

# 高雄榮民總醫院

## 直腸癌診療指引

大腸直腸癌醫療團隊 制定

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Kaohsiung Veterans General Hospital

Rectal Cancer Clinical Practice Guidelines

Colorectal Cancer Multidisciplinary Team

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# Rectal Cancer Clinical Practice Guidelines

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## <Revision Summary>

Updates in Version 1 2020 of the VGHKS RectalCancer Clinical Practice Guidelines from Version 1 2019 include:

1. [Pre-OP workup](#)(p.6):

- MMR/MSI testing
- MDT evaluation

2. [Adjuvant Therapy for cT3 or Stage III Rectal Cancer](#) (p.8):

- The following regimen was added: Short-course RT and adjuvant chemotherapy with FOLFOX or CAPEOX for clinical nodal-positive stage.

3. [Unresectable Synchronous Metastases or Medically Inoperable Treatment](#)(p.11):

- Add HIPEC regimen: oxaliplatin or mitomycin C

4. [Regimen added](#)(p.13):

Trifluridine + tipiracil +/- bevacizumab

Add backbone with FOLFOXIRI for BRAF-mutant.

Dabrafenib + trametinib + (cetuximab or panitumumab)

BRAF V600E mutation (+)

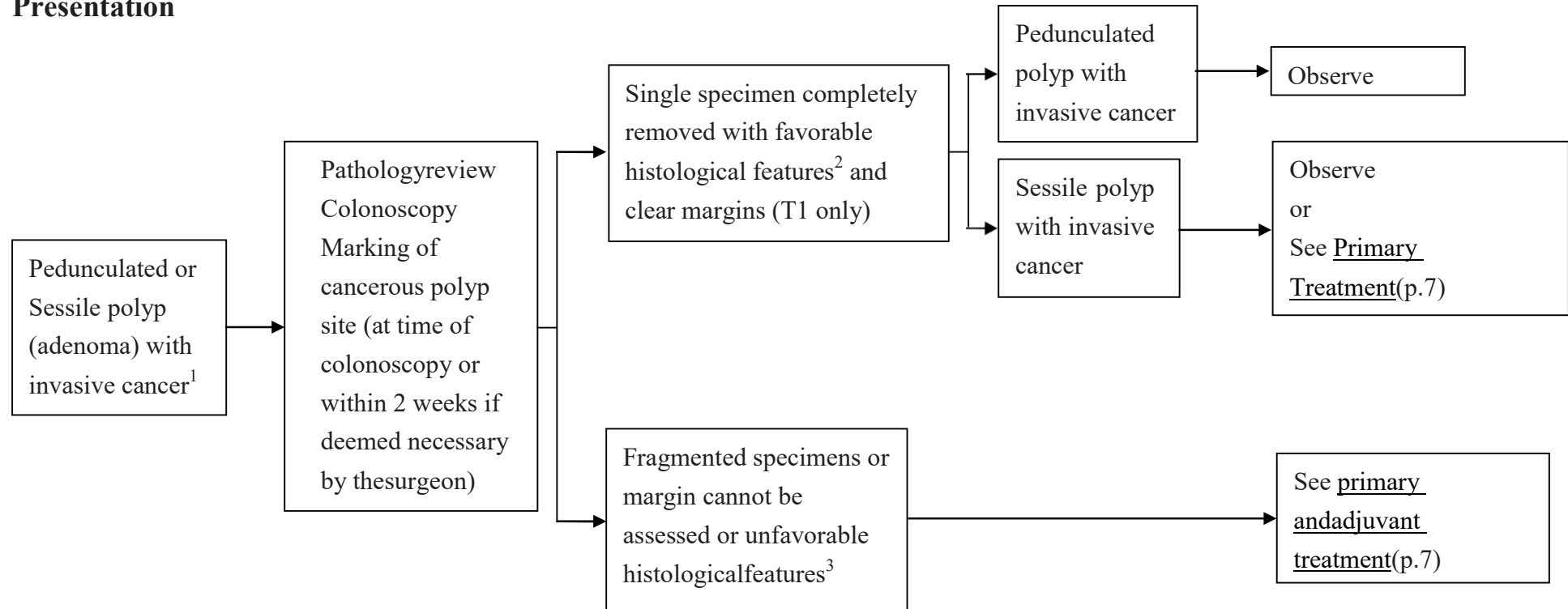


## Malignant polyp

### Clinical Presentation

### Workup

### Findings



<sup>1</sup>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”.

<sup>2</sup>Favorable histological features: Grade 1 & 2, no angiolymphatic invasion and negative margin of resection

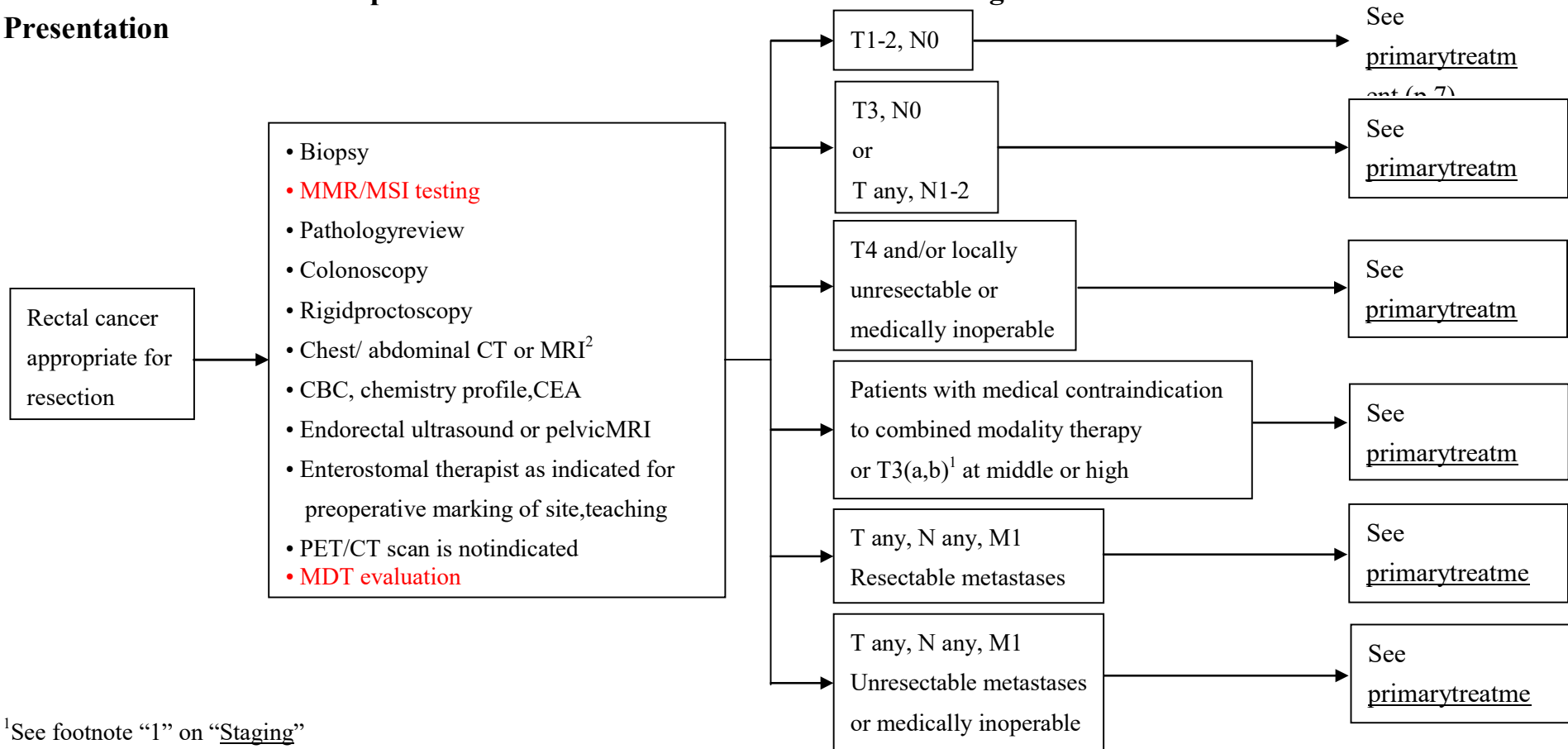
<sup>3</sup>Unfavorable histological features: Grade 3 & 4, or angiolymphatic invasion, or a “positive” margin (tumour < 1mm from the transected margin)

