❖Treatment Selection in Cholangiocarcinoma
A Practical Approach to Clinical Decision-Making

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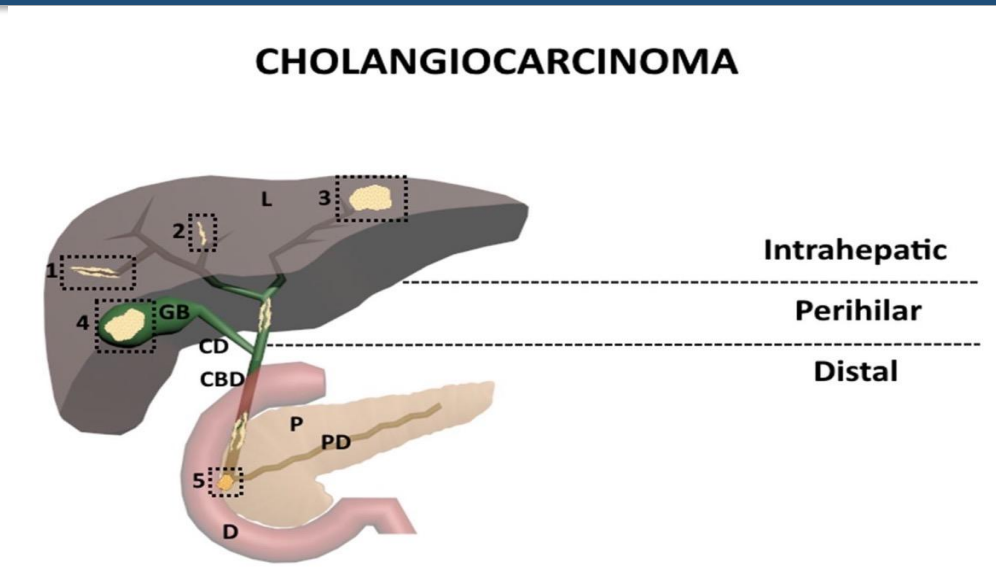
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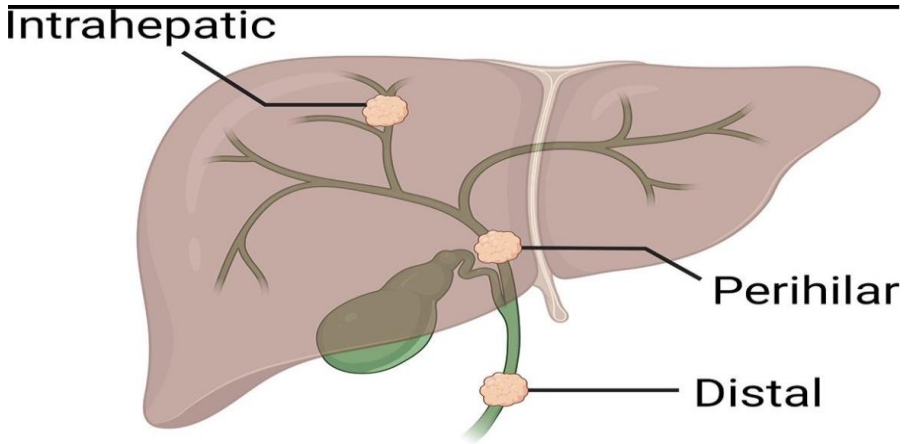
Anatomical Classification

- **Why is treatment selection challenging?**

The First Decision: Where Is the Tumor?

