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直　　腸　　癌　　診　　療　　指　　引

大腸直腸癌醫療團隊 制定

2022年 6月修訂

Kaohsiung Veterans General Hospital

Rectal Cancer Clinical Practice Guidelines

Colorectal Cancer Multidisciplinary Team

June 2022*version 1*

Rectal Cancer Clinical Practice Guidelines

Content

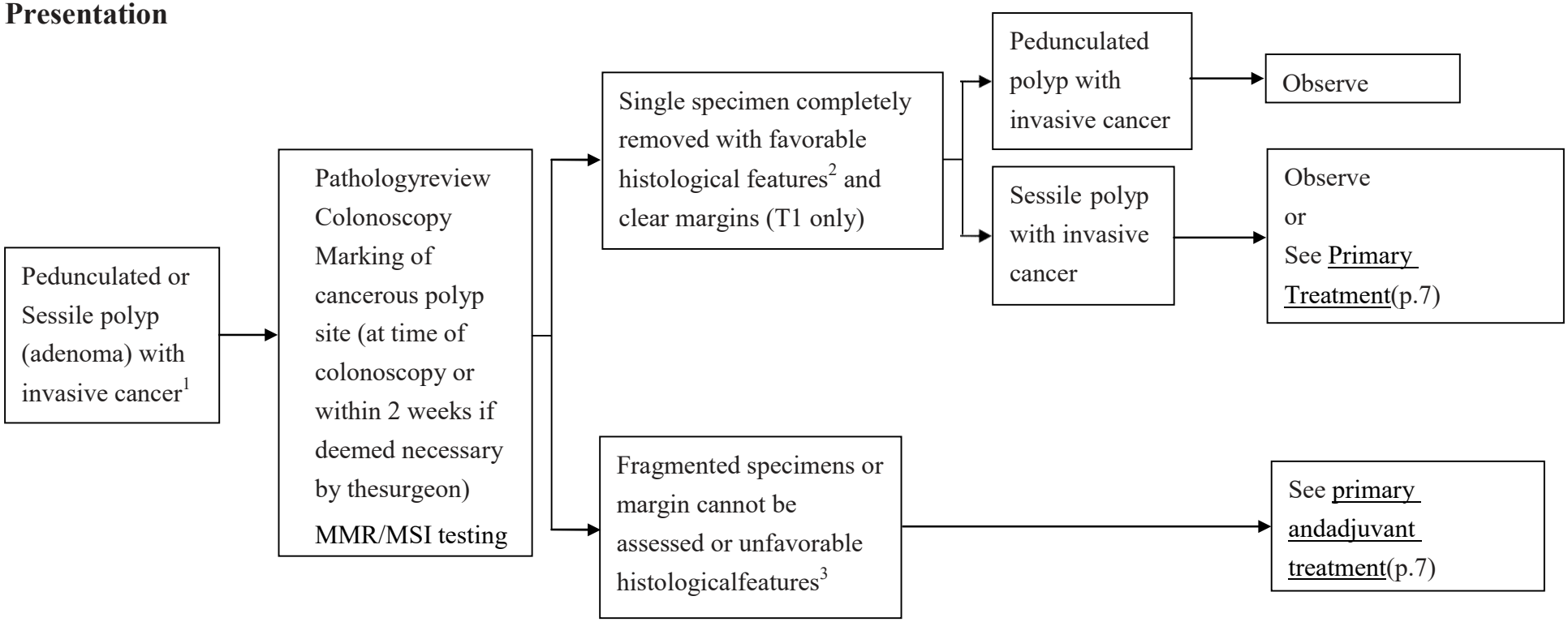
<Revision Summary>

Updatesin Version 1 2022 of the VGHKS ColonCancer Clinical Practice Guidelines from Version 1 2021 include:

FOLFOXIRI replaced with FOLFIRINOX

Total Neoadjuvant Therapy specified as preferred
FOLFOX or CAPEOX: 12 – 16 wk added

Malignant polyp

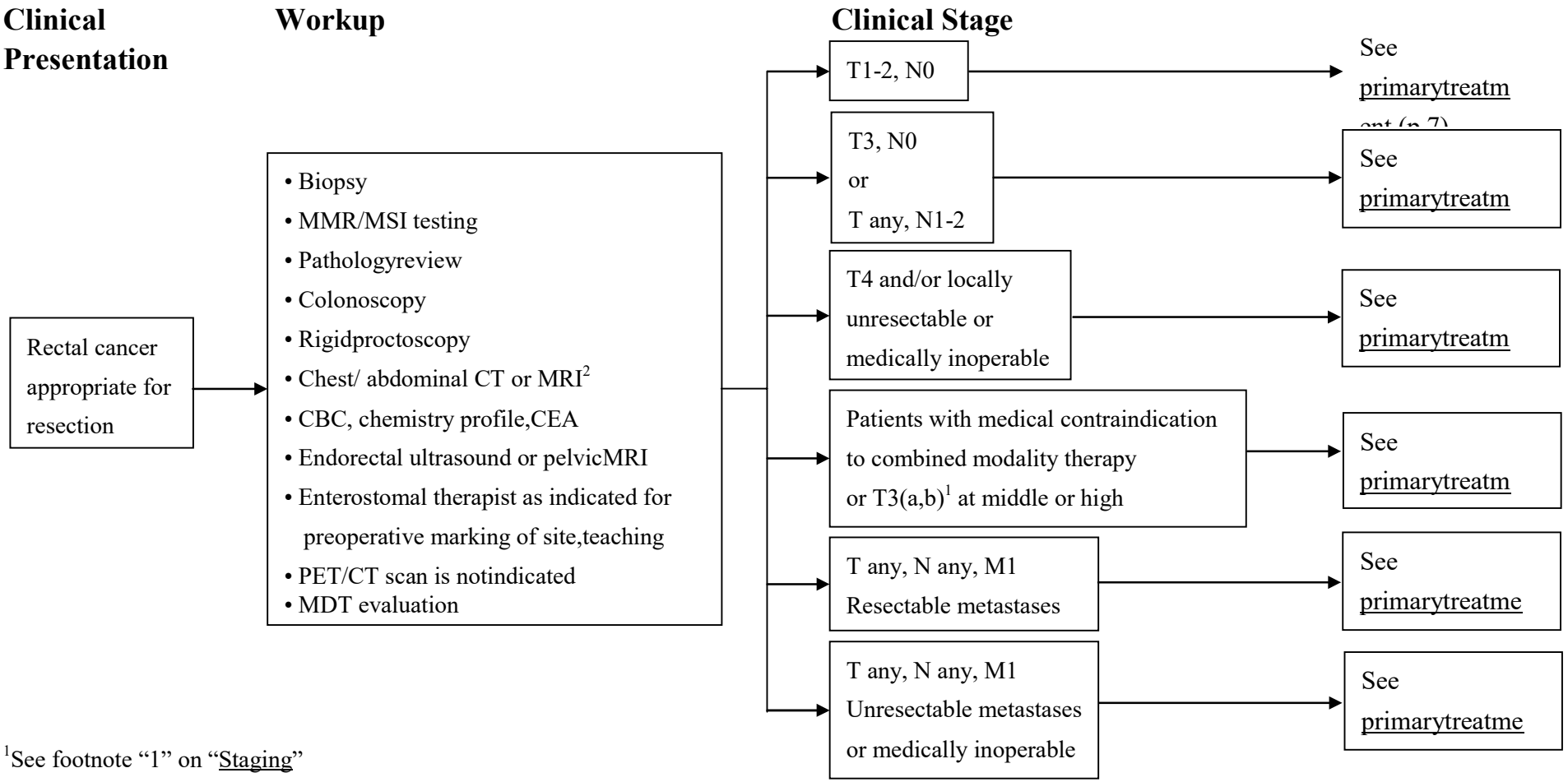


[1]A malignant polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1). pTis is not considered a "malignant polyp".