## Resectable Primary Rectal Cancer

### Clinical Presentation

### Workup

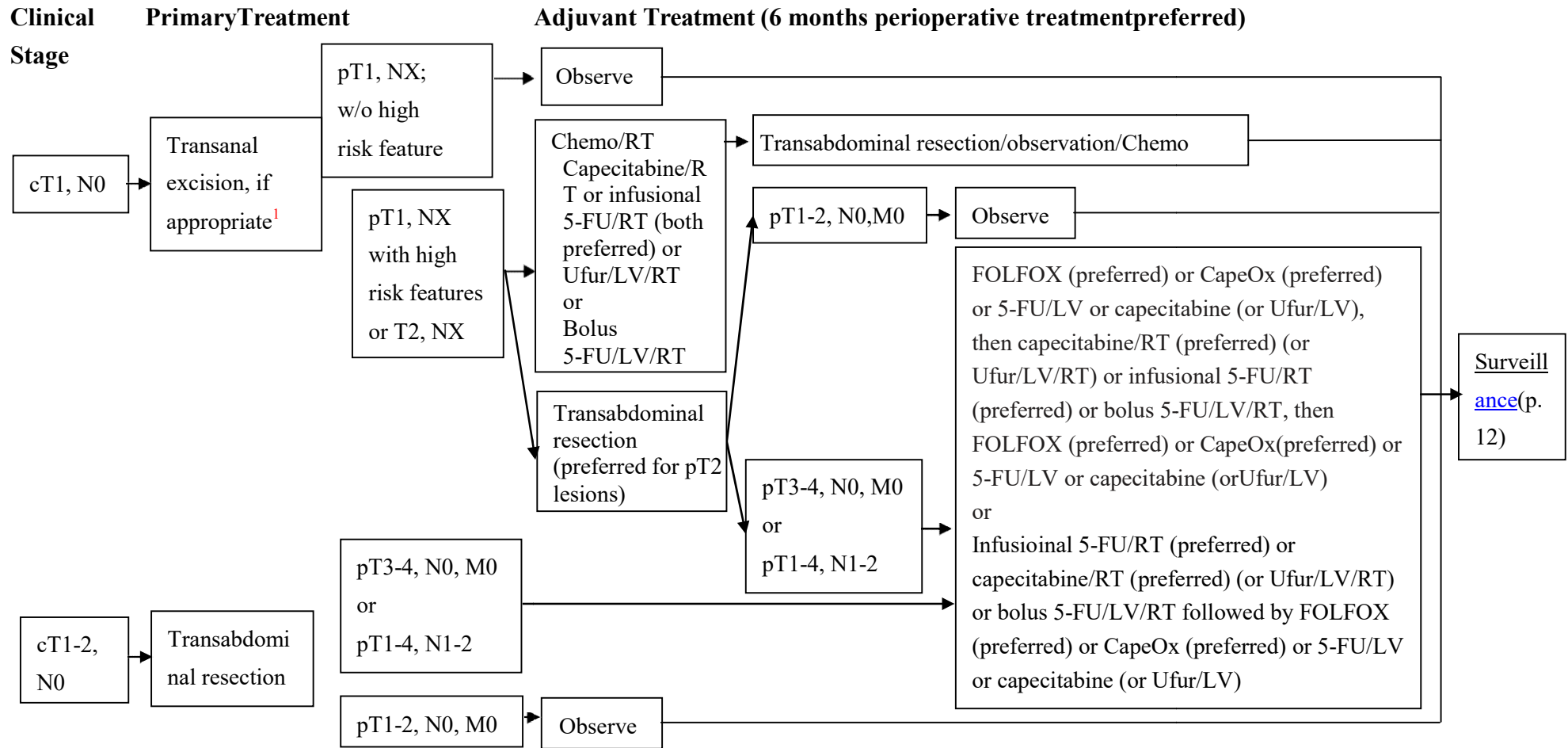
### Clinical Stage



<sup>1</sup>See footnote “1” on “[Staging](#)”

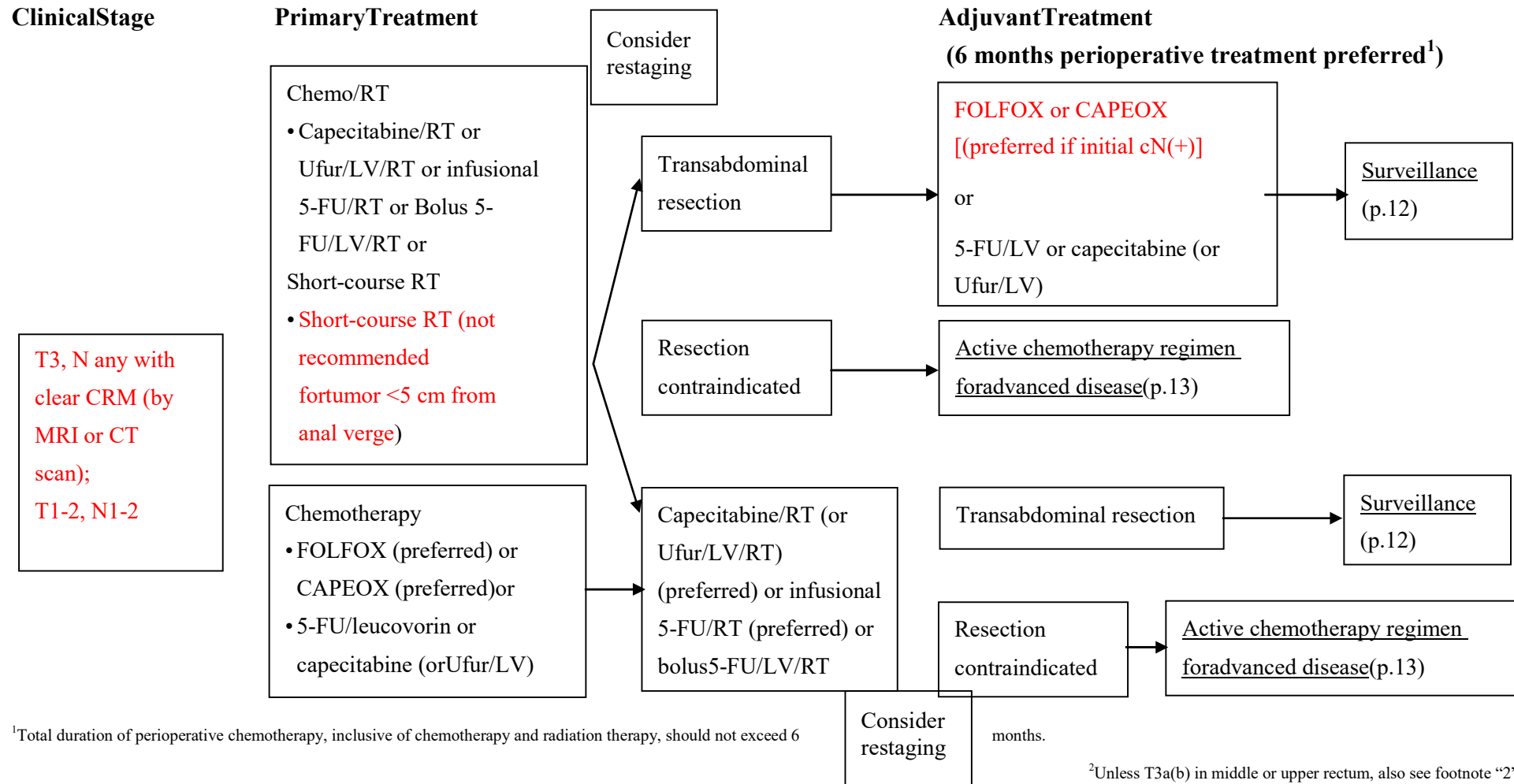
<sup>2</sup>CT should be with IV and oral contrast. Consider abd/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.

## Adjuvant Therapy for Stage I Rectal Cancer



<sup>1</sup>Unfavorable histopathologic features: >3cm in size, T1, with grade III, lymphovascular invasion, positive margin, or sm3 depth of tumor invasion. (positive margins, lymphovascular invasion, poorly differentiated tumors, or sm3 invasion)

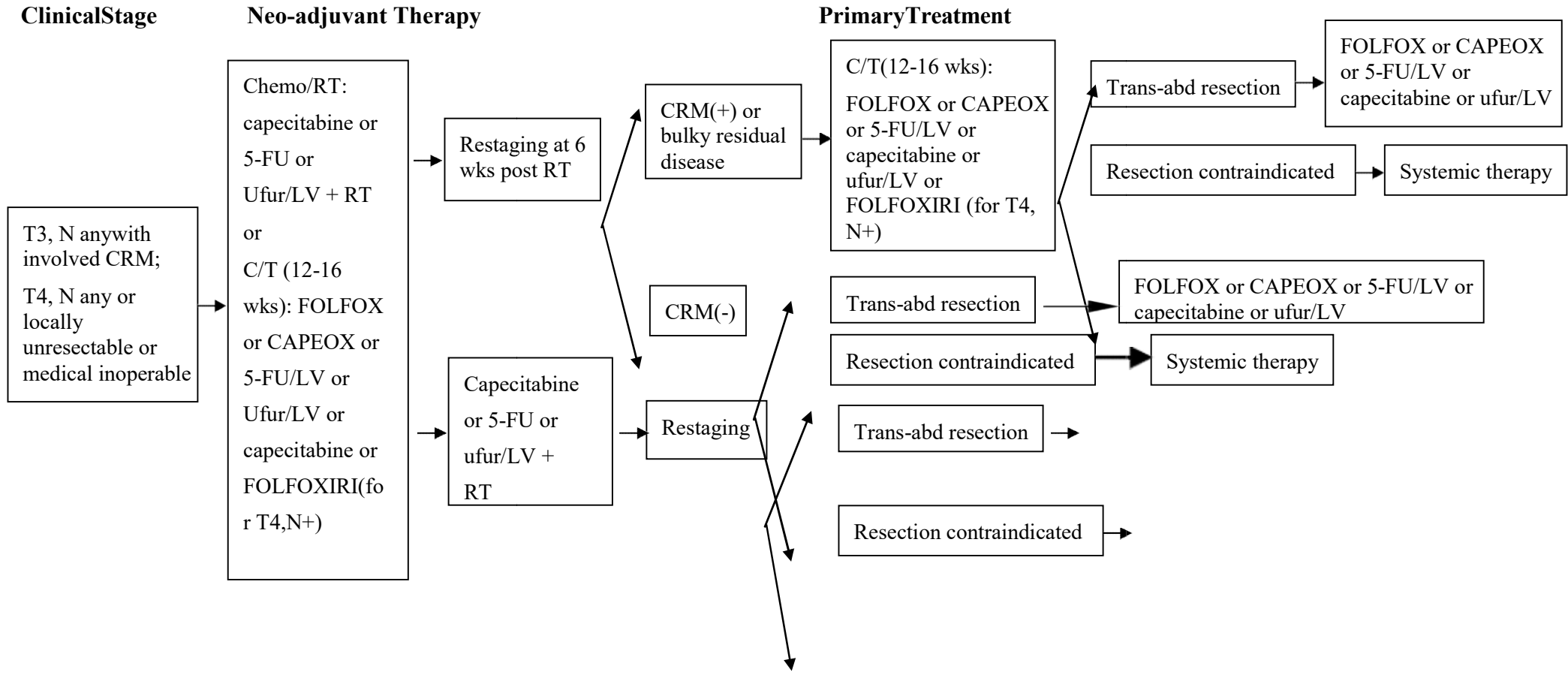
## Adjuvant Therapy for cT3 or Stage III Rectal Cancer



