台北榮民總醫院
Taipei Veterans General Hospital

# Colon Cancer

大腸直腸癌醫療團隊

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# Before Guidelines

- This panel is for medical fitted patients, adjustment might be considered for medical unfitted patients(elder..) or for individual considerations under clinical practices.
- Although the guidelines are believed to represent the optimal treatment strategy, the panel believes that, when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy
- Adenocarcinomas of the small bowel or appendix may be treated with systemic chemotherapy according to these guideline.

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# AJCC 8th
# Colon and Rectum

***Table 1.*** **Definitions for T, N, M**

| | |
|---|---|
| **T** | **Primary Tumor** |
| **TX** | Primary tumor cannot be assessed |
| **T0** | No evidence of primary tumor |
| **Tis** | Carcinoma *in situ*: intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae) |
| **T1** | Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria) |
| **T2** | Tumor invades the muscularis propria |
| **T3** | Tumor invades through the muscularis propria into the pericolorectal tissues |
| **T4** | Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure |
| T4a | Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum) |
| T4b | Tumor directly invades or is adheres to adjacent organs or structures |
| **N** | **Regional Lymph Nodes** |
| **NX** | Regional lymph nodes cannot be assessed |
| **N0** | No regional lymph node metastasis |
| **N1** | One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative |
| N1a | One regional lymph node is positive |
| N1b | Two or three regional lymph nodes are positive |
| N1c | No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic, or perirectal/ mesorectal tissues |
| **N2** | Four or more regional lymph nodes are positive |
| N2a | Four to six regional lymph nodes are positive |
| N2b | Seven or more regional lymph nodes are positive |
| **M** | **Distant Metastasis** |
| **M0** | No distant metastasis by imaging, etc.; no evidence of tumor in distant sites or organs |
| **M1** | Metastasis to one or more distant sites or organs or peritoneal metastasis is identified |
| M1a | Metastasis to one site or organ is identified without peritoneal metastasis |
| M1b | Metastasis to two or more sites or organs is identified without peritoneal metastasis |
| M1c | Metastasis to the peritoneal surface is identified alone or with other site or organ metastases |

***Table 2.*** **AJCC Prognostic Stage Groups**

| | T | N | M |
|---|---|---|---|
| **Stage 0** | Tis | N0 | M0 |
| **Stage I** | T1-T2 | N0 | M0 |
| **Stage IIA** | T3 | N0 | M0 |
| **Stage IIB** | T4a | N0 | M0 |
| **Stage IIC** | T4b | N0 | M0 |
| **Stage IIIA** | T1-T2 | N1/N1c | M0 |
| | T1 | N2a | M0 |
| **Stage IIIB** | T3-T4a | N1/N1c | M0 |
| | T2-T3 | N2a | M0 |
| | T1-T2 | N2b | M0 |
| **Stage IIIC** | T4a | N2a | M0 |
| | T3-T4a | N2b | M0 |
| | T4b | N1-N2 | M0 |
| **Stage IVA** | Any T | Any N | M1a |
| **Stage IVB** | Any T | Any N | M1b |
| **Stage IVC** | Any T | Any N | M1c |

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# Flowchart

# Initial Workup Colon & Rectum

- Present illness
- Physical examination
- Personal and family history
- CBC, chemistry profile, *±CEA ,±CA19-9*, ±AFP, ±CA125, ±FDP, ± aPTT/PT
- ± { RAS, BRAF, MSI, NTRK, UGT1A1,TMB, Her2}
- ± Abdominal ± Chest CT ± MRI
- Colonoscopy ± PES
- ± PET scan
- ± Whole Body Bone Scan
- ± Endorectal ultrasonography (Rectum)
- ± Brain CT

# Malignant polyp (pT1)
# Colon and rectum

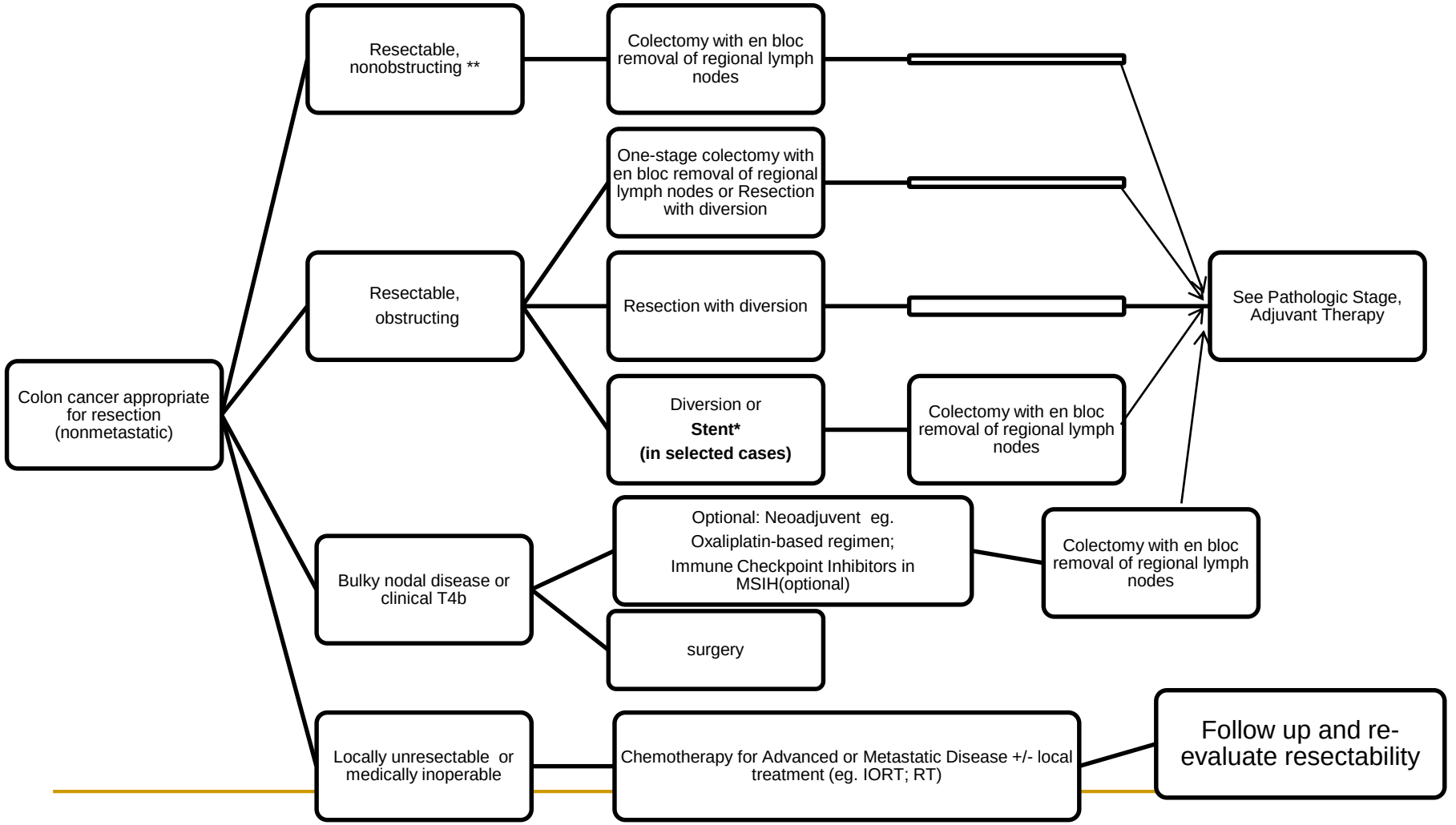
**Pedunculated or sessile polyp (adenoma) with invasive cancer**

- Single specimen, completely removed with favorable histologic features and clear margins
  - Pedunculated polyp with invasive cancer → Observe
  - Sessile polyp with invasive cancer → Observe or Colectomy with en bloc removal of regional lymph nodes
- Fragmented specimen or margin cannot be assessed, or unfavorable histologic features → Colectomy with en bloc removal of regional lymph nodes

