

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 2017 of the VGHKS rectal Cancer Clinical Practice Guidelines from Version 1 2016 include:

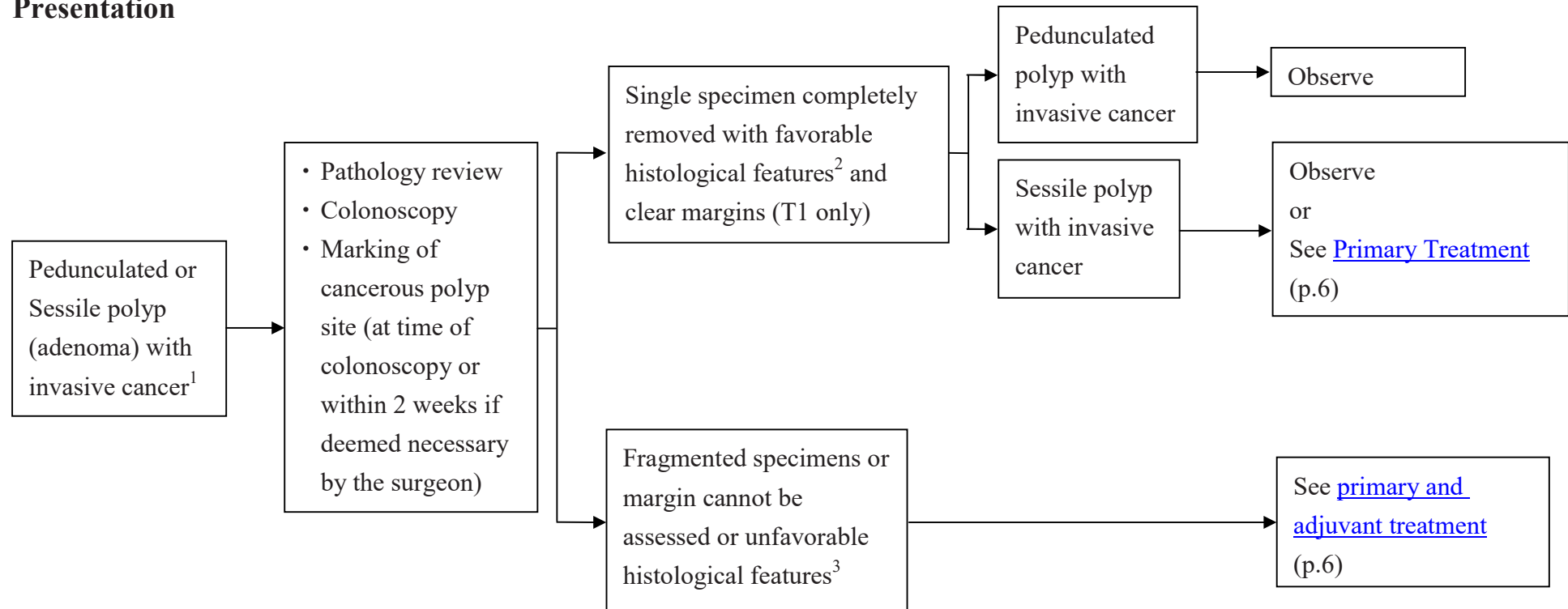
Version 2016	Version 2017
Adjuvant Therapy for T3-4 or Stage III Rectal Cancer (p.7)	Adjuvant Therapy for T3-4 or Stage III Rectal Cancer (p.7): a) Column 4, add “± followed by UFUR/LV(1-2 yrs) ³ ” behind the preferred treatment b) Add footnote 3: Based on Reference [11]
Chemotherapy for Advanced or 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 5 th column in topic 1 of 4, 2 of 4 and 3 of 4 b) Add footnote 4: “Based on Reference [13, 14]”
Principle of Chemotherapy (p.19)	Principle of Chemotherapy (p.19): Add “癌症藥物考慮停藥準則” and adjust font type
Reference (p.28-29)	Reference (p.28-29): Add reference [11], [12], [13] and [14]
	Revise page numbers

Malignant polyp

Clinical Presentation

Workup

Findings



¹A 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”.

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

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

Resectable Primary Rectal Cancer

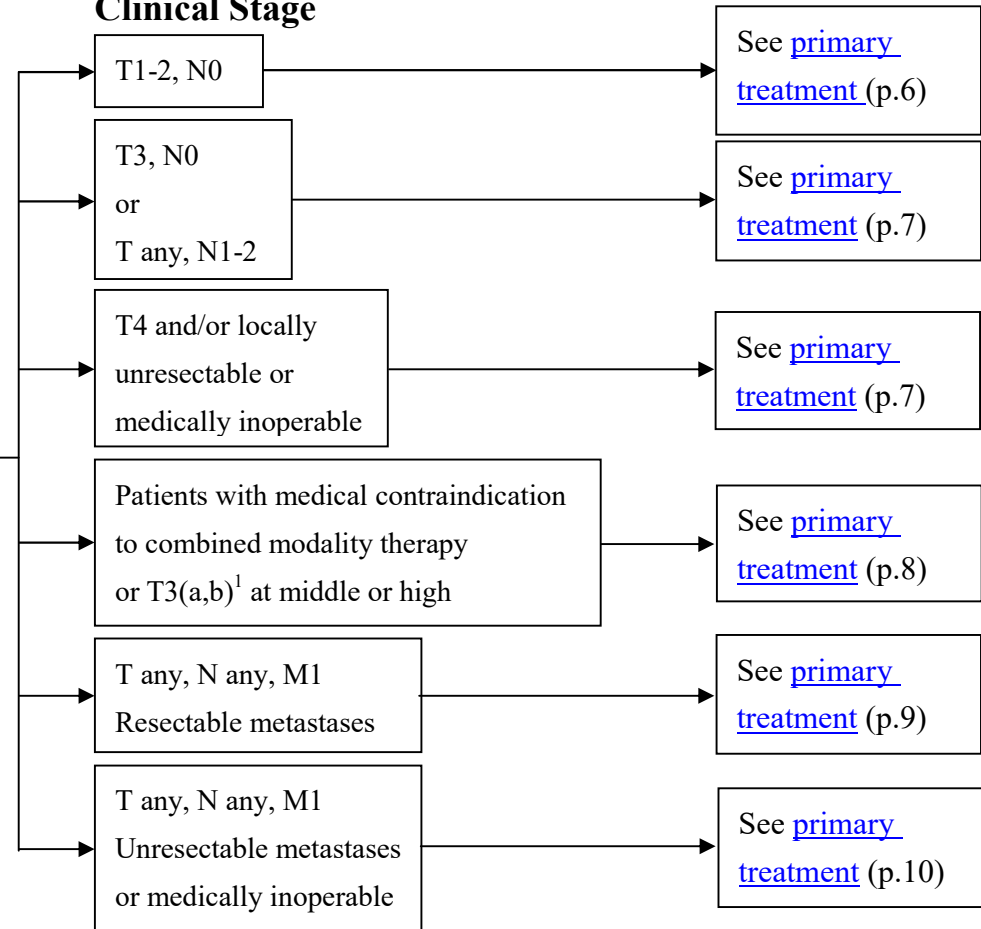
Clinical Presentation

Rectal cancer appropriate for resection

Workup

- Biopsy
- CXR
- Pathology review
- Colonoscopy
- Rigid proctoscopy
- Chest/abdominal/pelvic CT²
- CEA
- Endorectal ultrasound or pelvic MRI
- Enterostomal therapist as indicated for preoperative marking of site, teaching
- PET-CT scan is not routinely indicated

