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 2016 年 12 月 29 日修訂

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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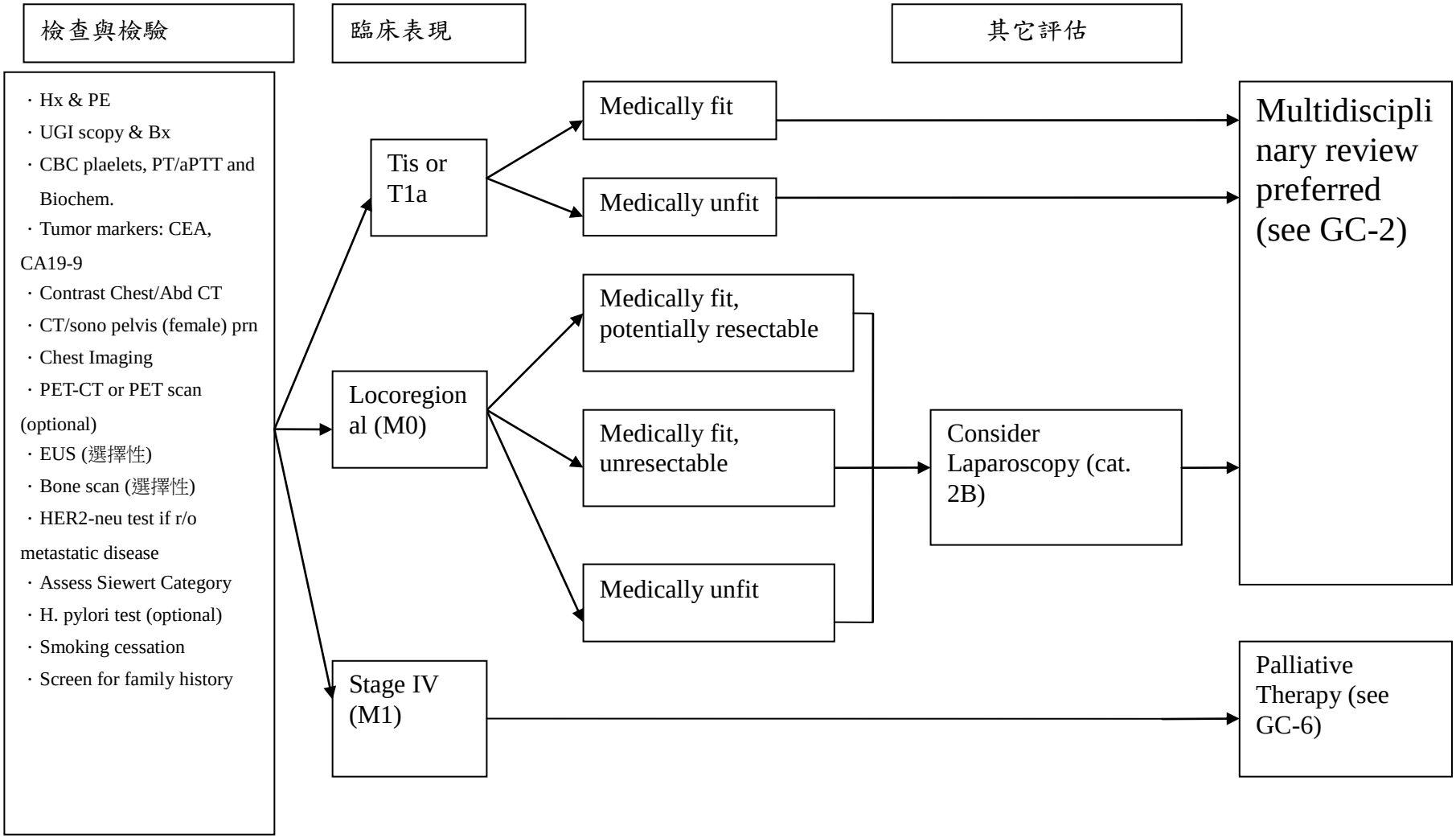

