# 大腸癌診療指引

大腸直腸癌醫療團隊修訂

2007 年 11 月制訂　2012 年 7 月修訂

2008 年 8 月修訂　2013 年 5 月修訂

2009 年 6 月修訂　2014 年 10 月修訂

2010 年 7 月修訂　2015 年 10 月修訂

2011 年 7 月修訂

參考資料：

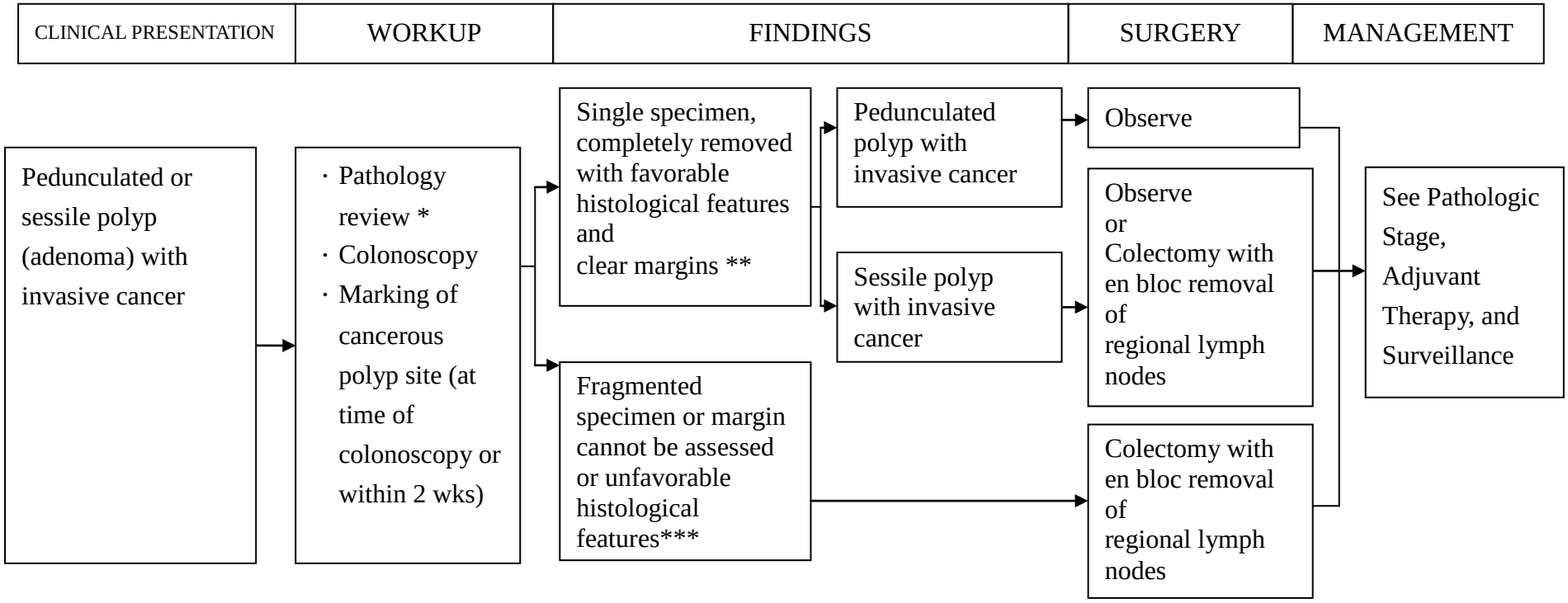
1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Colon Cancer version 2. 2015