[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)

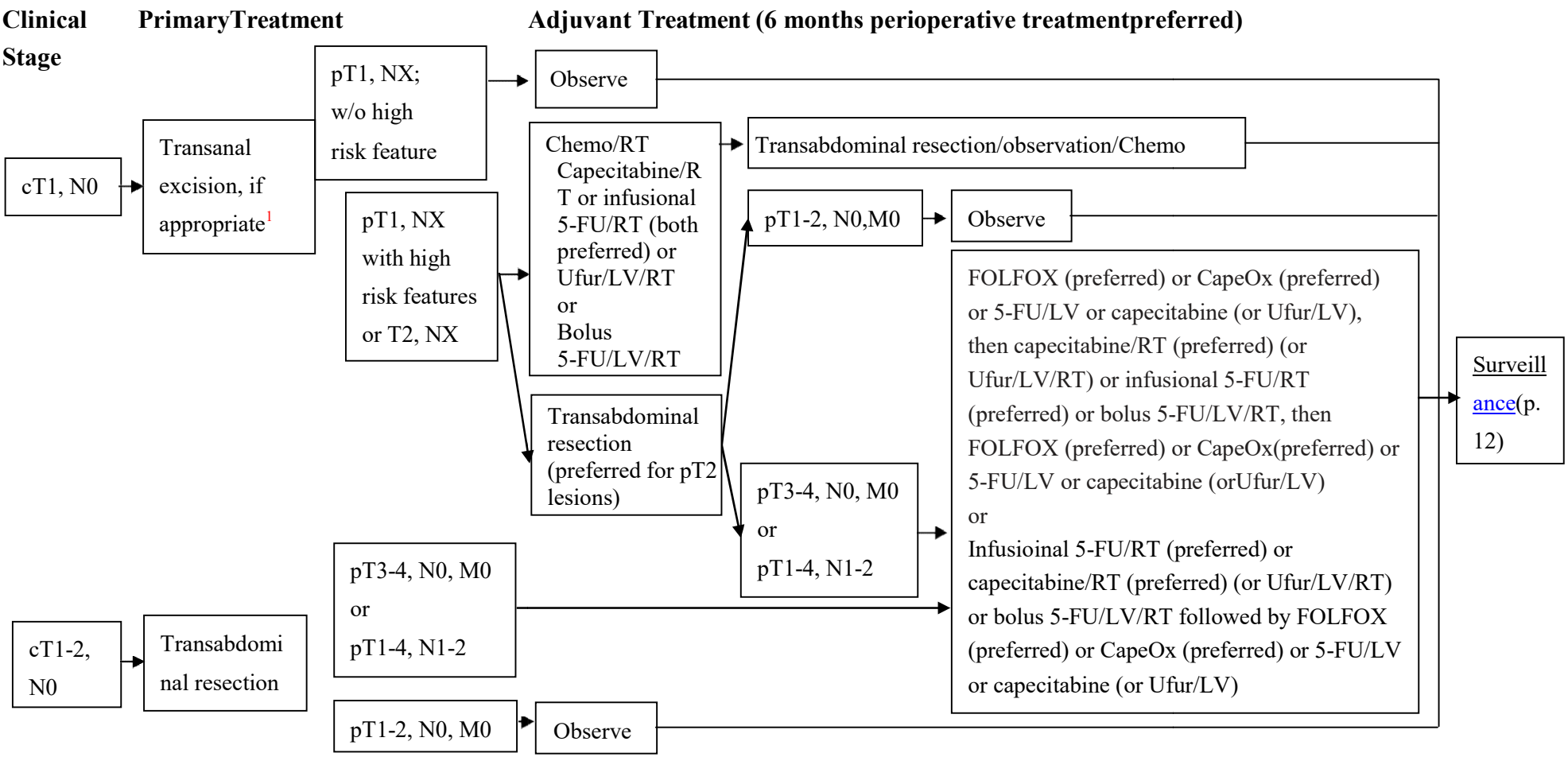
Resectable Primary Rectal Cancer



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

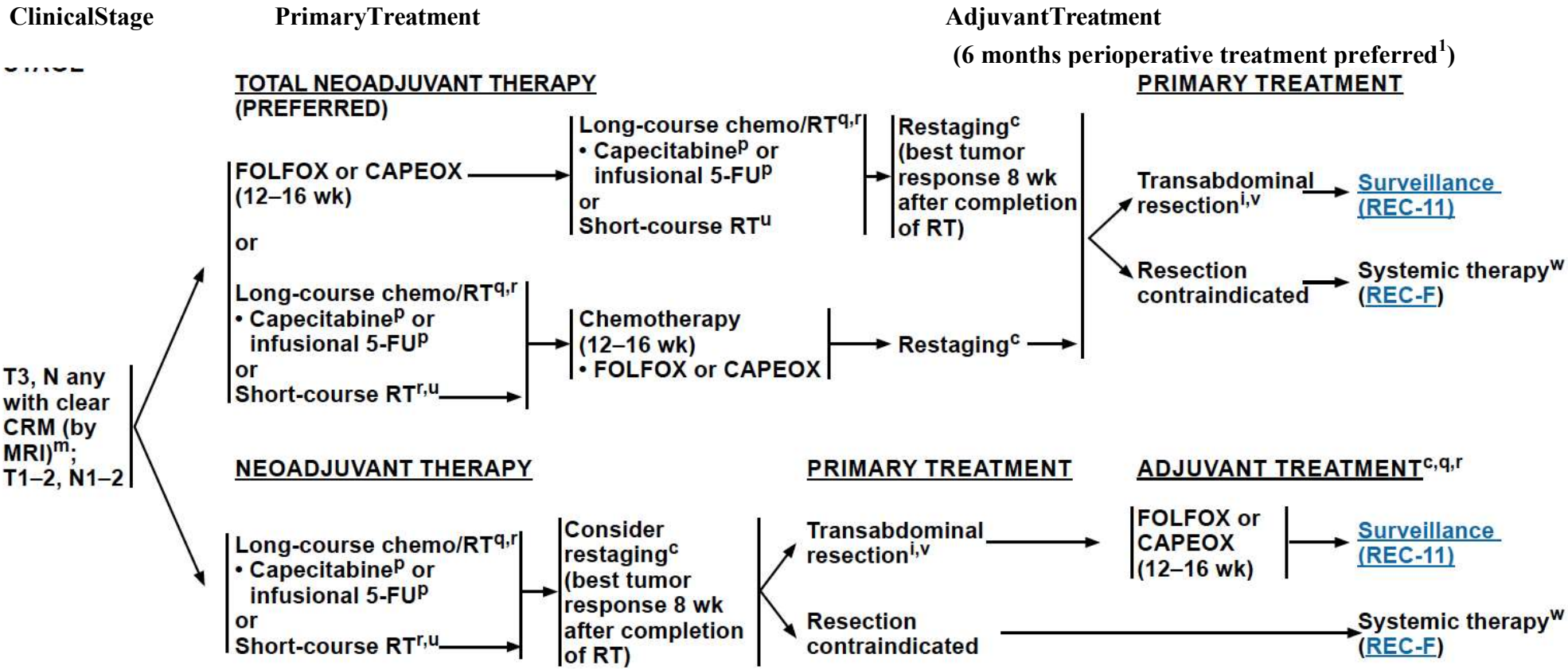
[2]CT should be with IV and oral contrast. Consider abd/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.