# Endoscopically Removed Malignant Polyps

- A malignant polyp is defined as one with cancer invading through the muscularis mucosa and into the submucosa (pT1).
- Favorable histologic features:
  - grade 1 or 2, no angiolymphatic invasion, and negative margin of resection. There is no consensus as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as: 1) tumor <1 mm from the transected margin; 2) tumor <2 mm from the transected margin; and 3) tumor cells present within the diathermy of the transected margin.
- Unfavorable histologic features:
  - grade 3 or 4, angiolymphatic invasion, or a “positive margin.” See the positive margin definition above. In several studies, tumor budding has been shown to be an adverse histologic feature associated with adverse outcome and may preclude polypectomy as an adequate treatment of endoscopically removed malignant polyps.
- There is controversy as to whether malignant colorectal polyps with a sessile configuration can be successfully treated by endoscopic removal. The literature seems to indicate that endoscopically removed sessile malignant polyps have a significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, and hematogenous metastasis, but not lymph node metastasis) than do pedunculated malignant polyps. However, when one closely looks at the data, configuration by itself is not a significant variable for adverse outcome, and endoscopically removed malignant sessile polyps with grade I or II histology, negative margins, and no lymphovascular invasion can be successfully treated with endoscopic polypectomy.

# Surgical management



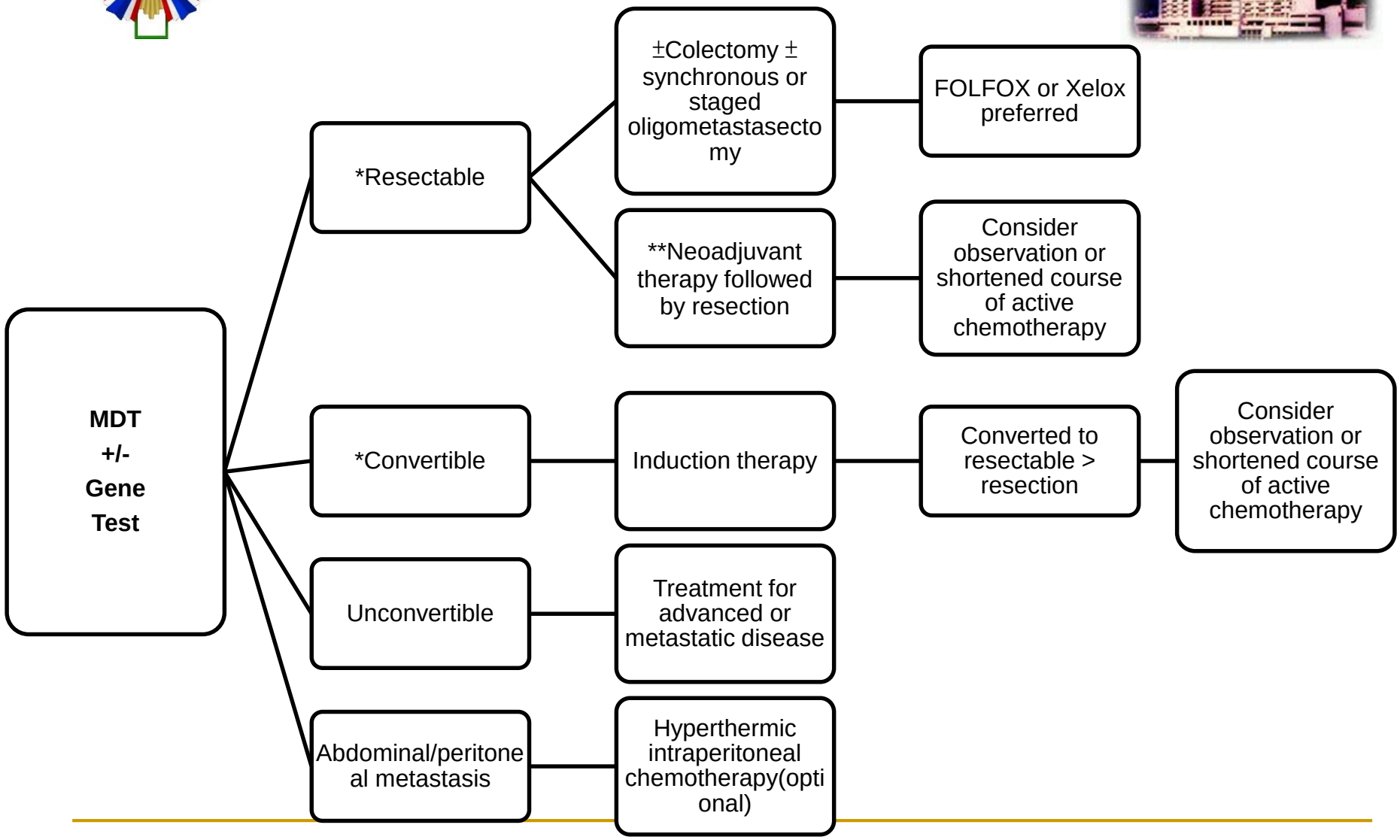
- Neo-adjuvant chemotherapy/RT  is an option for colon cancer.
  - Unfitted for surgery
  - cT4b
  - (cT3-4, N0-2,M0)

# Stage I-III Colon Cancer

- pStage I
  - Observation
- pStage II
  - MSI-H
    - Observation (preferred)
    - High risk (individual discussion)
      - Oxaliplatin + 5FU
  - MSS
    - No high risk
      - #observation
      - #Xeloda/5FU( 6 mo)
    - High risk*
      - #FOLFOX (6 mo) or Xelox (3 mo)
      - #Xeloda/5FU( 6 mo)
      - #observation
- pStage III
  - T1-3,N1 (low-risk III)
    - #Preferred: FOLFOX (3-6 mo) or Xelox (3 mo)
    - #Xeloda/5FU( 6 mo)
  - T4,N1-2;T any, N2 (high-risk III)
    - #Preferred: FOLFOX (6 mo) or Xelox (3-6 mo)
    - #Xeloda/5FU( 6 mo)

- High-risk factors for recurrence (exclusive of those cancers that are MSI-H): poorly differentiated/undifferentiated histology, lymphatic/vascular invasion, bowel obstruction, <12 lymph nodes examined, perineural invasion, localized perforation, or close, indeterminate, positive margins or tumor budding.
  - In high-risk stage II patients, there are no data that correlate risk features and selection of chemotherapy.
  - Diabetes(VGHTPE).; * Elder >=70 y/o: oxaliplatin (stage II :self pay) is optional

# Stage IV


MDT
+/-
Gene
Test
*Resectable
±Colectomy ± synchronous or staged oligometastasectomy
FOLFOX or Xelox preferred
**Neoadjuvant therapy followed by resection
Consider observation or shortened course of active chemotherapy
*Convertible
Induction therapy
Converted to resectable > resection
Consider observation or shortened course of active chemotherapy
Unconvertible
Treatment for advanced or metastatic disease
Abdominal/peritoneal metastasis
Hyperthermic intraperitoneal chemotherapy(optional)