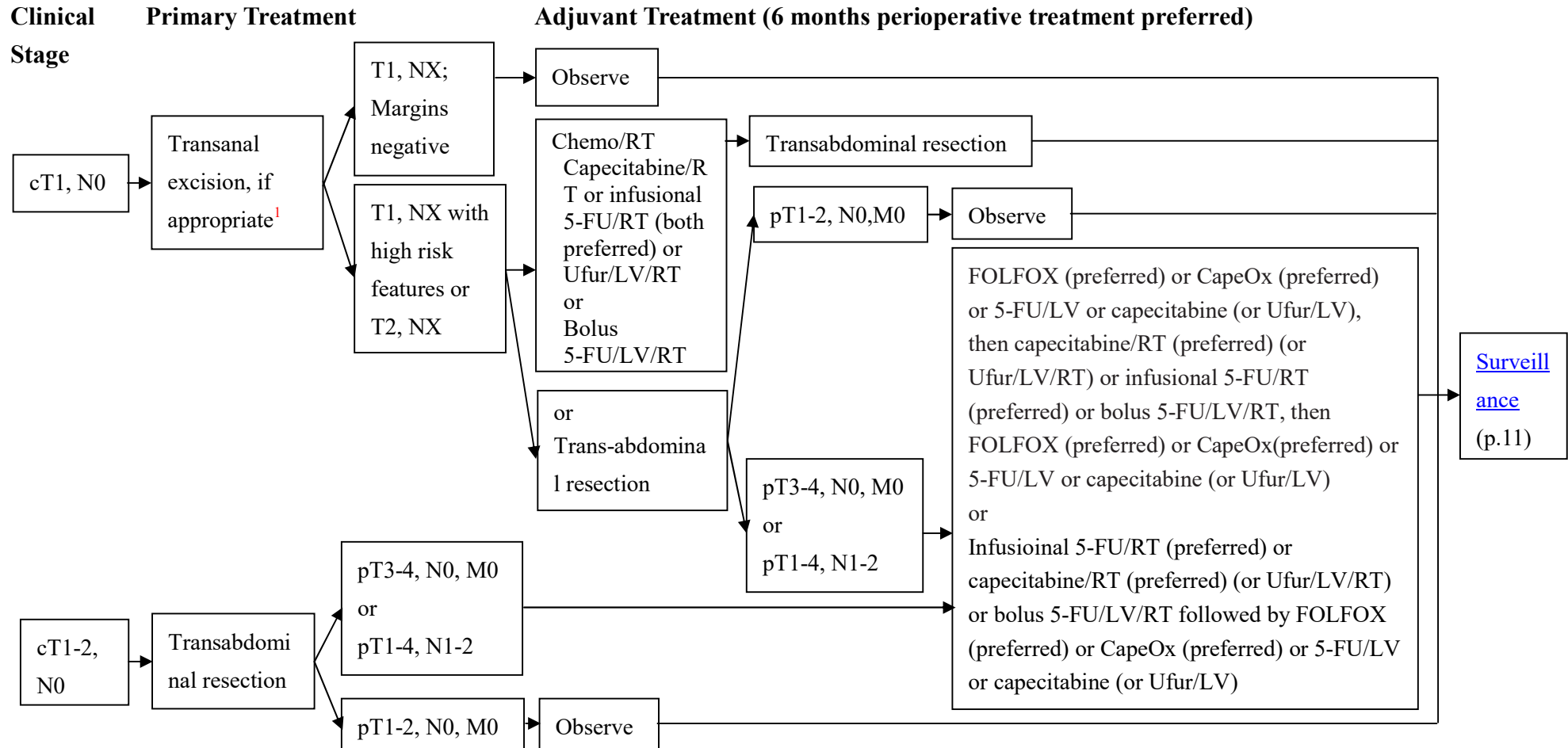
Clinical Stage



¹See footnote “1” on “[Staging](#)”

²CT 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.

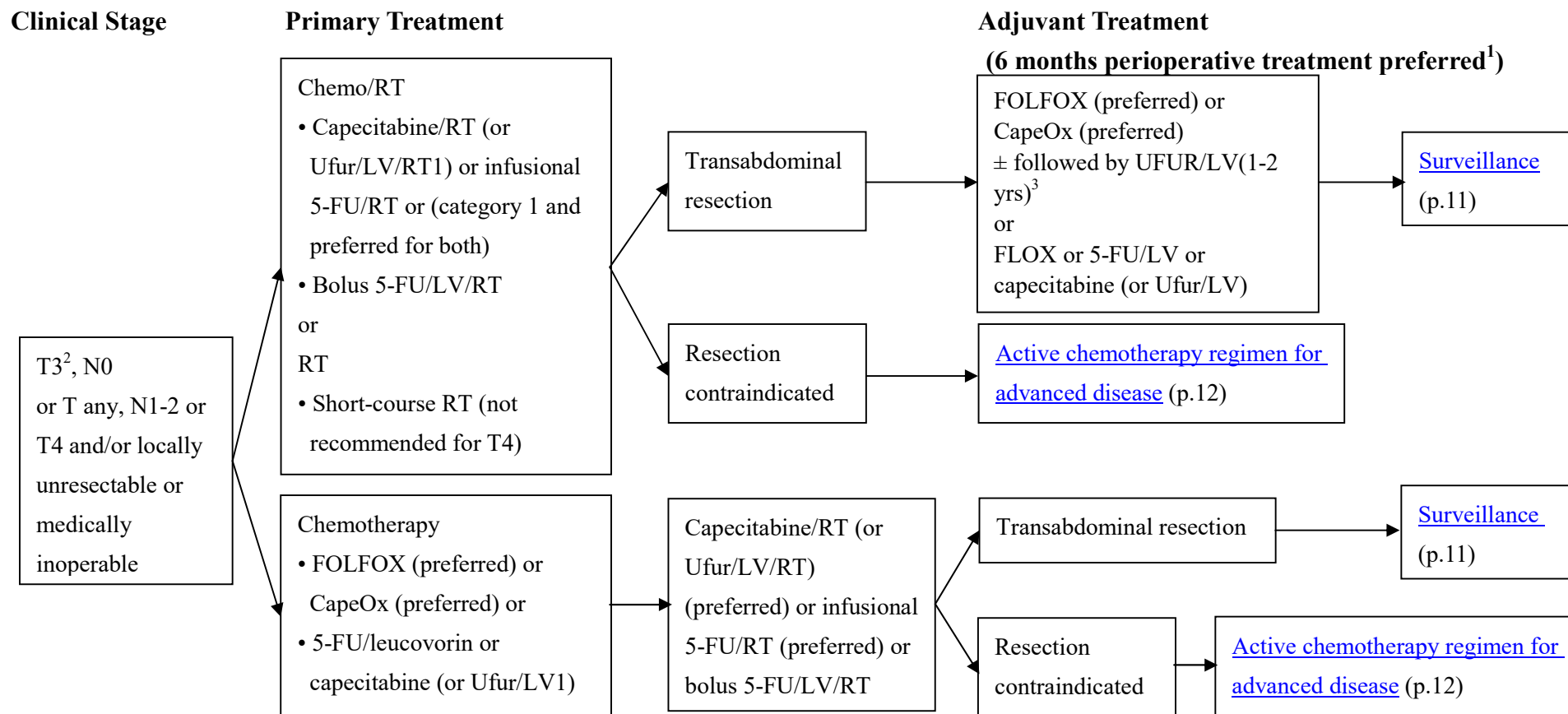
Adjuvant Therapy for Stage I Rectal Cancer



