Liver Metastasis of Colorectal Cancer: A Comprehensive Review

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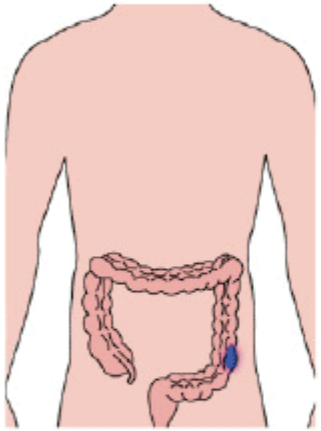
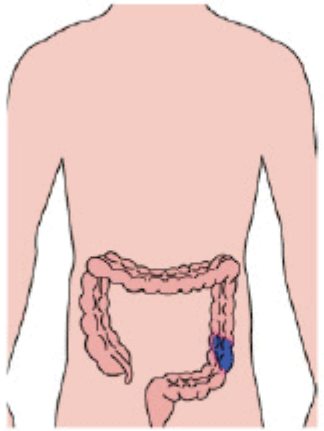
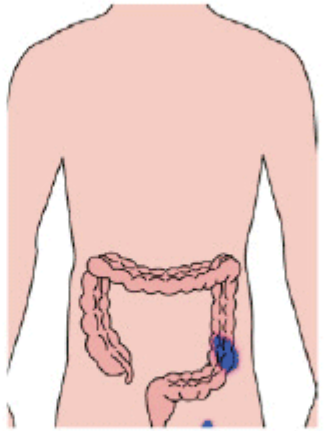
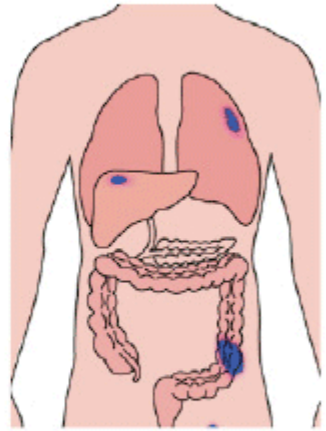
Agenda

- 1. Introduction (Epidemiology, Clinical Significance)
- 2. Anatomy (Liver Structure, Metastatic Pathways)
- 3. Etiology & Risk Factors
- 4. Pathophysiology (Metastatic Cascade, Molecular Mechanisms)
- 5. Investigations (Labs, Imaging, Pathology)
- 6. Management (Surgical, Systemic, Locoregional)
- 7. Complications
- 8. Follow-Up Protocols
- 9. Key Takeaways

Epidemiology of Colorectal Cancer (CRC)

- Global Burden: 3rd most common cancer, 2nd leading cause of cancer deaths.
- Metastasis: ~50% of CRC patients develop liver metastases.
- Survival: 5-year survival drops from 90% (localized) to 15% (metastatic).
- 20–30% of mets are detected synchronously

Colorectal cancer staging

STAGE 1 (I) ACPS/DUKES' A T1 OR T2, NO MO	STAGE 2 (II) ACPS/DUKES' B T2 OR T4, NO MO	STAGE 3 (III) ACPS/DUKES' C ANY T, N1 OR N2 MO	STAGE 4 (IV) ACPS/DUKES' D ANY T, ANY N, M1
			
Tumour has invaded several layers of bowel but has not spread outside the wall.	Cancer has grown through the muscle layer of the bowel or rectum and invaded nearby tissue, but has not spread to the lymph nodes.	Cancer has spread to nearby lymph nodes, but not to other parts of the body.	This is also known as METASTATIC BOWEL CANCER. The cancer has spread from where it started in the colon or rectum, to other organs often the liver and lung.

Why Liver Metastasis Matters

- Key Facts:
  - Liver = most common metastatic site in CRC (due to portal venous drainage).
  - Resectability = strongest predictor of survival (5-year survival up to 50% post-resection).

Clinical Presentation

- Symptoms
  - Asymptomatic (early)
  - RUQ pain, jaundice, weight loss (late).
- Signs:
  - Hepatomegaly, ascites (if portal hypertension).

