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直　　腸　　癌　　診　　療　　指　　引

大腸直腸癌醫療團隊 制定

2021年 5月修訂

Kaohsiung Veterans General Hospital

Rectal Cancer Clinical Practice Guidelines

Colorectal Cancer Multidisciplinary Team

May 2021*version 1*

Rectal Cancer Clinical Practice Guidelines

Content

<Revision Summary>

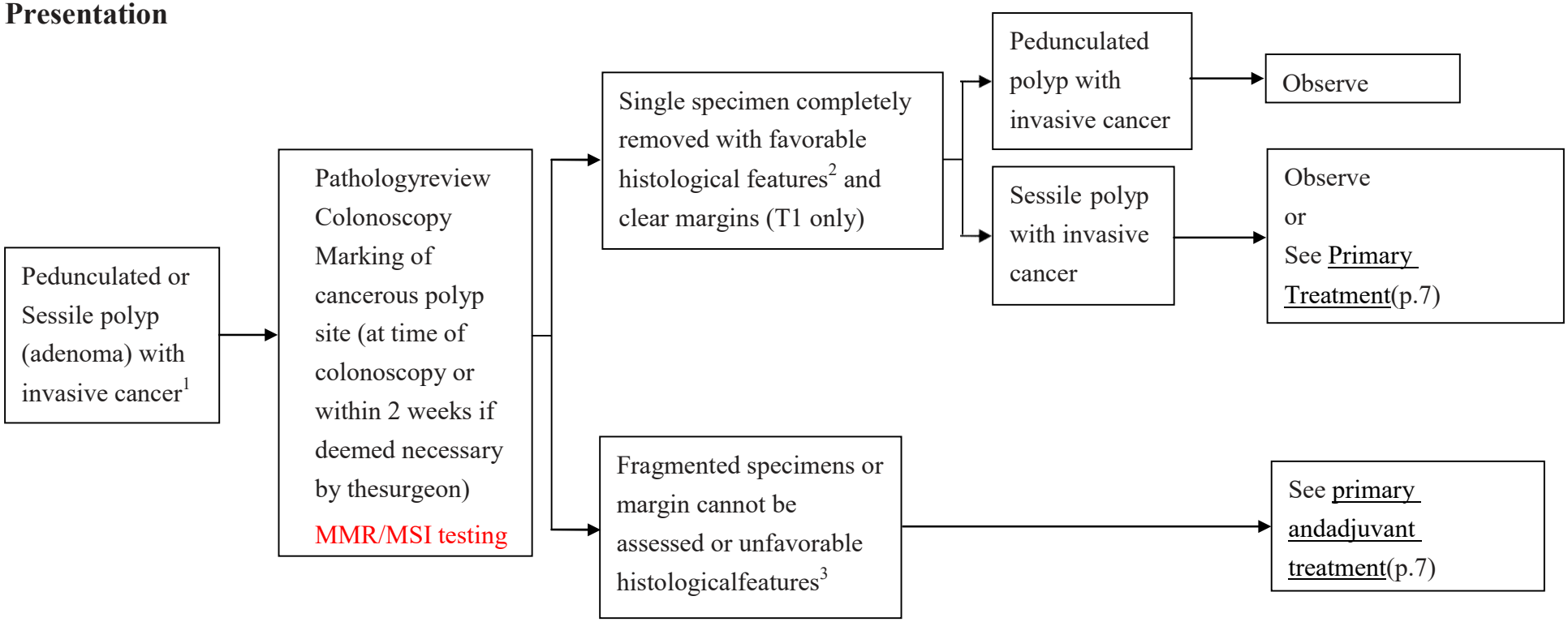
Updatesin Version 1 2021 of the VGHKS ColonCancer Clinical Practice Guidelines from Version 1 2020 include:

1. Pre-OP workup(p.6):
   - MMR/MSI testing
   - MDT evaluation

2. Unresectable Synchronous Metastases or Medically Inoperable Treatment (p.12):
   - Add HIPEC regimen: oxaliplatin or mitomycin C

3. Regimen added(p.13):
   Trifluridine + tipiracil +/- bevacizumab
   Add backbone with FOLFOXIRI for BRAF-mutant.
   Dabrafenib + trametinib + (cetuximab or panitumumab)
   BRAF V600E mutation (+)

Malignant polyp

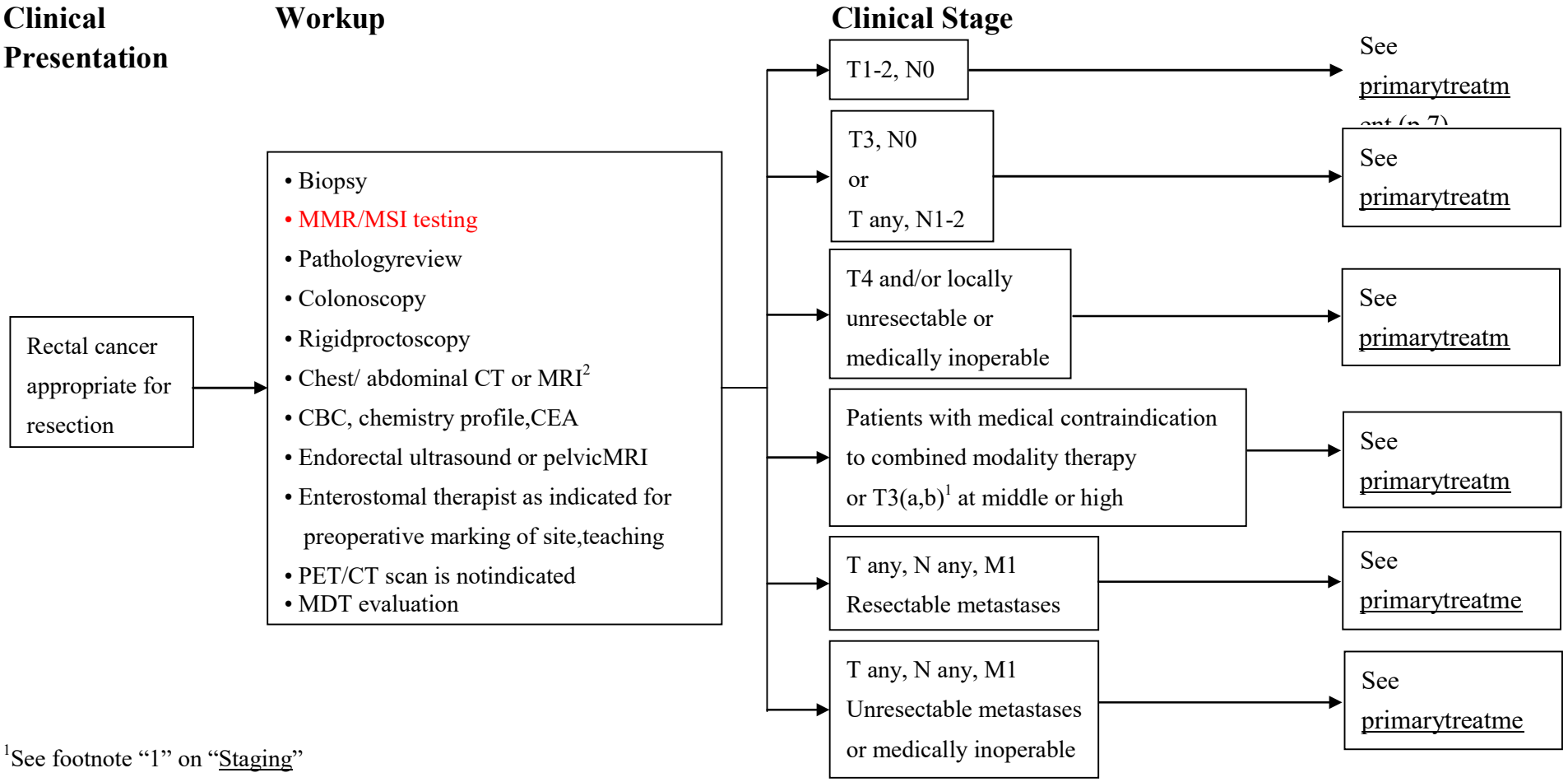


[1]A malignant polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1). pTis is not considered a "malignant polyp".