Adjuvant Therapy for Stage I Rectal Cancer



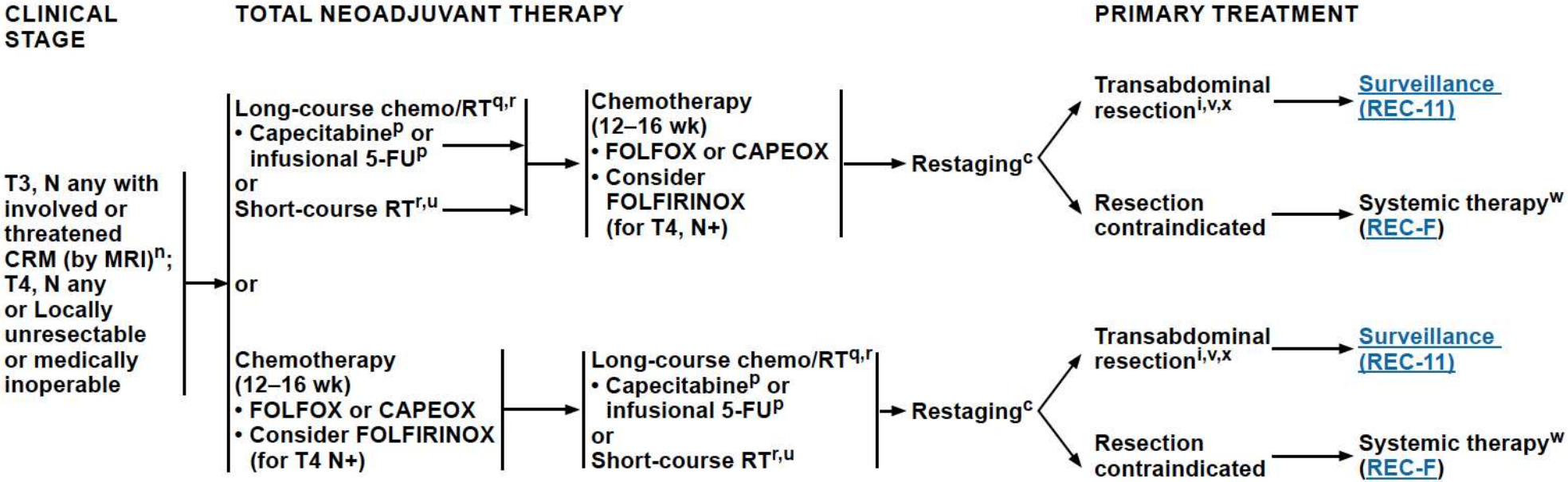
[1]Unfavorable histopathologic features:>3cm in size, T1, with grade III, lymphovascular invasion, positive margin, or sm3 depth of tumor invasion.(positive margins, lymphovascular invasion, poorly differentiated tumors, or sm3 invasion)

