ONCOLOGY KNOWLEDGE HUB · FOR HEALTH PROFESSIONALS

Colorectal Cancer

A mini review for clinicians

For postgraduate residents (medical, surgical and radiation oncology, general surgery, gastroenterology, medicine), practising clinicians and medical students

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Updated 9 October 2026. Educational summary written in our own words from current guidelines and primary trials; no drug doses; not advice for an individual patient. Verify current guidelines and Indian regulatory approvals before treatment decisions. Patients and families: please see the patient guides at drharitha.co.in.

Colorectal Cancer

Colon · Rectum · MMR/MSI · RAS · BRAF · HER2 · Key points for clinicians · Last updated 9 October 2026

01 At a glance

- Colorectal cancer is the third commonest cancer in the world and the second commonest cause of cancer death. India records roughly 65,000 new cases a year (GLOBOCAN 2022 estimates); age-standardised rates are lower than in the West but rising in cities, and Indian hospital series report a larger share of **rectal cancers** and of patients **under 50**, with more signet-ring and mucinous histology.
- Most cancers arise from a visible polyp over about a decade, so **colonoscopy prevents cancer as well as finding it**. India has no organised colorectal screening programme; a stool immunochemical test (FIT) is the practical first step for average-risk adults.
- Stage drives survival: about 90% of patients with localised disease are alive at 5 years, about 70% with nodal disease, and about 15% with distant metastases. Even so, selected patients with liver or lung metastases are **cured by resection**.
- Four decisions shape treatment: **site** (colon or rectum, and right or left), **stage** (CT for everyone, MRI pelvis for the rectum), **mismatch-repair status** (every new cancer) and, when metastatic, **RAS, BRAF and HER2**.
- The commonest avoidable harm in Indian practice is delay: rectal bleeding labelled as piles, anaemia treated with iron alone, and caecal masses treated as intestinal TB without tissue.

Approximate share by site; Indian hospital series often report a larger rectal share and more patients under 50 than Western series.

Right colon · ~30%	Left colon & sigmoid · ~30%	Rectum · ~40%
Caecum to transverse colon • Anaemia, fatigue, a mass; bleeding is occult • Older, more often women; more MSI-high and BRAF • Poorer prognosis when metastatic **Metastatic, RAS/BRAF wild-type: doublet + bevacizumab**	*Splenic flexure to sigmoid* • Change in bowel habit, bleeding, obstruction • Chromosomal-instability type; HER2 more often • Better prognosis when metastatic **Metastatic, RAS/BRAF wild-type: doublet + anti-EGFR**	*Up to 15 cm from the anal verge* • Bleeding, tenesmus, mucus; often called "piles" • Staged locally by MRI pelvis • Pelvic recurrence risk: radiotherapy matters **Total neoadjuvant therapy; organ preservation for some**

Figure 1. Three working sites. Where the tumour starts changes the symptoms, the staging (MRI for the rectum), the role of radiotherapy and, when metastatic, the choice of biological drug.

02 Clinical presentation, common traps & genetic causes

Who is at risk: ask about each of these

Factor	Approximate size of risk	Clinical note
Age	Risk rises steeply after 45–50	Early-onset cancer (under 50) is rising worldwide; Indian series often report a fifth to a third under 45. Symptoms in the young must not be dismissed.
One first-degree relative with colorectal cancer	About 2-fold; higher if diagnosed before 50 or several relatives	Start colonoscopy at 40, or 10 years before the youngest relative's diagnosis.
Lynch syndrome	Lifetime risk roughly 10–50% depending on the gene (highest MLH1/MSH2)	Also endometrial, ovarian, gastric, urothelial and small-bowel cancers. Section 04.
Polyposis syndromes (FAP, MUTYH, serrated polyposis)	Classic FAP near 100% without colectomy	Hundreds of adenomas from the teens; attenuated forms present later.
Inflammatory bowel disease	Rises with duration and extent of colitis	Surveillance colonoscopy with chromoendoscopy from about 8 years after onset of extensive colitis.
Primary sclerosing cholangitis (PSC) with IBD	About 3-fold higher than IBD alone (**meta-analysis**[1]); cancers are often right-sided, at a median age near 50	Colonoscopy at PSC diagnosis (colitis is often silent: take random biopsies), then **every year**; PSC without IBD: every 5 years. Ursodeoxycholic acid is not a chemopreventive.
Lifestyle	Each modest (relative risks 1.1–1.5)	Red and processed meat, obesity, inactivity, smoking, alcohol and diabetes raise risk; fibre, calcium and physical activity lower it.
Previous adenoma or colorectal cancer	Metachronous cancer about 1–2% over 5 years	Surveillance colonoscopy (section 08).
Pelvic radiotherapy, acromegaly, cystic fibrosis, Streptococcus gallolyticus bacteraemia	Increased	Colonoscopy after S. gallolyticus endocarditis or bacteraemia.

How it presents

Site	Typical symptoms	Clue that is often missed
Right colon	Fatigue, iron-deficiency anaemia, right iliac fossa mass, vague pain	Bleeding is occult: anaemia in a man or post-menopausal woman needs both endoscopies.
Left colon and sigmoid	Change in bowel habit, bright or dark blood mixed with stool, colicky pain, obstruction	Alternating constipation and loose stools; "pencil" stools.
Rectum	Bleeding, tenesmus, mucus, incomplete evacuation, pain at the anus if low	A digital rectal examination finds most low tumours; it is skipped surprisingly often.
Emergency (about 1 in 5)	Large-bowel obstruction, perforation, massive bleeding	Emergency presentation predicts worse survival; urgent CT, not repeated enemas.

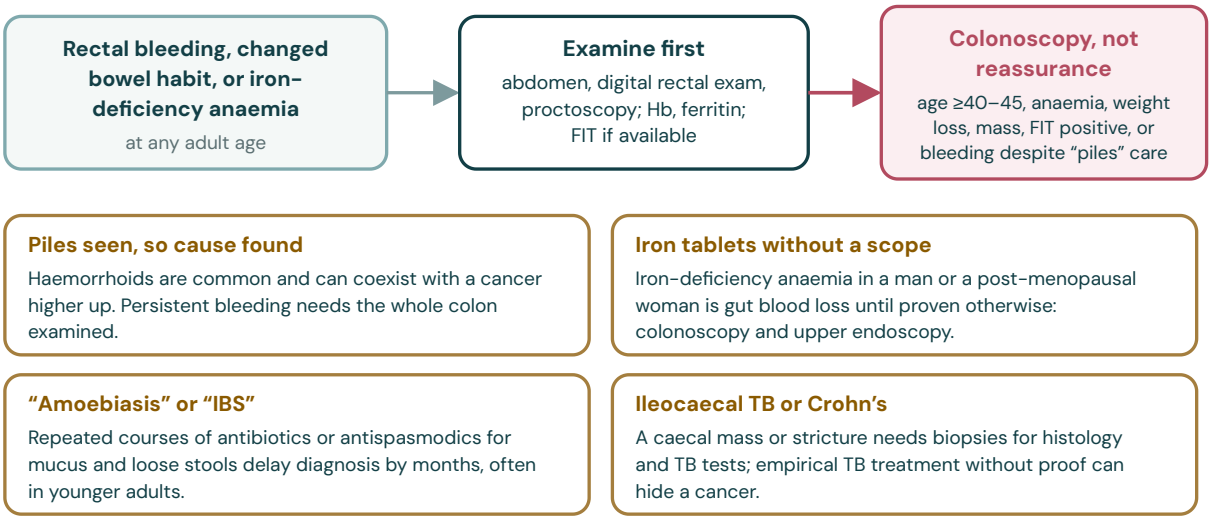


Figure 2. Rectal bleeding and anaemia: piles or cancer? The examination comes first, but persistent symptoms, anaemia or a positive FIT need colonoscopy whatever the age.

- **Urgent referral triggers** (2-week pathway): rectal bleeding with a change in bowel habit; unexplained iron-deficiency anaemia; a rectal or abdominal mass; a positive FIT in a symptomatic person; persistent change in bowel habit over 40–45; weight loss with abdominal symptoms. Same day: obstruction, perforation or heavy bleeding.
- **FIT in symptomatic patients**: a faecal haemoglobin at or above 10 µg/g identifies most cancers and is used in the UK to prioritise colonoscopy; a negative FIT does not override a mass, anaemia or rectal bleeding.
- **Atypical presentations**: fever of unknown origin, a malignant fistula, *Streptococcus gallolyticus* (bovis) bacteraemia or endocarditis, *Clostridium septicum* sepsis, or adenocarcinoma of unknown primary — each warrants colonoscopy.
- **CEA is not a diagnostic test**: it is normal in many early cancers and raised in smokers, liver disease and inflammation. Use it for baseline and follow-up only.
- **Ileocaecal TB versus cancer**: both cause a right iliac fossa mass, anaemia and weight loss. Take multiple biopsies for histology, TB PCR and culture; empirical antituberculous treatment without proof can hide a caecal cancer for months.

Hereditary syndromes to recognise

Syndrome	Gene	Clues	What to do
Lynch syndrome	MLH1, MSH2 (EPCAM), MSH6, PMS2	dMMR tumour; young; right colon; endometrial, ovarian, gastric, urothelial and small-bowel cancers in the family	Colonoscopy every 1–2 years from 20–25 (MLH1/MSH2) or every 1–3 years from 30–35 (MSH6/PMS2), or 2–5 years before the youngest family case; upper endoscopy with H. pylori treatment from 30–35; daily aspirin recommended for MLH1, MSH2, MSH6 and EPCAM carriers (**CAPP2**[2]), individualised for PMS2
Familial adenomatous polyposis	APC	>100 adenomas, often in the teens; desmoids, duodenal adenomas	Prophylactic colectomy; upper GI surveillance

Syndrome	Gene	Clues	What to do
MUTYH-associated polyposis	MUTYH, biallelic (recessive)	Usually up to 100 adenomas by the 50s–60s, but sometimes cancer with few or no polyps; serrated polyps too; siblings affected, parents not	Colonoscopy every 1–2 years from 25–30; upper endoscopy from 30–35 (interval by Spigelman stage); yearly thyroid examination and ultrasound. Single-allele carriers (1–2% of people) screen as the general population (Win 2014[3]); siblings have a 25% chance of being affected
Polymerase proofreading-associated polyposis (PPAP)	POLE, POLD1 exonuclease domain (dominant)	Typically 30–100 adenomas; colorectal cancer risk over 20%; duodenal adenomas; possibly endometrial cancer	Colonoscopy from 25–30 every 2–3 years (1–2 years once polyps appear); upper endoscopy from 25–30 (POLE) or 30–35 (POLD1) about every 3 years. Tumours are hypermutated and respond to immune checkpoint inhibitors (Palles 2022[4])
Serrated polyposis	Usually none found	Many serrated polyps, right colon	Clearance colonoscopy; relatives screened earlier
Peutz–Jeghers, juvenile polyposis	STK11; SMAD4/BMPR1A	Pigmented lips; hamartomas; HHT with SMAD4	Specialist surveillance of several organs

- Refer for genetic counselling when there is a dMMR tumour not explained by MLH1 methylation or BRAF, 10 or more adenomas, cancer under 50, or a strong family history. About one in six patients diagnosed under 50 carries a germline predisposition, so a germline panel for everyone diagnosed under 50 is reasonable where affordable.
- Family history alone misses most Lynch carriers, although about one in four patients with colorectal cancer has an affected relative. A variant of uncertain significance (VUS) does not change management: manage by the personal and family history and ask the laboratory for re-classification about once a year.

SHARE WITH PATIENTS: SYMPTOMS AND EARLY DIAGNOSIS

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

- Telugu–English handout: bowel cancer warning signs (తెలుగు · English)
- Blood in the stools is always caused by piles?
- Colorectal cancer occurs only in elderly people?
- If I am anaemic, iron tablets are all I need?
- A lump in the right side of the abdomen is usually intestinal TB?
- If I have no digestive problems, I can't have colorectal cancer?

03 Screening, workup & staging essentials

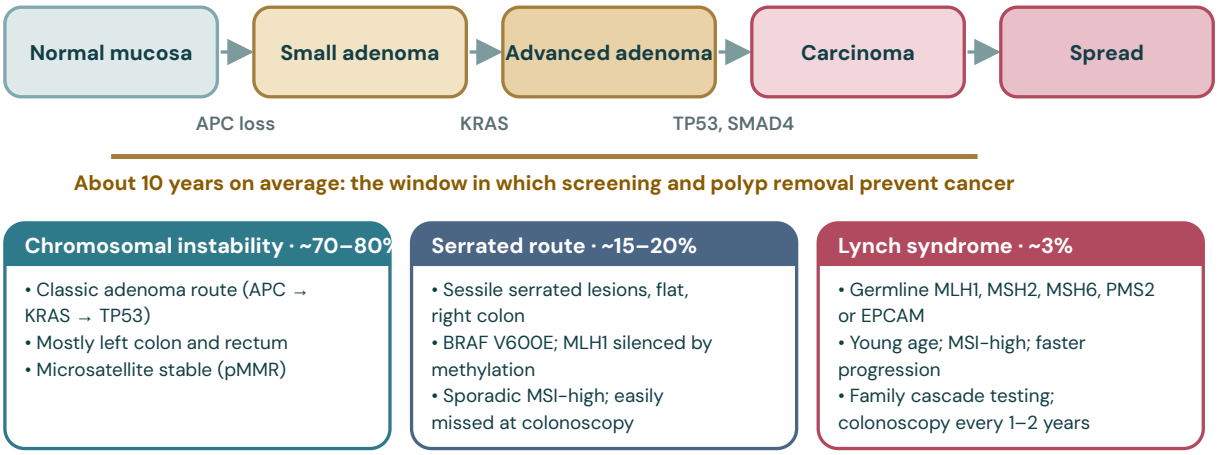


Figure 3. How colorectal cancer develops. Most cancers pass through a visible polyp stage, which is why colonoscopy can prevent cancer as well as find it. The route also predicts MMR status and BRAF, both of which change treatment.

