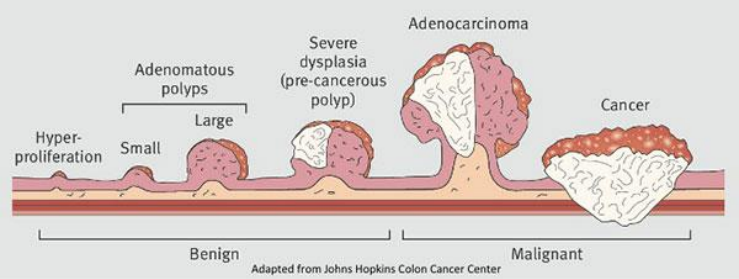
COLON CANCER

General Overview

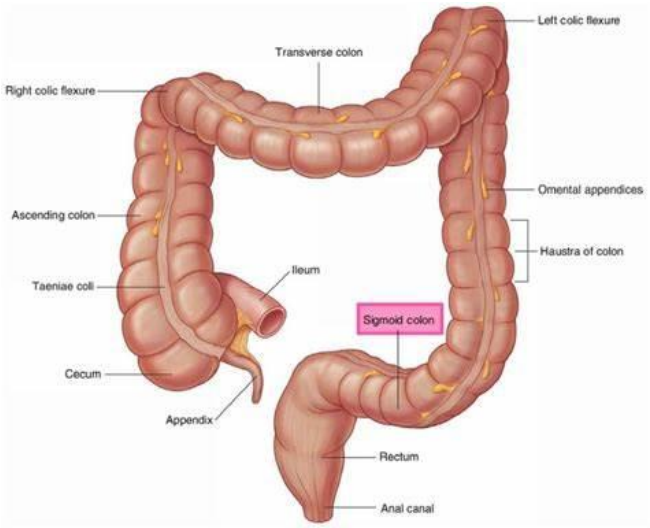
- 10% of all tumor types worldwide. 4th most common cancer-related cause of death worldwide.
- Risk factors: obesity, physical inactivity, alcohol, red meat intake, smoking, IBD
- Lifestyle + genetic factors (FAP, HNPCC, Lynch). 70% of CRC are >65y
- Rising trend in incidence in young adults (mainly 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, ….

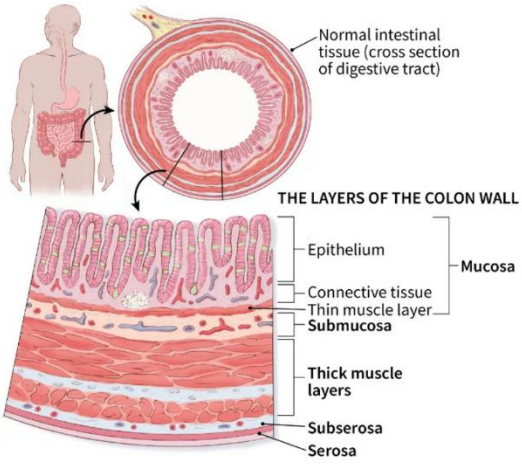
Staging (AJCC Version 8)

- 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



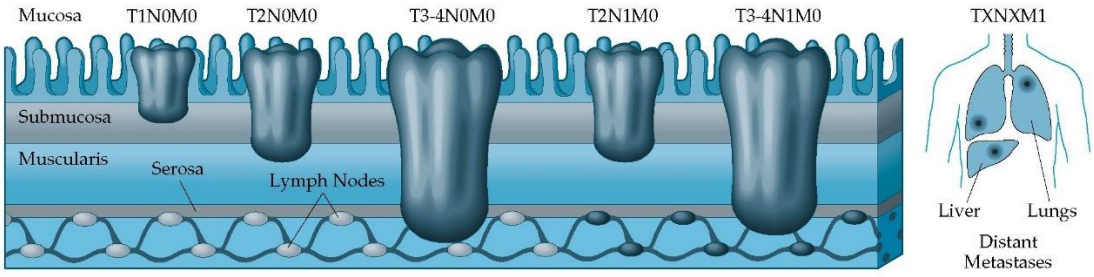
Update: December 2024

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



- Anatomic Stage
  - Stage I: T1-2N0M0
  - Stage IIA: T3N0M0
  - Stage IIB: T4aN0M0
  - Stage IIC: T4bN0MO
  - 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%

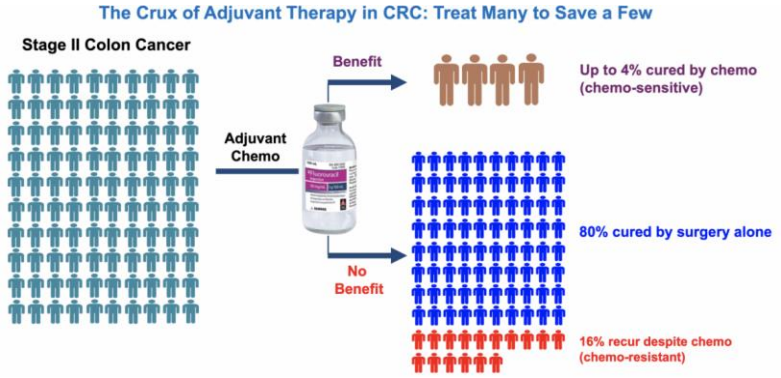


TNM Stage	*Description*
T1N0M0	Infiltration no deeper than submucosa
T2N0M0	Infiltration of muscularis; no penetration through colonic wall; no lymph node involvement
T3-4N0M0	Extension through colonic wall; no lymph node involvement
T2N1M0	Infiltration of muscularis; no penetration through colonic wall;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

Update: December 2024

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



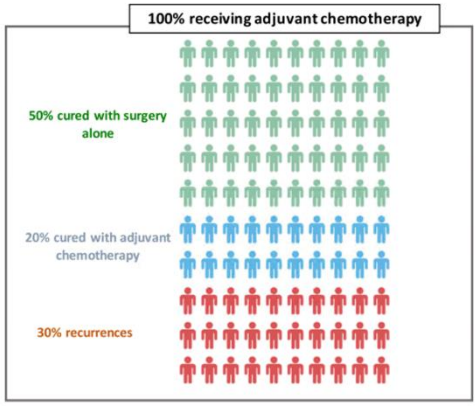


Fig. 1. Paradigm in stage III colon cancer.

