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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

November 2015*version 2*

Rectal Cancer Clinical Practice Guidelines

Content

<Revision Summary>

Updates in Version 2 2015 of the VGHKS Rectal Cancer Clinical Practice Guidelines from Version 1 2015 include:

1. Correct some typographical error and page numbers
2. Revise the page of workup for recurrence, resectable metachronous metastases and unresectable metachronous metastases
3. Unresectable Synchronous Metastases or Medically Inoperable Treatment (p.12)
   a) Column 3 and 4 : "± Cytoreductive surgery with HIPEC in selected case" was added as additional treatment option with resection of involved rectal segment; "Consider radioembolisation with yttrium-90 resin microspheres for liver limited mets" was added as treatment option for liver limited disease
   b) Footnote "2" and "3": added for additional items described above
4. Intensive chemotherapy for advanced or metastatic disease (p.14-17):
   a) p.14, Column 3: bevacizumab listed as preferred in combination with FOLFIRI or irinotecan. Ramucirumab[2] added as an option in combination with FOLFIRI or irinotecan, also in Intensive chemotherapy for advanced or metastatic disease (2,3 of 4) (p.15,16) and Unresectable metachronous metastases (p.20)
   b) Footnote "2" added: "Not available in routine clinical practice in Taiwan now", also as footnote "2" in Unresectable metachronous metastases (p.20)
   c) "Regorafenib + FOLFIRI" added as option for clinical trial
   d) Footnote "3" added: "Based on reference [10], also see footnote "3" in Chemotherapy Regimens for Advanced/Metastatic Disease (3 of 3)"
5. Principles of chemotherapy (p.21)
   a) NHI regulation added: Panitumumab combine with Irinotecan base regimens at the 3rd line treatment. Regorafenib at the third/fourth[K-ras wild type] line treatment
6. Chemotherapy regimens for advanced/metastatic disease (p.22-24)
   a) Add regimen: Ramucirumab, AIO (described in Weekly), Mayo clinic and modified AIO
   b) Footnote "2" added: "Not available in routine practice in Taiwan now"

c) Foornote “3” added: “As third/fourth line chemotherpy for advanced/metastatic disease, based on reference[10]”

d) Footnote “4” added: “At VGHKS”

7. Chemotherapy regimens of adjuvant therapy (p.25-26):

a) Add regimen: AIO, Mayo clinic and modified AIO

b) Divided Modified regimen for CRS@VGHKS as independent sheet

Updates in Version 1 2015 of the VGHKS Rectal Cancer Clinical Practice Guidelines from Version 2014 include:

1. Revise alignment of algorithms
2. Add titles for previous algorithms
3. Add hyperlinks
4. Divided “Chemotherapy regimens” into “Principle of Chemotherapy”, “Chemotherapy Regimens for Advanced/Metastatic disease” and “Chemotherapy Regimens for Adjuvant Therapy” as individual topics
5. Replace item “UFUR” by “UFUR/LV”
6. Malignant polyp (p.):

a) Clinical presentation modified: “Pedunculated or sessile polyp (adenoma [tubular, tubulovillous, or villous]) with invasive cancer.”

b) Workup, bullet 3 modified: “Marking of cancerous polyp site (at time of colonoscopy or within 2 weeks if deemed necessary by the surgeon).”

7. Adjuvant Therapy for Stage I Rectal Cancer (p.):

a) FOLFOX and CapeOx are noted as preferred (also applies to Adjuvant Therapy for T3-4 or Stage III Rectal Cancer Contraindicated to Combined Modality Therapy)

8. Adjuvant Therapy for T3-4 or Stage III Rectal Cancer (p.):

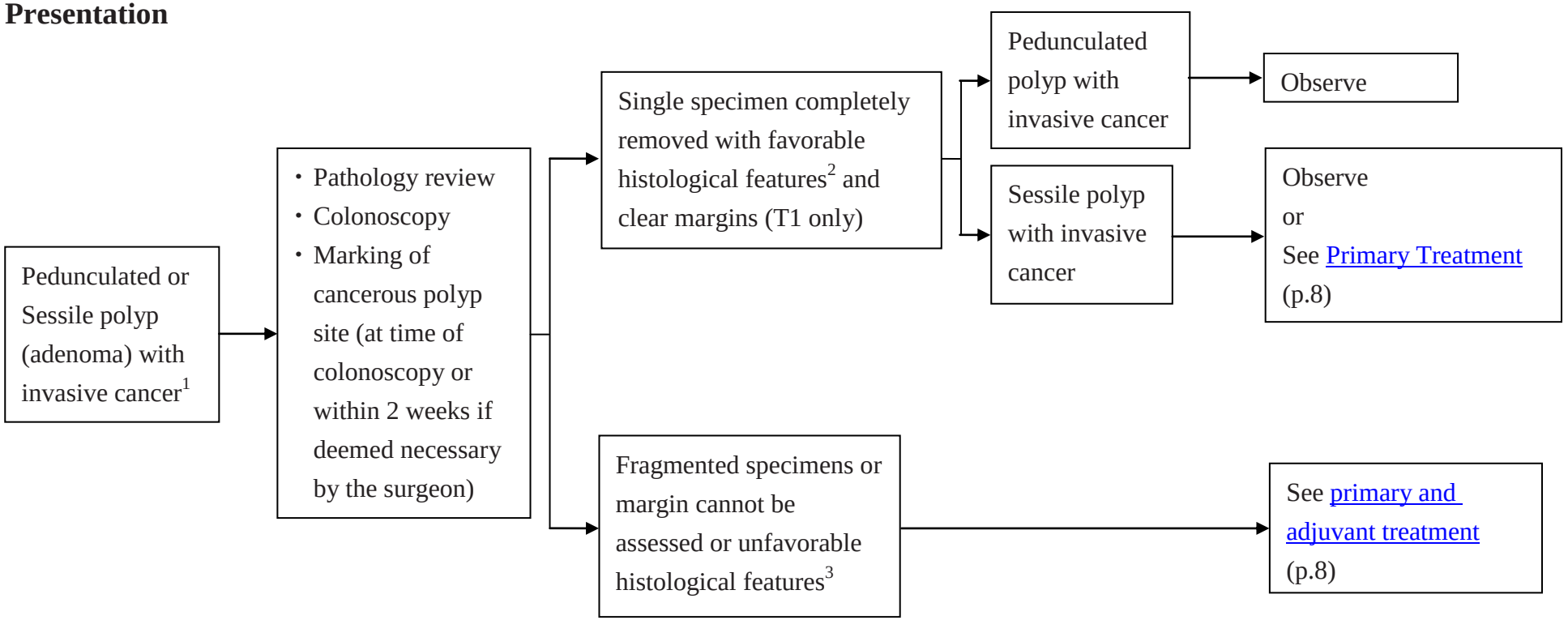
a) The clinical stages “T3, N0 or T any, N1-2” and “T4 and/or locally unresectable or medically inoperable” were combined.

