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大　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

Colon Cancer Clinical Practice Guidelines

Colorectal Cancer Multidisciplinary Team

May 2017 *version 1*

Colon Cancer Clinical Practice Guidelines

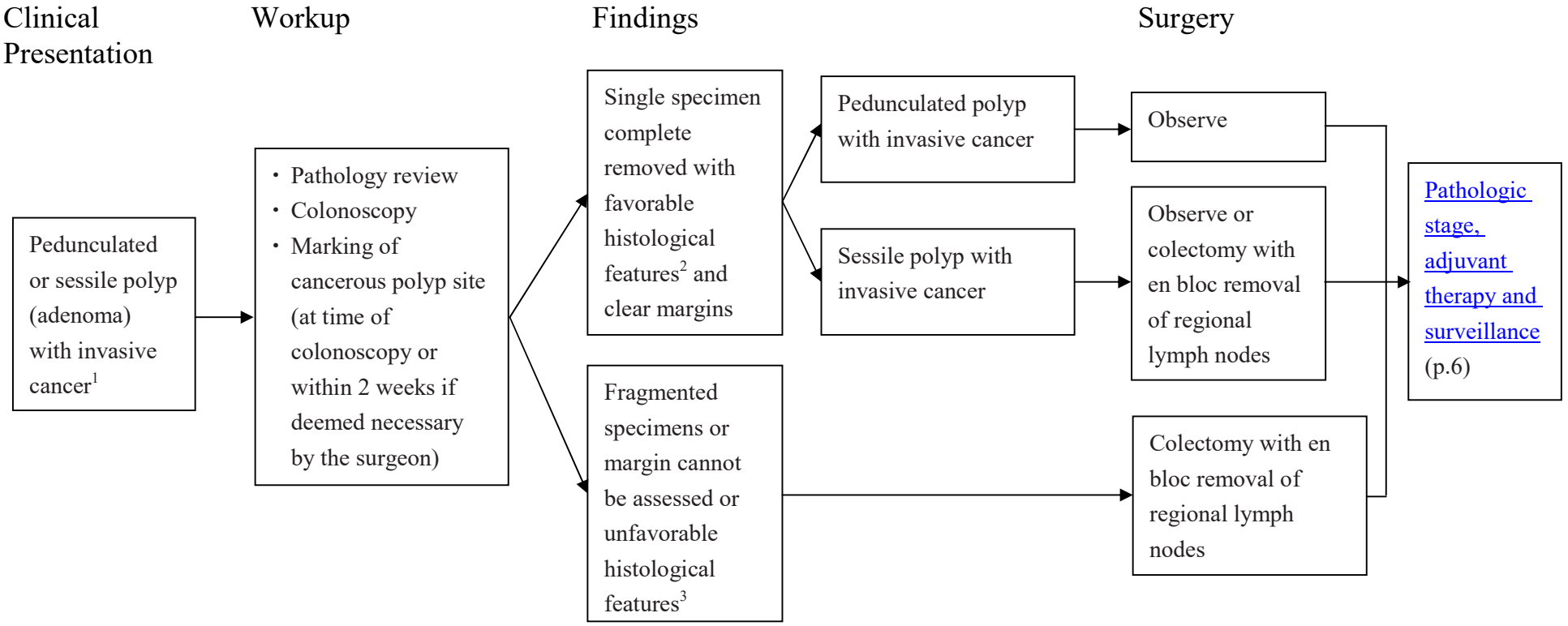
Content

<Revision Summary>

Updates in Version 1 2017 of the VGHKS colon Cancer Clinical Practice Guidelines from Version 1 2016 include:

Version 2016	Version 2017
Adjuvant therapy for stage III colon cancer (p.7)	Adjuvant therapy for stage III colon cancer (p.7): a) Column 2, add "± followed by UFUR/LV(1-2 yrs) [2]" behind the preferred treatment b) Add footnote 2: Based on Reference [11]
Resectable synchronous liver and/or lung metastases only (p.9)	Resectable synchronous liver and/or lung metastases only (p.9): a) Column 2, add "or FOLFIRI + bevacizumab[4]" b) Add footnote 4: Based on Reference [12]
Chemotherapy for advanced or metastatic disease (p.12-15)	Chemotherapy for advanced or metastatic disease (p.12-15): a) Add "or Nivolumab or Pembrolizumab (dMMR/MSI-H only)[4]" in all 5th column in topic 1 of 4, 2 of 4 and 3 of 4 b) Add footnote 4: "Based on Reference [13, 14]"
Principles of chemotherapy (p.19)	Principles of chemotherapy (p.19): Add "癌症藥物考慮停藥準則" and adjust font type
Reference (p.26-27)	Reference (p.26-27): Add reference [11], [12], [13] and [14]
	Revise page numbers

Malignant polyp

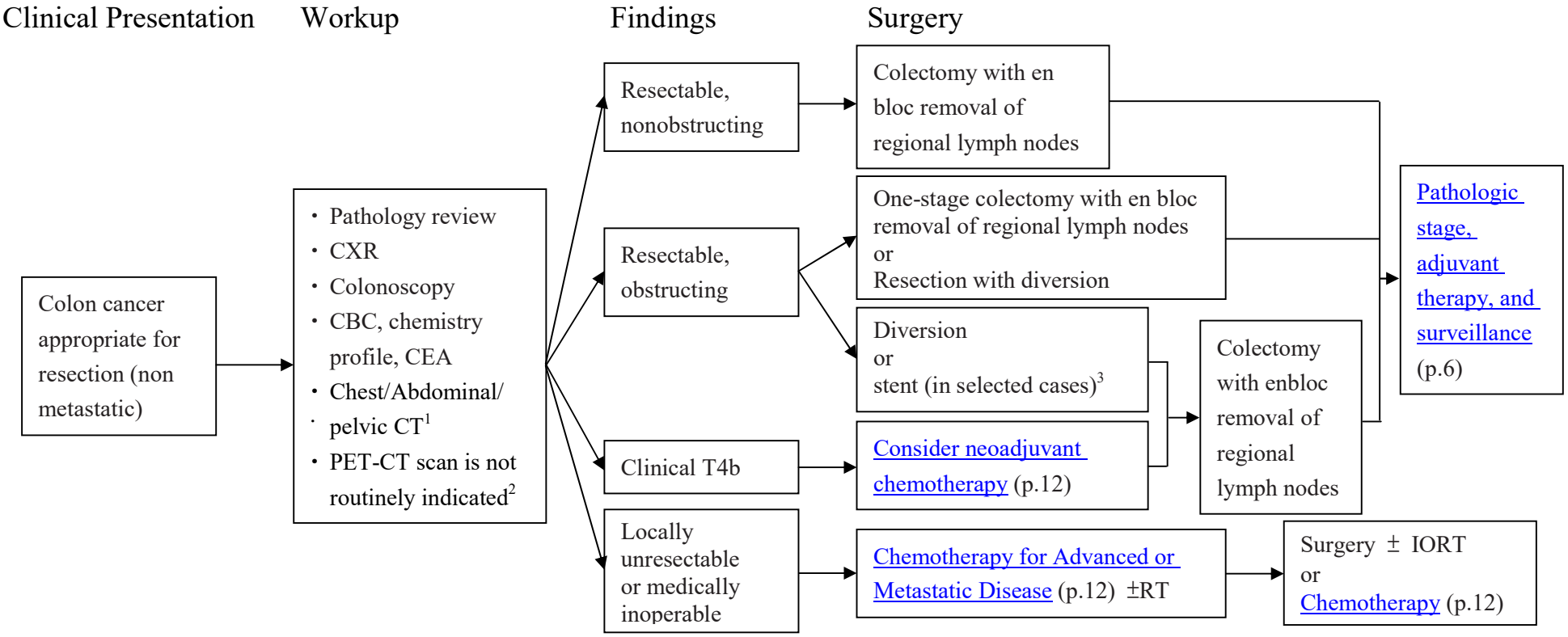


[1]A malignant polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1). pTis is not considered a "malignant polyp".