2. 全民健康保局醫療給付標準行政院衛生署一百零四年版

3. Physicians' Cancer Chemotherapy Drug Manual 2015

# Table of Contents

# Malignant Polyp of Colon

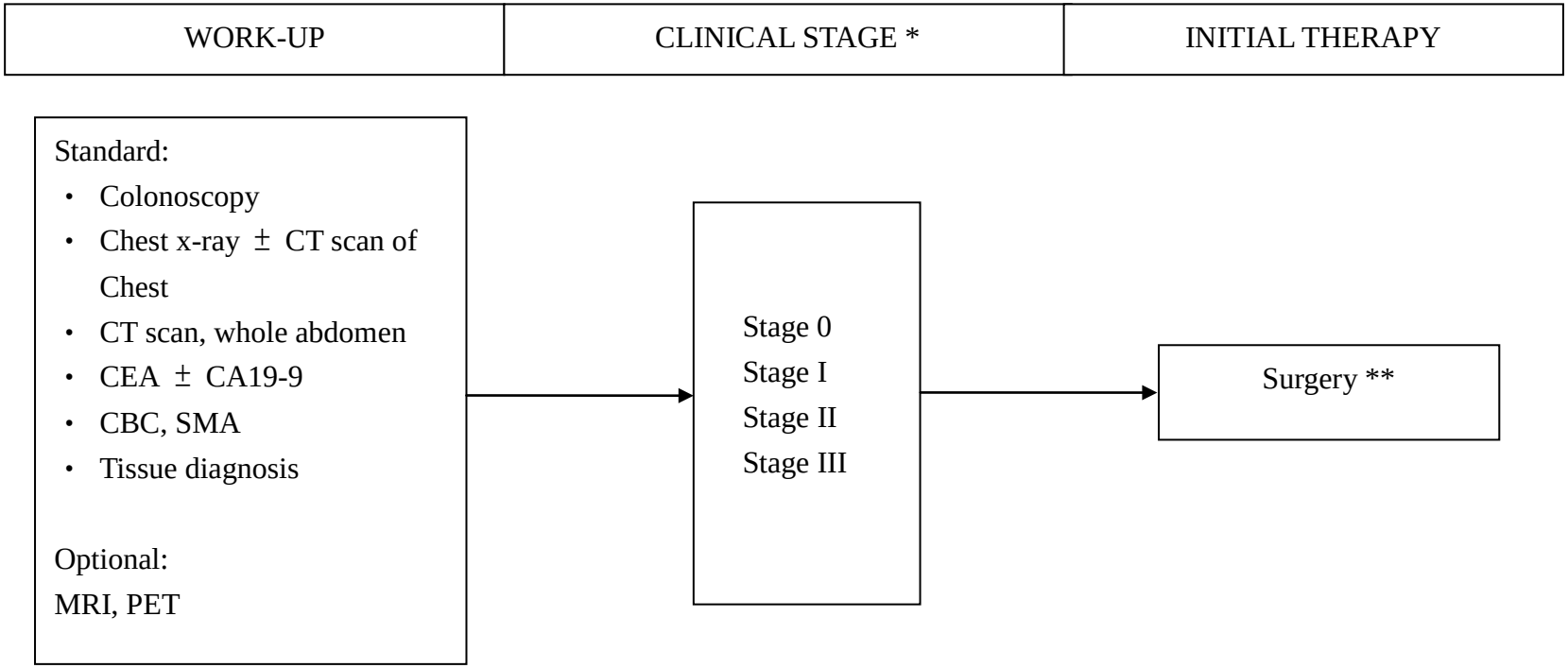



* A malignant polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1). pTis is not considered a “malignant polyp.”

** 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. [1-4]

*** 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:[2]

► The surgeon has experience performing laparoscopically assisted colorectal operations.[3,4]