[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)

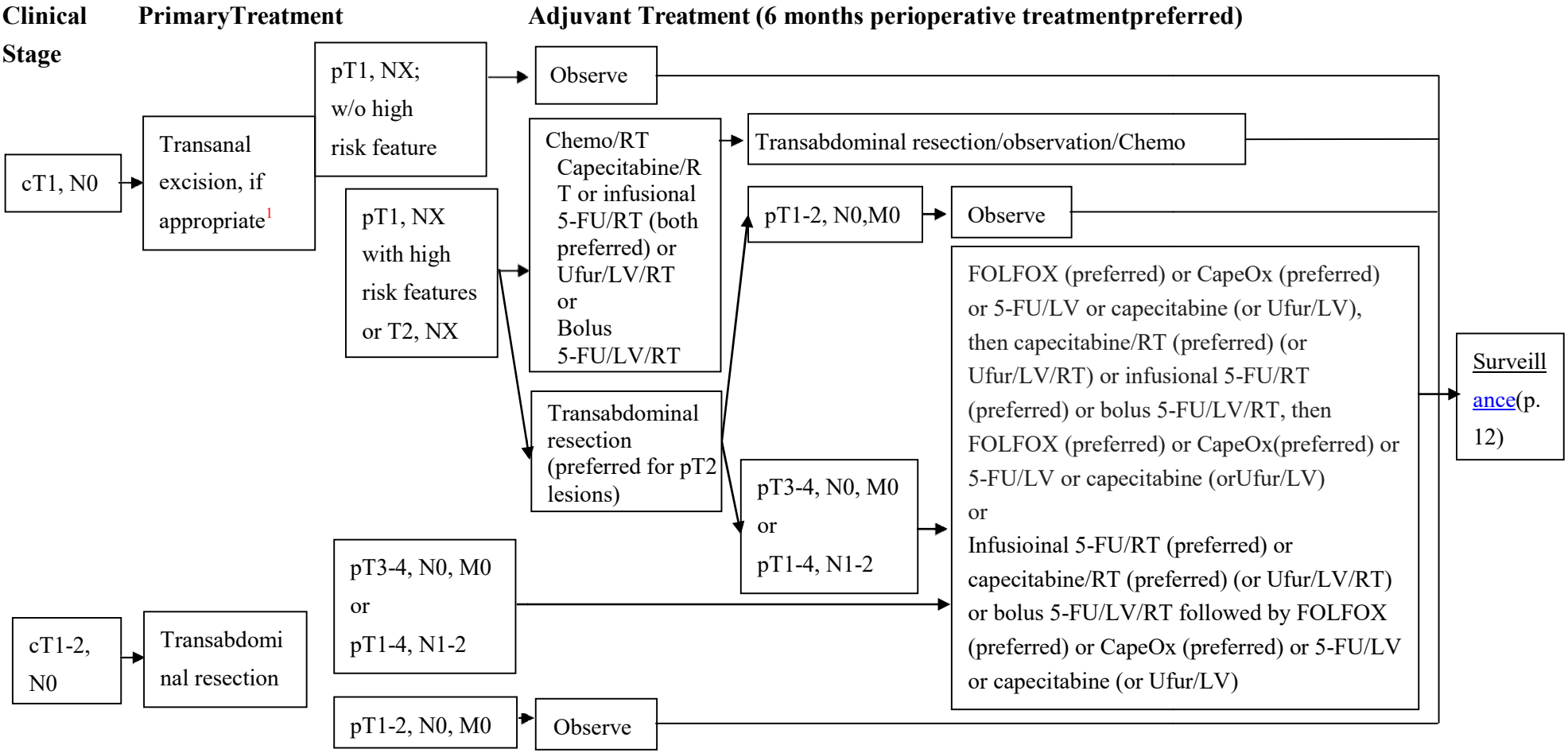
Resectable Primary Rectal Cancer



[1]See footnote "1" on "Staging"

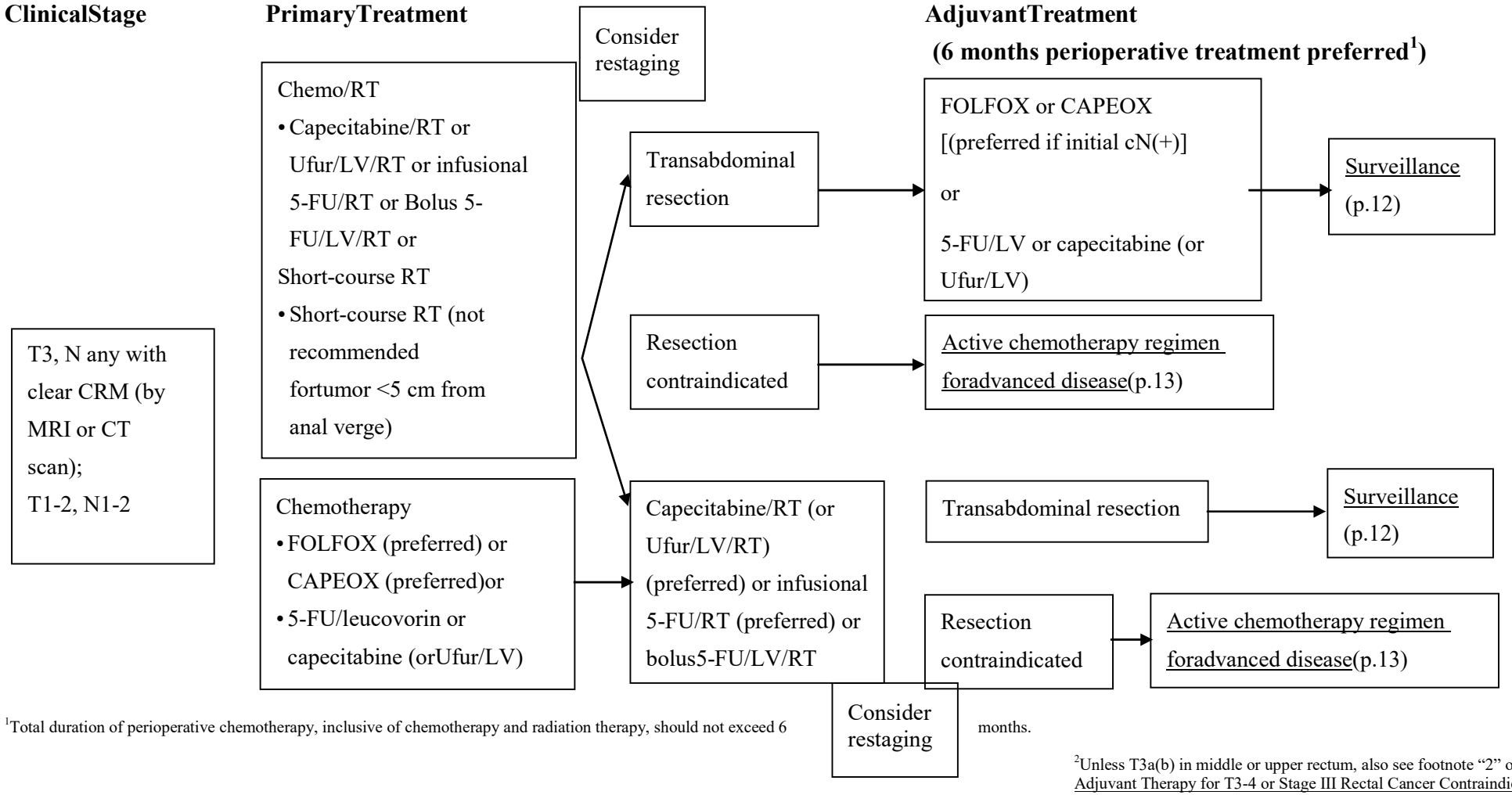
[2]CT should be with IV and oral contrast. Consider abd/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.