- 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)		HR (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)	*1.01* (0.90-1.12)
	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)	*1.12* (1.03-1.23)
	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.

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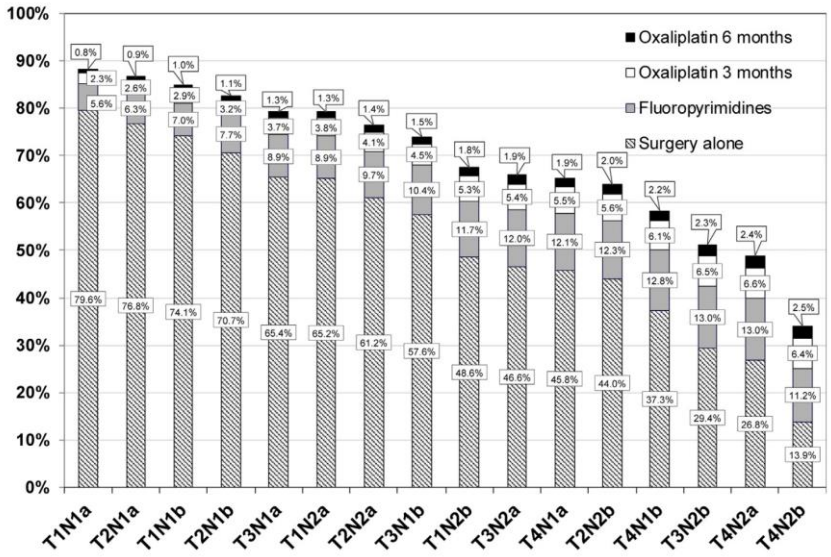
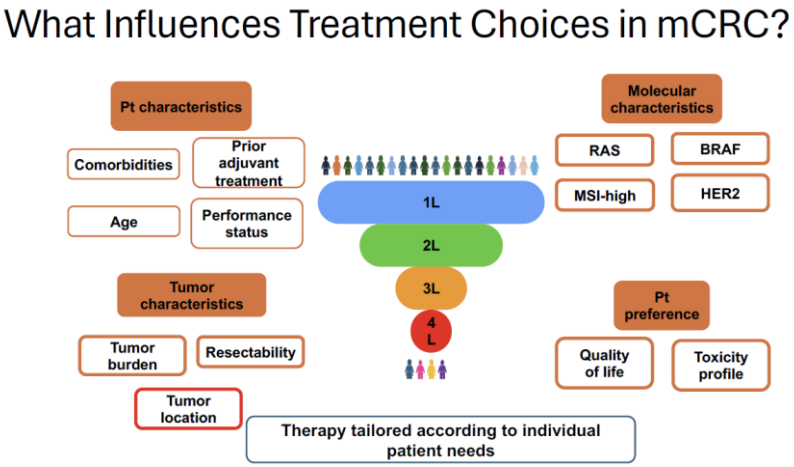
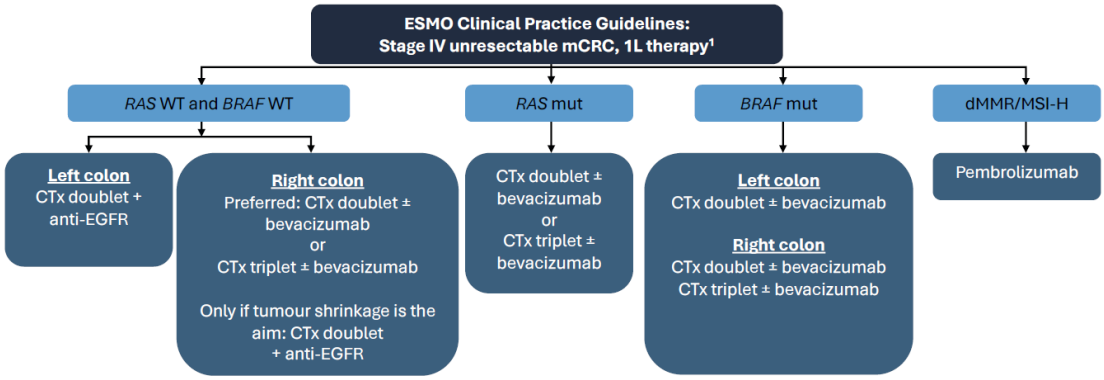
- Added value of 3 versus 6 months adj chemo (Sobrero AF et al. Eur J Cancer 2020)



- **<u>Metastatic colon cancer</u>**:



- 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

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- 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
    - No reimbursement yet in Belgium
    - 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 (no reimbursement): 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)
- 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

Update: December 2024

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)
- 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): ctDNA guiding adjuvant therapy in stage II 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)
- KRAS G12C mutated mCRC
  - Adagrasib +/- cetuximab (Yaeger et al. NEJM 2022) (Yaeger et al Cancer disc 2024)
  - Sotorasib plus panitumumab (Fakih et al NEJM 2023) (Kuboki et al Nature med 2024)
  - Divarasib plus cetuximab (Desai J et al Nat med 2024
- Fruquintinib vs placebo in chemorefractory mCRC (FRESCO-2) : Lancet july 2023
- 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