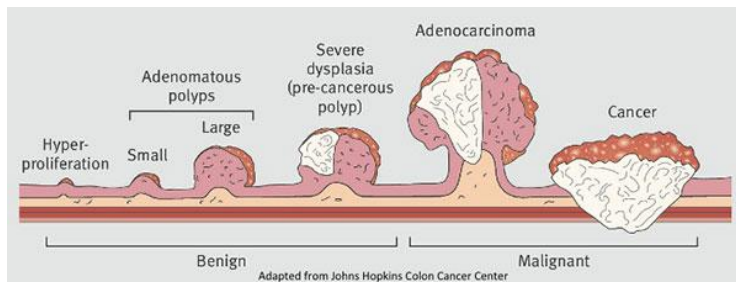


COLON CANCER

General Overview

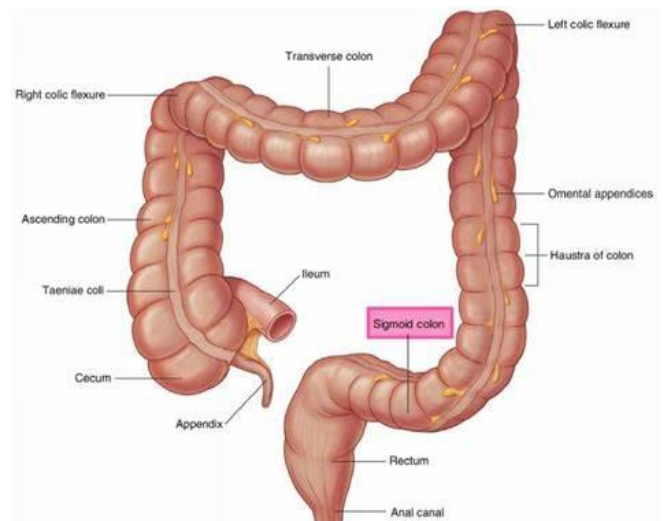
- 10% of all tumor types worldwide. 4th most common cancer-related cause of death worldwide.
- Risk factors: obesity, physical inactivity, alcohol, red meat intake, smoking, IBD
- Lifestyle + genetic factors (FAP, HNPCC, Lynch). 70% of CRC are >65y
- Rising trend in incidence in young adults (mainly in developed countries)
- CRC arises following progression of normal mucosa to premalignant and malignant lesions



- Molecular biology of colon cancer:
 - High genomic concordance between primary tumors and metastasis
 - Left versus right colon cancer is a continuum of molecular alterations
 - Always test for microsatellite instability (MSI) by either PCR or IHC
 - PMS2, MSH2/MSH6 or MSH6 loss: germline MMR gene testing
 - MLH1/PMS2 loss:
 - BRAFV600 mutated: sporadic
 - BRAFV600 wild type:
 - MLH1 hypermethylation: sporadic
 - No hypermethylation: germline MMR gene testing
 - In case of MSI-H and wild type BRAF/KRAS: test for fusions (NTRK, BRAF,...)
 - HER2 overexpression is present in 3-5% of mCRC: greater incidence of brain M+
 - Standard NGS: RAS (KRAS, NRAS), BRAF, ...

Staging (AJCC Version 8)

- Diagnostic work up: colonoscopy, CT thorax/abdomen, CEA (monitoring), (MRI liver if indicated)
- When not carried out before or during surgical procedure, complete colonoscopy should be carried out within 3-6 months following tumor resection