Adjuvant Therapy for Stage I Rectal Cancer



[1]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

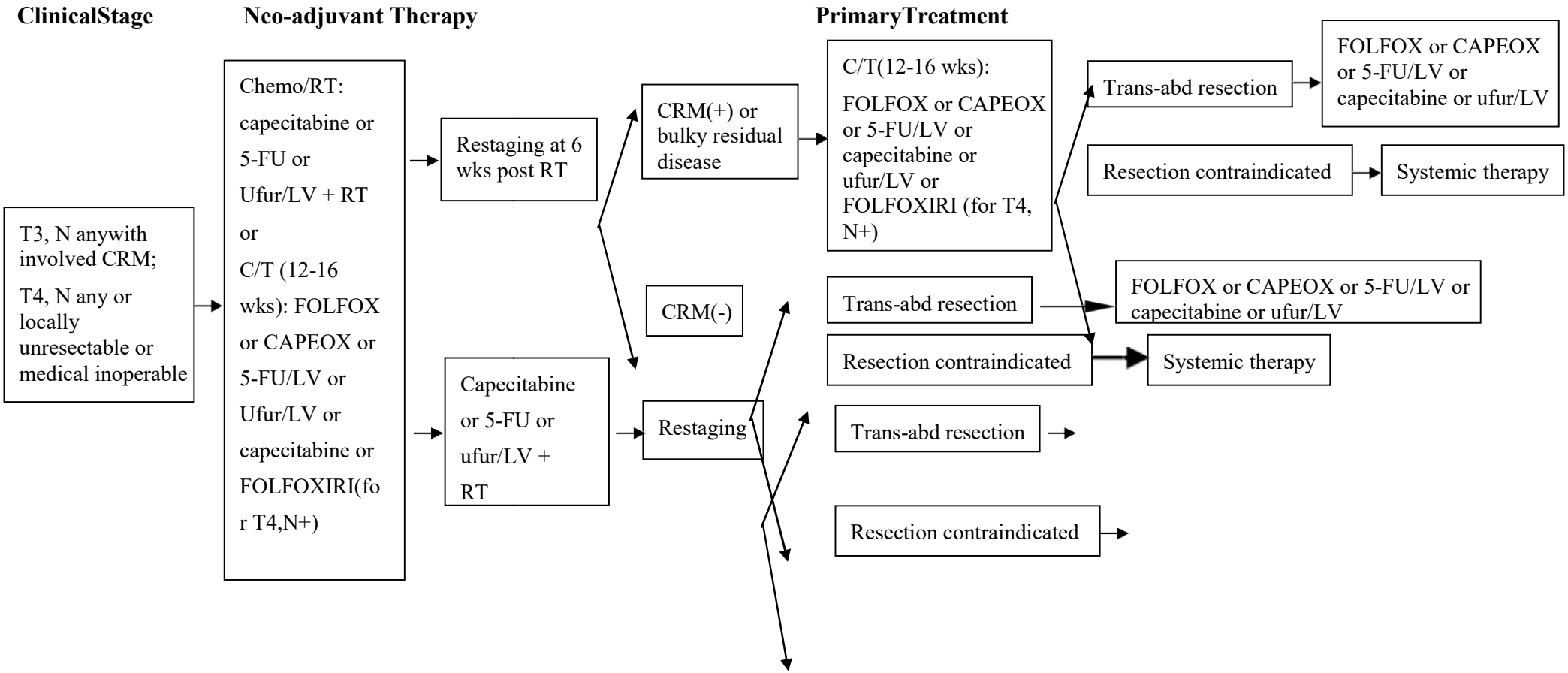


[1]Total duration of perioperative chemotherapy, inclusive of chemotherapy and radiation therapy, should not exceed 6 months.

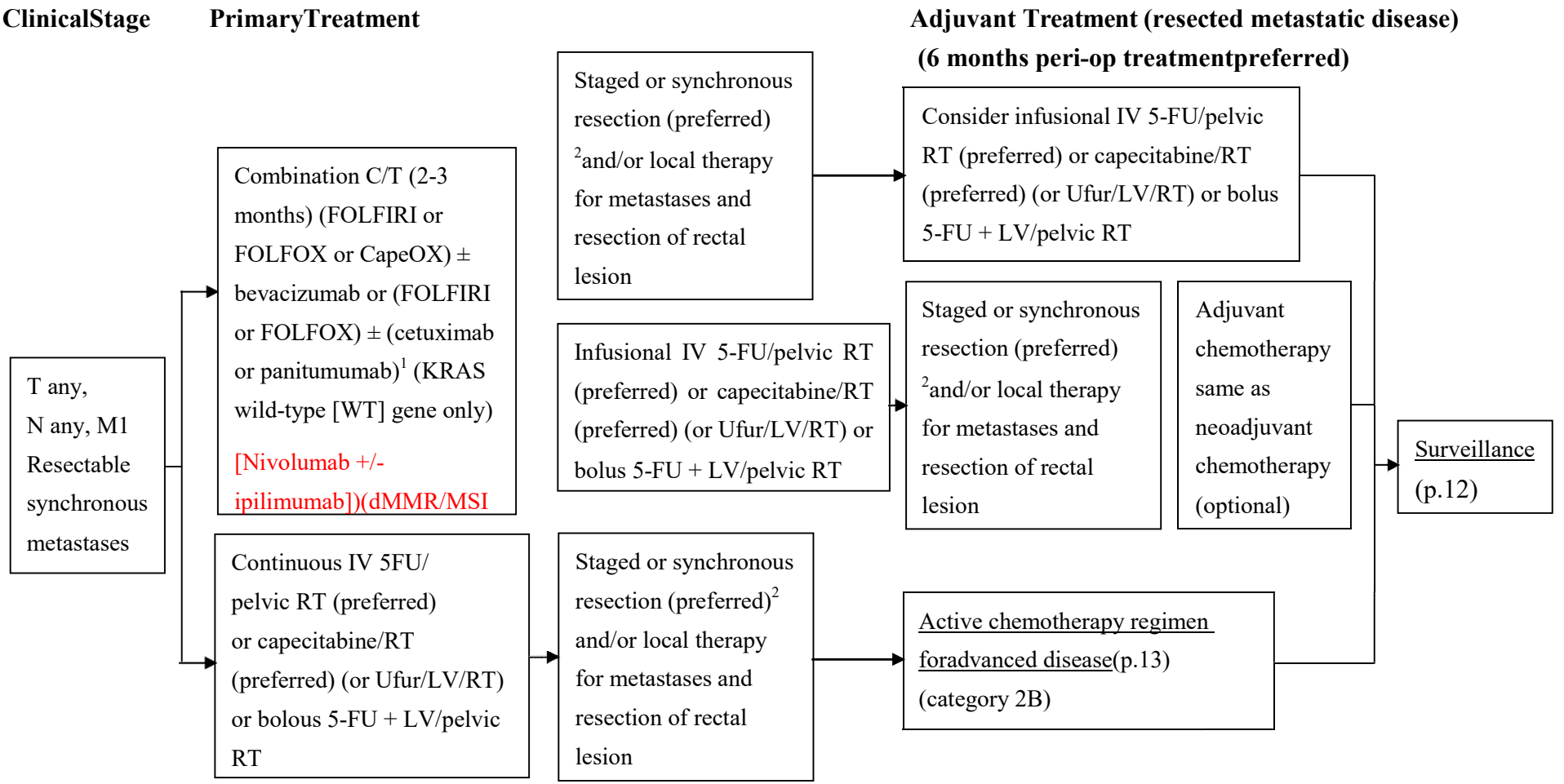
[2]Unless T3a(b) in middle or upper rectum, also see footnote "2" on Adjuvant Therapy for T3-4 or Stage III Rectal Cancer Contraindicated to Combined Modality Therapy