Prognostic Factors

- Favorable:
  - Solitary metastasis
  - R0 resection
  - low CEA.
- Poor:
  - Extrahepatic disease
  - RAS/BRAF mutations

Prognostic Factors

- FONG Clinical Risk Score:
  - Patients with Fong Score 0-2 are considered “low risk” and may proceed with surgical intervention.
  - Patients with Fong Score 3-5 are considered “high risk” and may benefit from close surveillance

Variables:

- Nodal status of primary.
- Disease-free interval from the primary to discovery of the liver metastases of <12 months.
- Number of tumors >1.
- Preoperative CEA level >200 ng/mL.
- Size of the largest tumor >5 cm.

Global Burden of CRC Liver Metastases

- Statistics: ~1.9 million new CRC cases/year, 50% develop liver mets.

Pathways of Metastatic Spread

- 1. Portal Venous Drainage (most common).
- 2. Lymphatic Spread.
- 3. Direct Invasion (rare).

Why the Liver is Vulnerable

- "Soil and Seed" Hypothesis: CRC cells express chemokines binding to liver sinusoids.

Etiology & Risk Factors

Primary CRC Risk Factors

Genetic:

- Lynch syndrome
- FAP
- RAS/BRAF mutations.

Lifestyle:

- Smoking
- red meat
- low fiber.

Risk Factors for Liver Metastasis

Tumor-Related:

- T4/N2 stage
- lymphovascular invasion
- poor differentiation.

Biomarkers:

- High CEA
- KRAS mutations.

Genetic Drivers of Metastasis

- Key Mutations:
  - APC (80% CRC)
  - TP53
  - KRAS (resistance to anti-EGFR).

Pathophysiology

Metastatic Cascade

- 1. Epithelial-mesenchymal transition → Intravasation → Circulation → Liver Colonization.
- 2. Extravasation: into liver parenchyma.

Tumor Microenvironment

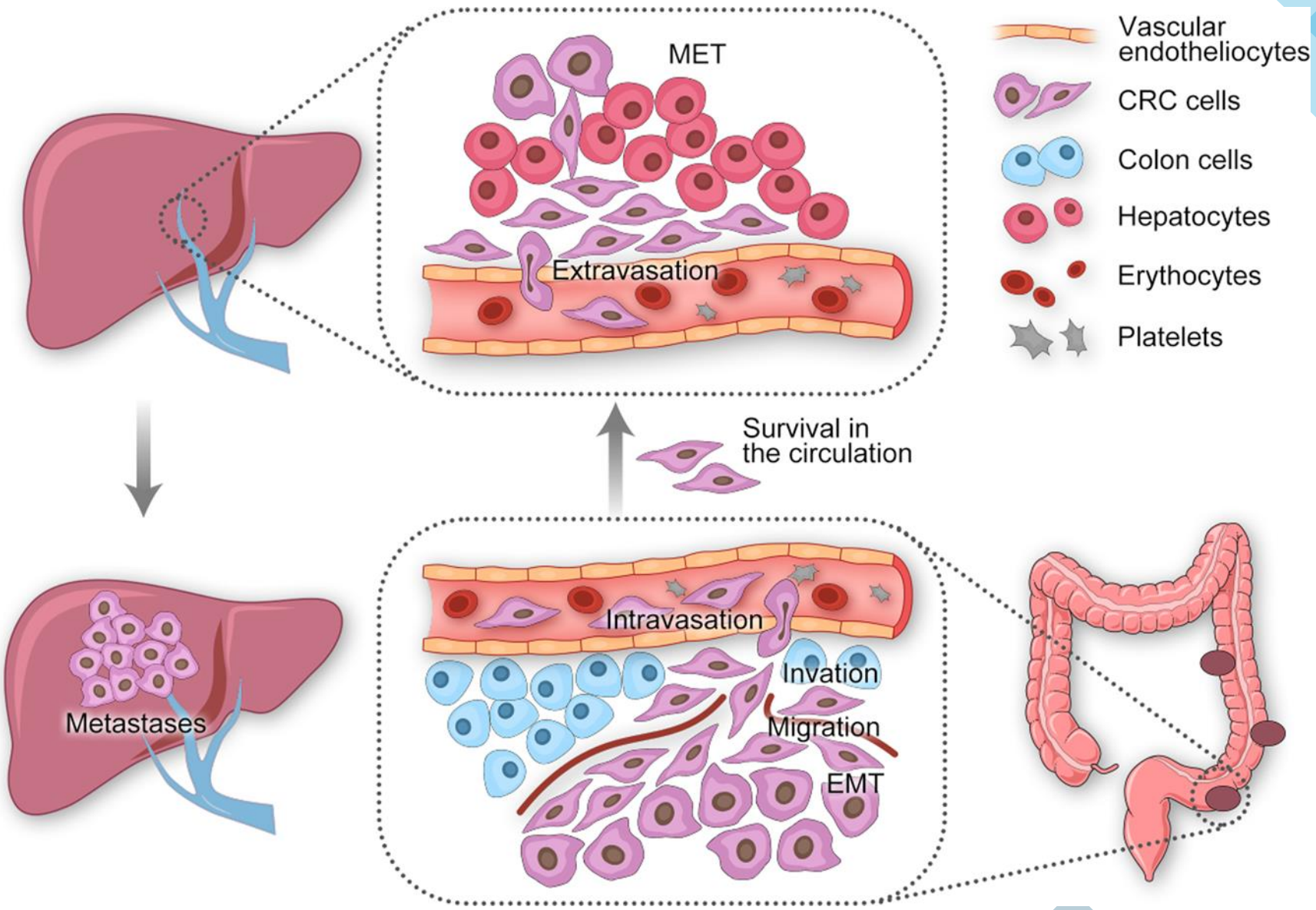
- Kupffer Cells: Initially attack, then promote growth via cytokines.
- Angiogenesis: VEGF-driven neovascularization.