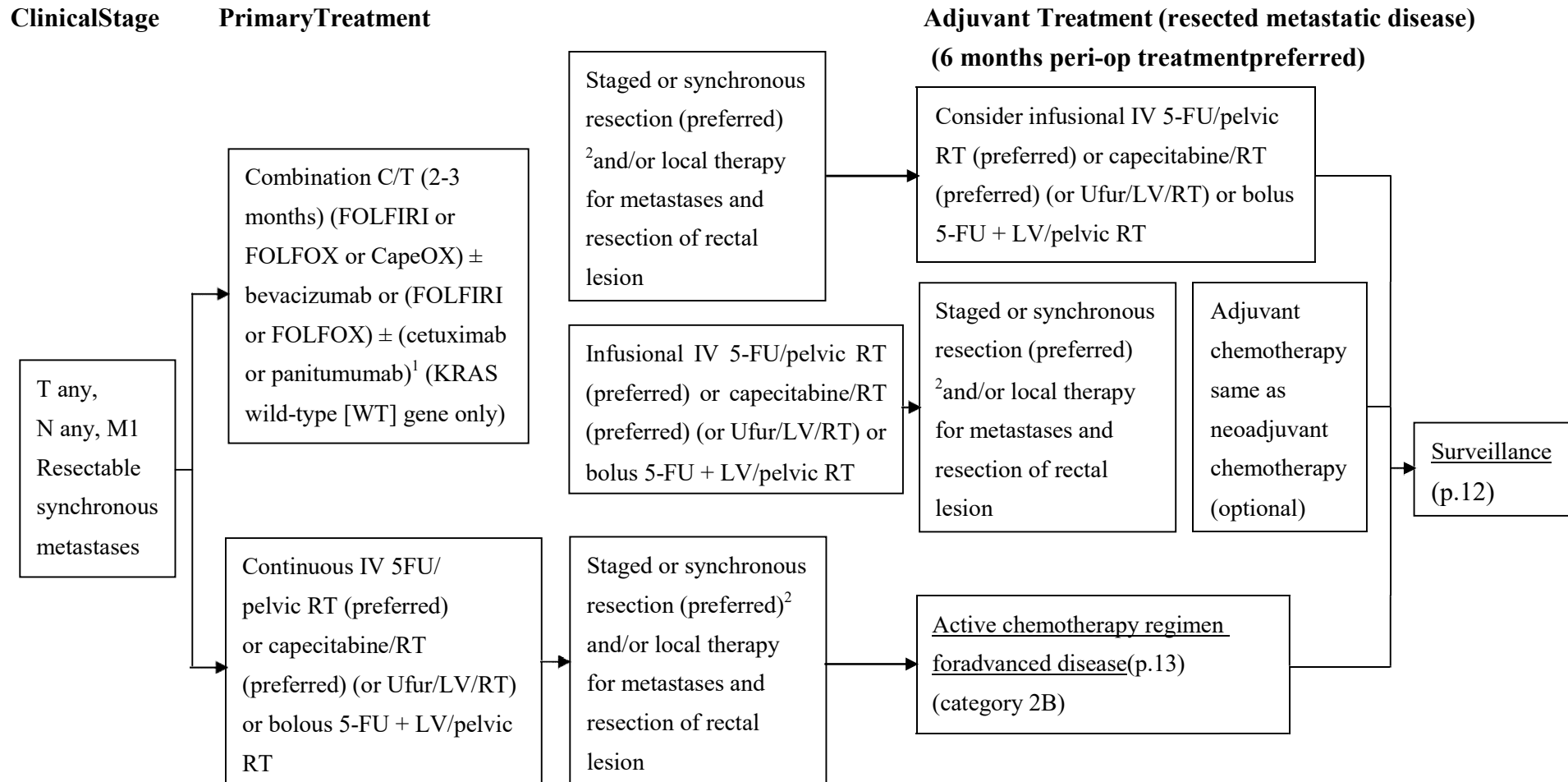
<sup>3</sup>PLoS One. 2017 Mar 22;12(3):e0174280. Oral tegafur-uracil as metronomic therapy following intravenous FOLFOX for stage III colon cancer.



## Adjuvant Therapy for Locally Advanced or Medical Inoperable Rectal Cancer



## Resectable Synchronous Metastases



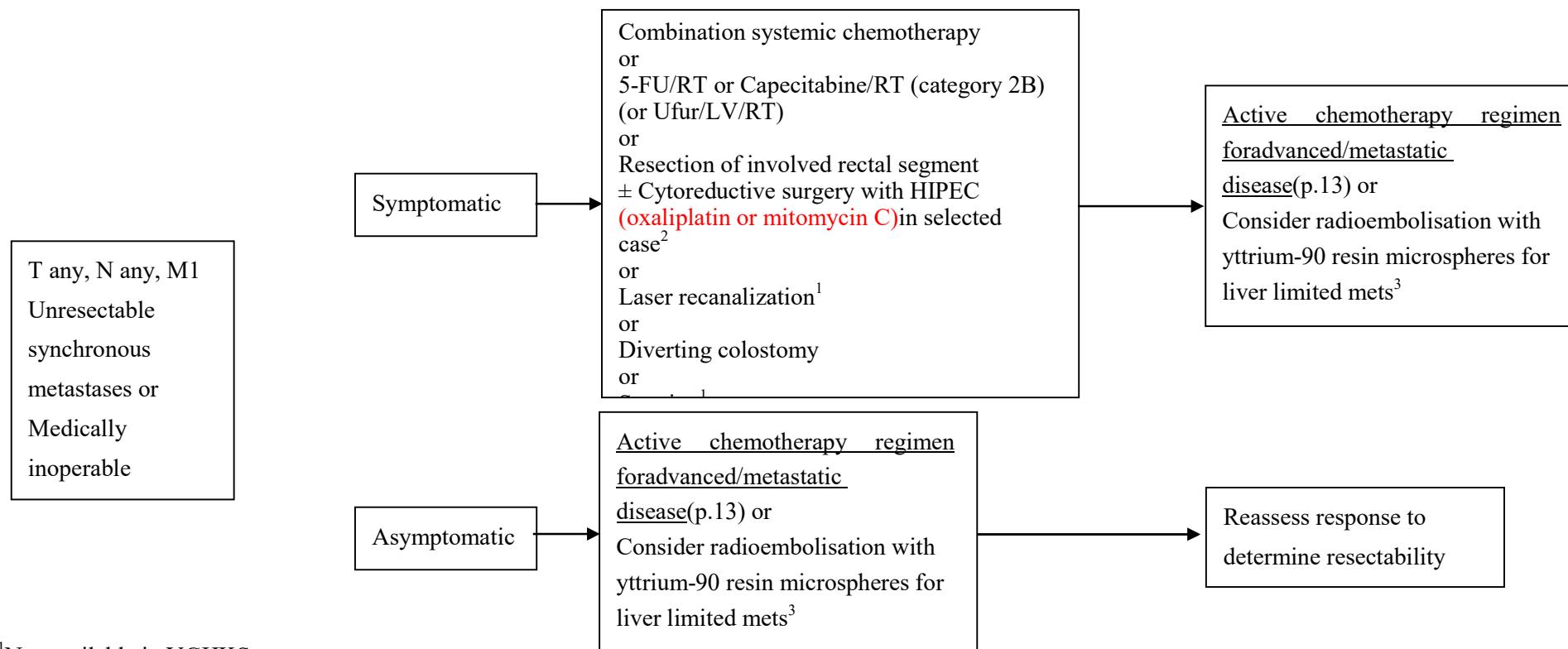
<sup>1</sup>There are conflicting data regarding the use of FOLFOX + cetuximab in patients who have potentially resectable liver metastases.