Screening options for average-risk adults

Test	Evidence	Practical points
FIT (faecal immunochemical test), yearly (one sample)	Guaiac stool testing cut colorectal cancer deaths by about a third with annual testing (Minnesota FOBT trial[5]); FIT is more sensitive and needs no diet change	Best suited to Indian practice: cheap, one sample, no preparation. One-time sensitivity for cancer is about 74% (lower for advanced adenomas), so yearly repetition matters. Return the sample within about 24 hours and keep it away from heat — delay and high temperatures reduce sensitivity, a real issue in Andhra summers. A positive result needs colonoscopy within weeks; it is not a test to repeat.
Colonoscopy every 10 years	Removing adenomas roughly halved colorectal cancer deaths (National Polyp Study[6]). In NordICC[7] an invitation to one colonoscopy reduced incidence by about a fifth at 10 years; the death reduction was not significant because only 42% attended	Diagnostic and therapeutic; quality matters (adenoma detection rate, caecal intubation, good bowel preparation). Small risk of bleeding and perforation.
CT colonography every 5 years	Sensitive for polyps ≥10 mm	Option when colonoscopy is incomplete or refused; findings still need colonoscopy.
Flexible sigmoidoscopy	Reduced distal cancer incidence and mortality in randomised trials	Misses right-sided lesions; less used now.
Multitarget stool DNA (with FIT), every 1–3 years	More sensitive than FIT for cancer; benefit on outcomes is indirect	A reasonable alternative where available; costly in India.
Blood-based cfDNA tests, stool RNA tests	Efficacy data not yet robust; poor sensitivity for advanced adenomas	Not recommended for screening at present. Never use a single in-office guaiac test after a rectal examination, or a barium enema.

- **When to start and stop**: screen average-risk adults from 45 to 75 (USPSTF 2021[8] lowered the start age to 45; benefit is clearest from 50); individualise from 76 to 85 by health and previous results (screening up to

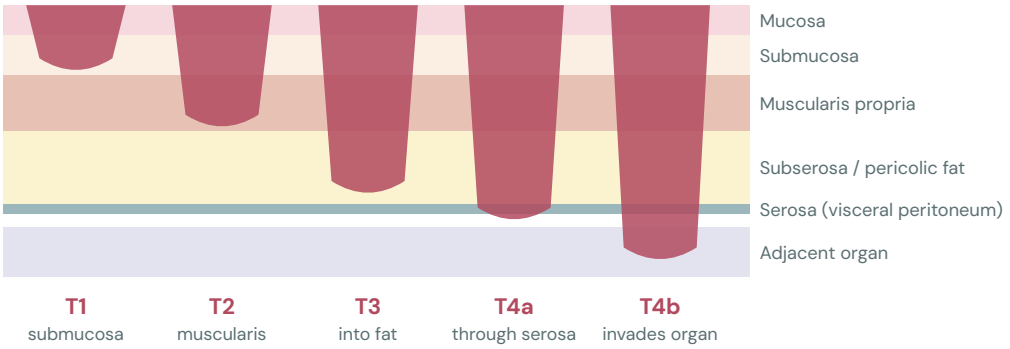
85 is reasonable if never screened). Colonoscopy every 10 years or yearly FIT are the preferred options; whatever the test, adherence matters more than the choice, and every positive non-colonoscopy test needs a prompt colonoscopy.

- **Family history**: one first-degree relative with colorectal cancer, an advanced adenoma or an advanced serrated lesion → colonoscopy from 40 (or 10 years before the relative's diagnosis, whichever is earlier), repeated every 5 years; yearly FIT if colonoscopy is declined. Ask every adult about family history before 40 and update it every few years.
- **An Indian approach**: opportunistic FIT for adults over 45–50 seen in clinics, colonoscopy for a positive FIT, symptoms, anaemia or a family history; quality colonoscopy capacity is the main constraint.
- **Polyps**: adenomas (risk rises with size, villous histology and high-grade dysplasia), sessile serrated lesions and traditional serrated adenomas are precancerous; small distal hyperplastic polyps are not. Inflammatory polyps need no removal unless symptomatic. Juvenile polyposis and Peutz–Jeghers syndrome carry cancer risk.
- **Malignant polyp** (cancer invading the submucosa in a removed polyp): no further surgery if it was removed in one piece with a clear margin (≥1 mm), grade 1–2, no lymphovascular invasion and low tumour budding; otherwise resection with nodes. Tattoo the site.

Workup before treatment: the checklist

Step	Why	Notes
Complete colonoscopy with biopsies and tattoo	Histology, synchronous cancers (3–5%) and polyps	If obstructing: CT (or MR) colonography — preferred over barium enema — or complete colonoscopy within 3–6 months after surgery.
CT chest, abdomen and pelvis with contrast	Distant staging; local extent of colon cancer	Radiological T4 or bulky T3 colon cancer may suit neoadjuvant chemotherapy (section 06).
MRI liver (with hepatocyte-specific contrast if available)	Indeterminate or potentially resectable liver lesions	Before any liver surgery or ablation.
MRI pelvis, rectal protocol (rectal cancer)	Local stage: T, CRM, EMVI, nodes, height, sphincter	Done before any treatment; repeat after neoadjuvant therapy. Endorectal ultrasound adds detail for early T1–T2 tumours.
CEA, before and after surgery	Baseline for follow-up; a high level carries a worse prognosis	Not for screening or diagnosis.
PET-CT	Selected cases only	Before resecting metastases, or for a rising CEA with normal CT. Not routine for staging.
Blood counts, liver and kidney function; DPYD genotype where available	Fitness and safety of chemotherapy	Correct anaemia; nutritional assessment; geriatric assessment over 70.
MMR immunohistochemistry on the biopsy	Changes treatment at every stage; screens for Lynch	Request at diagnosis so neoadjuvant options are not missed.

Depth of invasion (T)



N (regional nodes; examine ≥12)
N1a: 1 node · N1b: 2–3 nodes
N1c: tumour deposits, nodes negative
N2a: 4–6 nodes · N2b: 7 or more

M (distant)
M1a: one organ
M1b: two or more organs
M1c: peritoneum (± organs)

Stage groups
I: T1–2 N0 · IIA T3 · IIB T4a · IIC T4b
III: any T, N1–2 (IIIA–C)
IV: any M1 (IVA–C)

Figure 4. TNM at a glance (AJCC/UICC 8th edition). A pathology report with fewer than 12 lymph nodes may understage the cancer; tumour deposits without nodes count as N1c.

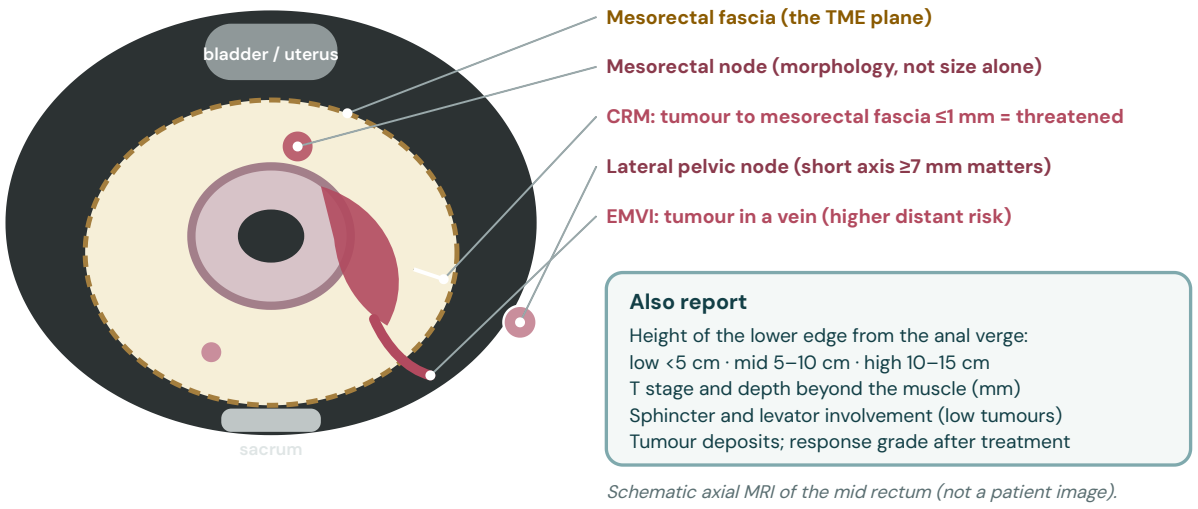


Figure 5. High-resolution MRI pelvis decides rectal cancer treatment. A threatened margin, EMVI, enlarged lateral nodes, a low tumour or T4 disease all push towards total neoadjuvant therapy.

- **Rectal cancer is defined** (and staged by MRI) when the lower edge lies within 15 cm of the anal verge on rigid sigmoidoscopy, or below the sigmoid take-off on MRI. Tumours above the peritoneal reflection behave more like colon cancer.
- The MRI items that change treatment: **CRM threatened or involved** (≤1 mm), **EMVI**, **T3 depth beyond the muscle** (>5 mm), **T4**, **tumour deposits**, **enlarged lateral nodes** (short axis ≥7 mm; Ogura 2019[9]), and the distance from the anal verge and sphincters. MERCURY[10] showed that MRI predicts a clear circumferential margin accurately.
- **Obstructing left-sided cancer**: emergency resection (Hartmann's or primary anastomosis with or without a stoma) or a self-expanding stent as a bridge to elective surgery a few weeks later in expert hands; stents are avoided if bevacizumab is planned.

- **Prognosis within stage III** varies widely: T1–2 N1 does as well as many stage II tumours, while T4 N2 does worse than some stage IV patients after metastasectomy.

04 Biomarkers that change treatment

- **Mismatch repair (MMR) / microsatellite instability (MSI)**: test every new cancer by immunohistochemistry (MLH1, MSH2, MSH6, PMS2) or PCR/NGS. About 15% of all colorectal cancers are dMMR (more in stage II, right colon), but only about 4% of metastatic ones. dMMR changes adjuvant treatment (no fluoropyrimidine alone in stage II), neoadjuvant treatment (immunotherapy is highly active) and metastatic treatment (immunotherapy first line).
- **RAS (KRAS and NRAS, exons 2, 3 and 4)**: mutated in about 45–50%. Any RAS mutation excludes anti-EGFR antibodies, which can harm these patients (**PRIME**[11]). Test all of KRAS and NRAS, not just KRAS exon 2.
- **KRAS G12C** (about 3%): sotorasib or adagrasib combined with an anti-EGFR antibody after chemotherapy (**CodeBreaK 300**[12]); alone they work poorly in colorectal cancer because EGFR signalling bypasses the block.
- **BRAF V600E** (about 8–10%): poor prognosis, right-sided, peritoneal spread. Encorafenib with cetuximab and FOLFOX in first line (**BREAKWATER**[13]), encorafenib with cetuximab later (**BEACON**[14]). Non-V600 BRAF mutations behave differently.
- **HER2 amplification** (about 3–5%, mostly RAS wild-type, left-sided): tucatinib with trastuzumab (**MOUNTAINEER**[15]) or trastuzumab deruxtecan (**DESTINY-CRC01**[16]). Use colorectal-specific scoring; HER2 also predicts resistance to anti-EGFR antibodies.
- **POLE / POLD1 proofreading mutations** (somatic or germline): ultramutated tumours (often >50 mutations per megabase) that respond to immune checkpoint inhibitors as dMMR tumours do; immunotherapy is suggested first line for such metastatic cancers.
- **PI3K-pathway alterations** (*PIK3CA* exon 9/20 and other *PIK3CA*, *PIK3R1* or *PTEN* mutations; roughly a third of cancers): after resection of stage I–III disease, low-dose aspirin for 3 years roughly halved recurrence in **ALASCCA**[17]. This makes NGS of the resected tumour useful even in early disease; aspirin can start once the patient has recovered from surgery and run alongside adjuvant chemotherapy.
- **Rare fusions** (NTRK, RET, ALK; under 1%, mainly MSI-high, RAS/BRAF wild-type): tumour-agnostic TRK or RET inhibitors.
- **Primary tumour side** works like a biomarker in metastatic RAS/BRAF wild-type disease: left-sided tumours gain survival from anti-EGFR antibodies (**PARADIGM**[18]), right-sided ones generally do not (**pooled analysis**[19]).
- **Liquid biopsy (ctDNA)**: useful when tissue is scant (RAS concordance with tissue is high in most patients), for anti-EGFR rechallenge (RAS wild-type in plasma again), and after surgery to estimate relapse risk (**DYNAMIC**[20]) — the latter still largely within trials and costly.
- **Germline pharmacogenomics**: DPYD variants (severe fluoropyrimidine toxicity) and UGT1A1*28 (irinotecan) — test before treatment where available.
- **Not useful for treatment choice**: CEA level, consensus molecular subtypes, immunoscore (prognostic only), and tumour mutational burden outside MSI-high.