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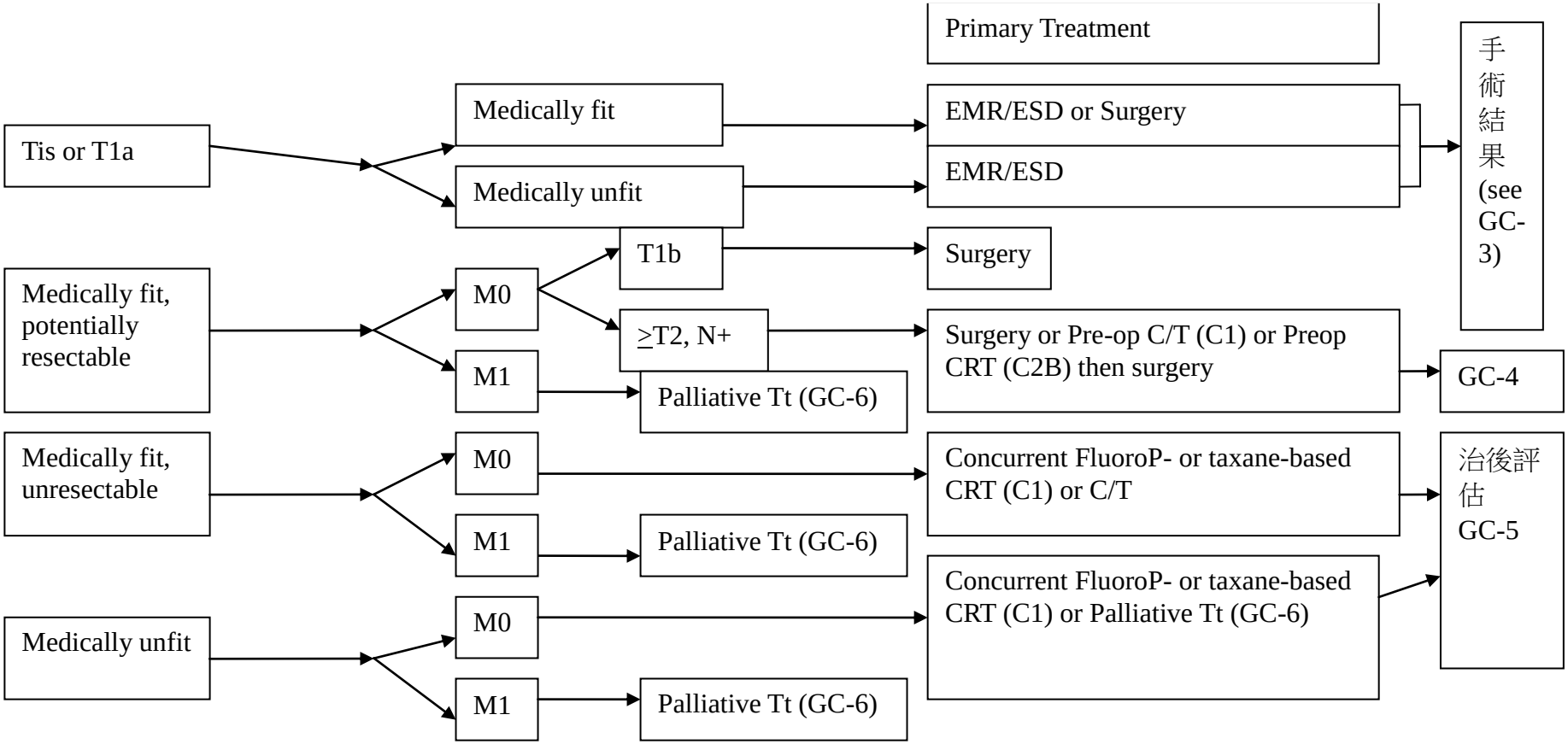