[2]Favorable histological features: Grade 1 & 2, no angiolymphatic invasion and negative margin of resection

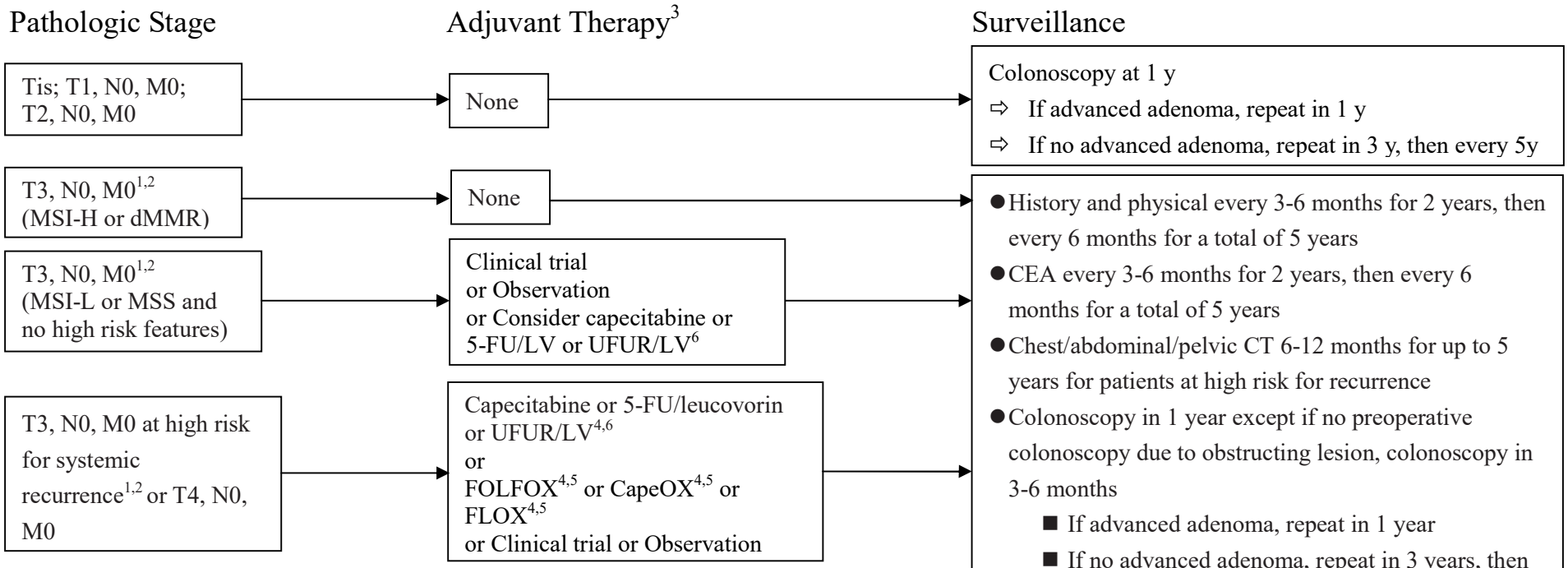
[3]Unfavorable histological features: Grade 3 & 4, or angiolymphatic invasion, or a "positive" margin (tumour <1mm from the transected margin)

Resectable primary colon cancer



[1]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.
[2]PET-CT does not supplant a contrast-enhanced diagnostic CT scan. PET-CT should only be used to evaluate an equivocal finding on a contrast-enhanced CT scan or in patients with strong contraindications to IV contrast.
[3]Not available in VGHKS now

Adjuvant therapy for stage I-II colon cancer



[1]High risk factors: Grade 3-4 differentiated (exclusive of those cancers that are MSI-H) , lymphatic/vascular invasion, bowel obstruction, < 12 lymph nodes examined, perineural invasion, localized perforation or close, indeterminate or positive margins. In high-risk stage II patients, there are no data that correlate risk features and selection of chemotherapy.

[2]Testing for mismatch repair proteins (MMR) should be considered for all patients <70 Y/O or with stage II disease. Stage II MSI-H patients may have a good prognosis and do no benefit from 5-FU adjuvant therapy.

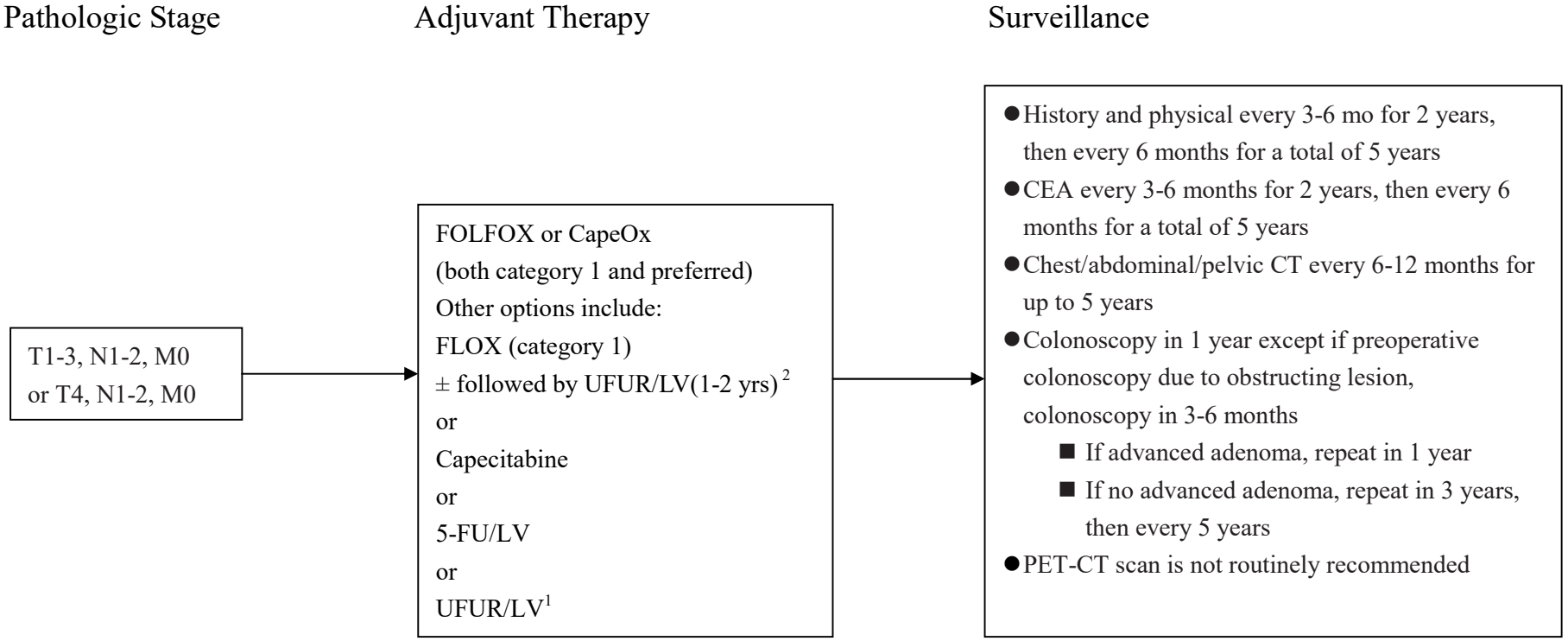
[3]Bevacizumab, cetuximab, panitumumab, or irinotecan should be not used in the adjuvant setting for stage II or III patients outside the setting of a clinical trial

