

大腸癌診療指引

大腸直腸癌醫療團隊修訂

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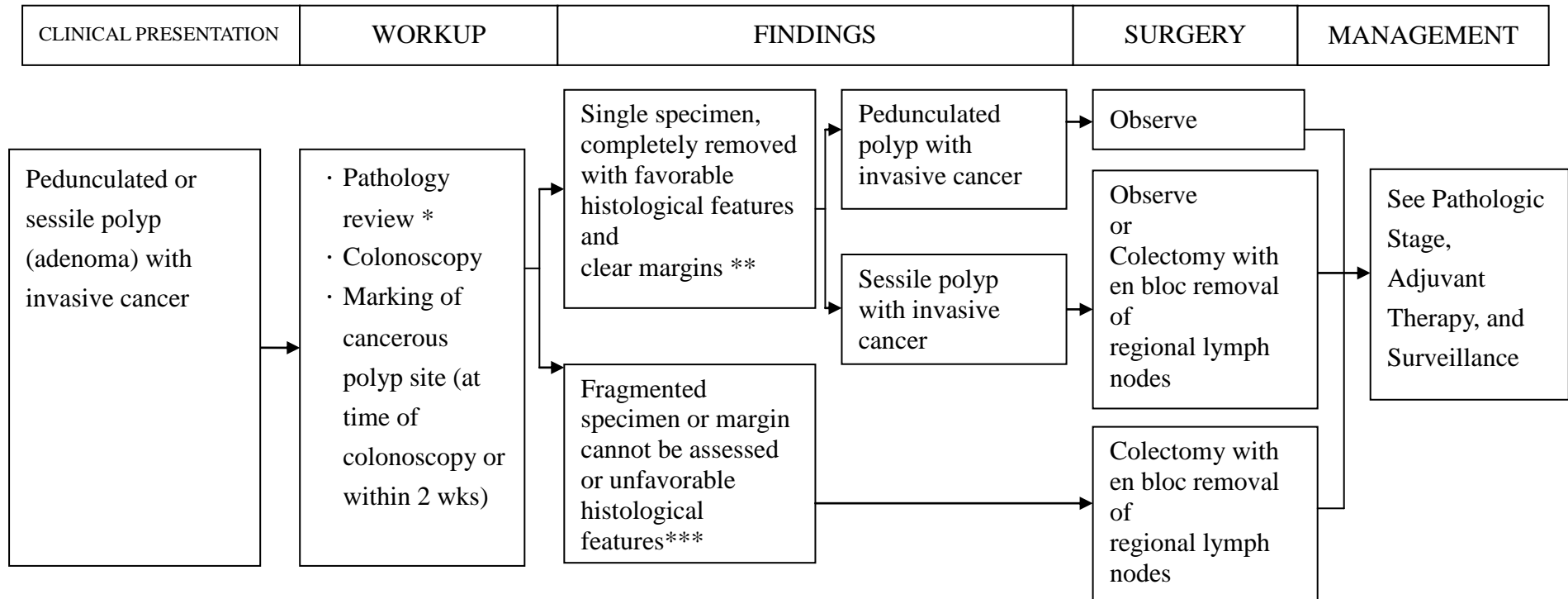
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Malignant Polyp of Colon