- The following treatment option was added prior to resection: Chemotherapy (FOLFOX [preferred] or CapeOx [preferred] or 5-FU/leucovorin or capecitabine) followed by chemoradiation (Capecitabine/RT [preferred] or infusional 5-FU/RT [preferred] or bolus 5-FU/leucovorin/RT).
- Adjuvant therapy modified with the addition of “preferred” to FOLFOX or CapeOx.

b) Footnote "1" added: "Total duration of perioperative chemotherapy, inclusive of chemotherapy and radiation therapy, should not exceed 6 months." (also applies to Adjuvant Therapy for T3-4 or Stage III Rectal Cancer Contraindicated to Combined Modality Therapy)

9. Adjuvant Therapy for T3-4 or Stage III Rectal Cancer Contraindicated to Combined Modality Therapy (p.):
   a) Treatment recommendations for patients with a medical contraindication to combined modality therapy moved from p. to p.
   b) Footnote "2" added: "Not 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)."
10. Resectable Synchronous Metastases (p.):
    a) The option of adjuvant chemotherapy was added after combination chemotherapy, chemoradiation, and surgery.
    b) FOLFOX + cetuximab added as a treatment option with the following footnote "1": "There are conflicting data regarding the use of FOLFOX + cetuximab in patients who have potentially resectable liver metastases."
11. Unresectable Synchronous Metastases or Medically Inoperable Treatment (p.):
    a) Primary treatment: "Diverting colostomy" changed to "Diverting ostomy." with following footnote "1": "Not available in VGHKS"; also applied to bullet: " Laser recanalization" in column 3
12. Surveillance (p.):
    a) The following bullet was removed: "Consider proctoscopy every 6 mo x 3-5 y for patient status post LAR or transanal excision."
13. Unresectable Metachronous Metastases (p.):
    a) First column: CapeOx listed in addition to FOLFOX in previous therapy Lymph node evaluation, first bullet
14. Chemotherapy for Advanced or Metastatic Disease (p.):
    a) FOLFOX + cetuximab (KRAS/NRAS WT gene only) added as a treatment option for Initial therapy.
    b) FOLFOXIRI ± bevacizumab: category recommendation changed from a 2B to a 2A
15. Staging (p.):
    a) Footnote "2" added: "Sampling of 12 lymph nodes may not be achievable in patients that received preoperative chemotherapy."

Malignant polyp

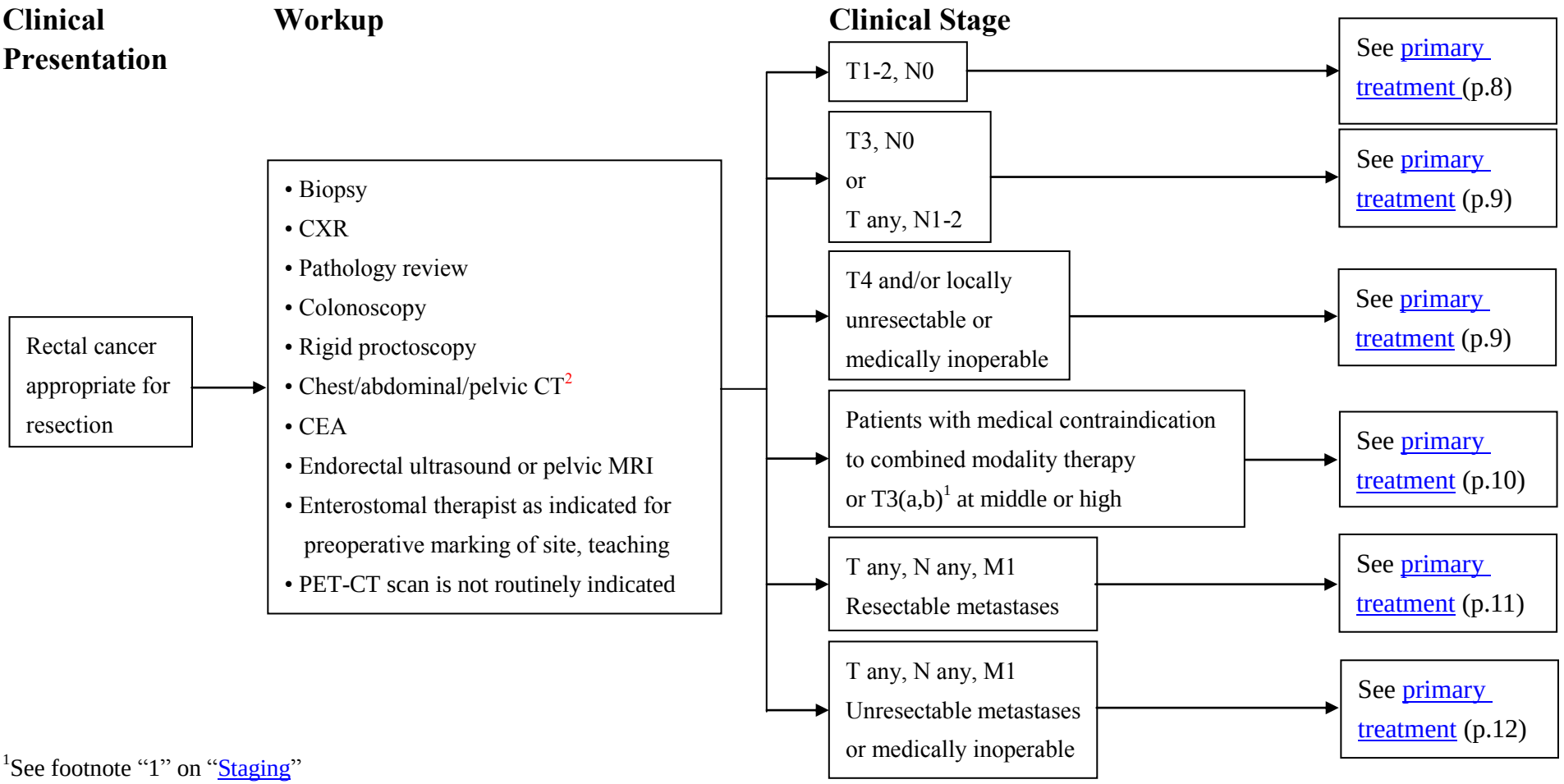


[1]A malignant polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1). pTis is not considered a "malignant polyp".

[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)