[4]Consider RT for T4 with penetration to a fixed structure

[5]A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven

[6]Japanese regimen, also see Chemotherapy Regimens

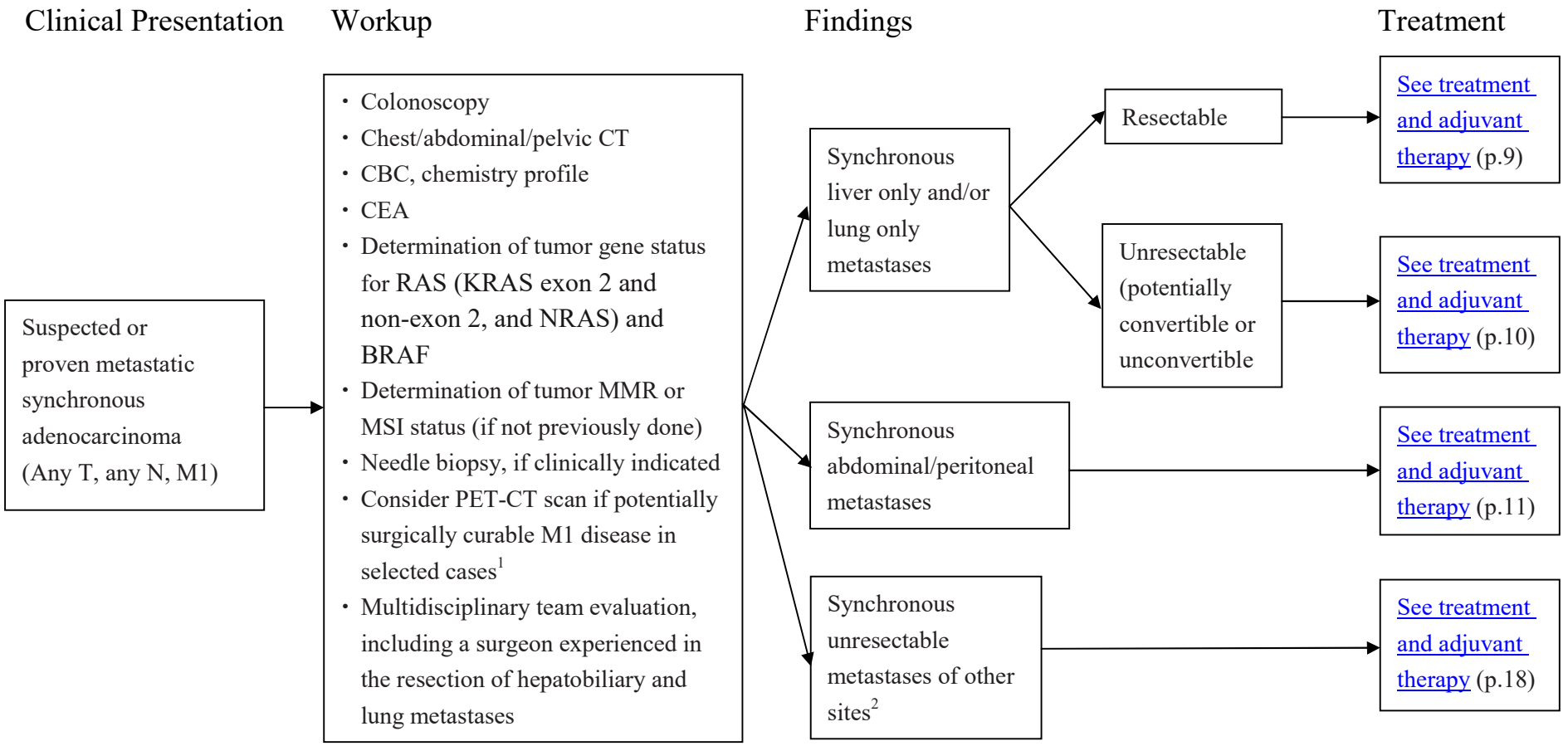
Adjuvant therapy for stage III colon cancer



[1] Japanese regimen, also see Chemotherapy Regimens

[2] Based on Reference [11]

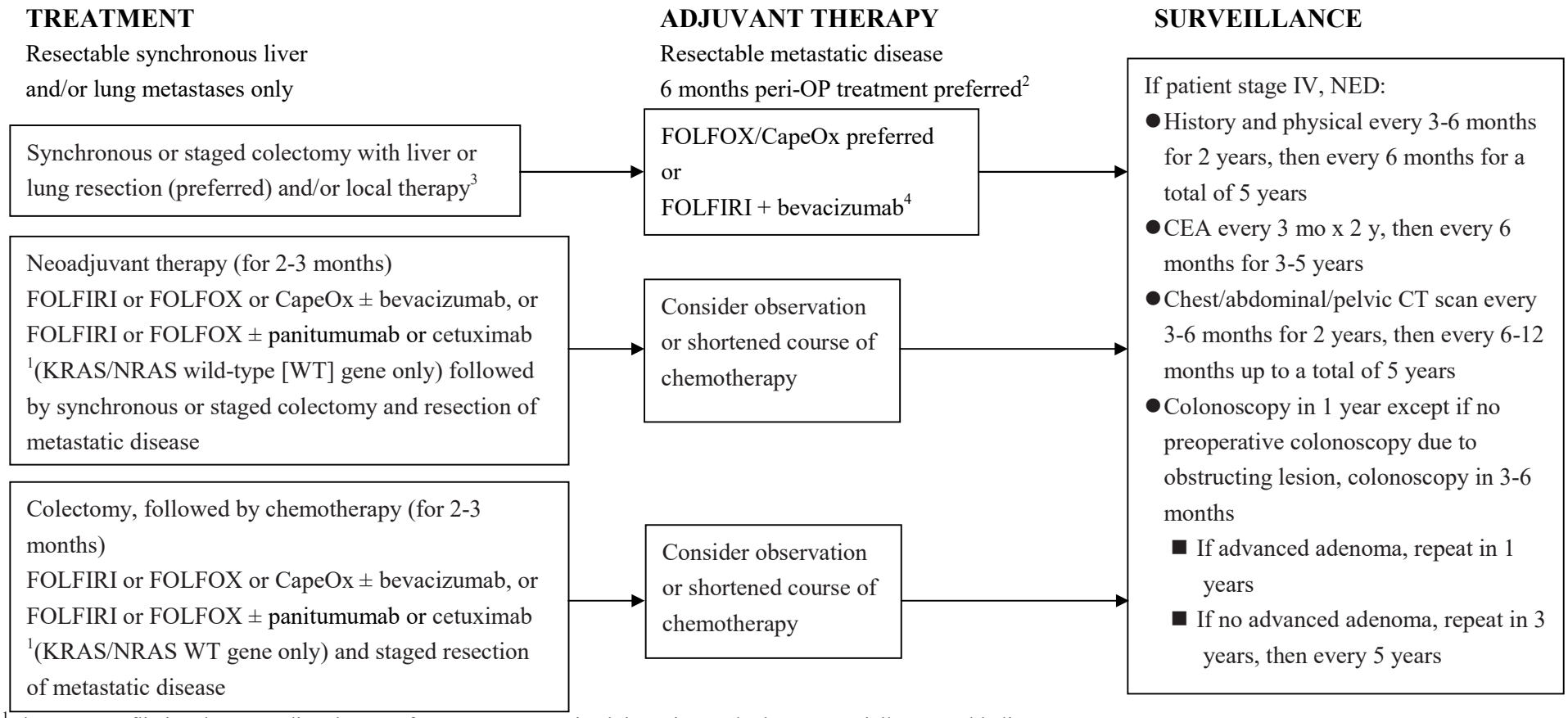
Metastatic synchronous adenocarcinoma from large bowel



[1]Moulton CA, Gu CS, Law CH, et al. Effect of PET before liver resection on surgical management for colorectal adenocarcinoma metastases: a randomized clinical trial. JAMA 2014;311:1863-1869.

[2]Consider colon resection only if imminent risk of obstruction or significant bleeding.

Resectable synchronous liver and/or lung metastases only



[1]There are conflicting data regarding the use of FOLFOX + cetuximab in patients who have potentially resectable liver metastases.

[2]Total duration of perioperative chemotherapy should not exceed 6 months.

[3]Resection is preferred over locally ablative precedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver oligometastases.