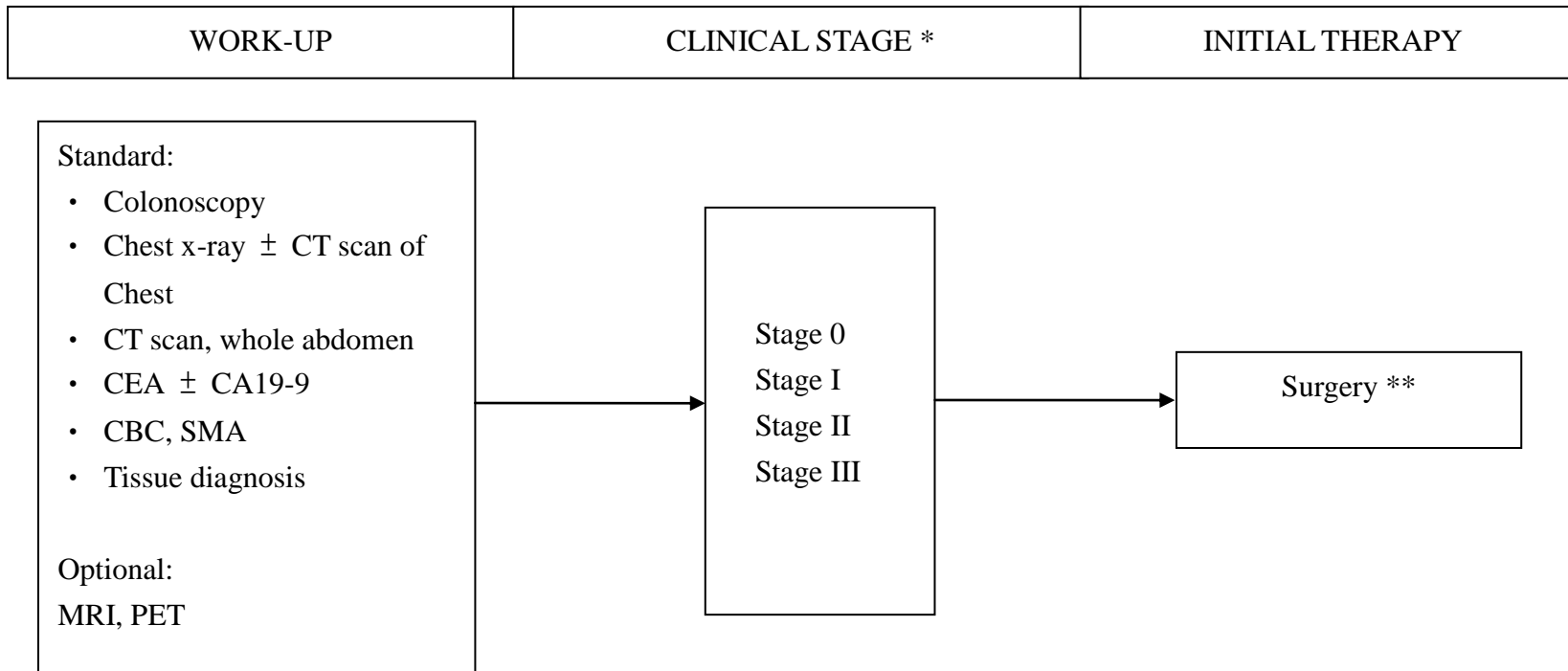


* A malignant polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1). pTis is not considered a “malignant polyp.”

** Favorable histologic features: grade 1 or 2, no angiolymphatic invasion, and negative margin of resection. There is no consensus as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as 1) tumor <1 mm from the transected margin, 2) tumor <2 mm from the transected margin, and 3) tumor cells present within the diathermy of the transected margin.

*** Unfavorable histologic features: grade 3 or 4, angiolymphatic invasion, or a “positive margin.” See the positive margin definition above.