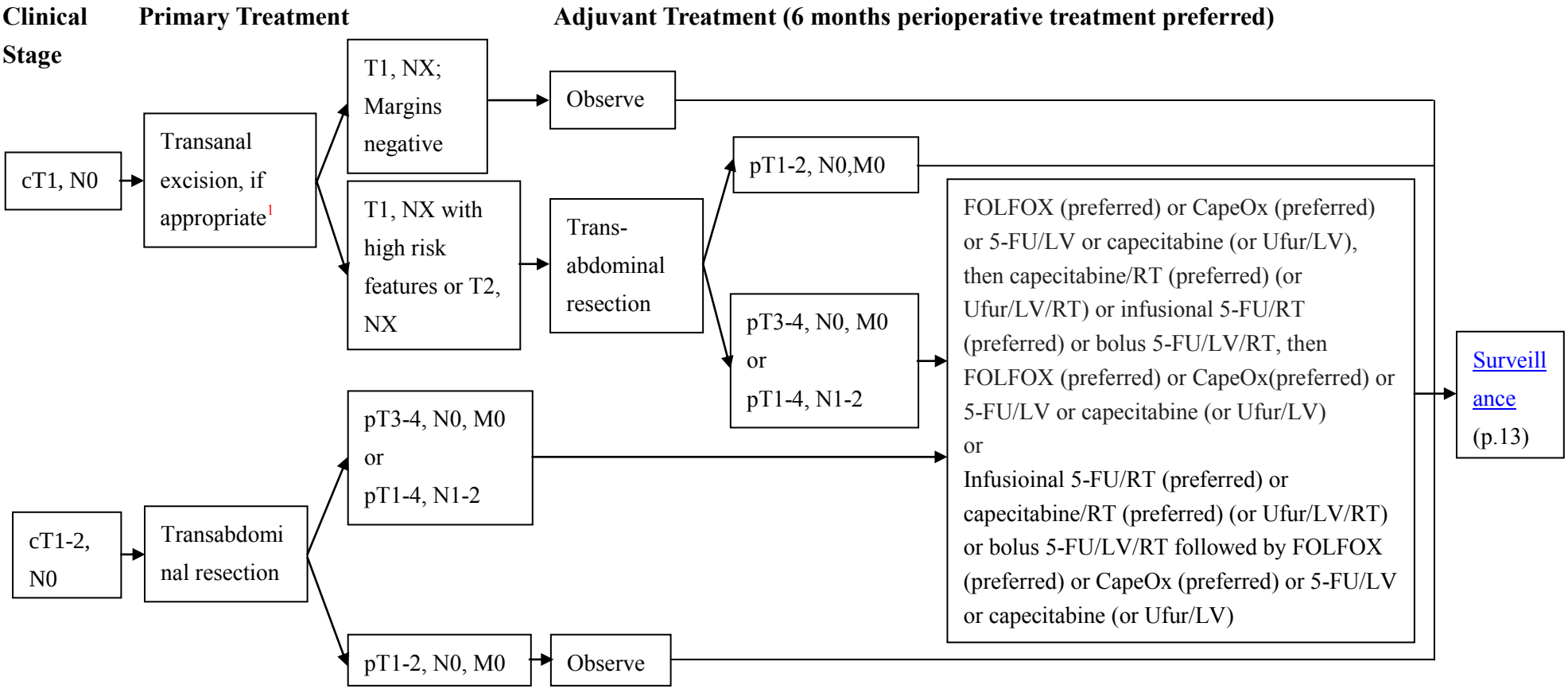
Resectable Primary Rectal Cancer



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

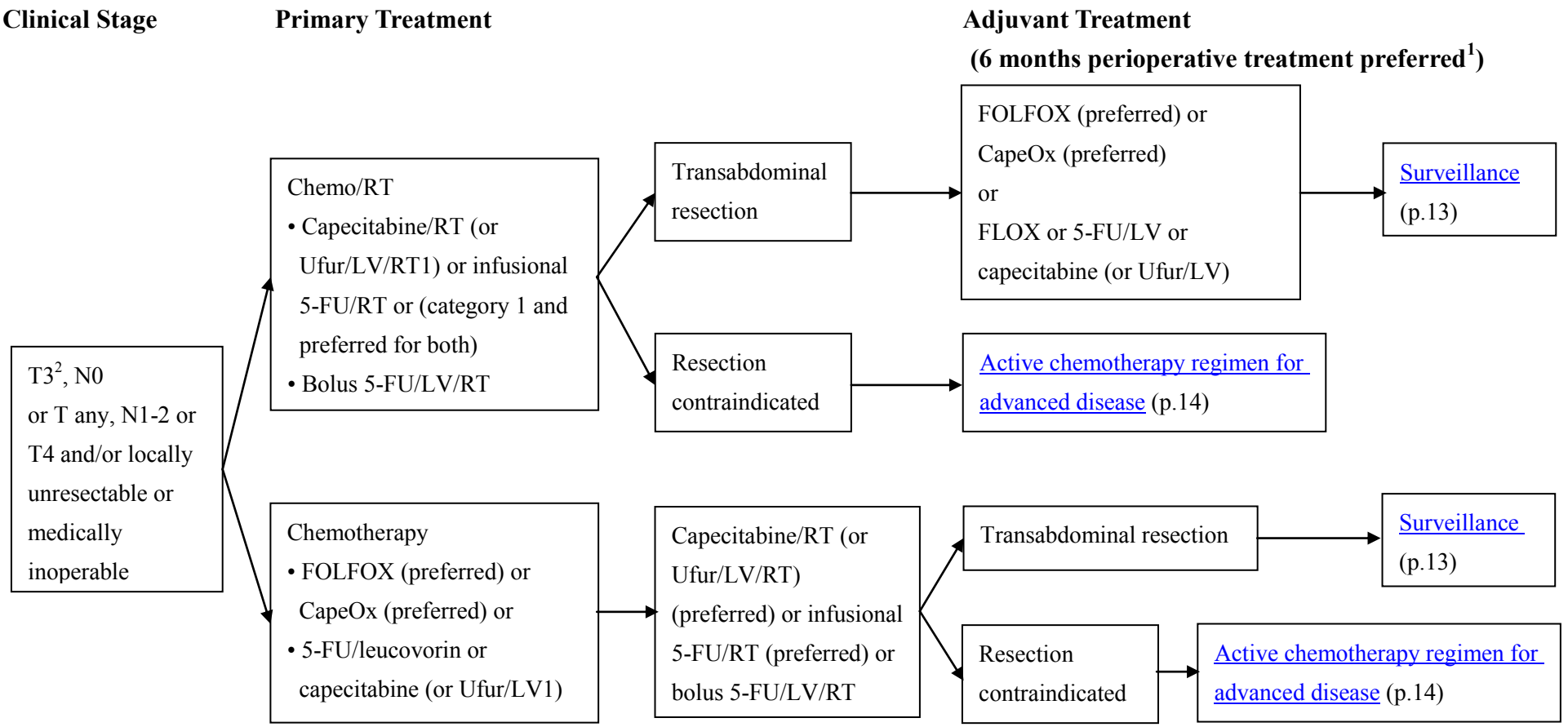
[2]CT should be with IV and oral contrast. Consider abd/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.

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)

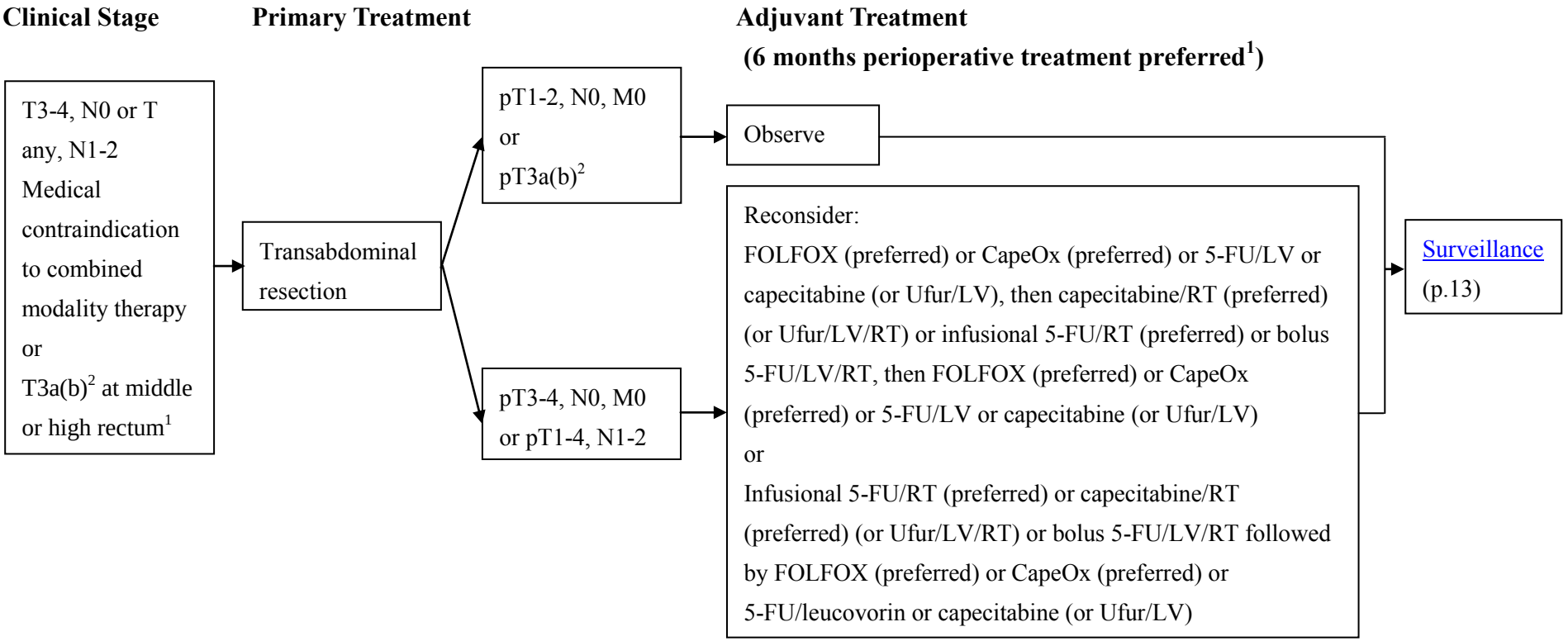
Adjuvant Therapy for Unresectable T3-4 or Stage III Rectal Cancer