[Surveillance](#)
(p.11)

¹Unfavorable 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 Unresectable T3-4 or Stage III Rectal Cancer

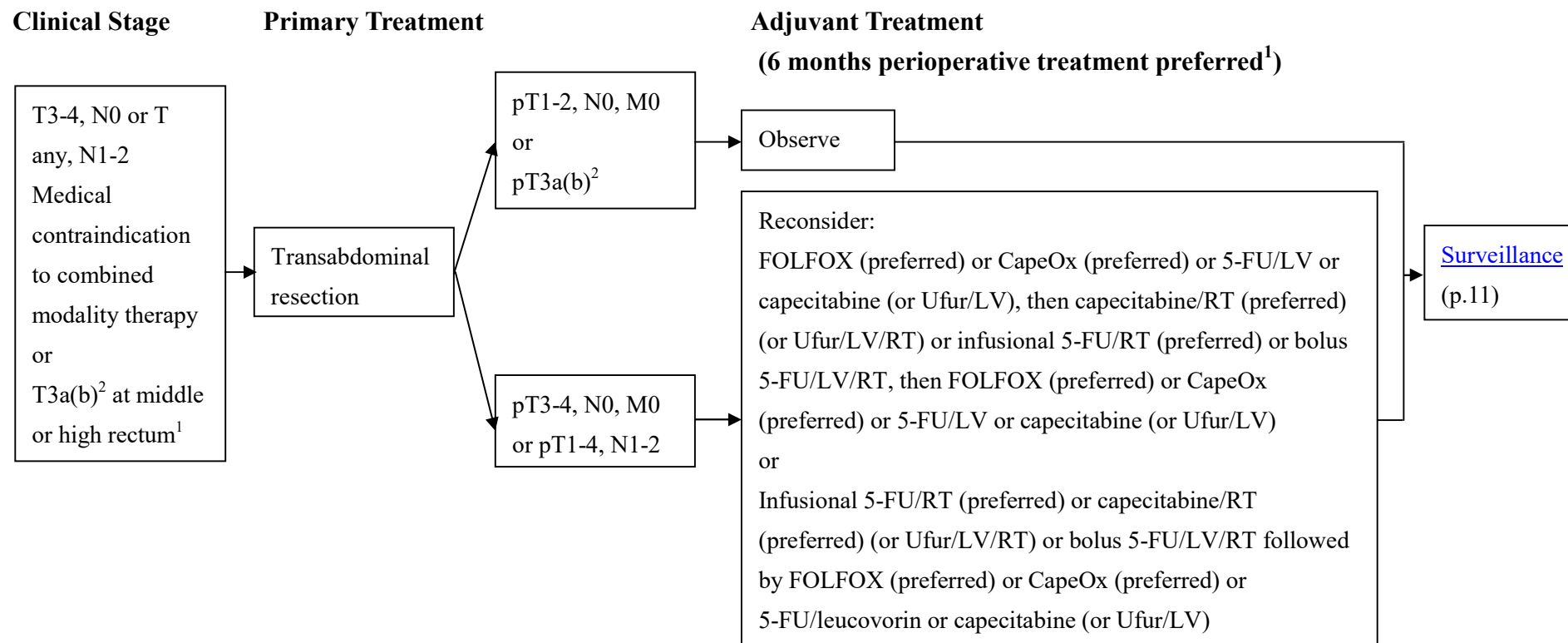


¹Total duration of perioperative chemotherapy, inclusive of chemotherapy and radiation therapy, should not exceed 6 months.

²Unless 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](#)

³Based on Reference [11]

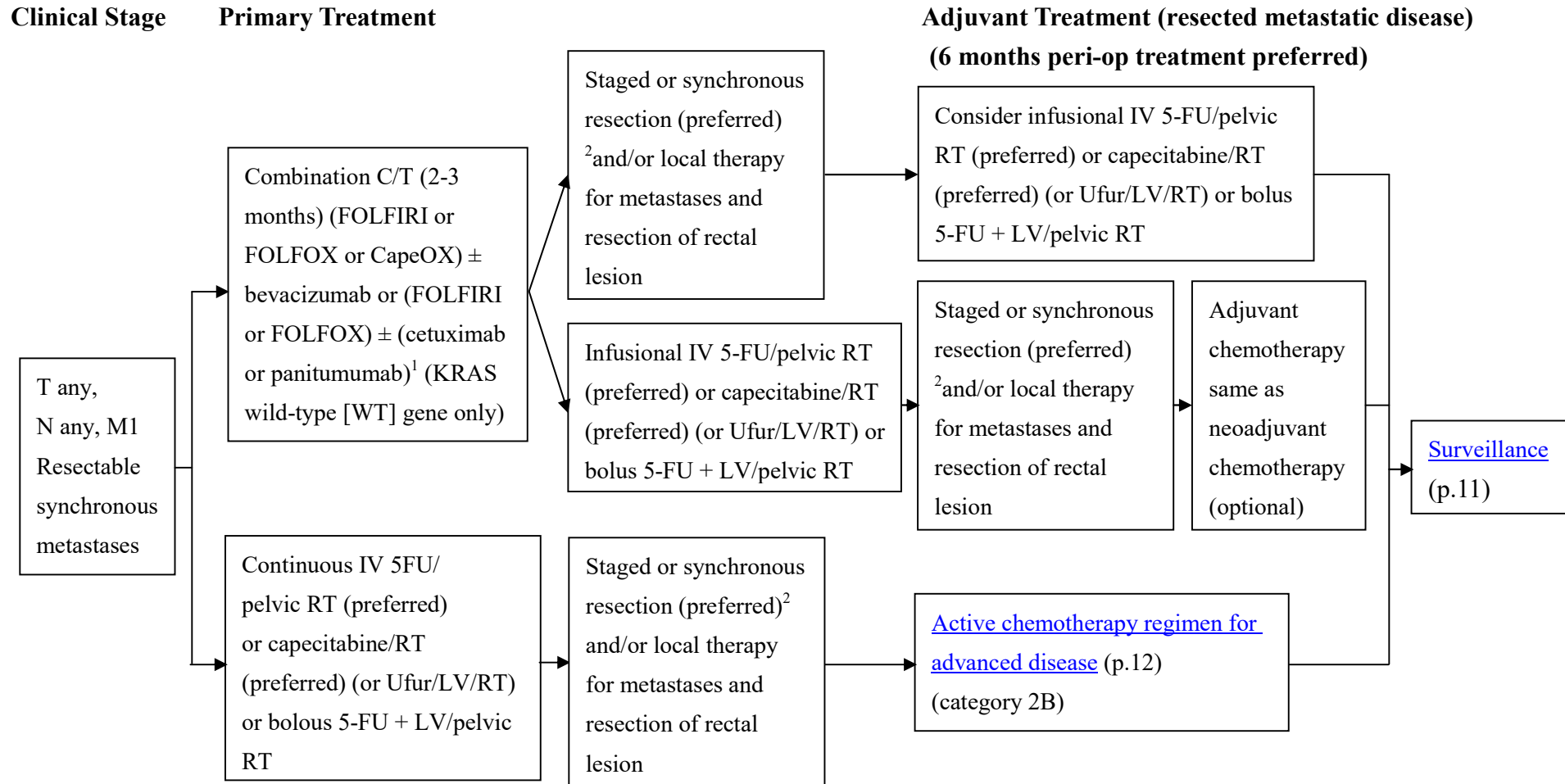
Adjuvant Therapy for T3-4 or Stage III Rectal Cancer Contraindicated to Combined Modality Therapy



