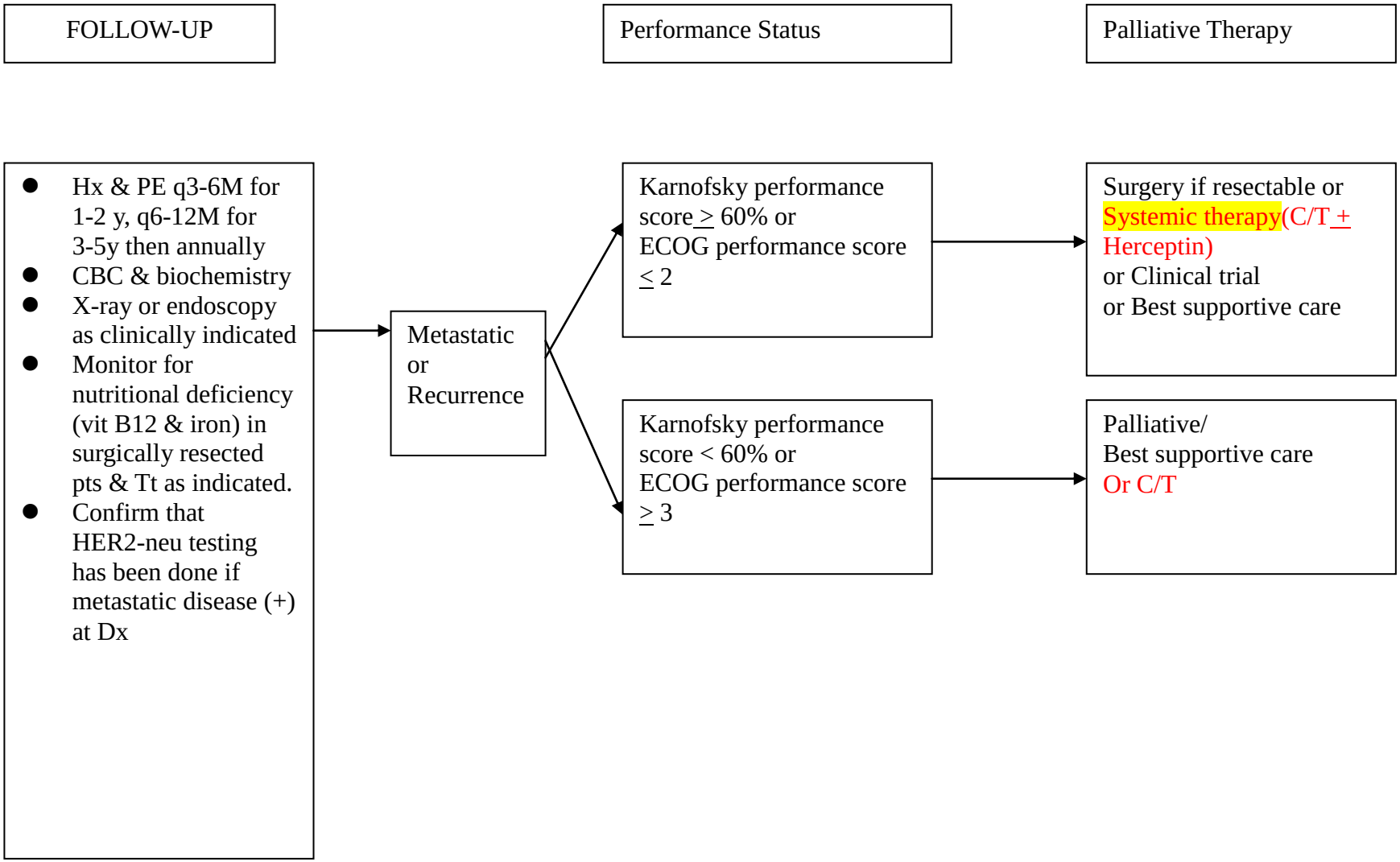

Principle of Surgery

- N Staging

- Determine extent of disease by CT scan (chest, abdomen, and pelvic) ± EUS (if no metastatic disease seen on CT).
- In patients being considered for surgical resection without preoperative therapy, laparoscopy may be useful in detecting radiographically occult metastatic disease in patients with T3 and/or N+ disease seen on preoperative imaging. If laparoscopy is performed as a separate procedure, peritoneal washings should be performed as well.
- In patients receiving preoperative therapy, a baseline laparoscopy along with peritoneal washings should be considered.
- Positive peritoneal cytology (performed in the absence of visible peritoneal implants), is associated with poor prognosis and is defined as M1 disease.