# Treatment for advanced or metastatic disease

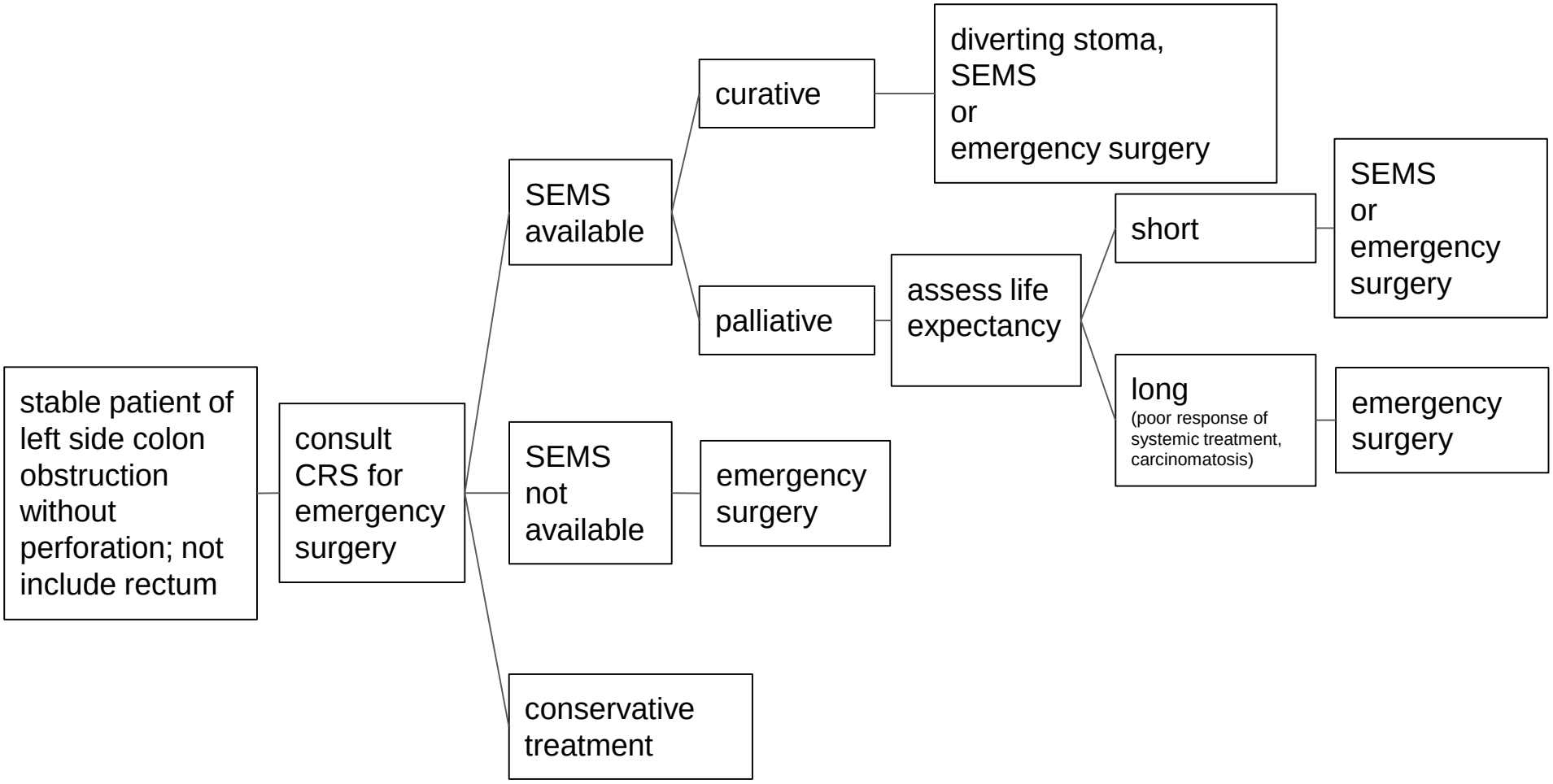
- Gene test is advised for all M1 sample including biopsy.
  - **+/-** {RAS, BRAF, MSI-H, NTRK , Her2, TMB}
  - Individual consideration for patients with gene finding.
- Optional treatment in tumor with MSI-H:
  - Pembrolizumab (preferred) or nivolumab+/-ipilimumab
- Anti-EGFR agent: limited to KRAS/NRAS/BRAF WT gene and left-sided tumors only
- *Resection of primary lesion and oligometastasectomy: individually consideration; Resection is preferred over locally ablative procedures
- Off-label use of treatment could be reserved to patients failed to standard treatment.
- Palliative resection: individual consideration
- Sequence of agents/regimens remains inconclusive
- Sequential use of following regimens in single or combination use (see regimen for metastatic colorectal cancer)

# HIPEC (optional)

- Highly selection of patients
- References
  - Prodige 7- ACCORD 15 trial
  - Portilla AG, Shigeki K, Dario B, Marcello D. The intraoperative staging systems in the management of peritoneal surface malignancy. J Surg Oncol. 2008;98:228-231.
  - Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Peritoneal carcinomatosis: principles of management. Boston, MA: Kluwer Academic Publishers; 1996;359-374.
  - Curr Oncol. 2015 Apr; 22(2): e100–e112. Guidelines on the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal surface malignancy arising from colorectal or appendiceal neoplasms

# Stent

- Must share with patients before stent


stable patient of left side colon obstruction without perforation; not include rectum
consult CRS for emergency surgery
SEMS available
curative
diverting stoma, SEMS or emergency surgery
palliative
assess life expectancy
short
SEMS or emergency surgery
long
(poor response of systemic treatment, carcinomatosis)
emergency surgery
SEMS not available
emergency surgery
conservative treatment

MUST SHARE WITH PATIENTS BEFORE STENT

| | Stent, BT | Emergency Surgery for tumor resection |
|---|---|---|
| **perforation** | 8.9-14% | - |
| recurrence | 35-40% | 24-26% |
| mortality | 3.6-9.6% | 5.6-9.9% |
| overall complication | 33% | 48.25% |
| permanent stoma | 22% | 35% |
| derivative stoma | 23-47.5% | - |

BTS success rate about 70%

Tan *et al. World Journal of Emergency Surgery* (2021) 16:11
https://doi.org/10.1186/s13017-021-00355-2

World Journal of Emergency Surgery

RESEARCH ARTICLE Open Access

# Comparison of the prognosis of four different treatment strategies for acute left malignant colonic obstruction: a systematic review and network meta-analysis

Ling Tan[1†], Zi-lin Liu[1†], Meng-ni Ran[2], Ling-han Tang[1], Yan-jun Pu[1], Yi-lei Liu[1], Zhou Ma[1], Zhou He[1] and Jiang-wei Xiao[1*]

**Table 3** Pairwise comparisons for 5-year survival outcomes

| | | | | |
|---|---|---|---|---|
| **DFS** | **CS-BTS** | **TCT-BTS** | **DS-BTS** | **ER** |
| | | **1.23 (0.88–1.72)** | **0.97 (0.88–1.07)** | **1.12 (1.06–1.35)** |
| | TCT-BTS | – | 0.79 (0.56–1.12) | 0.97 (0.70–1.36) |
| | DS-BTS | – | – | **1.23 (1.06–1.44)** |
| OS | CS-BTS | 1.29 (0.85–1.97) | **0.88 (0.80-0.98)** | **1.14 (1.04–1.26)** |
| | TCT-BTS | – | 0.68 (0.45–1.05) | 0.89 (0.59–1.34) |
| | DS-BTS | – | – | **1.29 (1.13–1.48)** |

Hazard ratio horizontal treatment over vertical treatment (95% credible intervals CI)