Initial management for stage 0, I, II, III disease

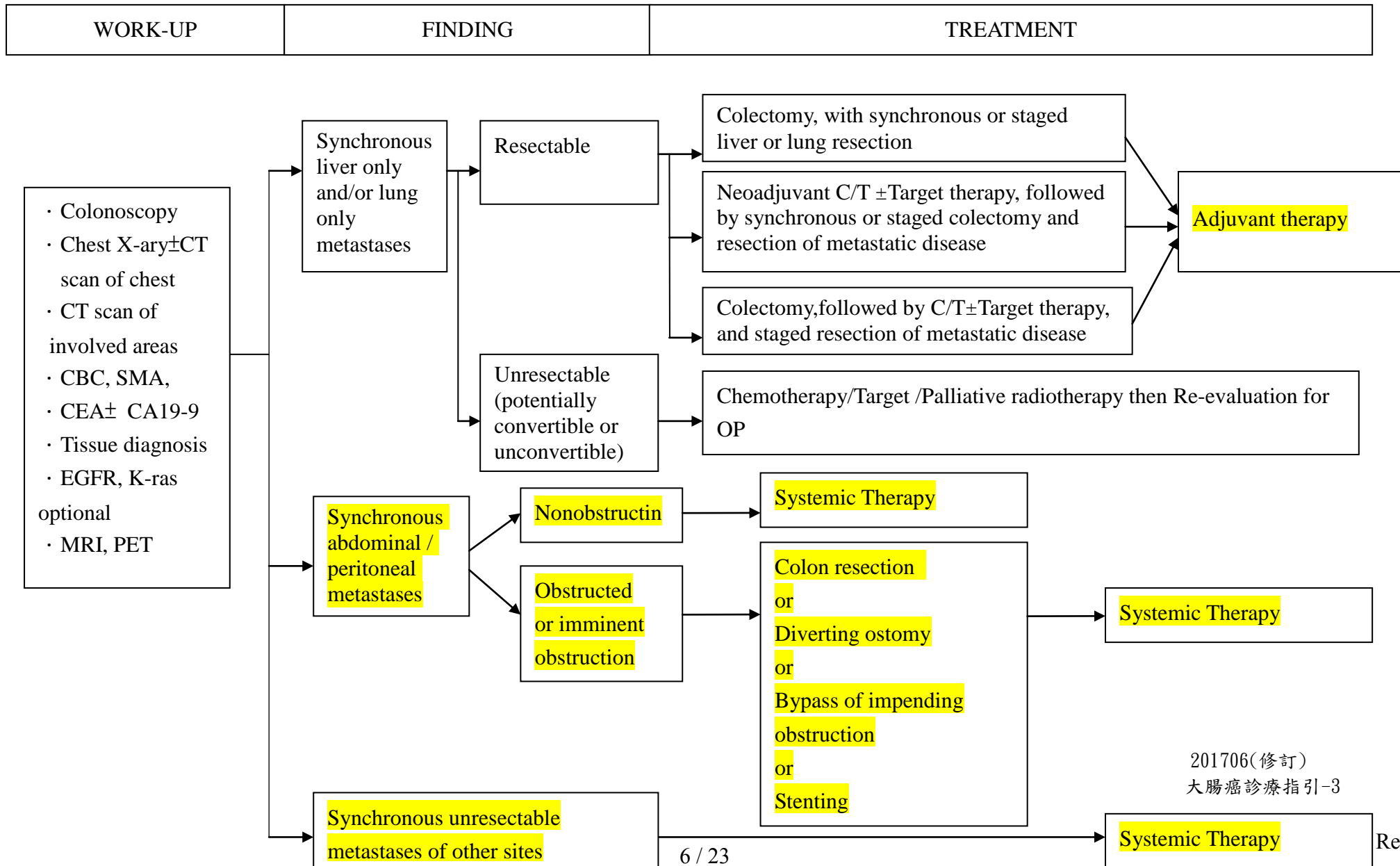


* Colon cancer 之分期依 7th AJCC staging.

** Laparoscopic-assisted colectomy may be considered based upon the following criteria.

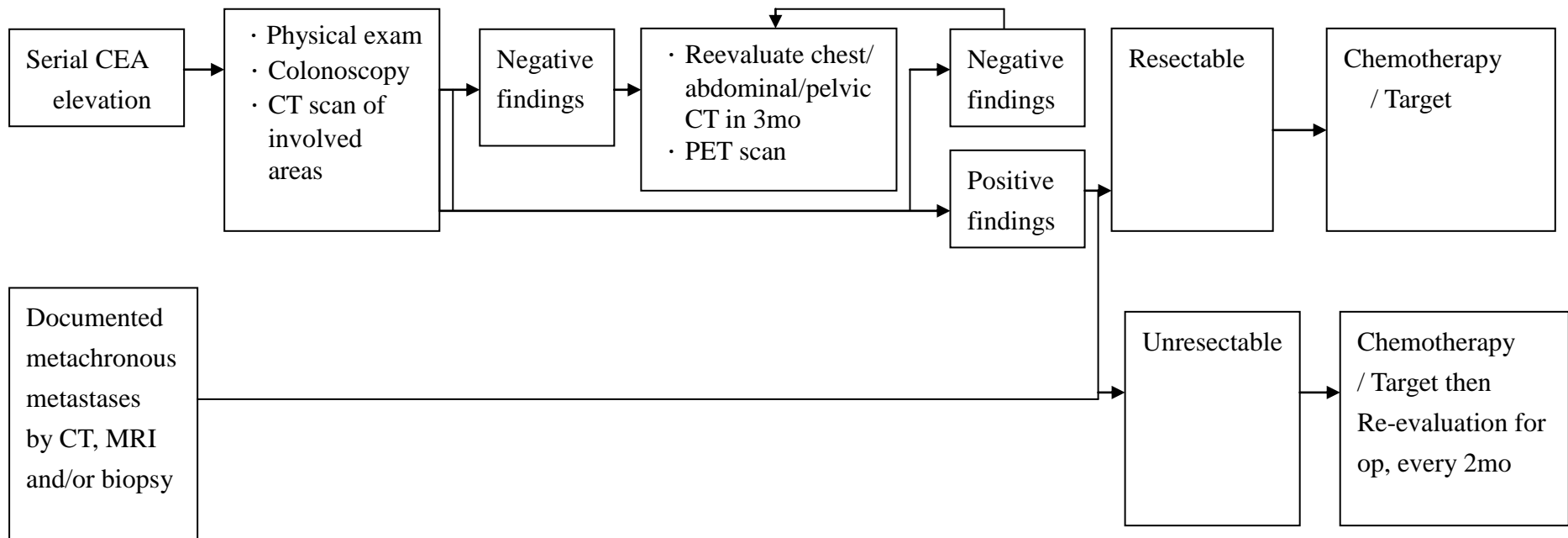
- ▶ The surgeon has experience performing laparoscopically assisted colorectal operations.
- ▶ There is no locally advanced disease.
- ▶ It is not indicated for acute bowel obstruction or perforation from cancer.
- ▶ Thorough abdominal exploration is required.
- ▶ Consider preoperative marking of small lesions.