<sup>2</sup>Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver oligometastases

## Unresectable Synchronous Metastases or Medically Inoperable Treatment

Clinical Stage

Primary Treatment



<sup>1</sup>Not available in VGHS

<sup>2</sup>HIPEC = Hyperthermic Intraperitoneal Chemotherapy; Not documented in NCCN guideline 2015 v2 but in ESMO guideline 2014 (evidence grade IVB). Also refer to Reference [7], [8]

<sup>3</sup>Not documented in NCCN guideline 2015 v2 but in ESMO guideline 2014 (evidence grade IVB). Also refer to reference [9]

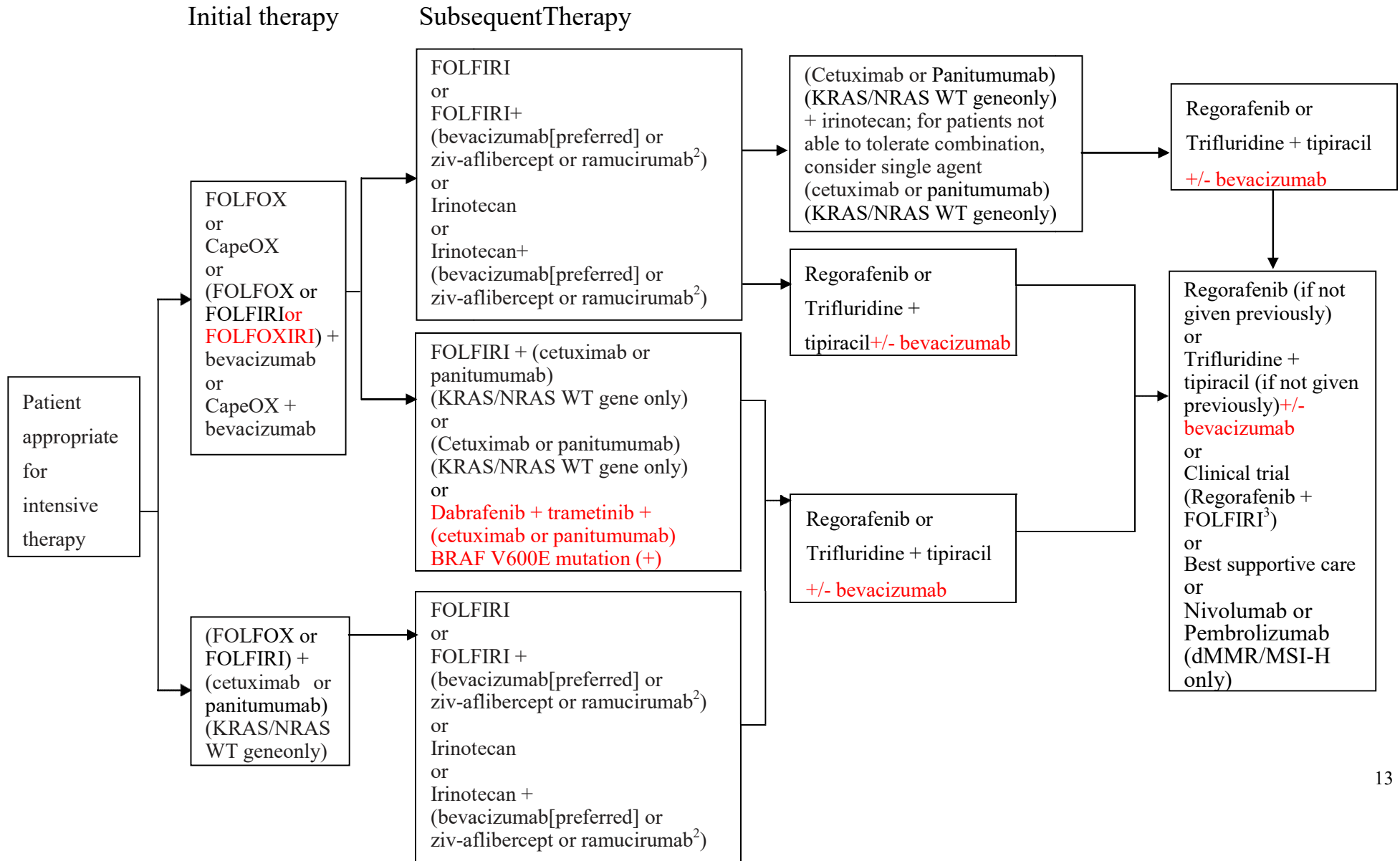
## Surveillance

- History and physical every 3-6 months for 2 years, then every 6 months for a total of 5 years
- CEA every 3-6 months for 2 years, then every 6 months for a total of 5 years for T2 or greater lesions
- Chest/abdominal/pelvic CT every 3-6 months x 2 years, then every 6-12 months for up to 5 years
- Colonoscopy in 1 year except if no preoperative colonoscopy due to obstruction lesion, colonoscopy in 3-6 months
  - If advanced adenoma, repeat in 1 year
  - If no advanced adenoma, repeat in 3 years, then every 5 years
- Proctoscopy (with EUS or MRI) every 3-6 months x 2 years, then every 6 months for a total 5 years (for patient with transanal excision only)
- PET-CT scan is not routinely recommended

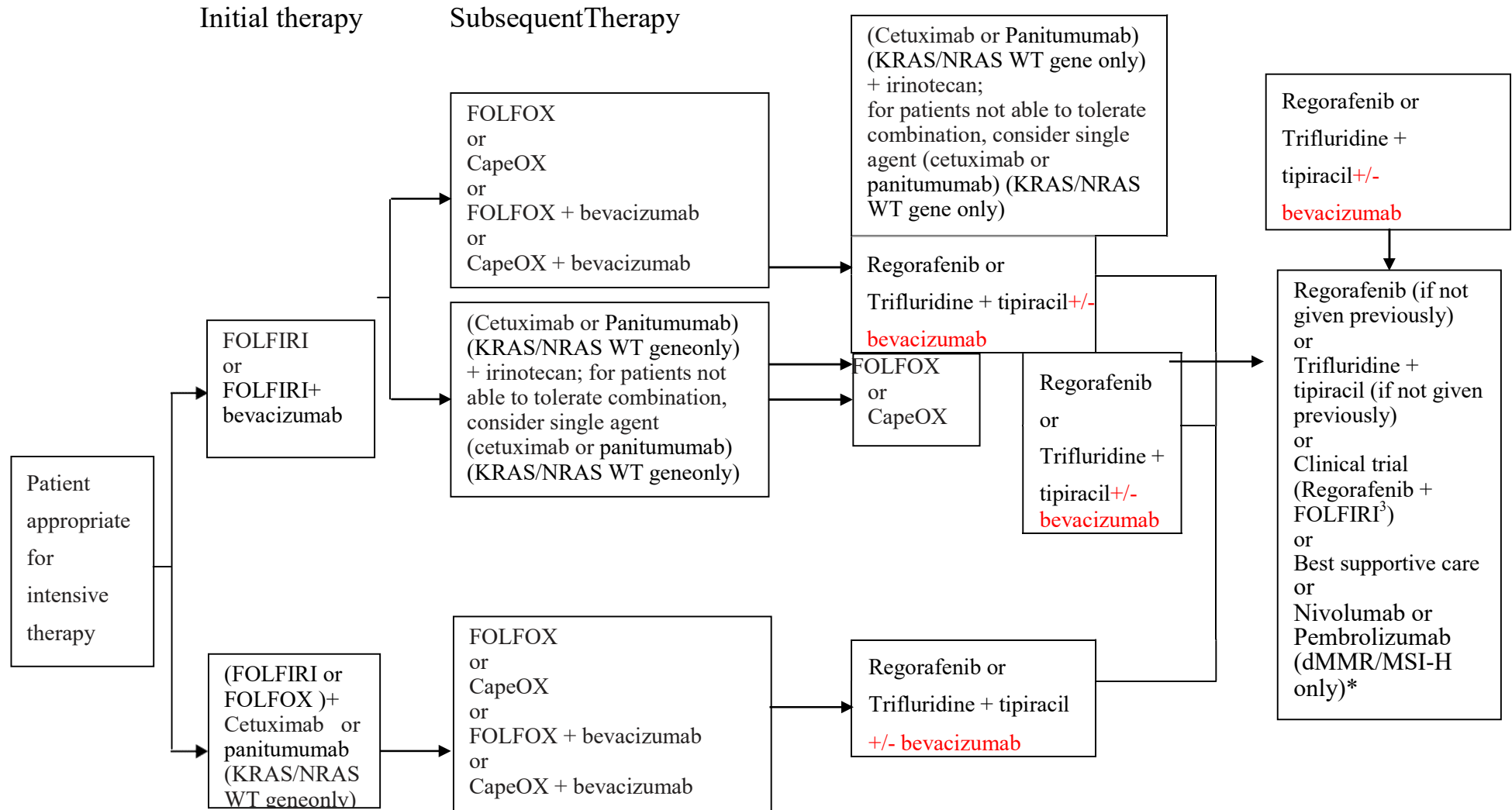
Serial CEA elevation or documented recurrence

See workup and treatment (p.17)