Every new colorectal cancer
MMR immunohistochemistry (or MSI)

All four proteins present — **pMMR / MSS (about 85%)**
No Lynch work-up unless the family history is strong; standard treatment

MLH1 + PMS2 lost — **Usually sporadic**
Test BRAF V600E or MLH1 promoter methylation: if present → sporadic; if absent → germline testing

MSH2 + MSH6, or MSH6, or PMS2 lost — **Lynch likely**
Genetic counselling and germline testing; cascade testing of relatives

Why test everyone

- dMMR stage II: no benefit from fluoropyrimidine alone
- dMMR metastatic: immunotherapy first
- dMMR localised: immunotherapy before surgery is highly active

Family history alone misses about half of Lynch carriers. Somatic "double hits" (two tumour mutations) explain many unexplained dMMR cases, but germline testing still comes first.

Figure 6. One test, three uses. MMR status changes adjuvant, neoadjuvant and metastatic treatment, and it is the screening test for Lynch syndrome.

Approximate frequency in metastatic colorectal cancer (overlaps exist; NTRK, RET and others are each under 1%).

RAS mutant ~45–50%	BRAF ~8%	MSI-H ~4%	HER2 ~3%	RAS/BRAF wild ~35%

RAS (KRAS, NRAS)

- Extended RAS test before any anti-EGFR
- Mutant: anti-EGFR harms or does not help
- KRAS G12C: sotorasib or adagrasib + anti-EGFR (later line)

BRAF V600E

- Aggressive; right-sided; peritoneal spread
- First line: encorafenib + cetuximab + FOLFOX
- Later: encorafenib + cetuximab

dMMR / MSI-high

- Immunotherapy first line (pembrolizumab, or nivolumab + ipilimumab)
- Localised: neoadjuvant IO trials, organ sparing in rectum

HER2 amplified

- IHC 3+ or ISH; usually RAS wild-type, left-sided
- Tucatinib + trastuzumab, or trastuzumab deruxtecan
- Predicts anti-EGFR resistance

All patients

- Sidedness + RAS/BRAF choose anti-EGFR vs bevacizumab
- NGS: KRAS G12C, NTRK, POLE (IO), PI3K (aspirin in stage I–III)
- DPYD and UGT1A1 where available

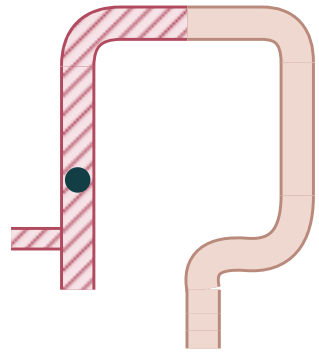
Test early
At diagnosis of metastatic disease: RAS, BRAF, MMR/MSI, HER2 (NGS panel preferred). Tissue first; plasma ctDNA if tissue is scant.
MMR for every new cancer.

Figure 7. Biomarkers that change treatment. Each result points to a specific drug, or away from one: anti-EGFR antibodies help only RAS and BRAF wild-type tumours, ideally left-sided.

05 Local therapy: surgery & radiotherapy

Colon cancer surgery

- **Principle**: remove the bowel segment with its mesentery and the lymph nodes along the feeding vessels, with clear margins (usually 5 cm or more of bowel on each side) and at least 12 nodes for staging.
- **Complete mesocolic excision with central vascular ligation** (CME/CVL, "D3") removes the mesocolon in its fascial envelope and the central nodes; it yields more nodes and may lower recurrence in observational series, at the cost of more vascular injury if done without experience.
- **Laparoscopic versus open**: equivalent long-term cancer outcomes in **COST**[21] and **COLOR**[22], with faster recovery; robotic surgery is an option where available. Enhanced recovery (ERAS) pathways shorten stay and complications.
- **T4b tumours** (adherent to another organ): resect en bloc; separating the adhesion risks tumour spill. Consider neoadjuvant chemotherapy first.
- **Synchronous cancers or polyposis**: subtotal or total colectomy; Lynch patients under about 60 may choose extended colectomy to reduce metachronous risk.

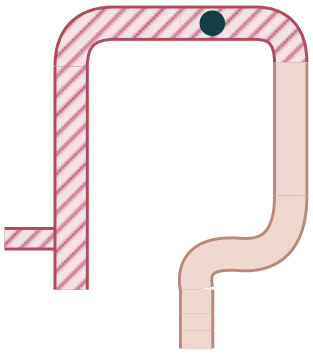


Right hemicolectomy

REMOVES
Terminal ileum, caecum, ascending colon, hepatic flexure with the ileocolic and right colic vessels

RESULT
Ileum joined to transverse colon

For: Caecum, ascending colon, hepatic flexure

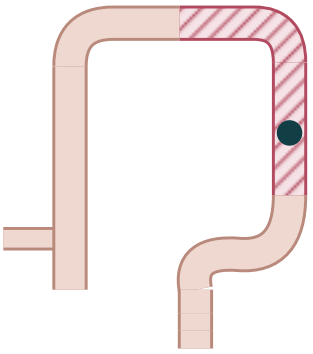


Extended right hemicolectomy

REMOVES
As right hemicolectomy plus the transverse colon (middle colic vessels)

RESULT
Ileum joined to descending colon

For: Transverse colon and splenic flexure

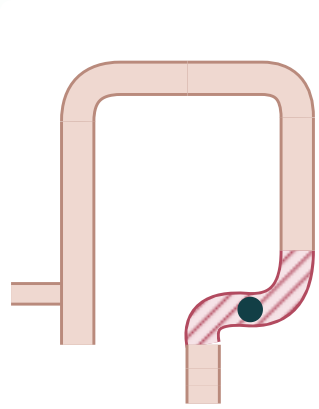


Left hemicolectomy

REMOVES
Distal transverse and descending colon (left colic vessels; inferior mesenteric artery for some)

RESULT
Transverse colon joined to sigmoid

For: Descending colon

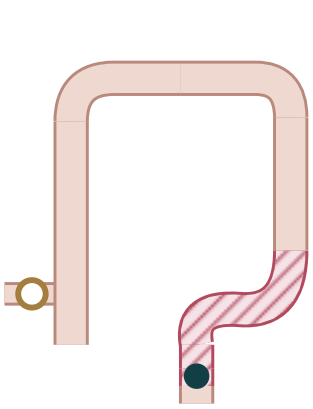


Sigmoid colectomy / high anterior resection

REMOVES
Sigmoid colon with the inferior mesenteric pedicle

RESULT
Descending colon joined to upper rectum

For: Sigmoid and rectosigmoid junction

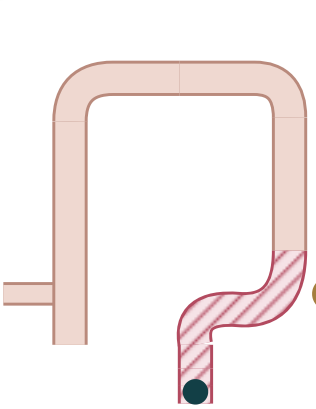


Low anterior resection with TME

REMOVES
Rectum with its whole mesorectum in the fascial envelope (TME)

RESULT
Colon joined low in the pelvis; temporary loop ileostomy

For: Mid and low rectum when the sphincter can be kept



Abdominoperineal resection

REMOVES
Rectum, anal canal and sphincters (extralevator when needed)

RESULT
Permanent end colostomy

For: Tumours invading the sphincter or levators; poor sphincter function

Bowel removed · Bowel kept · Tumour · Stoma

Figure 8. Types of colorectal resection (schematic large bowel, front view). Each operation removes the bowel with its blood supply and lymph nodes (at least 12 nodes); laparoscopic and robotic routes give equivalent cancer outcomes in experienced hands. Emergency obstruction or perforation may need a Hartmann's operation (resection, end colostomy, rectal stump closed) with later reversal.

Operation	Best suited to	Advantages	Disadvantages
Right / extended right hemicolectomy	Caecum, ascending, hepatic flexure, transverse colon	Safe ileocolic anastomosis; good node yield	Looser stools for some; middle colic dissection in extended resections

Operation	Best suited to	Advantages	Disadvantages
Left hemicolectomy / sigmoid colectomy	Descending and sigmoid colon	Bowel function usually normal afterwards	Splenic flexure mobilisation; anastomotic leak 2–5%
Subtotal / total colectomy	Synchronous cancers, Lynch (selected), obstructing left cancer with caecal damage	Removes the at-risk colon	Frequent stools
Low anterior resection with TME	Mid and low rectum when the sphincter can be preserved	Avoids a permanent stoma	Low anterior resection syndrome; temporary ileostomy; leak 5–15%
Abdominoperineal resection	Tumours invading the sphincter or levators; poor continence	Clear distal margin	Permanent colostomy; perineal wound problems
Local excision (TEM / TAMIS)	Selected cT1 low-risk rectal tumours; after a good response in trials	No stoma; minimal function loss	Nodes not removed: higher local recurrence unless the tumour is very favourable
Hartmann's operation	Emergency obstruction or perforation; frail patients	No anastomosis at risk	Stoma; reversal often never done

Rectal cancer surgery

- **Total mesorectal excision (TME)**: sharp dissection in the plane outside the mesorectal fascia removes the rectum with its fatty envelope and nodes intact; it cut local recurrence from 20–30% to under 10% and is the foundation of rectal cancer treatment. The pathologist grades the specimen (complete, nearly complete, incomplete) and the CRM.
- **Distal margin**: 1–2 cm is acceptable for low tumours after TME (1 cm, or even less after good neoadjuvant response); upper rectal tumours need a 5 cm mesorectal margin (partial mesorectal excision).
- **Laparoscopic TME** gave similar local recurrence and survival to open surgery in **COLOR II**[23]; trials in less specialised settings missed non-inferiority for pathological quality, so experience matters more than the route.
- **Lateral pelvic nodes**: enlarged nodes (short axis ≥7 mm before treatment) predict lateral recurrence even after chemoradiation and TME; consider a radiotherapy boost and/or lateral node dissection in an experienced centre.
- **Function after surgery**: low anterior resection syndrome (urgency, frequency, clustering, incontinence) affects up to half after low anastomoses; urinary and sexual dysfunction from pelvic nerve injury. Counsel before surgery; temporary ileostomy closure at about 3 months.
- **Watch-and-wait**: after a clinical complete response (no palpable tumour, flat white scar on endoscopy, no residual tumour on MRI), surgery can be deferred with intensive surveillance. About a quarter regrow, almost all within 2 years and most are salvageable by surgery (**International Watch & Wait Database**[24]).

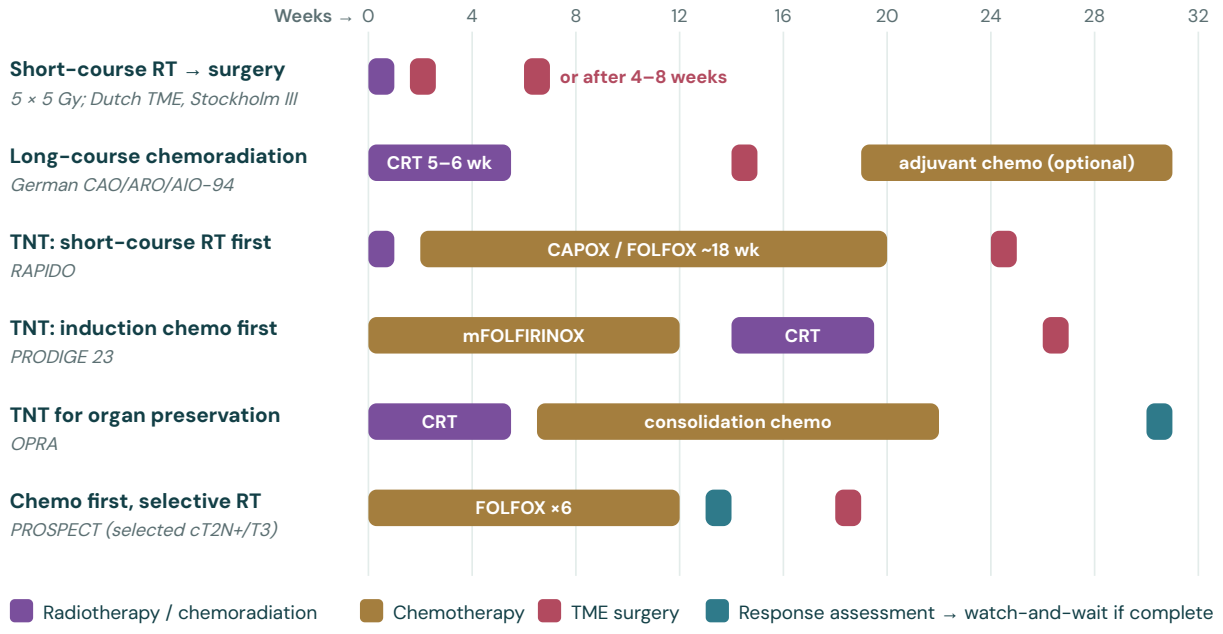


Figure 9. Rectal cancer sequences (illustrative timing). Total neoadjuvant therapy gives all chemotherapy before surgery, raises complete response rates and lets about half of selected patients keep the rectum when a clinical complete response is followed by watch-and-wait.

Radiotherapy schedules for rectal cancer

Schedule	How given	Pros	Cons
Short-course RT	5 fractions over 1 week (5 × 5 Gy)	Cheap, quick, convenient; no concurrent drug; ideal before chemotherapy in TNT or for frail patients	Little shrinkage if surgery is immediate; delayed surgery (4–8 weeks) needed for downstaging
Long-course chemoradiation	25–28 fractions over 5–6 weeks with capecitabine or 5-FU	More shrinkage; preferred for organ preservation and threatened CRM	Six weeks of daily travel; more acute toxicity
Boost / contact X-ray brachytherapy	Extra dose to the tumour	Raises complete response for organ preservation in selected small low tumours	Limited availability
Palliative pelvic RT	Short schedules	Controls bleeding, pain and tenesmus	—

- Pelvic radiotherapy causes infertility and early menopause: offer sperm banking, oocyte or embryo storage, and ovarian transposition where relevant before it starts. Late effects: bowel urgency, insufficiency fractures, second cancers (rare).