Adjuvant Therapy for cT3 or Stage III Rectal Cancer

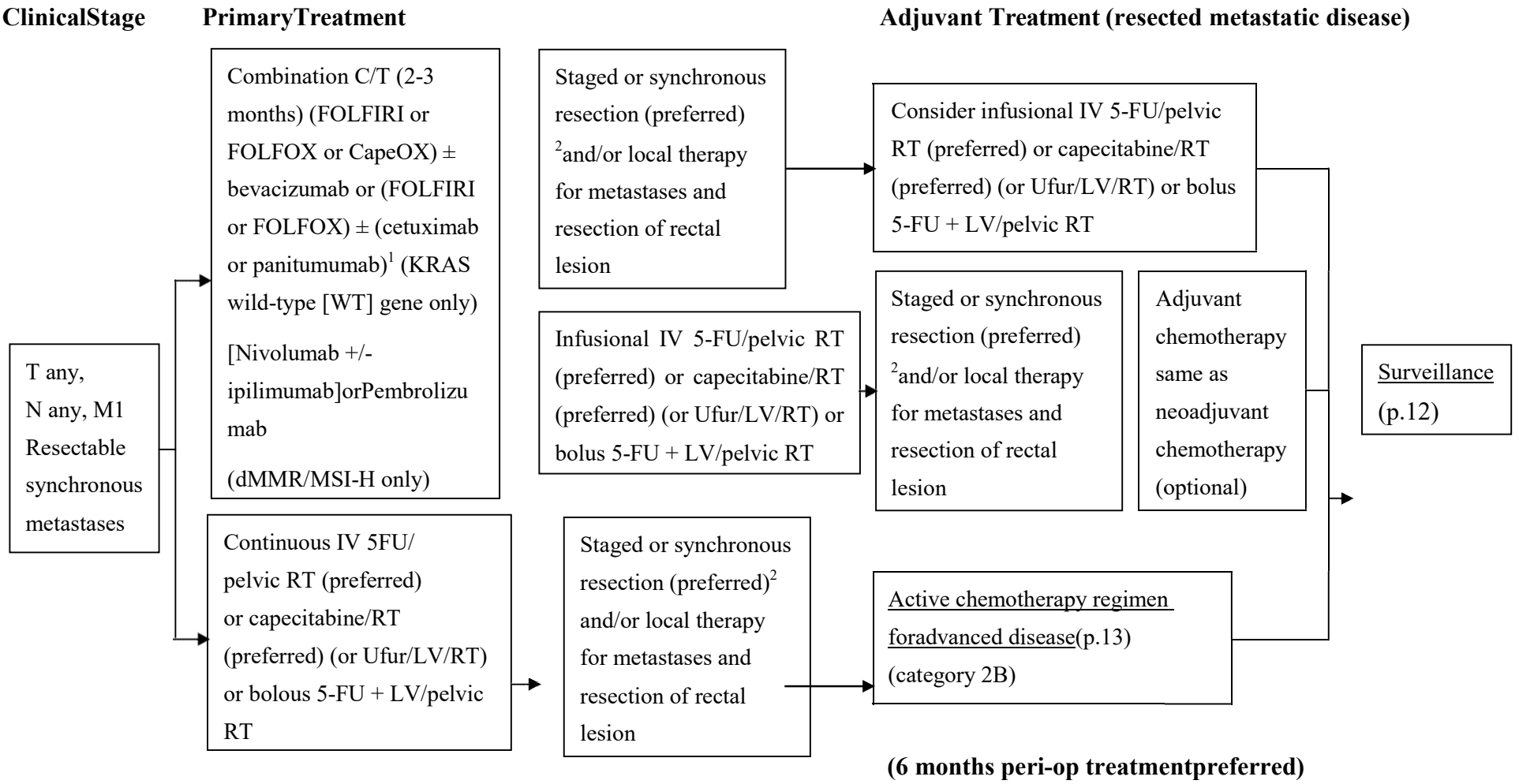


Adjuvant Therapy for Locally Advanced or Medical Inoperable Rectal Cancer

ClinicalStage **Neo-adjuvant Therapy** **PrimaryTreatment**



Resectable Synchronous Metastases

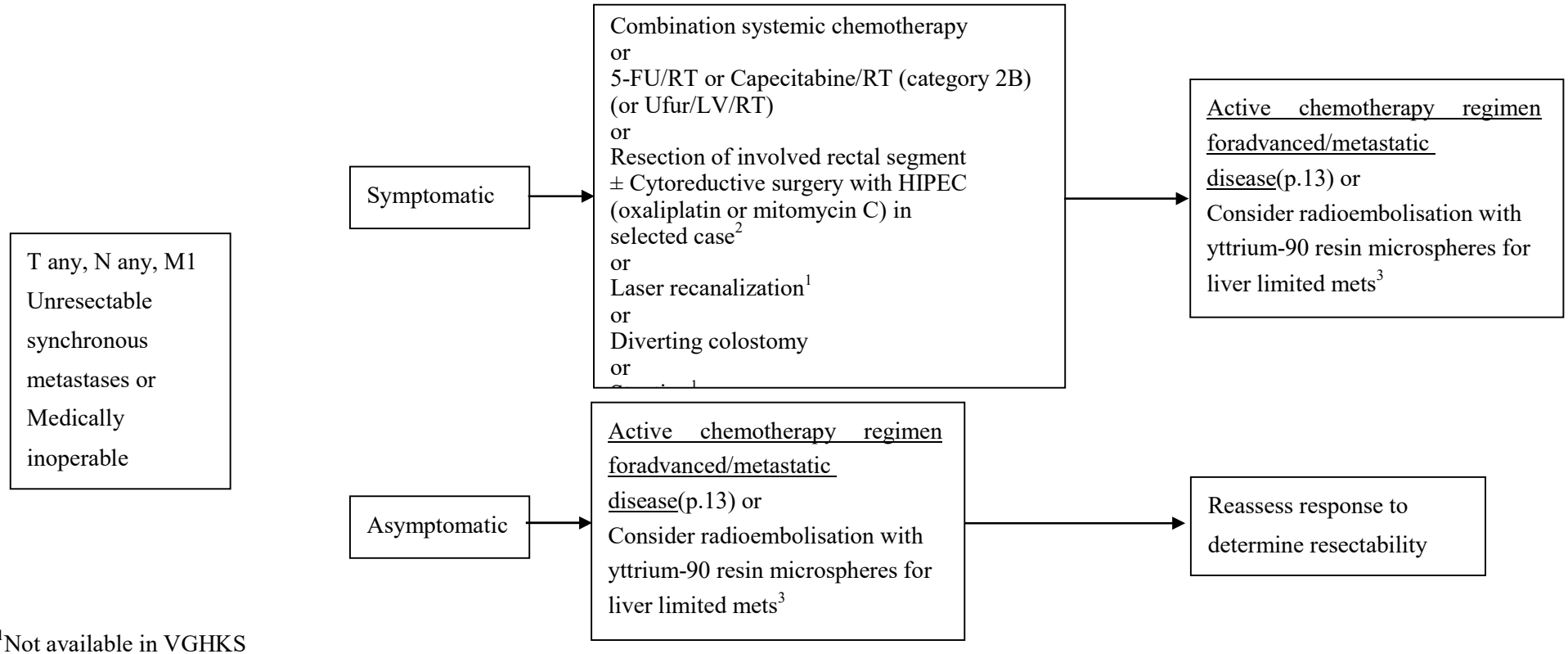


[1]There are conflicting data regarding the use of FOLFOX + cetuximab in patients who have potentially resectable liver metastases.