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

²Not documented in NCCN 2015 v2 but ESMO guideline 2014, see footnote “1” on “[Staging](#)”; Good prognostic factors included: T1-2; T3a(b) if middle or high rectum, N0 (or N1 if high rectum), circumferential resection margin negative (crm-), no extramural vascular invasion (EMVI)

Resectable Synchronous Metastases



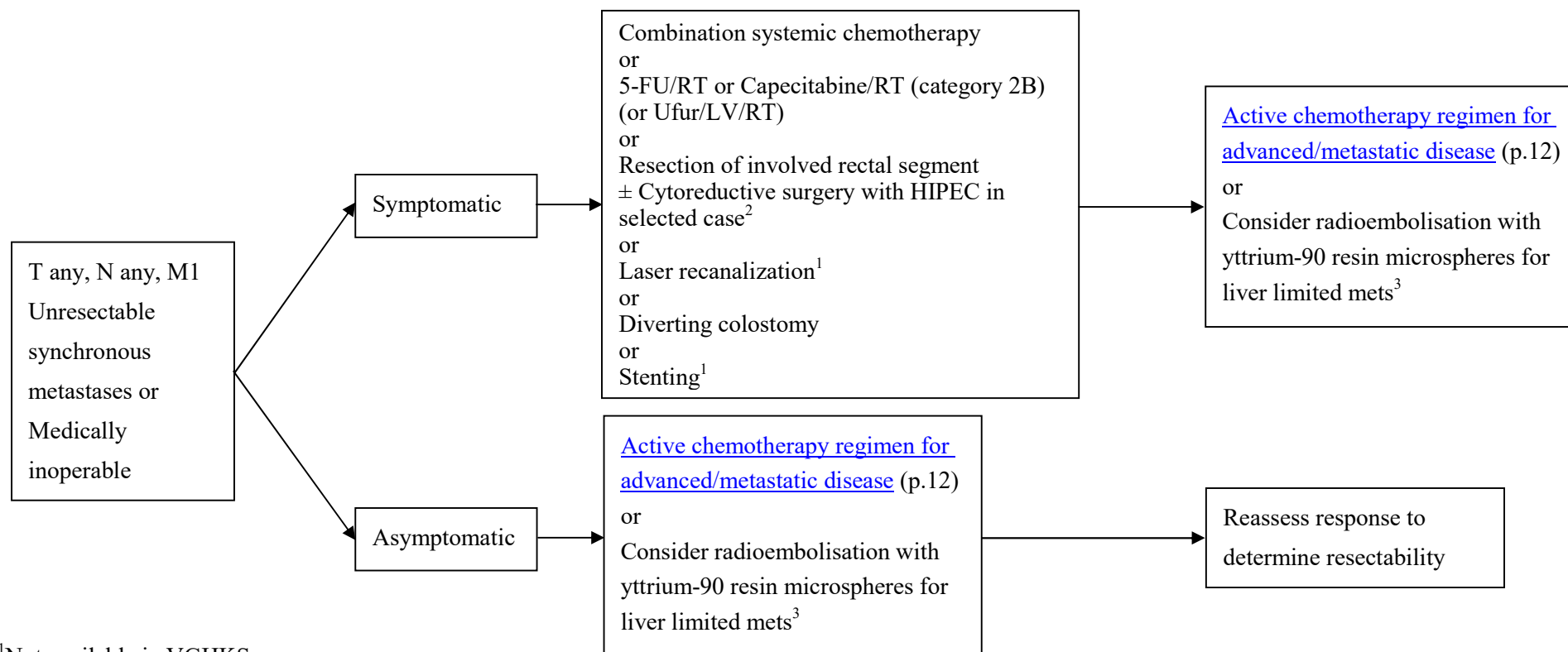
¹There are conflicting data regarding the use of FOLFOX + cetuximab in patients who have potentially resectable liver metastases.