**Table 4** Pairwise comparisons for short-term postoperative outcomes

| | | TCT-BTS | DS-BTS | ER |
|---|---|---|---|---|
| Primary anastomosis* | CS-BTS | 0.98 (0.26–3.71) | 0.61 (0.22–1.68) | **0.23 (0.13–0.38)** |
| | TCT-BTS | – | 0.63 (0.12-3.05) | **0.23 (0.06–0.84)** |
| | DS-BTS | – | – | 0.37 (0.13–1.06) |
| Mortality* | CS-BTS | 1.48 (0.29–6.29) | 0.71 (0.35-1.23) | **2.13 (1.59–3.22)** |
| | TCT-BTS | – | 0.48 (0.10-2.61) | 1.45 (0.35–8.01) |
| | DS-BTS | – | – | **3.03 (1.75–6.67)** |
| Anastomotic leak* | CS-BTS | 1.69 (0.35–7.88) | 0.75 (0.22–2.21) | 1.33 (0.84–2.21) |
| | TCT-BTS | – | 0.45 (0.07–3.11) | 0.79 (0.17–3.89) |
| | DS-BTS | – | – | 1.77 (0.61–6.11) |
| Permanent colostomy* | CS-BTS | 1.89 (0.50–7.14) | 0.98 (0.27–3.51) | **3.28 (1.75–6.41)** |
| | TCT-BTS | – | 0.52 (0.08–3.34) | 1.75 (0.45–6.77) |
| | DS-BTS | – | – | 3.35 (0.88–14.07) |
| Hospital stays† | CS-BTS | **−15.35 (−25.43–5.13)** | **13.76 (9.13–18.03)** | 2.10 (−0.44–5.27) |
| | TCT-BTS | – | **29.00 (18.02–39.73)** | **17.46 (6.24–27.77)** |
| | DS-BTS | – | – | **−11.58 (−15.60–6.77)** |

Statistically significant outcomes in bold: OR was significant if the 95% CI did not include the value 1, MD was significant if the 95% CI did not include the value 0

*Odds ratio of horizontal treatment over vertical treatment

†Mean difference of horizontal treatment minus vertical treatment, (95% credible intervals CI)

MUST SHARE WITH PATIENTS BEFORE STENT

| | Stent | Stent (adjusted) | Stoma (TPEVGH) |
|---|---|---|---|
| **perforation** | 8.9-14% | - | - |
| recurrence | 35-40% | 42.5% (38.5-46.8) | 41.2% |
| mortality | 3.6-9.6% | 0.7% (0.4-1.4) | 0.5% |
| overall complication | 33% | - | 43.6% |
| permanent stoma | 22% | 12.6% (3.5-45.6) | 12.3% |
| derivative stoma | 23-47.5% | - | - |

BTS success rate about 70%

# Safety and Oncological Outcomes of Bevacizumab Therapy in Patients With Advanced Colorectal Cancer and Self-expandable Metal Stents

obstructive metastatic CRC who underwent endoscopic stent placement between January 2012 and December 2017

**Table 1** Clinical and Demographics Characteristics of the Study Group

| Clinical Features | N (%) | | |
|---|---|---|---|
| | No Treatment | Chemotherapy Alone | BV-based Regimen |
| **Gender** | | | |
| Male | 13 (16) | 13 (34) | 3 (19) |
| **Primary Tumor Stage** | | | |
| cT1-cT3 | 6 (19) | 3 (9) | 3 (19) |
| cT4 | 14 (45) | 12 (39) | 5 (31) |
| Unknown | 11 (36) | 16 (52) | 8 (50) |
| **Sidedness** | | | |
| Left colon | 29 (94) | 29 (94) | 16 (100) |
| Right colon | 2 (6) | 2 (6) | 0 (0) |
| **RAS Status** | | | |
| Native | 2 (6) | 13 (42) | 5 (31) |
| Mutated | 6 (20) | 13 (42) | 10 (62.5) |
| Unknown | 23 (74) | 5 (16) | 1 (6.5) |
| Median OS (mo) | 11 | 20 | 43 |

Abbreviations: BV = bevacizumab; OS = overall survival.

**Table 2** Overall Complications According to Treatment

| Complications | N (%) | | |
|---|---|---|---|
| | No Treatment (n = 31) | Chemotherapy Alone (n = 31) | BV-based Regimen (n = 16) |
| Perforation | 2 (6) | 3 (9.7) | 2 (12.5) |
| Re-obstruction | 5 (16) | 7 (22.5) | 2 (12.5) |
| Minor bleeding | 0 | 2 (6.5) | 2 (12.5) |
| Stent migration | 1 (3) | 1 (3) | 0 |
| Total | 8 (26) | 13 (42) | 6 (37.5) |

Abbreviation: BV = bevacizumab.

**Table 3** Univariate Analysis of Factors Related to Overall Complications

| Variable | OR (95% CI) | *P* Value |
|---|---|---|
| Male gender | 1.10 (0.42-2.88) | .52 |
| cT3-cT4 | 0.54 (0.20-1.44) | .27 |
| RAS-native | 0.90 (0.28-2.88) | .54 |
| Chemotherapy | 2.39 (1.06-5.38) | .029[a] |
| BV-based regimen | 1.24 (0.39-3.95) | .46 |

# Treatment for advanced or metastatic disease

- Drugs
  - 5FU$^{base}$
  - Irinotecan
  - Oxaliplatin
  - Bevacizumab
  - Cetuximab$^{RAS/BRAF(wild)}$
  - Panitumumab$^{RAS/BRAF(wild)}$
  - Aflibercept
  - *Ramucirumab*
  - Regorafenib
  - Lonsurf

- Drugs
  - Pembrolizumab
  - Nivolumab Ipilimumab
  - Dostarlimab
  - OIND :duloxetine for neuropathy
  - Vemurafenib(Zelboraf)
  - Trastuzumab
  - Pertuzumab
  - Lapatinib
  - Dabrafenib +/-Trametinib
  - Encorafenib +/-Binimetinib
  - Larotrectinib

# Surveillance

- History and physical every 3-6 months for 2 years, then every 6 months for a total of 5 years
- Tumor markers (eg: CEA, CA19-9..etc):
  - every 3-6 months for 2 years, then every 6 months for a total of 5 years
- Images (eg: Chest/abdominal CT/sonography/X-ray/MRI..etc)
  - annually for 5 years(optional)
- Colonoscopy
  - in 1 year except if no preoperative complete colonoscopy, colonoscopy in 3-6 months.
  - If abnormal, repeat in 1-2 year
  - If no advanced adenoma, repeat in 3 years, then every 5 years
- PET-CT scan is not routinely recommended

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# Principle of Surgery

# Principle of Surgery

- Colectomy
  - Lymphadenectomy
    - Lymph nodes at the origin of feeding vessel should be identified for pathologic exam.
    - Clinically positive lymph nodes outside the field of resection that are considered suspicious should be biopsied or removed, if possible.
    - Positive nodes left behind indicate an incomplete (R2) resection.
    - A minimum of 12 lymph nodes need to be examined to establish N stage.
  - Laparoscopic-assisted colectomy may be considered based upon the following criteria:
    - The surgeon has experience performing laparoscopically assisted colorectal operations.
    - There is no locally advanced disease.
    - It is not indicated for acute bowel obstruction or perforation from cancer.
    - Thorough abdominal exploration is required.
  - Consider preoperative marking of small lesions
  - Management of patients with carrier status of known or clinically suspected HNPCC
    - Consider more extensive colectomy for patients with a strong family history of colon cancer or young age (<50 y).
  - Resection needs to be complete to be considered curative.

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# Principles of Radiation Therapy

# Principles of Radiation Therapy

- Optional/individual consideration
- Radiation therapy fields should include the tumor bed, which should be defined by preoperative radiological imaging and/or surgical clips.
- Radiation doses should be 45 Gy in 25-28 fractions.
  - Consider boost for close or positive margins.
  - Small bowel dose should be limited to 45 Gy.
  - 5-fluorouracil based chemotherapy should be delivered concurrently with radiation.
- If radiation therapy is to be used, conformal external beam radiation should be routinely used and intensity-modulated radiation therapy (IMRT) should be reserved only for unique clinical situations including re-irradiation of previously treated patients with recurrent disease.
- Intraoperative radiation therapy (IORT), if available, should be considered for patients with T4 or recurrent cancers as an additional boost. Preoperative radiation therapy with concurrent 5-FU-based chemotherapy is a consideration for these patients to aid resectability. If IORT is not available, additional 10-20 Gy external beam radiation and/or brachytherapy could be considered to a limited volume.
- In patients with a limited number of oligometastasis (liver or lung metastases), radiotherapy can be considered in highly selected cases or in the setting of a clinical trial.
- Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3-D conformal radiation therapy, IMRT, or stereotactic body radiation therapy (SBRT) (category 3).

