COLON CANCER

Initial Workup

- Personal and family history
- Physical examination
- Laboratory Tests:
  - Complete Blood Count (CBC), biochemistry
  - Baseline carcinoembryonic antigen (CEA) and carbohydrate antigen (CA 19-9)
- Colonoscopy (if not performed already, or was incomplete)
- CT thorax + abdomen + pelvis
- PET scan (not routinely)
- Mismatch Repair (MMR) protein testing: for all patients younger than 50 years to screen for Lynch syndrome

TNM Staging for Colon Cancer

Tumor Status	
T	Primary Tumor
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the peri-colorectal tissues
T4	Tumor directly invades or is adherent to other organs or structures

Node Status	
N	Regional Lymph Nodes
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in 1-3 regional lymph nodes

N1c	Tumor deposit(s) in the subserosa, mesentery or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis.
N2	Metastasis in four or more regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in seven or more regional lymph nodes

Metastasis	
M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis present
M1a	Metastasis confined to one organ or site (e.g. liver, lung, ovary, nonregional node)
M1b	Metastasis in more than one organ/site or the peritoneum

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

Stage I

- Surveillance only

Stage II:

• All patients	MMR testing (Genetic test or MSI by immunohistochemical (IHC))
• Patients with MSI-H	Adjuvant chemotherapy is not recommended. They have a good prognosis and do not get benefit from adjuvant therapy
• Low-risk patients	Surveillance and follow-up
• pT3N0 and • no other risk factors and • MSI-Low or Stable	Surveillance and follow-up May also consider Capecitabine or 5-FU/Leucovorin
• pT3, N0, M0 at high risk for systemic recurrence • or T4, N0, M0	Capecitabine, or
	5-FU/Leucovorin or
	FOLFOX or
	CAPEOX for 6 months or
	Observation

High-Risk Factors for Recurrence:

- Poorly differentiated histology (exclusive of those cancers that are MSI-H),
- Lymphatic/vascular invasion,
- Bowel obstruction,
- <12 lymph nodes examined,
- Perineural invasion,
- Localized perforation, or
- Close, indeterminate, or positive margins.

In high-risk stage II patients, there are no data that correlate risk features and selection of chemotherapy.

Stage III:	
Low-risk Stage III (pT1-3, N1)	
Preferred	CAPEOX for 3 months
	FOLFOX for 3–6 months (category 1 for 6 months)
Other options	Capecitabine or 5-FU for 6 months
	or XELOX or FOLFOX-6 (preferred)
	Alternatively: 5FU+FA, FLOX, or Capecitabine for 6 months
High-risk Stage III (pT4, N1-2; T Any, N2)	
Preferred	CAPEOX for 3–6 month (category 1 for 6 months)
	FOLFOX for 6 months (category 1)
Other options	Capecitabine or 5-FU for 6 months

Stage IV and Recurrent Colon Cancer – (Synchronous or Metachronous)	
Pretreatment Considerations	
Careful selection of patients appropriate for intensive treatment	Good performance status (PS)
	No contraindications for any or part of the chemotherapy regimen
Work up	Colonoscopy, Biopsy, CT chest/abdominal/pelvic, Lab: CBC, chemistry profile, CEA, PET/CT scan if potentially curable M1 disease.
Determination of tumor MMR or MSI status	
RAS mutational analysis	Codon 12,13 of K-RAS exon 2, exon3, exon 4 + NRAS exon 2,3 and 4
BRAF mutation status	Prognostic value only
Multidisciplinary team evaluation	Hepatobiliary and cardiothoracic surgeon

Treatment Considerations
Treatment re-challenged: All the chemotherapy regimens can be re-challenged upon progression if the patient has no documented progression while on that regimen in the past
Reassessment should be every 2-3 months and individualized
In case of primary colon or rectum obstruction, or imminent obstruction: • Colon resection, • Diverting colostomy, • Bypass of impending obstruction or • Stenting.
In case of primarily peritoneum limited metastatic disease: • Consider peritonectomy and HIPEC
In case of patients with active coronary artery disease/contraindications to 5FU based regimens: • IROX regimen might be considered.