[3] 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

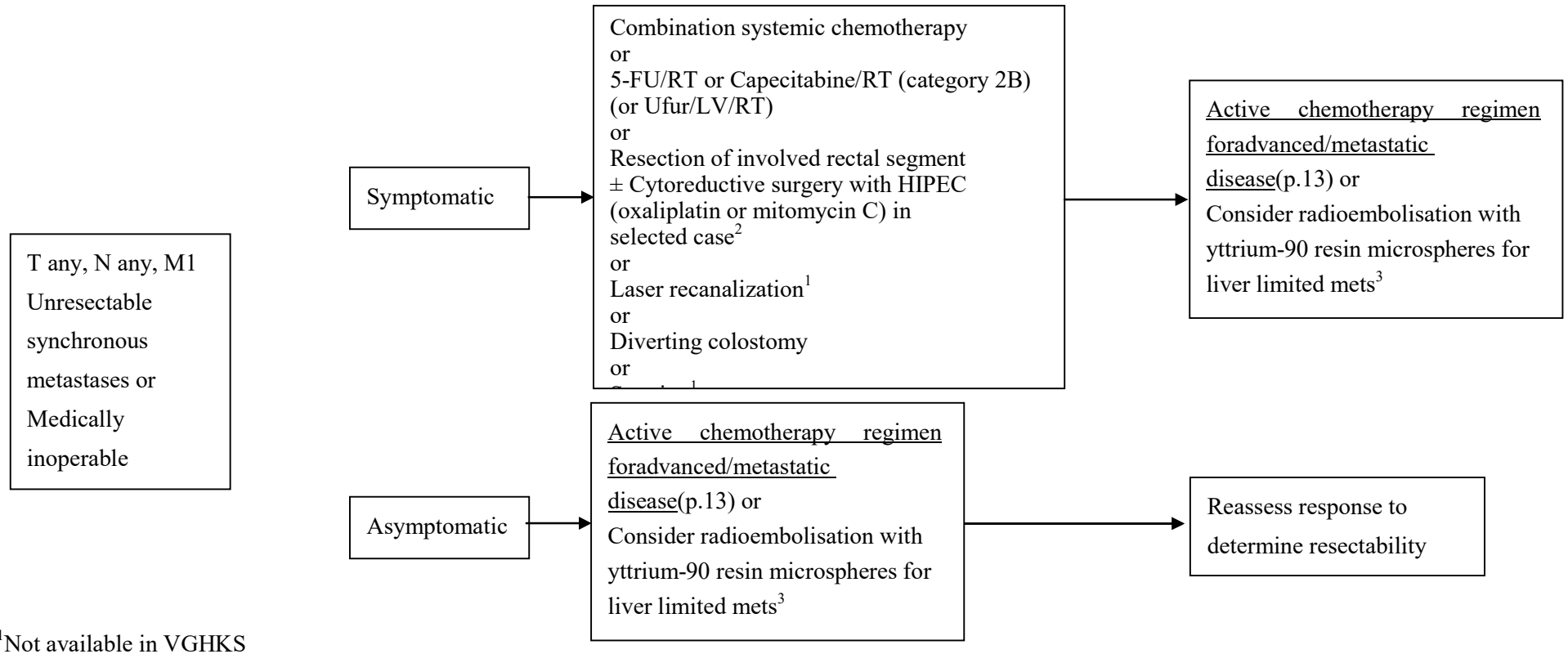


[1]There are conflicting data regarding the use of FOLFOX + cetuximab in patients who have potentially resectable liver metastases.