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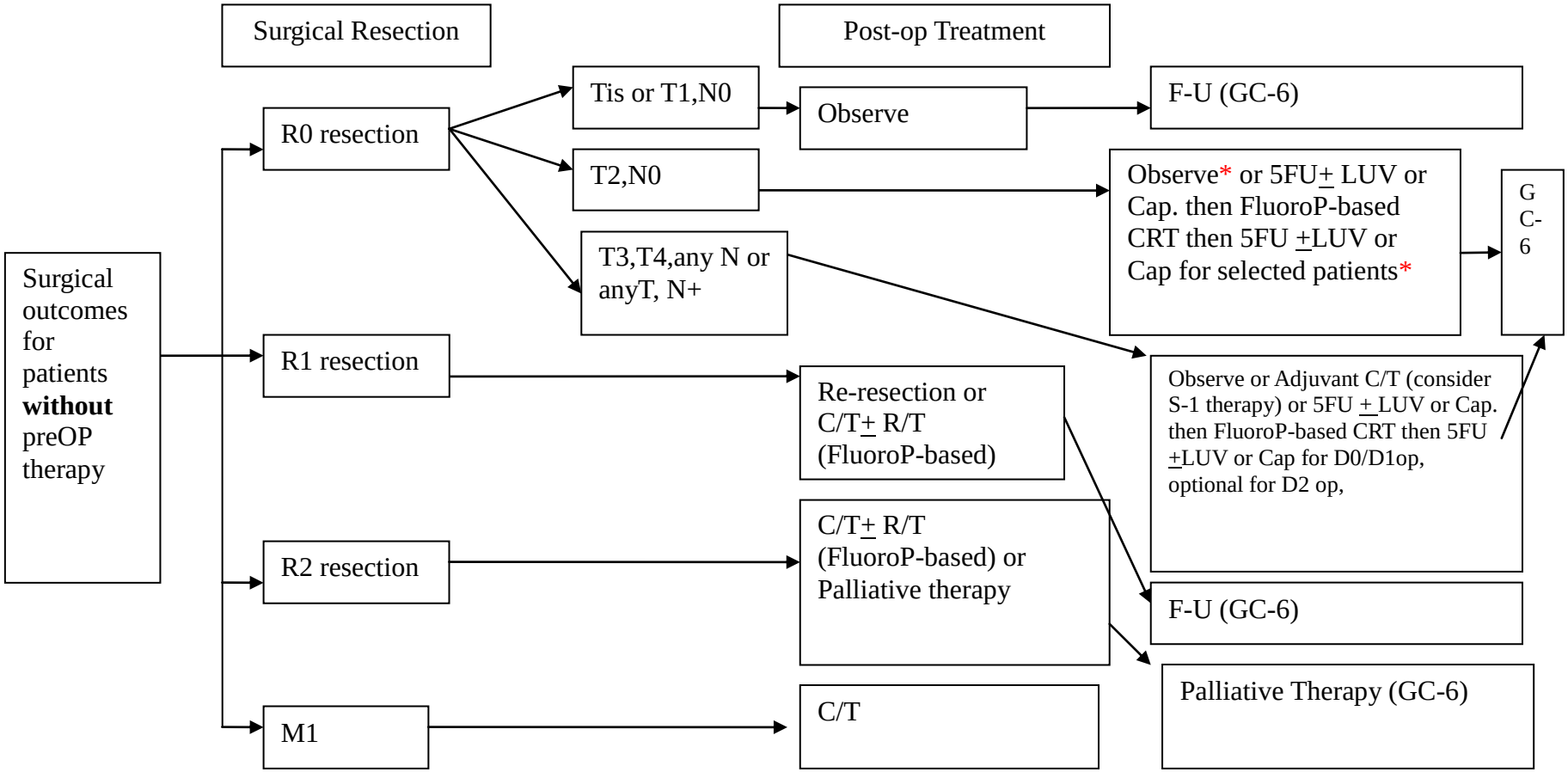

* **High risk features**: poorly differentiation or higher grade, lymphovascular invasion, neural invaision or < 50 y/o or patients who did not undergo D2 LN dissection.