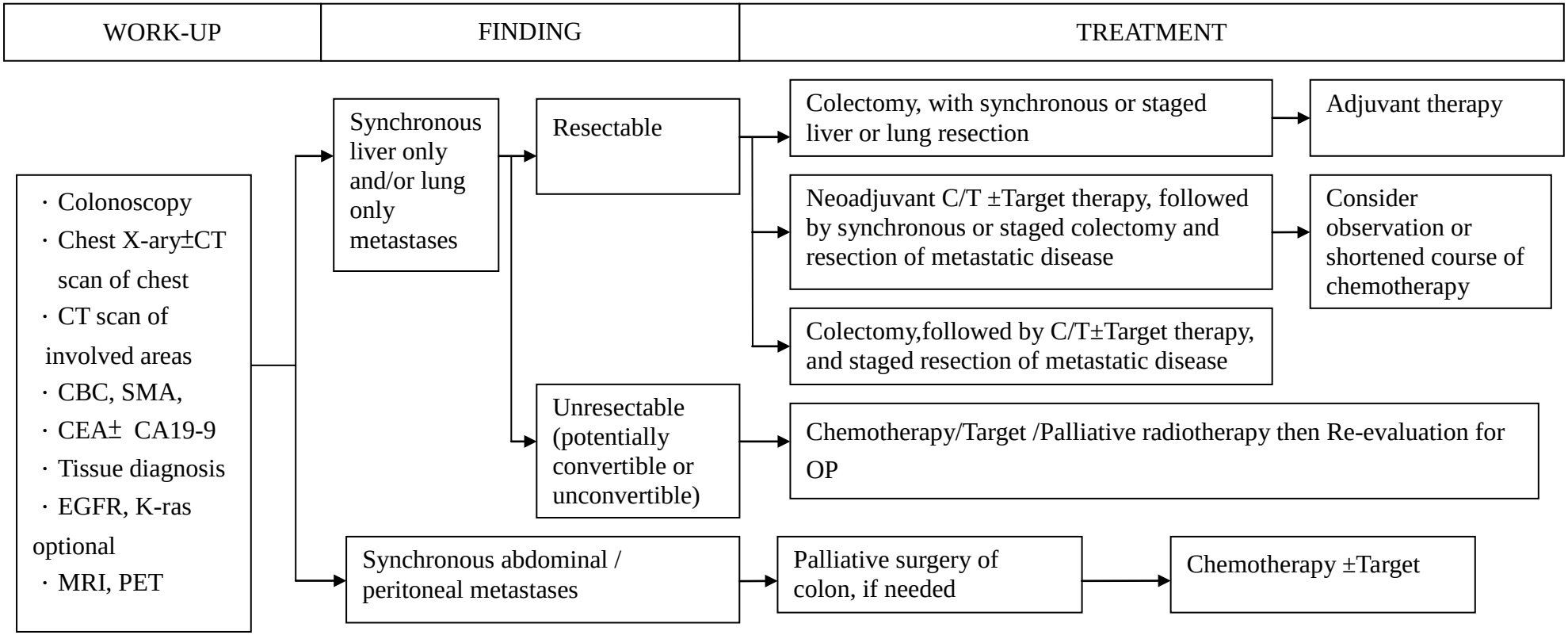
► There is no locally advanced disease.

► It is not indicated for acute bowel obstruction or perforation from cancer.