[4]Based on Reference [12]

Unresectable synchronous liver and/or lung metastases only

TREATMENT

Unresectable synchronous liver and/or lung metastases only

- Systemic therapy (FOLFIRI or FOLFOX or CapeOX ± bevacizumab,or FOLFIRI or FOLFOX ± panitumumab, or FOLFIRI ± cetuximab [KRAS /NRAS WT gene only] or, FOLFOXIRI ± bevacizumab)
- Consider colon resection only if imminent risk of obstruction or significant bleeding

→ Re-evaluate for conversion to resectable every 2 months if conversion to resectability is a reasonable goal

→ Converted to resectable → Synchronized or staged resection of colon and metastatic cancer

→ Remains unresectable → See chemotherapy for advanced or metastatic disease (p.12)

→ Consider radioembolisation with yttrium-90 resin microspheres for liver limited mets[1]

ADJUVANT THERAPY

6 months peri-OP treatment preferred

Active chemotherapy regimen for advanced Disease (Category 2B)
or
Consider observation or shortened course of chemotherapy

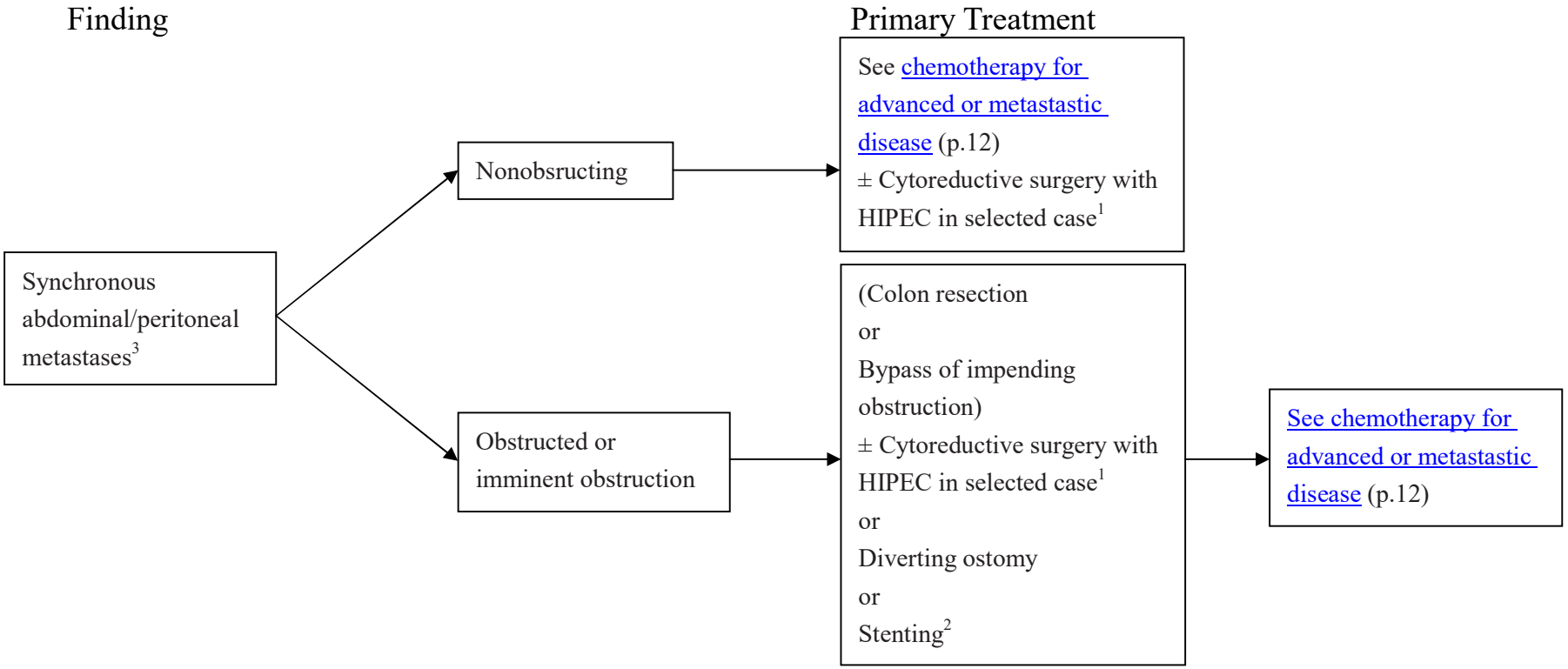
SURVEILLANCE

If patient stage IV, no eidence of disease (NED):

- History and physical every 3-6 months for 2 years, then every 6 months for a total of 5 years
- CEA every 3 months for 2 years, then every 6 months for 3-5 years
- Chest/abdominal/pelvic CT scan every 3-6 months for 2 years, then every 6-12 months up to a total of 5 years
- Colonoscopy in 1 year except if no preoperative colonoscopy due to obstructing 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

[1]Not documented in NCCN guideline 2015 v2 but in ESMO guideline 2014(evidence grade IVB). Also refer to reference [9]

Synchronous abdominal/peritoneal metastases

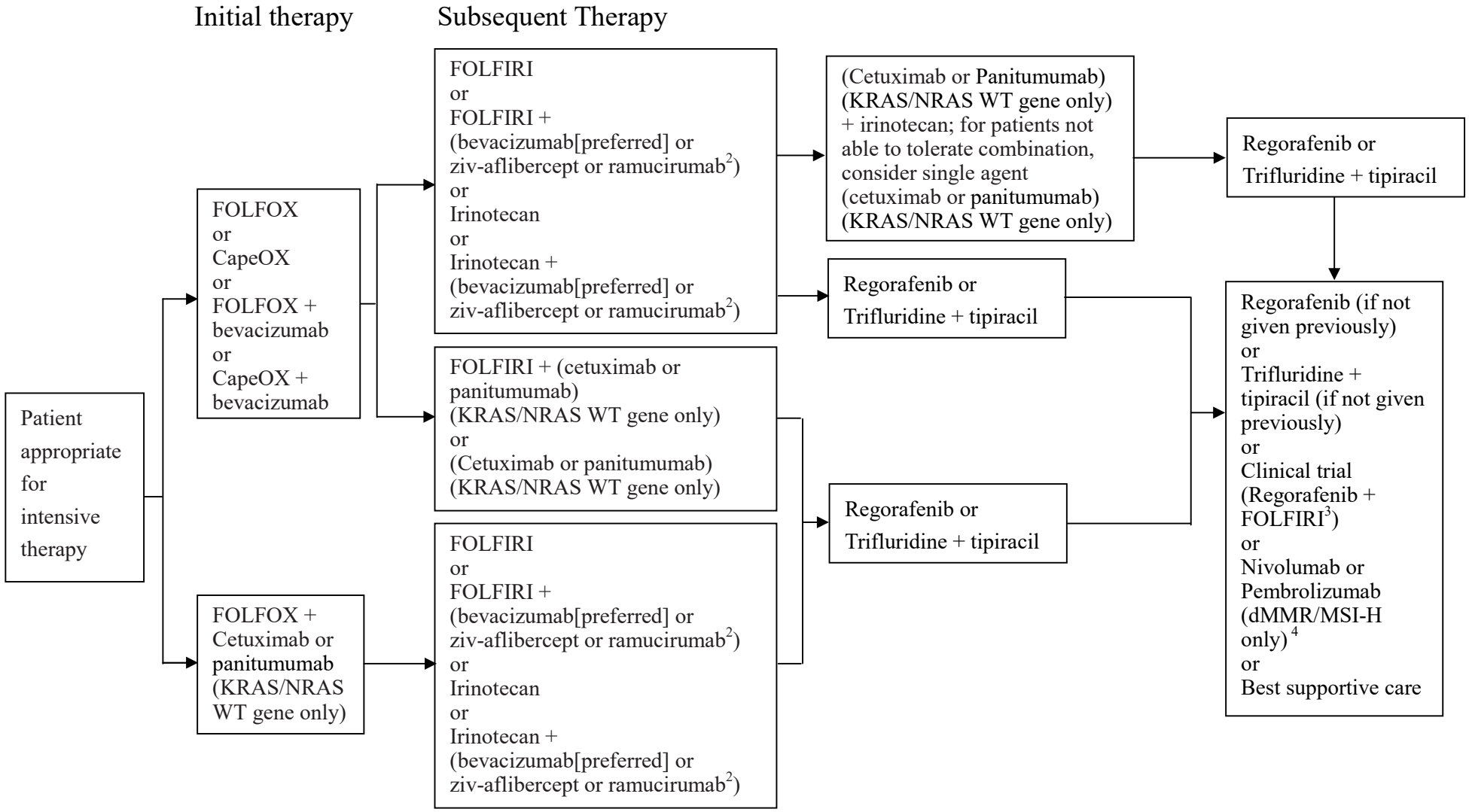


[1]HIPEC = Hyperthermic Intraperitoneal Chemotherapy; Not documented in NCCN guideline 2015 v2 but in ESMO guideline 2014(evidence grade IVB). Also refer to Reference [7], [8]