• Criteria of unresectability for cure

- Locoregionally advanced

-Disease infiltration of the root of the mesentery or para-aortic lymph node (Level 3 or 4 LNs) highly suspicious on imaging or confirmed by biopsy

-Invasion or encasement of major vascular structures (excluding the splenic vessels)

- Distant metastasis or peritoneal seeding (including positive peritoneal cytology)

Resectable tumors

- Tis or T1 tumors limited to mucosa (T1a) may be candidates for endoscopic mucosal resection
- T1b-T3 : Adequate gastric resection to achieve negative microscopic margins (typically **4 cm** from gross tumor). Distal/Subtotal/ total gastrectomy
- T4 tumors require en bloc resection of involved structures
- Gastric resection should include the regional lymphatics-- perigastric lymph nodes (D1) and those along the named vessels of the celiac axis (D2), with a goal of examining **15** or greater lymph

nodes

- Routine or prophylactic splenectomy is not required. Splenectomy is acceptable when the spleen or the hilum is involved.
- Consider placing feeding jejunostomy tube in select patients (especially if postoperative chemoradiation appears a likely recommendation)

Unresectable tumors (palliative procedures)

- Gastric resections should be reserved for the palliation of symptoms (eg, obstruction or uncontrollable bleeding) in patients with incurable disease.
- Lymph node dissection is not required.
- In patients fit for surgery and who have a reasonable prognosis, gastrojejunostomy (open or laparoscopic) is preferable to endoluminal stenting in patients with gastric outlet obstruction.
- Venting gastrostomy and/or jejunostomy tube may be considered.

PRINCIPLES OF RADIATION THERAPY

胃癌的治療指引以上消化道多專科團隊訂定的治療準則為依據。以下僅就放射治療的適應症、治療技術、治療劑量、以及正常組織的 劑量限制來說明肝癌放射治療政策及執行程序。

一、放射治療政策

放射治療的適應症:

(一) T2-4 and/or LN+ resectable and operable: post-op CCRT. (Not include T2N0M0 with R0)

(二) T2-4 and/or LN+ unresectable and inoperable: CCRT. C/T alone if patient not R/T candidate. R/T alone for palliation.

(三) M1: R/T for palliation.

二、放射治療執行程序**(procedures)**:

(一) 電腦斷層模擬攝影**(CT-based simulation)**

1. 病人禁食 4 小時。
2. 仰臥、双手置於頭頂，並以真空氣墊(vaccum pillow) or alpha cradle 固定姿勢
3. 以雷射光於病人腹部、身體兩側劃上等中心(isocenter)記號
4. 透過靜脈注射顯影劑，可加強判讀腫瘤侵犯之範圍，但如果病患腎功能差(creatinine>2.0 mg/dl)或其他禁忌症為例 外。
5. 每 3-5 毫米擷取一張電腦斷層影像
6. 將影像傳送至電腦治療計劃系統(radiation treatment plan, RTP system)

(二)　描繪標靶體積 **(contouring target volume)**

勾劃出腫瘤體積 (gross tumor volume, GTV)、臨床腫瘤體積(clinical tumor volume, CTV)和計劃靶區體積(planning target volume, PTV)的位置，定義如下:

Target volumes	Definition and description
GTV (gross tumor volume)	Primary: all gross tumor and enlarged lymph nodes (> 1cm) defined
CTV	Tumor bed, subsite nodal groups, remnant stomach, anastomosis
PTV	CTV + 0.5-1cm margin

(三)　體外放射治療技術 (external radiotherapy technique)：

1. 三維順形放射治療(3-Dimension Conformal Radiation Therapy, 3D-CRT)
2. 強度調控放射治療(Intensity Modulation Radiation Therapy, IMRT)
3. 影像導引放射治療(Image-guided Radiation Therapy, IGRT)

(四)　劑量處方 **(dose prescription)**：

1. 手術後進行輔助性合併化學放射治療 (adjuvant CCRT): 45Gy/25fx when CCRT. Boost to 50.4-54Gy for positive margins or residual disease
2. Palliative radiotherapy: 30-50Gy/15-25fx

(五) Organs At Risk (OAR):

1. Spinal cord:
   Dmax<= 45 Gy。

2. Heart

   V40Gy <50%

3 Liver:

   70% of volume < 30Gy

4. Kidney:

   70% of volume of each kidney <20Gy

(六) 治療驗證**(Treatment Verification)**

1. 三度空間放射治療或強度調控放射治療：治療前及每周應由放射師拍攝電腦斷層影像(Cone beam CT)來驗證照野之中心點。

2. 影像導引放射治療(IGRT)：如放射治療設備備有影像導引功能，每日治療前應由放射師拍攝電腦斷層影像(Cone beam CT)確認治療範圍。

(七) 參考資料:

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4. International Commission on Radiation Units and Measurements. ICRU Report No 62: Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50).Bethesda, MD: ICRU Publications 1999.
5. Target Volume Delineation and Field Setup: A Practical Guide for Conformal and Intensity-Modulated Radiation Therapy, Nancy Y. Lee & Jiade J. Lu, 2013
6. Handbook of Evidence-Based Radiation Oncology, Hansen, Eric, Roach III, Mack (Eds.), 2nd ed. 2010