[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**

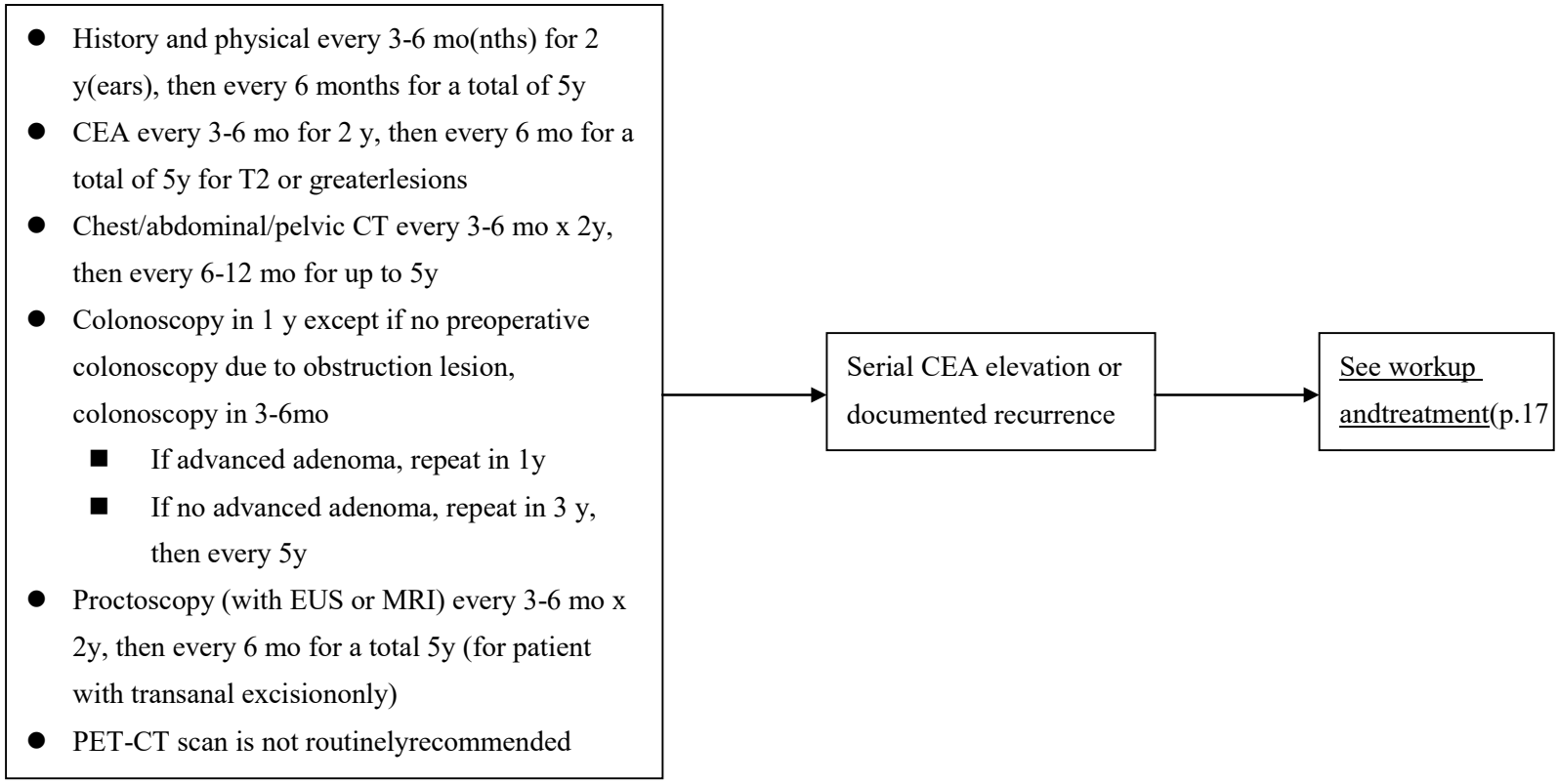


[1]Not available in VGHKS

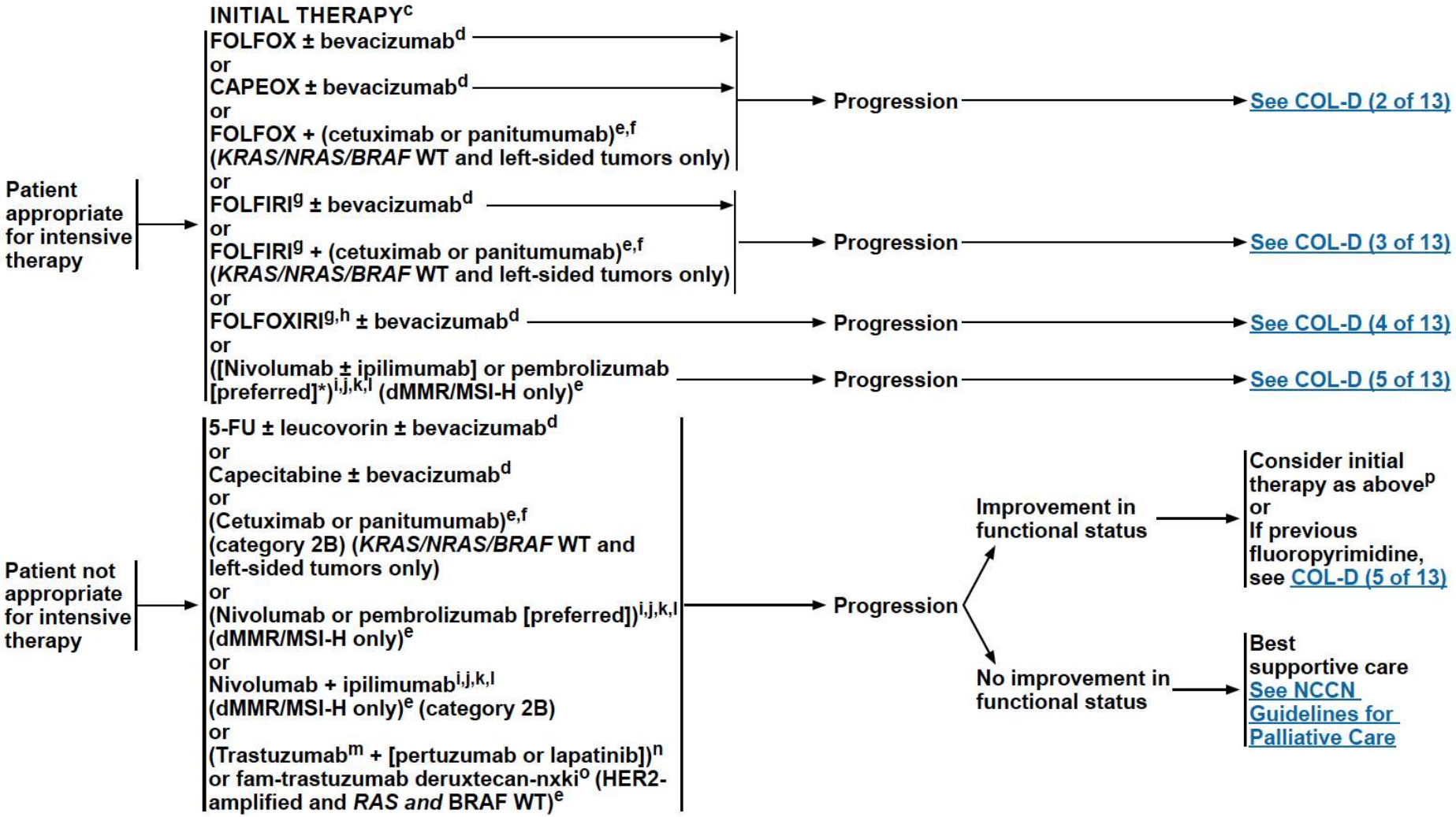
[2]HIPEC = Hyperthermic Intraperitoneal Chemotherapy; Not documented in NCCN guideline 2015 v2 but in ESMO guideline 2014(evidence grade IVB). Also refer to Reference [7], [8]