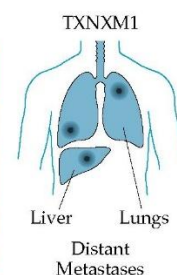
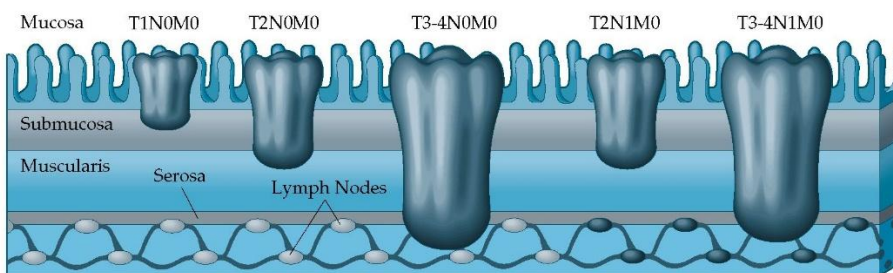
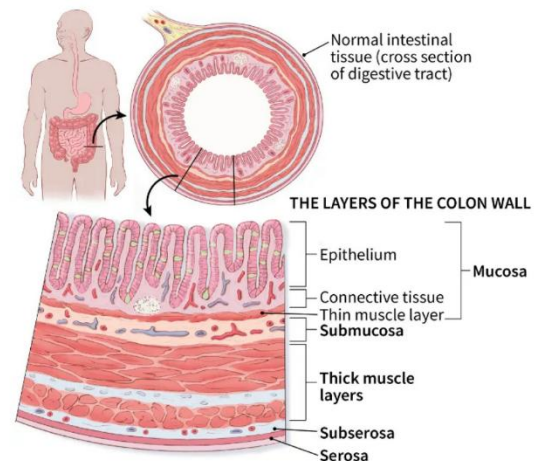
Primary Tumor (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
Tx: Primary tumor cannot be assessed	Nx: LN cannot be assessed	M0: no distant M+
T0: No evidence of primary tumor	N0: no regional LN	M1: distant M+
Tis: carcinoma in situ	N1: metastasis in 1-3 LN	M1a: 1 organ without peritoneal M+
T1: Tumor invades submucosa	N1a: 1 regional LN	M1b: more than 1 organ
T2: Tumor invades muscularis propria	N1b: 2-3 regional LN	M1c: peritoneum with or without organ involvement
T3: Tumor invades through muscularis propria into pericolic tissues	N1c: tumor deposits in subserosa, or in non-peritonealised pericolic or perirectal soft tissue without regional LN M+	
T4: Tumor invades visceral peritoneum (4a) or invades adjacent structures(4b)	N2: ≥ 4 (N2a: 4-6 ; N2b ≥ 7)	

- Anatomic Stage

- Stage I: T1-2N0M0
- Stage IIA: T3N0M0
- Stage IIB: T4aN0M0
- Stage IIC: T4bN0M0
- Stage IIIA: T1-2N1M0 or T1N2aM0
- Stage IIIB: T1-2N2bM0 or T2-3N2aM0 or T3-4aN1M0
- Stage IIIC: T3-4aN2bM0 or T4aN2aM0 or T4bN1-2M0

- Prognosis: [colon cancer survival calculator](#)

- Stage I 5y OS: 99%
- Stage II 5y OS: 68 – 83%
- Stage III 5y OS: 45 – 65%
- Stage IV 5y OS: 15%



TNM Stage	Description
T1N0M0	Infiltration no deeper than submucosa
T2N0M0	Infiltration of muscularis; no penetration through colonic wall; no lymph node involvement
T3-4N0M0	Extension through colonic wall; no lymph node involvement
T2N1M0	Infiltration of muscularis; no penetration through colonic wall; lymph node involvement
T3-4N1M0	Extension through colonic wall; lymph node involvement
TXNXM1	Distant metastases

Treatment

- Surgical resection is the only curative modality. Endoscopic resection only in favorable risk early stage colon cancer (no poor diff, LV/PNI, budding)
- Selected patients can be treated with neo-adjuvant chemo (FOXTROT JCO 2023 Morton et al)
- Surgery may be a curative option in selected patients with limited metastatic disease (liver, lung).
- No OS benefit for HIPEC with cytoreductive surgery (PRODIGE7 Lancet oncol 2021)
- **Adjuvant treatment of colon cancer:**
 - Stage 2 low risk (no pathological risk factors): follow-up
 - Stage 2 intermediate risk (LI or PNI or VI or gr 3 or obstruction or preoperative CEA >5):
 - MSS: adjuvant 6 months 5-FU or capecitabine
 - MSI: follow-up
 - Stage 2 high risk (pT4, < 12 LN, multiple risk factors from intermediate risk group)
 - Adjuvant therapy: FOLFOX 6m, CAPOX 3months or 6 months
 - Stage 3 low risk (pT1-3,N1): FOLFOX 6m or CAPOX 3months
 - Stage 3 high risk (pT4 and/or N2): FOLFOX or CAPOX 6 months