PRINCIPLES OF SYSTEMIC THERAPY

- **Systemic therapy regimens recommended for advanced esophageal and esophagogastric junction (EGJ) adenocarcinoma, squamous cell carcinoma of the esophagus, and gastric adenocarcinoma may be used interchangeably (except as indicated).**
- **Regimens should be chosen in the context of performance status (PS), medical comorbidities, and toxicity profile.**
- **For metastatic adenocarcinoma trastuzumab can be added to chemotherapy if tumor overexpresses HER2-neu.**
- **Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.**
- **Modifications of category 1 regimens or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting a more favorable toxicity profile without compromising efficacy.**
- **Doses and schedules for any regimen that is not derived from category 1 evidence are a suggestion, and are subject to appropriate modifications depending on the circumstances.**
- **Alternate combinations and schedules of cytotoxics based on the availability of the agents, practice preferences, and contraindications are permitted.**
- **Infusional fluorouracil and capecitabine may be used interchangeably without compromising efficacy (except as indicated). Infusion is the preferred route compared with bolus fluorouracil.**
- **Cisplatin and oxaliplatin may be used interchangeably depending on toxicity profile.**
- **Perioperative chemotherapy, or postoperative chemotherapy plus chemoradiation is the preferred approach for localized gastric cancer.**
- **Postoperative chemotherapy is recommended following primary D2 lymph node dissection.**
- **Induction chemotherapy may be appropriate as clinically indicated.**
- **In the adjuvant setting, upon completion of chemotherapy or chemoradiation, patients should be monitored for any long-term therapy-related complications.**

***Recommended regimens for adjuvant chemotherapy**

1. TS-1 (or S-1)[1] (Stage II, IIIA, IIIB, T1 excluded):TS-1 80mg/m2 per day (Bid) for 4 weeks every 6 weeks for 1 year

2. Xelox[2] (capecitabine/oxaliplatin)(IIIc: NHI paid, Other node +: self paid)

Oxaliplatin 135mg/m2 on D1, Capecitabine 1000mg/m2 BID for 14 days every 3 weeks for 6 months

Or

Oxaliplatin 85mg/m2 on D1, Capecitabine 1000mg/m2 BID for 10 days every 2 weeks for 6 months

3. C/T followed by CCRT (XP/XRT/XP)[27] (IIIA, IIIB, D2 dissection, self paid Xeloda)

XP(Capecitabine 2000 mg/m2 /day on days 1 to 14 and cisplatin 60 mg/m2 on day 1), repeated every 3 wks

The XP/XRT/XP arm received 2 cycles of XP followed by 45-Gy XRT (Capecitabine 1650 mg/m2/day x 5 wks) & 2 cycles of XP.

4. CCRT (McDonald trial 0116)(1, 3, 4 cycles)

Leucovorin (20mg/m2) IV on day 1-5 + 5FU (425 mg/m2)IV on day 1-5, cycled every 28 days

+

Leucovorin + 5 FU (2^{nd} cycle)

Leucovorin (20 mg/m2) IV on days 1-4 and 31-33

5FU (400 mg/m2) IV on days 1-4 and 31-33

***Recommended regimens for recurrent or metastatic gastric cancer**

First-line therapy regimens:

1. **Xelox (capecitabine/oxaliplatin, *preferred regimen*)**[4]
   Oxaliplatin 135 mg/m2 on D1, Capecitabine 1000mg/m2 BID for 14 days every 3 weeks
   Or Oxaliplatin 85mg/m2 on D1, Capecitabine 1000mg/m2 BID for 10 days every 2 weeks
2. **High dose PFL (cisplatin/fluorouracil/leucovorin)**
   Cisplatin 30mg/m2 IV, folinic acid 500 mg/m2 IV, 5-fluorouracil (5-FU) 2200 mg/m2 CIVD for 22 h, weekly x 6 months
   Or Cisplatin 75-100 mg/m^2 IV on Day 1
   Fluorouracil 750-1000 mg/ m^2 IV continuous infusion over 24 hours daily on Day 1-4
   Cycled every 28 days

3. TS-1 + cisplatin[5]

TS-1:40-60 mg BID for 21 days every 5 weeks, Cisplatin 60mg/m2 on D8

4. XP (Capecitabine & Cisplatin)

Cisplatin 80 mg/m^2 IV on Day 1

Capecitabine 1000 mg/m^2 PO BID on Day 1-14

Cycled every 21 days

5. FOLFOX[9]

Oxaplatin 85 mg/m2 IV, Leucovorin 400 mg/m2 IV, 5FU 400 mg/m2 IV on day 1and then 1200mg/m2 CIVD on D1, D2 , every 2 wks

6. Weekly OFL[10]

Oxaplatin 65 mg/m2 IV, Leucovorin 300 mg/m2 IV, 5FU 2600 mg/m2 CIVD for 24 hrs, weekly.