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# Other Modalities

# Other Modalities

- Used as palliative modalities
  - RFA (Radiofrequency Tumor Ablation)
  - TAE (Transarterial Embolization)
  - PEIT (Percutaneous Ethanol Injection Therapy)
  - Radioembolization withYttrium 90
    - Some institutions use arterially directed embolization in select patients with chemotherapyresistant/refractory disease, without obvious systemic disease, and with predominant hepatic metastases (category 3).
  - Cryotherapy
  - Tomotherapy
  - Cyberknife

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# Principles of liver metastasectomy

# Radiology evaluation of liver metastasis

- Thoraco-abdominal dynamic contrast-enhanced CT is the best option for initial staging
- MRI is more sensitive than CT for subcentimeter lesions, especially after neoadjuvant therapy.
- PET-CT may be used for detection of extrahepatic lesions, especially for recurrent disease or high tumor load( multinodular or large metastasis)

# Pathology evaluation on liver metastasis lesions

- Size and number of tumors
- Surgical margin
- Toxic effects of therapy on non-tumor tissue
  - Sinusoidal injury, steatohepatitis, steatosis
- Pathologic response to chemotherapy
  - Percentage of viable tumor cells
- Presence of hepatic micrometastases
- Biologic markers
  - RAS mutation, BRAF mutation

# Resectability

- Resectability
  - Planed resection (R0)
  - Adequate future remnant liver function
    - At least two contiguous functional liver segments
    - At least 30% of total liver volume
    - With adequate blood inflow, out blow and biliary drainage
  - Limited resectable extrahepatic metastasis

# Evaluate Resectability of Liver Metastatic Lesions of Colorectal Cancer

- Without chronic liver disease
  - Without previous chemotherapy → CT or MRI; FLR (Future liver remnant) > 30%
  - With previous prolonged chemotherapy → CT or MRI; FLR>30%-40%; Biopsy for non-tumor liver if necessary**
- With chronic liver disease*
  - Without previous prolonged chemotherapy → CT or MRI; FLR > 30%-40%; ICG test
  - With previous prolonged chemotherapy → CT or MRI; FLR>40%-50%; ICG test; Biopsy for non-tumor liver if necessary**

# Evaluate Resectability of Liver Metastatic Lesions of Colorectal Cancer

* Chronic liver disease refers to HBV infection, HCV infection, cirrhosis or alcoholic liver disease

** If severe steatosis or steatohepatitis was suspected, serum AST or ALT level > 2X upper normal limit, or major liver resection is planed

- Hepatectomy should be performed as soon as liver lesions are resectable
- Duration of chemotherapy should be limited before hepatectomy
- Radiology assessment frequency: 6-8 wks intervals
- At least 3-4 weeks interval between chemotherapy and hepatectomy
- At least 6 weeks interval between bevacizumab treatment and hepatectomy

# Preoperative Liver Function Assessment (ICG test)

Ascites absent or controllable

↓

Serum total bilirubin level

↓

| Normal | 1.1-1.5 mg/dl | 1.6-1.9 mg/dl | >2.0 mg/dl |
|---|---|---|---|
| ↓ | ↓ | ↓ | ↓ |
| ICG 15 value | Limited resection | Enucleation | Hepatectomy not indicated |

| Normal | 10%-19% | 20%-29% | 30-39% |
|---|---|---|---|
| ↓ | ↓ | ↓ | ↓ |
| Rt lobectomy Trisegmentectomy | Segmentectomy | Subsegmentectomy | Limited resection |

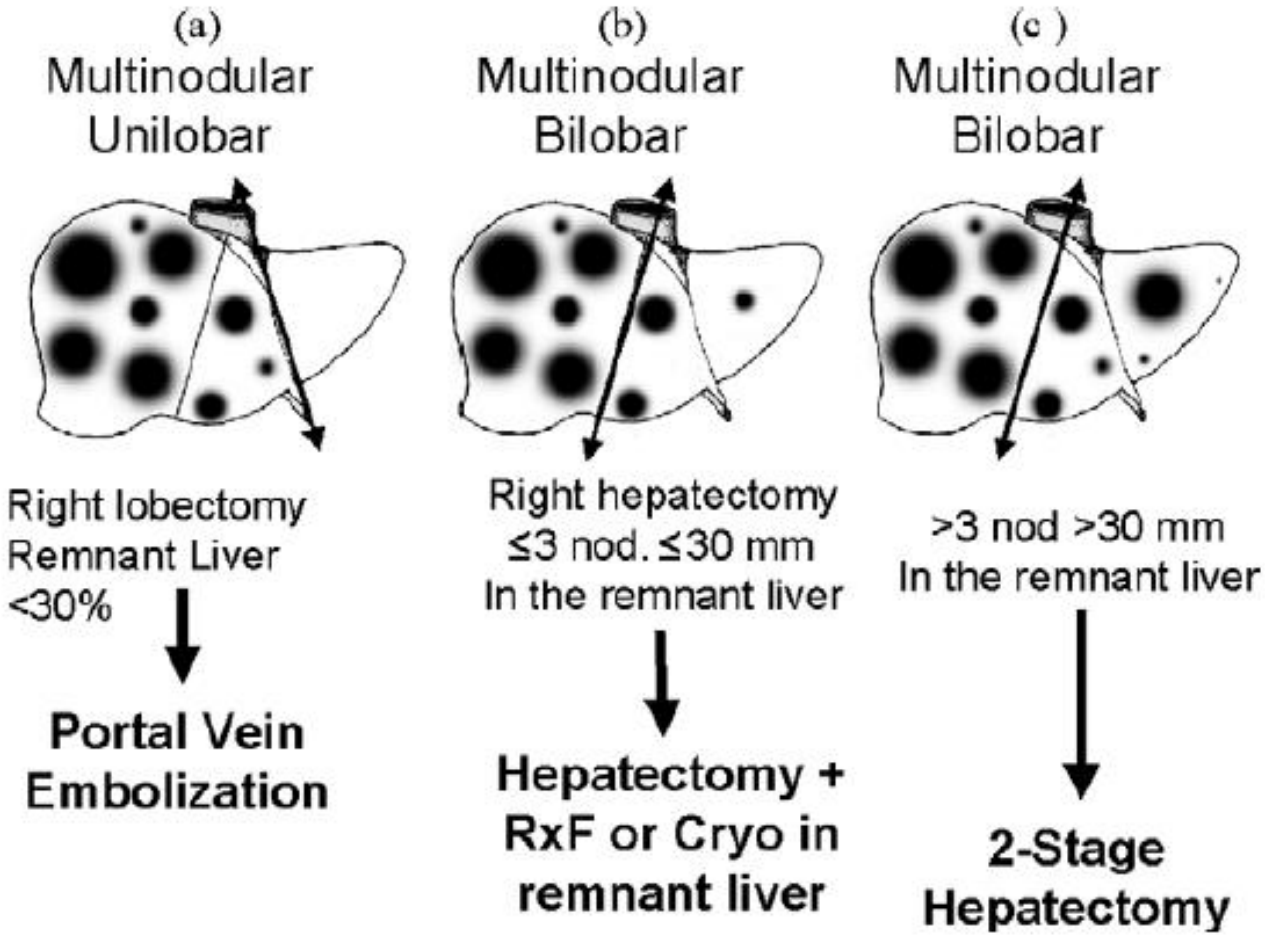
*Makuuchi M, et al. Criteria for safe hepatic resection Am J Surg 1995;169:589-594*

# Classic Strategy of Unresectable Liver Metastases due to Insufficient Remnant Liver Volume

- **Classic Strategy**
  - Preoperative systemic chemotherapy
  - Portal vein embolization
    - Multinodular unilobar
  - Combined radiofrequency ablation
    - Multinodualr bilobar/ small and few tumors in remnant liver
  - Two-stage hepatectomy
    - Multinodualr bilobar/ larger tumors in remnant liver

- **Alternative strategy**
  - Yttrium-90 radioembolization
  - ALPPS - Associating Liver Partition and Portal Vein Ligation

# Proposed strategy for primarily unresectable multinodular liver metastases




Adam. Surg Clin N Am (2004)

# Resectable synchronous liver metastases

1)Synchronous colon-liver resection

2) Neoadjuvant therapy followed by synchronous or staged colon-liver resection

3) Colectomy, followed by chemotherapy and staged liver resection

→ Adjuvant therapy (6 months total preoperative treatment)

For resectable metastatic lesion, resection is preferred over local ablative procedure

# Unresectable or potentially convertible synchronous liver metastases

1)Systemic therapy

2) Colon resection only if immediate risk of obstruction, bleeding, or perforation.