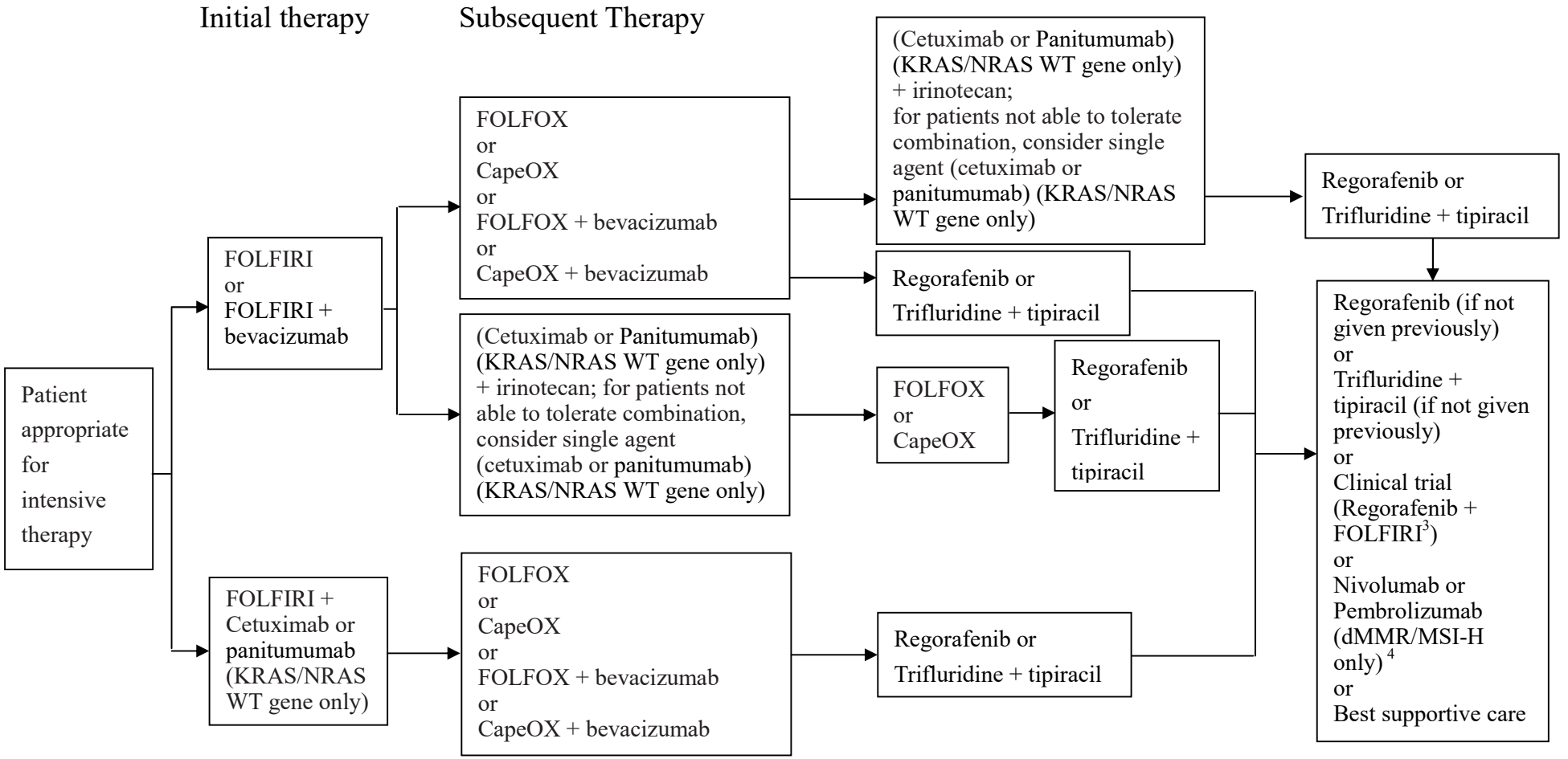
[2]Not available in VGHKS now

[3]Aggressive cytoreductive debulking and/or intraperitoneal chemotherapy are not recommended outside the setting of a clinical trial. If R0 resection can be achieved, surgical resection of isolated peritoneal disease may be considered at expertienced centers.

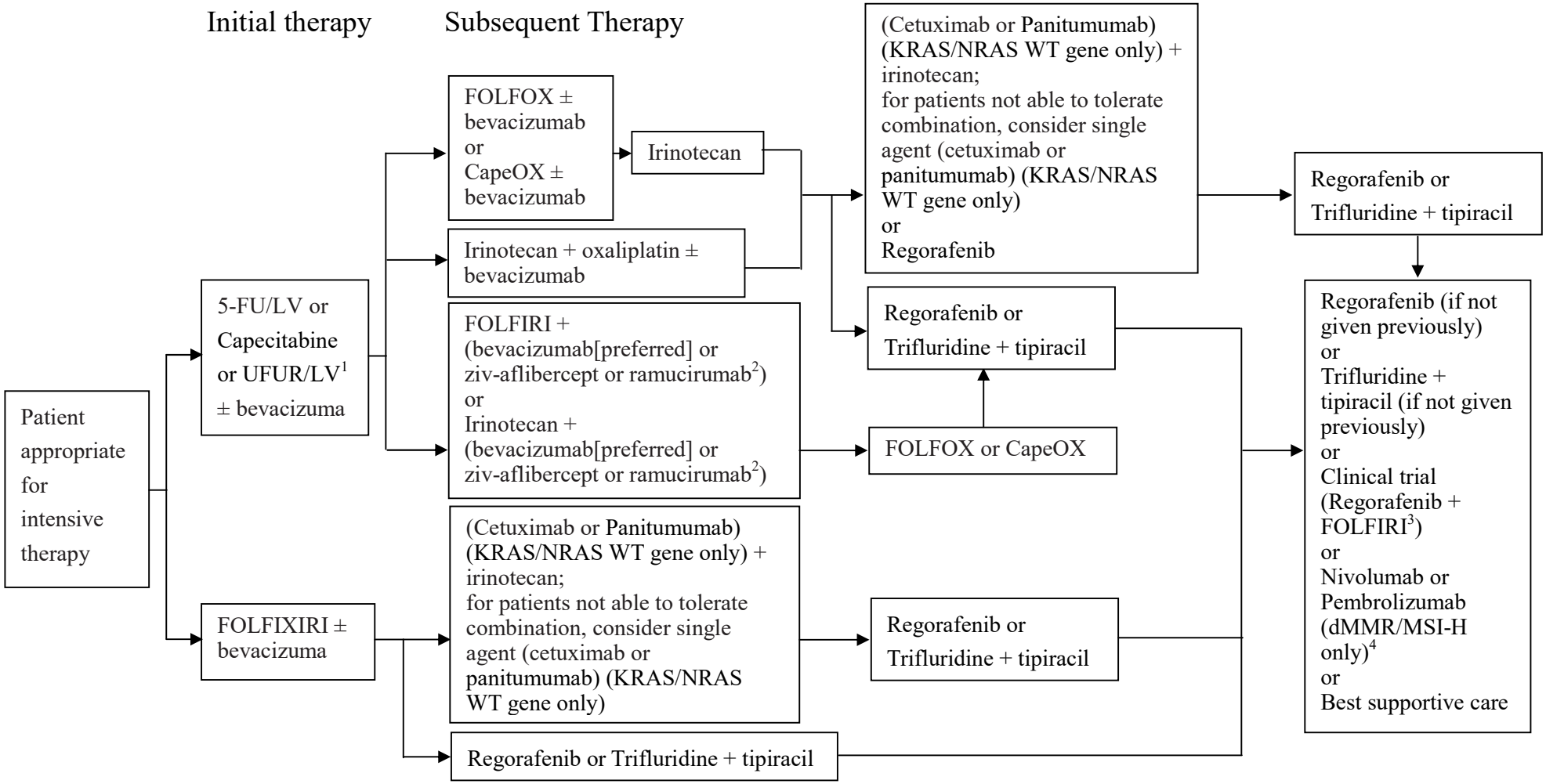
Chemotherapy for advanced or metastatic disease (1 of 4)