iCCA — Intrahepatic	pCCA — Perihilar	dCCA — Distal
Intrahepatic	Perihilar	Distal



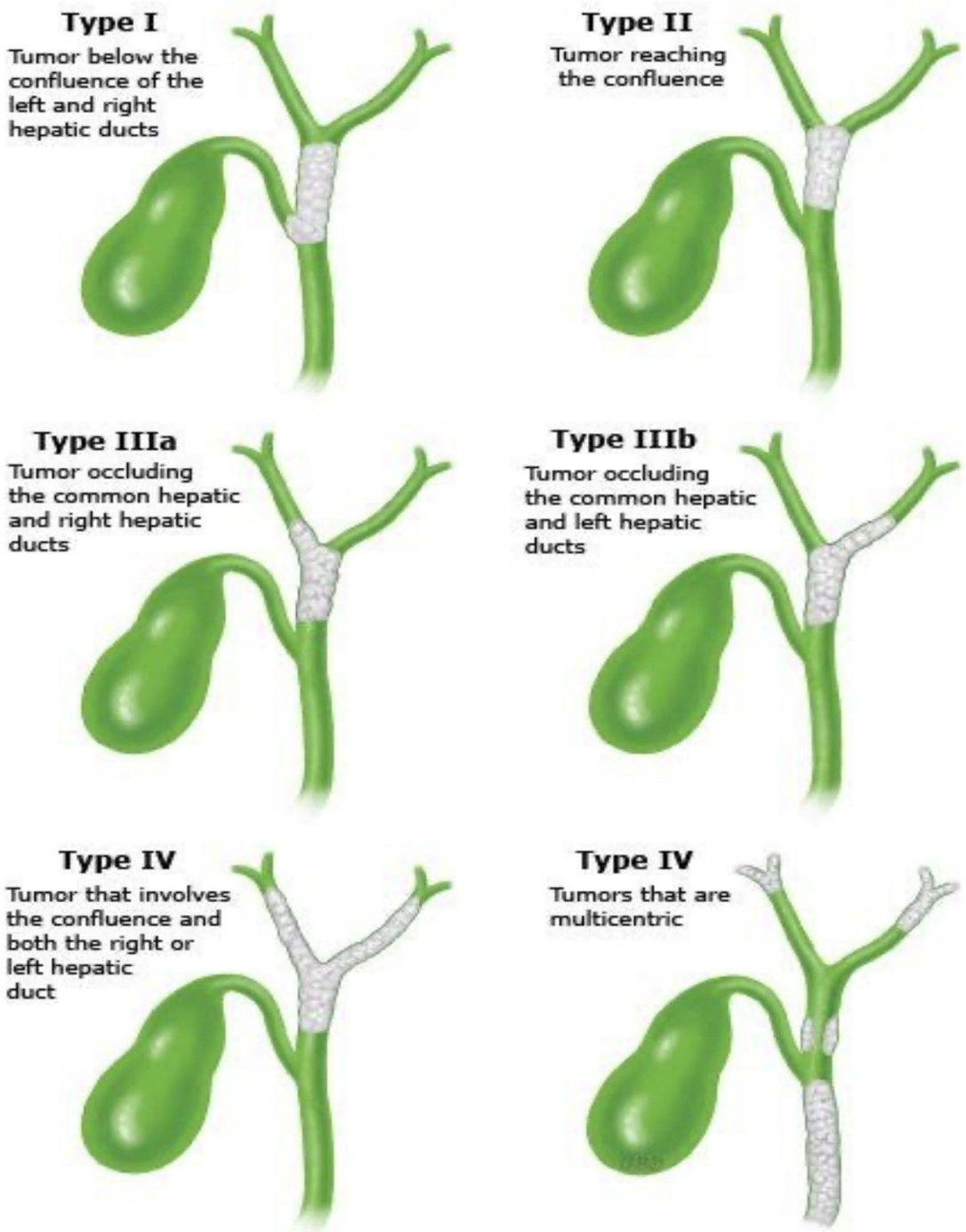


Three different diseases:

Different biology
Different molecular profile
Different surgical options
Different systemic treatment

Why does location matter? Different anatomy → different staging → different surgical strategy → different role of transplantation

BISMUTH CLASSIFICATION



Initial Staging and Resectability

- High-quality multiphasic CT of chest/abdomen/pelvis
- MRI/MRCP is particularly useful for biliary and vascular anatomy
- Assess vascular involvement, lobar atrophy, lymph nodes, and distant metastases
- PET/CT is not a routine substitute for anatomic staging; it may be useful selectively for occult metastatic disease
- Discuss potentially resectable disease in a hepatobiliary MDT.