→ Re-evalute for conversion to resectable every 2 months

→ Convert to resectable → synchronous or staged resection

→ Remain unresectable→ systemic therapy **+/-** Resection of primary tumor

# Surgical approach toward synchronous colorectal cancer with liver metastases

- One stage surgery( simultaneous liver and colorectal resection) could be adapted in with limited liver resection and colon resection.
- For patients needed complex surgery, major liver resection, old age, or with multiple co-morbidities, staged liver surgery and colorectal surgery should be considered according to patient's individual condition.
- Combined laparoscopic colorectal and minor liver resection could be safely performed in selected patients.
- In rectal cancer with liver metastasis, short-course radiotherapy could be considered followed by liver and rectal surgery.
- In initial unresectable liver metastasis, , short-course radiotherapy could be considered in initial treatment, followed by liver oriented chemotherapy to downsize liver metastatic lesions before rectal surgery

# Resectable metachronous liver metastases

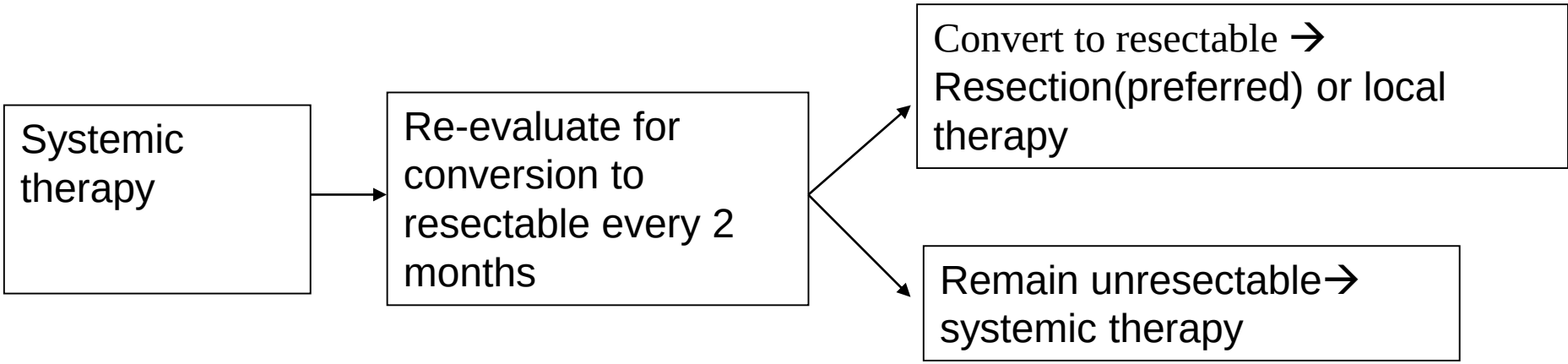
1)Resection(preferred) or local therapy

2) Neoadjuvant therapy followed by resection or local therapy

→ Adjuvant therapy

For resectable metastatic lesion, resection is preferred over local ablative procedure

# Unresectable or potentially convertible metachronous liver metastases



# Liver resection following neoadjuvant chemotherapy

- The optimal timing for assessing response to chemotherapy is considered to be every 2 months.
- At least 4 weeks interval between stopping chemotherapy and liver resection is suggested if the chemotherapy regimens contained FOLFOX, FOLFIRI or combined with targeted therapy cetuximab
- At least 6 weeks interval should be considered in patient receiving target therapy with bevacizumab
- (optional )Cetuximab or panitumumab should only be used for left-sided colon tumors. The panel defines the left side of the colon as splenic flexure to rectum. Evidence suggests that patients with tumors originating on the right side of the colon (hepatic flexure through cecum) are unlikely to respond to cetuximab and panitumumab. Data on the response to cetuximab and panitumumab in patients with primary tumors originating in the transverse colon (hepatic flexure to splenic flexure) are lacking

# Surgical approach to CRCLM with extrahepatic disease(EHD)

- Long-term survival for CRCLM with concurrent EHD after totally remove of metastatic lesions is possible
- Patients with favorable prognostic factors could be selected for surgery
  - Less liver metastatic lesion (tumor number<=5)
  - Single EHD metastatic site
  - Low CEA level
  - Resectable EHD
  - Patient tolerate and tumor shrinkage after initial intensive therapy (cytotoxic doublet + EGFR antibody or bevacizumab, or cytotoxic triplet + bevacizumab)
- BRAF mutation is a poor prognostic factor for liver metastases and should be tested before liver metastasectomy.

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# Evaluate Resectability of Lung Metastatic Lesions of Colorectal Cancer

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# Evaluate Resectability of Lung Metastatic Lesions of Colorectal Cancer

# Evaluate Resectability of Lung Metastatic Lesions of Colorectal Cancer

- For lesions <1.5-1.8 cm, it is hard to differentiate between neoplasm and normal lesions
- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.
- The primary tumor must have been resected for cure (R0).
- Re-resection can be considered in selected patients.
- Ablative techniques may be considered alone or in conjunction with resection for resectable disease.
- Ablative techniques can also be considered when unresectable and amenable to complete ablation.
- Patients with resectable synchronous metastases can be resected synchronously or using a staged approach.
- Conformal external bean radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgical resectable.

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# Pathology Reviews

- Colon cancer appropriate for resection
  - Histological confirmation of primary colonic malignant neoplasm
- Pathological stage
  - The following parameter should be reported
    - Grade of the tumor
    - Depth of penetration ( T )
    - Number of lymph nodes evaluated and number positive ( N)
    - Status of proximal, distal, and radial margins
    - Lymphovascular invasion
    - Perinural invasion
    - Extra-nodal tumor deposits

# Principles of Pathologic review

- Lymph node evaluation
  - The AJCC and College of American pathologists recommend examination of a minimum of 12 lymph nodes to accurately indentify stage II colorectal cancer.
  - For stage II colon cancer, if less than 12 lymph nodes are initially indentified, it is recommended that the pathologist go back to the specimen and resubmit more tissue for potential lymph nodes. If 12 lymph nodes are still not identified, a comment in the report should indicate that an extensive search for lymph nodes was undertaken.
  - The pathologist should attempt to retrieve as many lymph nodes as possible. It has been shown that the number of negative lymph nodes is an independent prognostic factor for patients with stage IIIB and IIIC colon cancer.
  - Sampling of 12 LNs may not be achievable in patients after preoperative therapy.