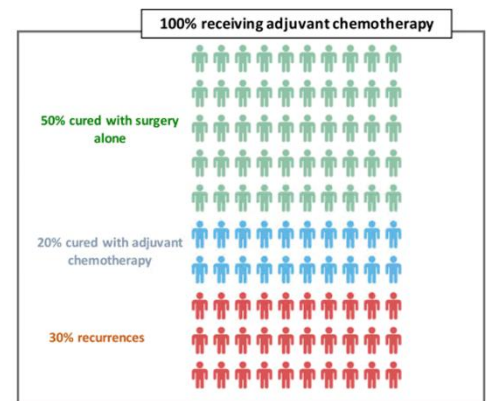
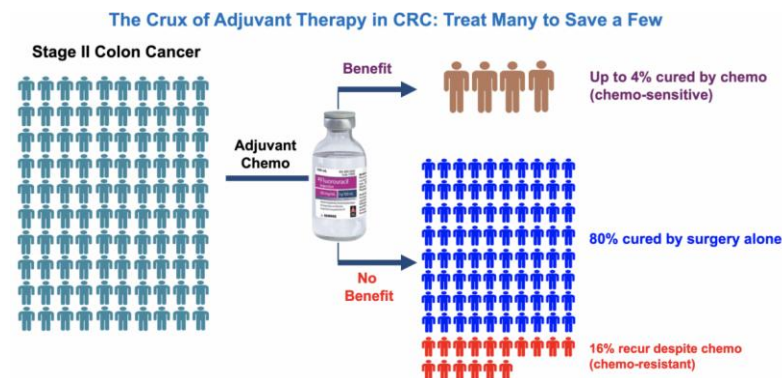


Fig. 1. Paradigm in stage III colon cancer.

- Benefit duration adjuvant chemo (stage III): IDEA

Table 2

Summary of 3-year DFS rates according to treatment arm and risk group from the IDEA study (Grothey et al., N Engl J Med, 2018).

3 yr DFS rate (%) and HR by regimen and risk group		Regimen							
		CAPOX			FOLFOX			CAPOX/FOLFOX combined	
		3 yr DFS, % (95% CI)		HR (95% CI)	3 yr DFS, % (95% CI)		HR (95% CI)	3 yr DFS, % (95% CI)	
		3 m	6 m		3 m	6 m		3 m	6 m
Risk group	Low-risk (T1-3 N1) ~60%	85.0 (83.1-86.9)	83.1 (81.1-85.2)	0.85 (0.71-1.01)	81.9 (80.2-83.6)	83.5 (81.9-85.1)	1.10 (0.96-1.26)	83.1 (81.8-84.4)	83.3 (82.1-84.6)
	High-risk (T4 or N2) ~40%	64.1 (61.3-67.1)	64.0 (61.2-67.0)	1.02 (0.89-1.17)	61.5 (58.9-64.1)	64.7 (62.2-67.3)	1.20 (1.07-1.35)	62.7 (60.8-64.4)	64.4 (62.6-66.4)
Risk groups combined		75.9 (74.2-77.6)	74.8 (73.1-76.6)	0.95 (0.85-1.06)	73.6 (72.2-75.1)	76.0 (74.6-77.5)	1.16 (1.06-1.26)	P-value interaction test: Regimen: 0.0061 Risk group: 0.11	