## Chemotherapy for advanced or metastatic disease (1 of 4)

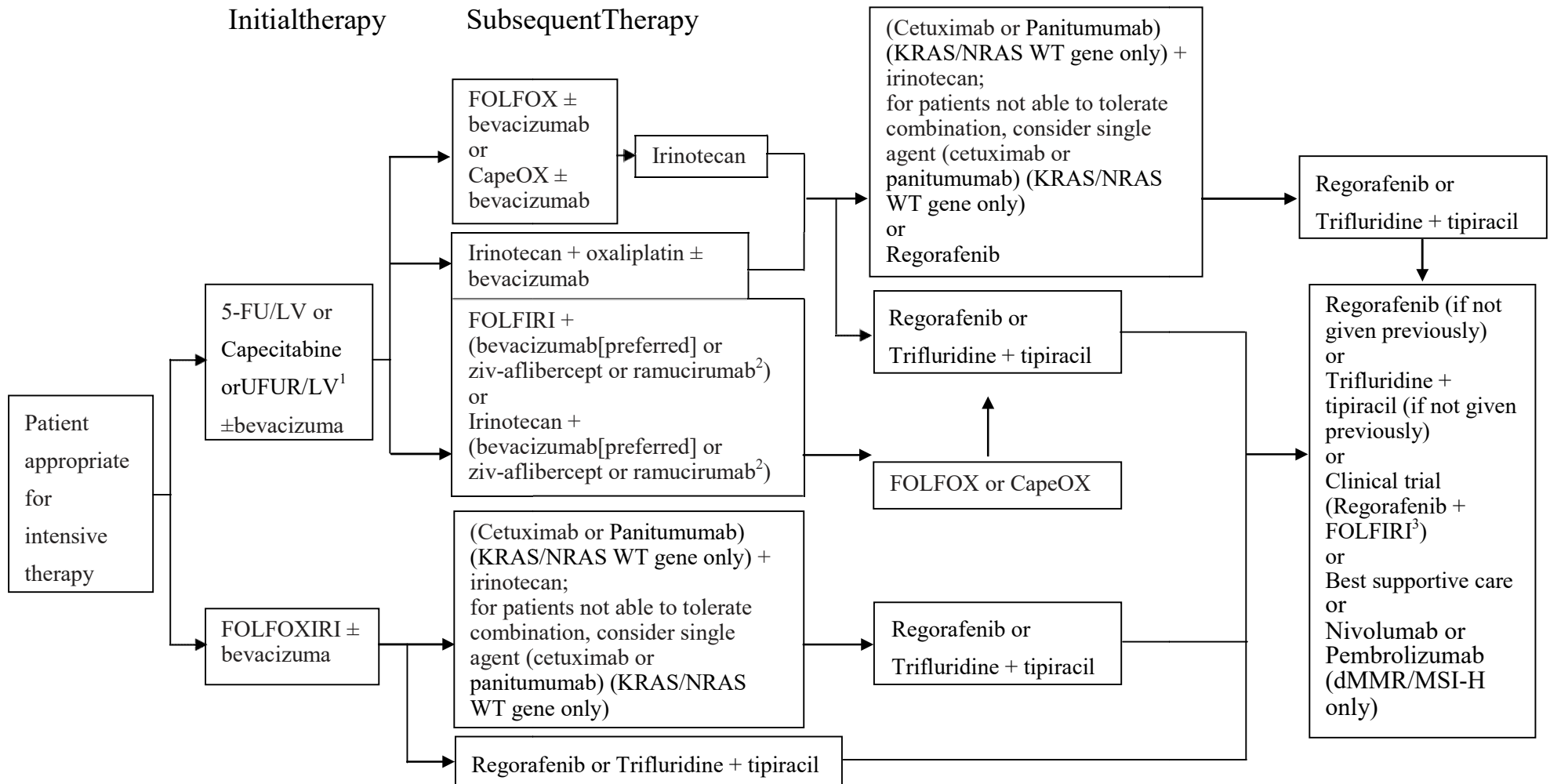


## Chemotherapy for advanced or metastatic disease (2 of 4)



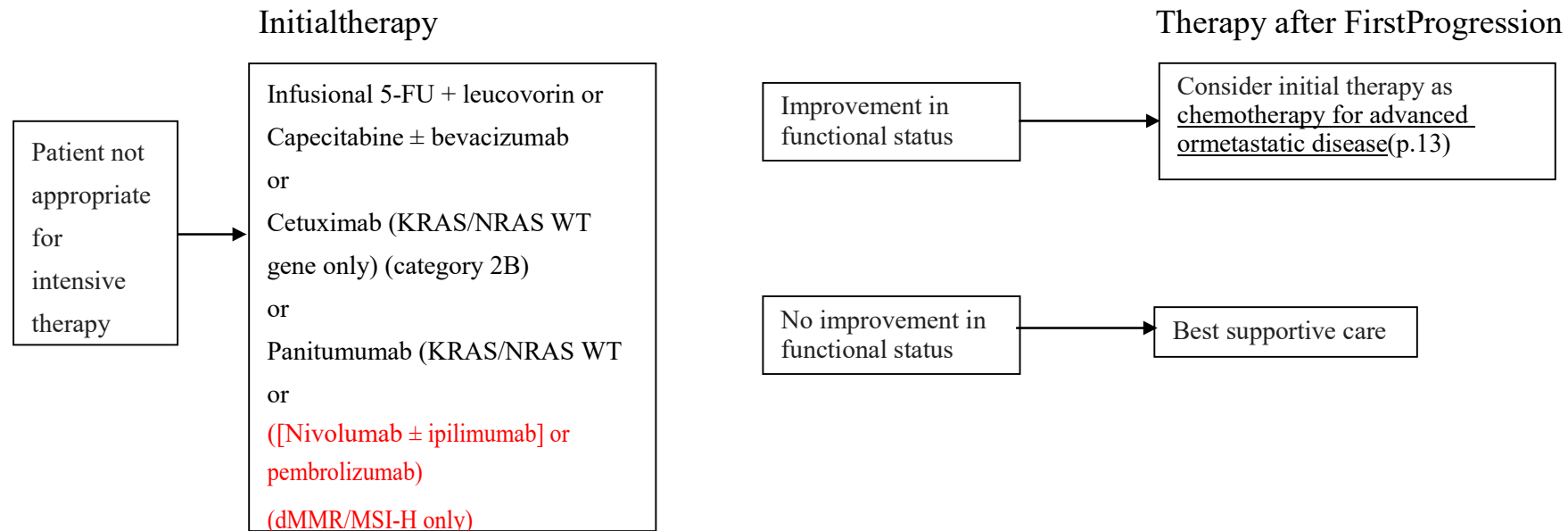
\*PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-2520. Nivolumab +/- ipilimumab in treatment of patients with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results [abstract]. ASCO Meeting Abstracts 2016;34:3501