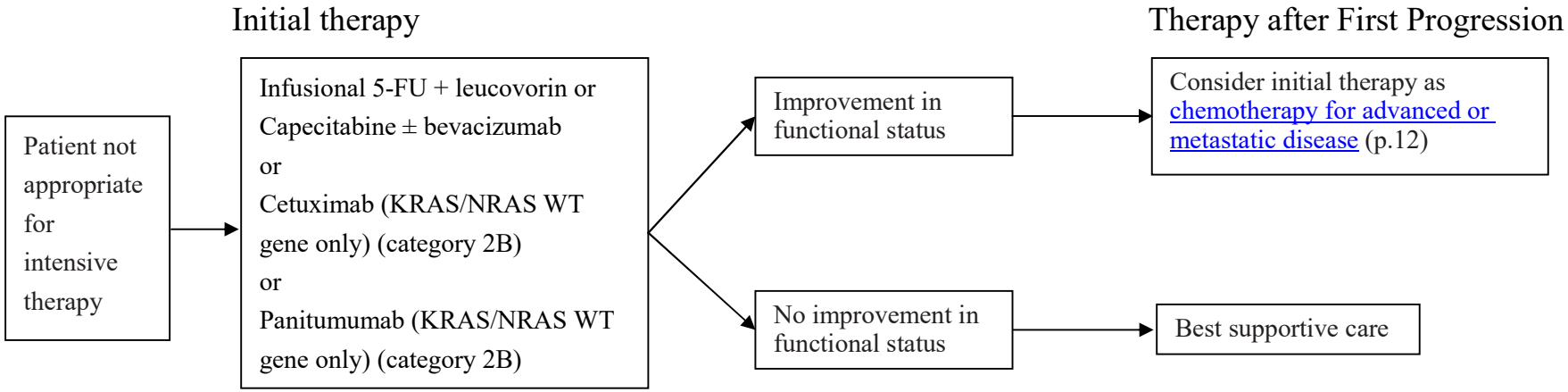
Chemotherapy for advanced or metastatic disease (2 of 4)



Chemotherapy for advanced or metastatic disease (3 of 4)



Chemotherapy for advanced or metastatic disease (4 of 4)



[1]Japanese regimen, also see Chemotherapy Regimens

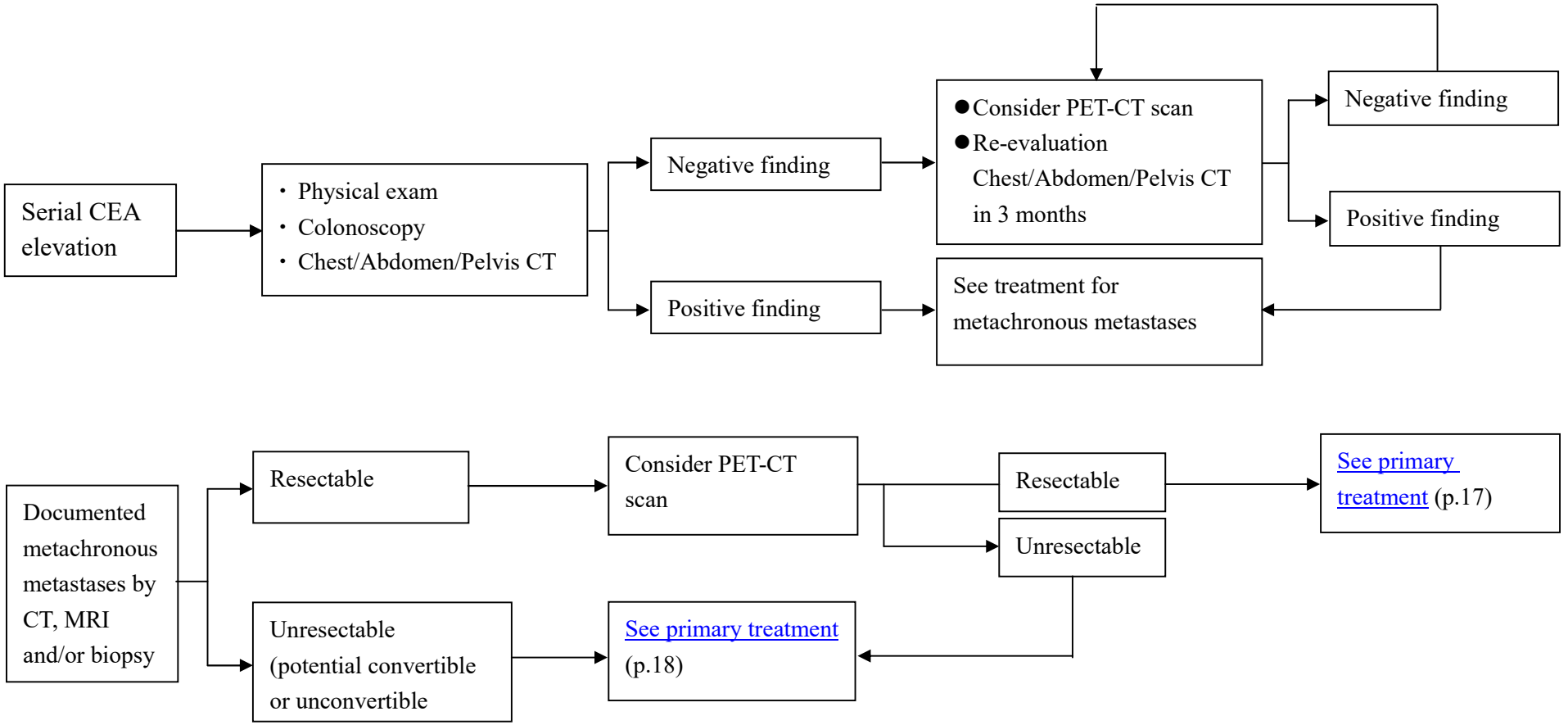
[2]Not available in routine clinical practice in Taiwan now