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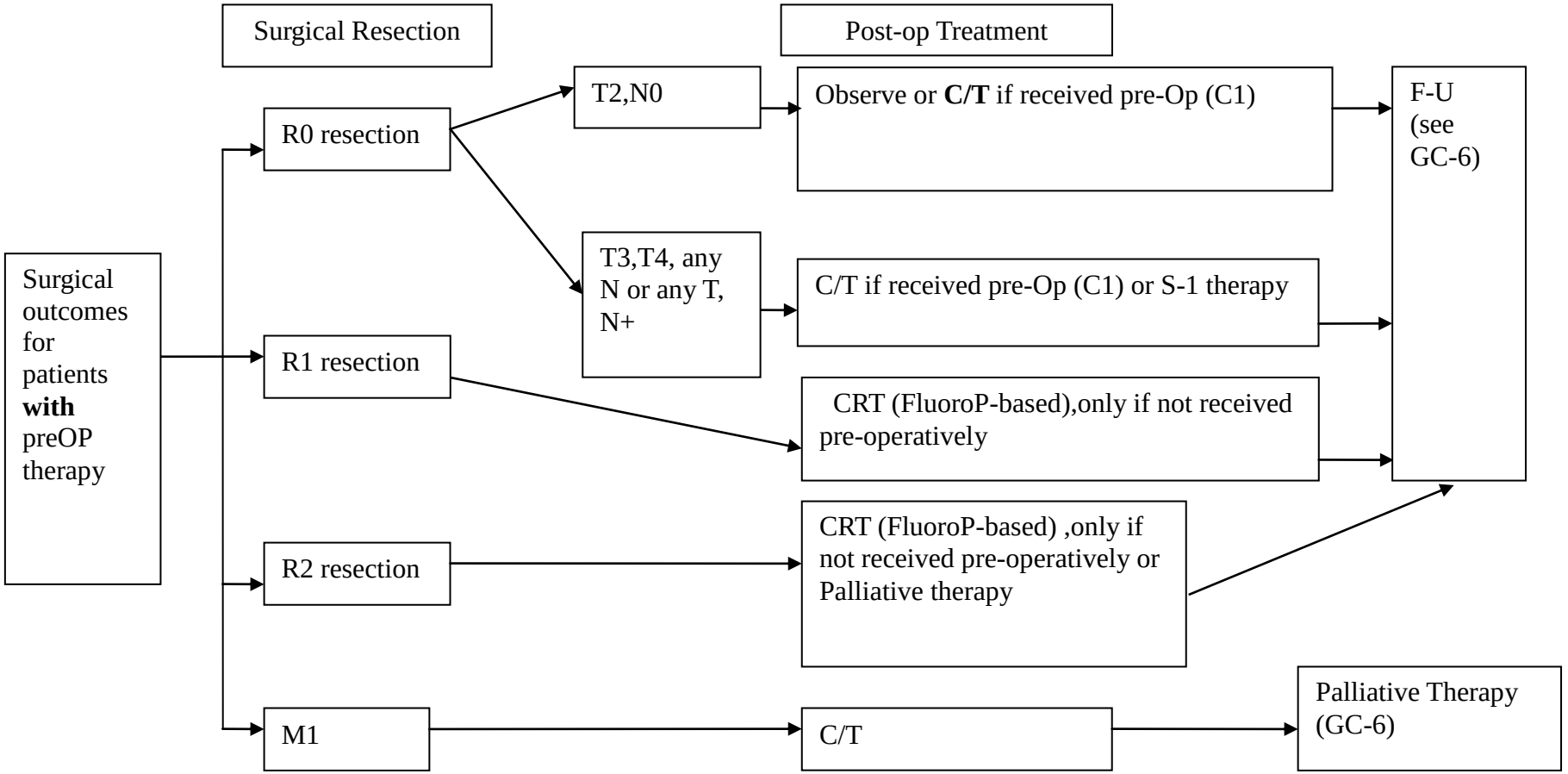

