中山醫學大學附設醫院

大腸癌診療指引

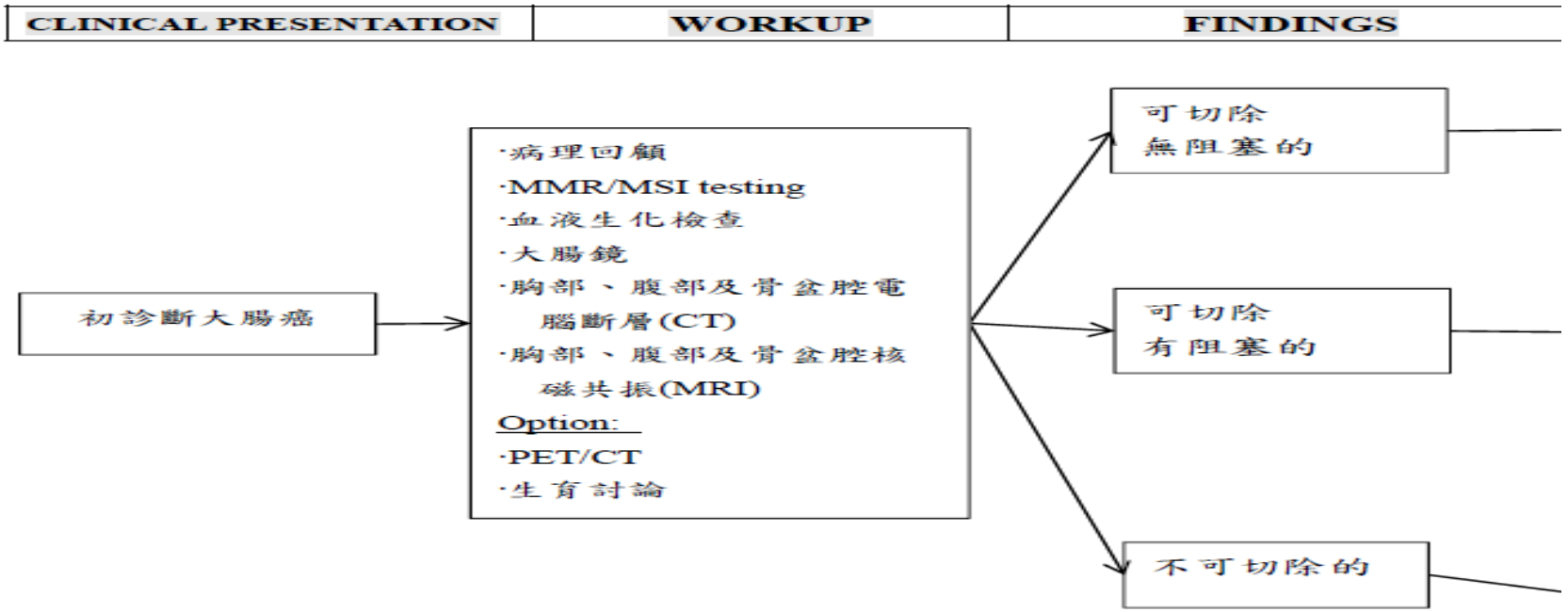
本臨床指引參考台灣國家衛生研究院、與美國NCCN版本

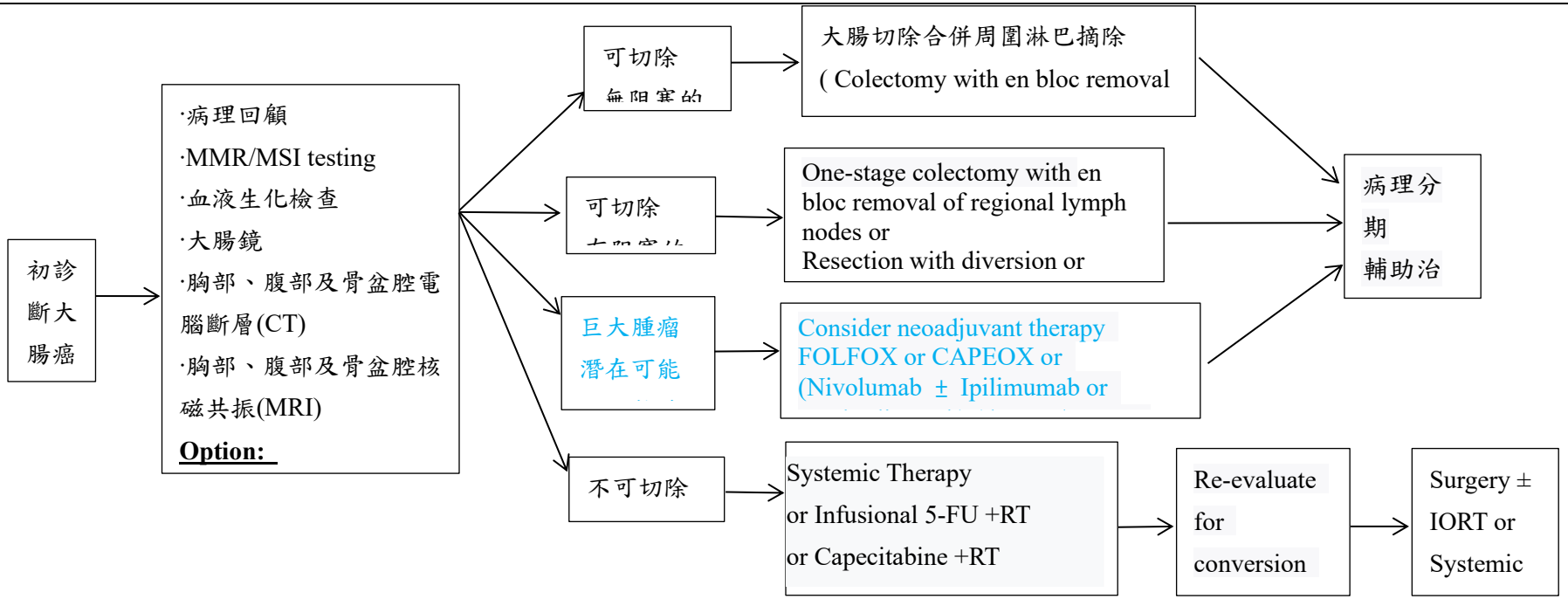
大腸直腸癌多專科團隊編修

2023/12/22	Version 17.0
2022/12/20	Version 16.0
2021/11/16	Version 15.0
2020/12/01	Version 14.0
2019/11/19	Version 13.0
2018/11/15	Version 12.0
2017/12/21	Version 11.0
2016/12/01	Version 10.0
2015/12/24	Version 9.0
2014/12/18	Version 8.0
2013/12/26	Version 7.0
2012/12/06	Version 6.0

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
P.10	

<table>
<tr><th>頁數</th><th>修訂/新增</th></tr>
<tr><td>P9-15</td><td> 
</td></tr>
<tr><td>P9-15</td><td>重新修訂流程因全部更動故沒有放置修改前後比較</td></tr>
<tr><td>P.29</td><td>無</td><td>Immunotherapy
Pembrolizumab (keytruda) (Optional)
1.建議劑量為 10mg/kg，每三週靜脈輸注一次。
KEYTRUDA® (pembrolizumab). Whitehouse Station,NJ: Merck & Co, Inc.; 2018.
OPDIVO (nivolumab) (Optional)</td></tr>
</table>

		1. 建議劑量為 3mg/kg，每兩週靜脈輸注一次。 OPDIVO (nivolumab) injection. Princeton, NJ: Bristol-Myers Squibb Company; 2018.

目 錄

一、 前言

本大腸癌治療指引內所提之各種診治意見，為實證醫學原則之建議，希望能為癌症患者及其家屬提供一個正確的指引；但對臨床醫師之醫療行為無絕對之法律性約束力！由於醫藥科技持續在進步，每位患者的病情亦不盡相同；醫師應就病人之病情做個別特殊性的考量，病人和家屬亦應與醫師溝通討論，以決定最適當之診治方式。

自民國七十一年起，癌症已躍居為國人十大死因第一位。我國於民國九十二年公布施行「癌症防治法」，並依據該法衍生「國家癌症防治五年計畫」。為達成上述計畫訂定之目標，提升民眾對癌症防治之認識，本院於 2004 年 11 月正式成立癌症委員會，配合國民健康局之癌症防治中心計畫，積極推動癌症防治相關工作，提供癌症診療與癌症篩檢服務，以確保民眾之健康。

二、組織病理分類與分化

腺癌 (Adenocarcinoma)佔所有病例的 90%以上，次多的黏液性腺癌(Mucinous adenocarcinoma)，及管性絨毛狀腺癌(Adenocarcinoma in tubulovillous adenoma)，其餘其他型態如戒指細胞癌 (Signet ring cell carcinoma)、鱗狀細胞癌 (Squamous cell carcinoma)、腺鱗狀癌 (Adenosquamous carcinoma)、未分化癌 (Undifferentiated carcinoma) Papillary adenocarcinoma、Carcinoid tumor 等。

大腸直腸癌的病理組織分化分為：

1. 分化良好 (grade 1)
2. 分化中度 (grade 2)
3. 分化不良或未分化 (grade 3)
4. 分化無法評估 (grade x)

cTNM 是臨床分期，
pTNM 是病理分期；
前綴 y 用於接受新輔助治療後的腫瘤分期（如 ypTNM），病理學完全緩解的患者分期為 ypT0N0cM0，可能類似於 0 期或 1 期。
前綴 r 用於經治療獲得一段無瘤間期後復發的患者（rTNM）。
Tis 包括腫瘤細胞局限於腺體基底膜(上皮內)或黏膜固有層(黏膜內)，未穿過黏膜肌層到達黏膜下層。
T4 的直接侵犯包括穿透漿膜侵犯其他腸段，並得到鏡下診斷的證實(如盲腸癌侵犯乙狀結腸)，或者，位於腹膜後或腹膜下腸管的腫瘤，穿破腸壁固有基層後直接侵犯其他的髒器或結構，例如降結腸後壁的腫瘤侵犯左腎或側腹壁，或者中下段直腸癌侵犯前列腺、精囊腺、宮頸或陰道。腫瘤肉眼上與其他器官或結構粘連則分期為 cT4b。但是，若顯微鏡下該粘連處未見腫瘤存在則分期為 pT3。
V 和 L 亞分期用於表明是否存在血管和淋巴管浸潤，而 PN 則用以表示神經浸潤（可以是部位特異性的）。