Local therapy for metastases

Resectable now	Potentially resectable	Never resectable
• RO resection keeping inflow, outflow and biliary drainage • Future liver remnant >20% (>30% after chemotherapy liver injury) • Low risk (≤4 lesions, one lobe, RAS/BRAF wild-type): surgery first; higher risk: chemotherapy first • Ablation for ≤3 cm (COLLISION); SBRT if unsuitable	• RAS/BRAF wild-type: oxaliplatin doublet/triplet (± anti-EGFR if left); mutant: FOLFOXIRI + bevacizumab • Fiducials for small, deep lesions; re-image every 6–8 weeks; operate as soon as resectable • Portal vein embolisation or two-stage hepatectomy to grow the remnant	• Systemic therapy for control • Ablation, SBRT, TACE or Y-90 for limited or refractory liver-predominant disease • No radioembolisation added to first-line chemotherapy • Selected liver-only disease: transplant in expert centres (TRANSMET)
5-year survival up to 50–60%	**About 15–30% convert**	**Median survival now often 2–3 years**

Decide in a liver multidisciplinary meeting with a hepatobiliary surgeon, before chemotherapy starts.
Extrahepatic disease limited to the lungs does not exclude cure.

Figure 10. Colorectal liver metastases are curable in a meaningful minority. Resectability is judged by what will remain, not by the number of lesions.

- **Liver resection** is the only curative option for liver metastases: 5-year survival after resection now approaches 50–60% in modern series, with operative mortality under 5% (under 1% in high-volume centres). Resectability depends on what remains — inflow, outflow, biliary drainage and a future liver remnant above 20% (above 30% after chemotherapy-related liver injury) — not on the number of lesions. Aim for margins over 10 mm, but resect if more than 1 mm is achievable; parenchyma-sparing resections are favoured, with wider margins for RAS- or BRAF-mutant tumours. Repeat hepatectomy is feasible for recurrence.
- **Sequencing with chemotherapy**: fit patients with up to 4 lesions in one lobe and RAS/BRAF wild-type tumours usually go straight to surgery; higher-risk disease (more than 4 lesions, bilobar, RAS/BRAF-mutant, suspicious portal nodes or extrahepatic disease) has chemotherapy first. Perioperative FOLFOX improved progression-free but not overall survival in **EPOC**[25] (**long-term results**[26]). Give no more than about 4 cycles before surgery, re-image every 6–8 weeks, operate as soon as lesions become resectable (at least 4 weeks after chemotherapy, 6–8 weeks after bevacizumab), and complete about 6 months of treatment in total. Mark small (<2 cm) or deep (>1 cm from the surface) lesions with fiducials before chemotherapy: they may vanish on imaging but rarely disappear pathologically, and should still be resected.
- **Conversion therapy** for initially unresectable liver-only disease: RAS/BRAF wild-type → oxaliplatin-based doublet or triplet (with an anti-EGFR antibody for left-sided tumours); RAS- or BRAF-mutant and fit → FOLFOXIRI with bevacizumab, which raised resection rates in **CAIRO5**[27]. Even dMMR potentially resectable disease is usually treated with chemotherapy rather than upfront immunotherapy, although this is evolving. Hepatic arterial infusion remains a trial or expert-centre option.
- **Synchronous metastases**: a bleeding, obstructing or perforated primary is resected first; extensive bilobar disease suits a planned two-stage hepatectomy with portal vein embolisation; a right-colon primary with limited liver disease can be removed in one operation (liver first); a reverse (liver-first) approach is an option when the liver disease dominates.
- **Ablation and other liver-directed therapy**: for up to a few lesions of 3 cm or less, thermal ablation (radiofrequency or microwave) gave similar survival with fewer complications than resection in **COLLISION**[28] (long-term follow-up awaited); SBRT, irreversible electroporation, TACE or yttrium-90 radioembolisation suit selected unresectable or chemotherapy-refractory liver-predominant disease.

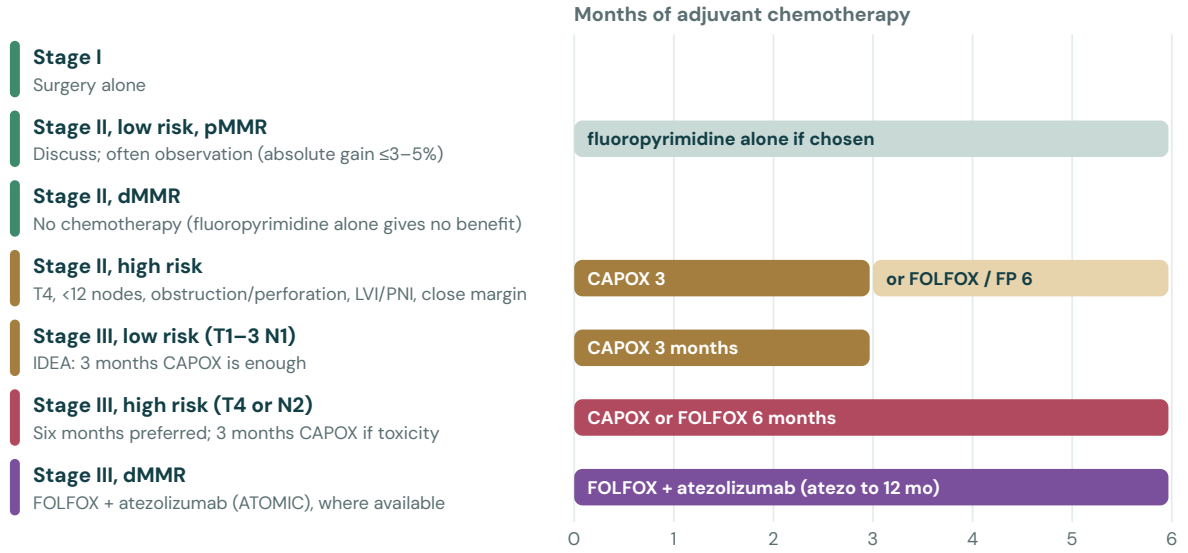
Adding radioembolisation to first-line chemotherapy did not improve survival (**FOXFIRE/SIRFLOX combined analysis**[29]).

- **Lung**: resection or SBRT for limited, slow-growing lung metastases; long-term survival is common when the disease-free interval is long.
- **Other sites**: selected isolated retroperitoneal nodal, adrenal or bulky symptomatic ovarian metastases can be resected; multi-organ disease responding to chemotherapy is not debulked (no survival gain, more toxicity).
- **Peritoneum**: complete cytoreductive surgery in expert centres for limited disease without extraperitoneal spread (low peritoneal cancer index), after shared decision-making about its morbidity; adding oxaliplatin HIPEC gave no survival benefit and more late complications in **PRODIGE 7**[30].
- **The primary tumour in stage IV**: in patients with unresectable metastases and an asymptomatic primary, upfront resection did not improve survival (**JCOG1007**[31]; **SYNCHRONOUS/CCRe-IV**[32]); resect, bypass, divert or stent only for obstruction, bleeding or perforation. With an asymptomatic primary and resectable metastases, systemic therapy usually comes first so that the biology declares itself.
- **Liver transplant**: for highly selected unresectable liver-only disease after good response to chemotherapy, transplant plus chemotherapy improved 5-year survival to about 57% versus 13% with chemotherapy alone (**TRANSMET**[33]); needs organ allocation policy and expert centres.

06 Systemic therapy: indications & options

Indications and options only; no doses. Benefits are given in absolute terms where possible. Trial names link to the primary publications.

Adjuvant therapy after resection of colon cancer



Start within 6–8 weeks of surgery. Over 70: oxaliplatin adds little; DPYD testing before fluoropyrimidines where available.

Figure 11. Adjuvant therapy after colon cancer surgery (no doses). Duration follows risk: the IDEA collaboration showed that three months of CAPOX is enough for low-risk stage III, with far less permanent neuropathy.

- **Stage III**: adding oxaliplatin to a fluoropyrimidine raised 6-year overall survival by about 4 percentage points (MOSAIC[34], OS update[35]; NSABP C-07[36]); capecitabine can replace infusional 5-FU (X-ACT[37]). Start within about 8 weeks of surgery; late starts lose benefit.
- **Duration** (IDEA[38]): three months of CAPOX is enough for low-risk stage III (T1–3 N1), with much less lasting neuropathy; high-risk stage III (T4 or N2) does better with 6 months, especially with FOLFOX. If oxaliplatin causes troublesome neuropathy, stop it and continue the fluoropyrimidine.
- **Stage II**: the absolute gain from chemotherapy is about 3–4% (QUASAR[39]). Offer it for high-risk features (T4, fewer than 12 nodes, obstruction or perforation, lymphovascular or perineural invasion, poorly differentiated pMMR tumours, close margins, high tumour budding). Low-risk pMMR: discuss, often observe. dMMR stage II: no fluoropyrimidine alone (no benefit; may harm); T4 dMMR can be considered for oxaliplatin-based treatment.
- **Stage III dMMR**: adding atezolizumab to 6 months of FOLFOX, continued alone to 12 months, roughly halved the risk of recurrence or death (ATOMIC[40]); overall survival did not differ at 5 years, and grade 3–4 toxicity was higher. Where atezolizumab is not accessible, standard oxaliplatin-based adjuvant therapy remains appropriate.
- **Older patients**: oxaliplatin adds little over the age of 70; a fluoropyrimidine alone is reasonable for many. Use geriatric assessment rather than age alone.
- **Adjunctive aspirin**: in unselected patients, randomised trials of aspirin (ASCOLT[41]) and celecoxib (CALGB/SWOG 80702[42]) after adjuvant therapy did not improve disease-free or overall survival, despite favourable observational data; discuss it, or reserve it for those with another indication. For stage I–III

cancers with a PI3K-pathway alteration, low-dose aspirin for 3 years reduced recurrence (about 8% vs 14–17%) in **ALASCCA**[17] (celecoxib also helped the *PIK3CA*-mutant subgroup of **80702**[43], but aspirin is safer).

- **Vitamin D**: low levels are linked with worse outcomes, but supplementation has not been proven to improve survival (**meta-analysis of trials**[44]). It is reasonable to measure 25-hydroxyvitamin D at diagnosis and replace it when below 20 ng/mL, mainly for bone health.
- **ctDNA-guided treatment**: in stage II, giving chemotherapy only to ctDNA-positive patients halved its use without losing recurrence-free survival (**DYNAMIC**[20]). Promising, but not yet standard and expensive in India.
- **Neoadjuvant chemotherapy for colon cancer**: for radiologically locally advanced (T4 or bulky T3) pMMR tumours, 6 weeks of FOLFOX before surgery reduced 2-year residual or recurrent disease from about 22% to 17% and downstaged tumours (**FOxTROT**[45]). dMMR tumours respond poorly to this chemotherapy but extraordinarily to immunotherapy: two cycles of nivolumab with ipilimumab gave a major pathological response in 95% and a complete response in two-thirds (**NICHE-2**[46]). For dMMR tumours that are locally unresectable, immunotherapy is an appropriate alternative to chemotherapy, ideally in a trial; most resectable colon cancers still go straight to surgery.

Systemic therapy in rectal cancer

- **Total neoadjuvant therapy (TNT)** gives chemotherapy and radiotherapy before surgery. It improves completion of chemotherapy, raises complete response and allows organ preservation. Options: short-course RT then 18 weeks of CAPOX/FOLFOX (**RAPIDO**[47]); induction mFOLFIRINOX then chemoradiation (**PRODIGE 23**[48], which also improved overall survival with longer follow-up); chemoradiation then consolidation chemotherapy, favoured for organ preservation (**OPRA**[49]).
- **Who needs TNT**: high-risk features on MRI — T4, N2, threatened or involved CRM, EMVI, enlarged lateral nodes, or low tumours where organ preservation is a goal.
- **Who can avoid radiotherapy**: in **PROSPECT**[50], patients with cT2N1 or cT3N0–1 tumours suitable for sphincter-sparing surgery and a clear margin had FOLFOX first, with chemoradiation only for a poor response; disease-free survival was non-inferior and about nine in ten avoided pelvic radiation (and its effects on fertility and bowel function).
- **Early rectal cancer** (cT1–2 N0): TME alone; selected T1 tumours by local excision.
- **dMMR rectal cancer**: anti-PD-1 therapy alone for 6 months produced a clinical complete response in every one of the first patients treated, allowing omission of chemoradiation and surgery (**Cercek 2022**[51]). An expanded series confirmed durable organ preservation with PD-1 blockade across dMMR rectal and other early tumours (**Cercek 2025**[52]). Confirm dMMR before planning neoadjuvant chemoradiation in every rectal cancer.
- **Adjuvant chemotherapy after chemoradiation and surgery** (when TNT was not used): evidence is weaker than in colon cancer; it is usually offered for ypN+ disease.