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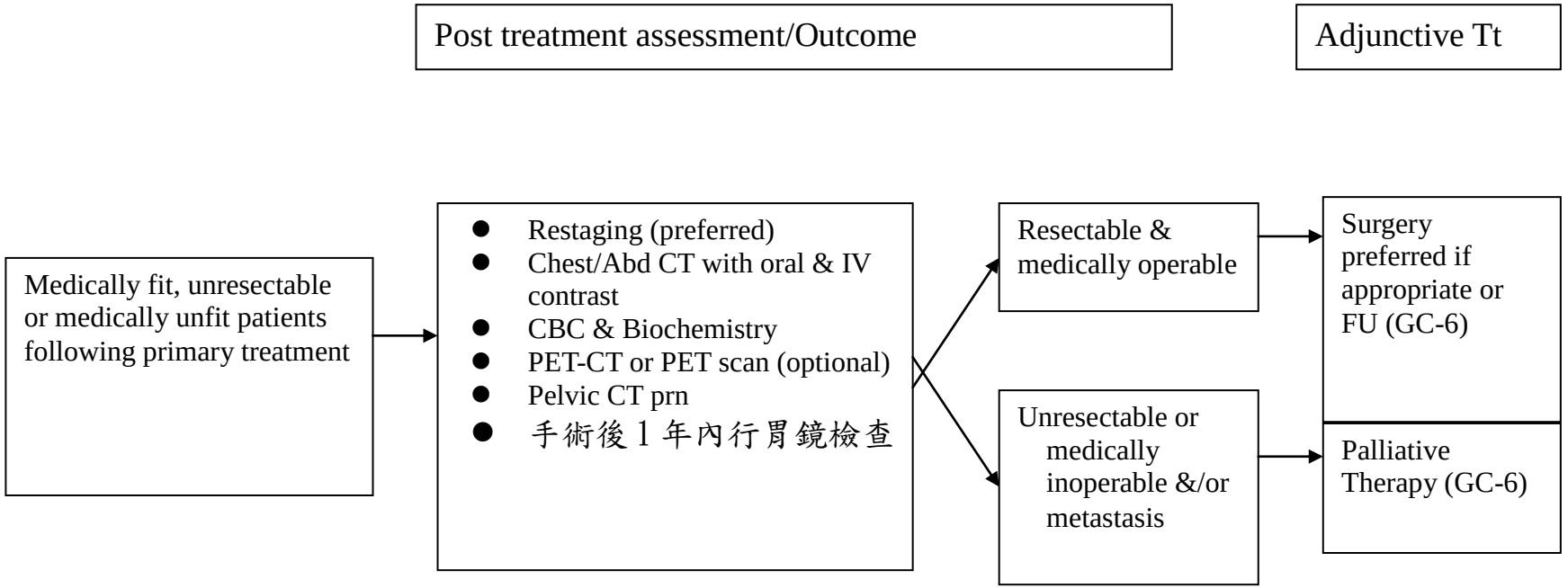