三、分期表 (依照 AJCC 第 8 版 TNM 分期)

表 1. T、N、M 的定義

原發腫瘤（T）	
Tx	原發腫瘤無法評估
T0	無原發腫瘤證據
Tis	原位癌：局限于上皮內或侵犯黏膜固有層
T1	腫瘤侵犯黏膜下層
T2	腫瘤侵犯固有肌層
T3	腫瘤穿透固有肌層到達漿膜下層，或侵犯無腹膜覆蓋的結直腸旁組織
T4a	腫瘤穿透腹膜髒層
T4b	腫瘤直接侵犯或粘連於其他器官或結構 c
區域淋巴結（N）	
Nx	區域淋巴結無法評估
N0	無區域淋巴結轉移
N1	有 1-3 枚區域淋巴結轉移
N1a	有 1 枚區域淋巴結轉移
N1b	有 2-3 枚區域淋巴結轉移
N1c	漿膜下、腸系膜、無腹膜覆蓋結腸/直腸周圍組織內有腫瘤種植 (TD tumor deposit），無區域淋巴結轉移
N2	有 4 枚以上區域淋巴結轉移
N2a	4-6 枚區域淋巴結轉移
N2b	7 顆及更多區域淋巴結轉移
遠處轉移（M）	
Mx	遠處轉移無法評估
M0	無遠處轉移
M1	有遠處轉移
M1a	遠處轉移局限於單個器官或部位（如肝、肺、卵巢、非區域淋巴結）
M1b	遠處轉移分佈於一個以上的器官/部位
M1c	腹膜表面轉移

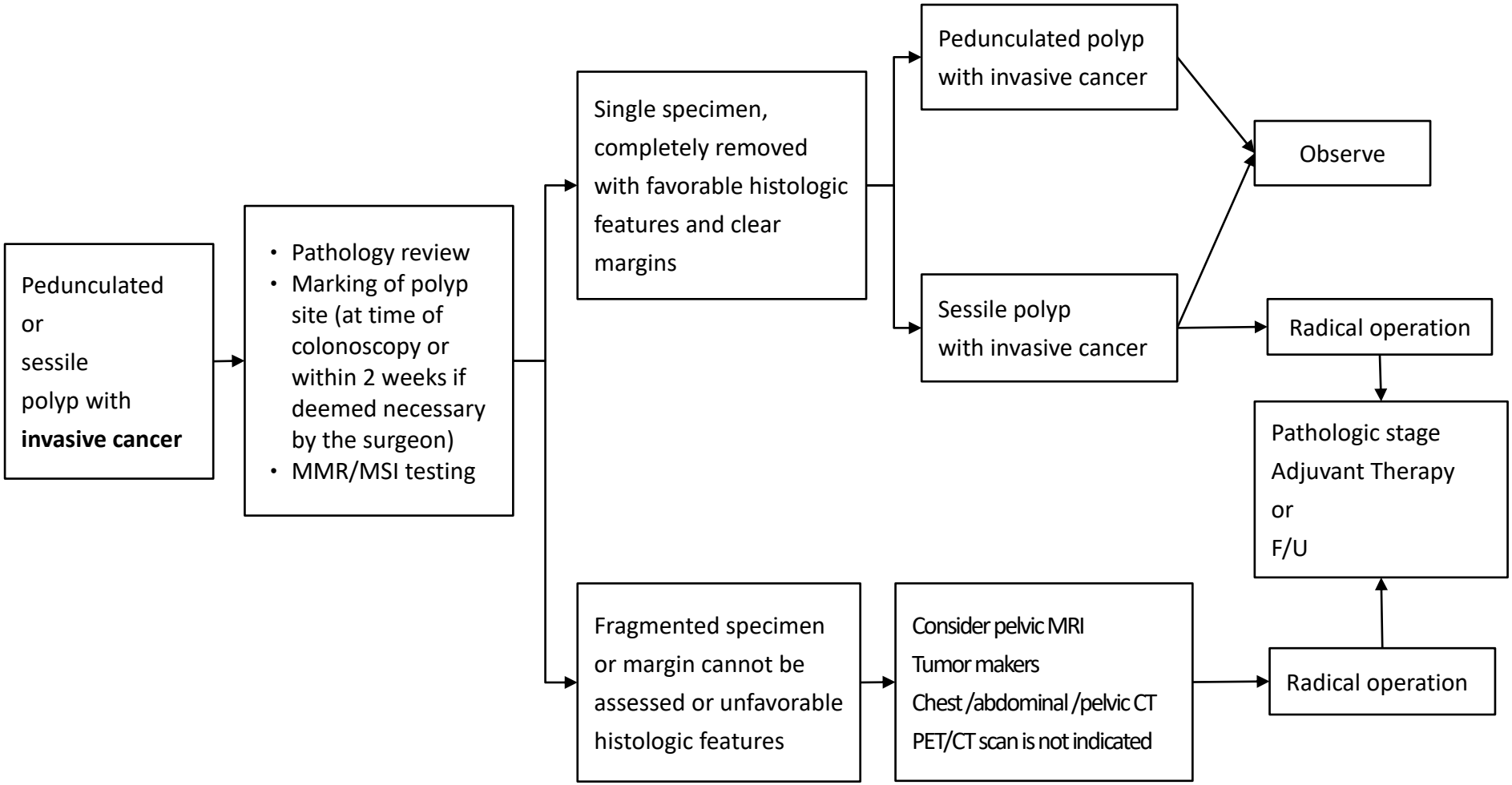
表 2. 分期組合(**Anatomic stage/prognostic groups)**