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

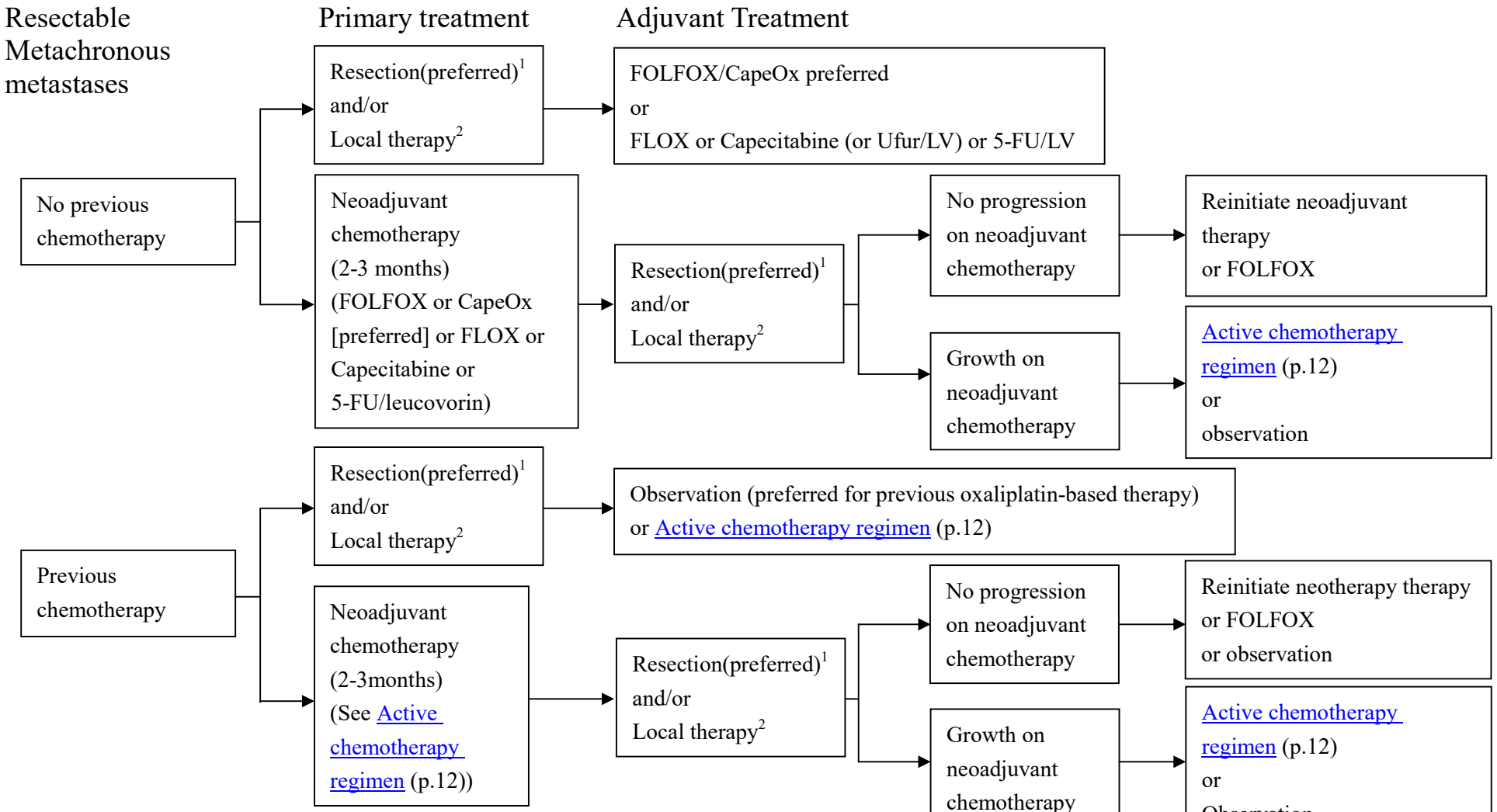
[4]Based on Reference [13, 14]

Workup for recurrence

Recurrence Workup



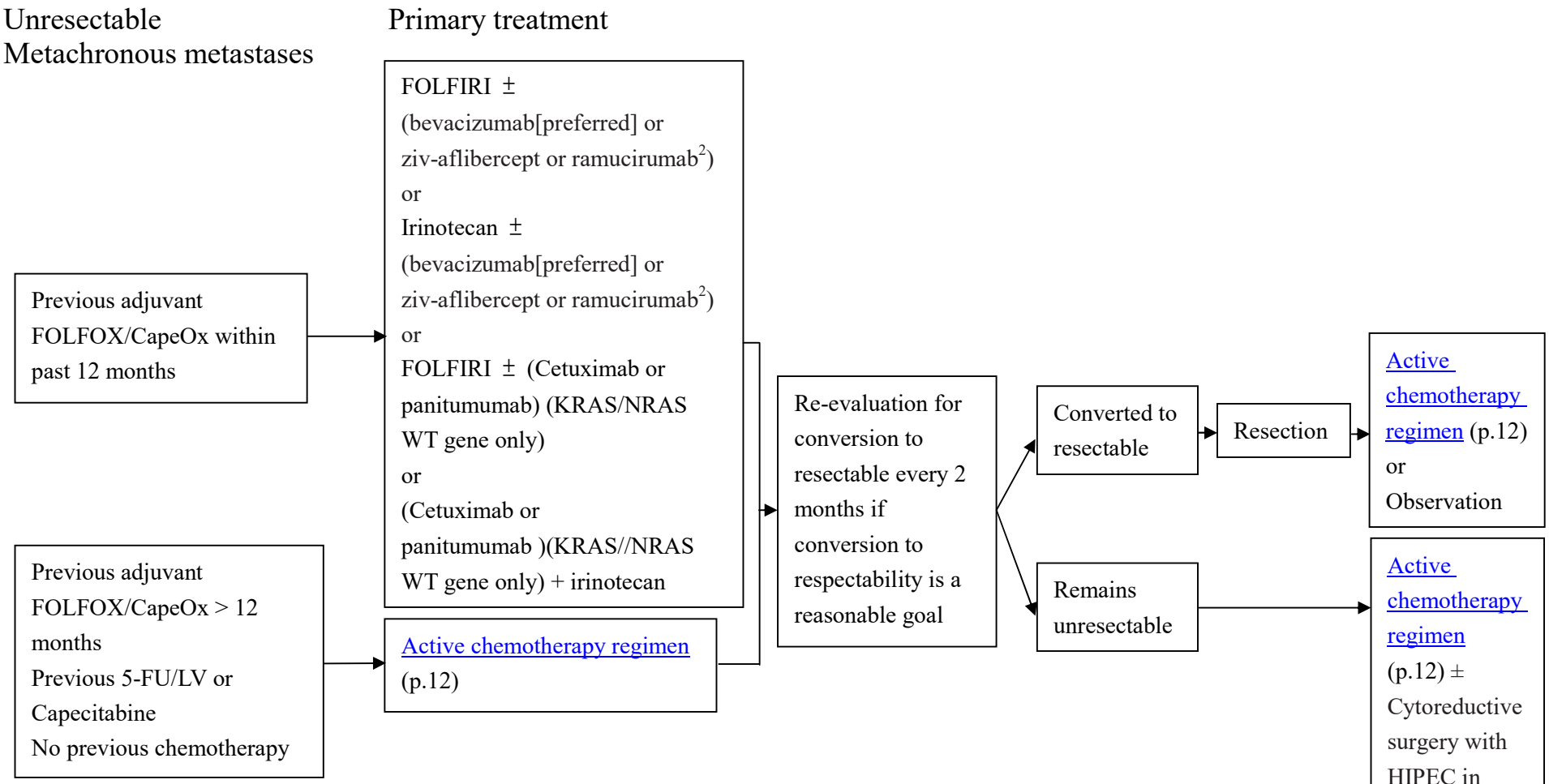
Resectable metachronous metastases



[1]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.

[2]Resection is preferred over locally ablative precedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver oligometastases

Unresectable metachronous metastases



[1]See footnote "1" in Synchronous abdominal/peritoneal metastases

[2]Not available in routine practice in Taiwan now

Principles of Chemotherapy

LV Dosage

Leucovorin 400 mg/m2 is the equivalent of levoleucovorin 200 mg/m2

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 1st line treatment

Cetuximab combine with Irinotecan base regimens at the 1st line & the 3rd line treatment

Panitumumab combine with Irinotecan base regimens at the 3rd 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

癌症藥物考慮停藥準則：

a. 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。

b. 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。

c. 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。

d. 評估Eastern Cooperative Oncology Group(ECOG) Performance Status≧3者。

e. 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。

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

FOLFOX
mFOLFOX6 (may add with Bevacizumab/Panitumumab/Cetuximab)
Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1 Leucovorin 400 mg/m^2 IV over 2 hours, day 1 5-FU 400 mg/m^2 IV bolus on day 1, then 1200 mg/m^2 /day x 2 days (total 2400 mg/m^2 over 46–48 hours) IV continuous infusion Repeat every 2 weeks
CapeOX (may add with Bevacizumab)
Oxaliplatin 130 mg/m^2 IV over 2 hours, day 1 Capecitabine 850–1000mg/m^2 twice daily PO for 14 days Repeat every 3 weeks
FOLFIRI *(may add with Bevacizumab/Panitumumab/Cetuximab/Ziv-aflibercept/Ramucirumab)*
Irinotecan 180 mg/m^2 IV over 30–90 minutes, day 1 Leucovorin* 400 mg/m^2 IV infusion to match duration of irinotecan infusion, day 1 5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46–48 hours) continuous infusion Repeat every 2 weeks
FOLFOXIRI *(may add with Bevacizumab)*
Irinotecan 165 mg/m^2 IV day 1, oxaliplatin 85 mg/m^2 day 1, leucovorin 400 mg/m^2 day 1, fluorouracil 1600 mg/m2/day x 2 days (total 3200 mg/m^2 over 48 hours) continuous infusion starting on day 1. Repeat every 2 weeks