[2] 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

ClinicalStage **Primary Treatment**

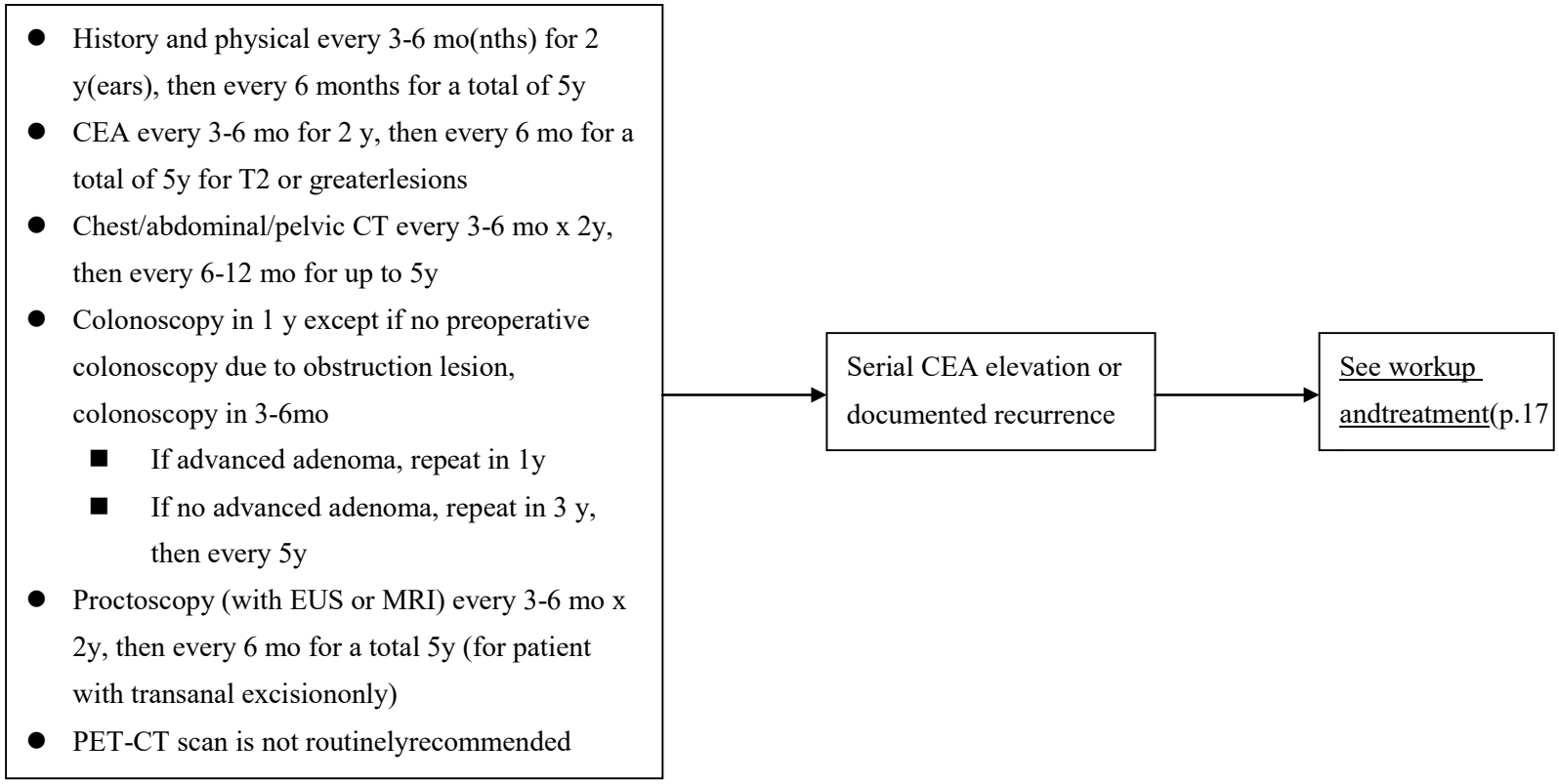


[1]Not available in VGHKS

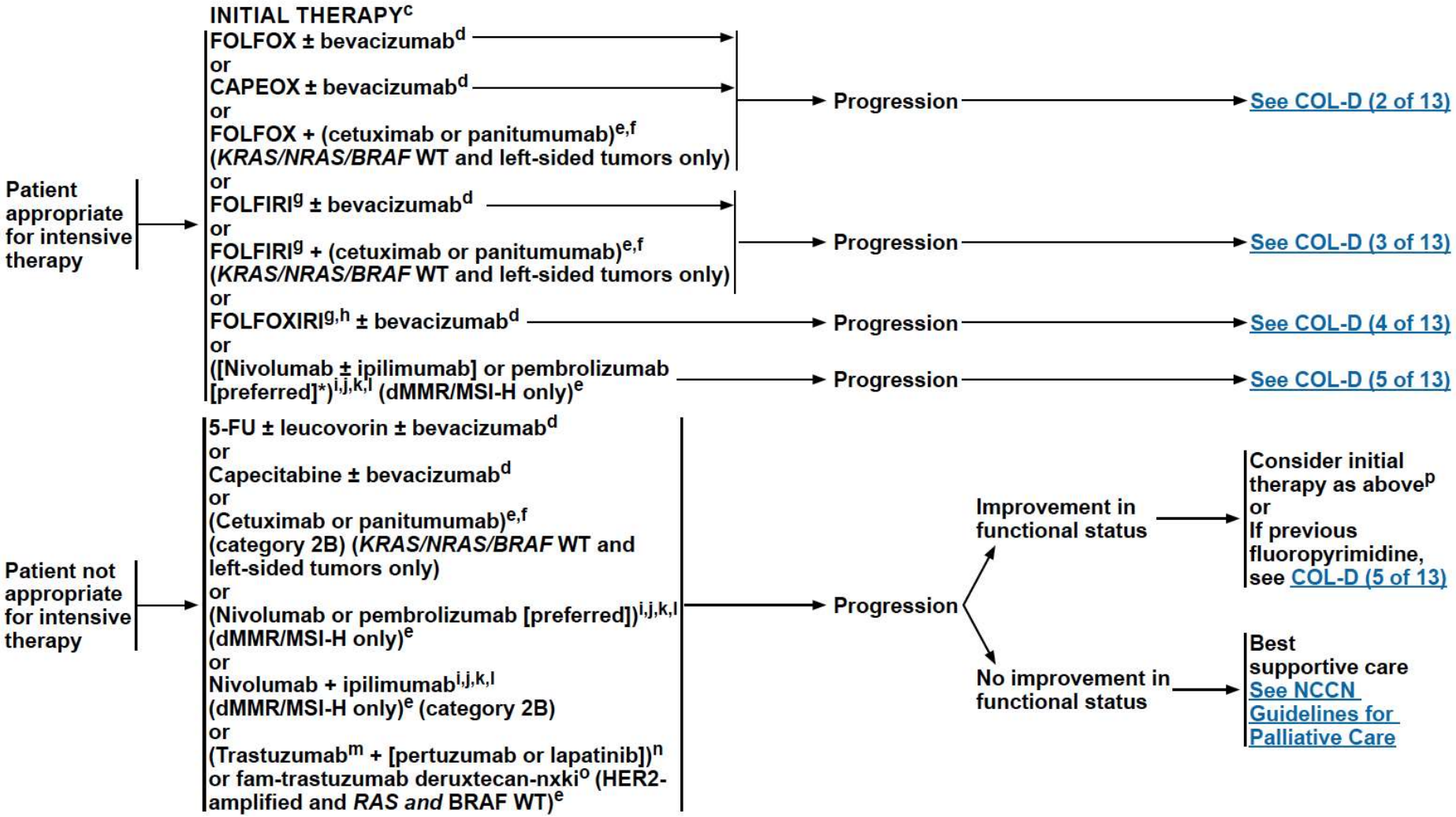
[2]HIPEC = Hyperthermic Intraperitoneal Chemotherapy; Not documented in NCCN guideline 2015 v2 but in ESMO guideline 2014(evidence grade IVB). Also refer to Reference [7], [8]