0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b
IVC	Any T	Any T	M1c

CLINICAL PRESENTATION	WORKUP	FINDINGS	PRIMARY TREATMENT

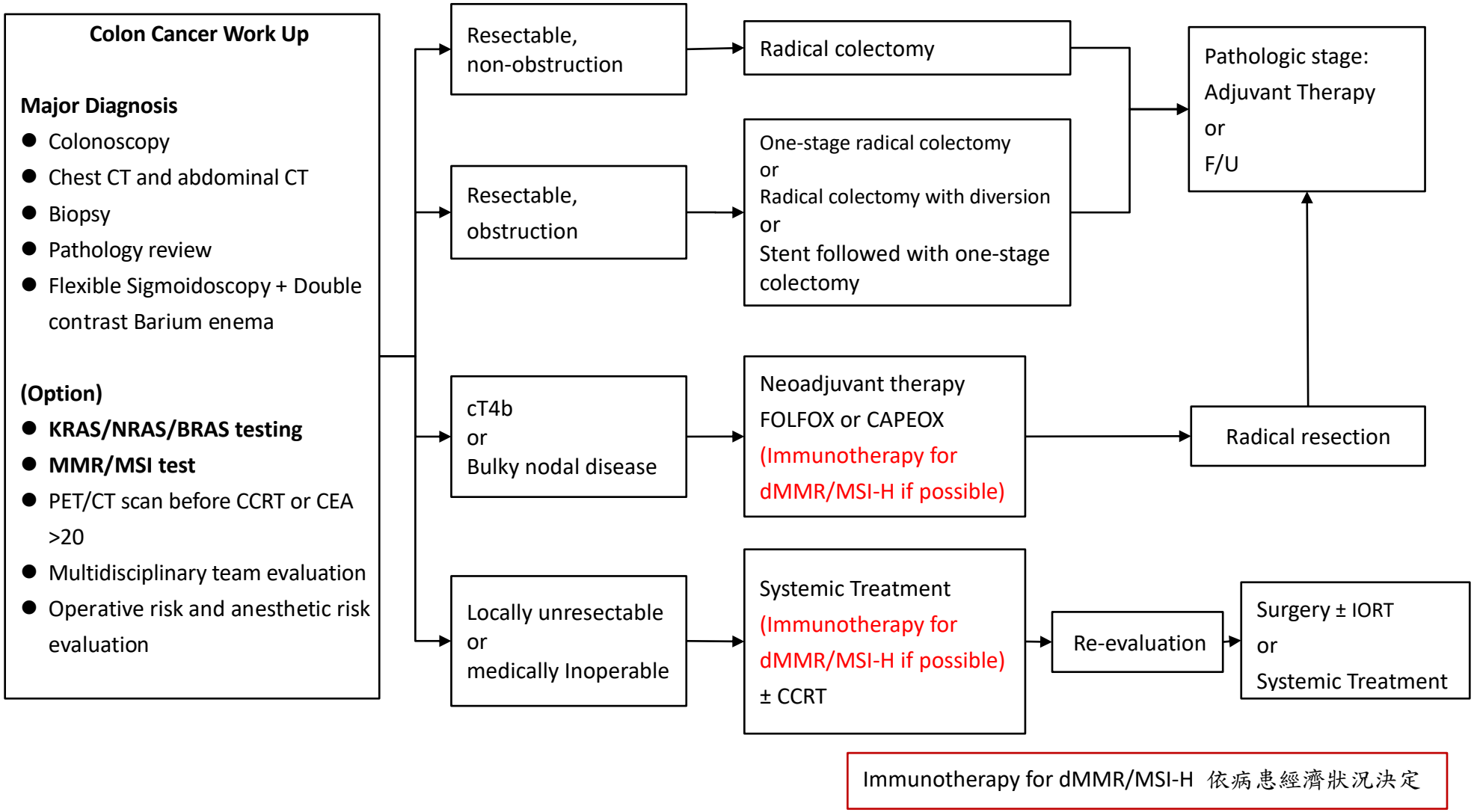
四、大腸癌診療指引

A: Malignant polyp



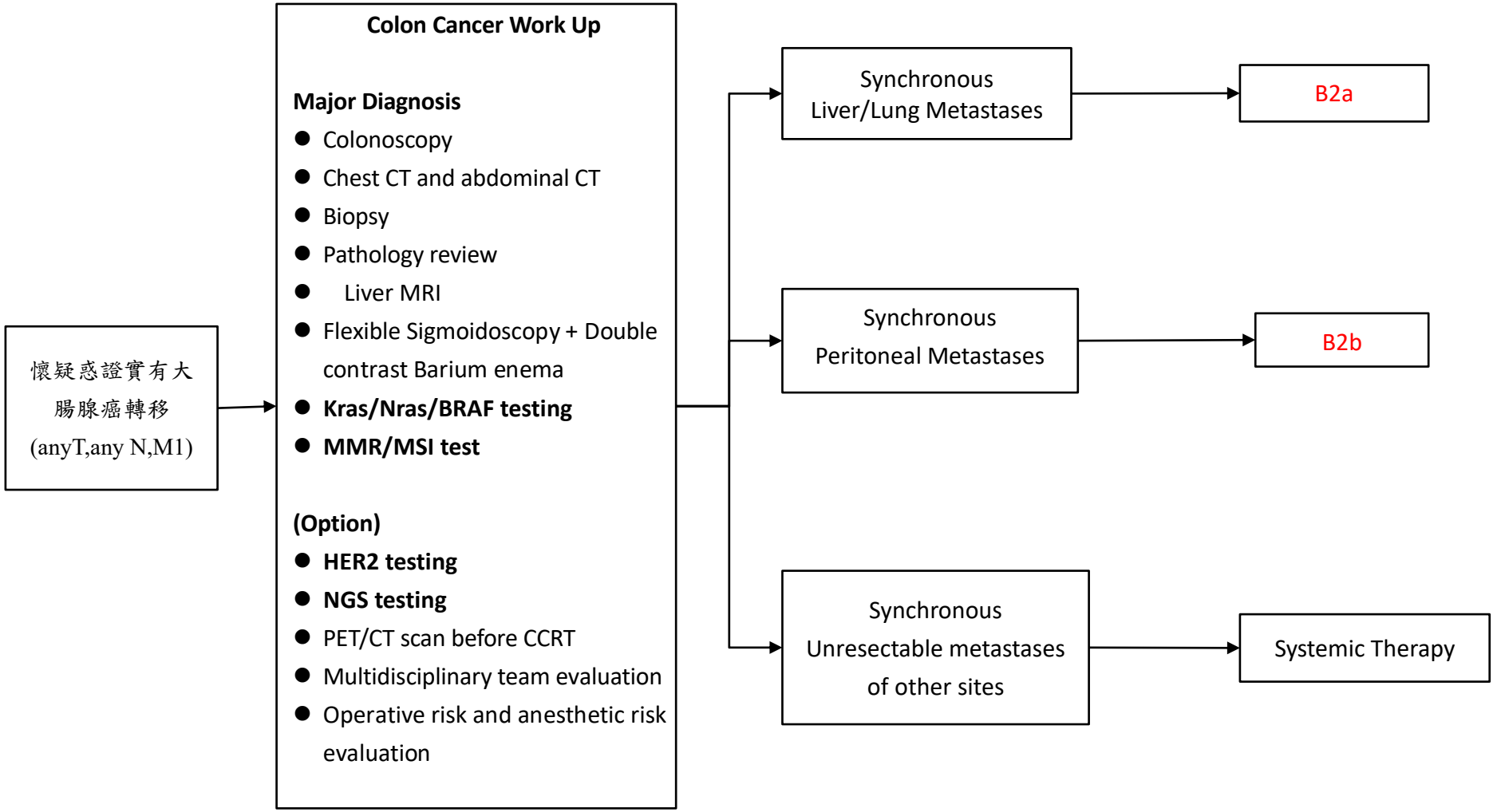
WORKUP	FINDINGS	PRIMARY TREATMENT

B1: 大腸癌(無遠端轉移)