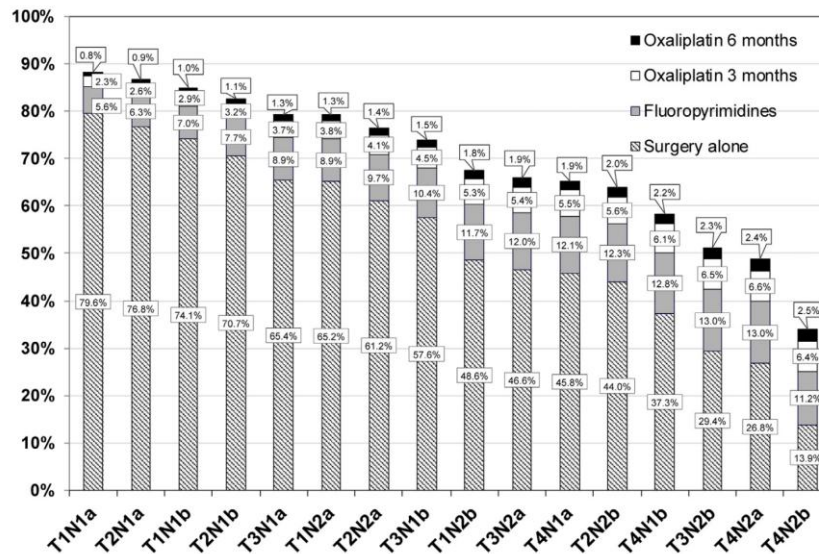
Non-inferior

Not proven

Inferior

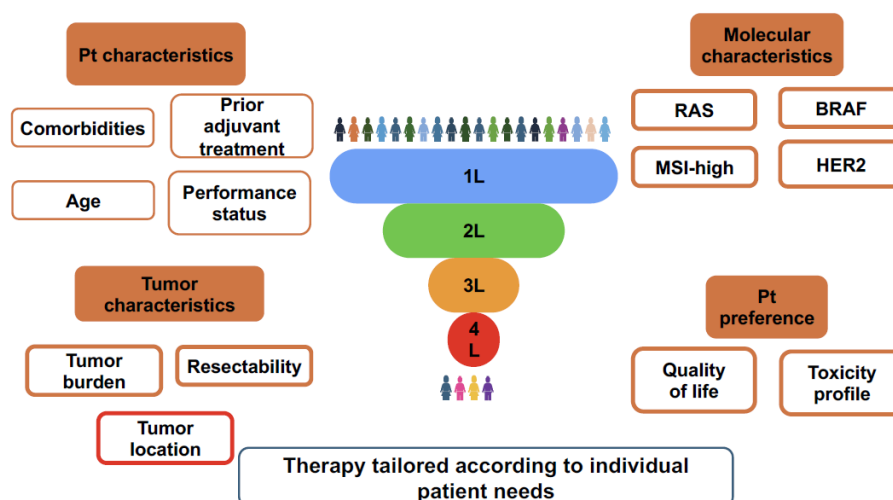
Abbreviations: 3 yr: three years; DFS: disease-free survival; CAPOX: capecitabine + oxaliplatin; FOLFOX: 5 fluorouracil + oxaliplatin.

- Added value of 3 versus 6 months adj chemo (Sobrero AF et al. Eur J Cancer 2020)