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

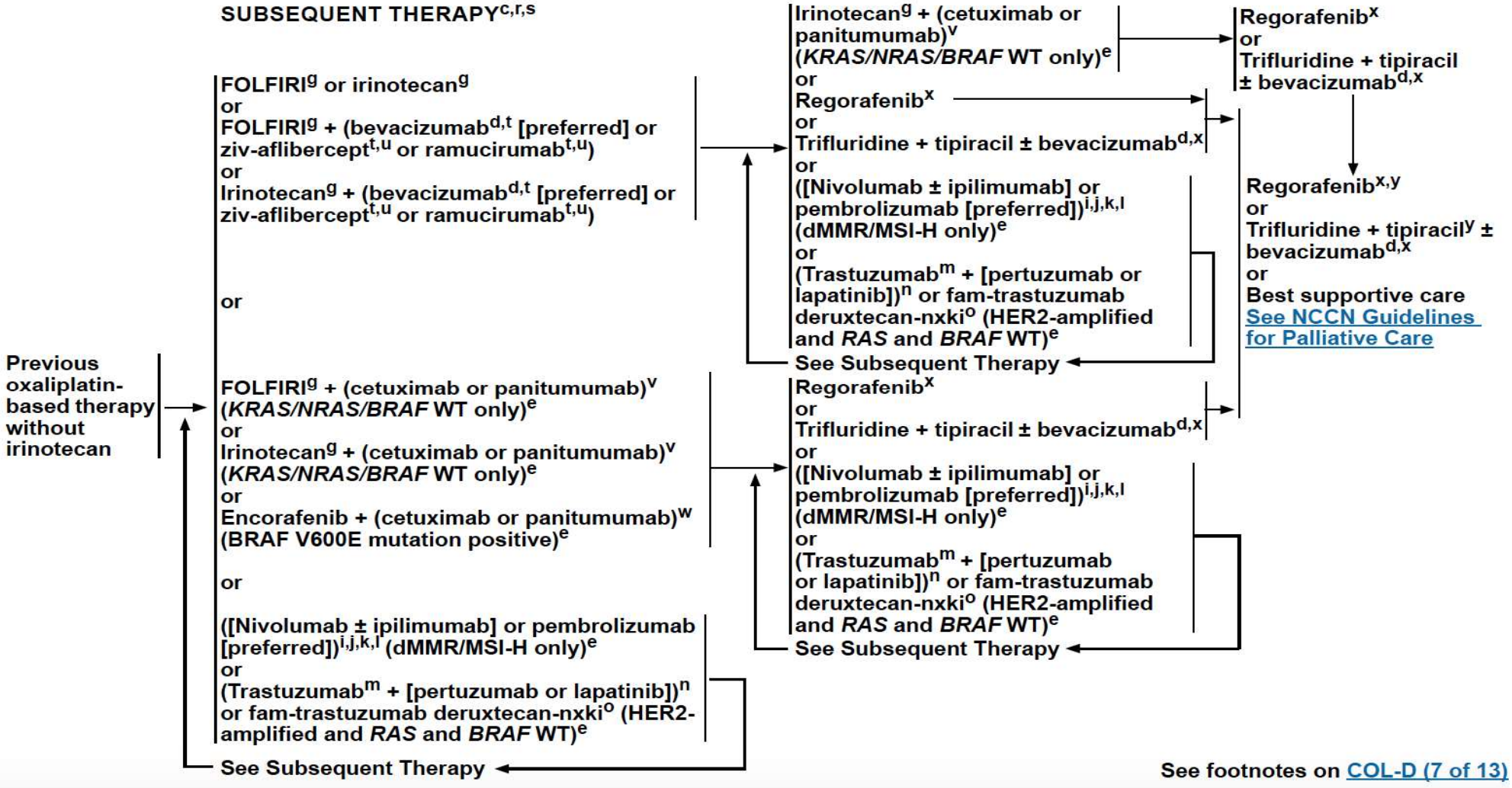
Surveillance



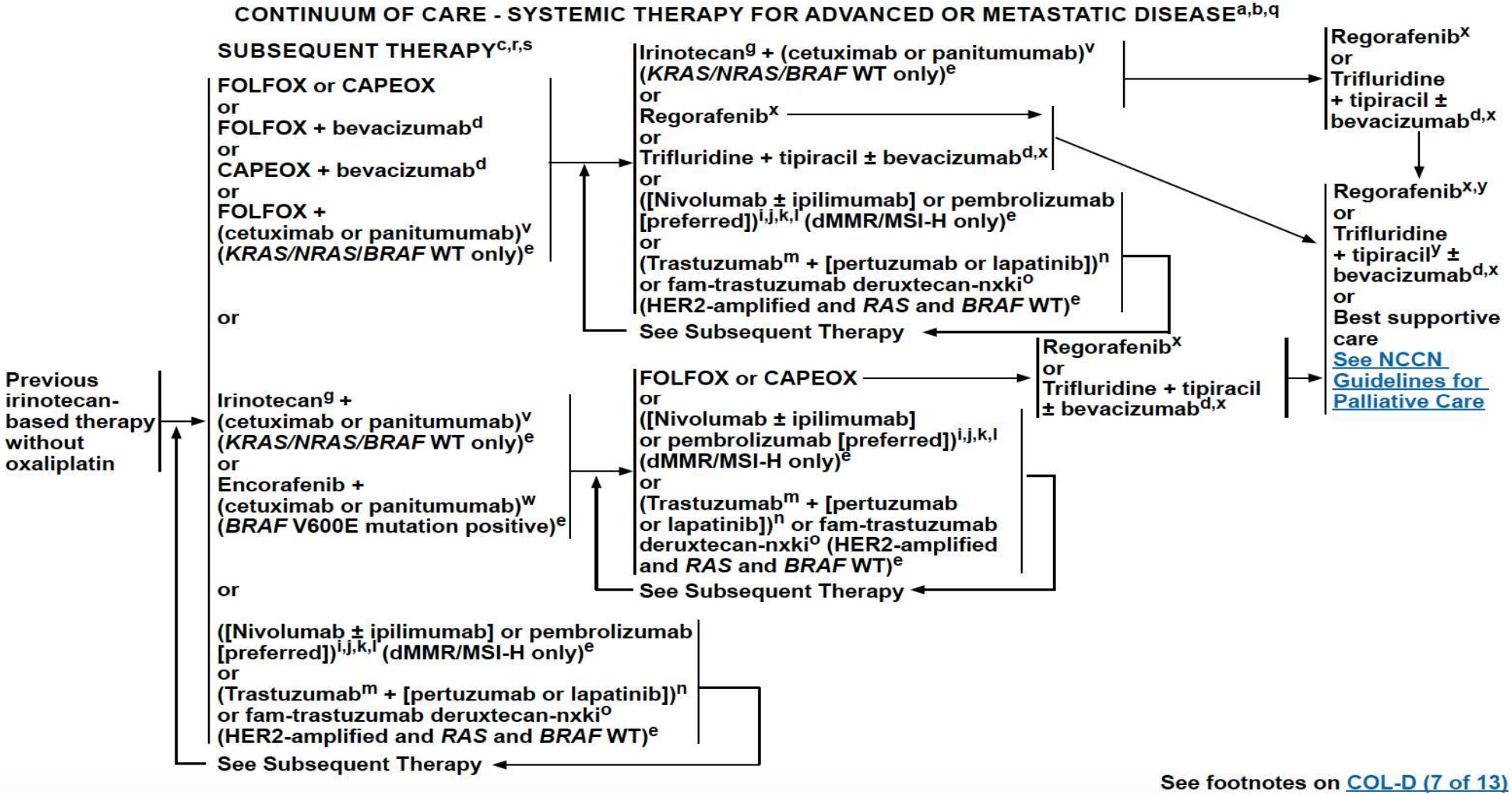
Chmotherapy for advanced or metastastic disease (1 of 4)



Chemotherapy for advanced or metastastic disease (2 of 4)

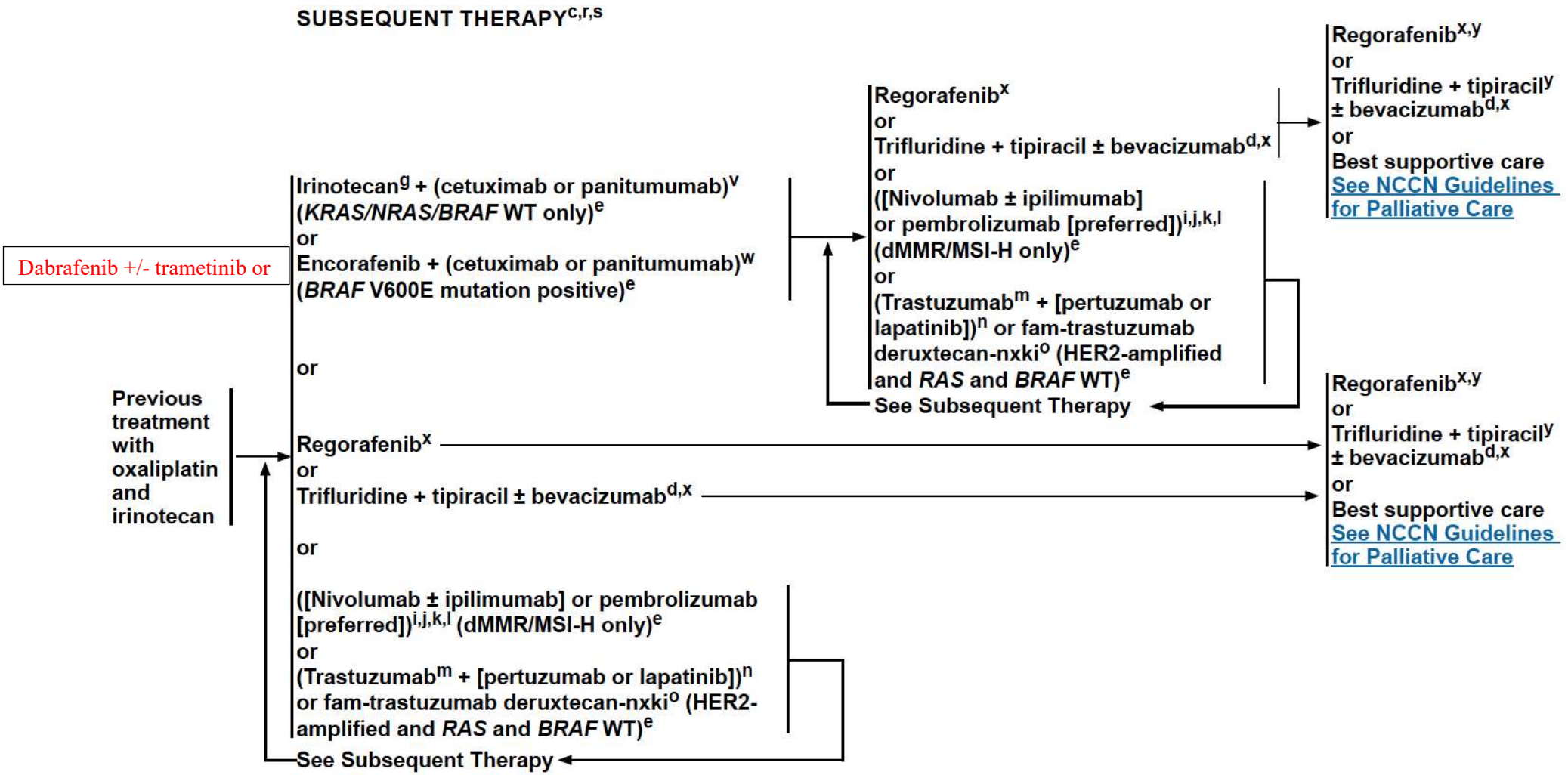


Chemotherapy for advanced or metastatic disease (3 of 4)

