

Lever, galwegen en galblaas

Leverkanker omvat:

1. **Hepatocellulair carcinoom** (HCC) – 80-90%
2. **Cholangiocarcinoom** (CCA) – 10-20%
3. **Galblaascarcinoom**

Andere meer zeldzame vormen:

- Hepatoblastoma
- Fibrolamellair HCC
- Mixed tumoren (overlap HCC en cholangiocarcinoom)

# Hepatocellulair carcinoom

# 1. Etiologie en risicofactoren

90% van de gevallen ontstaan in de context van cirrose veroorzaakt door:

- Virale hepatitis (B en C)
- Metabool syndroom (MASLD)
- Alcohol
- Andere zeldzamere oorzaken: hemochromatose, alfa-1 anti-trypsine deficiëntie, aflatoxine B1, acute hepatische porfyrie...

Indicatie voor zes maandelijks **screening** met echografie lever en AFP bij:

- alle cirrose patienten
- F3 fibrose in functie van individueel risico
- hoog risico Hepatitis B (PAGE-B score  $\geq 10$ )

# 2. Diagnose en staging

## ***Oncologisch bilan***

- Anamnese en klinisch onderzoek: stigmata chronisch leverlijden?
- Labo: standaard + TSH + AFP + leverfunctie (INR, albumine) + hepatobilan met virale serologie en auto-immuunscreening bij nieuwe diagnose cirrose
- CT-thorax + abdomen met IV-contrast (tri-fasisch)
- Bij twijfel aan te vullen met MRI lever gezien hogere sensitiviteit vooral voor kleine letsels
- Biopsie primaire tumor: percutaan of echo-endoscopisch ifv ligging.
- Alternatief: biopsie van metastatische lokalisatie.
- Gastroscopie ter uitsluiting van slokdarmvarices

### 3. TNM-classificatie (8e editie)

**T—primary tumour**

TX Primary tumour cannot be assessed  
 T0 No evidence of primary tumour  
 T1a Solitary tumour 2 cm or less in greatest dimension with or without vascular invasion  
 T1b Solitary tumour more than 2 cm in greatest dimension without vascular invasion  
 T2 Solitary tumour with vascular invasion more than 2 cm dimension or multiple tumours, none more than 5 cm in greatest dimension  
 T3 Multiple tumours any more than 5 cm in greatest dimension  
 T4 Tumour(s) involving a major branch of the portal or hepatic vein with direct invasion of adjacent organs (including the diaphragm), other than the gallbladder or with perforation of visceral peritoneum

**N—regional lymph nodes**

NX Regional lymph nodes cannot be assessed  
 N0 No regional lymph node metastasis  
 N1 Regional lymph node metastasis

**M—distant metastasis**

M0 No distant metastasis  
 M1 Distant metastasis

**Stage—liver**

Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

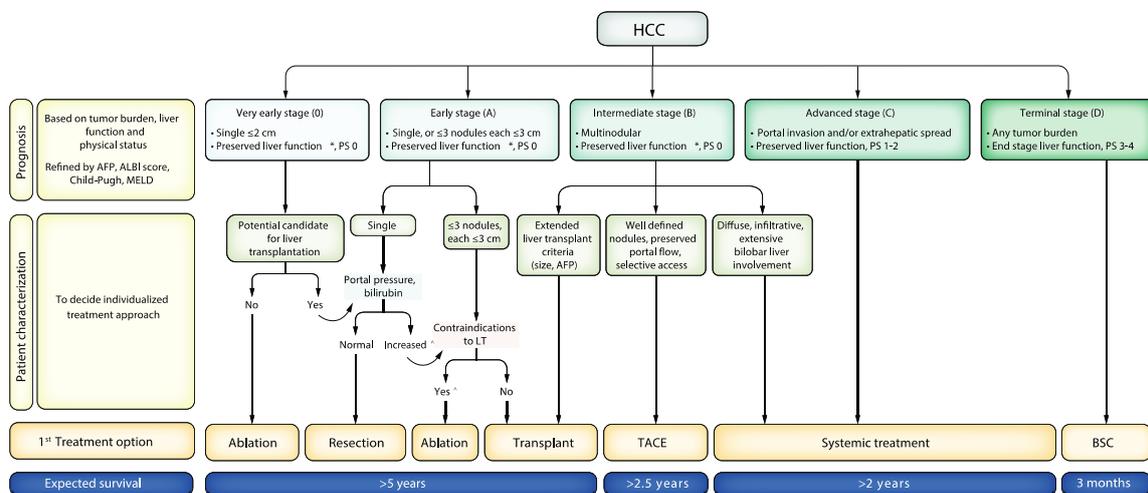
UICC, Union for International Cancer Control.