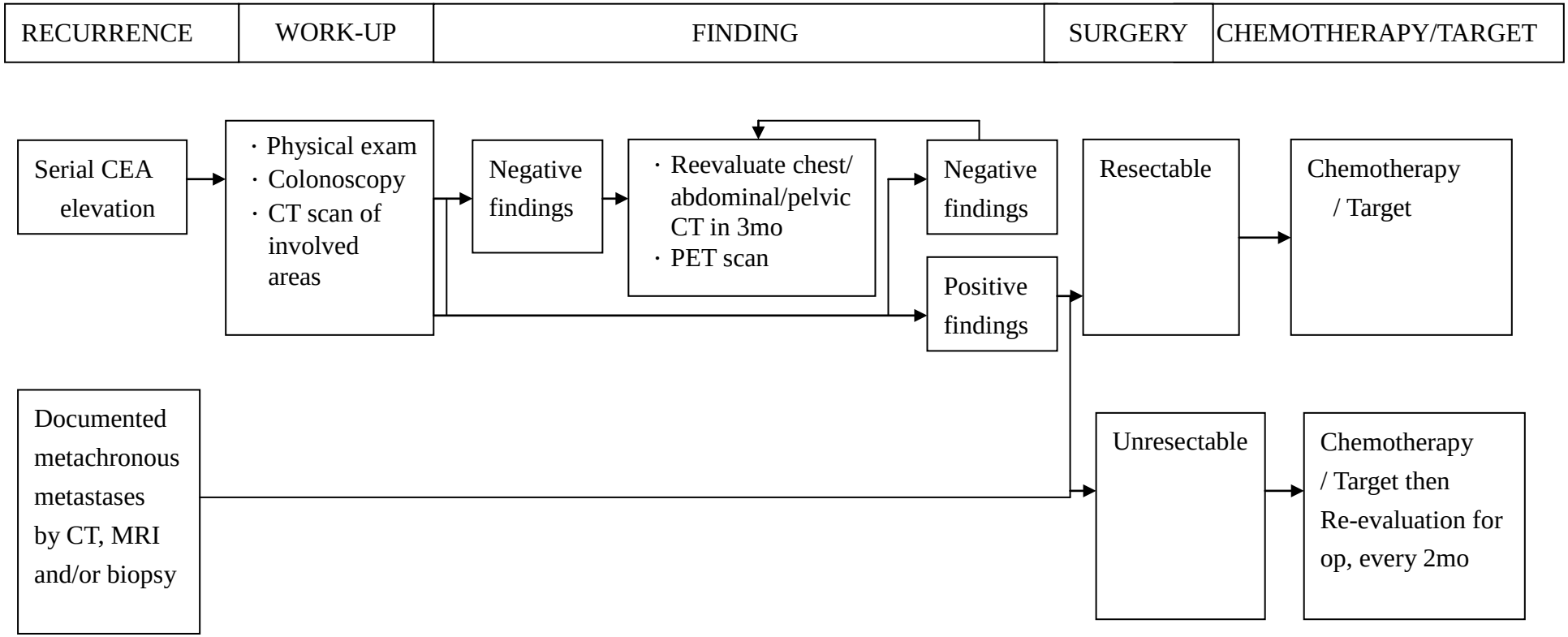
► Thorough abdominal exploration is required.[5]

► Consider preoperative marking of small lesions.

Initial management for stage IV disease



Initial management for recurrence



| PATHOLOGIC STAGE | ADJUVANT THERAPY |
|---|---|
| Stage 0 / stage I | None |
| Stage II A (Without risk factors * ) | None / UFUR / Capecitabine |
| Stage II A (With risk factors *)<br>Stage II B<br>Stage II C *** | 5FU / LV / UFUR / FOLFOX. / Capecitabine |
| Stage III *** | 5FU / LV / FOLFOX / UFUR / Capecitabine / CapeOx / FLOX |
| Stage IV | Salvage / palliative chemotherapy / Target therapy **<br>/ 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)** (K-ras wild-type only) 健保適應症：

(1)與 FOLFIRI (Folinic acid/5-fluorouracil/irinotecan)合併使用於治療具表皮生長因子受體表現型(EGFR expressing)，K-ras 基因沒有突變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 12 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 24 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 24 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 12 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。

**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 |

## Chemotherapy Regimens

**1. 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

**2. Capecitabine***

850-1250 mg/m² PO twice daily, days 1-14

Repeat every 3 weeks x 8 cycles

*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. Capecitabine + Bevacizumab**

Capecitabine 850-1250mg/m² PO twice daily,days 1-14

Bevacizumab 7.5mg/kg IV,day 1

Repeat every 3 weeks

**4. DeGramont (5-Fu x2 days)**

Leucovorin 200mg/m² IV 2 hours, days 1-2

5-Fluorouracil 400 mg/m² IV bolus, days 1-2

5-Fluorouracil 600 mg/m² IV continuous infusion, days 1-2

Repeat every 2 weeks x 12 cycles

**5. Bolus or infusional 5-FU/leucovorin (Roswell-Park regimen)**

Leucovorin 500 mg/m² IV over 2 hours, days 1, 8, 15, 22, 29, and 36

5-Fluorouracil 500 mg/m² IV bolus 1 hour after start of leucovorin, days 1, 8, 15, 22, 29, 36