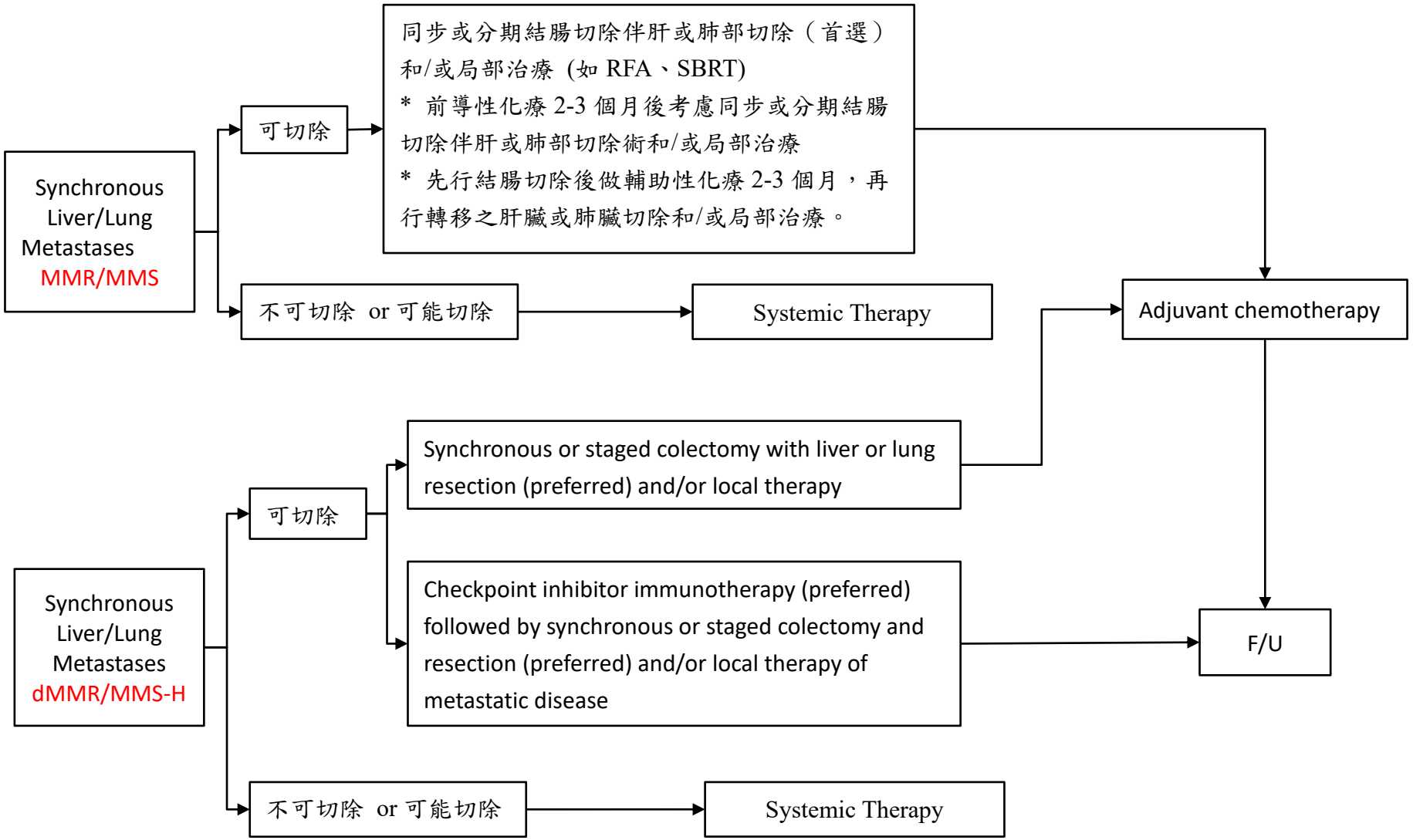
WORKUP	FINDINGS	PRIMARY TREATMENT

B2: 大腸癌（有遠端轉移）



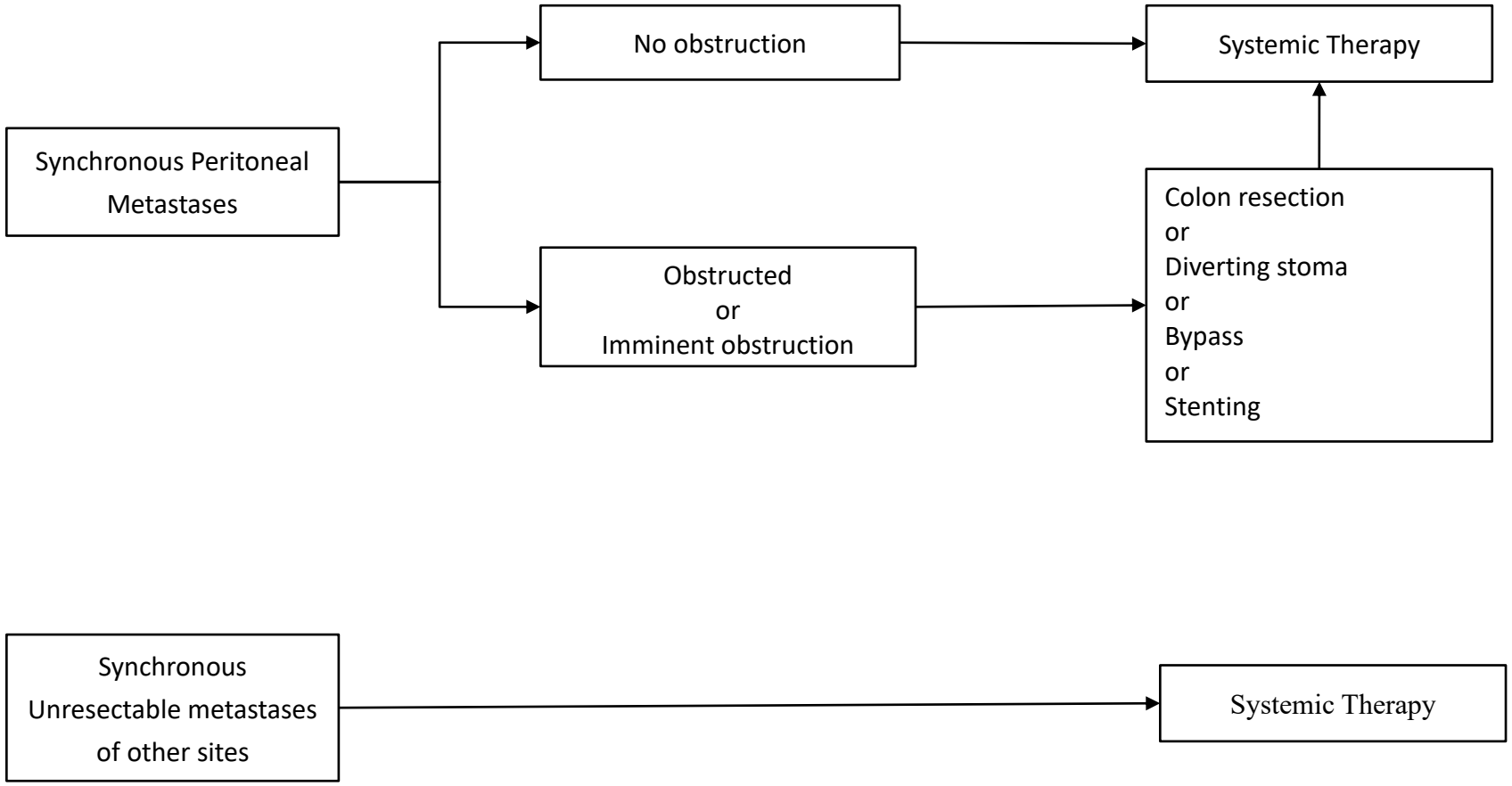
WORKUP	FINDINGS	PRIMARY TREATMENT

B2a: 大腸癌 (有遠端轉移)

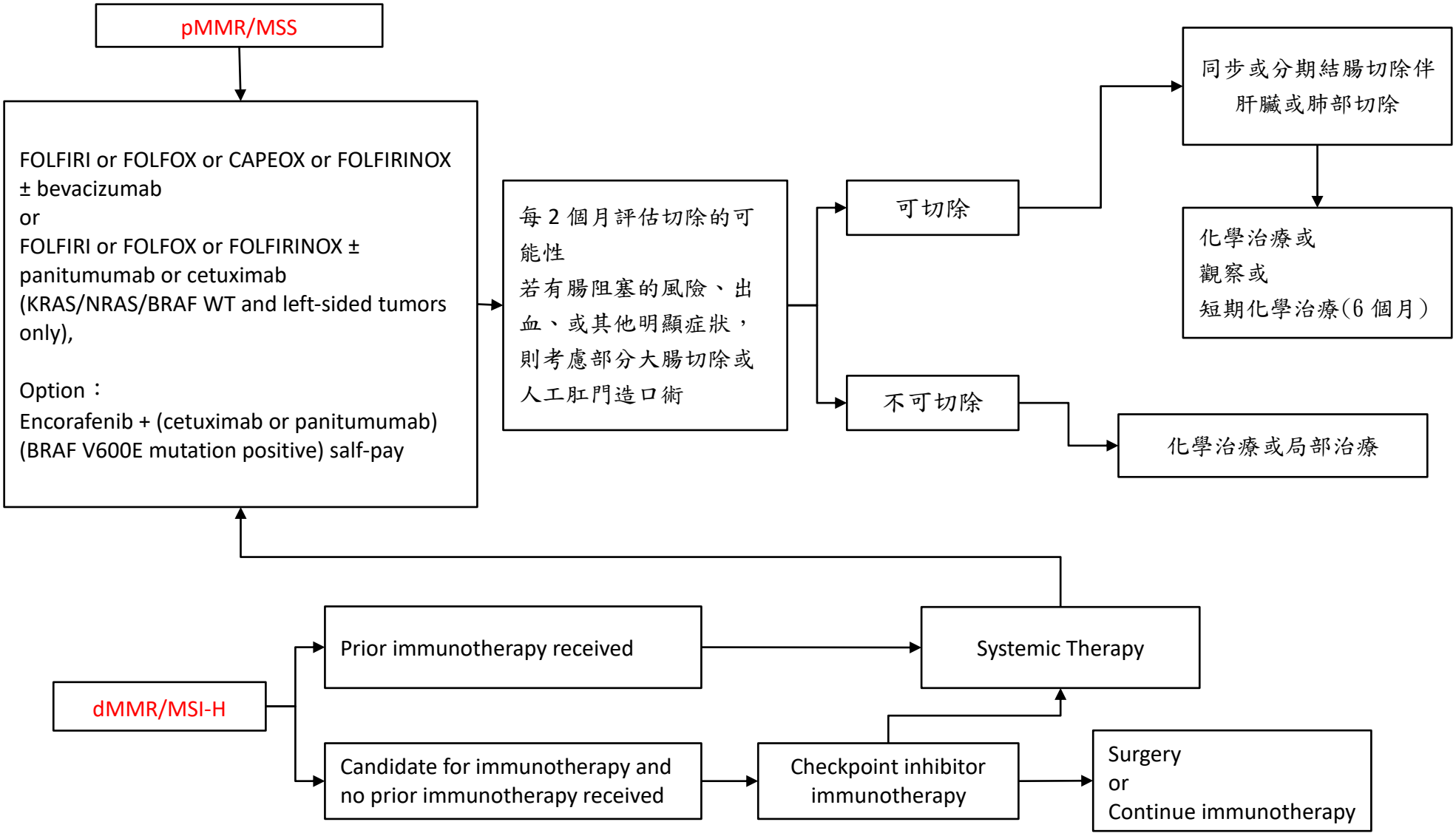


WORKUP	FINDINGS	PRIMARY TREATMENT

B3: 大腸癌 (有遠端轉移)