Initial management for stage IV disease



Initial management for recurrence

RECURRENCE	WORK-UP	FINDING	SURGERY	CHEMOTHERAPY/TARGET
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PATHOLOGIC STAGE	ADJUVANT THERAPY
Stage 0 / stage I	None
Stage II A (Without risk factors *)	None / UFUR / Capecitabine
Stage II A (With risk factors *) Stage II B Stage II C ***	5FU / LV / UFUR / FOLFOX. / Capecitabine
Stage III ***	5FU / LV / FOLFOX / UFUR / Capecitabine / CapeOx
Stage IV	Salvage / palliative chemotherapy / Target therapy ** / Palliative radiotherapy ***

* risk factor: poor differentiation, LVI, PNI, perforation, obstruction, < 12 lymph nodes examined, positive margins

** See page 6

*** 放射治療的適應症(大腸癌): (1)手術中放射線治療(Intraoperative radiation therapy)可適用於考慮手術切除後邊緣非常接近或陽性、患者屬於 T4 及復發性癌症。
(2)Stage IV: 針對轉移部位(如骨骼、腦等部位)施行緩解性放射治療 (3)對於 T4 合併侵犯其他固定的器官,可考慮 RT (4) 手術後病理檢驗結果證實沒有淋巴轉移,但在原發腫瘤切除邊緣接近或侵犯,而且能夠明確勾畫出此位置。

劑量給予:

1. 建議療程應以標準分次進行(每日一次、每週 5-6 次)。
2. 若手術前放射治療,劑量應為 45.0 – 50.4 Gy / 25 – 28 fractions
3. 若手術中放射治療(Intraoperative radiation therapy),劑量應為 12.0-20.0Gy
- 4 若手術後放射治療,首先給予劑量應為 45.0 – 50.4 Gy / 25 – 28 fractions to whole pelvis 後,進行局部劑量追加 (tumor bed),再給予劑量 5.4 – 9.0 Gy / 3 – 5 fractions

**** Target therapy:****Cetuximab(Erbitux)健保適應症：**

(1) 與 FOLFIRI (Folinic acid/ 5- fluorouracil/irinotecan)或 FOLFOX (Folinic acid/ 5-fluorouracil /oxaliplatin) 合併使用於治療具表皮生長因子受體表現型 (EGFR expressing)，RAS 原生型之轉移性直腸結腸癌病患之第一線治療。

I. 本藥品需經事前審查核准後使用，每次申請事前審查之療程以 18 週為限，再次申請必須提出客觀證據（如：影像學）證實無惡化，才可繼續使用。

II. 使用總療程以 36 週為上限。

III. 本藥品不得與 bevacizumab 併用。

(2) 與 irinotecan 合併使用，治療已接受過含 5-fluorouracil (5-FU)、irinotecan 及 oxaliplatin 二線以上之細胞毒性治療失敗、具有表皮生長因子受體(EGFR)表現型且 K-ras 基因沒有突變的轉移性直腸結腸癌的病患。

I. 本藥需經事前審查核准後使用，每次申請事前審查之療程以 9 週為限，再次申請必須提出客觀證據（如：影像學）證實無惡化，才可繼續使用。

II. 使用總療程以 18 週為上限

**** Target therapy:****Bevacizumab (Avastin) 健保適應症：**

- (1) Bevacizumab 與含有 irinotecan/ 5-fluorouracil/ leucovorin 或 5-fluorouracil/ leucovorin 的化學療法合併使用，作為轉移性大腸或直腸癌患者的第一線治療。
- (2) 使用總療程以 36 週為上限。
- (3) 本藥須經事前審查核准後使用，每次申請事前審查之療程以 18 週為限，再次申請必須提出客觀證據（如：影像學）證實無惡化，才可繼續使用。