Repeat every 8 weeks for 3-4 cycles

**6. CapeOx (Oxaliplatin+ Capecitabine)**

Oxaliplatin 130 mg/ m² IV over 2 hours, day 1

Capecitabine 850-1000mg/ m² twice daily PO for 14 days

Repeat every 3 weeks x 8 cycles

**7. CapeOX+ Bevacizumab**

Oxaliplatin 130mg/m² IV over 2 hours, day 1

Capecitabine 850-1000mg/m² PO twice daily for 14 days

Bevacizumab 7.5 mg/kg IV , day 1

Repeat every 3 weeks

**8. FLOX**

Oxaliplatin 85 mg/m² IV administered on weeks 1, 3, and 5

5-Fluorouracil 500 mg/m² IV bolus weekly x 6

Leucovorin 500 mg/m² IV weekly x 6,

Repeat of each 8 week for tatol of 3 cycle for 3 cycles

**9. FOLFOX4**

Oxalip<oxalipatin> 85mg/m² IV 2 hours, days 1

Leucovorin 200mg/m² IV 2 hours, days 1-2

5-Fluorouracil 400 mg/m² IV bolus, days 1-2

5-Fluorouracil 600 mg/m² IV continuous infusion, days 1-2

Repeat every 2 weeks x 12 cycles

**10. mFOLFOX 6**

Oxalip<oxalipatin> 85mg/m² IV 2 hours, days 1

Leucovorin 400mg/m² IV 2 hours, days 1

5-Fluorouracil 400 mg/m² IV bolus, days 1

5-Fluorouracil 1200 mg/m² IV continuous infusion, days 1-2

Repeat every 2 week x 12 cycles

**11. FOLFIRI + ziv-aflibercept**

Irinotecan 180 mg/ m² IV over 30-90 minutes , day 1

Leucovorin 400mg/m² IV ,day 1

5-Fu 400mg/m² IV bolus day 1,then 1200mg/m2/day x2 days , continuous infusion.

Ziv-aflibercept 4mg/kg IV

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。

**12. Regorafenib**

Regorafenib 160mg PO daily days 1-21

Repeat every 28 days

**13. FOLFIRI + Bevacizumab**

Irinotecan 180mg/m² IV over30-90 minutes, day 1

Leucovorin 400mg/m² IV infusion to match duration of irinotecan infusion day 1

5-FU 400mg/m² IV bolus day 1,then 1200mg/m²/day x 2 days (total 2400mg/m² over 46-48 hrs) IV continuous infusion

Bevacizumab 5mg/kg IV, day 1

Repeat every 2 weeks

**14. Cetuximab + FOLFOX**

Oxaliplatin 85mg/m² IV over 2 hours, day 1

Leucovorin 400mg/m² IV over 2 hours, day 1

5-FU 400mg/m² IV bolus on day 1, then 1200mg/m²/day x 2 days (total 2400mg/m² over 46-48 hrs) IV continuous infusion

Repeat every 2 weeks

Cetuximab 400mg/m² IV over 2 hours first infusion, 250mg/m² IV over 60 minutes weekly

or Cetuximab 500mg/m² IV over 2 hours, day 1, every 2 weeks

Repeat every 2 weeks

**15. Cetuximab + FOLFIRI**

Irinotecan 180mg/m² IV over30-90 minutes, day 1
Leucovorin 400mg/m² IV infusion to match duration of irinotecan infusion day 1
5-FU 400mg/m² IV bolus on day 1, then 1200mg/m²/day x 2 days (total 2400mg/m² over 46-48 hrs) IV continuous infusion
Repeat every 2 weeks
Cetuximab 400mg/m² IV over 2 hours first infusion, 250mg/m² IV over 60 minutes weekly
or Cetuximab 500mg/m² IV over 2 hours, day 1, every 2 weeks
Repeat every 2 weeks

**16. IROX**

Oxaliplatin 85mg/m² IV over 2 hours, followed by irinotecan 200mg/m² over 30~90 minutes every 3 weeks

**17. FOLFOXIRI**

Irinotecan 165mg/m² IV day 1, oxaliplatin 85mg/m² day 1,leucovorin 400 mg/m² day 1, fluorouracil 1600mg/m²/day x 2 days (total 3200mg/m² over 48 hours) continuous infusion starting on day 1.
Repeat every 2 weeks