[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

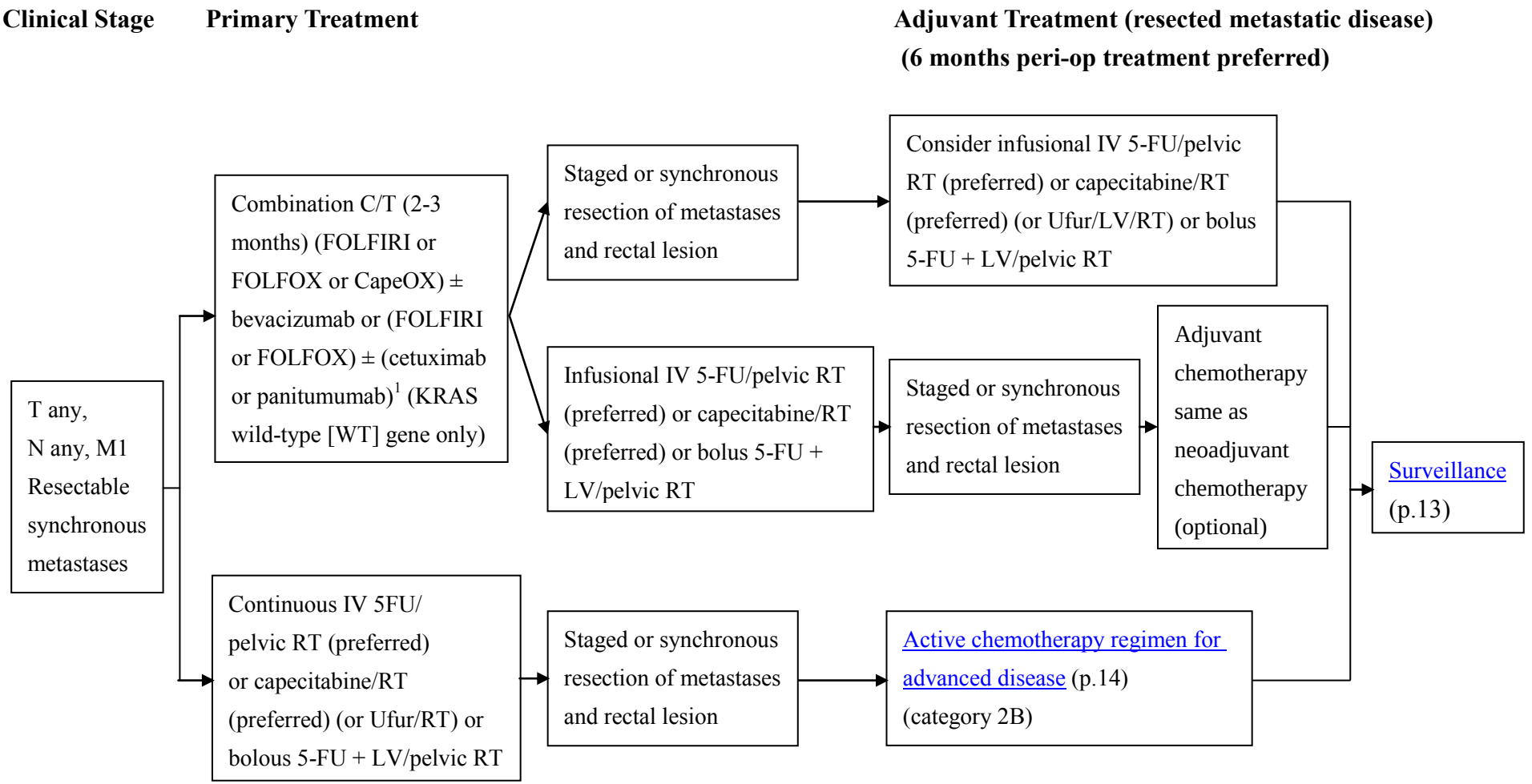
Adjuvant Therapy for T3-4 or Stage III Rectal Cancer Contraindicated to Combined Modality Therapy



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

[2]Not 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)