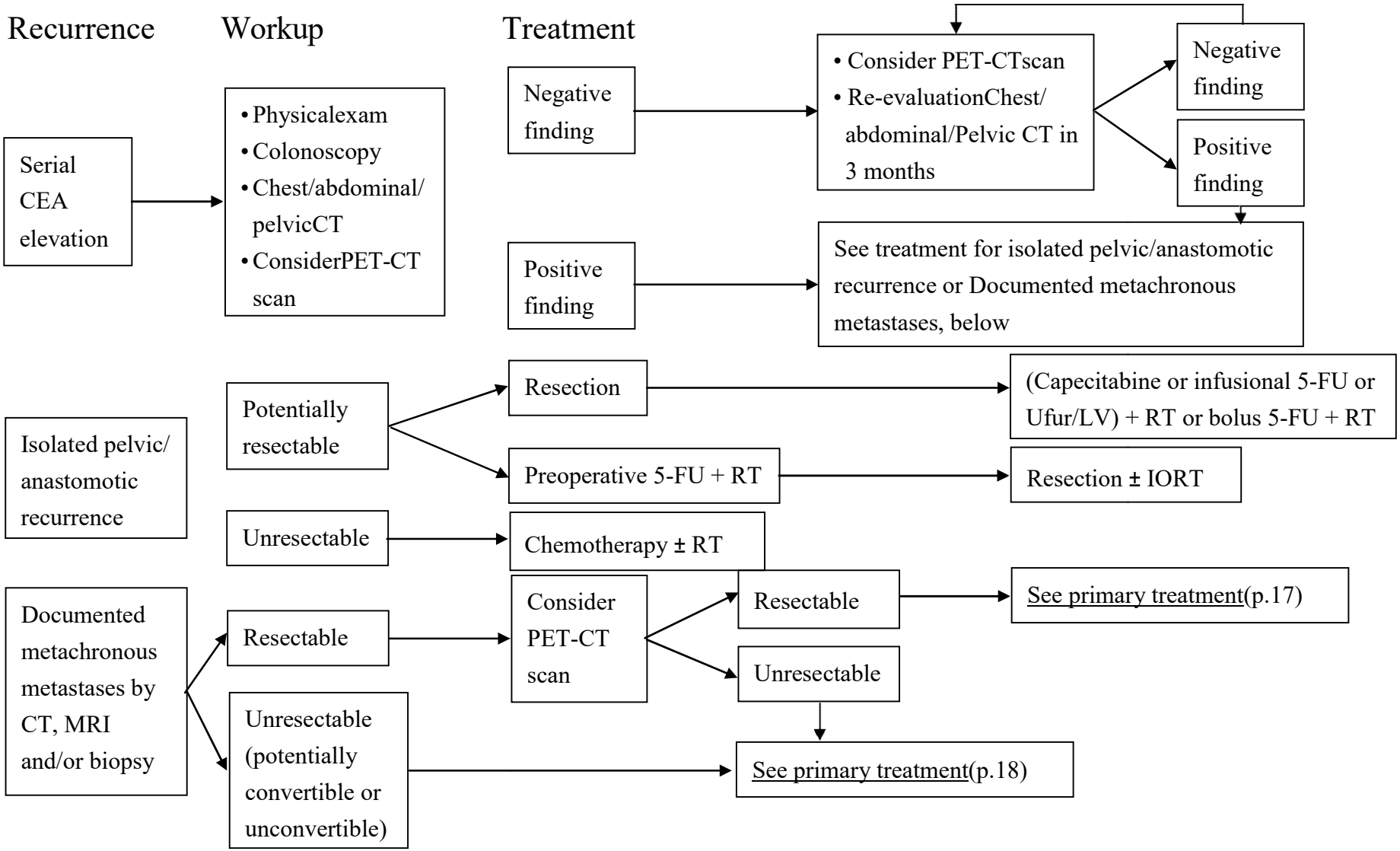


See footnotes on COL-D (7 of 13)

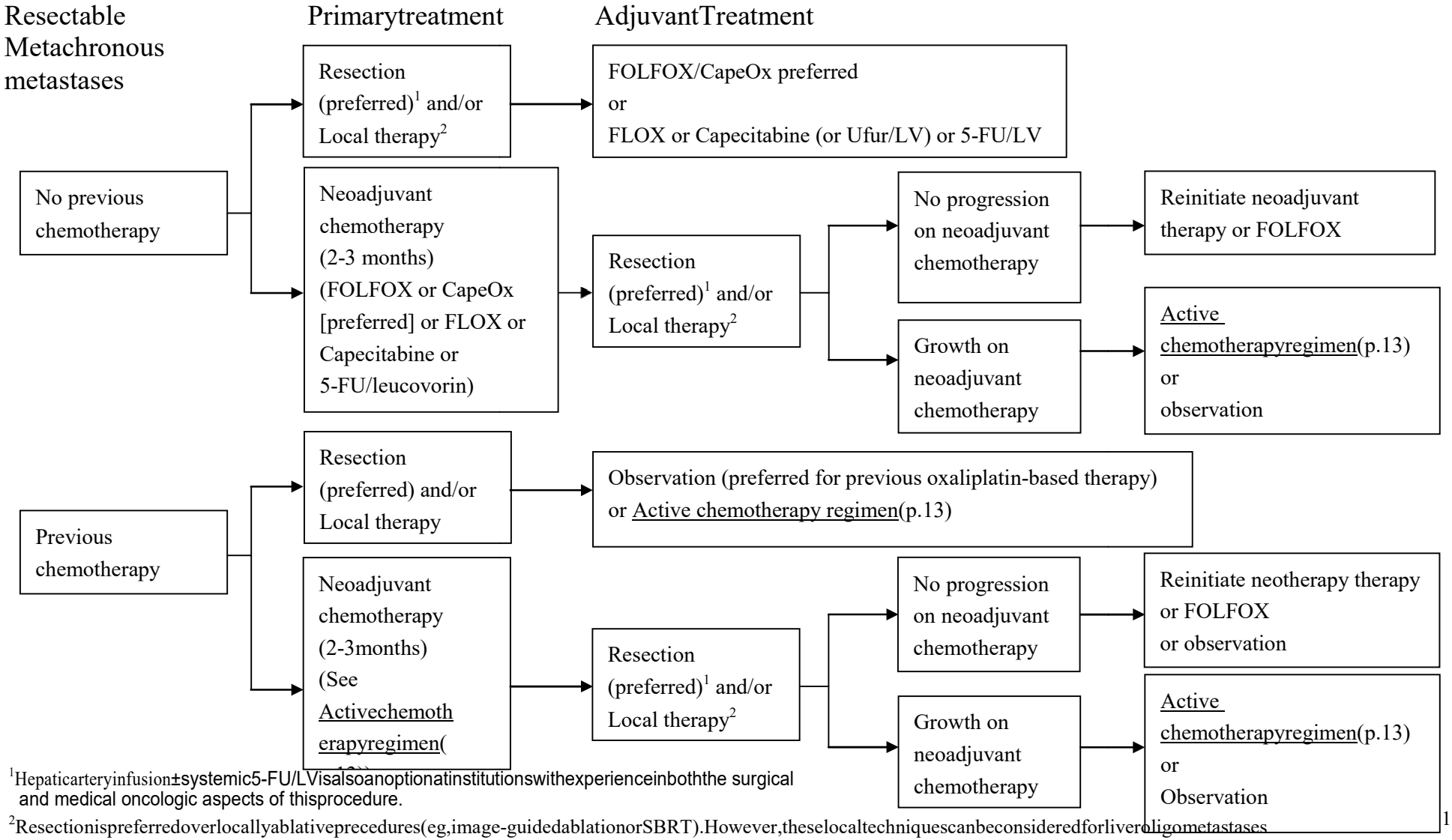
Chemotherapy for advanced or metastatic disease (4 of 4)