Imaging and Staging

- **Cross-sectional imaging is the foundation**

Multiphasic contrast-enhanced CT

- Vascular involvement
- Lymph nodes
- Distant metastases

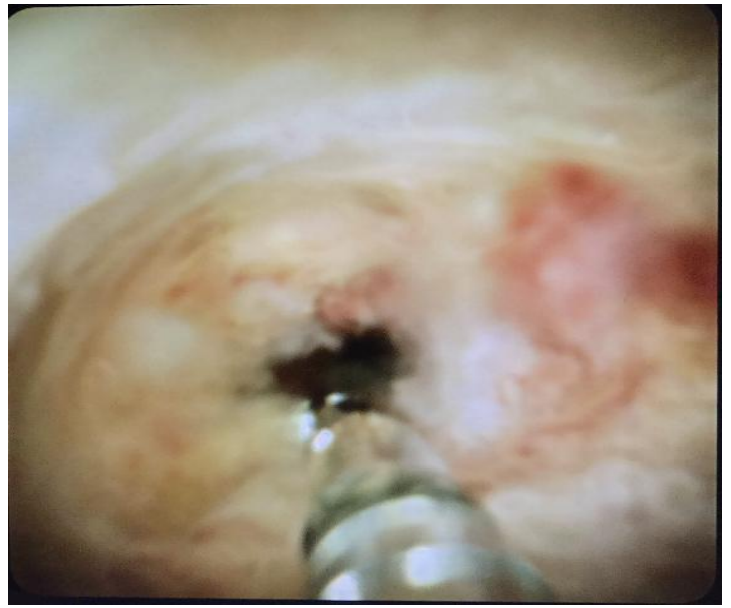
MRI + MRCP

- Biliary anatomy
- Longitudinal tumor extent
- Liver involvement

- Complete staging before biliary stenting whenever possible.

Tissue Diagnosis: When Is It Needed?

- Metastatic or unresectable disease: tissue confirmation is generally required before systemic therapy
- Avoid transperitoneal biopsy of a potentially transplant-eligible perihilar tumor when it could compromise transplantation strategy
- For distal lesions, EUS-guided sampling may be useful when tissue is needed
- ERCP is primarily therapeutic, but brushings/biopsies can provide tissue in selected patients.
- cholangioscopy :permits direct inspection or obtain biopsies



Is Preoperative Biopsy Mandatory?

Potentially resectable CCA

If imaging is convincing + MDT recommends curative surgery:

Preoperative biopsy is NOT routinely mandatory.

Diagnosis can be confirmed on the surgical specimen.

Biopsy becomes important when:

- Unresectable / metastatic disease
- Systemic therapy planned
- Diagnosis remains uncertain

→ Histology + IHC + Molecular profiling / NGS(next generation seq.)

Does PET Replace Biopsy?

- FDG-PET/CT is a STAGING tool — not a substitute for histology.
- iCCA: useful for occult nodal/distant metastases in potentially resectable disease.
- pCCA / dCCA: not for diagnosis or local staging; role mainly in distant disease detection and remains limited.
- **PET ≠ Biopsy**

PSC + Suspected pCCA: What Changes?

PSC can produce inflammatory biliary strictures that mimic CCA.

Suggested approach:

MRI/MRCP + contrast CT

↓

ERCP: brush cytology ± FISH ± intraductal sampling

↓

EUS: suspicious regional lymph nodes

Important:

A negative brush cytology does NOT reliably exclude CCA.

PSC therefore makes the diagnostic pathway more challenging.

PSC + pCCA: What Is the Role of FDG-PET?

FDG-PET is NOT routinely recommended for transplant staging in PSC-associated pCCA.

Its role in this setting remains limited / unclear.

Main staging tools:

- Contrast-enhanced CT
- MRI/MRCP
- EUS for suspicious lymph nodes

PET should NOT be used to establish the diagnosis of pCCA.

Key message:

PET does not solve the diagnostic problem in PSC.

The Biopsy Trap in Transplant Candidates

AVOID:

- Percutaneous / transperitoneal biopsy of the primary hilar tumor
- EUS-FNA/FNB of the primary hilar tumor

PREFERRED:

- ERCP brush cytology
- Intraductal forceps biopsy
- FISH when appropriate
- EUS-guided sampling of suspicious lymph nodes

Why?

Tumor seeding of the primary tumor may compromise transplant eligibility.

pCCA + Liver Transplant: Is Biopsy Mandatory?

Mayo-type transplant pathway:

Suspicious pCCA → diagnostic evidence → neoadjuvant chemoradiation → restaging → liver transplantation

Definitive histology from the PRIMARY TUMOR is NOT always mandatory before neoadjuvant therapy.

However: obtain cytology / tissue when feasible and stage carefully.

Resectable Disease: Surgery Is the Only Potentially Curative Option

- iCCA: anatomical liver resection when technically and oncologically appropriate
- pCCA: selected patients may require major hepatectomy with bile duct resection and lymphadenectomy
- dCCA: pancreaticoduodenectomy is standard for resectable distal tumors
- Aim for R0 resection while preserving adequate future liver remnant
- Perihilar transplant protocols apply only to highly selected patients.