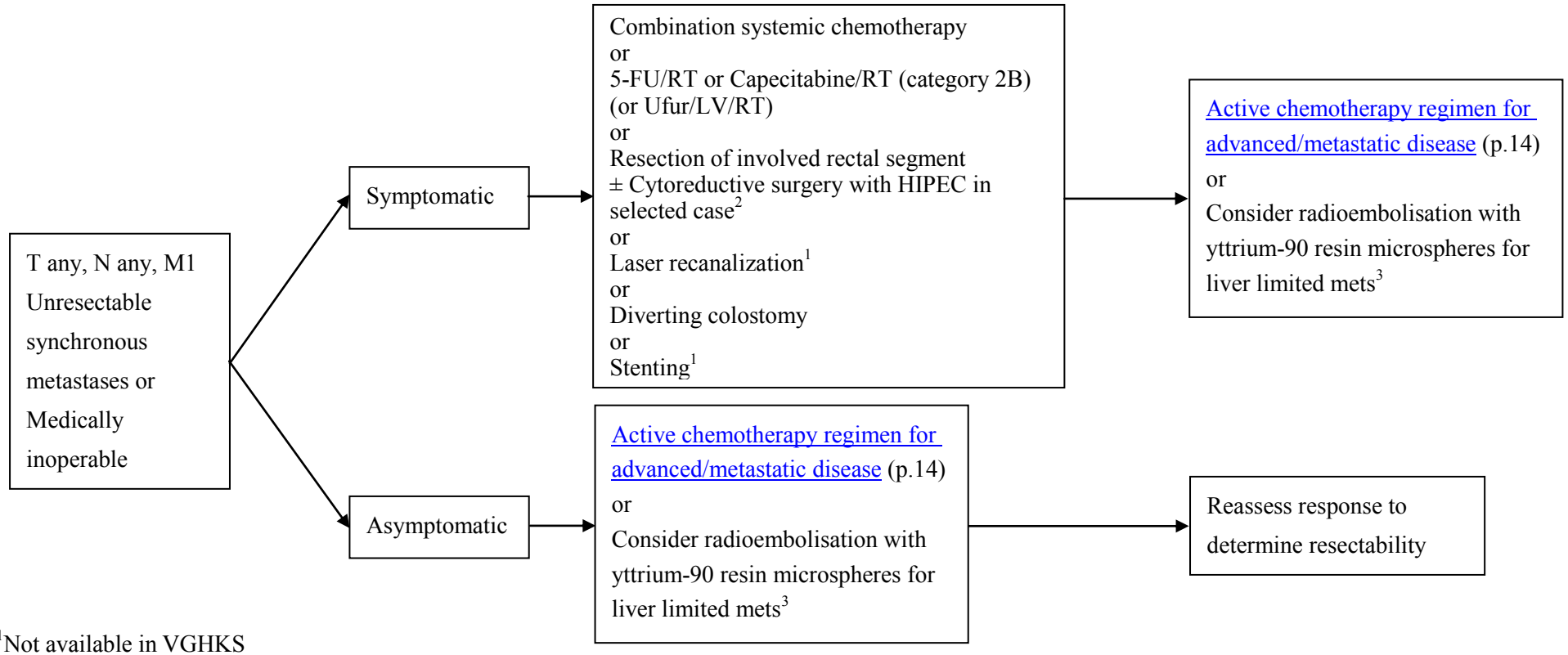
Resectable Synchronous Metastases



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

Unresectable Synchronous Metastases or Medically Inoperable Treatment

Clinical Stage **Primary Treatment**

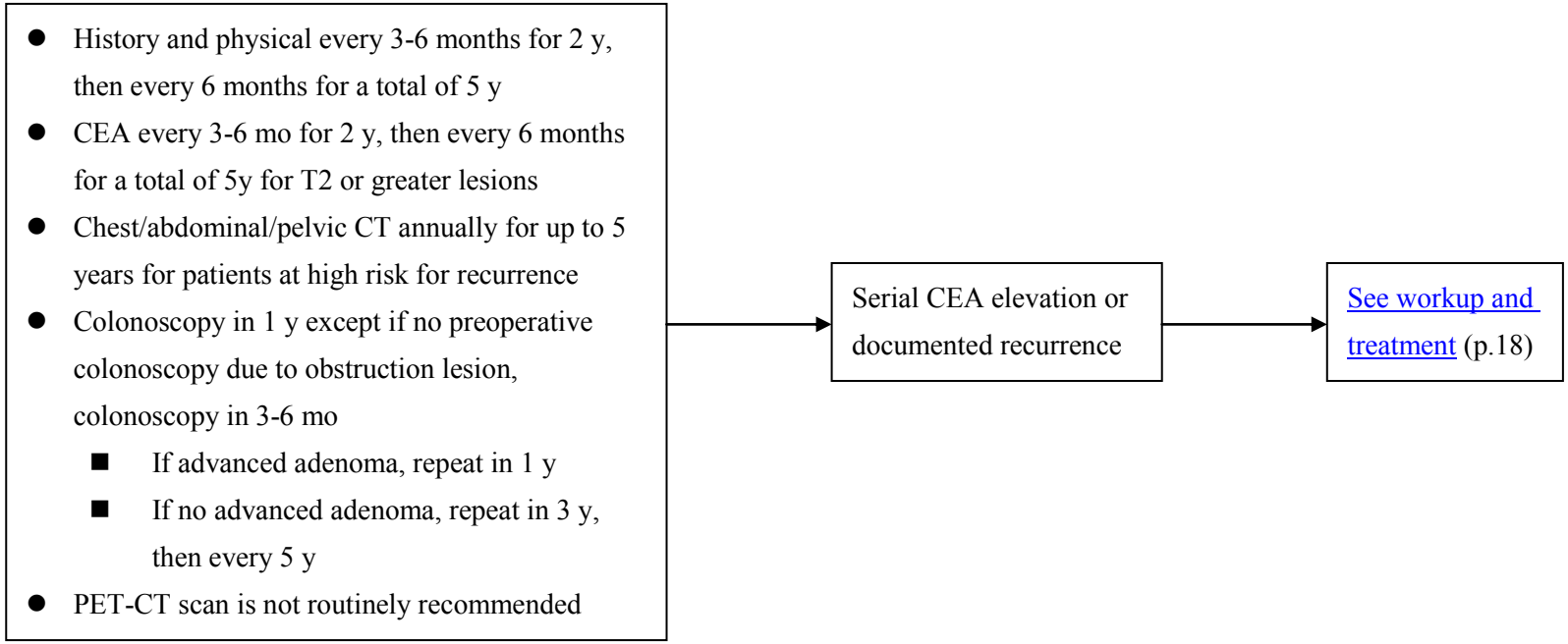


[1]Not available in VGHKS

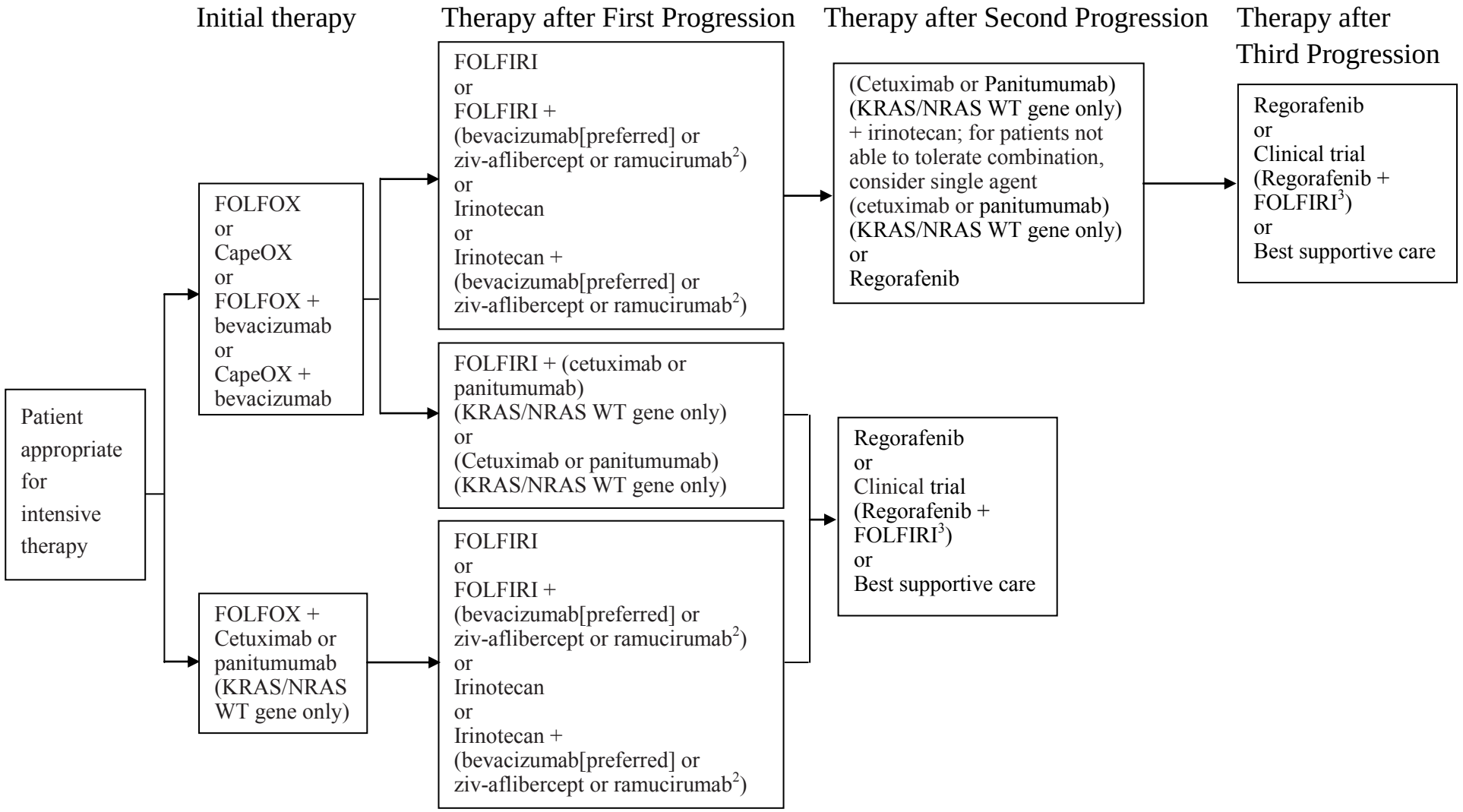
[2]HIPEC = Hyperthermic Intraperitoneal Chemotherapy; Not documented in NCCN guideline 2015 v2 but in ESMO guideline 2014(evidence grade IVB). Also refer to Reference [7], [8]