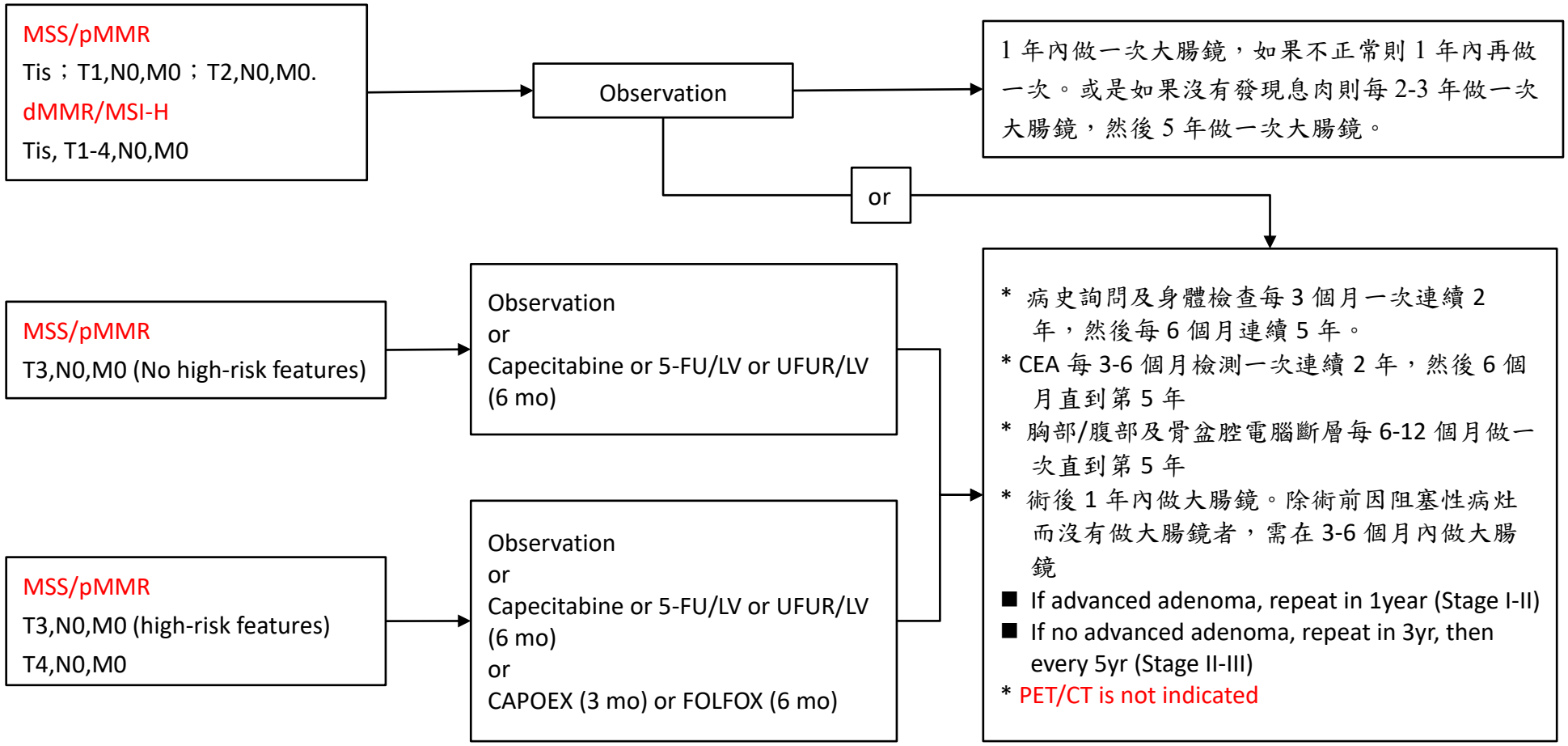


SYSTEMIC THERAPY and EVALUATION



Post OP

PATHOLOGIC STAGE	ADJUVANT THERAPY	FOLLOW-UP

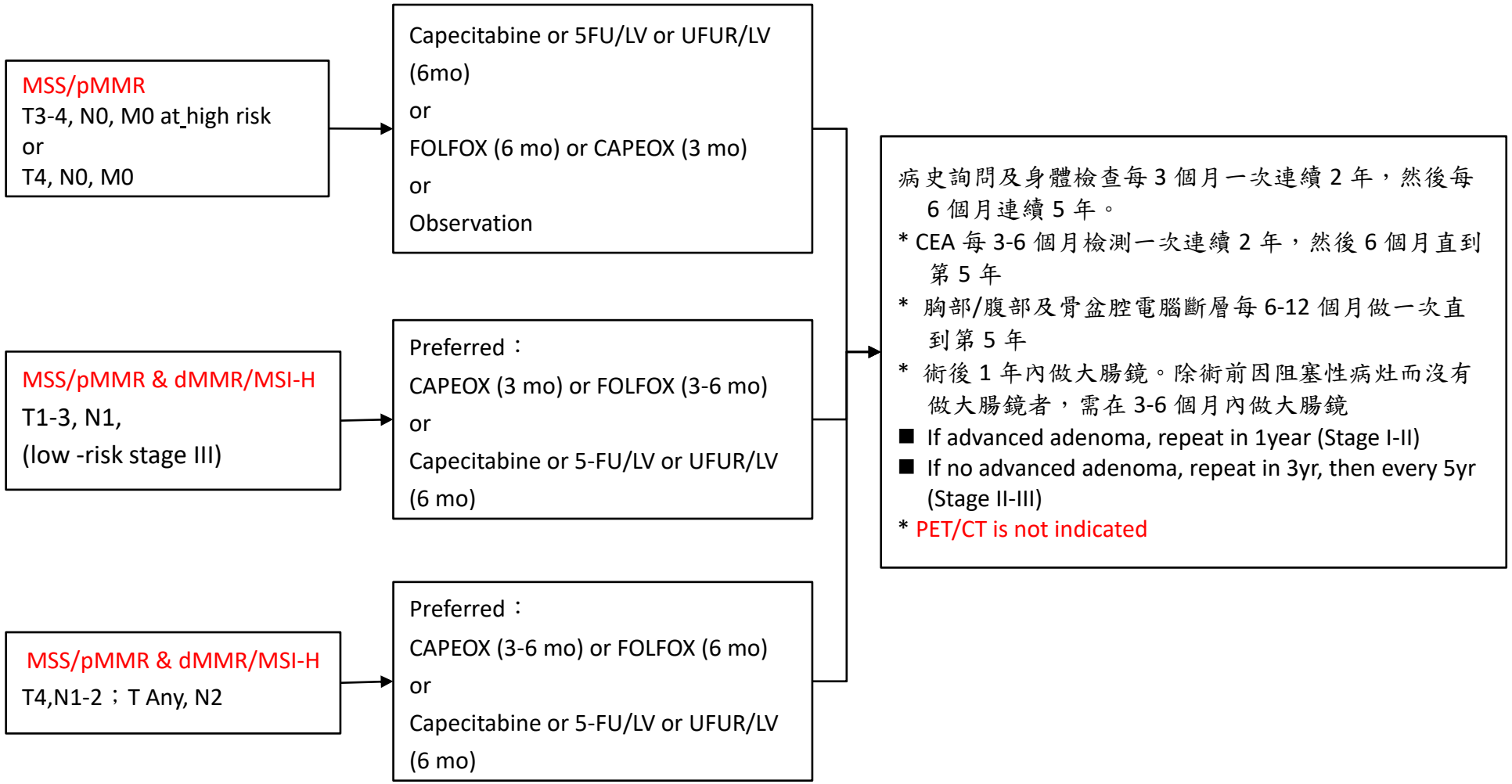


◎ Stage II, MSI high(MSI-H) patient may have a good prognosis and do not benefit from 5-FU adjuvant therapy

◎ 3 mo: 3 months； 6 mo: 6 months

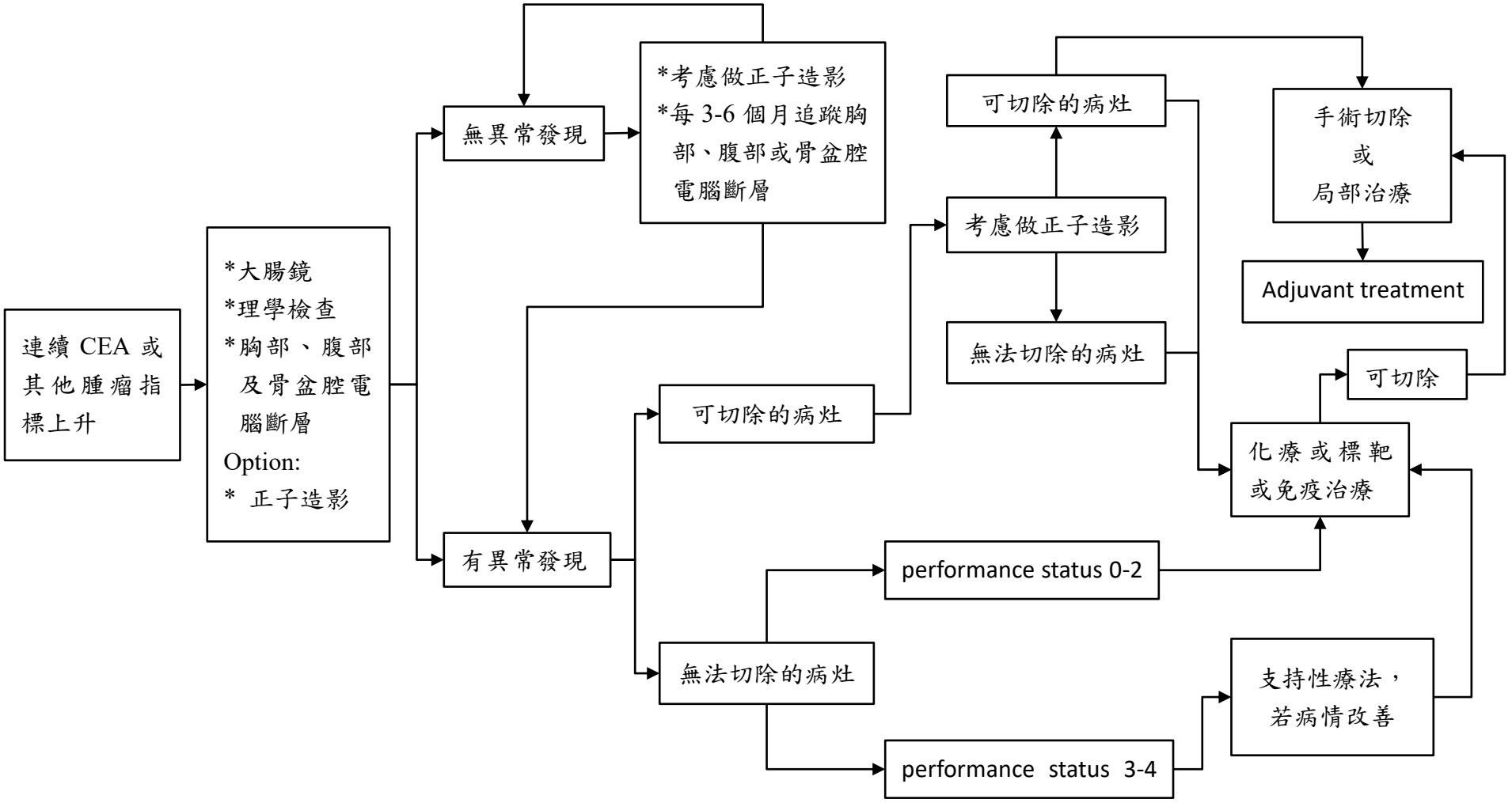
Post OP

PATHOLOGIC STAGE	ADJUVANT THERAPY	FOLLOW-UP



五、復發的評估

RECURRENCE	WORKUP



化學治療處方

Adjuvant chemotherapy

Uracil-Tegafur

Uracil-Tegafur	**250-300 mg/m2/day po**	
7 days/week x 24 weeks		

Lembersky BC et al. Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from national surgical adjuvant breast and bowel project protocol C-06. J Clin Oncol 2006; 24:2059

mFOLFOX

Leucovorin	**200 mg/m2 iv over 46 hrs**	**d1**
5-FU	**2400 -3000 mg/m2 iv over 46 hrs**	**d1**
Oxaliplatin	**85 mg/m2 iv**	**d1**
Q2w x 12 cycles		

de Gramont A et al. Oxaliplatin/5FU/LV in adjuvant colon cancer: updated efficacy results of the MOSAIC trial, including survival, with a medium follow-up of six years. 2007 ASCO annual meeting. Abstract 4007

Tournigand, C et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. J Clin Oncol 2004; 22:229

CAPOEX

Capecitabine	**825mg/m2 po bid**	**d1-14**
Oxaliplatin	**50 mg/m2 iv**	**d1**
Q2w		

Rodel C et al. Multicenter phase II trial of chemoradiation with oxaliplatin for rectal cancer. J Clin Oncol 2007; 25:110.