TARGET THERAPY Repeat every 2 weeks (unless additional mention)
+ *Bevacizumab*
Bevacizumab 5 mg/kg IV, day 1 or Bevacizumab 7.5 mg/kg IV, day 1 (for Capecitabine based)
+ *Panitumumab (KRAS/NRAS WT gene only)*
Panitumumab 6 mg/kg IV over 60 minutes, day 1
+ *Cetuximab (KRAS/NRAS WT gene only)*
Cetuximab 400 mg/m^2 IV over 2 hours first infusion, then 250 mg/m^2 IV over 60 minutes weekly or Cetuximab 500 mg/m^2 IV over 2 hours, day 1
+ *Ziv-aflibercept (FOLFIRI)*
Ziv-aflibercept 4 mg/kg IV, day 1
+ *Ramucirumab[2] (FOLFIRI)*
Ramucirumab 8mg/kg over 60 minutes, day 1
+ *Regorafenib (Single use or with FOLFIRI[3])*
Regorafenib 160 mg PO daily days 1-21 Repeat every 28 days
Trifluridine + tipiracil[2]
35mg/m2 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)

Bolus or infusional 5-FU/leucovorin	**Irinotecan based**
Roswell Park regimen	*IROX*
Leucovorin 500 mg/m^2 IV over 2 hours, days 1, 8, 15, 22, 29, and 36 5-FU 500 mg/m^2 IV bolus 1 hour after start of leucovorin, days 1, 8, 15, 22, 29, and 36 Repeat every 8 weeks	Oxaliplatin 85 mg/m^2 IV over 2 hours, followed by irinotecan 200 mg/m2 over 30-90 minutes every 3 weeks
Simplified biweekly infusional 5-FU/LV (sLV5FU2)	*Irinotecan (may add with Cetuximab)*
Leucovorin 400 mg/m^2 IV over 2 hours on day 1, followed by 5-FU bolus 400 mg/m^2 and then 1200 mg/m^2 /day x 2 days (total 2400 mg/m^2 over 46-48 hours) continuous infusion Repeat every 2 weeks	Irinotecan 125 mg/m^2 IV over 30-90 minutes, days 1 and 8 Repeat every 3 weeks or Irinotecan 180 mg/m^2 IV over 30-90 minutes, day 1 Repeat every 2 weeks or Irinotecan 300-350 mg/m^2 IV over 30-90 minutes, day 1 Repeat every 3 weeks
Weekly	
Leucovorin 20 mg/m^2 IV over 2 hours on day 1, 5-FU 500 mg/m^2 IV bolus injection 1 hour after the start of leucovorin. Repeat weekly. 5-FU 2600 mg/m^2 by 24-hour infusion plus leucovorin 500 mg/m^2 . Repeat every week (*AIO regimen*[4]: lecovorin 500 mg/m^2 in N/S 250ml over 2 hours followed by 5-FU 2600 mg/m^2 in N/S 500ml by 24-hour infusion weekly x6 and 2 weeks off, repeat every 8 weeks)	**Capecitabine** *(may add with Bevacizumab)*
	850–1250 mg/m^2 PO twice daily, days 1–14 Repeat every 3 weeks
Mayo Clinic regimen[4]	**Ufur/LV**[1]
Leucovorin 20 mg/m^2/day IV over 30 minutes followed by 5-FU IV bolus 425 mg/m^2/day x 5 days. Repeat every 5 weeks	Leucovorin 20-30 mg/m^2 + Ufur 300-500 mg/ m^2 PO at day 1 to 28 in every 35 days

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

Modified regimen for CRS@VGHKS
modified mFOLFOX
Oxaliplatin 85-100 mg/ m^2 IV over 3 hours on day 1 Leucovorin 200 mg/ m^2 IV over 1 hours after Oxaliplatin on day 1 5-FU 2600 mg/m^2 IV continuous infusion over 18 hours (start on day 1) Repeat every 2 weeks
modified FOLFIRI
Irinotecan 180 mg/m^2 IV over 90 minutes, day 1 Leucovorin 200 mg/m^2 IV infusion for 1 hours after irinotecan infusion, day 1 5-FU 2400-3000 mg/m^2 continuous infusion over 18 hours (start on day 1) Repeat every 2 weeks
modified AIO regimen
lecovorin 250 mg/m^2 in N/S 250ml over 1 hours followed by 5-FU 2600 mg/m^2 in N/S 500ml by 18-hour infusion weekly x6 and 2 weeks off, repeat every 8 weeks

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

[2]Not available in routine practice in Taiwan now

[3]As third/fourth line chemotherpy for advanced/metastatic disease, based on reference[10]

[4]At VGHKS

Chemotherapy Regimens for Adjuvant Therapy (1 of 2)

<table>
<tr><td>mFOLFOX6[3]</td><td>5-FU/leucovorin</td></tr>
<tr><td rowspan="2">Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1
Leucovorin 400 mg/m^2 IV over 2 hours, day 1
5-FU 400 mg/m^2 IV bolus on day 1, then 1200 mg/m^2 /day x 2 days (total 2400 mg/m^2 over 46–48 hours) IV continuous infusion
Repeat every 2 weeks</td><td>Rosewell Park regimen (?)</td></tr>
<tr><td rowspan="3">Leucovorin 500 mg/m^2 given as a 2-hour infusion and repeated weekly x 6. 5-FU 500 mg/m^2 given bolus 1 hour after the start of leucovorin and repeated weekly x 6. Every 8 weeks for 4 cycles</td></tr>
<tr><td>FLOX[2]</td></tr>
<tr><td>5-FU 500 mg/m^2 IV bolus weekly x 6 + leucovorin 500 mg/m^2 IV weekly x 6, each 8-week cycle x 3 with oxaliplatin 85 mg/m^2 IV administered on weeks 1, 3, and 5 of each 8-week cycle x 3</td><td rowspan="3">Simplified biweekly infusional 5-FU/LV (sLV5FU2)
Leucovorin 400 mg/m^2 IV over 2 hours on day 1, followed by 5-FU bolus 400 mg/m^2 and then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours) continuous infusion
Repeat every 2 weeks</td></tr>
<tr><td>Capecitabine</td></tr>
<tr><td>1250 mg/m^2 PO twice daily, days 1–14 every 3 weeks x 24 wks</td></tr>
<tr><td>CapeOX</td><td>AIO regimen[4]</td></tr>
<tr><td>Oxaliplatin 130 mg/m^2 IV over 2 hours, day 1
Capecitabine 850–1000mg/m^2 twice daily PO for 14 days
Repeat every 3 weeks x 24 weeks</td><td>Lecovorin 500 mg/m^2 in N/S 250ml over 2 hours followed by 5-FU 2600 mg/m^2 in N/S 500ml by 24-hour infusion weekly x6 and 2 weeks off, repeat every 8 weeks</td></tr>
<tr><td>Ufur/LV[1]</td><td>Mayo Clinic regimen[4]</td></tr>
<tr><td>Leucovorin 20-30 mg/m^2 + Ufur 300-500 mg/ m^2 PO at day 1 to 28 in every 35 days</td><td>Leucovorin 20 mg/m2/day IV over 30 minutes followed by 5-FU IV bolus 425 mg/m2/day x 5 days. Repeat every 5 weeks</td></tr>
</table>

[1]Japanese regimen, is the equavalent of 5-FU/LV or capecitabine in adjuvant and advanced/metastatic therapy. Also refer to Reference[4], [5] and [6]
[2]FLOX is an alternative to FOLFOX or CapeOx but FOLFOX or CapeOx are preferred
[3]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
[4]At VGHKS

Chemotherapy Regimens for Adjuvant Therapy (2 of 2)

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

Definitions for T, N, M	
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[a]
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum[b]
T4b	Tumor directly invades or is adherent to other organs or structures[b,c]
Regional Lymph Nodes (N)	
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
Distant Metastasis (M)	
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

7th 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

Reference

1. Major base on NCCN Colon Cancer Clinical Practice Guidelines Version 2.2016
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
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Appendix and Additional Information

1. Dosage of irinotecan in mFOLFIRI + Avstin regimen could be titrated up to 260mg/m^2 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