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

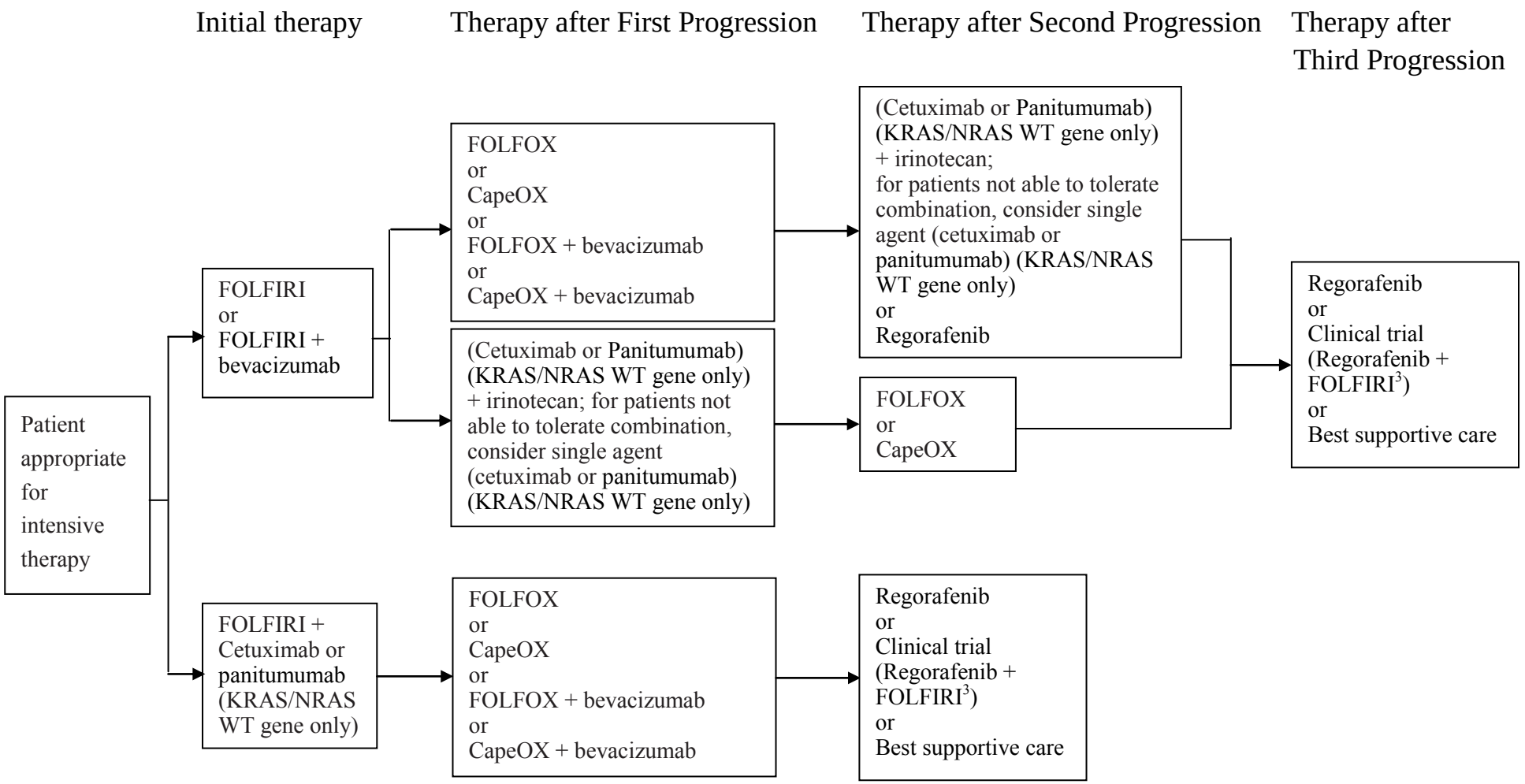
Surveillance



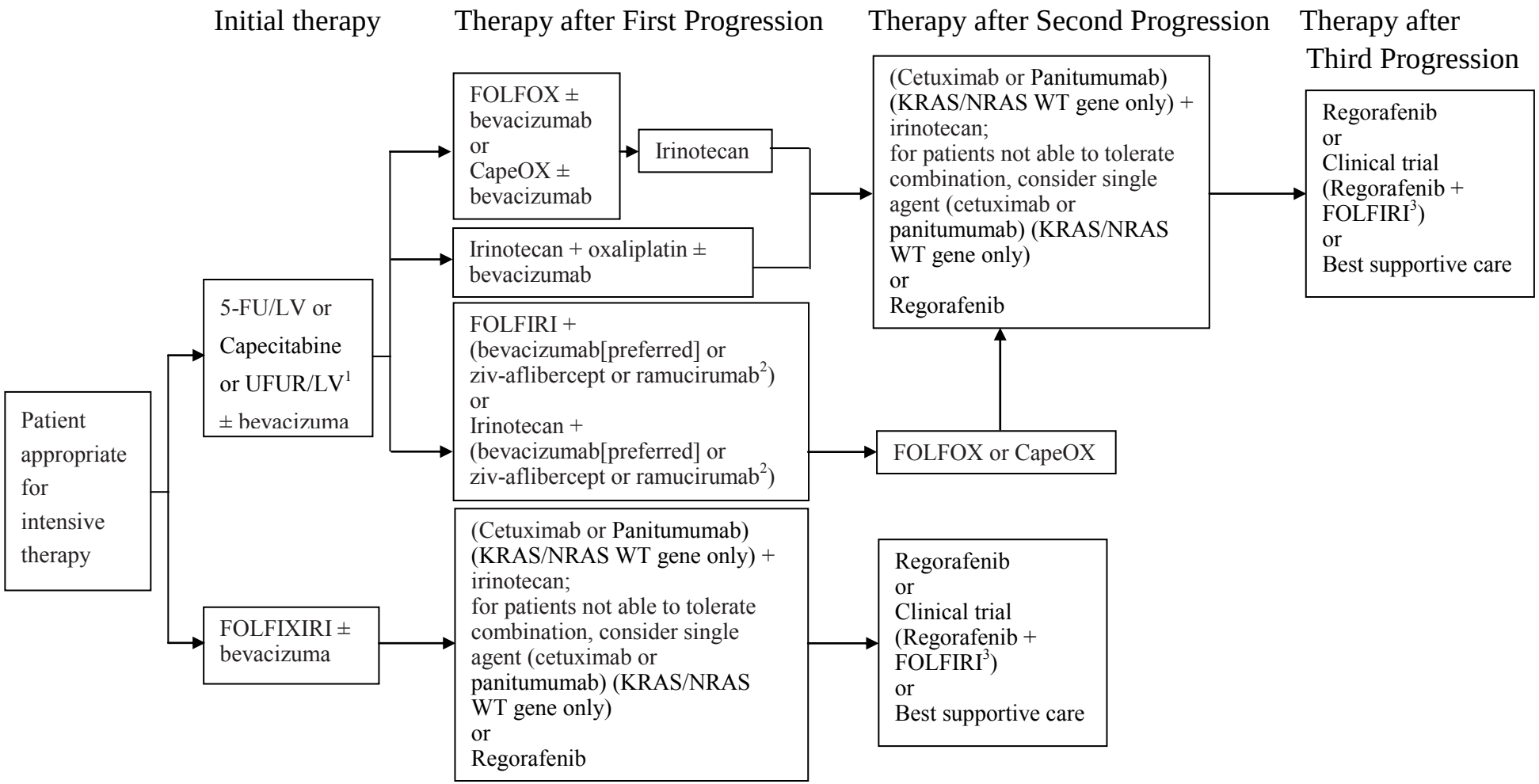
Chemotherapy for advanced or metastatic disease (1 of 4)