## Chemotherapy for advanced or metastatic disease (3 of 4)





## Chemotherapy for advanced or metastatic disease (4 of 4)

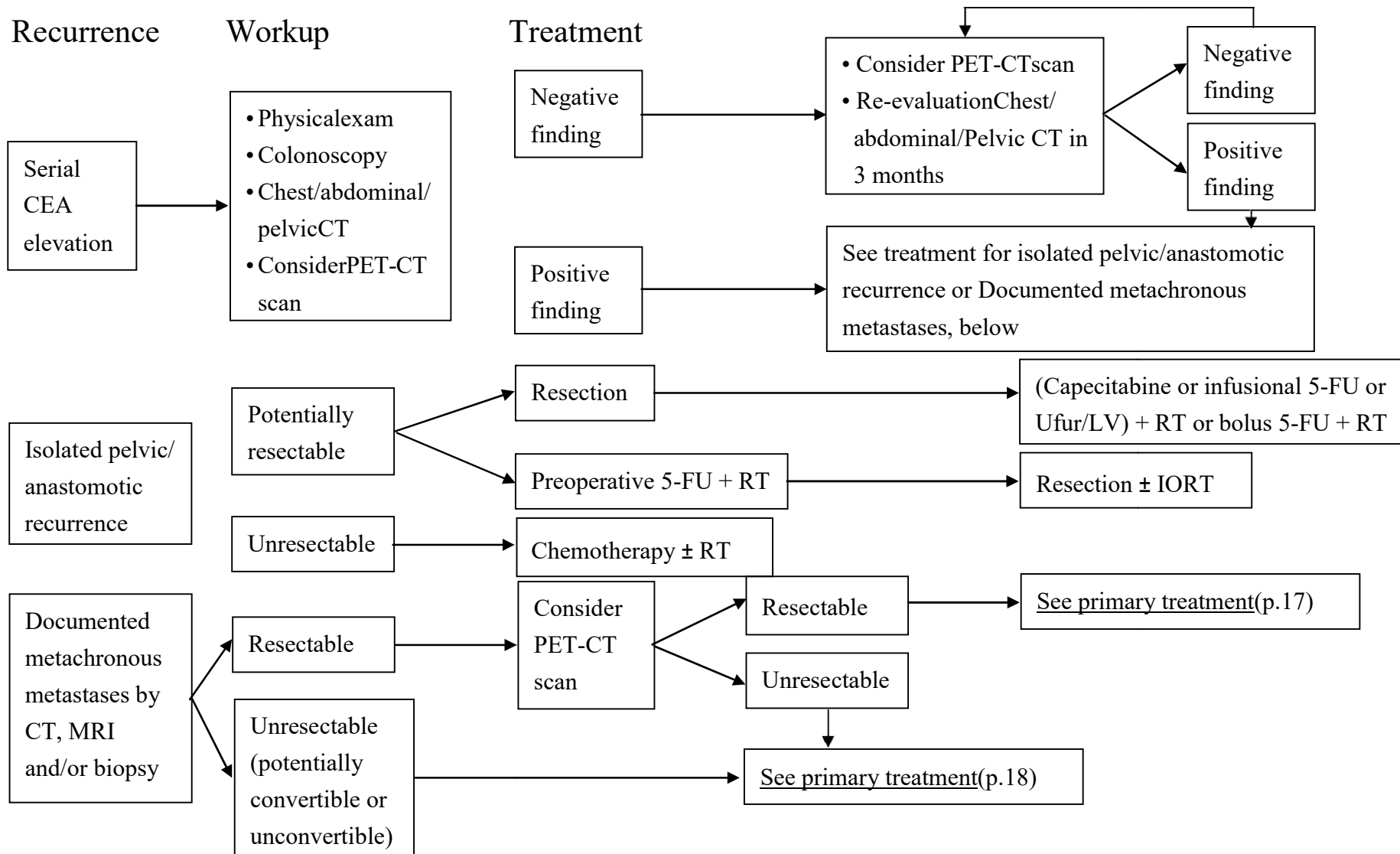


<sup>1</sup>Japanese regimen, also see Chemotherapy Regimens

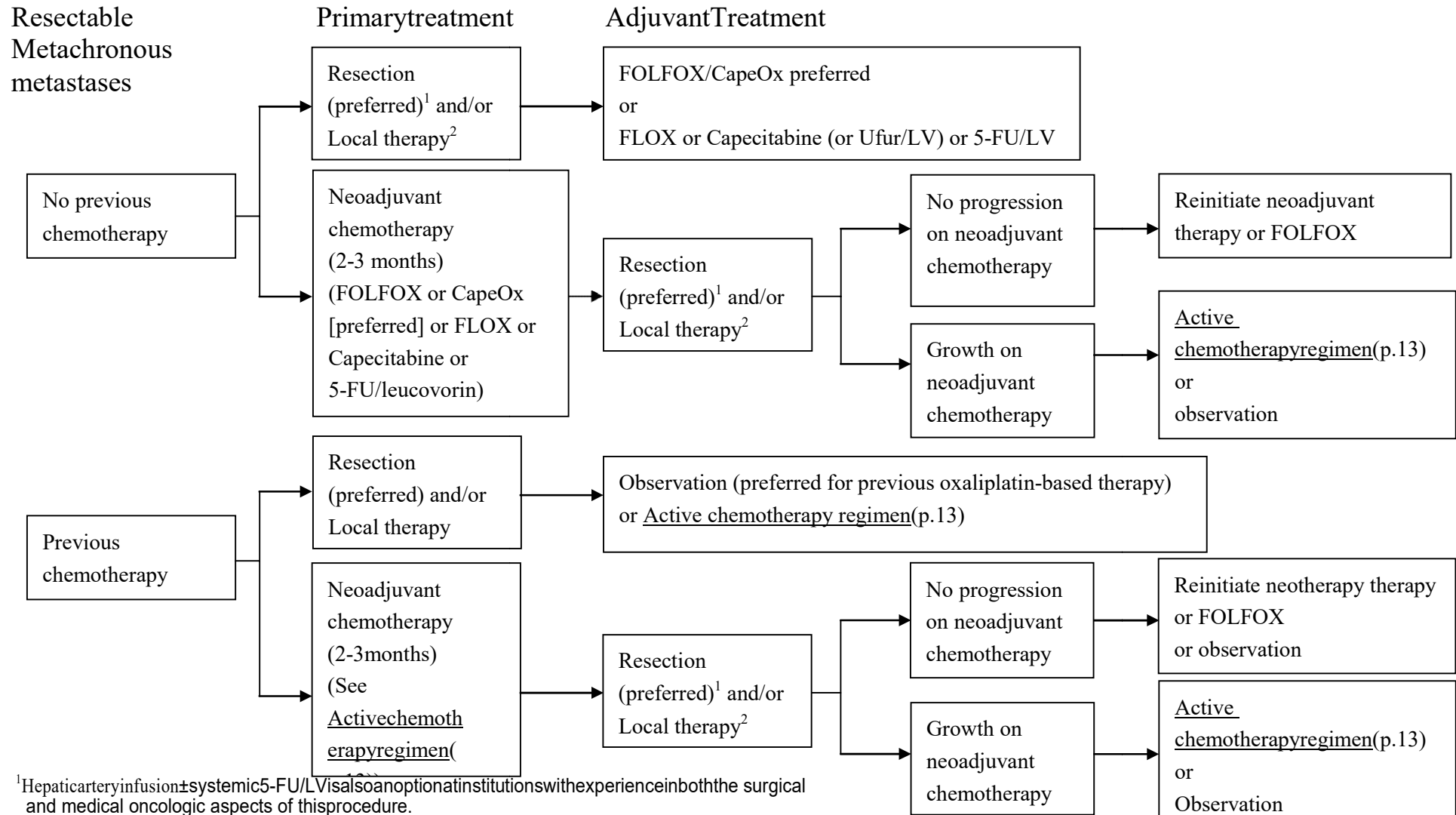
<sup>2</sup>Not available in routine clinical practice in Taiwan now

<sup>3</sup>Based on Reference [10], also see footnote "3" in Chemotherapy Regimens for Advanced/Metastatic Disease (3 of 3)

## Recurrence and Workup



## Resectable metachronous metastases



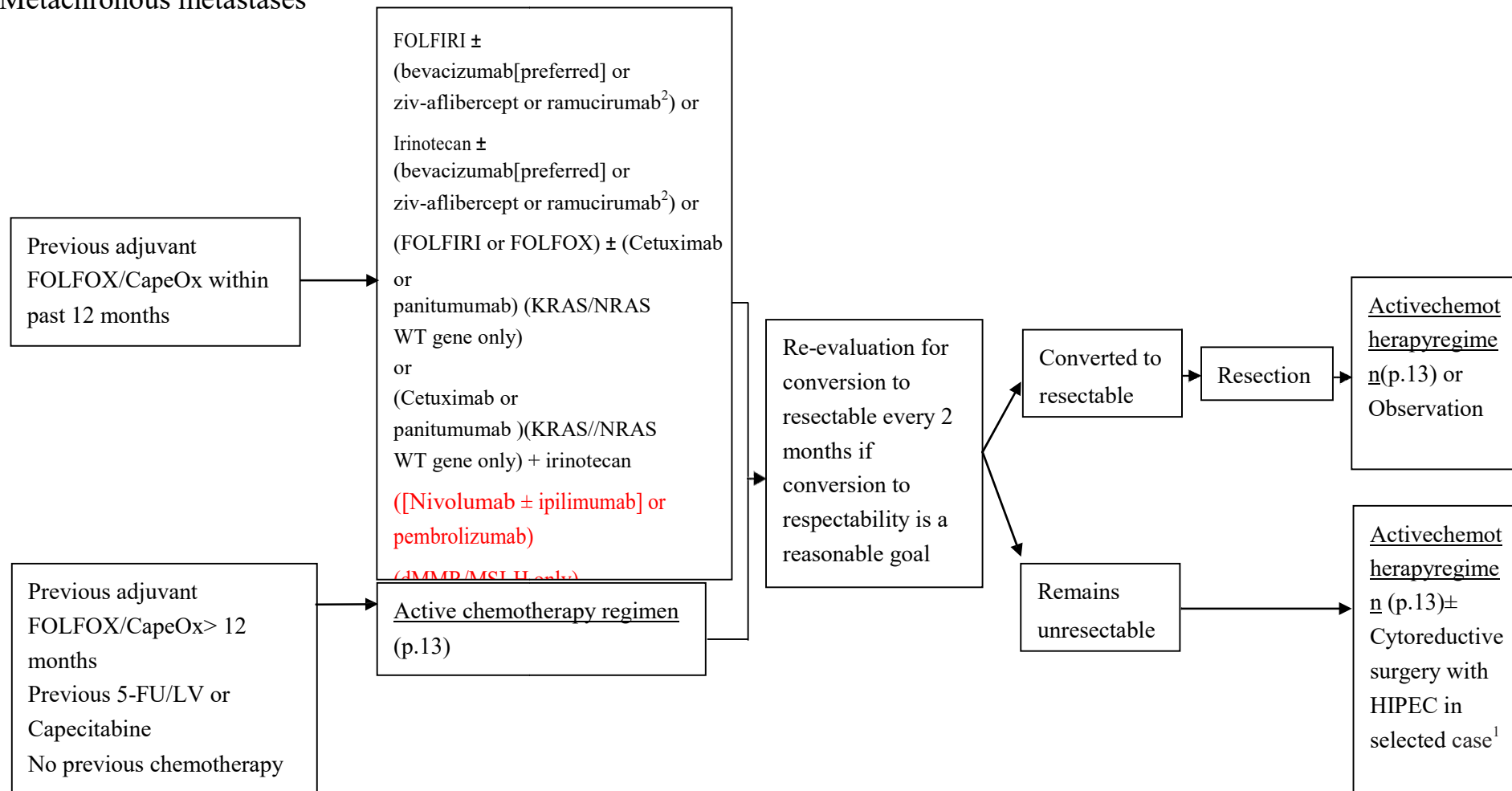
<sup>1</sup>Hepatic artery infusion ± systemic 5-FU/LV is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.

<sup>2</sup>Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver oligometastases.