Metastatic disease

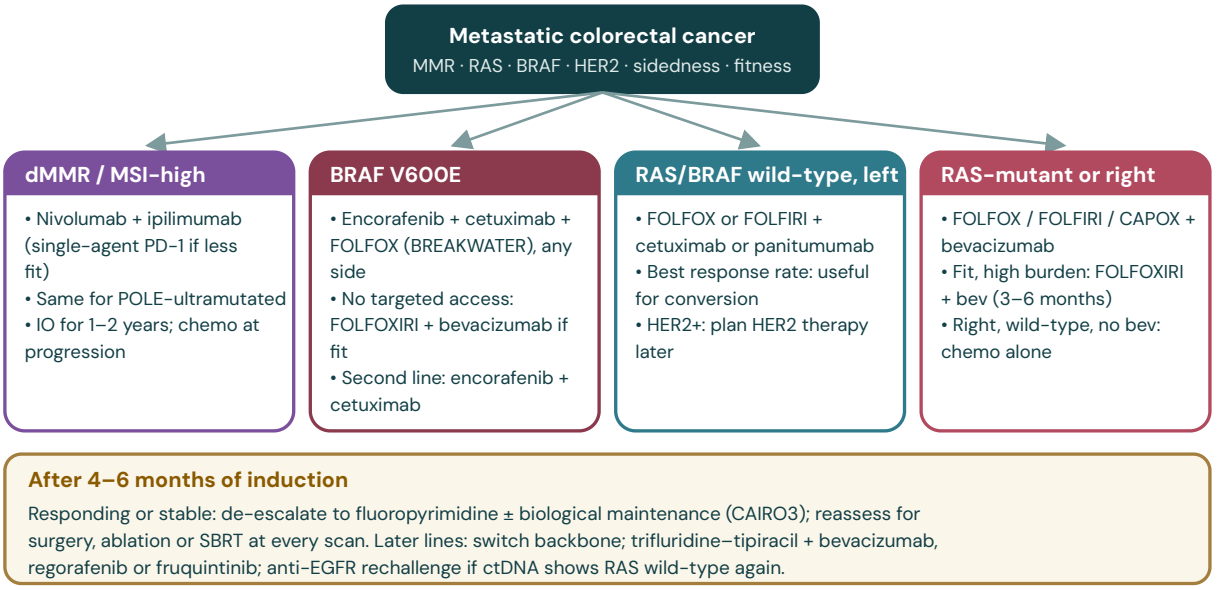


Figure 12. Choosing first-line therapy (no doses). Biomarkers come first, sidedness second, fitness and goals third. Ask at the start whether the disease could become resectable, because that changes the intensity of the first regimen.

- **First line, pMMR, RAS/BRAF wild-type, left-sided**: FOLFOX or FOLFIRI with panitumumab or cetuximab improved overall survival over bevacizumab in left-sided tumours (PARADIGM[18]; FIRE-3[53], CALGB/SWOG 80405[54], CRYSTAL[55]). Response rates are highest, which matters when conversion to resection is the aim.
- **Right-sided or RAS-mutant**: doublet chemotherapy with bevacizumab (Hurwitz[56]); for a right-sided RAS/BRAF wild-type tumour where bevacizumab is contraindicated, use chemotherapy alone rather than an anti-EGFR antibody. For fit patients with a large tumour burden, FOLFOXIRI with bevacizumab raises response and survival at the price of more toxicity (TRIBE[57]); limit the triplet to 3–6 months, then fluoropyrimidine maintenance.
- **Choosing the backbone**: FOLFOX, CAPOX and FOLFIRI are equally effective first line; choose by toxicity, and prefer FOLFIRI if adjuvant oxaliplatin was given within the past 12 months. Start chemotherapy early, before symptoms, rather than waiting. Stop oxaliplatin after 3–4 months (before disabling neuropathy) and continue the rest; planned breaks are reasonable for responding, low-volume disease. Judge response by imaging: a rising CEA alone should be confirmed radiologically before changing treatment.
- **dMMR / MSI-high (and POLE/POLD1-ultramutated)**: immunotherapy first. Nivolumab with ipilimumab was superior to chemotherapy and to nivolumab alone (CheckMate 8HW[58]; second report[59]) and is preferred for fit patients; pembrolizumab (KEYNOTE-177[60], which doubled progression-free survival over chemotherapy), nivolumab or dostarlimab alone suit less fit patients. Continue for 1–2 years if responding; stop after at least a year if a complete response is confirmed on two scans. On progression, switch to fluoropyrimidine-based chemotherapy ± a biological agent.
- **BRAF V600E**: encorafenib + cetuximab + mFOLFOX6 roughly doubled median overall survival over standard first-line chemotherapy (about 30 vs 15 months; BREAKWATER[13]), whatever the side; FOLFOX is the preferred backbone, FOLFIRI an alternative with less neuropathy. After first line without it, encorafenib + cetuximab improved survival over chemotherapy (BEACON[14]); after progression on the triplet, FOLFIRI or irinotecan with bevacizumab. Anti-EGFR antibodies alone do not work in BRAF-mutant disease.
- **Maintenance**: after 4–6 months of induction, de-escalate to a fluoropyrimidine with bevacizumab (CAIRO3[61]) or with anti-EGFR; full treatment breaks suit selected patients. Reintroduce oxaliplatin on

progression if neuropathy allows.

- **Second line**: switch the chemotherapy backbone (FOLFOX ↔ FOLFIRI). After first-line bevacizumab, continue an antiangiogenic agent (bevacizumab preferred over aflibercept); after FOLFOX + anti-EGFR, give FOLFIRI + bevacizumab (and vice versa). Combine chemotherapy with an antiangiogenic or an anti-EGFR antibody, never both. Patients who cannot tolerate intensive therapy can have sequential single agents, capecitabine + bevacizumab, or supportive care alone.
- **Later lines**: trifluridine–tipiracil with bevacizumab (median survival 10.8 vs 7.5 months over trifluridine–tipiracil alone; **SUNLIGHT**[62], after **RECOURSE**[63]); regorafenib (**CORRECT**[64]); fruquintinib (**FRESCO-2**[65]). Gains are measured in weeks to months: weigh them with the patient against toxicity and cost.
- **HER2-overexpressing** (pMMR, RAS wild-type) after chemotherapy: tucatinib + trastuzumab preferred (**MOUNTAINEER**[15]); trastuzumab with lapatinib or pertuzumab if unavailable; trastuzumab deruxtecan later (**DESTINY-CRC01**[16]; **DESTINY-CRC02**[66]), and as the second-line choice for HER2-positive RAS-mutant disease. **KRAS G12C** after chemotherapy and anti-VEGF: sotorasib + panitumumab (**CodeBreaK 300**[12]; **survival analysis**[67]) or adagrasib + cetuximab (**KRYSTAL-1**[68]). **NTRK fusion**: larotrectinib, entrectinib or repotrectinib. **Anti-EGFR rechallenge** works mainly when plasma ctDNA shows RAS wild-type again after a break; rechallenge with earlier regimens is also an option when everything has been used.
- **Older and less fit patients**: decide on function and comorbidity, not age (geriatric assessment; CARG or CRASH toxicity scores; dose renally cleared drugs by creatinine clearance). Fit older adults get the same treatment as younger ones, often a doublet without the 5-FU bolus; avoid bevacizumab within 6–12 months of a stroke, myocardial infarction or arterial thrombosis. Less fit: reduced-intensity doublet, fluoropyrimidine ± bevacizumab, or trifluridine–tipiracil + bevacizumab; dMMR → single-agent immunotherapy. ECOG 2: treat selected patients, especially when the decline is due to the cancer; ECOG 3–4: supportive care for most.
- **In India**: biosimilar bevacizumab and generic capecitabine, oxaliplatin and irinotecan make doublet chemotherapy with bevacizumab widely affordable; anti-EGFR antibodies, immunotherapy and BRAF/HER2 drugs often need assistance programmes. Chemotherapy alone remains a valid, evidence-based choice when biologicals are unaffordable.

	5-FU / cape	Oxaliplatin	Irinotecan	Bevacizumab	Anti-EGFR	Regorafenib	FTD-TPI	Encorafenib	IO
Diarrhoea	●	○	●		○	○	○	○	○
Neutropenia	○	○	●				●		
Neuropathy (cold-triggered, cumulative)		●							
Hand-foot skin reaction	●					●		○	
Acneiform rash, paronychia					●				
Low magnesium					●				
Hypertension, proteinuria				●		●			
Bleeding, perforation, poor wound healing				●		○			
Chest pain (coronary spasm)	○								
Infusion / allergic reaction		○			○				
Liver injury		○	○			●			○
Colitis, thyroid, hepatitis (immune)									●

● Common or signature ○ Occasional but important

*DPYD variants → severe fluoropyrimidine toxicity; UGT1A1*28 → irinotecan neutropenia.*

Figure 13. Side effects by drug (schematic). Signature toxicities guide counselling: cold-triggered neuropathy with oxaliplatin, rash and low magnesium with anti-EGFR antibodies, hypertension and bleeding with anti-VEGF drugs.

Quick-reference tables (also printable as one PDF from the Printable Teaching Resources page). No doses; check current approvals and product information.

Table A. Biomarkers and matched therapy

Biomarker	Frequency	Test	What it changes	Key trials	Watch for
dMMR / MSI-high	~15% of stage II, ~4% of metastatic	IHC for MLH1, MSH2, MSH6, PMS2 (or PCR/NGS MSI) on every new cancer	Stage II: no fluoropyrimidine alone. Stage III: FOLFOX + atezolizumab. Localised: neoadjuvant IO (organ sparing in rectum). Metastatic: nivolumab + ipilimumab preferred; single-agent PD-1 if less fit	KEYNOTE-177[60], CheckMate 8HW[58], NICHE-2[46], Cercek 2022[51], ATOMIC[40]	Lynch work-up; immune side effects; pseudoprogression early
RAS (KRAS/NRAS exons 2, 3, 4)	~45–50%	Extended RAS by NGS or PCR before any anti-EGFR	Mutant → no cetuximab or panitumumab	PRIME[11], CRYSTAL[55]	Do not use KRAS exon 2 alone
KRAS G12C	~3%	NGS	Sotorasib + panitumumab (or adagrasib + cetuximab) after chemotherapy and anti-VEGF	CodeBreaK 300[12], KRYSTAL-1[68]	Single-agent KRAS inhibitors work poorly in colorectal cancer

Biomarker	Frequency	Test	What it changes	Key trials	Watch for
BRAF V600E	~8–10%	NGS or PCR; (also used to sort MLH1 loss)	First line (any side): encorafenib + cetuximab + FOLFOX (FOLFIRI alternative); later: encorafenib + cetuximab	BREAKWATER[13], BEACON[14]	Rapid course; arthralgia, skin papillomas, fatigue
HER2 amplification	~3–5% (RAS wild-type, left)	IHC 3+, or 2+ with ISH; NGS copy number	After chemotherapy: tucatinib + trastuzumab preferred; trastuzumab deruxtecan later (or second line if RAS-mutant)	MOUNTAINEER[15], DESTINY-CRC01[16], DESTINY-CRC02[66]	Predicts anti-EGFR resistance; ILD with deruxtecan
POLE / POLD1 proofreading mutation	About 1%; ultramutated (TMB often >50/Mb)	NGS (somatic); germline testing if suspected PPAP	Metastatic: immune checkpoint inhibitor first line, as for dMMR	Guideline-based	Germline PPAP: colonoscopy from 25–30
PI3K pathway (PIK3CA, PIK3R1, PTEN)	About a third	NGS on the resected tumour	Stage I–III after surgery: low-dose aspirin for 3 years	ALASCCA[17]	Bleeding risk; not shown in unselected patients
NTRK, RET fusions	<1% (mostly MSI-high, right)	RNA NGS	Larotrectinib or entrectinib; selpercatinib (tumour-agnostic)	Basket trials	Rare: test if pan-wild-type
DPYD variants	A few per cent	Germline genotype (or phenotype) before fluoropyrimidines	Reduce or avoid 5-FU/capecitabine	Guidance (EMA, CPIC)	Severe mucositis, diarrhoea, neutropenia
UGT1A1*28	Common in South Asians (heterozygous)	Germline genotype	Lower irinotecan exposure in homozygotes	Guidance	Neutropenia, diarrhoea

Table B. Systemic therapy by setting (indications only; no doses)

Setting	Preferred options	Alternatives / when to modify	Evidence
Stage II high-risk colon	CAPOX 3 months, or FOLFOX 6 months	Fluoropyrimidine alone if over 70 or unfit for oxaliplatin; none if dMMR	MOSAIC[34], QUASAR[39], IDEA[38]
Stage III colon, low risk (T1–3 N1)	CAPOX 3 months	FOLFOX 6 months; capecitabine or 5-FU alone if oxaliplatin unsuitable	IDEA[38], X-ACT[37]
Stage III colon, high risk (T4 or N2)	CAPOX or FOLFOX 6 months	CAPOX 3 months if neuropathy or poor tolerance	IDEA[38], MOSAIC OS[35]
Stage III colon, dMMR	FOLFOX + atezolizumab	Standard FOLFOX/CAPOX where atezolizumab unavailable	ATOMIC[40]
Stage I–III, PI3K-pathway altered	Low-dose aspirin for 3 years after surgery (with or after adjuvant therapy)	Unselected patients: discuss; trials negative	ALASCCA[17], ASCOLT[41]