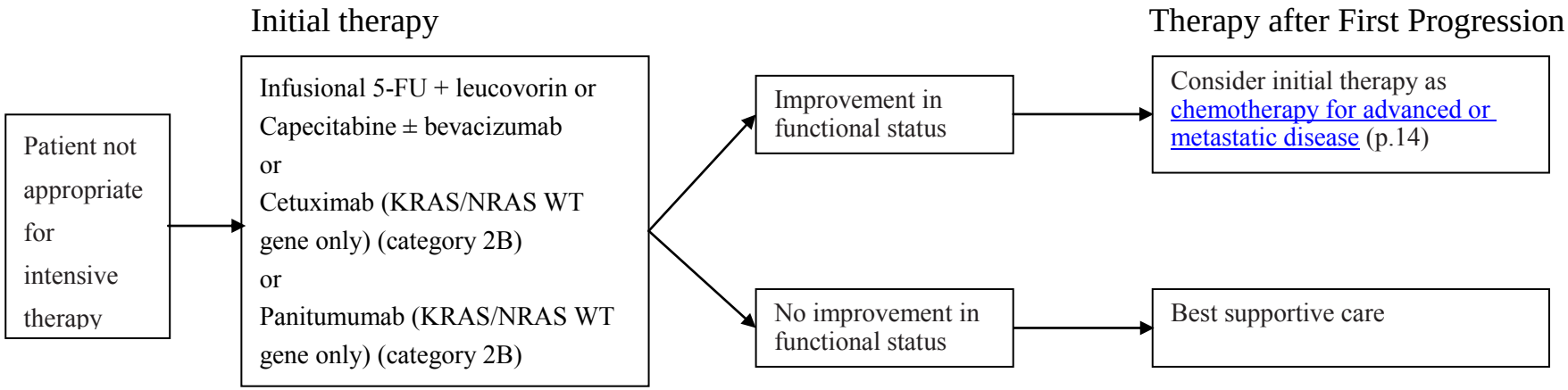
Chemotherapy for advanced or metastatic disease (2 of 4)



Chemotherapy for advanced or metastatic disease (3 of 4)



Chemotherapy for advanced or metastatic disease (4 of 4)