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

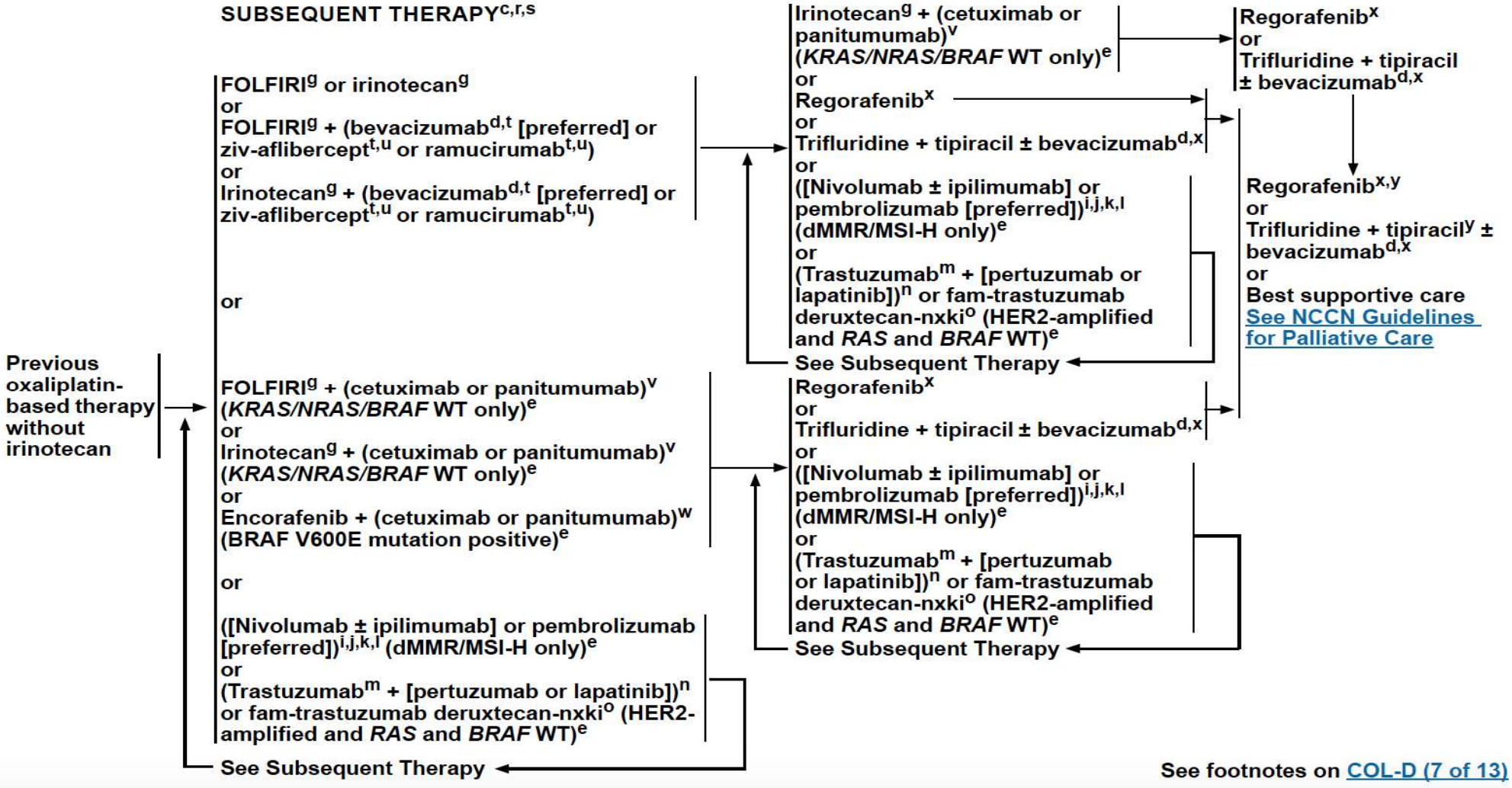
Surveillance



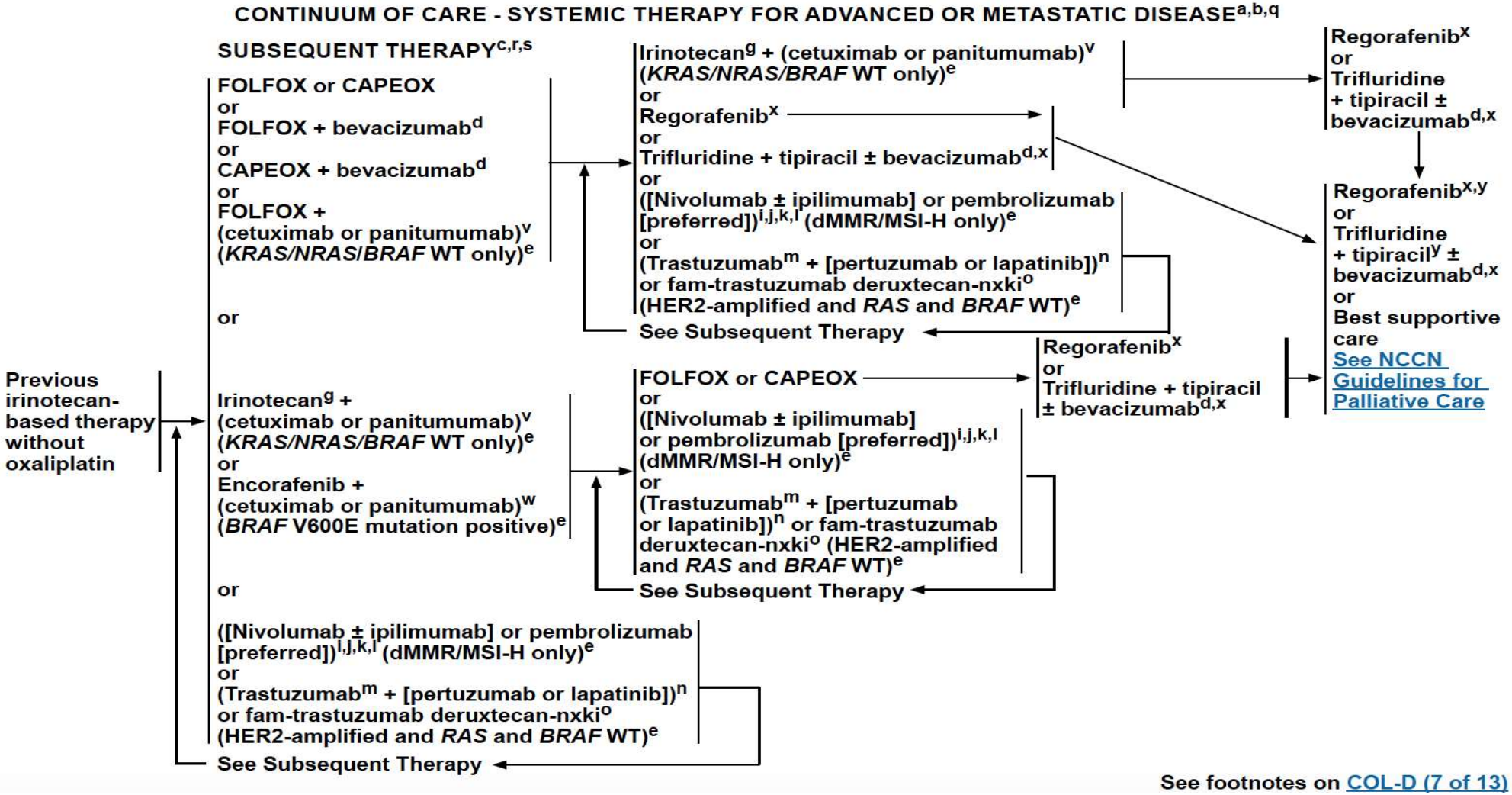
Chmotherapy for advanced or metastastic disease (1 of 4)



Chemotherapy for advanced or metastastic disease (2 of 4)