# Gene Test

- Optional
- RAS
- BRAF
- MMR/MSI
- NTRK
  - wild type RAS BRAF and arguably to MSI-H
  - 0.35% in CRC
- Her2
- UGT1A1
- TMB

# CHEMOTHERAPY

# ADJUVANT THERAPY for COLON CANCER

- FOLFOX is superior to 5-FU/leucovorin for patients with stage III colon cancer.(1, 2)
- Capecitabine/oxaliplatin is superior to bolus 5-FU/leucovorin for patients with stage III colon cancer. FLOX is an alternative to FOLFOX or CapeOx but FOLFOX or CapeOx are preferred. (3)
- Capecitabine appears to be equivalent to bolus 5-FU/leucovorin in patients with stage III colon cancer.(4)
- A survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer.(5) FOLFOX is reasonable for high-risk stage II patients and is not indicated for good- or average-risk patients with stage II colon cancer.
- Adjuvant therapy should be administered as soon as the patient is medically able.(after tumor resection 4-6 weeks)

- Adjuvant Chemoradiation: considered for very select patients with disease characterized as T4 tumors
- Adjuvant Regimens: FOLFOX or XELOX preferred
- Treatment times:12 cycle
- **5-FU based regimens**
  - **De Gramont (dG) :** Leucovorin 200 mg/m$^2$ IV (2h inf), day 1,2 .5-FU 400 mg/m$^2$ IV( bolus) x 2 days then 600 mg/m2 (22h inf)day x 2 days.To be repeated every 2 weeks. (6-8)
  - **5-FU/leucovorin :** Leucovorin 500 mg/m$^2$ given as a 2-hour infusion and repeated weekly x 6. 5-FU 500 mg/m2 given bolus 1 hour after the start of leucovorin and repeated 6 x weekly. Every 8 weeks for 4 cycles. (9)
  - **Simplified biweekly infusional 5-FU/LV (sLV5FU2) :** Leucovorin 400** mg/m$^2$ IV 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. **(10)**

- **UFT+folinic acid ：** UFT 100 mg/$m^2$ PO tid daily day 1-28 .Folinic acid 25mg or 30 mg /$m^2$ PO tid daily days 1-28.To be repeated every 5 weeks .Duration 6-24 months (11, 12)
- **Xeloda(** Capecitabine) ： Xeloda 1250 mg/$m^2$ twice daily days 1-14 every 3 weeks x 24 weeks (4)

- **Oxaliplatin_5-FU based regimens**
  - **mFOLFOX6** ：Oxaliplatin 85 mg/$m^2$ IV, day 1* .Leucovorin 400 mg/$m^2$ IV, 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) continuous infusion. Repeat every 2 weeks.(1, 13, 14)
  - **FOLFOX4** ： Leucovorin 200(or 100) mg/$m^2$ IV(2h inf), day 1,2.Oxaliplatin 85 mg/$m^2$ IV(2 hour inf), day 1 concurrent with folonic acid.5-FU 400 mg/$m^2$ IV( bolus) x 2 days then 600 mg/$m^2$(22h inf)day x 2 days .To be repeated every 2 weeks. (1)
  - **mFOLFOX7 :**Oxaliplatin 130 mg/$m^2$ IV , day 1*.Leucovorin** 400 mg/$m^2$ IV, day 1**.5-FU 2400 mg/$m^2$/2day iv 46 hrs .Repeat every 2 weeks (15)

- **FLOX :** 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. (3)
- **CapeOx :** Oxaliplatin 130 mg/m$^2$ over 2 hours, day 1 .Capecitabine 1000 mg/m$^2$ twice daily days 1–14 every 3 weeks x 24 weeks. (16)

- Note

*Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m$^2$/minute. Leucovorin infusion should match infusion time ofoxaliplatin. Cercek A, Park V, Yaeger RD, et al. Oxaliplatin can be safely infused at a rate of 1mg/m$^2$/min. J Clin Oncol 33, 2015 (suppl; abstr e14665).**Leucovorin 400 mg/m$^2$ is the equivalent of levoleucovorin 200 mg/m$^2$.†NCCN recommends limiting chemotherapy orders to 24-h units (ie, 1200 mg/m2/day NOT 2400 mg/m$^2$ over 48 hours) to minimize medication errors.

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# Chemotherapy for advanced or metastatic colorectal cancer

- **5-FU based regimens**
  - **de Gramont** : Leucovorin 200 mg/m$^2$ IV (2h inf), day 1,2.5-FU 400 mg/m$^2$ IV( bolus) x 2 days then 600 mg/m2 (22h inf)day x 2 days. To be repeated every 2 weeks. (1-3)
  - **Capecitabine** : 850–1250 mg/m$^2$ PO twice daily, days 1–14 .Repeat every 3 weeks(4)
- **Bolus or infusional 5-FU/leucovorin**
  - **Roswell Park regimen** : 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 (5)
  - **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 (6)

- **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. (7) 5-FU 2600 mg/m$^2$ by 24-hour infusion plus leucovorin 500 mg/m$^2$ .Repeat every week (8)
- **UFUR :** UFT (300 mg/m$^2$/d) and LV (75 or 90 mg/d) for 28 days every 35 days (9)

- **FOLFOX**
  - **mFOLFOX6 :** Oxaliplatin 85 mg/m$^2$ IV , day 1*Leucovorin** 400 mg/m$^2$ IV, 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 (10-12)
  - **FOLFOX4 :** Leucovorin 200(or 100) mg/m$^2$ IV(2h inf), day 1,2 .Oxaliplatin 85 mg/m$^2$ IV(2 hour inf), day 1 concurrent with folonic acid .5-FU 400 mg/m$^2$ IV( bolus) x 2 days then 600 mg/m$^2$(22h inf)day x 2 days .To be repeated every 2 weeks. (13)
  - **mFOLFOX7 :** Oxaliplatin *130 mg/m$^2$ IV , day 1* Leucovorin** 400 mg/m$^2$ IV, day 1** .5-FU 2400 mg/m$^2$/2day iv 46 hrs .Repeat every 2 weeks (14)

- **mFOLFOX6 + Bevacizumab :** Oxaliplatin 85 mg/m$^2$ IV, day 1* Leucovorin 400 mg/m$^2$ IV, 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 .Bevacizumab 5 mg/kg IV, day 1 .Repeat every 2 weeks(10, 15)
- **mFOLFOX6 + Panitumumab (*KRAS/NRAS* WT gene only) :** Oxaliplatin 85 mg/m$^2$ IV, day 1* Leucovorin 400 mg/m$^2$ IV, 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 Panitumumab 6 mg/kg IV over 60 minutes, day 1. Repeat every 2 weeks (10, 16)
- **FOLFOX + Cetuximab (*KRAS/NRAS* WT gene only) :** Oxaliplatin 85 mg/m$^2$ IV, day 1* Leucovorin 400 mg/m$^2$ IV, 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 .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, every 2 weeks(10, 17)

- **CapeOX :** Oxaliplatin 130 mg/m$^2$ IV over 2 hours, day 1 Capecitabine 850–1000 mg/m$^2$ twice daily PO for 14 days Repeat every 3 weeks (11, 13) or Oxaliplatin 85 mg/m$^2$ IV over 2 hours, day 1 .Capecitabine 1000 mg/m$^2$ twice daily PO for days 1-7 .Repeat every 2 weeks (18)
- **CapeOX (11) + Bevacizumab (19) :** Oxaliplatin 130 mg/m$^2$ IV over 2 hours, day 1 .Capecitabine 850–1000 mg/m$^2$ PO twice daily for 14 days .Bevacizumab 7.5 mg/kg IV, day 1 .Repeat every 3 weeks(11,19
- **FOLFIRI :** 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 (6)
- **FOLFIRI (6) + Bevacizumab (20) :** Irinotecan 180 mg/m$^2$ IV over 30–90 minutes, day 1 .Leucovorin** 400 mg/m2 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)† IV continuous infusion .Bevacizumab 5 mg/kg IV, day 1 .Repeat every 2 weeks

- **FOLFIRI (6) + Cetuximab (21) (KRAS/NRAS WT gene only) :** 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)† IV continuous infusion. Repeat every 2 weeks
- **Cetuximab :** 400 mg/m$^2$ IV over 2 hours first infusion, then 250 mg/m$^2$ IV over 60 minutes weekly (22) or Cetuximab 500 mg/m$^2$ IV over 2 hours, day 1, every 2 weeks (23)
- **FOLFIRI (6) + Panitumumab(24) (KRAS/NRAS WT gene only) :** 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,day1 .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)† IV continuous infusion .Panitumumab 6 mg/kg IV over 60 minutes, day 1. Repeat every 2 weeks