²Resection 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



¹Not available in VGHKS

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

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

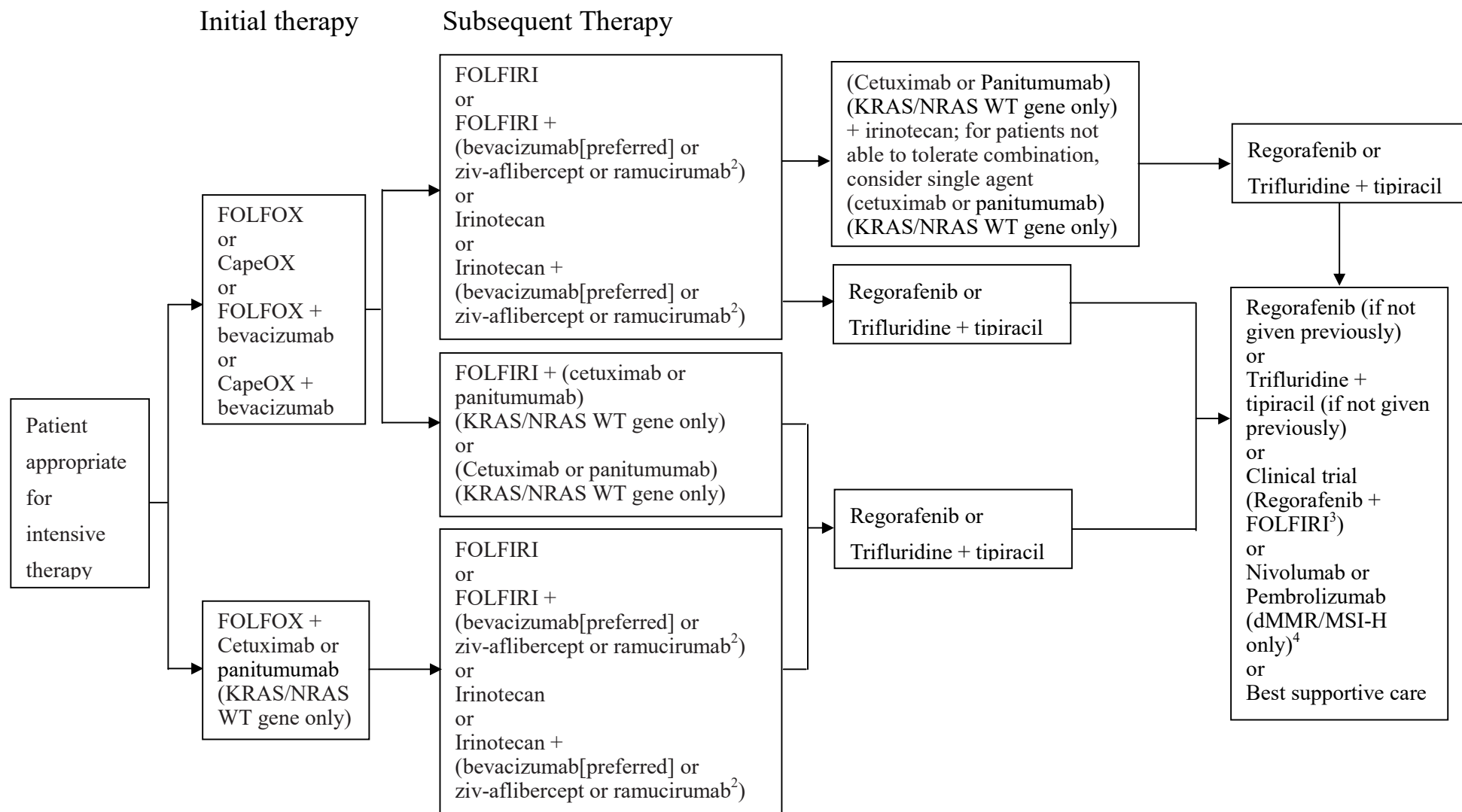
Surveillance

- 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

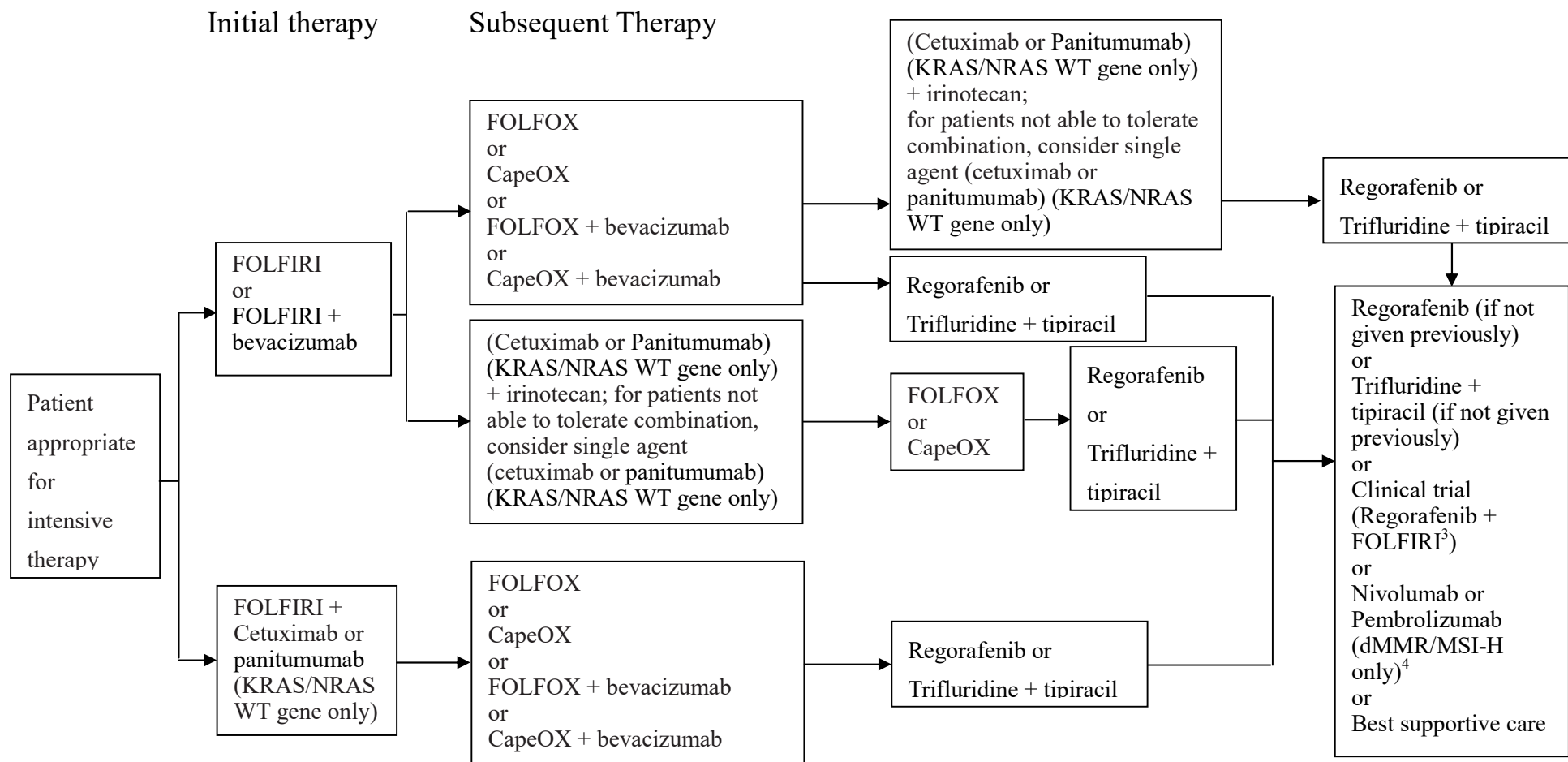
Serial CEA elevation or documented recurrence

[See workup and treatment](#) (p.16)