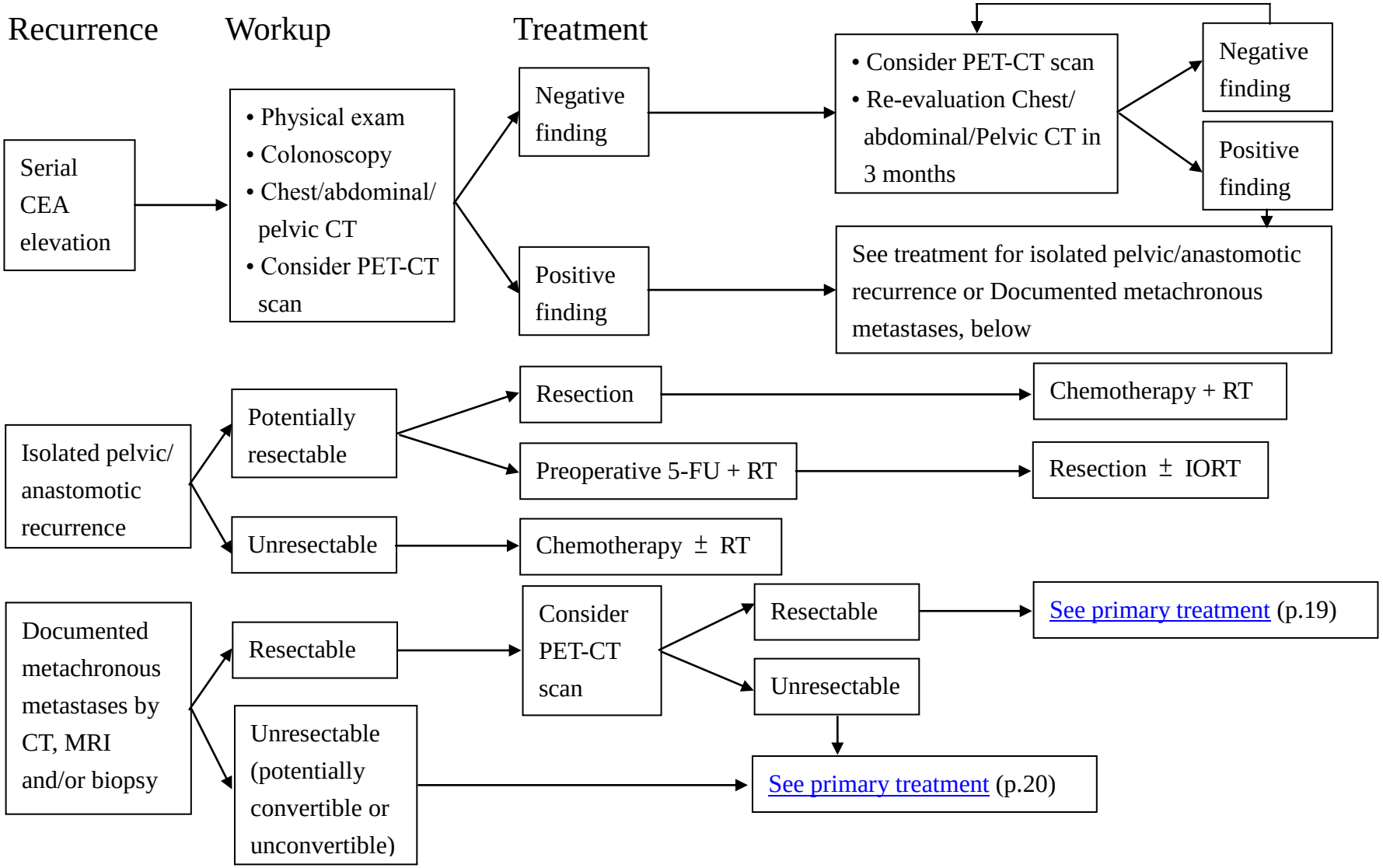


[1]Japanese regimen, also see Chemotherapy Regimens

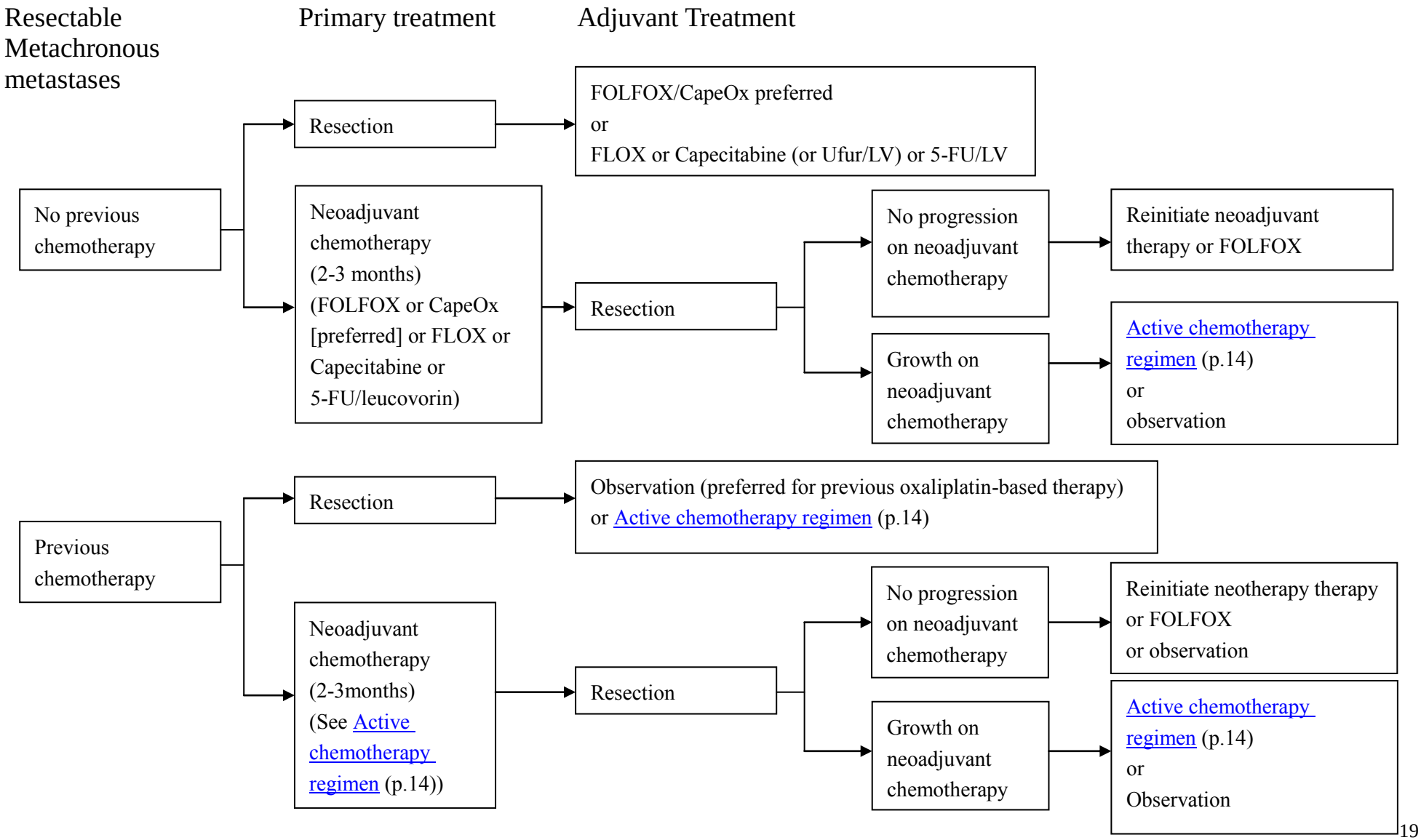
[2]Not available in routine clinical practice in Taiwan now

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

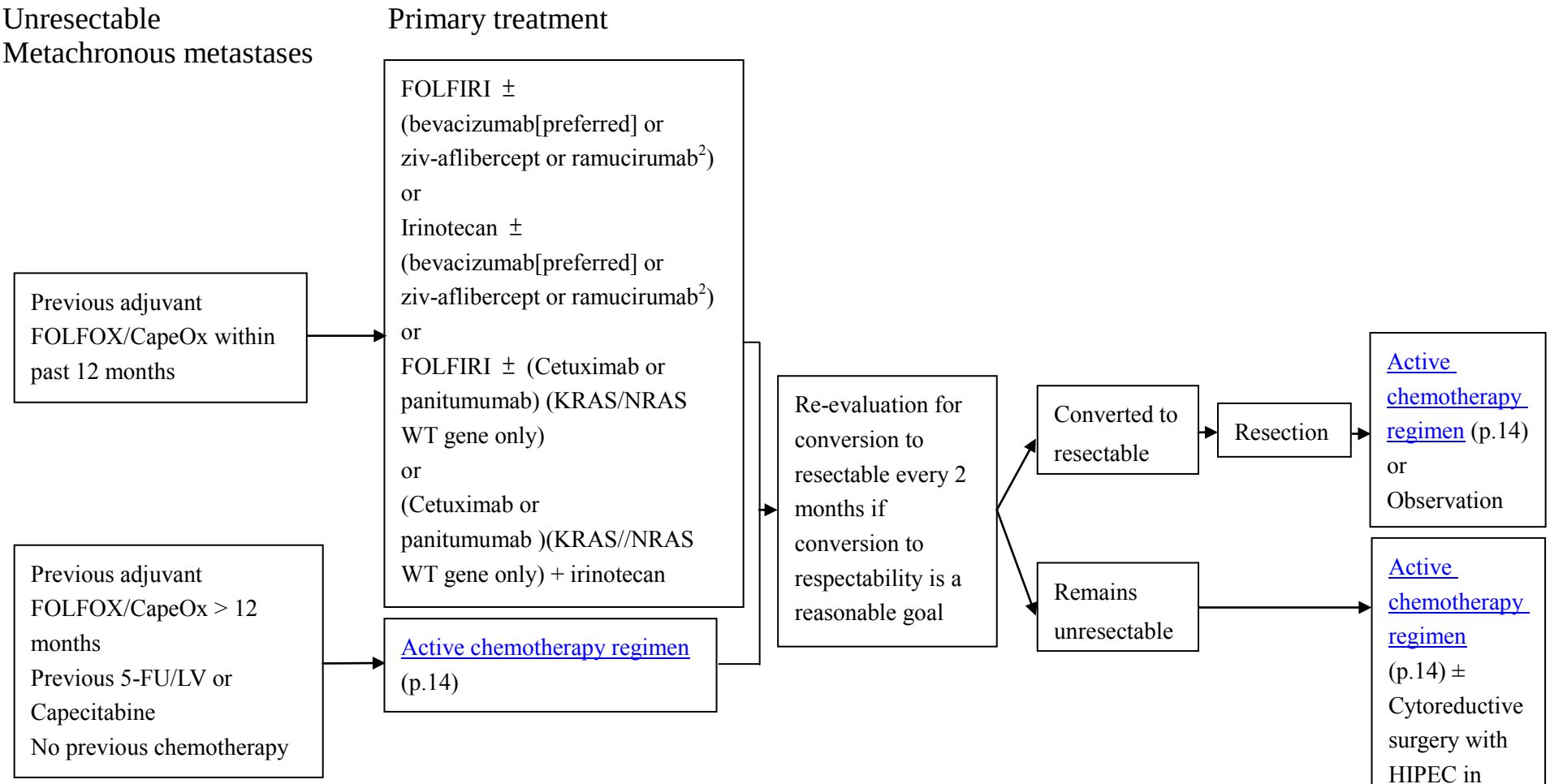
Recurrence and Workup



Resectable metachronous metastases



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 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

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 withBevacizumab/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

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)

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 2 weeks	*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 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 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

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

[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.

Reference

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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