7. ECF

Epirubicin (50 mg/m2) IV on day 1

Cisplatin (60 mg /m2)IV on day 1

Capecitabine (625 mg/m2) po bid on day 1-21 (self paid)

Cycles every 21 days.

8. ECF (metastatic ca)

Epirubicin (50 mg/m2) IV on day 1

Cisplatin (130 mg /m2)IV on day 1

Capecitabine (625 mg/m2) po bid on day 1-21 (self paid)

Cycles every 21 days.

***Preferred targeted therapy:**

Trastuzumab (self paid) + chemotherapy in HER-2 (+)[11]

- **Second line therapy**

-Folfiri[31]

Irinotecan 180 mg/ m^2 IV on D1, folinic acid 400 mg/m2 iv on D1, 5FU 400 mg/m2 IV bolus then 5FU 1200 mg/m2 iv on D1, D2, then every 2 wks

-Ramucirumab[15]

Ramucirumab 8 mg/kg IV on Day 1
Cycled every 14 days

-Ramucirumab + paclitaxel[16]

Ramucirumab 8 mg/kg IV on Day 1 and Day 15
Paclitaxel 80 mg/m2 on Day 1, 8, and Day 15
Cycled every 28 days

-Docetaxel[17]

Docetaxel 75-100 mg/ m^2 IV on Day 1
Cycled every 21 days

-Paclitaxel[18]

Paclitaxel 135-250 mg/ m^2 IV on Day 1
Cycled every 21 days Or
Paclitaxel 80 mg/ m^2 IV on Day 1 weekly
Cycled every 28 days

Or

Paclitaxel 80 mg/ m^2 IV on Day 1, 8, and Day 15
Cycled every 28 days

- **Irinotecan**[18]

- Irinotecan 250-350 mg/ m^2 IV on Day 1
  Cycled every 21 days
- Irinotecan 150-180 mg/ m^2 IV on Day 1
  Cycled every 14 days
- Irinotecan 125 mg/ m^2 IV on Day 1 and 8
  Cycled every 21 days

- **Second line therapy**

Immunotherapy (Anti-PD1/Anti-PDL1 therapy)

- Nivolumab 3mg/kg IV on D1[34] (2nd line, self paid)

  Cycle every 14 days

- Pembrolizumab 10mg/kg on D1 in Patients with PD-L1 positive[35]

  Cycle every 14 days (3rd line, self paid)

Pathological TNM Staging System: UICC/AJCC 2017 8th Edition

	pN0 0	pN1 1-2	pN2 3-6	pN3a 7-15	pN3b >15
pT1	IA	IB	IIA	IIB	IIIB
pT2	IB	IIA	IIB	IIIA	IIIB
pT3	IIA	IIB	IIIA	IIIB	IIIC
pT4a	IIB	IIIA	IIIA	IIIB	IIIC
pT4b	IIIA	IIIB	IIIB	IIIC	IIIC

Amin MB, Edge S, Greene F, et al. (eds.)
AJCC cancer staging manual 8th edition.
New York: Springer International

Clinical TNM Staging System: UICC/AJCC 2017 8th Edition

	T1	T2	T3	T4a	T4b
N0	I	I	IIB	IIB	IVA
N+	IIA	IIA	III	III	IVA
M1	IVB	IVB	IVB	IVB	IVB

Amin MB, Edge S, Greene F, et al. (eds.) AJCC cancer staging manual 8th edition. New York: Springer International Publishing, 2017.

Table 1

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Carcinoma of the Stomach
(7th ed., 2010)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria
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 penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures**,***
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures**,***
T4a	Tumor invades serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures

Regional Lymph Nodes (N)

NX	Regional lymph node(s) 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
N3a	Metastasis in 7 - 15 regional lymph nodes
N3b	Metastasis in 16 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
G4	Undifferentiated

*Note: A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified T4.

**The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

***Intramural extension to the duodenum or esophagus is classified by the depth of the greatest invasion in any of these sites, including the stomach.

§A designation of pN0 should be used if all examined lymph nodes are negative, regardless of the total number removed and examined.

Table 1 - Continued

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Carcinoma of the Stomach
(7th ed., 2010)

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

NCCN Categories of Evidence and Consensus

- **Category 1:** The recommendation is based on high level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.
- **Category 2A:** The recommendation is based on lower level evidence and there is uniform NCCN consensus.
- **Category 2B:** The recommendation is based on lower level evidence and there is nonuniform NCCN consensus (but no major disagreement).
- **Category 3:** The recommendation is based on any level of evidence but reflects major disagreement.

- All recommendations are category 2A unless otherwise noted.

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.

Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

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