Recurrence and Workup



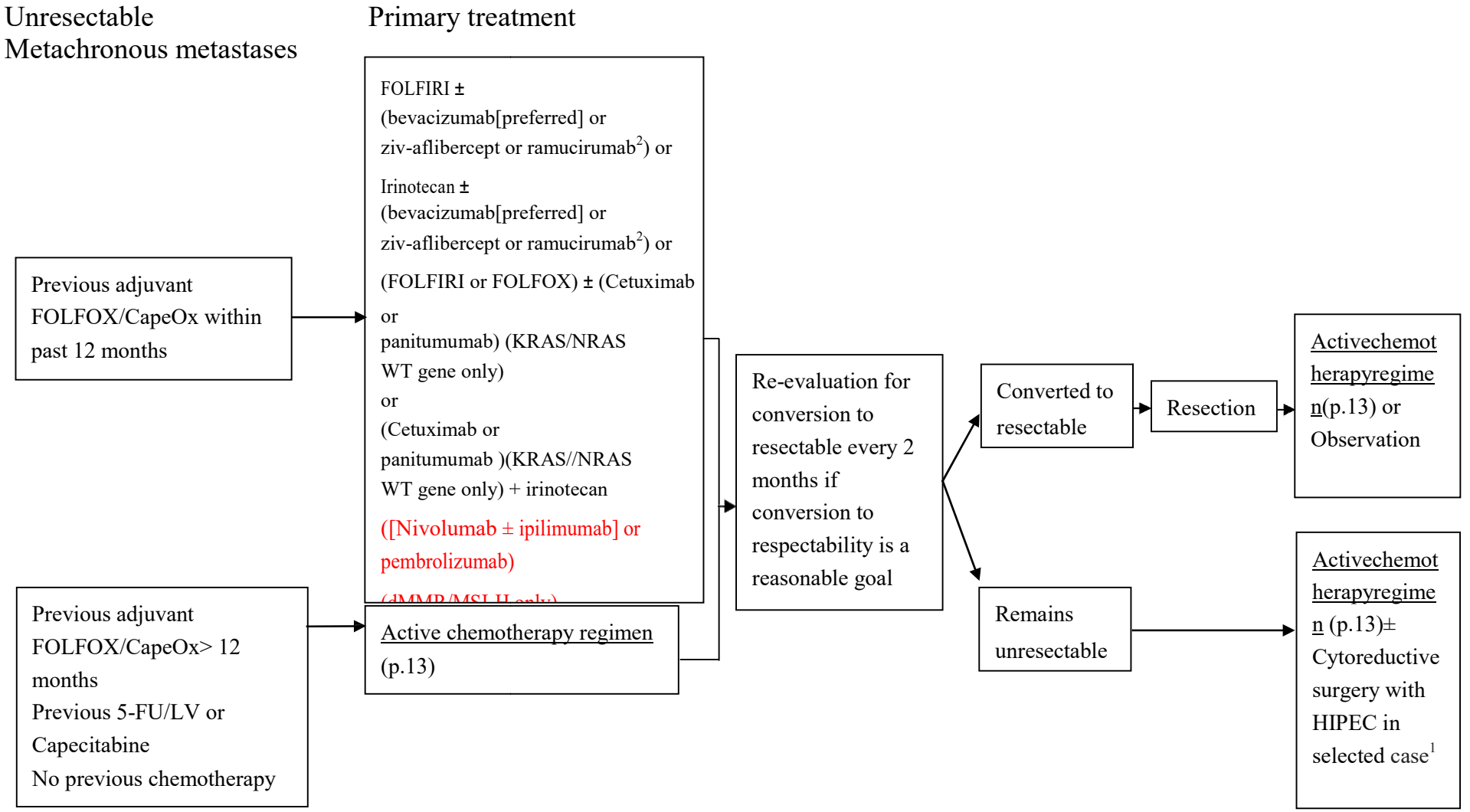
Resectablemetachronous metastases



[1]Hepaticarteryinfusion±systemic5-FU/LVisalsoanoptionatinstitutionswithexperienceinboththe surgical and medical oncologic aspects of thisprocedure.

[2]Resectionispreferredoverlocallyablativeprecedures(eg,image-guidedablationorSBRT).However,theselocaltechniquescanbeconsideredforliveroligometastases

Unresectable metachronous metastases



[1]See footnote “2” in Unresectable Synchronous Metastases or Medically Inoperable Treatment

[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 Irinotecanor oxaliplatin base regimens at the 1st line & the 3rd line treatment

Panitumumab combine with Irinotecanor oxalipatin 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)

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)

<table>
<tr><th>Bolus or infusional 5-FU/leucovorin</th><th>Irinotecan based</th></tr>
<tr><td>Roswell Park regimen</td><td>IROX</td></tr>
<tr><td>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</td><td>Oxaliplatin 85 mg/m^2 IV over 2 hours, followed by irinotecan 200 mg/m2 over 30-90 minutes every 3 weeks</td></tr>
<tr><td>Simplified biweekly infusional 5-FU/LV (sLV5FU2)</td><td>Irinotecan (may add with Cetuximab)</td></tr>
<tr><td>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><td rowspan="4">Irinotecan 125 mg/m^2 IV over 30-90 minutes, days 1 and 8
Repeat every 3weeks
or Irinotecan 180 mg/m^2 IV over 30-90 minutes, day1
Repeat every 2weeks
or Irinotecan 300-350 mg/m^{2}IV over 30-90 minutes, day 1
Repeat every 3weeks</td></tr>
<tr><td>Weekly</td></tr>
<tr><td>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 (<u>AIO regimen</u>[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)</td><td>Capecitabine (may add with Bevacizumab)</td></tr>
<tr><td>850–1250 mg/m^2 PO twice daily, days 1–14
Repeat every 3 weeks</td></tr>
<tr><td>Mayo Clinic regimen[4]</td><td>Ufur/LV[1]</td></tr>
<tr><td>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</td><td>Leucovorin 20-30 mg/m^2 + Ufur 300-500 mg/ m^2 PO at day 1 to 28 in every 35 days</td></tr>
</table>

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

Modified regimen for CRS@VGHKS	**IO**
modified mFOLFOX	*Nivolumab + ipilimumab*
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	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.
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)

mFOLFOX6[3]	**5-FU/leucovorin**
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 2weeks	*Rosewell Park regimen (?)* 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
FLOX[2]	*Simplified biweekly infusional 5-FU/LV (sLV5FU2)*
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 **Capecitabine** 1250 mg/m^2 PO twice daily, days 1–14 every 3 weeks x 24 wks	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
CapeOX	*AIO regimen*[4]
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	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
Ufur/LV[1]	*Mayo Clinic regimen*[4]
Leucovorin 20-30 mg/m^2 + Ufur 300-500 mg/ m^2 PO at day 1 to 28 in every 35 days	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

[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

Regimens for Concurrent Chemotherapy/RT

XRT + continuous infusional 5-FU
5-FU 225 mg/m^2 over 24hours 5 or 7 days/weekduringXRT
XRT + 5-FU/leucovorin
5-FU 400 mg/m^2 IV bolus + leucovorin 20 mg/m^{2}IVbolus for4 days during week 1 and 5 of XRT
XRT + Capecitabine
Capecitabine 825 mg/m^2 twice daily5 days/week+XRT x5 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 oflamina propria[a]
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3[1]	Tumor invades through the muscularis propria into the pericolorectal
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)[2]	
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

[1]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

[2]Sampling of 12 lymph nodes may not be achievable in patients that received preoperative chemotherapy.

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

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 adverseeffects(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 CooperativeOncologyGroup(ECOG)PerformanceStatus≧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 Version1.2021
2. ESMO Clinical Practice Guidelines 2014: Gastrointestinal cancers -- section: Metastatic Colorectal Cancer, Early Colon Cancer, Rectal Cancerand AnalCancer
3. NHI regulations for CRCchemotherapy
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. 2002Mar;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.*
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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