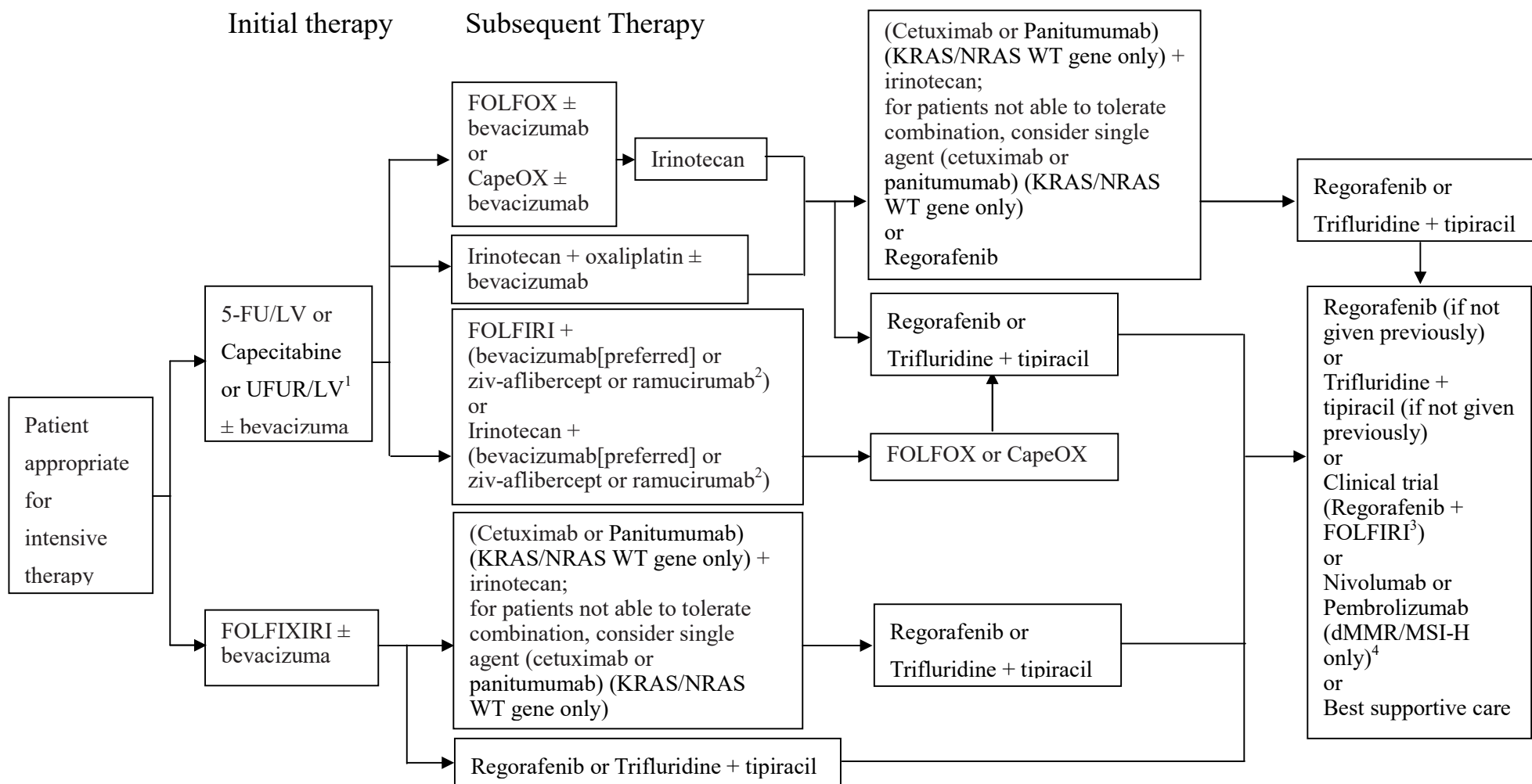
Chemotherapy for advanced or metastatic disease (1 of 4)



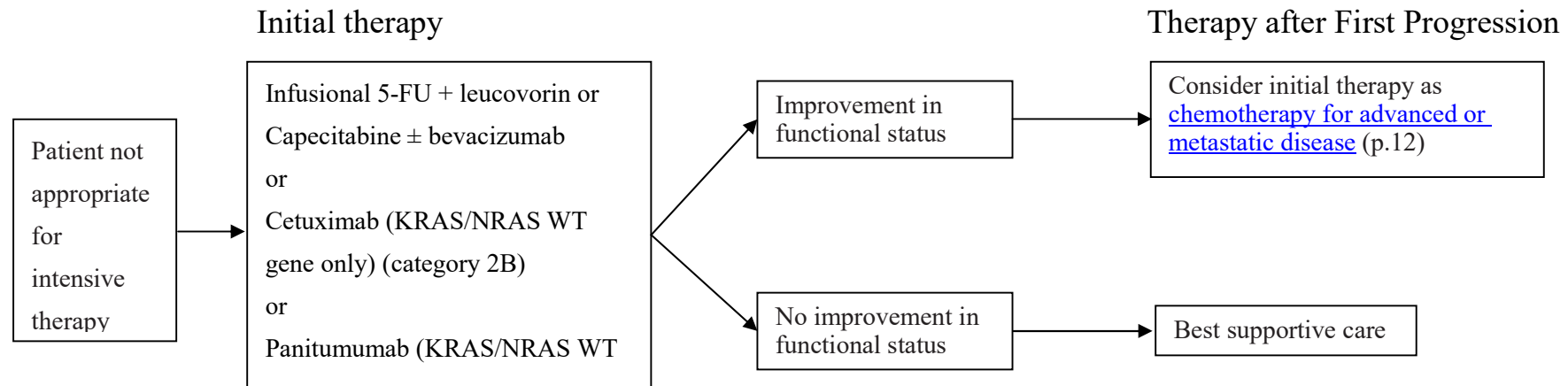
Chemotherapy for advanced or metastatic disease (2 of 4)



Chemotherapy for advanced or metastatic disease (3 of 4)



Chemotherapy for advanced or metastatic disease (4 of 4)