## Unresectable metachronous metastases

Unresectable  
Metachronous metastases

Primary treatment



<sup>1</sup>See footnote “2” in Unresectable Synchronous Metastases or Medically Inoperable Treatment

<sup>2</sup>Not available in routine practice in Taiwan now

## Principles of Chemotherapy

### LV Dosage:

Leucovorin 400 mg/m<sup>2</sup> is the equivalent of levoleucovorin 200 mg/m<sup>2</sup>

### Chemotherapy for Advanced/Metastatic disease

All CRC chemotherapy regimens according to patient's condition and guidelines

NHI regulation:

Bevacizumab combine with Irinotecan base or 5-FU base regimens at the 1<sup>st</sup> line treatment

Cetuximab combine with Irinotecan or oxaliplatin base regimens at the 1<sup>st</sup> line & the 3<sup>rd</sup> line treatment

Panitumumab combine with Irinotecan or oxaliplatin base regimens at the 1st line treatment

Regorafenib at the third/fourth [K-ras wild type] line treatment

### Adjuvant Chemotherapy Regimen

Oxaliplatin base (including mFOLFOX6, CapeOX, FLOX)

5-FU base chemotherapy (IV form 5-FU, Capecitabine, Ufur/LV)

NHI regulation:

Oxaliplatin: Stage III colon cancer

Xeloda: Stage III colon cancer, stage IV colorectal cancer

5-FU/LV: High risk stage II, stage III and stage IV colorectal cancer

Ufur/LV: High risk stage II, stage III and stage IV colorectal cancer

## Chemotherapy Regimens for Advanced/Metastatic Disease (1 of 3)

<b>FOLFOX</b>
<i>mFOLFOX6 (may add with Bevacizumab/Panitumumab/Cetuximab)</i>
Oxaliplatin 85 mg/m <sup>2</sup> IV over 2 hours, day 1 Leucovorin 400 mg/m <sup>2</sup> IV over 2 hours, day 1 5-FU 400 mg/m <sup>2</sup> IV bolus on day 1, then 1200 mg/m <sup>2</sup> /day x 2 days (total 2400 mg/m <sup>2</sup> over 46–48 hours) IV continuous infusion Repeat every 2 weeks
<i>CapeOX(may add with Bevacizumab)</i>
Oxaliplatin 130 mg/m <sup>2</sup> IV over 2 hours, day 1 Capecitabine 850–1000mg/m <sup>2</sup> twice daily PO for 14 days Repeat every 3 weeks
<b>FOLFIRI</b> <i>(may add with Bevacizumab/Panitumumab/Cetuximab/Ziv-aflibercept/Ramucirumab)</i>
Irinotecan 180 mg/m <sup>2</sup> IV over 30–90 minutes, day 1 Leucovorin* 400 mg/m <sup>2</sup> IV infusion to match duration of irinotecan infusion, day 1 5-FU 400 mg/m <sup>2</sup> IV bolus day 1, then 1200 mg/m <sup>2</sup> /day x 2 days (total 2400 mg/m <sup>2</sup> over 46–48 hours) continuous infusion Repeat every 2 weeks
<b>FOLFOXIRI</b> <i>(may add with Bevacizumab)</i>
Irinotecan 165 mg/m <sup>2</sup> IV day 1, oxaliplatin 85 mg/m <sup>2</sup> day 1, leucovorin 400 mg/m <sup>2</sup> day 1, fluorouracil 1600 mg/m <sup>2</sup> /day x 2 days (total 3200 mg/m <sup>2</sup> over 48 hours) continuous infusion starting on day 1. Repeat every 2 weeks

<b>TARGET THERAPY</b>
Repeat every 2 weeks (unless additional mention)
+ <i>Bevacizumab</i>
Bevacizumab 5 mg/kg IV, day 1 or Bevacizumab 7.5 mg/kg IV, day 1 (for Capecitabine based)
+ <i>Panitumumab (KRAS/NRAS WT gene only)</i>
Panitumumab 6 mg/kg IV over 60 minutes, day 1
+ <i>Cetuximab (KRAS/NRAS WT gene only)</i>
Cetuximab 400 mg/m <sup>2</sup> IV over 2 hours first infusion, then 250 mg/m <sup>2</sup> IV over 60 minutes weekly or Cetuximab 500 mg/m <sup>2</sup> IV over 2 hours, day 1
+ <i>Ziv-aflibercept (FOLFIRI)</i>
Ziv-aflibercept 4 mg/kg IV, day 1
+ <i>Ramucirumab<sup>2</sup> (FOLFIRI)</i>
Ramucirumab 8mg/kg over 60 minutes, day 1
+ <i>Regorafenib (Single use or with FOLFIRI<sup>3</sup>)</i>
Regorafenib 160 mg PO daily days 1-21 Repeat every 28 days
<i>Trifluridine + tipiracil<sup>2</sup></i>
35mg/m <sup>2</sup> up to a Max doas of 80 mg per dose (based on trifluridine component) PO twice daily days 1-5 and 8-12 repeat every 28 days

## Chemotherapy Regimens for Advanced/Metastatic Disease (2 of 3)

<b>Bolus or infusional 5-FU/leucovorin</b>	<b>Irinotecan based</b>
<i>Roswell Park regimen</i>	<i>IROX</i>
Leucovorin 500 mg/m <sup>2</sup> IV over 2 hours, days 1, 8, 15, 22, 29, and 36 5-FU 500 mg/m <sup>2</sup> IV bolus 1 hour after start of leucovorin, days 1, 8, 15, 22, 29, and 36 Repeat every 8 weeks	Oxaliplatin 85 mg/m <sup>2</sup> IV over 2 hours, followed by irinotecan 200 mg/m <sup>2</sup> over 30-90 minutes every 3 weeks
<i>Simplified biweekly infusional 5-FU/LV (sLV5FU2)</i>	<i>Irinotecan (may add with Cetuximab)</i>
Leucovorin 400 mg/m <sup>2</sup> IV over 2 hours on day 1, followed by 5-FU bolus 400 mg/m <sup>2</sup> and then 1200 mg/m <sup>2</sup> /day x 2 days (total 2400 mg/m <sup>2</sup> over 46-48 hours) continuous infusion Repeat every 2 weeks	Irinotecan 125 mg/m <sup>2</sup> IV over 30-90 minutes, days 1 and 8 Repeat every 3 weeks or Irinotecan 180 mg/m <sup>2</sup> IV over 30-90 minutes, day 1 Repeat every 2 weeks or Irinotecan 300-350 mg/m <sup>2</sup> IV over 30-90 minutes, day 1 Repeat every 3 weeks
<i>Weekly</i>	
Leucovorin 20 mg/m <sup>2</sup> IV over 2 hours on day 1, 5-FU 500 mg/m <sup>2</sup> IV bolus injection 1 hour after the start of leucovorin. Repeat weekly. 5-FU 2600 mg/m <sup>2</sup> by 24-hour infusion plus leucovorin 500 mg/m <sup>2</sup> . Repeat every week ( <i>AIO regimen</i> <sup>4</sup> : leucovorin 500 mg/m <sup>2</sup> in N/S 250ml over 2 hours followed by 5-FU 2600 mg/m <sup>2</sup> in N/S 500ml by 24-hour infusion weekly x6 and 2 weeks off, repeat every 8 weeks)	<b>Capecitabine</b> ( <i>may add with Bevacizumab</i> ) 850–1250 mg/m <sup>2</sup> PO twice daily, days 1–14 Repeat every 3 weeks
<i>Mayo Clinic regimen</i> <sup>4</sup>	<b>Ufur/LV</b> <sup>1</sup>
Leucovorin 20 mg/m <sup>2</sup> /day IV over 30 minutes followed by 5-FU IV bolus 425 mg/m <sup>2</sup> /day x 5 days. Repeat every 5 weeks	Leucovorin 20-30 mg/m <sup>2</sup> + Ufur 300-500 mg/ m <sup>2</sup> PO at day 1 to 28 in every 35 days



## Chemotherapy Regimens for Advanced/Metastatic Disease (3 of 3)

<b>Modified regimen for CRS@VGHKS</b>	<b>IO</b>
<i>modified mFOLFOX</i>	<i>Nivolumab + ipilimumab</i>
<p>Oxaliplatin 85-100 mg/ m<sup>2</sup> IV over 3 hours on day 1                  Leucovorin 200 mg/ m<sup>2</sup> IV over 1 hours after Oxaliplatin on day 1                  5-FU 2600 mg/m<sup>2</sup> IV continuous infusion over 18 hours (start on day 1)                  Repeat every 2 weeks</p>	<p>Nivolumab 3 mg/kg (30 minute IV infusion) and ipilimumab 1 mg/kg (30 minute IV infusion) once every 3 weeks for four doses, then nivolumab 3 mg/kg IV or nivolumab 240 mg IV every 2 weeks.</p>
<i>modified FOLFIRI</i>	
<p>Irinotecan 180 mg/m<sup>2</sup> IV over 90 minutes, day 1                  Leucovorin 200 mg/m<sup>2</sup> IV infusion for 1 hours after irinotecan infusion, day 1                  5-FU 2400-3000 mg/m<sup>2</sup> continuous infusion over 18 hours (start on day 1)                  Repeat every 2 weeks</p>	
<i>modified AIO regimen</i>	
<p>leucovorin 250 mg/m<sup>2</sup> in N/S 250ml over 1 hours followed by 5-FU 2600 mg/m<sup>2</sup> in N/S 500ml by 18-hour infusion weekly x6 and 2 weeks off, repeat every 8 weeks</p>	

<sup>1</sup>Japanese regimen, is the equivalent of 5-FU/LV or capecitabine in adjuvant and advanced/metastatic therapy. Also refer to Reference[4], [5] and [6]

<sup>2</sup>Not available in routine practice in Taiwan now

<sup>3</sup>As third/fourth line chemotherapy for advanced/metastatic disease, based on reference[10]