Immune Invasion Mechanisms

- PD-L1 expression, T-cell exhaustion.
- Pre-Metastatic Niche Formation:
  - Bone Marrow-Derived Cells
  - prepare liver before metastasis.

Liquid Biopsy in Metastasis Detection

- ctDNA: as a biomarker for minimal residual disease (e.g., DYNAMIC trial).
- Sensitivity vs. imaging (80% for lesions >1cm).


MET
Extravasation
Vascular endotheliocytes
CRC cells
Colon cells
Hepatocytes
Erythocytes
Platelets
Survival in the circulation
Intravasation
Invation
Migration
EMT
Metastases

Investigations

Laboratory Workup

- CEA (>10 ng/mL = poor prognosis).
- LFTs (AST/ALT ↑, ALP ↑ if biliary obstruction).

Imaging Modalities**

- CT (Triple-Phase):Arterial/portal/delayed phases.
- MRI (Eovist): 95% sensitivity for lesions <1 cm.
- PET-CT: to Detect extrahepatic disease (FDG-avid lesions).

AI in Imaging Detection

- Deep learning (e.g., Google’s LYNA) improves sensitivity for sub-1cm lesions.
- Example: AI flagged 12% more mets than radiologists

Biopsy & Pathology

- IHC Markers: CK20+, CDX2+, SATB2+.

Pathologic Margins Matter

- R0 resection (≥1mm margin) vs. R1 (microscopic+) → 5-yr survival 45% vs. 20%

Management

Resectable vs. Unresectable

- Criteria: ≤3 lesions, no extrahepatic disease, FLR ≥30%.
- Surgical Options
  - Hepatectomy (anatomical/non-anatomical).
  - Associating Liver Partition and Portal vein Ligation for Staged hepatectomy ALPPS (for large tumors).
- Systemic Therapy:
  - FOLFOX/FOLFIRI + Bevacizumab/Cetuximab.
- Locoregional Therapies
  - TACE, SBRT, Microwave Ablation.