Resectable pCCA and dCCA

pCCA

Localized + technically resectable

↓

Hepatobiliary resection ± vascular reconstruction

↓

R0 resection

Selected pCCA

If transplant criteria are fulfilled:

Neoadjuvant therapy → Liver transplantation

dCCA

Localized + resectable

↓

Pancreaticoduodenectomy (Whipple)

iCCA: A Distinct Treatment Pathway

Resectable iCCA

↓

Complete surgical resection

Goal: R0 resection

+

Regional lymph-node assessment

↓

Adjuvant capecitabine × 6 months

Unresectable / metastatic iCCA

↓

Gemcitabine + Cisplatin + Durvalumab

↓

Early molecular profiling / NGS → Targeted therapy when an actionable alteration is identified

Important:

iCCA is NOT treated according to the HCC/BCLC algorithm.

Adjuvant Therapy After Resection

- Adjuvant capecitabine remains a standard evidence-based option after curative-intent resection
- Consider margin status, nodal disease, performance status, and postoperative recovery
- Routine postoperative chemoradiation is not universal; consider selectively, particularly in high-risk local disease
- MDT review is essential.

Molecular Biology: Three CCA Subtypes

- Comprehensive molecular profiling should be considered in advanced disease
- iCCA: FGFR2 fusions and IDH1 mutations
- pCCA: KRAS, TP53, ARID1A
- dCCA and extrahepatic CCA :KRAS/TP53 وHER2

Important:

These are characteristic patterns, NOT absolute subtype-specific rules.

There is substantial molecular overlap among CCA subtypes.

Biliary Drainage: Palliation and Bridge to Therapy

- Drainage is indicated for cholangitis and clinically significant obstruction
- For distal malignant obstruction, endoscopic drainage is usually preferred when feasible
- For unresectable hilar obstruction, drainage should be planned according to anatomy and the liver segments that need drainage
- EUS-guided drainage and percutaneous drainage are important alternatives when ERCP is unsuccessful or inappropriate
- Avoid unnecessary instrumentation of ducts that do not need drainage.

Biliary Drainage Before Surgery

Routine preoperative drainage is NOT recommended.

Consider drainage with:

- Cholangitis
- High bilirubin
- Renal dysfunction
- Severe/intractable pruritus
- Need for neoadjuvant therapy
- Major hepatectomy / extensive surgery
- Expected delay before surgery

Important: EASL does NOT define a fixed bilirubin cut-off for preoperative drainage.

The Role of Endoscopy in Modern Cholangiocarcinoma Care

- ERCP: decompression, stenting, tissue acquisition in selected cases
- EUS: staging information, tissue acquisition, and biliary drainage in selected patients
- Cholangioscopy: targeted visualization/biopsy in indeterminate strictures
- Endoscopic intervention should be integrated with surgery, radiology, oncology, and transplant expertise.

A Practical MDT Algorithm

- 1. Confirm anatomy and stage
- 2. Define resectability and transplant eligibility
- 3. If resectable → hepatobiliary surgery
- 4. If unresectable/metastatic → biliary optimization + molecular profiling + systemic therapy
- 5. First line → gemcitabine/cisplatin + durvalumab when appropriate
- 6. Progression → actionable target if present; otherwise evidence-based second-line therapy/clinical trial

Treatment Selection in Cholangiocarcinoma — Take-Home Algorithm

CCA

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Define anatomy: iCCA | pCCA | dCCA

↓

Complete staging: CT + MRI/MRCP ± EUS nodal assessment

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Resectable?

YES → Curative-intent treatment

- iCCA → Liver resection
- pCCA → Hepatobiliary resection
- dCCA → Whipple
- Selected pCCA/PSC → Neoadjuvant therapy → Liver transplantation

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Adjuvant therapy

Take-Home Messages

- Resectability—not histology alone—drives the first major treatment decision
- Perihilar disease requires particularly careful surgical, biliary, and transplant planning
- Durvalumab plus gemcitabine/cisplatin is a key first-line standard for advanced disease
- Early comprehensive molecular profiling is essential for precision treatment
- Biliary drainage is a therapeutic intervention, not merely a technical procedure
- Complex cases should be managed in a high-volume multidisciplinary center.