Panitumumab (Vectibix) 健保適應症：

單獨使用治療已接受過含 5-fluorouracil(5-FU)、irinotecan 與 oxaliplatin 二線以上之細胞毒性治療失敗、具有表皮生長因子受體(EGF 表現型且 K-RAS 基因沒有突變的轉移性直腸結腸癌的病患。

Regorafenib (Stivarga) 健保適應症：

- (1) 用於治療先前曾接受下列療法的轉移性大腸直腸癌(mCRC)患者，療法包括 fluoropyrimidine-、oxaliplatin-、irinotecan- 為基礎的化療，和抗血管內皮生長因子(anti-VEGF)等療法；若 K-ras 為原生型(wild type)，則需接受過抗表皮生長因子受體(anti-EGFR)療法。
- (2) 須經事前審查核准後使用，每次申請事前審查之療程以 8 週為限，再次申請必須提出客觀證據（如：影像學）證實無惡化，才可繼續使用。

Follow-up

Time	Pre-Treatment	3M	6M	9M	1yr	3M	6M	9M	2yrs	6M	3yrs	6M	4yrs	6M	5yrs
Physical exam	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
CEA	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
CXR	O				O				O		O		O		O
Sono of liver			O				O			O		O		O	
Whole abdominal. CT	O				O				O		O		O		O
Colonoscopy	O				O				O						O

ADJUVANT THERAPY - CHEMOTHERAPY REGIMENS

1.mFOLFOX

Oxaliplatin 85 mg/m² IV over 2 hours, day 1.
Leucovorin* 400 mg/m² IV over 2 hours, day 1.
5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† continuous infusion. Repeat every 2 weeks.

2. Capecitabine

Capecitabine 1250 mg/m² twice daily days 1–14 every 3 wks x 24 wks.

*健保適應症:第三期結腸癌患者手術後的輔助性療法,以八個療程為限

3. UFUR <Tegafur 100mg + Uracil 224mg >*

350-500 mg/m² PO once daily for 24 months

*健保適應症:直腸癌、結腸癌第II、III期患者之術後輔助性治療,且使用期限不得超過2年

4. LV5FU2 (de Gramont regimen)

- 5-Fluorouracil: 400 mg/m² IV bolus, followed by 600 mg/m² IV continuous infusion for 22 hours on days 1 and 2
- Leucovorin: 200 mg/m² IV on days 1 and 2 as a 2-hour infusion before 5-fluorouracil
- Repeat cycle every 2 weeks for a total of 12 cycles

5. FLOX

5-FU 500 mg/m² iv bolus 1 hr after start of leucovorin qw x 6 weeks every 8 weeks for 3 cycles

Leucovorin 500 mg/m² iv over 2 hrs qw x 6 weeks every 8 weeks for 3 cycles

Oxaliplatin 85 mg/m² iv over 2 hrs before 5-FU and Leucovorin week 1, 3, 5 of each 8-week cycle for 3 cycles

CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS**1.FOLFIRI**

Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1,
then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)[†] continuous infusion
Repeat every 2 weeks

2.FOLFIRI + Bevacizumab

Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1,
then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)[†] IV continuous infusion
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

3.FOLFIRI + Cetuximab

Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1,
then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)[†] IV continuous infusion
Repeat every 2 weeks
Cetuximab 400 mg/m² IV over 2 hours first infusion, then 250 mg/m² IV over 60 minutes weekly
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks

4.FOLFIRI + ziv-aflibercept

Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin* 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1,
then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)[†] continuous infusion
Ziv-aflibercept 4 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

* Irinotecan 健保適應症：限轉移性大腸直腸癌之第一線治療藥物
(1)與 5-FU 及 folinic acid 合併，使用於未曾接受過化學治療之患者。
(2)單獨使用於曾接受 5-FU 療程治療無效之患者。

5.Capecitabine

850–1250 mg/m² PO twice daily, days 1–14
Repeat every 3 weeks

*健保適應症：第三期結腸癌患者手術後的輔助性療法，以八個療程為限

6.Capecitabine+ Bevacizumab

Capecitabine 850–1250 mg/m² PO twice daily, days 1–14
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