First-line Treatment

Resectable Synchronous or Metachronous Liver and/or Lung Metastases only: (Group A)

1) Resected staged primary and metastatic disease

- FOLFOX-6 or XELOX adjuvant (Preferred)

↓

2) Neoadjuvant chemotherapy for 2-3 months (consider early re-assessment in 8 weeks)

- FOLFOX-6 or XELOX adjuvant (Preferred)
- FOLFOX-6 or FOLFIRI or XELOX ± Bevacizumab.
- FOLFOX-6 or FOLFIRI or XELOX ± Panitumumab (RAS gene wild type)
- FOLFIRI ± Cetuximab (RAS gene wild type).
- FOLFEXIRI ± Bevacizumab

↓

3) Followed by

- Synchronous or staged resection of the primary tumor and metastatic sites

↓

4) Followed by

- Shortened course adjuvant treatment (to complete 6 months perioperatively)

↓

5) Surveillance
○ As per stage IV no evidence of disease (NED).

Potentially Resectable Synchronous or Metachronous Metastases (Group B)

1) Neoadjuvant chemotherapy for 2-3 months (consider early re-assessment in 8 weeks)
○ FOLFOX-6 or FOLFIRI or XELOX ± Bevacizumab. ○ FOLFOX-6 or FOLFIRI ± Panitumumab (RAS gene wild type) ○ FOLFIRI ± Cetuximab (RAS gene wild type)

2) Re-evaluation for conversion to resectable	
If resectable	**If remains unresectable**
Synchronous or staged resection of the primary tumor and metastatic sites. **Followed by** Continuation of original regimen or observation or shortened course adjuvant treatment	Continuation of original regimen till progression

3) Surveillance: As per stage IV or stage IV NED

Unresectable Synchronous Metastases (Group C)

1) Neoadjuvant chemotherapy for 2-3 months (consider early re-assessment in 8 weeks)
○ FOLFOX-6 or FOLFIRI or XELOX ± Bevacizumab. ○ FOLFOX-6 or FOLFIRI ± Panitumumab (RAS gene wild type) ○ FOLFIRI ± Cetuximab (RAS gene wild type) ○ Irinotecan ± Bevacizumab. ○ Capecitabine ± Bevacizumab ○ 5FU+ LV ± Bevacizumab

2) Re-evaluation for conversion to resectable	
If resectable	**If remains unresectable**
Resection of all or most of the metastatic sites or combinations with radiofrequency ablation (RFA), transarterial chemoembolization (TACE), transarterial radioembolization (TARE).	Continuation of original regimen till progression

Followed by Continuation of original regimen or Observation or Shortened course adjuvant treatment	

3) Surveillance: As per stage IV or stage IV NED

Unresectable Metachronous Metastases (Group D)

1) Received Oxaliplatin-based adjuvant chemotherapy within the past 12 months

- (FOLFIRI or Irinotecan) ± (Bevacizumab [preferred], or Ziv-aflibercept or Ramucirumab)
- If KRAS/NRAS WT gene only: (FOLFIRI or Irinotecan) ± (Cetuximab or Panitumumab)
- If BRAF V600E mutation positive: (Irinotecan + [Cetuximab or Panitumumab] + Vemurafenib)
- In dMMR/MSI-H only: (Nivolumab ± Ipilimumab) or Pembrolizumab
- Capecitabine ± Bevacizumab.
- 5FU+ leucovorin (LV) ± Bevacizumab.

2) Received Oxaliplatin-based adjuvant chemotherapy >12 months before

a) Patient fit for aggressive chemotherapy:

- Consider re-challenge with Oxaliplatin-based regimen:
- FOLFOX ± Bevacizumab or
- CAPEOX ± Bevacizumab or
- FOLFOX + (Cetuximab or Panitumumab) in KRAS/NRAS WT and left-sided tumors only.

If progress on above regimens then consider the following

- (FOLFIRI or Irinotecan) + (Bevacizumab [preferred] or Ziv-aflibercept or Ramucirumab)
- If KRAS/NRAS WT only: (FOLFIRI or Irinotecan) + (Cetuximab or Panitumumab)
- If BRAF V600E mutation positive: Irinotecan + (Cetuximab or Panitumumab) + Vemurafenib
- If dMMR/MSI-H only: (Nivolumab ± Ipilimumab) or Pembrolizumab

Other treatment options include

- FOLFIRI ± Bevacizumab.
- FOLFIRI + (Cetuximab or Panitumumab) in KRAS/NRAS WT and left-sided tumors only.
- FOLFOXIRI ± Bevacizumab.
- 5-FU/Leucovorin (infusional preferred) ± Bevacizumab.
- Capecitabine ± Bevacizumab

b) Patient unfit for aggressive chemotherapy:
○ Infusional 5-FU + Leucovorin ± Bevacizumab. ○ Capecitabine ± Bevacizumab ○ In KRAS/NRAS WT and left-sided tumors only: Cetuximab or Panitumumab (category 2B) ○ If dMMR/MSI-H only: Nivolumab or Pembrolizumab ○ If dMMR/MSI-H only: Nivolumab + ipilimumab (category 2B)