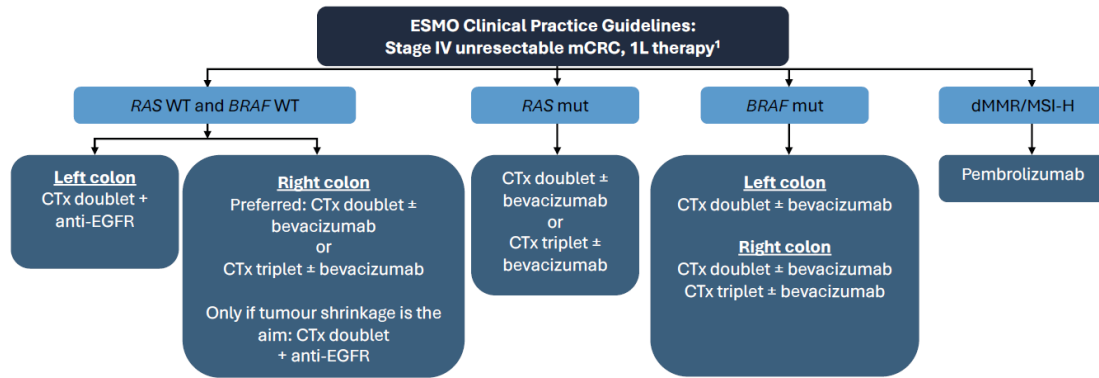


- **Adjuvant treatment:**
 - Structured **exercise** (NEJM June 2025 Courneya et al)
 - 889 patients randomized to exercise or health education for 3years
 - 5y DFS 80.3 vs 73.9 %
 - **Low dose aspirin** for PI3K altered (ALASCCA study, Martling et al NEJM sept 2025)
 - 160 mg aspirin
 - Mutations in exon 9 and 20 of PIK3CA, PIK3R1 or PTEN
- **Metastatic colon cancer:**

What Influences Treatment Choices in mCRC?



- Benefit of systemic therapy: 6 m OS (BSC) vs >20months OS (combination chemotherapy)



Treatment of metastatic colorectal cancer: ASCO guideline²

- Anti-EGFR + doublet CTx should be offered as 1L therapy to patients with MMS/pMMR, left-sided, RAS WT mCRC
 - Although anti-EGFR therapy is preferred, anti-VEGF therapy remains an active treatment option
 - Anti-EGFR therapy with triplet CTx is not recommended

- Principal phase III clinical trials with cetuximab and Panitumumab in RAS wt mCRC
 - CRYSTAL (2015): FOLFIRI cetux vs FOLFIRI
 - CALGB/SWOG 80405 (2014): FOLFOX / FOLFIRI + cetuximab or bevacizumab
 - FIRE3 (2014): FOLFIRI + cetux vs FOLFIRI + beva
 - PRIME (2013): FOLFOX/panitumumab vs FOLFOX
 - VOLFI (2019): FOLFOXIRI/panitumumab vs FOLFOXIRI
- PARADIGM study: Principal ph3 study comparing anti-EGFR / anti-VEGF 1st line RAS WT
 - Watanabe J et al, JAMA 2023: FOLFOX Pmab vs FOLFOX beva
 - mOS 36.3m (Pmab) vs 31.3 (beva) ; mOS left sided: 37.9 vs 34.3m
- Immunotherapy 1st line in MSI-H
 - Pembrolizumab (NEJM 2020, Andre T et al) vs chemotherapy 1st line
 - mPFS 16.5 vs 8.2m ; KEYNOTE-177 study (update Ann oncol 2024)
 - Nivolumab + Ipilimumab (CheckMate 8HW trial): NEJM nov 2024 ; Lancet 2025
 - Nivo reimbursed / Ipi MNP program since 17/9/25
 - 24m PFS 72% for IO vs 14% with chemotherapy
- *Second line treatment:*
 - oxaliplatin or irinotecan based depending on 1st line
 - bevacizumab beyond progression
 - RAS wild type and anti-EGFR naïve: anti-EGFR
 - BRAF V600 mutant:
 - Encorafenib + cetuximab (Kopetz S et al NEJM 2019, Tabernero J JCO 2021) (no reimbursement in Belgium): mOS 9.3 vs 5.9m
 - RNF43 mutations predict response (Elez E et al Nat med 2022)
 - MSI-H:
 - Ipi – nivo (reimbursement in first line): checkmate 142 (Lenz et al, JCO 2021)
 - Avelumab (Taieb et al, Jama oncol 2023) (no reimbursement)
- Third line and beyond:
 - If HER2 positive (expression):
 - anti-HER2 drugs (no reimbursement)
 - Role of HER2 mutations: resistance to anti-EGFR and HER2 targeting
 - Trifluridine-tipiracil-bevacizumab (Prager et al NEJM 2023): sunlight study