Unresectable mCRC first line therapy

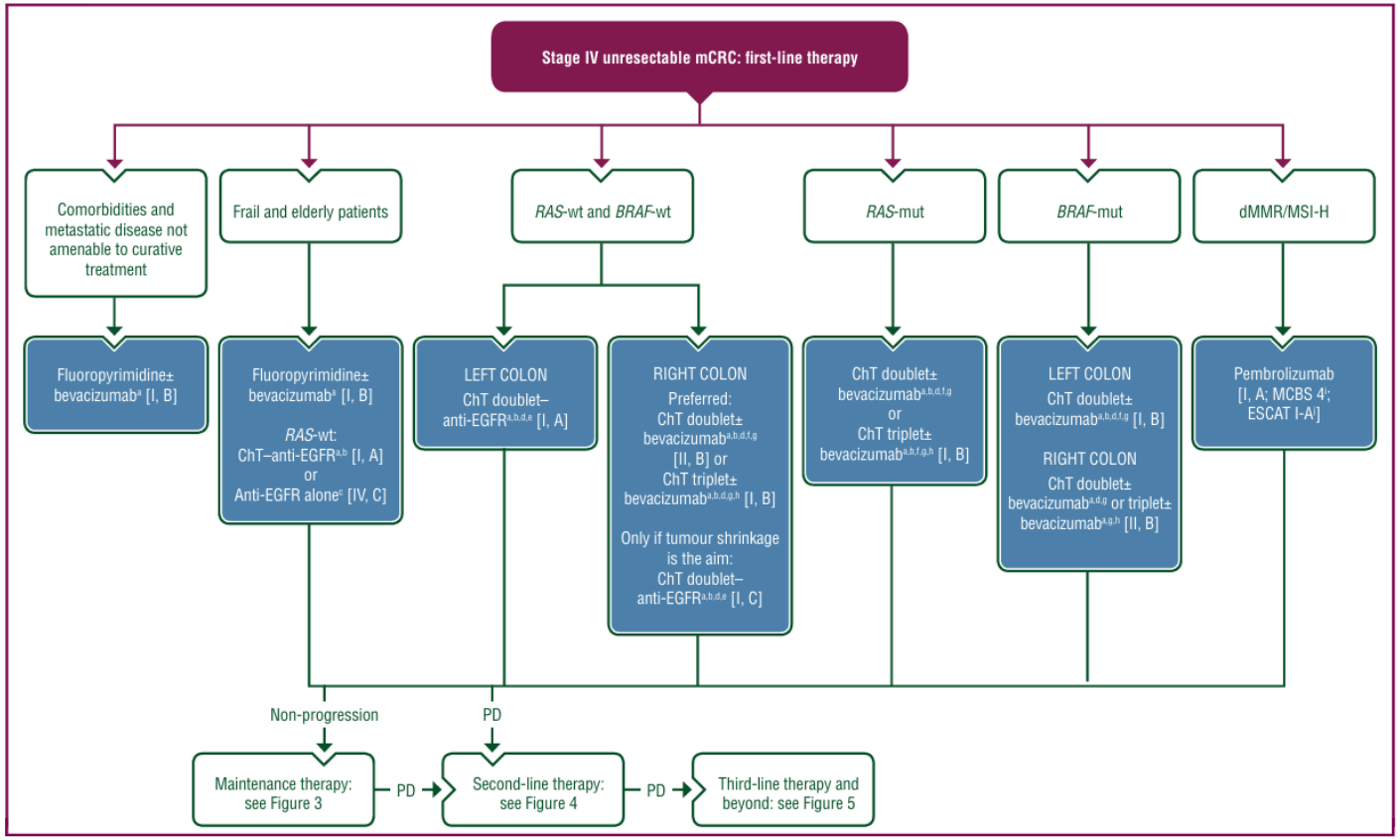


Figure 2. Management of stage IV unresectable mCRC in first-line therapy. Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.