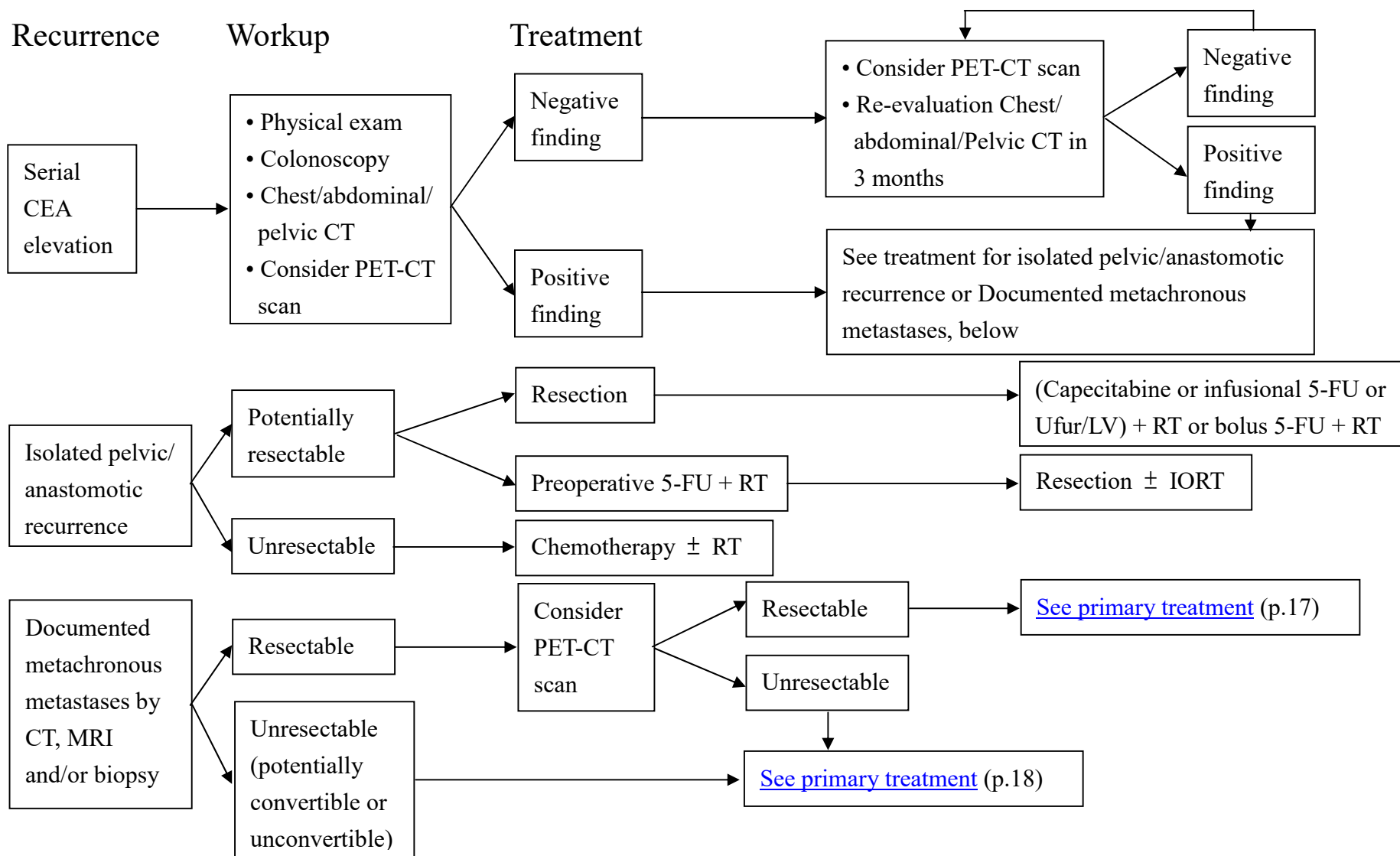
¹Japanese regimen, also see [Chemotherapy Regimens](#)

²Not available in routine clinical practice in Taiwan now

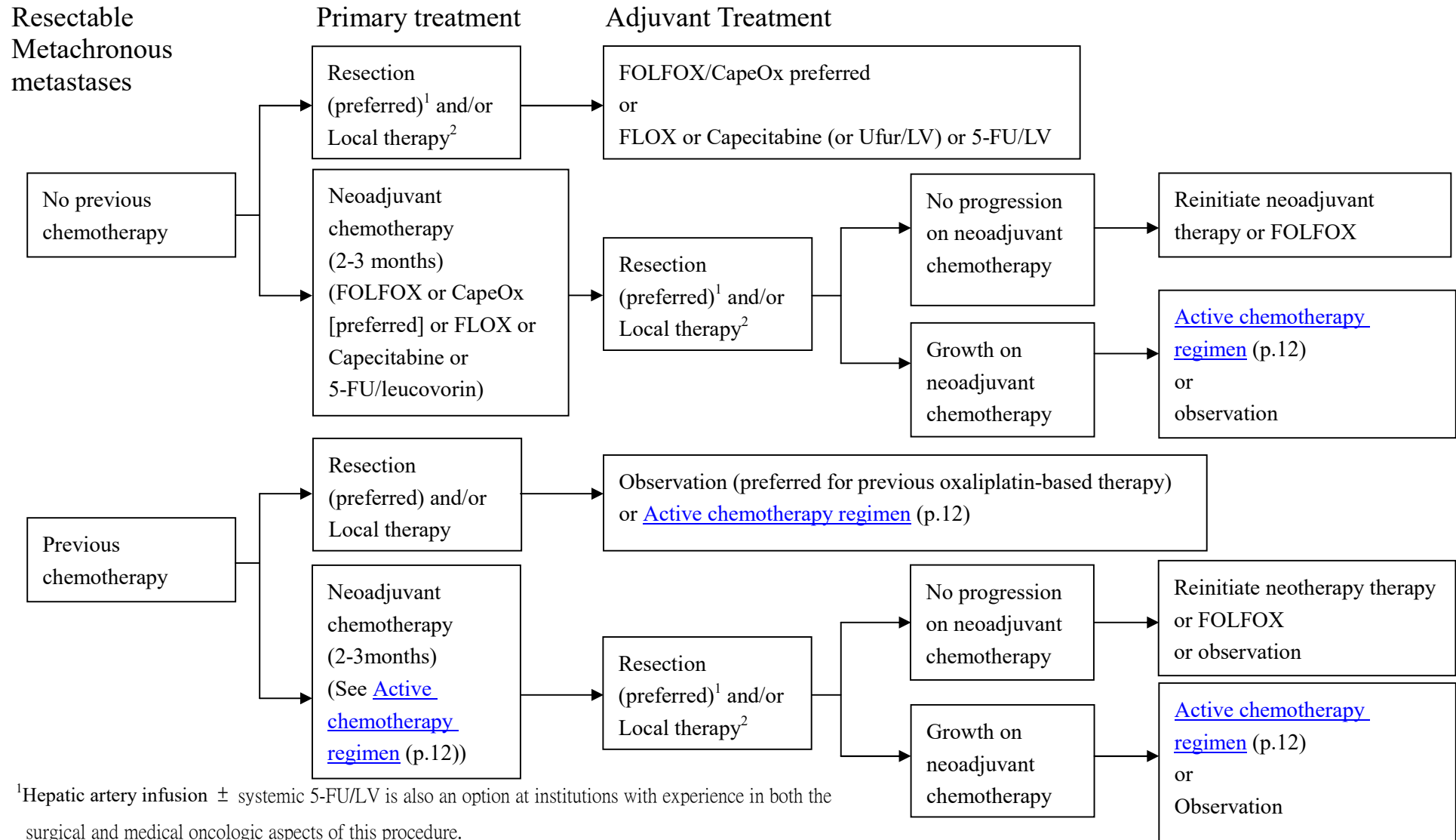
³Based on Reference [10], also see footnote "3" in Chemotherapy Regimens for Advanced/Metastatic Disease (3 of 3)

⁴Based on Reference [13, 14]