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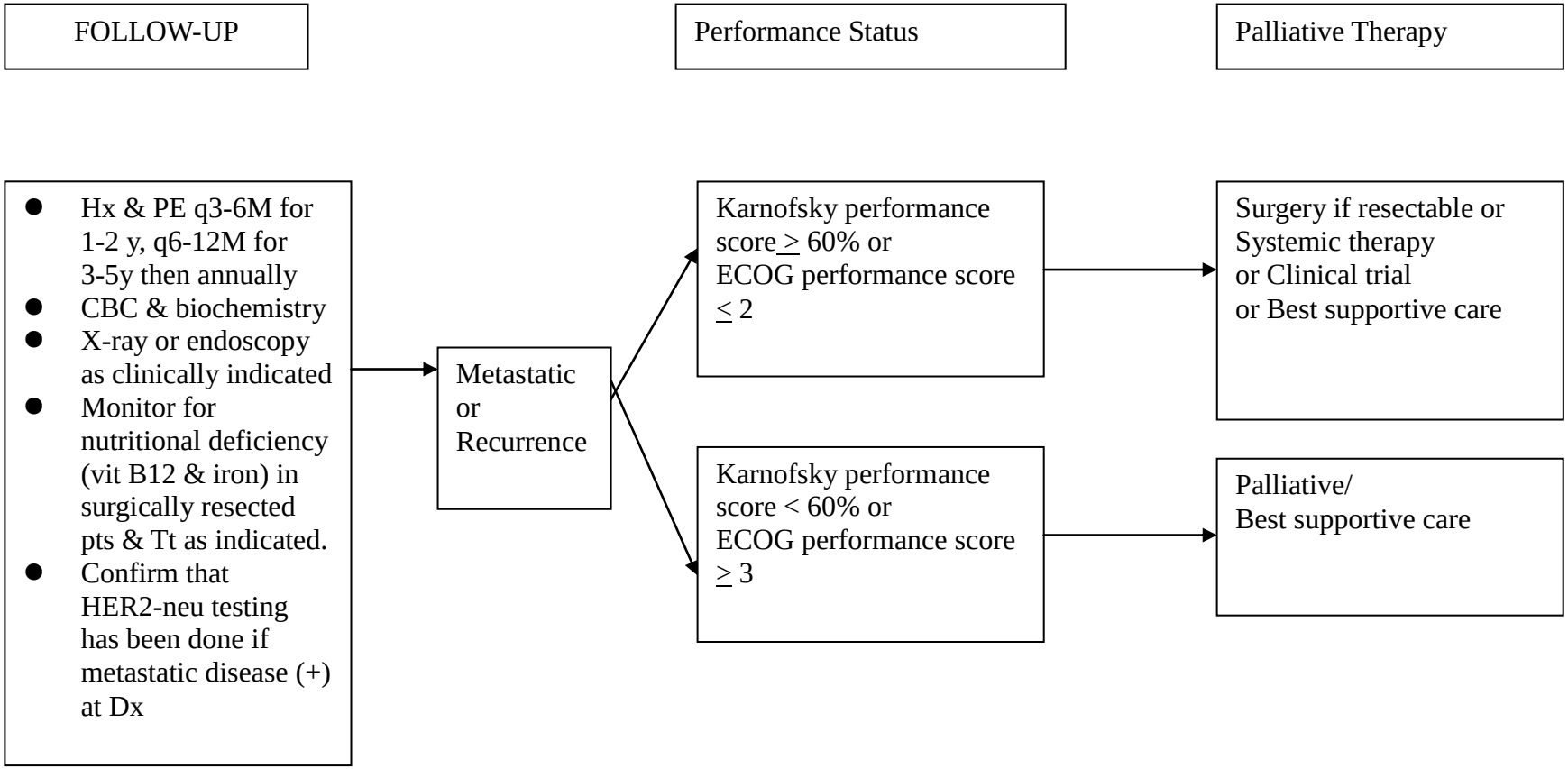

Principle of Surgery

- 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 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.