7. UFUR <Tegafur 100mg + Uracil 224mg >*

350-500 mg/m² PO once daily for 24 months

*健保適應症：直腸癌、結腸癌第 II、III 期患者之術後輔助性治療，且使用期限不得超過 2 年

*Reference: see page 13

8. Oxaliplatin + 5-fluorouracil + leucovorin (mFOLFOX)

- Oxaliplatin: 85 mg/m² IV on day 1
- 5-Fluorouracil: 400 mg/m² IV bolus on day 1, followed by 2400 mg/m² IV continuous infusion for 46 hours
- Leucovorin: 400 mg/m² IV on day 1 as a 2-hour infusion, before 5-fluorouracil
- Repeat cycle every 2 weeks

9. XELOX

Capecitabine (Xeloda) 1000 mg/m² po bid x 14 days
Oxaliplatin (Eloxatin) 130 mg/m² iv over 2 hrs d1

10. mFOLFOX + Bevacizumab

- Oxaliplatin: 85 mg/m² IV on day 1
- 5-Fluorouracil: 400 mg/m² IV bolus on day 1, followed by 2400 mg/m² IV continuous infusion for 46 hours
- Leucovorin: 400 mg/m² IV on day 1 as a 2-hour infusion, before 5-fluorouracil
- Bevacizumab: 5 mg/kg IV on day 1 every 2 weeks
- Repeat cycle every 2 weeks

11. FOLFOXIRI (for BRAF mutant)

Irinotecan (Camptosar, CPT-11) 165 mg/m² iv over 1 h d1
Oxaliplatin (Eloxatin) 85 mg/m² iv over 2 hrs d1
Leucovorin 200 mg/m² iv over 2 hrs d1
5-FU 3200 mg/m² civi over 48 hrs d1-2
Q2w x 12 cycles

12. FOLFOX4 + Cetuximab (for patients with wild-type KRAS)

Leucovorin 200 mg/m² iv over 2 hrs before 5-FU, d1 and 2 q2w
5-FU 400 mg/m² iv bolus and then 600 mg/m² iv over 22 hrs, d 1 and d2 q2w
Oxaliplatin (Eloxatin) 85 mg/m² iv over 2 hrs d1q2w
Cetuximab (Erbitux) 400 mg/m² iv loading over 2 hours d1, and then 250 mg/m² iv over 1 hour qw
Until progression

13. FOLFOX4 + Panitumumab (for patients with wild-type KRAS)

Panitumumab (Vectibix) 6 mg/kg iv over 60 min q2w

Leucovorin 200 mg/m² iv over 2 hrs before 5-FU, d1 and 2

5-FU 400 mg/m² iv bolus and then 600 mg/m² iv over 22 hrs, d1 and d2

Oxaliplatin (Eloxatin) 85 mg/m² iv d1

Q2w until progressive disease

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5. FLOX

Wolmark N et al. A phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: survival results of NSABP protocol C-07. 2008 ASCO annual meeting. LBA4005 (link to the abstract).

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10.mFOLFOX + Bevacizumab

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6.Capecitabine+ Bevacizumab

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STAGE CATEGORY DEFINITIONS	
PRIMARY TUMOR (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria*
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum**
T4b	Tumor directly invades or is adherent to other organs or structures [^] ,**
<p>*Note: Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or mucosal lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.</p> <p>[^]Note: Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retro-peritoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (i.e., respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix or vagina).</p> <p>**Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN site-specific factor should be used for perineural invasion.</p>	

REGIONAL LYMPH NODES (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4 to 6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
<p>Note: A satellite peritumoral nodule in the pericorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule may represent discontinuous spread, venous invasion with extravascular spread (V1/2) or a totally replaced lymph node (N1/2). Replaced nodes should be counted separately as positive nodes in the N category, whereas discontinuous spread or venous invasion should be classified and counted in the Site-Specific Factor category Tumor Deposits (TD).</p>	

DISTANT METASTASIS (M)	
M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (e.g., liver, lung, ovary, non-regional node).
M1b	Metastases in more than one organ/site or the peritoneum.

ANATOMIC STAGE • PROGNOSTIC GROUPS					
GROUP	T	N	M	Dukes*	MAC*
0	Tis	N0	M0	-	-
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1-T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3-T4a	N1/N1c	M0	C	C2
	T2-T3	N2a	M0	C	C1/C2
	T1-T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3-T4a	N2b	M0	C	C2
	T4b	N1-N2	M0	C	C3
IVA	Any T	Any N	M1a	-	-
IVB	Any T	Any N	M1b	-	-
*Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (Any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.					
Stage unknown					