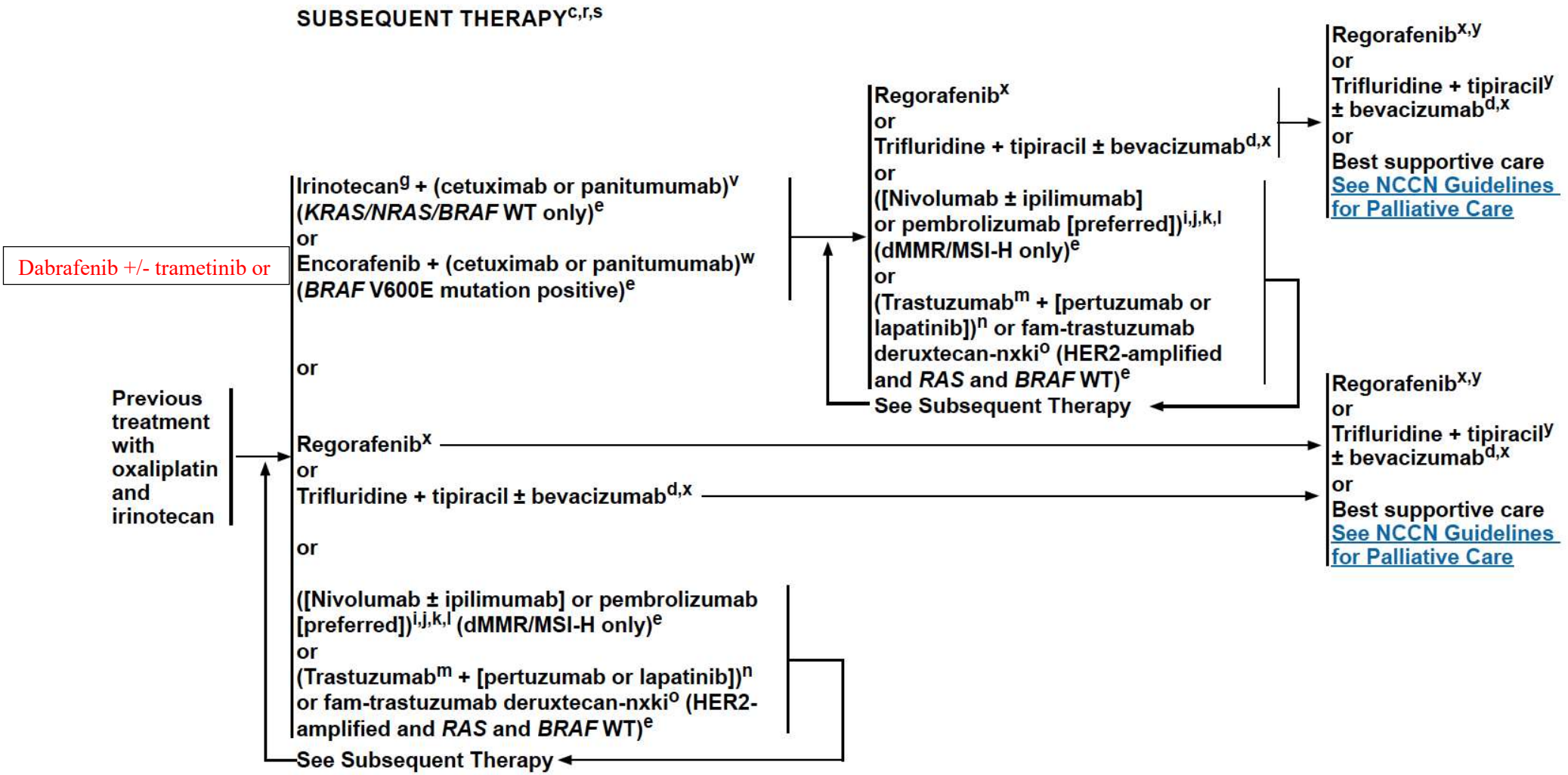


Chemotherapy for advanced or metastatic disease (3 of 4)

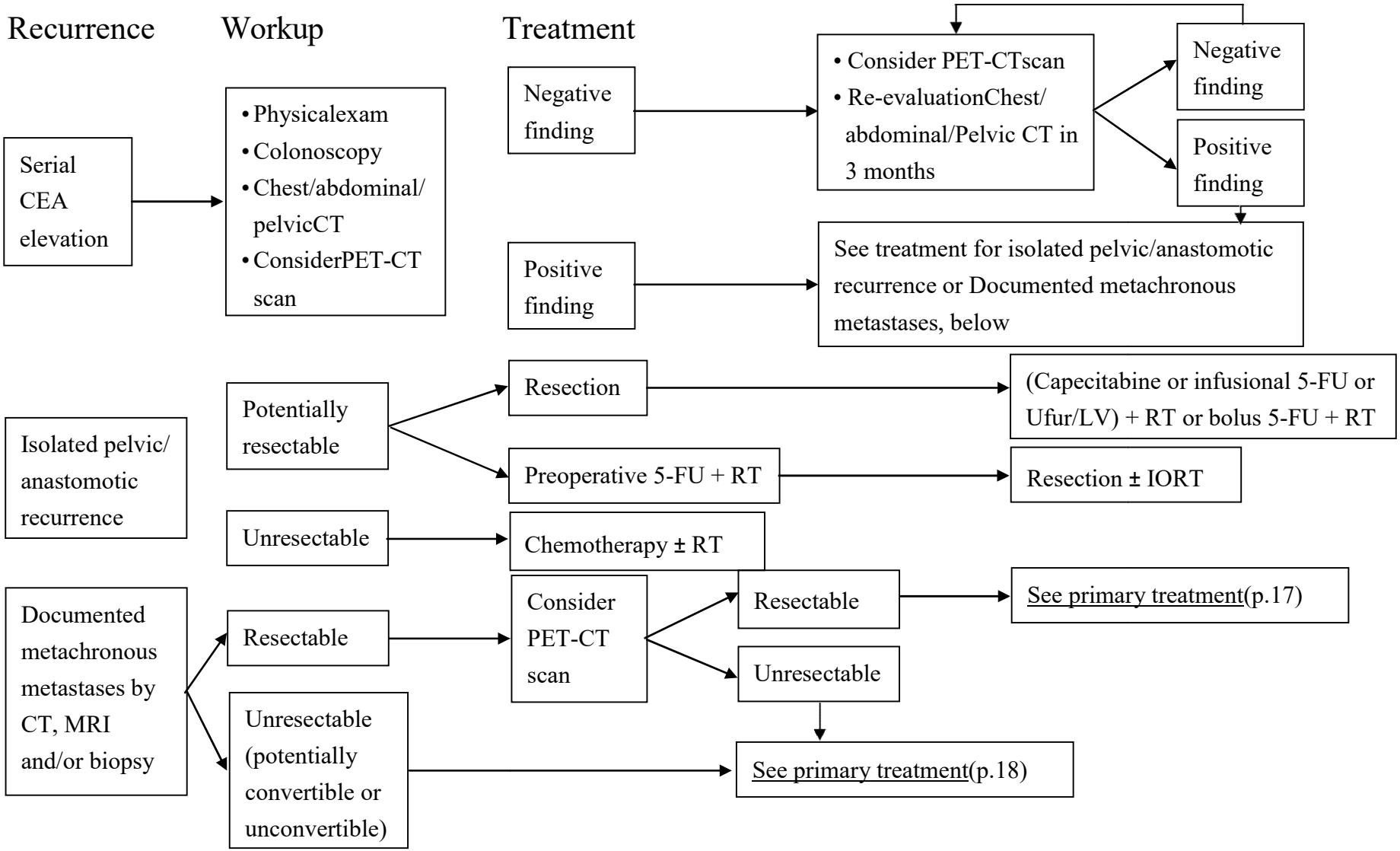


See footnotes on COL-D (7 of 13)