(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/12-25fx

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]: TS-1 80mg/m2 per day (Bid) for 4 weeks every 6 weeks for 1 year (105年10月20日健保給付條件：(1)胃癌術後輔助性化療，用於罹患TNM Stage II（排除T1）、IIIA 或IIIB 胃癌且接受過胃癌根除性手術的成年患者，限用1年。(2)需經事前審查核准後使用）

2. XELOX[2、4、5] (capecitabine(在 **adjuvant 要**自費)**/oxaliplatin)**

Oxaliplatin **130**mg/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. **Capecitabine**(在 **adjuvant 要**自費)**+Cisplatin**[31]

Cisplatin (80 mg/m2) IV Daily on day 1
Capecitabine (1000mg/m2) PO BID on day 1-14 Cycled every 21 day

4. Fluorouracil and Cisplatin
Fluorouracil 800 mg/m2 IV continuous infusion over 24 hrs daily on days 1-5
Cisplatin 75-80 mg/m2 IV on days 1
Cycles every 28 days for 6 Cycles

CCRT

1.Leucovorin+5-FU(1、3、4 Cycles**)**（院內藥局主套有的）

Leucovorin (20 mg/m2) IV on 1-5 DAY
5-FU (425 mg/m2) IV on 1-5 DAY
Cycles every 28 days
+
Leucovorin+5-FU(**2 nd** Cycles)
Leucovorin (20 mg/m2) IV on 1-4 DAY and 31-33
5-FU (400 mg/m2) IV on 1-4 DAY and 31-33

*Recommended regimens for recurrent or metastatic gastric cancer(optional)

1. XELOX (capecitabine/oxaliplatin, *preferred regimen*)[4、6]

Oxaliplatin 130 mg/m2 on D1, Capecitabine 1000mg/m2 BID for 14 days every 3 weeks

2. High dose PFL (cisplatin/fluorouracil/leucovorin) [10]

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（自費）+ cisplatin[5、7]

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

4. XP (Capecitabine（自費） & Cisplatin)

Cisplatin 80 mg/m^2 IV on Day 1
Capecitabine 1000 mg/m^2 PO BID on Day 1- 10（自費）
Cycles every 21 days

5. mFOLFOX6[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.Trastuzumab + chemotherapy in HER-2 (+)[11]（自費）

Trastuzumab 8mg/kg IV loading dose on day 1of cycle 1,then Trastuzumab 6mg/kg IV EVERY 21 DAYS

7. DCF regimen[12]

Docetaxel 75mg/m2 IV and Cisplatin 75mg/m2 IV on D1（自費）

5-FU 750mg/m2 CIVD on D1-5, every 3 weeks

8. **ECF**
Epirubicin (50mg/m2) IV on DAY 1
Cisplatin (60 mg/m^2) IV on Day 1
Capecitabine (625 mg/m^2) PO BID on Day 1-21（自費）
Cycled every 21 days

10. ECF(轉移性胃癌)

Epirubicin (50mg/m2) IV on DAY 1
Oxaliplatin (130 mg/m^2) IV on Day 1
Capecitabine (625 mg/m^2) PO BID on Day 1-21
Cycled every 21 days

10. Paclitaxel with Cisplatin
Paclitaxel 80-90 mg/m^2 IV on D1（自費）
Cisplatin 50 mg/m2 IV on D1
Cycled every 2 Weeks

11. FOLFIRI

Irinotecan 150-180 mg/ m^2 IV on D1(自費)

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016 Staging Gastric Cancer

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.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016 Staging Gastric Cancer

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.

References

1. *Sasako M, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol. 2011 Nov 20;29(33):4387-93. Epub 2011 Oct 17*

2. Y Bang et al. Adjuvant capecitabine and oxaliplatin for gastric cancer: Results of the phase III CLASSIC trial. Lancet. 2012 ;379:315-21

3. Paoletti X, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: A meta-analysis: GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group. JAMA 303:1729–1737

4. Park YH et al. Capecitabine in combination with Oxaliplatin (XELOX) as a first -line therapy for advanced gastric cancer. Cancer Chemother Pharmacol. 2008;61(4):623-9.

5. Kuo YC, et al. Modified biweekly oxaliplatin and capecitabine for advanced gastric cancer: a retrospective analysis from a medical center. Biomed J. 2014 ;37(3):141-6.

6. Chao Y, et al. A multicenter phase II study of biweekly capecitabine in combination with

oxaliplatin as first-line chemotherapy in patients with locally advanced or metastatic gastric cancer. Cancer Chemother Pharmacol. 2014;73:799-806.