- Regorafenib: correct trial (Grothey et al Lancet 2013)
- Trifluridine-tipiracil monotherapy (KRAS G12 are biomarkers for reduced OS benefit Nat med 2023)
- Fruquintinib vs placebo in chemorefractory mCRC (FRESCO-2) : Lancet july 2023 (reimbursed in Belgium since 1 nov 2025)
- Anti-EGFR rechallenge: liquid biopsy/ctDNA analysis may help select candidates
 - Phase 2 CRICKET and CHRONOS study (Nat med 2022)
 - Panitumumab + TAS102 (JAMA oncol 2023 Napolitano et al)
- Locoregional therapies for colorectal liver metastases:
 - Radioembolization: Mulcahy et al. JCO 2021

References

- 1) MOSAIC study (adjuvant colon): Andre et al NEJM 2004
- 2) Duration adjuvant chemo stage III: Grothey et al NEJM 2018

What's new ?

- Neoadjuvant immunotherapy in MSI-H colon cancer :
 - **NICHE1** study (Chalabi et al Nature med 2020)(included also MMR proficient) : nivo + ipi
 - Pembrolizumab : Ludford et al JCO 2023
 - **NICHE2** study : Nivo + ipilimumab (Chalabi et al NEJM 2024) ; 111 patients ; 98% RR
 - **NICHE3** study : Nivo + relatlimab (De Gooyer et al Nat med 2024 Nov)
 - Neoadjuvant immunotherapy in MSS CRC (Tan et al, Nature oct 2025)
 - Ipi/nivo in 31 pts. RR 26%
 - HER2 expressing CRC:
 - DESTINY-CRC01 (Lancet oncol 2021 and Nat commun 2023) : Trastuzumab deruxtecan in chemorefractory disease, 45% RR
 - Mountaineer (Lancet Oncol 2023) : tucatinib + trastuzumab in chemorefractory RAS wild type disease, RR 38%
 - DRUP : trastuzumab plus pertuzumab (Eur J Cancer 2024 Spiekman et al) 29% RR
 - DESTINY-CRC02 : randomised phase 2 with trastuzumab deruxtecan (Lancet oncol 2024)
 - Future role of ctDNA to detect minimal residual disease after surgery:
 - Dynamic trial (Tie et al, NEJM 2022, Nat med 2025): ctDNA guiding adjuvant therapy in stage II /III CRC
 - Circulate – galaxy trial (Nature medicine jan 2023 and sept 2024)
 - BRAFV600 :
 - phase 2 of combined PD-1, BRAF and MEK-I (Tian J et al Nat med 2023)
 - Anchor phase 2 study 1st line encorafenib-binimetinib-cetuximab (JCO 2023)
 - Molecular profiling in BEACON (Kopetz et al Nat med 2024)
 - **BREAKWATER** : encorafenib + cetuximab + FOLFOX 1st line (Kopetz et al Nat med 2025, Elez et al NEJM 2025) : longer PFS and OS
 - KRAS G12C mutated mCRC
- Update: December 2025

- Adagrasib +/- cetuximab (Yaeger et al. NEJM 2022 ; Cancer discov 2024)
- Sotorasib plus panitumumab (Fakih et al NEJM 2023, Kuboki et al Nature med 2024, JCO 2025 Pietrantonio et al)
- Divarasib plus cetuximab (Desai J et al Nat med 2024)
- POLE and POLD1 mCRC treated with immune CPI. Ambrosini M et al. Ann oncol 2024
- Bullock et al Nat med 2024 : botensilimab (anti-CTLA-4) + balstilimab (anti-PD1) in MSS mCRC
- TransMET study (liver transplant for CRC liverM+) : Lancet 2024 Rene adam *et al*
- Precectabart tocentecan (anti-CAECAM5 ADC), phase 1 : Nat med Oct 2025 Kopetz et al
- Stellar-303 : Zanzalintinib (TKI) + atezolizumab (anti-PDL1) vs regorafenib in chemorefractory CRC (Lancet nov 2025). OS 10.9m vs 8.4m