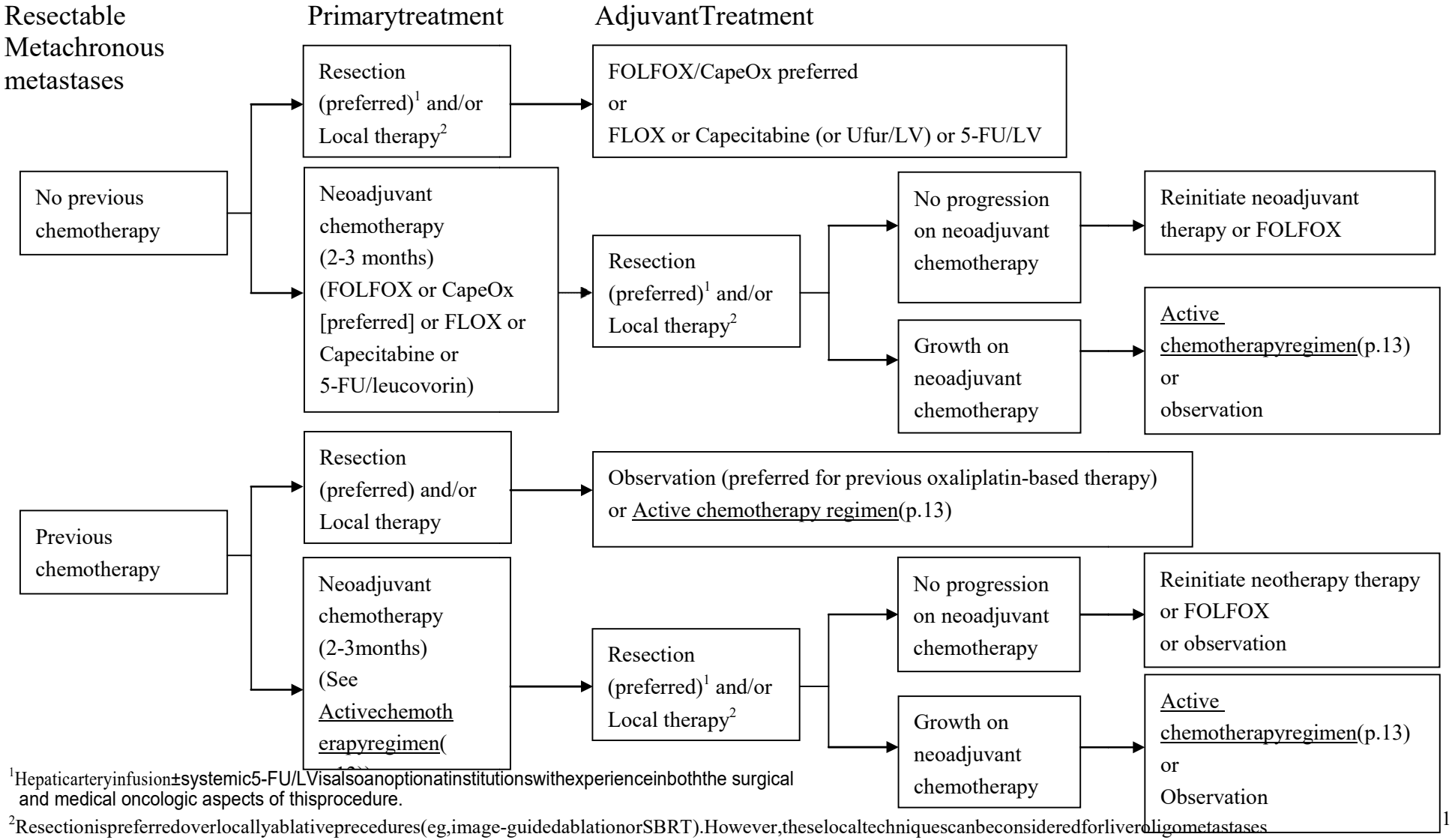
Chemotherapy for advanced or metastatic disease (4 of 4)



Recurrence and Workup



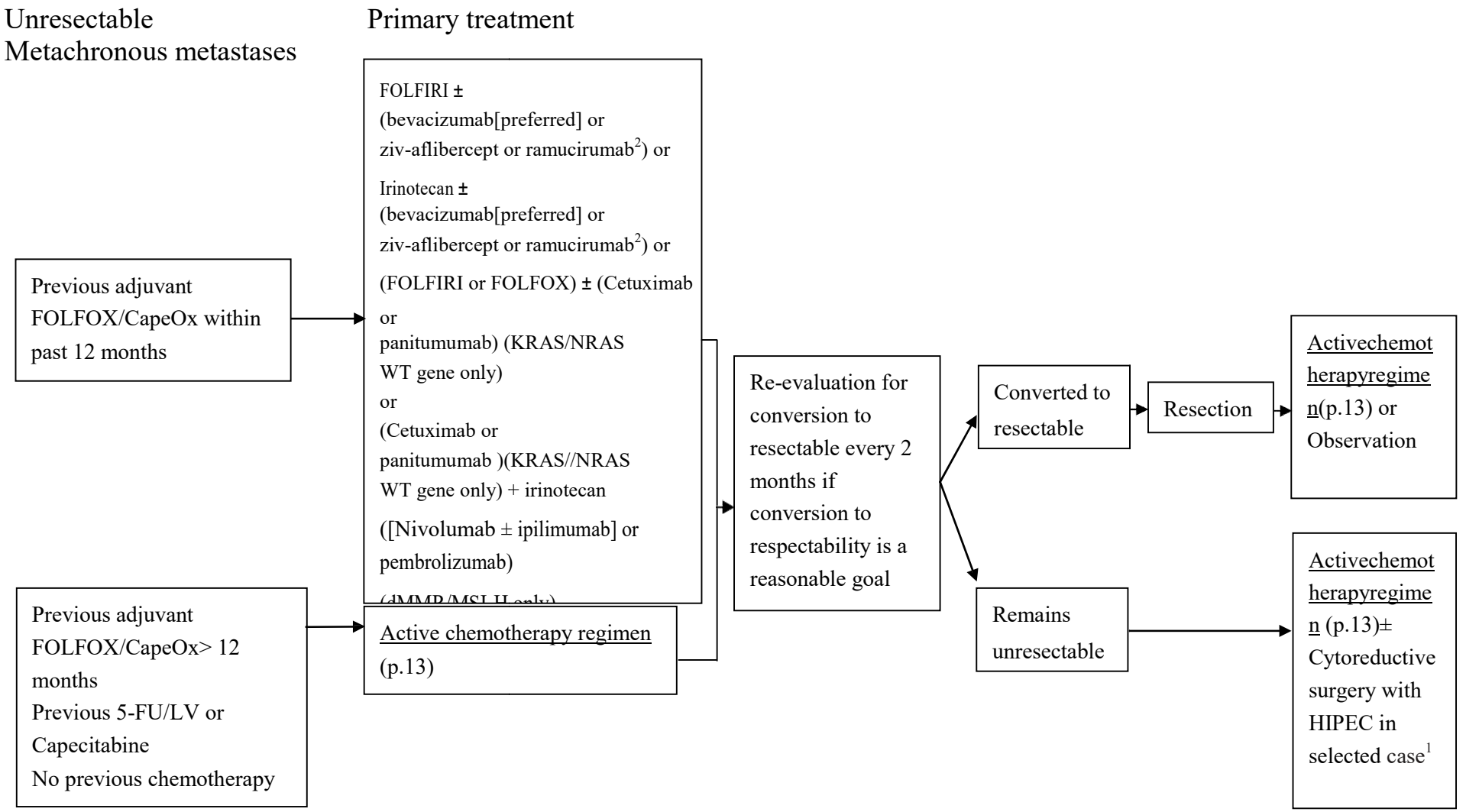
Resectablemetachronous metastases



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

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

Unresectable metachronous metastases



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 Irinotecan or 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

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.*
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, ColangeloLH, 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 ChemohyperthermiaWith Oxaliplatin for Peritoneal Carcinomatosis of Colorectal Origin, *J Clin Oncol* 27:681-685.2008
8. *Vic J. Verwaalet 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^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