<sup>4</sup>At VGHKS

## Chemotherapy Regimens for Adjuvant Therapy (1 of 2)

<b>mFOLFOX<sup>3</sup></b>	<b>5-FU/leucovorin</b>
Oxaliplatin 85 mg/m <sup>2</sup> IV over 2 hours, day 1 Leucovorin 400 mg/m <sup>2</sup> IV over 2 hours, day 1 5-FU 400 mg/m <sup>2</sup> IV bolus on day 1, then 1200 mg/m <sup>2</sup> /day x 2 days (total 2400 mg/m <sup>2</sup> over 46–48 hours) IV continuous infusion Repeat every 2 weeks	<i>Rosewell Park regimen (?)</i>  Leucovorin 500 mg/m <sup>2</sup> given as a 2-hour infusion and repeated weekly x 6. 5-FU 500 mg/m <sup>2</sup> given bolus 1 hour after the start of leucovorin and repeated weekly x 6. Every 8 weeks for 4 cycles
<b>FLOX<sup>2</sup></b>	<i>Simplified biweekly infusional 5-FU/LV (sLV5FU2)</i>
5-FU 500 mg/m <sup>2</sup> IV bolus weekly x 6 + leucovorin 500 mg/m <sup>2</sup> IV weekly x 6, each 8-week cycle x 3 with oxaliplatin 85 mg/m <sup>2</sup> IV administered on weeks 1, 3, and 5 of each 8-week cycle x 3	Leucovorin 400 mg/m <sup>2</sup> IV over 2 hours on day 1, followed by 5-FU bolus 400 mg/m <sup>2</sup> and then 1200 mg/m <sup>2</sup> /day x 2 days (total 2400 mg/m <sup>2</sup> over 46-48 hours) continuous infusion Repeat every 2 weeks
<b>Capecitabine</b>	
1250 mg/m <sup>2</sup> PO twice daily, days 1–14 every 3 weeks x 24 wks	
<b>CapeOX</b>	<i>AIO regimen<sup>4</sup></i>
Oxaliplatin 130 mg/m <sup>2</sup> IV over 2 hours, day 1 Capecitabine 850–1000mg/m <sup>2</sup> twice daily PO for 14 days Repeat every 3 weeks x 24 weeks	Leucovorin 500 mg/m <sup>2</sup> in N/S 250ml over 2 hours followed by 5-FU 2600 mg/m <sup>2</sup> in N/S 500ml by 24-hour infusion weekly x6 and 2 weeks off, repeat every 8 weeks
<b>Ufur/LV<sup>1</sup></b>	<i>Mayo Clinic regimen<sup>4</sup></i>
Leucovorin 20-30 mg/m <sup>2</sup> + Ufur 300-500 mg/ m <sup>2</sup> PO at day 1 to 28 in every 35 days	Leucovorin 20 mg/m <sup>2</sup> /day IV over 30 minutes followed by 5-FU IV bolus 425 mg/m <sup>2</sup> /day x 5 days. Repeat every 5 weeks

<sup>1</sup>Japanese regimen, is the equivalent of 5-FU/LV or capecitabine in adjuvant and advanced/metastatic therapy. Also refer to Reference[4], [5] and [6]

<sup>2</sup>FLOX is an alternative to FOLFOX or CapeOx but FOLFOX or CapeOx are preferred

<sup>3</sup>FOLFOX is reasonable for high-risk or intermediate-risk stage II patients and is not indicated for good- or average-risk patients with stage II colon cancer

<sup>4</sup>At VGHKS

## Chemotherapy Regimens for Adjuvant Therapy (2 of 2)

<b>Modified regimen for CRS@VGHKS</b>
<i>modified mFOLFOX</i>
Oxaliplatin 85-100 mg/ m <sup>2</sup> IV over 3 hours on day 1 Leucovorin 200 mg/ m <sup>2</sup> IV over 1 hours after Oxaliplatin on day 1 5-FU 2600 mg/m <sup>2</sup> IV continuous infusion over 18 hours (start on day 1) Repeat every 2 weeks
<i>modified AIO regimen</i>
Lecovorin 250 mg/m <sup>2</sup> in N/S 250ml over 1 hours followed by 5-FU 2600 mg/m <sup>2</sup> in N/S 500ml by 18-hour infusion weekly x6 and 2 weeks off, repeat every 8 weeks

## Regimens for Concurrent Chemotherapy/RT

<b>XRT + continuous infusional 5-FU</b>	
5-FU 225 mg/m <sup>2</sup> IV bolus + leucovorin 20 mg/m <sup>2</sup> IV bolus	24 hours 5 or 7 days/week during XRT
<b>Primary Tumor (T)</b>	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
<b>XRT + Capecitabine</b>	
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3 <sup>1</sup>	Tumor invades through the muscularis propria into the pericolorectal
T4a	Tumor penetrates to the surface of the visceral peritoneum <sup>b</sup>
T4b	Tumor directly invades or is adherent to other organs or structures <sup>b,c</sup>
<b>Regional Lymph Nodes (N)<sup>2</sup></b>	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1a	Metastasis in one regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis

N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in seven or more regional lymph nodes
<b>Distant Metastasis (M)</b>	
M0	M0 No distant metastasis
M1	M1 Distant metastasis
M1a	Metastasis confined to one organ or site (eg, liver, lung, ovary, onregional node)
M1b	Metastases in more than one organ/site or the peritoneum

<sup>1</sup>T3 lesion could be divided into T3a, T3b, T3c and T3d on the MRI image (documented in ESMO guideline for rectal cancer, 2014). The definition of the divisions of T3 lesion are listed in following sheet:

Classification	Invasion depth
T3a	<1mm
T3b	1-5mm
T3c	5-15mm
T3d	15+mm

<sup>2</sup>Sampling of 12 lymph nodes may not be achievable in patients that received preoperative chemotherapy.

7 <sup>th</sup> AJCC Colorectal cancer staging				Dukes*	MAC*
Group	T	N	M		
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	T1-2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3-4a	N1/N1c	M0	C	C2
	T2-3	N2a	M0	C	C1/C2
	T1-2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3-4a	N2b	M0	C	C2
	T4b	N1-2	M0	C	C3
IVA	anyT	anyN	M1a	-	-
IVB	anyT	anyN	M1b	-	-

Note: cTNM = clinical classification, pTNM = pathologic classification. Prefix “y” = classification after neoadjuvant pretreatment (eg, ypTNM). Patients who have a complete pathologic response are ypT0N0cM0 that may be similar to Stage Group 0 or I. Prefix “r” = recurred after a disease-free interval (rTNM).

\*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

癌症藥物停藥準則:

1. 根據影像學檢查或臨床依據，針對目前癌症用藥反應效果不良者。
2. 癌症用藥期間，產生藥物不良反應者，或初次發生輕微藥物不良反應後，經調降劑量或處置，仍再次發生藥物不良或更嚴重之反應者。
3. 評估 **adverse effects(AEs)**分級為第三級以上或任何無法承受之併發症者。
4. 評估 Eastern Cooperative Oncology Group(ECOG) Performance Status  $\geq 3$  者。
5. 經病人意願無法接受及配合持續治療，但經醫師解釋說明後，仍是無法接受癌症用藥或拒絕持續治療者。

## Reference

1. Major base on NCCN Rectal Cancer Clinical Practice Guidelines Version 2.2015
2. ESMO Clinical Practice Guidelines 2014: Gastrointestinal cancers -- section: Metastatic Colorectal Cancer, Early Colon Cancer, Rectal Cancer and Anal Cancer
3. NHI regulations for CRC chemotherapy
4. Efficacy of oral UFT as adjuvant chemotherapy to curative resection of colorectal cancer: multicenter prospective randomized trial. Kato T, Ohashi Y, Nakazato H, Koike A, Saji S, Suzuki H, Takagi H, Nimura Y, Hasumi A, Baba S, Manabe T, Maruta M, Miura K, Yamaguchi A. *Langenbecks Arch Surg.* 2002 Mar; 386(8):575-81.
5. The role of UFT in metastatic colorectal cancer. Bennouna J, Saunders M, Douillard JY. *Oncology.* 2009; 76(5):301-10.
6. 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. Lembersky BC, Wieand HS, Petrelli NJ, O'Connell MJ, Colangelo LH, Smith RE, Seay TE, Giguere JK, Marshall ME, Jacobs AD, Colman LK, Soran A, Yothers G, Wolmark N. *J Clin Oncol.* 2006 May 1; 24(13):2059-64.
7. Dominique Elias et al. Complete Cytoreductive Surgery Plus Intraperitoneal Chemohyperthermia With Oxaliplatin for Peritoneal Carcinomatosis of Colorectal Origin, *J Clin Oncol* 27:681-685. 2008
8. Vic J. Verwaal et al. 8-Year Follow-up of Randomized Trial: Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy Versus Systemic Chemotherapy in Patients with Peritoneal Carcinomatosis of Colorectal Cancer, *Annals of Surgical Oncology* 15(9):2426–2432. 2008
9. Hendlisz A, Van den Eynde M, Peeters M et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard. *J Clin Oncol* 2010; 28:3687–3694.
10. Chien-Yu Lu et al. FOLFIRI and regorafenib combination therapy with dose escalation of irinotecan as fourth-line treatment for patients with metastatic colon cancer according to *UGT1A1* genotyping, *OncoTargets Ther.* 2014; 7:2143–2146

## Appendix and Additional Information

1. Dosage of irinotecan in mFOLFIRI + Avstin regimen could be titrated up to 260mg/m<sup>2</sup> in patient with 6TA/6TA in genotyping of UGT1A1. This is based on the ongoing reseach: **Prospective analysis of *UGT1A1* promoter polymorphism for irinotecan dose escalation in metastatic colorectal cancer patients treated with bevacizumab combined with FOLFIRI as the first-line setting** by Dr. Wang