Chemotherapy for Advanced or Metastatic Disease

Modified FOLFOX (mFOLFOX)

Leucovorin	**150 mg/m2 iv over 46 hrs**	**d1**
5-FU	**2400 -3000 mg/m2 iv over 46 hrs**	**d1**
Oxaliplatin	**85 mg/m2 iv**	**d1**
q2w		

Tournigand, C et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. J Clin Oncol 2004; 22:229

FOLFOX + bevacizumab[5,d,cc]

Leucovorin	**150 mg/m2 iv over 46 hrs**	**d1**
5-FU	**2400 -3000 mg/m2 iv over 46 hrs**	**d1**
Oxaliplatin	**85 mg/m2 iv**	**d1**
Bevacizumab	**5 mg/kg IV**	**d1**
q2w		

Emmanouilides C, Sfakiotaki G, Androulakis N, et al. Front-line bevacizumab in combination with oxaliplatin, leucovorin and 5-fluorouracil (FOLFOX) in patients withmetastatic colorectal cancer: a multicenter phase II study. BMC Cancer 2007;7:91.

FOLFOX + panitumumab[6] (*KRAS/NRAS/BRAF* WT only)

Leucovorin	**150 mg/m2 iv over 46 hrs**	**d1**
5-FU	**2400 -3000 mg/m2 iv over 46 hrs**	**d1**
Oxaliplatin	**85 mg/m2 iv**	**d1**
Panitumumab	**6 mg/kg IV over 60 minutes**	**d1**
q2w		

Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol 2010;28:4697-4705.

FOLFOX + cetuximab[7] (*KRAS/NRAS/BRAF* WT only)

Leucovorin	**150 mg/m2 iv over 46 hrs**	**d1**
5-FU	**2400 -3000 mg/m2 iv over 46 hrs**	**d1**
Oxaliplatin	**85 mg/m2 iv**	**d1**
Cetuximab	**400 mg/m2 IV over 2 hours first infusion then 250 mg/m2 IV over 60 minutes weekly**	
Cetuximab	**500 mg/m2 IV over 2 hours**	**d1**
q2w		

Venook AP, Niedzwiecki D, Lenz HJ, et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild- type advanced or metastatic colorectal cancer: A randomized clinical trial. JAMA 2017;317:2392-2401.

CAPEOX + bevacizumab8,d,cc

Capecitabine	**1000mg/m2 po bid**	**d1-14**
Oxaliplatin	**85 mg/m2 iv**	**d1**
Bevacizumab	**5 mg/kg IV**	**d1**
By weekly		

Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin- based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26:2013-2019.

FOLFIRI + bevacizumab[11,d,cc]

Leucovorin	**400 mg/m2 iv over 2 hrs before 5-FU**	**d1**
5-FU	**400 mg/m2 iv bolus d1, and then 2400 mg/m2 iv over 46 hrs**	**d1**
Irinotecan	**150 - 180 mg/m2 iv**	**d1**
Bevacizumab	**5 mg/kg IV**	**d1**
q2w		

Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomized, open-label, phase 3 trial. Lancet Oncol 2014;15:1065-1075.

FOLFIRI + cetuximab (KRAS/NRAS/BRAF WT only)

Leucovorin	**400 mg/m2 iv over 2 hrs before 5-FU**	**d1**
5-FU	**400 mg/m2 iv bolus d1, and then 2400 mg/m2 iv over 46 hrs**	**d1**
Irinotecan	**150 - 180 mg/m2 iv**	**d1**
Cetuximab	**400 mg/m2 IV over 2 hours first infusion then 250 mg/m2 IV over 60 minutes weekly**	
Cetuximab	**500 mg/m2 IV over 2 hours**	**d1**
q2w		

Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337-345.

FOLFIRI + panitumumab[14] (KRAS/NRAS/BRAF WT only)

Leucovorin	**400 mg/m2 iv over 2 hrs before 5-FU**	**d1**
5-FU	**400 mg/m2 iv bolus d1, and then 2400 mg/m2 iv over 46 hrs**	**d1**
Irinotecan	**150 - 180 mg/m2 iv**	**d1**
Panitumumab	**6 mg/kg IV over 60 minutesCetuximab**	**d1**
q2w		

Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol 2010;28:4706-4713.

FOLFIRI+ ziv-aflibercept[15]

Leucovorin	**400 mg/m2 iv over 2 hrs before 5-FU**	**d1**
5-FU	**400 mg/m2 iv bolus d1, and then 2400 mg/m2 iv over 46 hrs**	**d1**
Irinotecan	**150 - 180 mg/m2 iv**	**d1**
Ziv-aflibercept	**4 mg/kg IV over 60 minutes**	**d1**
q2w		

Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin- based regimen. J Clin Oncol 2012;30:3499-3506.

FOLFIRI+ ramucirumab[16]

Leucovorin	**400 mg/m2 iv over 2 hrs before 5-FU**	**d1**
5-FU	**400 mg/m2 iv bolus d1, and then 2400 mg/m2 iv over 46 hrs**	**d1**
Irinotecan	**150 - 180 mg/m2 iv**	**d1**
Ramucirumab	**8 mg/kg IV over 60 minutes**	**d1**
q2w		

Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomized, double-blind, multicentre, phase 3 study. Lancet Oncol 2015;16:499-508.

Modified FOLFIRI

Leucovorin	**150 mg/m2 iv over 46 hrs**	**d1**
5-FU	**2400 - 3000 mg/m2 iv over 46 hrs**	**d1**
Irinotecan	**150 - 180 mg/m2 iv**	**d1**
q2w		

Fuchs CS et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropymidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C study. J Clin Oncol 2007; 25:4779.

Van Cutsem E et al. Randomized phase III study of irinotecan and 5-FU/FA with or without cetuximab in the first-line treatment of patients with metastatic colorectal cancer (mCRC): The CRYSTAL trial. 2007 ASCO annual meeting. Abstract 4000.

Capecitabine

Capecitabine	850-1250 mg/m2 po bid	14 days
q3w till disease progression		

Van Cutsem, E et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: Results of a large phase III

study. J Clin Oncol 2001; 19:4097.

Capecitabine + bevacizumab[23,d,cc]

Capecitabine	850-1250 mg/m2 po bid	14 days
Bevacizumab	7.5 mg/kg IV	d1
q3w till disease progression		

Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. Lancet Oncol 2013;14:1077-1085.

Irinotecan

Irinotecan	180 mg/m2 IV over 30 – 90 minutes	d1
q2w		

Cunningham D, Pyrhonen S, James R, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. The Lancet 1998;352:1413-1418.

Cetuximab[13]

Cetuximab	500 mg/m^2 IV over 2 hours	d1
q2w		

Martín-Martorell P, Roselló S, Rodríguez-Braun E, et al. Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. Br J Cancer 2008;99:455-458.

Irinotecan+ panitumumab[14,27] (KRAS/NRAS/BRAF WT only)

Irinotecan	180 mg/m2 IV over 30 – 90 minutes	d1
Panitumumab	6 mg/kg IV over 60 minutes	d1
q2w		

Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337-345.
Andre T, Blons H, Mabro M, et al. Panitumumab combined with irinotecan for patients with KRAS wild-type metastatic colorectal cancer refractory to standard chemotherapy: a GERCOR efficacy, tolerance, and translational molecular study. Ann Oncol 2013;24:412-419.

Irinotecan+ bevacizumab[28,d,cc]

Irinotecan	180 mg/m2 IV over 30 – 90 minutes	d1
Bevacizumab	5 mg/kg IV	d1
q2w		

Yildiz R, Buyukberber S, Uner A, et al. Bevacizumab plus irinotecan-based therapy in metastatic colorectal cancer patients previously treated with oxaliplatin-based regimens. Cancer Invest 2010;28:33-37.

Irinotecan+ ramucirumab[16]

Irinotecan	180 mg/m2 IV over 30 – 90 minutes	d1
Ramucirumab	8 mg/kg IV over 60 minutes	d1
q2w		

Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomized, double-blind, multicentre, phase 3 study. Lancet Oncol 2015;16:499-508.

Irinotecan+ ziv-aflibercept

Irinotecan	180 mg/m2 IV over 30 – 90 minutes	d1
Ziv-aflibercept	4 mg/kg IV	d1
q2w		

Regorafenib

Regorafenib	160 mg PO daily
days 1–21	

Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:303- 312.

Trifluridine + tipiracil[32]

Trifluridine + tipiracil and 8–12	35 mg/m2 -80mg/m2 po twice daily days 1–5
every 28 days	

Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer (RECOURSE). N Engl J Med 2015;372:1909-19.

Trastuzumabdd + pertuzumab[36](HER2-amplified and RAS and BRAF WT)

Trastuzumab 8 mg/kg IV loading dose on day 1 of cycle 1, then 6 mg/kg IV every 21 days Pertuzumab 840 mg IV loading dose on day 1 of cycle 1, then 420 mg IV every 21 days
every 28 days

Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol 2019;20:518-530.

Modified Uracil-Tegafur

Uracil-Tegafur	**250 - 300 mg/m2/day**
7 days/week	

Hochster HS et al. Phase II study of uracil-tegafur with leucovorin in elderly (> 75 years old) patients with colorectal cancer: ECOG 1299. J Clin Oncol 2007; 25:5397.