4) Re-evaluation for conversion to resectable (2-3 monthly)	
If resectable	**If remains unresectable**
Resection of all or most of the metastatic sites or combinations with RFA, TACE, TARE. **Followed by** Continuation of original regimen or Observation or Shortened course adjuvant treatment	Continuation of original regimen till progression

3) Surveillance: As per stage IV or stage IV NED

Continuation Treatment

If previously treated with	Second Line Treatment	Third Line Treatment	Fourth Line Treatment
FOLFOX-6 or XELOX ± Bevacizumab	(FOLFIRI or Irinotecan) ± (Bevacizumab or Ziv- aflibercept or Ramuciromab)	Irinotecan + (Cetuximab or Panitumumab)	Regorafenib or Trifluridine + Tipiracil or Best supportive care
	In RAS & NRAS wild type: (FOLFIRI, Irinotecan) ± (Panitumumab or Cetuximab)	or Regorafenib	
	In RAS & NRAS wild type: Cetuximab or Panitumumab	or Trifluridine + Tipiracil.	
	In BRAF V600E mutation positive: Irinotecan + (Cetuximab or Panitumumab) + Vemurafenib	**If dMMR/MSI-H only:** (Nivolumab ± ipilimumab) or Pembrolizumab	
	If dMMR/MSI-H only: (Nivolumab ± Ipilumumab) or Pembrolizumab		

Continuation Treatment

If previously treated with	Second Line Treatment	Third Line Treatment	Fourth Line Treatment
FOLFOX-6 or XELOX + Panitumumab or Cetuximab **(RAS wild type)**	(FOLFIRI or Irinotecan) ± (Bevacizumab or Ziv- aflibercept or Ramuciromab	Regorafenib	Regorafenib or Trifluridine + Tipiracil or Best supportive care
		or Trifluridine + Tipiracil.	
	If dMMR/MSI-H only: (Nivolumab ± Ipilumumab) or Pembrolizumab	**If dMMR/MSI-H only:** (Nivolumab ± ipilimumab) or Pembrolizumab	

Continuation Treatment

If previously treated with	Second Line Treatment	Third Line Treatment	Fourth Line Treatment
FOLFOX-6 or XELOX ± Bevacizumab	**If RAS/NRAS wild type:** (FOLFOX-6 or XELOX) ± (Bevacizumab, Panitumumab or Cetuximab)	Regorafenib	Regorafenib or Trifluridine + Tipiracil or Best supportive care
		or Trifluridine + Tipiracil.	
	If KRAS/NRAS WT only: Irinotecan ± (Cetuximab or Panitumumab)	Nivolumab ± ipilimumab or Pembrolizumab	
	If BRAF V600E mutation positive: Irinotecan + (Cetuximab or Panitumumab) + Vemurafenib		
	If MSI-H only: (Nivolumab ± Ipilimumab) or Pembrolizumab		

Surveillance

Stage I (T1N0M0 and T2N0M0):

Colonoscopy

- Performed after 1 year of surgery
- If no pre-operative colonoscopy due to obstructive tumor:
  - Colonoscopy in 3-6 months after surgery
- If advanced adenoma:
  - Repeat colonoscopy in 1 year
- If no advanced adenoma:
  - Repeat colonoscopy in 3 years,
  - Then every 5 years.

Stage II (low and high-risk) and Stage III:

History and Physical Examination

- 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

Contrast-enhanced CT scan of chest + abdomen + pelvis

- Annually for 3-5 years; as clinical indicated

Colonoscopy

- Performed after 1 year of surgery
- If no pre-operative colonoscopy due to obstructive tumor:
  - Colonoscopy in 3-6 months after surgery
- If advanced adenoma:
  - Repeat colonoscopy in 1 year
- If no advanced adenoma:
  - Repeat colonoscopy in 3 years,
  - Then every 5 years.

Laboratory (CBC, biochemistry)

- As clinically indicated

Stage IV and Stage IV NED:
History and Physical Examination
• 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
Contrast-enhanced CT scan of chest + abdomen + pelvis
• Every 3-6 monthly for 2 years • Then every 6-12 months up to a total of 5 years.
Colonoscopy

• After 1 year of surgery
• If no pre-operative colonoscopy due to obstructive tumor:
  ○ Colonoscopy in 3-6 months after surgery
• If advanced adenoma:
  ○ Repeat colonoscopy in 1 year
• If no advanced adenoma:
  ○ Repeat colonoscopy in 3 years,
  ○ Then every 5 years.