Setting	Preferred options	Alternatives / when to modify	Evidence
Locally advanced colon (radiological T4, bulky T3)	Neoadjuvant FOLFOX (6 weeks) then surgery	Neoadjuvant nivolumab + ipilimumab if dMMR (trial or expert setting)	FOxTROT[45], NICHE-2[46]
Locally advanced rectum (pMMR)	Total neoadjuvant therapy: short-course RT → chemo, or CRT + consolidation chemo, or induction chemo → CRT	Selected cT2N1/cT3N0–1 with clear MRF: FOLFOX first, RT only if poor response	RAPIDO[47], OPRA[49], PRODIGE 23[48], PROSPECT[50]
Locally advanced rectum, dMMR	Anti-PD-1 alone (dostarlimab) with close MRI/endoscopy follow-up	Chemoradiation if IO unavailable (response to chemotherapy is poorer)	Cercek 2022[51]
Metastatic, first line, pMMR, RAS/BRAF wild-type, left	FOLFOX or FOLFIRI + panitumumab or cetuximab	Bevacizumab instead if anti-EGFR unaffordable or poorly tolerated	PARADIGM[18], FIRE-3[53], CALGB/SWOG 80405[54]
Metastatic, first line, right-sided or RAS-mutant	FOLFOX / CAPOX / FOLFIRI + bevacizumab; FOLFOXIRI + bevacizumab if fit with high burden	Right, wild-type, bevacizumab contraindicated: chemotherapy alone (not anti-EGFR); FOLFIRI if oxaliplatin within 12 months; frail: capecitabine ± bevacizumab	Hurwitz[56], TRIBE[57], sidedness analysis[19]
Metastatic, first line, dMMR / MSI-high or POLE-ultramutated	Nivolumab + ipilimumab	Pembrolizumab, nivolumab or dostarlimab alone if less fit; 1–2 years	CheckMate 8HW[58], KEYNOTE-177[60]
Metastatic, first line, BRAF V600E	Encorafenib + cetuximab + FOLFOX	FOLFIRI backbone if neuropathy	BREAKWATER[13]
Liver-only, potentially resectable (conversion)	RAS/BRAF wild-type: oxaliplatin doublet/triplet (± anti-EGFR if left); RAS/BRAF-mutant: FOLFOXIRI + bevacizumab	≤4 cycles before surgery; about 6 months in total	CAIRO5[27], EPOC[25]
Maintenance	Fluoropyrimidine + bevacizumab after 4–6 months of induction; stop oxaliplatin at 3–4 months	Treatment break with close scans for selected patients	CAIRO3[61]
Second line	Switch backbone (FOLFOX ↔ FOLFIRI) ± continue bevacizumab, or aflibercept / ramucirumab with FOLFIRI	Encorafenib + cetuximab (BRAF); KRAS G12C or HER2 options	BEACON[14]
Older or less fit	Doublet without 5-FU bolus if fit; otherwise fluoropyrimidine ± bevacizumab or trifluridine–tipiracil + bevacizumab	ECOG 3–4: supportive care; avoid bevacizumab within 6–12 months of arterial events	Geriatric assessment
Third line and later	Trifluridine–tipiracil + bevacizumab	Regorafenib; fruquintinib; anti-EGFR rechallenge if ctDNA RAS wild-type	SUNLIGHT[62], CORRECT[64], FRESCO-2[65], RECOURSE[63]

Table C. Neoadjuvant strategies for rectal cancer compared

Strategy	Best suited to	Main result	Caveat
Short-course RT (5 × 5 Gy) → surgery	Elderly or frail; when chemotherapy is not planned	Halved local recurrence vs surgery alone (Dutch TME[69])	Little downstaging if surgery is immediate; delay 4–8 weeks lowers complications (Stockholm III[70])

Strategy	Best suited to	Main result	Caveat
Long-course chemoradiation → surgery → adjuvant	Traditional standard	Preoperative better than postoperative for local control and toxicity (German CAO/ARO/AIO-94[71])	No survival gain; adjuvant chemotherapy often not completed
TNT: short-course RT → 18 weeks chemo → TME	High risk: T4, N2, threatened CRM, EMVI, lateral nodes	Fewer disease-related treatment failures; pathological complete response doubled (RAPIDO[47])	Higher local recurrence at 5 years than CRT in the trial: careful surgery and follow-up
TNT: induction FOLFIRINOX → CRT → TME	Fit patients, high distant risk	Better disease-free and overall survival (PRODIGE 23[48])	Intensive; needs good performance status
TNT: CRT → consolidation chemo → watch-and-wait if cCR	Low tumours where keeping the rectum matters	About half keep the rectum at 3–5 years (OPRA[49])	Regrowth in about a third of watch-and-wait patients; strict surveillance
FOLFOX → selective CRT → TME	cT2N1, cT3N0–1, MRF clear, suitable for sphincter-sparing surgery	Non-inferior disease-free survival; most avoid pelvic RT (PROSPECT[50])	Not for T4, threatened margin or low tumours
Anti-PD-1 alone	dMMR / MSI-high rectal cancer	Clinical complete response in nearly all patients in the first series (Cercek 2022[51])	Small numbers; confirm MMR status; surveillance as for watch-and-wait

Table D. Managing common side effects (principles; follow local protocols)

Problem	Usual cause	Do	Hold or stop when
Cold-triggered tingling, cramps; later persistent numbness	Oxaliplatin	Warn about cold drinks and metal; check function every cycle; stop-and-go strategy	Persistent numbness affecting function (grade 2 lasting, or 3): stop oxaliplatin, continue the rest
Diarrhoea	Irinotecan, fluoropyrimidines, IO	Loperamide plan given in advance; fluids; check for neutropenia	Severe, bloody, febrile or with dehydration: admit; on IO consider colitis (stool tests, steroids)
Severe toxicity in cycle 1 (mucositis, diarrhoea, neutropenia)	DPD deficiency	Stop fluoropyrimidine; supportive care; uridine triacetate where available	Do not rechallenge at full intensity; genotype DPYD
Chest pain on infusion or capecitabine	Fluoropyrimidine coronary vasospasm	Stop, ECG and troponin	Recurrence is common: switch to raltitrexed or non-fluoropyrimidine regimen
Painful red palms and soles	Capecitabine; regorafenib (hand-foot skin reaction)	Emollients, urea cream, avoid friction; dose delay	Blistering or limits self-care
Acneiform rash, paronychia	Cetuximab, panitumumab	Pre-emptive doxycycline/minocycline, moisturiser, sunscreen; rash often tracks with benefit	Severe or infected rash; hold then resume at lower intensity
Low magnesium, cramps, arrhythmia	Anti-EGFR antibodies	Check magnesium, calcium, potassium regularly; replace	Symptomatic or refractory hypomagnesaemia
Hypertension, proteinuria	Bevacizumab, regorafenib, fruquintinib	BP every visit; urine dipstick	Uncontrolled BP, nephrotic-range proteinuria

Problem	Usual cause	Do	Hold or stop when
Bleeding, perforation, wound problems	Anti-VEGF drugs	Stop 4–6 weeks before elective surgery; restart after wound heals	Perforation, major bleeding, arterial thrombosis: stop permanently; avoid with an uncovered stent
Neutropenia	Irinotecan, trifluridine–tipiracil, FOLFOXIRI	Count before each cycle; G-CSF per risk	Febrile neutropenia: emergency antibiotics
Colitis, hepatitis, thyroid, adrenal problems	Pembrolizumab, nivolumab ± ipilimumab	Baseline and periodic TSH, cortisol, liver tests; report diarrhoea early	Grade ≥2 colitis or hepatitis: hold, steroids; grade 4: stop

07 Management algorithms

These decision paths pull together sections 02–06. Colours: teal for early or favourable paths, purple for intermediate, rose for high-risk or later-line paths.

ALGORITHM 1

Non-metastatic colon cancer

Colon cancer on biopsy: complete colonoscopy · CT chest-abdomen-pelvis · CEA · MMR immunohistochemistry · fitness and nutrition · tumour board

RESECTABLE (MOST)

Surgery: segmental resection with ≥12 nodes (laparoscopic if expertise)

Obstruction → resection, or stent as a bridge; perforation → emergency resection

Stage I → follow-up

Stage II low-risk → follow-up (discuss fluoropyrimidine if pMMR)

Stage II high-risk → CAPOX 3 mo or FOLFOX/FP 6 mo

Malignant polyp, favourable features → surveillance only

STAGE III

Low risk (T1–3 N1) → CAPOX 3 months

High risk (T4 or N2) → CAPOX or FOLFOX 6 months

Over 70 or oxaliplatin unsuitable → capecitabine or 5-FU alone

dMMR → FOLFOX + atezolizumab where available

LOCALLY ADVANCED ON CT (T4, BULKY T3)

pMMR → FOLFOX 6 weeks → surgery → complete adjuvant therapy

dMMR → neoadjuvant immunotherapy (trial / expert centre) → surgery

T4b: en bloc resection of the adherent organ

Unresectable locally → systemic therapy, reassess for surgery

All patients: Lynch work-up if dMMR without BRAF V600E or MLH1 methylation (Lynch: consider total colectomy with ileorectal anastomosis) · start adjuvant therapy within about 8 weeks · DPYD testing where available · PI3K-pathway alteration on NGS → low-dose aspirin for 3 years · replace vitamin D if below 20 ng/mL · colonoscopy at 1 year · exercise and weight advice from the first visit.

ALGORITHM 2

Non-metastatic rectal cancer

Rectal cancer on biopsy: MRI pelvis (T, CRM, EMVI, nodes, height) · CT chest-abdomen-pelvis · colonoscopy · CEA · **MMR status before any treatment** · fertility counselling · tumour board

EARLY: CT1–2 N0

TME surgery (low or ultralow anterior resection, or APR if the sphincter is involved)

Selected cT1, low risk → local excision (TAMIS/TEM)

pT1–2 N0 → follow-up

Upstaged (pT3 or N+) → chemoradiation or chemotherapy as for locally advanced

Wants organ preservation → discuss chemoradiation ± consolidation in a trial or expert centre

INTERMEDIATE: CT3 OR N+, CRM CLEAR

Selected (PROSPECT-like) → FOLFOX × 6 → MRI → TME; chemoradiation only if poor response

Or short-course RT → delayed TME, or long-course CRT → TME

Upper rectum, cT3a–b N0, clear MRF → TME alone is acceptable

Adjuvant chemotherapy if ypN+ and no TNT

HIGH RISK: T4, N2, CRM ≤1 MM, EMVI, LATERAL NODES, OR LOW TUMOUR

pMMR → TNT: SCRT → chemo (RAPIDO), or FOLFIRINOX → CRT, or CRT → consolidation chemo (OPRA)

MRI + endoscopy 8–12 weeks after the last treatment

Clinical complete response → watch-and-wait (MRI + endoscopy every 3–4 months)

Incomplete → TME (lateral node dissection if lateral nodes persist)

dMMR → anti-PD-1 alone for 6 months; chemoradiation only if not responding

All patients: confirm MMR status before chemoradiation · TME by an experienced rectal surgeon · temporary ileostomy after low anastomosis, reverse at about 3 months · counsel about LARS, sexual and urinary function · regrowth after watch-and-wait is usually salvageable if found early.

ALGORITHM 3

Metastatic colorectal cancer

New stage IV: CT ± MRI liver (PET only before metastasectomy) · **MMR, RAS, BRAF, HER2** (NGS) · DPYD · sidedness · fitness and goals · hepatobiliary/thoracic surgeon at the first MDT

RESECTABLE OR POTENTIALLY RESECTABLE

Low risk (≤4 lesions in one lobe, RAS/BRAF wild-type) → surgery first; ablation for ≤3 cm

Higher risk (>4, bilobar, RAS/BRAF-mutant) → chemotherapy first (≤4 cycles)

Unresectable liver-only → conversion: oxaliplatin doublet/triplet (± anti-EGFR if left, wild-type); FOLFOXIRI + bev if RAS/BRAF-mutant

Re-image every 6–8 weeks → operate as soon as resectable; about 6 months of treatment in total

Fiducials for small, deep lesions before chemotherapy · asymptomatic primary: no upfront resection

UNRESECTABLE: FIRST LINE

dMMR or POLE-ultramutated → nivolumab + ipilimumab (single-agent anti-PD-1 if less fit)

BRAF V600E → encorafenib + cetuximab + FOLFOX (any side)

Left, RAS/BRAF wild-type → doublet + anti-EGFR

Right or RAS-mutant → doublet (triplet if fit, high burden) + bevacizumab; FOLFIRI if oxaliplatin within 12 months

Frail → capecitabine ± bevacizumab; biologicals unaffordable → chemotherapy alone

Maintenance after 4–6 months; local therapy for oligoprogression

LATER LINES

Second line: switch backbone ± anti-VEGF (never with anti-EGFR); after IO → chemotherapy; BRAF → encorafenib + cetuximab; HER2 → tucatinib + trastuzumab (T-DXd later, or second line if RAS-mutant); G12C → sotorasib + panitumumab

Third line: trifluridine–tipiracil + bevacizumab, regorafenib, fruquintinib; anti-EGFR rechallenge if ctDNA RAS wild-type

Early palliative care; clinical trials at every line

All patients: discuss goals early · obstruction → stent or diversion (avoid stents with bevacizumab) · peritoneal disease → expert-centre opinion on cytoreduction · selected unresectable liver-only disease → transplant evaluation in specialised programmes.