**18. Irinotecan**

Irinotecan 125mg/m² IV over 30~90 minutes, day1 and day 8
Repeat every 3 weeks
or Irinotecan 180mg/m² IV over 30~90 minutes, day1
Repeat every 2 weeks
or Irinotecan 300~350mg/m² IV over 30~90 minutes, day1
Repeat every 3 weeks

**19. FOLFOX + Bevacizumab**

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

**Reference**

1. UFUR<Tegafur 100mg + Uracil 224mg >:
- Journal of Clinical Oncology Volume 24, Number 13, May 1, 2005
- Int.J. Raditiona Oncology Biol.Phys., Vol.79, No. 1,pp.102-110, 2008
- Langenbeck's Arch Surg(2002)386;575-581
- British Journal of Cancer(2007)96, 1170-1177
- Journal of Clinical Oncology Volume 22, Number 15, August 1, 2004
- Int.J. Raditiona Oncology Biol.Phys., Vol.45, No. 3,pp.629-634, 1999
- Annals of Oncology Advance Access published April 1, 2008/10/14 Jpn Clin Oncol 2006;36(4)237-244
- J Gastrointest Surg. 2011 Dec;15(12):2239-45.
2. Capecitabine
- ournal of Clinical Oncology 2004; Vol 22:145(Abstract 8105)
- N Engl J Med 352;26-30, 2005
- F. Hoffmann-La Roche, data on file
- Schmoll et al. J Clin Oncol 2007
- J Clin Oncol 26: 2008 (May 20 suppl; abstr 15074)
- Van Cutsem et al. Br J Cancer 2004
- J Clin Oncol. 2008;26(12):2006–12.
- Schmiegel et al. ASCO 2007 (Abst 4034)
-Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352:2696-2704

**Reference**

3. Bolus or infusional 5-FU/leucovorin

-Haller DG, Catalano PJ, Macdonald JS Mayer RJ. Phase III study of fluorouracil, leucovorin and levamisole in high risk stage II and III colon cancer: final report of Intergroup 0089. J Clin Oncol 2005:23:8671-8678

4. FOLFOX4:

- British Journal of Cancer(2006)94, 69-73

- Goldberg R, et al. J Clin Oncol 2004; 22:23.

- Andre T, Bensmaine MA, Louvet C, et al: Multicenter phase II study of bimonthly high-dose leucovorin, fluorouracil infusion, and oxaliplatin for metastatic colorectal cancer resistant to the same leucovorin and fluorouracil regimen. *J Clin Oncol* 1999; 17:3560-3568.

5. XELOX

-Schmoll HJ, Cartwright T, Tabernero J, et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. J Clin Oncol 2007;25:102-109. Haller DG, Tabernero J, Maroun J, et al. Capecitabine Plus Oxaliplatin Compared With Fluorouracil and FolinicAcidAs Adjuvant Therapy for Stage III Colon Cancer. J Clin Oncol 2011;29:1465-1471.Available at: http://www.ncbi.nlm.nih.gov/pubmed/21383294

6. FLOX

-Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol 2007;25:2198-2204.

7. mFOLFOX 6

Cassidy J, Clarke S, Diaz Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 2008;26:2006-12.

**Reference**

8. FOLFIRI + ziv-aflibercept

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.Available at: http://www.ncbi.nlm.nih.gov/pubmed/22949147

9. Regorafenib

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; 26;381:303-12. Available at : http://www.ncbi.nlm.nih.gov/pubmed/23177514

| 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^,** |

*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.

^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).

**Tumor that is adherent to other organs or structures, grossly, is classified cT4b.However, if no tumor is present in the adhesion, microscopically, the classificationshould be pT1-4a depending on the anatomical depth of wall invasion. The V andL 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.

| 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 |
| Note: A satellite peritumoral nodule in the pericolorectal 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). | |

| 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 • P ROGNOSTIC 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 | | | | | |