FOLFIRINOX

Irenotecan	**160→mg/m2 60 min**	**d1**
Oxaliplatin	**65→ mg/m2 iv**	**d1**
Leucovorin	**400 mg/m2 iv over 46 hrs**	**d1**
5-FU	**2400→mg/m2 iv over 48hrs**	**d1**
Q2w		

FOLFOXIRI plus bevacizumab versus FOLFIRI plis bevacizumab as first –line treatment of patients with metastatic colorectal cancer:updated overall survival and molecular subgroup analyses of the open-label,phase3 TRIBE study Chiara Cremolini et al Vol 16.october 2015;1308

註:依病人狀況調整劑量

FOLFIRINOX + bevacizumab[18,d,cc]

Irenotecan	**160→mg/m2 60 min**	**d1**
Oxaliplatin	**65→ mg/m2 iv**	**d1**
Leucovorin	**400 mg/m2 iv over 46 hrs**	**d1**
5-FU	**2400→mg/m2 iv over 48hrs**	**d1**
Bevacizumab	**5 mg/kg IV**	**d1**
Q2w		

Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. Lancet Oncol 2015;16:1306- 1315.

FOLFIRINOX+ cetuximab (KRAS/NRAS/BRAF WT only)

Leucovorin	**400 mg/m2 iv over 2 hrs before 5-FU**	**d1**
5-FU	**400 mg/m2 iv bolus d1, and then 2400 mg/m2 iv over 46 hrs**	**d1**
Irinotecan	**150 - 180 mg/m2 iv**	**d1**
Cetuximab	**400 mg/m2 IV over 2 hours first infusion**	
	then 250 mg/m2 IV over 60 minutes weekly	
Cetuximab	**500 mg/m2 IV over 2 hours**	**d1**
q2w		

Cremolini C, Antoniotti C, Lonardi S, et al. Activity and safety of cetuximab plus modified FOLFOXIRI followed by maintenance with cetuximab or bevacizumab for RAS and BRAF wild-type metastatic colorectal cancer: A randomized phase 2clinical trial. JAMA Oncol 2018;4:529-536.

FOLFIRINOX + panitumumab[19] (KRAS/NRAS/BRAF WT only)

Leucovorin	**400 mg/m2 iv over 2 hrs before 5-FU**	**d1**
5-FU	**400 mg/m2 iv bolus d1, and then 2400 mg/m2 iv over 46 hrs**	**d1**
Irinotecan	**150 - 180 mg/m2 iv**	**d1**
Panitumumab	**6 mg/kg IV over 60 minutesCetuximab**	**d1**
q2w		

Cremolini C, Antoniotti C, Lonardi S, et al. Activity and safety of cetuximab plus modified FOLFOXIRI followed by maintenance with cetuximab or bevacizumab for RAS and BRAF wild-type metastatic colorectal cancer: A randomized phase 2clinical trial. JAMA Oncol 2018;4:529-536.

IROX

Oxaliplatin	**85 mg/m2 IV**	**d1**
irinotecan	**200 mg/m² over 30–90 minutes**	**d1**
q3w		

Haller DG, Rothenberg ML, Wong AO, et al. Oxaliplatin plus irinotecan compared with irinotecan alone as second-line treatment after single agent fluoropyrimidine therapy for metastatic colorectal carcinoma. J Clin Oncol 2008;26:4544-4550.

IROX + bevacizumab[d]

Oxaliplatin	**85 mg/m2 IV**	**d1**
irinotecan	**200 mg/m² over 30–90 minutes**	**d1**
Bevacizumab	**5 mg/kg IV**	**d1**
q3w		

Haller DG, Rothenberg ML, Wong AO, et al. Oxaliplatin plus irinotecan compared with irinotecan alone as second-line treatment after single agent fluoropyrimidine therapy for metastatic colorectal carcinoma. J Clin Oncol 2008;26:4544-4550.

Target therapy for Advanced or Metastatic Disease

Bevacizumab + chemotherapy

Bevacizumab	**5 mg/kg iv**	**d1**
q2w		

Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 2003; 21:60

Saltz LB et al. Bevacizumab (Bev) in combination with XELOX or FOLFOX4: efficacy results from XELOX-1/No 16966, a randomized phase III trial in the first-line treatment of metastatic colorectal cancer (MCRC). 2007 Gastrointestinal Cancers Symposium. Abstract 238.

Giantonio, BJ et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007; 25:1539.

Hurwitz, H et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350:2335.

Cetuximab +/- chemotherapy (for patients with wild-type KRAS)

Cetuximab	**400 mg/m2 iv d1, and then 500 mg/m2 iv over 1 hour**
q2w	

Bokemeyer C et al. KRAS status and efficacy of first-line treatment of patients with metastatic colorectal cancer (mCRC) with FOLFOX with or without cetuximab: the OPUS experience. 2008 ASCO annual meeting. Abstract 4000.

Van Cutsem E et al. KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with or without cetuximab: the CRYSTAL experience. 2008 ASCO annual meeting. Abstract 2.

Jonker DJ et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med 2007; 357-2040.

Sobrero AF et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. J Clin Oncol 2008; 26:2311.

Target therapy(Optional)	**STIVARGA (regorafenib) 400 mg/㎡ x4 po QD**
	21 days/cycle

STIVARGA (regorafenib) tablets, oral. Wayne, N.J.:Bayer HealthCare Pharmaceuticals; 2018.

Target therapy +/- chemotherapy–

Target therapy(Optional)	**ZALTRAP 4 mg/kg iv over 1 hour**
	q2w

ZALTRAP® (ziv-aflibercept). Bridgewater, NJ:Regeneron Pharmaceuticals, Inc. / sanofi-aventis U.S. LLC; 2016.

TAS-102(Trifluridine+tipiracil) 20mg/tab(35 mg/㎡) (Optional)

1.建議劑量及療程: 每天給藥兩次，在第 1~5 天與第 8~12 天，每 28 天為一個療程。

2.最大劑量不可超過 82mg。

Bendell JC, Rosen LS, Mayer RJ, et al. Phase 1 study of oral TAS-102 in patients with refractory metastatic colorectal cancer. Cancer Chemother Pharmacol 2015;76:925-932

TS-1 (Tegafur) 20mg/cap(Optional)

1.建議劑量如下表格:

體表面積	早餐後 30 分鐘	晚餐後 30 分鐘	一天總劑量
<1.25 ㎡	服用 2 顆 20mg TS-1	服用 2 顆 20mg TS-1	80mg/天
1.25 ㎡~1.5 ㎡	服用 2 顆 25mg TS-1	服用 2 顆 25mg TS-1	100mg/天
1.5 ㎡	服用 3 顆 20mg TS-1	服用 3 顆 20mg TS-1	120mg/天

2.服藥週期:連續服用 28 天(4 周)，接著休息 14 天(2 周)。

3.TS-1 與 Irinotecan 合併使用於已使用含有 Oxaliplatin 化學療法失敗之轉移性大腸直腸癌患者。

4. TS-1與Irinotecan合併使用:Irinotecan的劑量為125mg/m2，靜脈輸注，每兩週給藥一次。TS-1的劑量根據病人體表面積，每天兩次，連續吃兩週，接著休息兩週，重複以上方式治療。

5.禁忌並用化療藥物(TS-1 不可與下列藥品併用)，如下:

藥品名稱
fluoropyrimidine類抗惡性腫瘤劑
fluorouracil(5-FU)
tegafur/uracil(UFT)
tegafur(futraful)
doxifluridine(furtulon)
capecitabine(Xeloda)
carmofur(mifurol)
葉酸+tegafur-uracil合併治療 (UZEL/UFT)
Levofolinate與fluorouracil合併治療(Isovorin/5-FU)
fluoropyrimidine類抗真菌劑
Flucytosine(ancotil)

Zaltrap(Aflibercept) 25mg/vail (Optional)

1.建議劑量及療程: 4 mg/kg 以靜脈輸注給藥，每 2 週一次，每次輸注時間超過 1 小時。

2.與 5-fluorouracil、leucovorin、irinotecan-(FOLFIRI) 合併使用，治療已使用含有 oxaliplatin 化學療法無效或惡化之轉移性大腸直腸癌病患。

ZALTRAP® (ziv-aflibercept). Bridgewater, NJ:Regeneron Pharmaceuticals, Inc. / sanofi-aventis U.S. LLC; 2016.

CYRAMZA(ramucirumab) (Optional)

1. 建議劑量為 8mg/kg，每兩週靜脈輸住一次，每次輸注約 60 分鐘，在投予 FOLFIRI 之前。

CYRAMZA (ramucirumab) injection. Indianapolis, IN:Eli Lilly and Company; 2018.

Trastuzumab+ pertuzumab (HER2-amplified and RAS WT) (Optional)

Trastuzumab can be given after completion of chemotherapy as well, loading dose 8mg/kg . followed by 6mg/kg . iv q3w
Trastuzumab can be given after completion of chemotherapy as well . loading Dose 840mg , followed by 420mg . iv q3w

Trastuzumab+ lapatinib (HER2-amplified and RAS WT) (Optional)

Trastuzumab can be given after completion of chemotherapy as well, loading dose 8mg/kg . followed by 6mg/kg . iv q3w
Lapatinib 1000mg PO daily.

Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. Lancet Oncol 2016;17:738-746.

Immunotherapy

Pembrolizumab (keytruda) (Optional)

1.建議劑量為 10mg/kg，每三週靜脈輸注一次。

KEYTRUDA® (pembrolizumab). Whitehouse Station,NJ: Merck & Co, Inc.; 2018.

OPDIVO (nivolumab) (Optional)

2. 建議劑量為 3mg/kg，每兩週靜脈輸注一次。

OPDIVO (nivolumab) injection. Princeton, NJ: Bristol-Myers Squibb Company; 2018.