7. Koizumi W et al.S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9(3):215-21.

8. Ryu MH et al. ML17032 trial: capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in advanced gastric cancer. Expert Rev Anticancer Ther. 2009;9(12):1745-51.

9. Enzinger PC et al. CALGB 80403/ECOG 1206: A randomized phase II study of three standard chemotherapy regimens (ECF, IC, FOLFOX) plus cetuximab in metastatic esophageal and GE junction cancer. J Clin Oncol 28:15s, 2010 (suppl; abstr 4006)

10. Chao Yee, et al. Phase II study of weekly oxaliplatin and 24-h infusion of high-dose 5-

fluorouracil and folinic acid in the treatment of advanced gastric cancer. Br J Cancer. 2004 91:453-8

11. Bang YJ et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet, 2010;376(9742):687-97.

12. Van Cutsem E et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol. 2006 Nov 1;24(31):4991-7.

13. Chao Y et al. An open, multi-centre, phase II clinical trial to evaluate the efficacy and safety of paclitaxel, UFT, and leucovorin in patients with advanced gastric cancer. Br J Cancer. 2006;95(2):159-63.

14. Dank M et al. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol. 2008;19(8):1450-7.

15. Fuchs CS, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014 ;383(9911):31-9.

16. Wilke H, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction

adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol.

2014 Oct;15(11):1224-35.

17. Ford HE, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol. 2014 Jan;15(1):78-86

18. Hironaka S, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after

failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol. 2013 Dec 10;31(35):4438-44.

19. Ajani AJ, Winter K, Okawara GS, et al. Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): Quality of combined modality therapy and pathologic response. JCO 2006;24:3953-3958.

20. Willett CG, Gunderson LL. Stomach, in: Perez and Brady's principles and practice of radiation oncology, 5th ed. Lippincott Williams & Wilkins, 2007;1318-1335.

21. Smalley SR, Gunderson L, Tepper J, et al. Gastric surgical adjuvant radiotherapy consensus report: rationale and treatment implementation. Int J Radiat Oncol Biol Phys 2002;52:283-293.

22. Macdonald JS, Smalley S, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 345:725-730, 2001.

23. Tepper JE, Gunderson LE, Radiation treatment parameters in the adjuvant postoperative therapy of gastric cancer. Semin Radiat Oncol 2002;12(2):187-195.

24. Hazard L, O'Connor J, Scaife C. Role of radiation therapy in gastric adenocarcinoma. World J Gastroenterol 2006;12:1511-1520.

25. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725-730.

26. Smalley SR, Benedetti JK, Haller DG, et al. Updated Analysis of WOG-Directed Intergroup Study 0116: A Phase III Trial of Adjuvant Radiochemotherapy Versus Observation After Curative Gastric Cancer Resection. Journal of Clinical Oncology 2012;30:2327-2333.

27. Lee J, Lim do H, Kim S, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. J Clin Oncol 2012;30:268-273.

28. 日本胃癌治療指南(JGCA) 第 3 版

29. NCCN Gastric cancer Version 2. 2011

30. Huang SF, et al Increased risk of tuberculosis after gastrectomy and chemotherapy in gastric cancer: a 7-year cohort study. Gastric Cancer. 2011;14:257-65

31. Guimbaud R, Louvet C, Ries P, et al. Prospective, Randomized, Multicenter, Phase III Study of Fluorouracil, Leucovorin, and Irinotecan Versus Epirubicin, Cisplatin, and Capecitabine in Advanced Gastric Adenocarcinoma: A French Intergroup (Federation Francophone de Cancerologie Digestive, Federation Nationale des Centres de Lutte Contre le Cancer, and Groupe Cooperateur

Multidisciplinaire en Oncologie) Study. J Clin Oncol 2014;32:3520-3526. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25287828.