- **FOLFIRI + ziv-aflibercept :** 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 .Ziv-aflibercept 4 mg/kg IV over 60 minutes, day 1 .Repeat every 2 weeks (25)
- **ziv-aflibercept :** Ziv-aflibercept 4 mg/kg IV over 60 minutes, day 1

  Repeat every 2 weeks (25)
- **FOLFIRI + ramucirumab :** Irinotecan 180 mg/m$^2$ IV over 90 minutes, day 1 Leucovorin** 400 mg/m$^2$ IV 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)† IV continuous infusion Ramucirumab 8 mg/kg over 60 minutes, day 1 .Repeat every 2 weeks(26)
- **XELIRI :** Irinotecan 240 or 250 mg/m$^2$ IV over 90 minutes, day 1 .Capecitabine1000 mg/m$^2$ PO twice daily days 2-15 .To be repeated every 3 weeks (27, 28) or Irinotecan 175 mg/m$^2$ IV over 30 minutes, day 1 .Capecitabine 1000 mg/m2 PO twice daily days 2-8 .To be repeated every 2 weeks (29)

- **IROX :** Oxaliplatin 85 mg/m$^2$ IV over 2 hours, followed by irinotecan 200 mg/m$^2$ over 30-90 minutes every 3 weeks(30)
- **FOLFOXIRI :** 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(31, 32)± Bevacizumab (33) 5 mg/kg IV, day 1
- **Irinotecan :** Irinotecan 125 mg/m$^2$ IV over 30-90 minutes, days 1 and 8 .Repeat every 3 weeks (34, 35) 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
- **Cetuximab (*KRAS/NRAS* WT gene only) :** Cetuximab 400 mg/m$^2$ first infusion, then 250 mg/m$^2$ IV weekly (36) or Cetuximab 500 mg/m$^2$ IV over 2 hours, day 1, every 2 weeks (23)

- **Cetuximab (*KRAS/NRAS* WT gene only) + irinotecan :** Cetuximab 400 mg/m$^2$ first infusion, then 250 mg/m$^2$ IV weekly (36) or Cetuximab 500 mg/m$^2$ IV over 2 hours, day 1, every 2 weeks (23) Irinotecan 300-350 mg/m$^2$ IV over 30-90 minutes, day 1 .Repeat every 3 weeks or Irinotecan 180 mg/m$^2$ IV over 30-90 minutes, day 1 .Repeat every 2 weeks or Irinotecan 125 mg/m$^2$ IV over 30-90 minutes, days 1 and 8Repeat every 3 weeks
- **Panitumumab (*KRAS/NRAS* WT gene only) :** Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks(38)
- **Regorafenib :** Regorafenib 160 mg PO daily days 1-21 .Repeat every 28 days(37) or First cycle: Regorafenib 80 mg PO daily on days 1-7, then 120 mg PO daily on days 8-14, then 160 mg PO daily on days 15-21 Subsequent cycles: Regorafenib 160 mg PO daily on days 1-21 Repeat every 28 days(ReDOS)
- **(TAS-102) Trifluridine + tipiracil 35 mg/m$^2$ up to a maximum dose of 80 mg per dose (based on the trifluridine component) :** PO twice daily days 1-5 and 8-12 .Repeat every 28 days (39)
- **Trifluridine + tipiracil ± bevacizumab**
  Trifluridine + tipiracil 35 mg/m$^2$ up to a maximum dose of 80 mg per dose (based on the trifluridine component) PO twice daily days 1–5 and 8–12 Bevacizumab 5 mg/kg on days 1 and 15 Repeat every 28 days

- Pembrolizumab (dMMR/MSI-H only)
  - Pembrolizumab 2 mg/kg IV every 3 weeks
  - Pembrolizumab 200 mg IV every 3 weeks
  - Pembrolizumab 400 mg IV every 6 weeks

- Nivolumab34 (dMMR/MSI-H only)
  - Nivolumab 3 mg/kg every 2 weeks
  - Nivolumab 240 mg IV every 2 weeks
  - Nivolumab 480 mg IV every 4 weeks

- Nivolumab + ipilimumab (dMMR/MSI-H only)
  - 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 or Nivolumab 480 mg IV every 4 weeks
- Dostarlimab-gxly (dMMR/MSI-H only)
  - Dostarlimab-gxly 500 mg IV every 3 weeks for 4 doses followed by 1000 mg IV every 6 weeks

- Trastuzumabdd + pertuzumab (HER2-amplified and RAS and BRAF WT)
  - Trastuzumab 8 mg/kg IV loading dose on day 1 of cycle 1, then 6 mg/kg IV every 21 days
  - Pertuzumab 840 mg IV loading dose on day 1 of cycle 1, then 420 mg IV every 21 days
- Trastuzumabdd + lapatinib (HER2-amplified and RAS and BRAF WT)
  - Trastuzumab 4 mg/kg IV loading dose on day 1 of cycle 1, then 2 mg/kg IV weekly
  - Lapatinib 1000 mg PO daily
- ENHERTU (fam-trastuzumab deruxtecan-nxki) 6.4 mg/kg iv on day1 , q3wks (HER2-amplified and RAS and BRAF WT)
- Encorafenib + cetuximab(BRAF V600E mutation positive)
  - Encorafenib 300 mg PO daily
  - Cetuximab 400 mg/$m^2$ followed by 250 mg/$m^2$ weekly
- Encorafenib + panitumumab(BRAF V600E mutation positive)
  - Encorafenib 300 mg PO daily
  - Panitumumab 6 mg/kg IV every 14 days
- Larotrectinib (NTRK gene fusion positive)
  - 100 mg PO twice daily
- Entrectinib(NTRK gene fusion positive)
  - 600 mg PO once daily

# Optional

- Dabrafenib +/- trametinib +  cetuximab(BRAF V600E mutation positive)
  - Dabrafenib 150 mg PO twice daily;
  - Trametinib 2 mg PO daily
  - Cetuximab 400 mg/m$^2$ followed by 250 mg/m$^2$ weekly
- Dabrafenib +/- trametinib + panitumumab (BRAF V600E mutation positive)
  - Dabrafenib 150 mg PO twice daily
  - Trametinib 2 mg PO daily
  - Panitumumab 6 mg/kg IV every 14 days
- Encorafenib +/- binimetinib + cetuximab(BRAF V600E mutation positive)
  - Encorafenib 300 mg PO daily
  - Binimetinib 45 mg PO twice daily
  - Cetuximab 400 mg/m$^2$ followed by 250 mg/m$^2$ weekly
- Encorafenib +/- binimetinib + panitumumab(BRAF V600E mutation positive)
  - Encorafenib 300 mg PO daily
  - Binimetinib 45 mg PO twice daily
  - Panitumumab 6 mg/kg IV every 14 days

# Drugs under good clinical practice

- Optional
- **Definition of Drugs(Regimens) under good clinical practice**
  - **Mimic or modification of global clinical trial or paper-based regimens, due the poor efficacy of late-line agents intreating metastatic colorectal cancer.**
  - **For example, Lenvatinib , taxol, IP with anti-VEGF agents ….etc**
- Dosage of Lonsurf from D1-5 8-12 to D 1-5 15-19
- Anti-VEGF for brain and ascites (IP/IV)control
- Lenvatinib +/- biochemotherapy or  check points inhibitors
- BRAFi+/-Meki+/-biochemotherapy
- Biosimilar

- **Note**

*Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/$m^2$/minute. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger RD, et al. Oxaliplatin can be safely infused at a rate of 1mg/m2/min. J Clin Oncol 33, 2015 (suppl; abstr e14665).

**Leucovorin 400 mg/$m^2$ is the equivalent of levoleucovorin 200 mg/$m^2$.

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