七、病理檢查原則

1. 內鏡切除的惡性息肉

惡性息肉被定義為癌細胞穿透粘膜肌層到達粘膜下層(pT1)。pTIS 不認為是“惡性息肉”。

病理特徵良好：1/2 級，無血管/淋巴管侵犯和切緣陰性。

在認定切緣陽性的定義是不一致的。陽性切緣被定義為：1）腫瘤距切緣 < 1 ㎜， 2）腫瘤距切緣 < 2 ㎜，3）腫瘤細胞穿透切緣。

病理特徵不良：3/4 級，或血管/淋巴管侵犯，或切緣陽性

結腸癌適合切除

組織學證實的原發結腸惡性腫瘤

病理學分期

應報告以下項目：

癌細胞分級

浸潤深度(T)

檢出淋巴結數目和陽性數目(N)

遠端、近端、側面切緣狀況(radial)

2.淋巴結評估

AJCC 和病理學家學會建議至少應檢測 12 個淋巴結以準確確定 II 期結腸癌。準確確定 II 期結腸癌應檢測最少淋巴結數目的資料是不統一的。最少淋巴結數目被報導>7, >9, >13, >20, >30。能找到的淋巴結數目和年齡、性別、腫瘤的分期、腫瘤的位置有關。

尖淋巴結(供養血管的起點)被定義為“在結紮的血管根部的最頂端 1 cm 以內的最近淋巴結”。尖淋巴結應被外科醫生標記。多因素分析提示尖淋巴結受侵與不良預後明顯相關。

前哨淋巴結和用 IHC 檢測微轉移

用嚴格的組織學和/或 IHC 檢測前哨淋巴結以發現轉移癌是允許的。已有資料報導用大量的 H & E 切片和/或 IHC 來檢測細胞角蛋白陽性細胞。雖然研究資料被看到了希望，但是在檢測細胞的何種物質與轉移相關方面的意見是不統一的。NCCN 專家組定義轉移癌是微轉移（腫瘤在 0.2 mm to 2 mm 之間）或肉眼可見的轉移。僅被 IHC 發現的單個細胞的意義是有爭論的。一些研究認為是微轉移灶，然而大多數認為是 ITC，而不是微轉移。一些研究發現在 II (N0)期結腸癌(用 H & E 定義)，IHC 檢測的細胞角蛋白陽性與預後差有關，但其他研究卻沒有發現。在這些研究中 ITC 被認為是微轉移。目前，使用前哨淋巴結和僅用 IHC 檢測的癌細胞的方法，在臨床使用中應謹慎

八、外科手術原則

1.大腸切除術

淋巴結廓清術

應通過病理學檢查明確位於供養血管起點的淋巴結。

位於切除野外的可疑淋巴結應進行活檢或切除。

陽性淋巴結殘留表明切除不徹底（R2）。

至少應檢測 12 顆淋巴結送檢，以明確結腸癌Ⅱ期（T3-4,N0）分期。

即使Ⅲ期，淋巴結數目也與存活有關。

經腹腔鏡進行結腸切除術的條件

有經腹腔鏡進行大(直)腸手術經驗的外科醫生

無直腸、橫結腸病變

無局部晚期或轉移性疾病

無急性腸阻塞或癌性穿孔徵象

需要徹底的腹部探查

小病灶的術前標記

遺傳性非息肉性大(直)腸癌的處理

有明顯結腸癌家族史或年輕（小於 50 歲）發病的病人，考慮行更廣泛結腸切除術。

需要完全切除以達到治癒的目的。

2.轉移部位-肝臟

從肝臟解剖、病變範圍及肝功能維持方面綜合判斷完全切除病灶的可行性

無不能切除的肝外病灶

不能切除的病人給予新輔助治療後，重新評價能否切除

肝臟切除是可切除肝轉移的結腸癌病人的一種治療手段

對於不能單純切除的病人，可考慮聯合應用消融術與切除術

肝臟轉移的孤立病灶較多發病灶預後好

動脈內栓塞不應常規使用（除臨床試驗外）

原發病灶必須是被治癒性切除（R0）

可以考慮有選擇的進行再次切除

3.轉移部位-肺臟

完全切除需要從解剖位置、病變範圍及肺功能維持方面綜合判斷

一併切除可切除的肺外轉移病灶

原發病灶必須是被治癒性切除（R0）

可以考慮有選擇的進行再次切除

4.手術治療

腹腔鏡手術要由熟練掌握該技術的外科醫生實施，術中應進行細緻全面的腹腔探查。目前不推薦對中低位直腸腫瘤、腫瘤所致梗阻或穿孔、腫瘤明顯侵犯周圍組織（如 T4 病灶）者施行腹腔鏡手術。有腹膜粘連高危因素的患者應避免接受腹腔鏡手術，如術中發現患者有腹膜粘連應當即轉為開放手術治療。 CLASSIC 研究和 COST 研究長期隨訪的結果顯示，兩種手術方式有著相似的總生存期（OS）和局部復發率。特別是對 COLOR 試驗近期事件的分層分析發現，醫院腹腔鏡手術開展得越多，患者獲益越明顯。

病理評估對淋巴結給予更多重視鑒於手術淋巴結情況與術後生存相關，認為至少要取足 12 顆淋巴結才能準確判斷病理分期，而且在新證據的基礎上，對淋巴結的病理評估給予了更多的重視。INT-0089 研究顯示，手術切除淋巴結的數目不僅與準確進行病理分期相關；而且，無論淋巴結是陰性還是陽性，手術時增加淋巴結切除數目對患者生存的改善均有益。同時，有研究顯示，淋巴結轉移率也是疾病復發和 OS 的

預後指標。Ⅲ期結腸癌輔助化療地位鞏固，Ⅱ期仍有爭議。

MOSAIC 研究的 3 年、4 年、6 年隨訪資料均表明，Ⅲ期患者採用 FOLFOX 方案較 5-FU/LV 有明顯優勢，6 年 OS 率分別為 72.9%和 68.7%（P=0.023）。NSABP C-07 研究結果也證實 FOLFOX 輔助化療可以改善Ⅱ、Ⅲ期結腸癌患者的 4 年無病生存時間（DFS）。研究者對 18 項研究（20 898 例患者）進行薈萃分析，進一步證實了 FOLFOX 方案輔助化療對Ⅲ期患者的價值。因此，Ⅲ期結腸癌患者輔助化療的推薦方案也調整為 FOLFOX（1 類證據）。 基於 MOSAIC 研究的初步結果，對於有高危因素（分化程度差、脈管侵犯、梗阻、穿孔、受檢淋巴結(12 顆、切緣陽性或接近陽性）的 T3N0M0 和 T4N0M0 患者推薦採用 FOLFOX、5-FU/LV 或 Capecitabine 行術後輔助化療。 對 T3N0M0 期無高危因素的患者，可以考慮行 5FU/LV 或 Capecitabine 輔助化療，也可以參加臨床試驗或觀察；具有高危因素的Ⅱ期患者可以考慮行 FOLFOX、5FU/LV 或 Capecitabine 輔助化療、參加臨床試驗或觀察。臨床實踐中，我們應充分告知Ⅱ期患者，輔助治療的絕對生存獲益不超過 5%，要根據患者實際情況和個人意願酌情實施。

立足於根治，進一步強調轉移性病灶的治療。

近年來，隨著新型化療藥物及方案的應用和對轉移灶手術適應證的重新認識，轉移性結腸癌的手術率有了明顯提高。新近的證據顯示，可以手術完全切除的轉移性結腸癌患者的 5 年生存率超過了 50%。 考慮到疾病進展及新輔助化療不良反應對後續手術可能存在的影響，對於明確能手術切除的轉移性結腸癌，更傾向於建議首選手術治療，而非新輔助化療。新輔助化療療效應每 2 個月評估一次，對所謂“完全緩解”者的結論態度應審慎。因為研究顯示，大多數患者僅為影像學完全緩解，並非病理完全緩解，可能給後續手術切除定位帶來很大麻煩，如不選擇手術治療，絕大多數患者都會復發。由於手術完全切除的意義重大，對一些潛在的可手術切除的轉移性結腸癌，應給予更加積極、有效的治療。 消融術(RFA)可配合手術治療進行，對於不能耐受手術的患者可以考慮選擇施行。但應該明確，無論手術還是消融術(RFA)均應以根治為目的，不推薦以減瘤為目的的治療。

分子標靶治療強調檢測標誌物已經明確，患者腫瘤組織 EGFR 表達狀態對 EGFR 單株抗體療效預測並無意義，不能作為接受抑或排除 EGFR 單株抗體治療的根據。但多項研究發現，KRAS 基因突變與 EGFR 單株抗體耐藥密切相關。這是一個具有里程碑意義的發現，是歷史上第一個可以對結腸癌療效進行預測的生物標誌。強烈推薦所有轉移性結腸癌患者都應檢測 KRAS 基因狀態，突變患者不應接受含 EGFR 單株抗體方案治療。研究也發現，KRAS 突變是結腸癌發病的早期事件，原發灶與轉移灶 KRAS 狀態高度一致，無論對原發灶還是轉移灶進行 KRAS 狀態檢測都是合理的。

九、早期緩和照護原則

若病人疾病分期為第四期，醫療團隊預估病人生命存活期約大於 6 個月，若病人拒絕治療、第二線化療及標靶藥物治療無效或經主治

醫師及醫療團隊評估當病人身體狀況不適用常規治療方式，上述三項條件則一符合時，緩和醫療與安寧療護轉介機制便會啟動（鄭等，2018）。

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）

十一、實症醫學

Categories of Evidence and Consensus :

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower- level evidence including clinical experience, that the recommendationis appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

NCCN 對證據和共識的分類

1 類：基於高水準證據（如隨機對照試驗）提出的建議，專家組一致同意。

2A 類：基於低水準證據提出的建議，專家組一致同意。

2B 類：基於低水準證據提出的建議，專家組基本同意，無明顯分歧。

3 類：基於任何水準證據提出的建議，專家組意見存在明顯的分歧。除非特別指出， NCCN 對所有建議均達成 2A 類共識。

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