08 Survivorship, follow-up & reducing recurrence

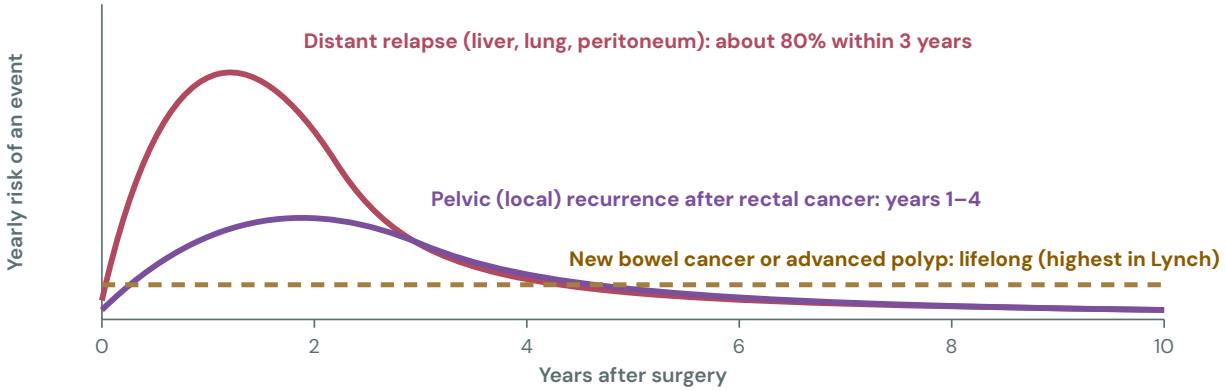
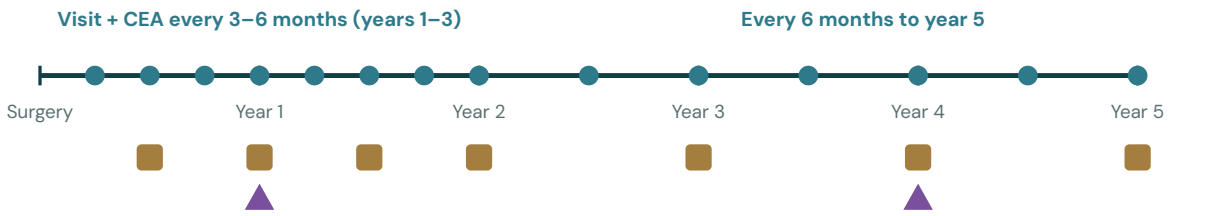


Figure 14. When relapses happen (illustrative shape, not to scale). Intensive CEA and CT surveillance is concentrated in the first 3 years because that is when a resectable relapse can still be found; colonoscopy continues for new polyps and cancers.



- Clinic visit + CEA: symptoms, weight, bowel and bladder function, neuropathy, stoma and LARS, mood
- CT chest and abdomen (± pelvis) every 6–12 months to 5 years, or at least yearly for 3 years (stage II–III)
- Colonoscopy at 1 year; again at 1 year if advanced adenoma, otherwise every 3–5 years

Rectum: watch-and-wait/local excision → MRI + endoscopy 3–4-monthly (2 years); LAR without RT → endoscopy + EUS/MRI 6-mon
Not routine when well: PET-CT, other tumour markers. A rising CEA needs CT (± PET) and an MDT review for a curable relapse.

Figure 15. A simple follow-up rhythm (NCCN, ESMO, ASCO). More intensive testing than this did not improve survival in the FACS and COLOFOL trials, but surveillance still finds resectable relapses.

Follow-up protocol (NCCN, ESMO, ASCO)

What	How often	Notes
History, examination, CEA	Every 3–6 months for 3 years, then every 6 months in years 4–5 (CEA at least for the first 2–3 years)	Stage II–III and after resection of metastases, if the patient would be fit for further curative treatment; rectal examination after low anterior resection or local excision. A confirmed rising CEA triggers imaging.
CT chest and abdomen (pelvis for rectal cancer)	Every 6–12 months up to 5 years (NCCN), or at least yearly for 3 years	Stage I: CT not routine (except after local or endoscopic excision alone). Earlier relapses are more often resectable.
Colonoscopy	At 1 year (or 3–6 months if not complete before surgery); if an advanced adenoma is found, again at 1 year, otherwise every 3–5 years	Every 1–2 years in Lynch syndrome; yearly in PSC-associated colitis.

What	How often	Notes
Rectal endoscopy and MRI pelvis (rectum)	Watch-and-wait or local excision: every 3–4 months for 2 years, then 6-monthly to year 5. Low anterior resection without pelvic RT: proctosigmoidoscopy with endorectal ultrasound or MRI every 6 months for up to 5 years	Regrowth is usually luminal and salvageable when found early.
Not routine	—	PET-CT, other tumour markers, ctDNA outside trials.

- **Intensity**: more intensive CEA and CT schedules found more resectable relapses but did not improve overall survival in FACS[72] and COLOFOL[73]; the schedule above is a balance, not a minimum.
- **Exercise**: a structured 3-year programme of aerobic activity after adjuvant chemotherapy reduced recurrence or new cancer (5-year disease-free survival 80% vs 74%) and improved overall survival (CHALLENGE[74]). Prescribe it like a drug: about 150 minutes a week of brisk walking, built up with support.
- **Other risk factors**: healthy weight (severe obesity, BMI over 35, is linked with worse outcomes); in observational studies of stage III colon cancer, a Western-style diet (red and processed meat, sweets, refined grains) and a high dietary glycaemic load were linked with more recurrence, and a prudent diet (vegetables, fruit, whole grains, fish, pulses) with less; no smoking, little or no alcohol, a plant-rich diet with less red and processed meat. Aspirin: see section 06 (PI3K-altered cancers, Lynch syndrome). Check and replace vitamin D if low.
- **Late effects**: oxaliplatin neuropathy (may persist; about 1% have chronic severe painful neuropathy needing duloxetine-type drugs or other analgesics), fatigue, depression, work and money worries, higher rates of diabetes and cardiovascular disease, radiation proctitis and pelvic fractures, low anterior resection syndrome, stoma care, urinary and sexual dysfunction, infertility and early menopause after pelvic RT, insufficiency fractures, anxiety about recurrence.
- **Stoma**: stoma nurse before and after surgery; hernia and dehydration (high-output ileostomy) are common problems; most people return to work, travel and religious practice.
- **Family**: first-degree relatives start colonoscopy at 40 (or 10 years before the patient's age at diagnosis); cascade genetic testing in Lynch and polyposis families.
- **Shared care**: give the family doctor the stage, the follow-up schedule and the red flags (below).

SHARE WITH PATIENTS: LIFE AFTER TREATMENT

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

- 🖨 Telugu–English handout: living with a stoma (తెలుగు · English)
- 🖨 Telugu–English handout: stool test (FIT) and colonoscopy (తెలుగు · English)
- Once colorectal cancer treatment is finished, follow-up isn't needed?
- Every rectal cancer patient needs a permanent colostomy bag?
- Living with a stoma (bag) means a normal life is over?
- After bowel cancer treatment, rest is best and exercise should be avoided?
- When one person in the family has bowel cancer, the others do not need any tests?

09 Landmark trials

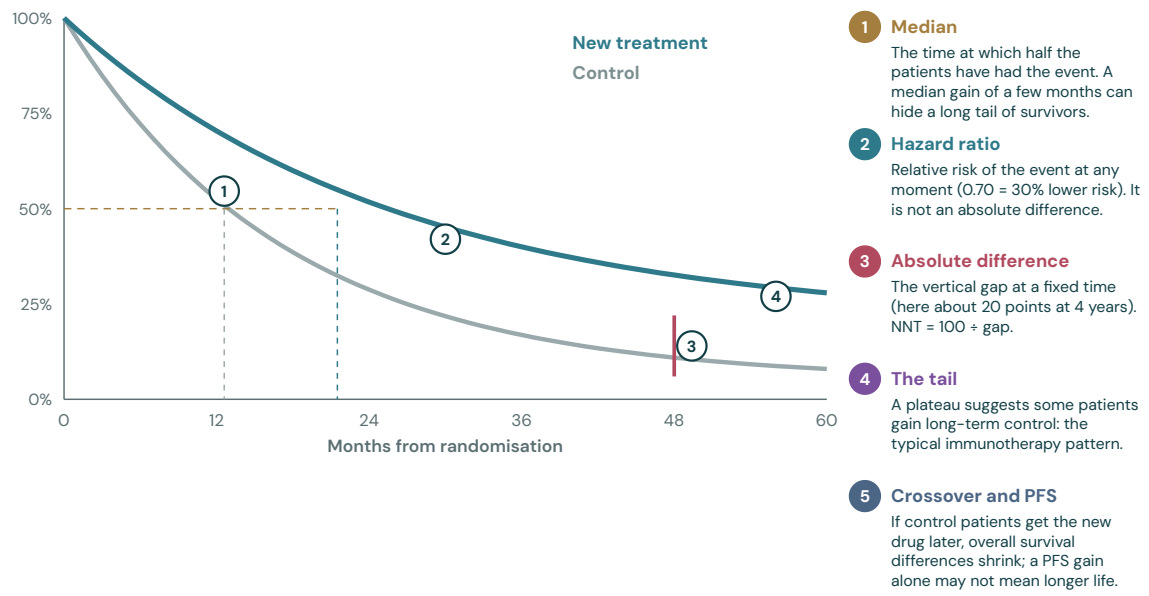


Figure 16. How to read a survival curve (illustrative). Use the absolute gap at a fixed time and overall survival, not the median or PFS alone, when weighing benefit against toxicity and cost.

- National Polyp Study[6] and NordICC[7]: does finding and removing polyps prevent death? Polypectomy roughly halved colorectal cancer deaths; a population invitation to one colonoscopy cut incidence by about a fifth, limited by low uptake. → Screening works only if people attend and positive tests are followed up.
- MOSAIC[34] and IDEA[38]: oxaliplatin added to fluoropyrimidine adjuvant therapy improved survival in stage III; three months of CAPOX is enough for low-risk stage III. → Match duration to risk and spare nerves.
- FOxTROT[45] and NICHE-2[46]: treatment before colon surgery. Six weeks of FOLFOX downstaged locally advanced pMMR cancers; two cycles of immunotherapy eradicated most dMMR cancers. → Test MMR on the biopsy, before surgery.
- Dutch TME[69] and German CAO/ARO/AIO-94[71]: short-course RT halved local recurrence after TME, and preoperative chemoradiation beat postoperative. → The foundation of neoadjuvant rectal treatment.
- RAPIDO[47], PRODIGE 23[48] and OPRA[49]: total neoadjuvant therapy improves disease control, doubles complete responses and lets about half of selected patients keep the rectum. PROSPECT[50]: many intermediate-risk patients can skip radiotherapy. → Rectal treatment is now risk-adapted.
- Cercek 2022[51]: anti-PD-1 therapy alone gave complete clinical responses in all of the first patients with dMMR rectal cancer. → MMR status first, then decide on radiotherapy and surgery.
- KEYNOTE-177[60] and CheckMate 8HW[58]: immunotherapy beats chemotherapy for metastatic MSI-high cancer, with long-lasting responses. → MMR testing at diagnosis of metastatic disease is mandatory.
- PARADIGM[18]: panitumumab versus bevacizumab with FOLFOX in RAS wild-type disease. Overall survival improved in left-sided tumours (median about 38 vs 34 months). → Sidedness and RAS together choose the biological.
- BREAKWATER[13]: first-line encorafenib + cetuximab + FOLFOX for BRAF V600E roughly doubled median survival. → BRAF testing belongs at diagnosis.

- **CHALLENGE**[74]: a supported exercise programme after adjuvant chemotherapy reduced recurrence and death. → Exercise is part of treatment.
- **ALASCCA**[17]: low-dose aspirin for 3 years after surgery for PI3K-altered stage I–III colorectal cancer roughly halved recurrence, whereas trials in unselected patients were negative. → A cheap drug, selected by a tumour biomarker.
- **COLLISION**[28]: thermal ablation versus resection for small liver metastases (3 cm or less). Survival was similar with fewer complications. → Ablation is a curative-intent option, chosen in the MDT.

10 Practice pearls & pitfalls

- Piles do not explain anaemia. Iron-deficiency anaemia in a man or a post-menopausal woman means colonoscopy and upper endoscopy, not iron tablets alone.
- Do a digital rectal examination in every patient with rectal bleeding; most low rectal cancers are within reach of a finger.
- A negative FIT does not override red-flag symptoms, and CEA never rules cancer in or out.
- Take multiple biopsies of any ileocaecal mass for histology and TB tests; do not start antituberculous treatment without proof.
- Request MMR status on the first biopsy. It decides neoadjuvant immunotherapy, adjuvant chemotherapy in stage II and screening of the family.
- MRI pelvis before any rectal treatment, including emergency diverting stomas where possible; a threatened CRM, EMVI or lateral nodes change the plan.
- Ask every patient with low rectal cancer whether keeping the rectum matters to them; organ preservation is now an evidence-based choice, not an experiment.
- Offer sperm banking or egg/embryo storage before pelvic radiotherapy; young Indian patients are often not asked.
- Fewer than 12 nodes in the specimen is a quality problem and a high-risk feature, not reassurance.
- Start adjuvant chemotherapy within about 8 weeks; three months of CAPOX is enough for low-risk stage III.
- Test DPYD where available, and stop a fluoropyrimidine at once after severe cycle-1 toxicity.
- Never give anti-EGFR antibodies without an extended RAS (and BRAF) result; prefer them for left-sided tumours.
- Show every patient with liver or lung metastases to a hepatobiliary or thoracic surgeon before chemotherapy starts.
- Chemotherapy with biosimilar bevacizumab is an evidence-based, affordable first-line option; do not let unaffordable biologicals delay treatment.
- Send the resected tumour for NGS where affordable: a PI3K-pathway alteration means 3 years of low-dose aspirin (ALASCCA), and POLE/POLD1 or dMMR results change metastatic treatment.
- Patients with primary sclerosing cholangitis need colonoscopy at diagnosis and yearly if they have colitis; right-sided cancers in their 40s are typical.
- A positive germline result is rarely an emergency; a variant of uncertain significance changes nothing. Single MUTYH carriers screen like everyone else.
- Prescribe exercise, check neuropathy at every visit, and arrange colonoscopy for first-degree relatives.

11 Case vignettes: lines of management

Seven cases, written for postgraduates and practising clinicians. Read the presentation, decide on stage, workup and plan, then open the line of management. No doses are given; durations follow the evidence.

CASE 1 Colon · stage III · dMMR · Lynch

Six months of iron tablets in a 34-year-old

34 years, woman | pT3 N1b (stage IIIB) | MSH2 and MSH6 lost

A 34-year-old teacher has had fatigue for a year and was treated with iron tablets twice for haemoglobin of 8 g/dL with low ferritin. Her stools are normal. Her father had "intestinal cancer" at 48 and her aunt had uterine cancer at 50.