Recurrence and Workup



Resectable metachronous metastases



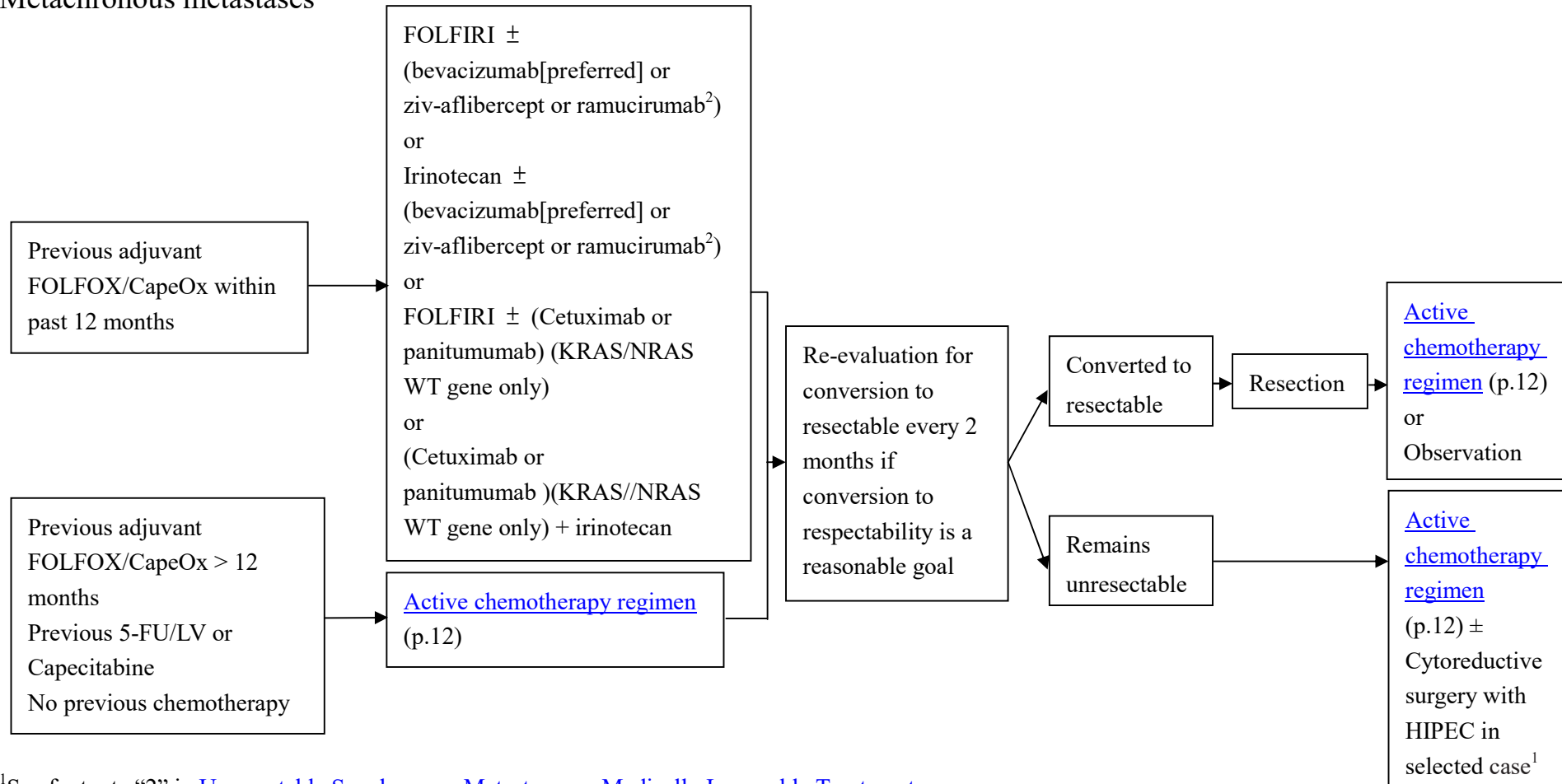
¹Hepatic artery infusion ± systemic 5-FU/LV is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.

²Resection 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



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

²Not 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：

- 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。
- 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。
- 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。
- 評估Eastern Cooperative Oncology Group(ECOG) Performance Status ≥ 3 者。
- 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
<i>mFOLFOX6 (may add with Bevacizumab/Panitumumab/Cetuximab)</i>
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
<i>CapeOX (may add with Bevacizumab)</i>
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 <i>(may add with Bevacizumab/Panitumumab/Cetuximab/Ziv-aflibercept/Ramucirumab)</i>
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 <i>(may add with Bevacizumab)</i>
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/m ² /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)
+ <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 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
+ <i>Ziv-aflibercept (FOLFIRI)</i>
Ziv-aflibercept 4 mg/kg IV, day 1
+ <i>Ramucirumab² (FOLFIRI)</i>
Ramucirumab 8mg/kg over 60 minutes, day 1
+ <i>Regorafenib (Single use or with FOLFIRI³)</i>
Regorafenib 160 mg PO daily days 1-21 Repeat every 28 days
<i>Trifluridine + tipiracil²</i>
35mg/m ² 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
<i>Roswell Park regimen</i>	<i>IROX</i>
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/m ² 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 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
<i>Weekly</i>	
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 (<i>AIO regimen</i> ⁴ : leucovorin 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 (<i>may add with Bevacizumab</i>) 850–1250 mg/m ² PO twice daily, days 1–14 Repeat every 3 weeks
<i>Mayo Clinic regimen</i> 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
<i>modified mFOLFOX</i>
<p>Oxaliplatin 85-100 mg/ m² IV over 3 hours on day 1 Leucovorin 200 mg/ m² IV over 1 hours after Oxaliplatin on day 1 5-FU 2600 mg/m² IV continuous infusion over 18 hours (start on day 1) Repeat every 2 weeks</p>
<i>modified FOLFIRI</i>
<p>Irinotecan 180 mg/m² IV over 90 minutes, day 1 Leucovorin 200 mg/m² IV infusion for 1 hours after irinotecan infusion, day 1 5-FU 2400-3000 mg/m² continuous infusion over 18 hours (start on day 1) Repeat every 2 weeks</p>
<i>modified AIO regimen</i>
<p>leucovorin 250 mg/m² in N/S 250ml over 1 hours followed by 5-FU 2600 mg/m² in N/S 500ml by 18-hour infusion weekly x6 and 2 weeks off, repeat every 8 weeks</p>

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

²Not available in routine practice in Taiwan now

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

⁴At VGHKS

Chemotherapy Regimens for Adjuvant Therapy (1 of 2)

mFOLFOX³ 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	5-FU/leucovorin <i>Rosewell Park regimen (?)</i> 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
FLOX² 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	<i>Simplified biweekly infusional 5-FU/LV (sLV5FU2)</i> 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
Capecitabine 1250 mg/m ² PO twice daily, days 1–14 every 3 weeks x 24 wks	
CapeOX 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	<i>AIO regimen⁴</i> 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/LV¹ Leucovorin 20-30 mg/m ² + Ufur 300-500 mg/ m ² PO at day 1 to 28 in every 35 days	<i>Mayo Clinic regimen⁴</i> 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

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

²FLOX is an alternative to FOLFOX or CapeOx but FOLFOX or CapeOx are preferred

³FOLFOX 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

⁴At VGHKS

Chemotherapy Regimens for Adjuvant Therapy (2 of 2)

Modified regimen for CRS@VGHKS
<i>modified mFOLFOX</i>
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
<i>modified AIO regimen</i>
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 24 hours 5 or 7 days/week during XRT
XRT + 5-FU/leucovorin
5-FU 400 mg/m ² IV bolus + leucovorin 20 mg/m ² IV bolus for 4 days during week 1 and 5 of XRT
XRT + Capecitabine
Capecitabine 825 mg/m ² twice daily 5 days/week + XRT x 5 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 ¹	Tumor invades through the muscularis propria into the pericorectal
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

7 th 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

¹T3 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

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

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.
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Appendix and Additional Information

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