Laboratory (CBC, biochemistry)
• As clinically indicated

Established Regimens

FOLFOX 6	
Oxaliplatin then	85 mg/m^2 IV 2 hours, day 1
Leucovorin	400 mg/m^2 IV over 2 hours, day 1
5-FU	400 mg/m^2 IV bolus Then 1200 mg/m^2 /day x 2 days (total 2400 mg/m^2 over 46-48 hours) continuous infusion, days 1 and 2
Repeat every 2 weeks.[1,2,3]	

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
Oxaliplatin	85 mg/m^2 IV administered on weeks 1, 3 and 5 of each 8-week cycle x 3

Capecitabine	
Capecitabine	1250 mg/m^2 twice daily, days 1-14
Repeat every 3 weeks x 24 weeks.	

CapeOx	
Oxaliplatin	130 mg/m^2 over 2 hours, day 1
Capecitabine	1000 mg/m^2 twice daily days 1-14
Repeat every 3 weeks x 24 weeks	

5-FU/Leucovorin	
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 6 x weekly
Repeat every 8 weeks for 4 cycles	

sLV5FU2 [Simplified biweekly infusional 5FU/LV]	
Leucovorin	400 mg/m^2 IV over 3 hours on day 1
5 FU	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	

mFOLFOX 6	
Oxaliplatin	85 mg/m^2 IV 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.[1,2,3]	

mFOLFOX 6 + Bevacizumab[4]	
Oxaliplatin	85 mg/m^2 IV 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
Bevacizumab	5 mg/Kg IV, day 1
Repeat every 2 weeks.	

mFOLFOX 6 + Panitumumab[5]	
Oxaliplatin	85 mg/m^2 IV 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
Panitumumab	6 mg/kg IV, over 60 minutes, day 1
Repeat every 2 weeks.	

CapeOx + Bevacizumab [1,6,7]	
Oxaliplatin	130 mg/m^2 IV over 2 hours, day 1
Capecitabine	850 – 1000↕ mg/m^2 twice daily PO for 14 days
Bevacizumab	7.5 mg/kg IV, day 1
Repeat every 3 weeks	

FOLFIRI

FOLFIRI[8]
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

FOLFIRI[8] **+ Bevacizumab**[9,¶]
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
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

FOLFIRI[8] **+ Cetuximab**
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[10]
or Cetuximab 500 mg/m^2 IV over 2 hours, day 1, every 2 weeks[11]

FOLFIRI[7] **+ Panitumumab**[12]
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
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRI + ziv-aflibercept[13]
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
Repeat every 2 weeks

Capecitabine[14]
850-1250 mg/m^2 PO twice daily, days 1-14
Repeat every 3 weeks

Capecitabine[14] **+ Bevacizumab**[7¶]
Capecitabine 850-1250 mg/m^2 PO twice daily, days 1-14
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

Bolus or infusional 5-FU/leucovorin
Roswell Park regimen[15]
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

Simplified biweekly infusional 5-FU/LV (sLV5FU2)[8]
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

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.[16]
5-FU 2600 mg/m^2 by 24-hour infusion plus leucovorin 500 mg/m^2
Repeat every week[17]

IROX[18]
Oxaliplatin 85 mg/m^2 IV over 2 hours, followed by irinotecan 200 mg/m^2 over 30 or 90 minutes every 3 weeks

FOLFOXIRI[19]
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
± Bevacizumab[20] 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[21,22]
Irinotecan 300-350 mg/m^2 IV over 30-90 minutes, day 1
Repeat every 3 weeks

Cetuximab (KRAS WT gene only) ± irinotecan[11,23]
Cetuximab 400 mg/m^2 first infusion, then 250 mg/m^2 IV weekly
or Cetuximab 500 mg/m^2 IV every 2 weeks[11]
±
Irinotecan 300-350 mg/m^2 IV every 3 weeks
or Irinotecan 180 mg/m^2 IV every 2 weeks
or Irinotecan 125 mg/m^2 on days 1 and 8 and repeat every 3 weeks

Cetuximab (KRAS WT gene only)
Cetuximab 400 mg/m^2 first infusion, then 250 mg/m^2 IV weekly[23]
or Cetuximab 500 mg/m^2 IV over 2 hours, day 1, every 2 weeks[11]

Panitumumab[24] **(KRAS WT gene only)**
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Regorafenib[25]
Regorafenib 160 mg PO daily days 1-21
Repeat every 28 days

IMPORTANT NOTE REGARDING LEUCOVORIN SHORTAGE, PLEASE SEE MS-14