Before you open the answer: what is the stage, what must be done before treatment, and what is the plan?

1. **INVESTIGATE THE ANAEMIA**
   Iron deficiency without an obvious cause needs both endoscopies, even at 34. Colonoscopy: ulcerated caecal cancer; biopsy adenocarcinoma, poorly differentiated with tumour-infiltrating lymphocytes.
2. **STAGE AND TEST**
   CT chest-abdomen-pelvis: no metastases. CEA normal. MMR immunohistochemistry: loss of MSH2 and MSH6 — Lynch syndrome likely.
3. **SURGERY**
   Lynch syndrome is suspected before surgery, so total colectomy with ileorectal anastomosis is offered to cut the roughly 20% 10-year risk of a new colon cancer after segmental resection; she chooses it after discussing bowel function. 31 nodes, 3 positive (pT3 N1b).
4. **ADJUVANT THERAPY**
   Stage III dMMR: FOLFOX with atezolizumab for 6 months where available (ATOMIC); otherwise CAPOX or FOLFOX.
5. **GERMLINE AND FAMILY**
   Germline MSH2 pathogenic variant confirmed. Yearly endoscopy of the remaining rectum; upper endoscopy from 30–35 with H. pylori treatment; yearly urinalysis (MSH2 carries urothelial risk); risk-reducing hysterectomy and salpingo-oophorectomy after childbearing; daily aspirin. Cascade testing offered to siblings and children (from 18–20).

TEACHING POINTS

- Anaemia in a young adult with low ferritin is a gut question, not a dietary one.
- MMR status changes adjuvant therapy, the extent of surgery and the family's screening.
- MSH2/MSH6 loss is not explained by MLH1 methylation: go straight to germline testing.

See: Sections 02, 04, 06 · Algorithm 1 · ATOMIC[40], CAPP2[2], Parry 2011[75]

CASE 2 Colon · obstruction · stage II

A distended abdomen in a 72-year-old farmer

72 years, diabetic | pT4a N0 (stage IIB) | pMMR

A 72-year-old man presents with 4 days of absolute constipation, colicky pain and a distended abdomen. He was treated for "gas" and "piles" over the past 3 months.

Before you open the answer: what is the stage, what must be done before treatment, and what is the plan?

1. **RESUSCITATE AND IMAGE**
   Drip and suck; contrast CT: obstructing sigmoid tumour, dilated colon with a caecum of 9 cm, no perforation, no metastases.
2. **CHOOSE THE OPERATION**
   Options: emergency resection (Hartmann's, or primary anastomosis ± covering stoma), or a self-expanding stent as a bridge to elective laparoscopic surgery in 1–2 weeks in an experienced centre. He had a stent, recovered, completed staging and colonoscopy, and had an elective sigmoid colectomy.
3. **PATHOLOGY**
   pT4a N0, 16 nodes, pMMR, no lymphovascular invasion. Obstruction and T4 are both high-risk features.
4. **ADJUVANT THERAPY**
   High-risk stage II: 3 months of CAPOX, or a fluoropyrimidine alone given his age and neuropathy from diabetes; absolute benefit is modest and is discussed with him.
5. **FOLLOW-UP**
   CEA and CT for 5 years; colonoscopy at 1 year; exercise programme.

TEACHING POINTS

- Emergency presentation is common and carries worse survival; earlier colonoscopy would have helped.
- Stent as a bridge allows staging and elective surgery but needs expertise.
- Stage II benefit from chemotherapy is small: risk features and fitness decide.

See: Sections 02, 03, 05, 06 · Algorithm 1 · IDEA[38], QUASAR[39]

CASE 3 Rectum · high risk · TNT

A 52-year-old with "piles" and a threatened margin

52 years, man | cT3c N2 EMVI+, CRM 0.5 mm | Mid rectum, 7 cm

A 52-year-old shopkeeper has bled per rectum for 8 months and was treated with piles ointments. He now has tenesmus and has lost 5 kg. A finger reaches a hard, fixed lesion at the tips.

Before you open the answer: what is the stage, what must be done before treatment, and what is the plan?

1. **DIAGNOSE**
   Proctoscopy and colonoscopy: mid-rectal adenocarcinoma; pMMR. CEA 12.
2. **MRI PELVIS**
   Lower edge 7 cm from the anal verge; cT3c, tumour 0.5 mm from the mesorectal fascia (threatened CRM), EMVI positive, 5 mesorectal nodes (N2), lateral nodes not enlarged.
3. **DISTANT STAGING**
   CT chest-abdomen-pelvis: no metastases.
4. **TOTAL NEOADJUVANT THERAPY**
   Short-course RT followed by about 18 weeks of CAPOX (RAPIDO), or induction mFOLFIRINOX then chemoradiation (PRODIGE 23) given his fitness. Fertility counselling and sperm banking first.
5. **REASSESS AND OPERATE**
   MRI and endoscopy after TNT: good partial response, CRM now clear. Laparoscopic low anterior resection with TME and a temporary loop ileostomy; ypT2 N0, complete mesorectum. Ileostomy reversal at 3 months.
6. **AFTER SURGERY**
   No further chemotherapy (all given before surgery). Follow-up CEA, CT and pelvic MRI as scheduled; LARS advice and pelvic floor exercises.

TEACHING POINTS

- Persistent bleeding despite piles treatment demands a rectal examination and endoscopy.
- Threatened CRM, EMVI and N2 define high-risk disease: TNT is preferred.
- Fertility counselling must precede pelvic radiotherapy.

See: Sections 03, 05, 06 · Algorithm 2 · RAPIDO[47], PRODIGE 23[48]

CASE 4 Rectum · organ preservation

A low rectal cancer in a woman who does not want a stoma

61 years, woman | cT2 N1, 4 cm from verge | pMMR

A 61-year-old retired nurse has a low rectal cancer 4 cm from the anal verge. Surgery would need an ultralow anterior resection with likely poor function, or an abdominoperineal resection. She asks whether there is any way to avoid a stoma.

Before you open the answer: what is the stage, what must be done before treatment, and what is the plan?

1. **STAGE**
   MRI: cT2 N1, CRM clear, no EMVI, sphincter not involved. CT: no metastases. pMMR.
2. **ORGAN-PRESERVATION PLAN**
   Long-course chemoradiation followed by consolidation chemotherapy (OPRA approach), aiming for a clinical complete response.
3. **RESPONSE ASSESSMENT**
   At 8–12 weeks: flat white scar on endoscopy, no palpable tumour, no residual tumour signal on MRI — a clinical complete response.
4. **WATCH-AND-WAIT**
   Digital examination, endoscopy and MRI every 3–4 months for 2 years, then every 6 months; CEA and CT as usual.
5. **IF REGROWTH**
   About a quarter regrow, mostly within 2 years; salvage TME is usually possible. She understands and accepts the surveillance.

TEACHING POINTS

- Organ preservation is an evidence-based option for selected low tumours.
- Strict surveillance is the price of keeping the rectum.
- Discuss bowel, sexual and urinary function, not only survival.

See: Sections 05, 06, 08 · Algorithm 2 · OPRA[49], International Watch & Wait Database[24]

CASE 5 Rectum · dMMR · immunotherapy

A 29-year-old with dMMR rectal cancer

29 years, man | cT3 N1, 6 cm from verge | MLH1 and PMS2 lost; BRAF wild-type

A 29-year-old software engineer has rectal bleeding. Biopsy shows a mid-rectal adenocarcinoma. The pathology report includes MMR immunohistochemistry: MLH1 and PMS2 are lost. He is booked for chemoradiation the following week.

Before you open the answer: what is the stage, what must be done before treatment, and what is the plan?

1. **PAUSE**
   dMMR changes the plan. BRAF V600E is negative and MLH1 promoter methylation is absent: germline testing (likely Lynch).
2. **STAGE**
   MRI pelvis cT3 N1, CRM clear; CT no metastases.
3. **TREATMENT**
   Anti-PD-1 therapy alone (dostarlimab or another anti-PD-1, in a trial or expert setting) for 6 months, with MRI and endoscopy every 2–3 months; chemoradiation and surgery are held in reserve for non-response.
4. **OUTCOME**
   Clinical complete response at 6 months; watch-and-wait surveillance. Fertility, function and work are preserved.
5. **FAMILY**
   Germline MLH1 variant: cascade testing, colonoscopy for relatives.

TEACHING POINTS

- Know the MMR status before planning radiotherapy.
- dMMR rectal cancer responds poorly to chemotherapy but very well to immunotherapy.
- Young age plus dMMR: germline testing is mandatory.

See: Sections 04, 06 · Algorithm 2 · Cercek 2022[51], NICHE-2[46]

CASE 6 Metastatic · liver-only · conversion

Six liver metastases in a 55-year-old

55 years, man | Sigmoid primary, 6 liver lesions | RAS/BRAF wild-type, pMMR, HER2-negative

A 55-year-old accountant has a sigmoid cancer with six liver metastases in both lobes, the largest 6 cm near the right hepatic vein. CT chest is clear. He is fit (ECOG 0).

Before you open the answer: what is the stage, what must be done before treatment, and what is the plan?

1. **MDT WITH A LIVER SURGEON**
   Not resectable now: the remnant would be too small. Potentially resectable if the tumours shrink.
2. **CONVERSION THERAPY**
   Left-sided, RAS/BRAF wild-type: FOLFOX (or FOLFIRI) with panitumumab or cetuximab for the highest response rate.
3. **RESTAGE EVERY 2–3 MONTHS**
   After 4 months: 60% shrinkage; now resectable with a two-stage approach (left lateral clearance, portal vein embolisation, then right hepatectomy).
4. **SURGERY**
   Liver resections and sigmoid colectomy in staged procedures; R0. Ablation for a small residual lesion.
5. **AFTER**
   Complete about 6 months of perioperative chemotherapy in total; CEA and CT every 3–4 months; about 4 in 10 such patients are alive at 5 years, though most relapse at some point.

TEACHING POINTS

- Show liver metastases to a hepatobiliary surgeon before chemotherapy.
- Choose the most active regimen for the biomarkers when conversion is the goal.
- Operate as soon as resectable: “vanishing” lesions and chemotherapy liver injury complicate late surgery.

See: Sections 05, 06 · Algorithm 3 · **PARADIGM**[18], **EPOC**[25]

CASE 7 Metastatic · BRAF V600E

Ascites and right-sided cancer in a 47-year-old

47 years, woman | Ascending colon, peritoneal + liver | BRAF V600E, pMMR

A 47-year-old homemaker presents with abdominal distension and weight loss. CT shows an ascending colon mass, omental cake, ascites and three liver metastases. Biopsy: adenocarcinoma.

Before you open the answer: what is the stage, what must be done before treatment, and what is the plan?

1. **BIOMARKERS FIRST**
   NGS: BRAF V600E, RAS wild-type, pMMR, HER2-negative. DPYD normal. ECOG 1.
2. **FIRST LINE**
   Encorafenib + cetuximab + mFOLFOX6 (BREAKWATER) where accessible; otherwise FOLFOXIRI + bevacizumab if fit, or FOLFOX + bevacizumab. Anti-EGFR alone with chemotherapy is ineffective in BRAF-mutant disease.
3. **SUPPORTIVE**
   Early palliative care; nutrition; drainage of ascites as needed; watch for bowel obstruction from peritoneal disease.
4. **SECOND LINE**
   If not given first: encorafenib + cetuximab (BEACON). Later: trifluridine–tipiracil + bevacizumab, regorafenib or fruquintinib; clinical trials.
5. **GOALS**
   Discuss prognosis honestly: BRAF V600E disease progresses fast, but targeted combinations have substantially improved survival.

TEACHING POINTS

- Test BRAF at diagnosis of metastatic disease: it changes first-line therapy.
- Right-sided, peritoneal and BRAF often go together.
- Plan supportive and palliative care from the start.

See: Sections 04, 06 · Algorithm 3 · **BREAKWATER**[13], **BEACON**[14]

12 References & guidelines

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- ASCO guidelines: treatment of metastatic colorectal cancer; surveillance after curative treatment; management of locally advanced rectal cancer.
- AJCC/UICC TNM Classification, 8th edition; College of American Pathologists colorectal reporting protocol; ESGAR rectal MRI consensus.
- US Multi-Society Task Force and USPSTF 2021 screening recommendations; British Society of Gastroenterology / NICE DG30 guidance on FIT in symptomatic patients; ESGE guidance on colonic stenting.
- ICMR consensus document for the management of colorectal cancer; Indian Council of Medical Research National Cancer Registry Programme reports; GLOBOCAN 2022.
- Cross-checked in October 2026 against current evidence summaries (UpToDate topic reviews on epidemiology and risk factors, molecular genetics, polyps, screening strategies and tests, family-history screening, Lynch syndrome, MUTYH and POLE/POLD1 gene-test interpretation, PSC-associated colitis, presentation and staging, pathology and prognosis, management of primary colon cancer, adjunctive aspirin and vitamin D, survivorship, diet and exercise, post-treatment surveillance, systemic therapy principles, initial and later-line therapy for metastatic disease, older adults, liver resection and potentially resectable liver metastases, non-surgical liver-directed therapy and locoregional management). All text is written in our own words and cites primary sources; regimen dose tables were not used.
- Trial names above link to PubMed searches for the primary publications.

Core trials cited on this page (75)

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> Educational summary for health professionals, written in our own words from current guidelines and primary trials. No drug doses are given. Verify current guidelines, Indian regulatory approvals and individual patient factors before treatment decisions.