Unresectable mCRC maintenance therapy

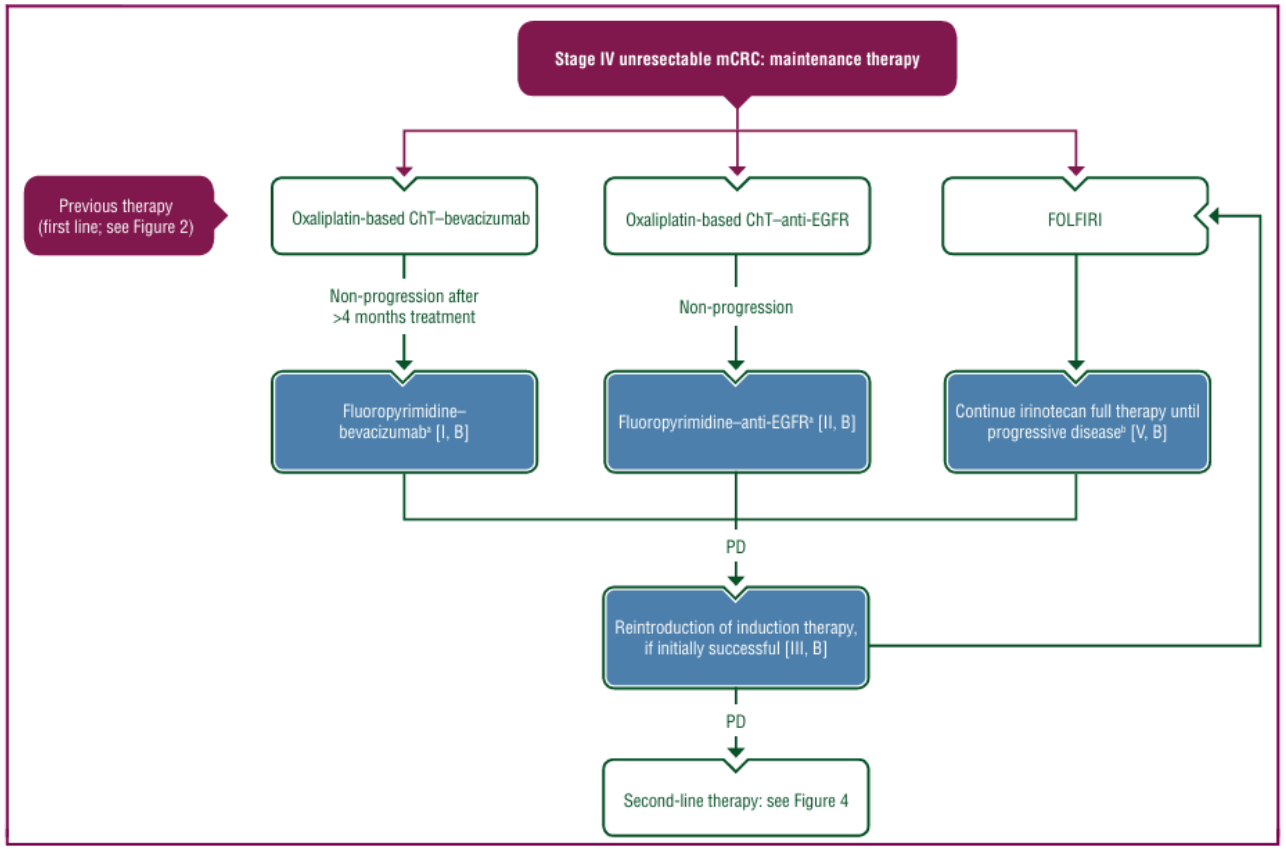


Figure 3. Management of stage IV unresectable mCRC with maintenance therapy. Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.

Unresectable mCRC 2nd line therapy

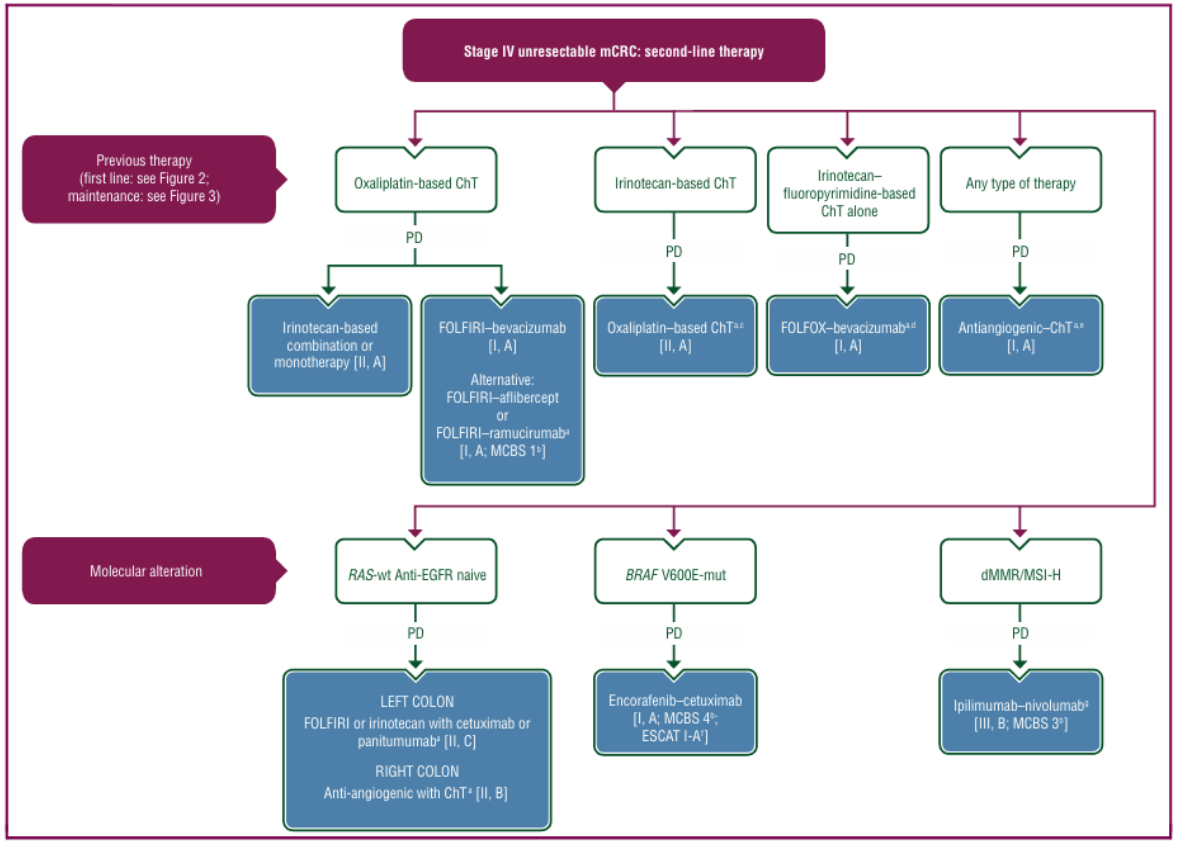
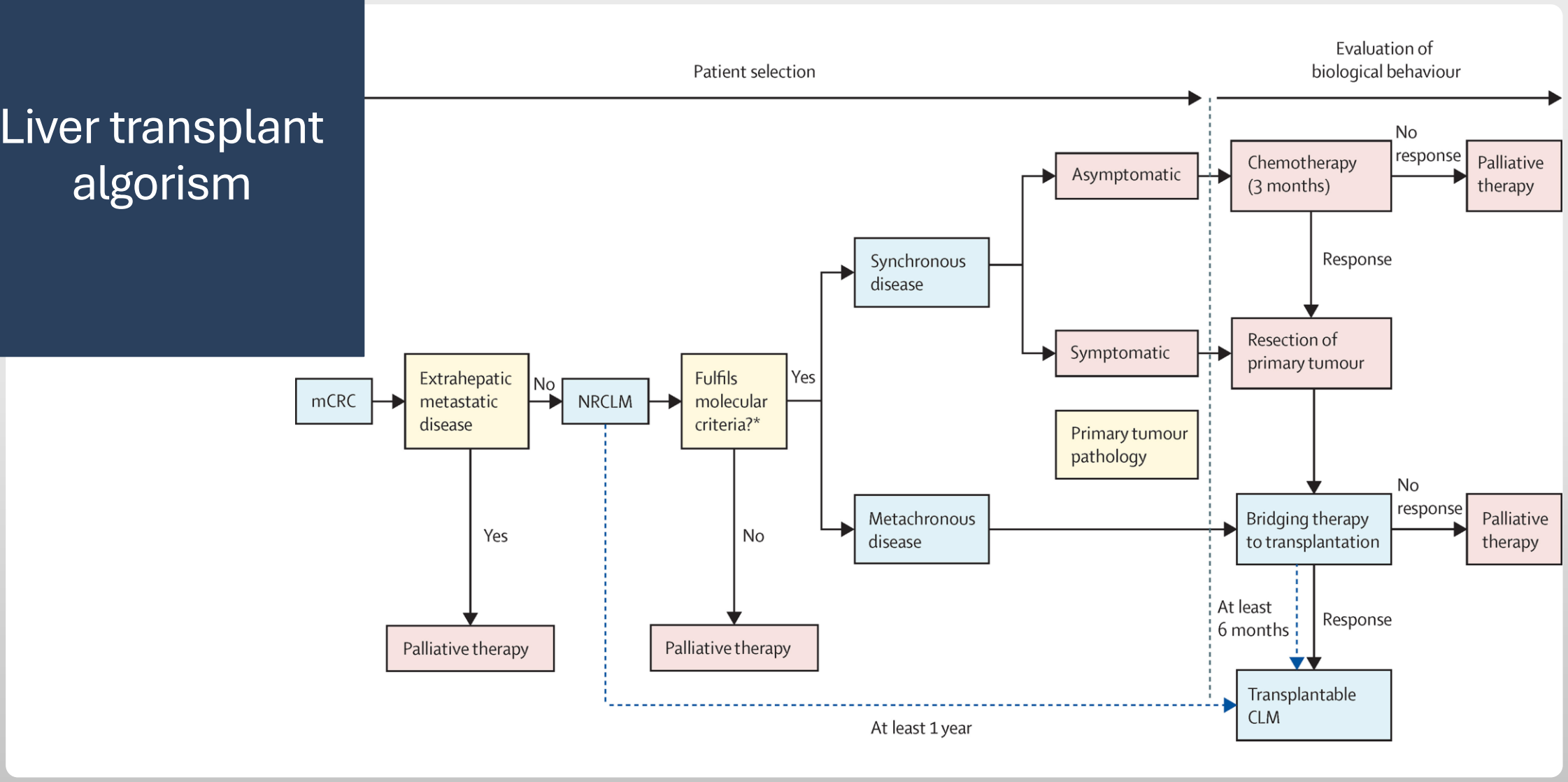


Figure 4. Management of stage IV unresectable mCRC in the second line. Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.

Liver transplant algorism



Complications

- Post-Resection Liver Failure (15–20% mortality if FLR <20%).
- Chemotherapy-Induced Steatohepatitis (CASH): Irinotecan → hepatic steatosis; Oxaliplatin → sinusoidal obstruction
- Post-Embolization Syndrome: Fever (60%), pain (40%), liver abscess (5%).
- Recurrence

Follow-Up

- CEA + CT/MRI
  - High-risk patients: q3mo.
  - Low-risk: q6mo.

Take-Home Message

- 1. Early detection improves resectability.
- 2. Multidisciplinary care (surgeon, oncologist, radiologist).
- 3. Emerging therapies (immunotherapy, liquid biopsy).
- 4. Multimodal therapy (surgery + systemic) is gold standard.
- 5. Liquid biopsy: may replace surveillance imaging.

Thank you