### 4. Behandeling

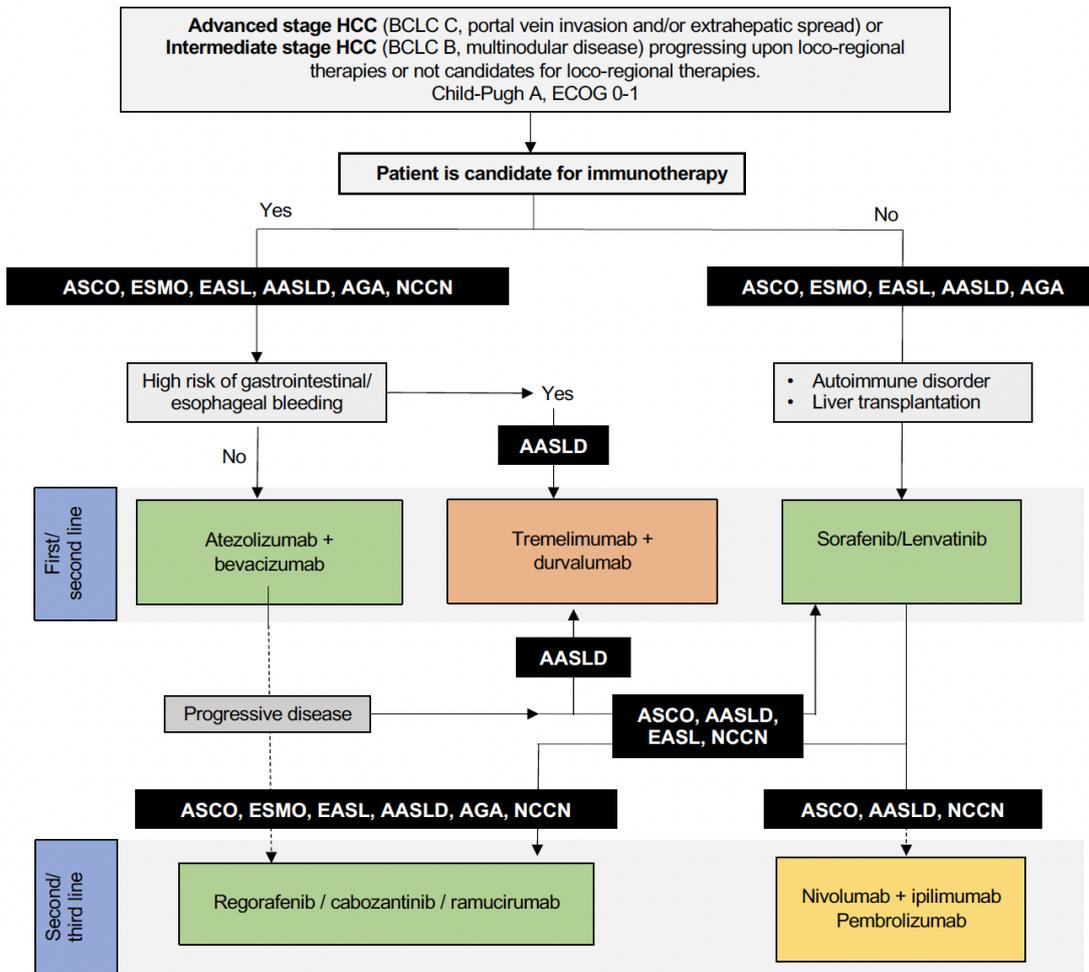
Algoritme gebaseerd op de BCLC classificatie, rekening houdend met algemene toestand van de patiënt (ECOG PS), tumorkarakteristieken (aantal nodules, portale invasie, extrahepatische ziekte), leverfunctie (Child-Pugh Score) en kanker-gerelateerde symptomen.

Steeds bespreking in multidisciplinair overleg.

Bij kleine letsels (BCLC A), vroegtijdig doorverwijzen naar transplant centrum.



## Systemtherapie voor HCC



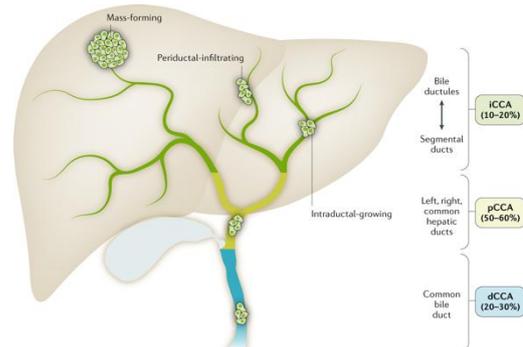
# Cholangiocarcinoom

# 1. Definitie en risicofactoren

Meestal adenocarcinomen

Indeling op basis van anatomische lokalisatie:

- Intra-hepatisch cholangiocarcinoom (iCCA)
  - Perihilair cholangiocarcinoom (pCCA)
  - Distaal cholangiocarcinoom (dCCA)
- **Extrahepatic (pCCA + dCCA)**



NB. Verschillende subtypes verschillen in risicofactoren, histologie, prognose en (epi-)genetische kenmerken.

Risicofactoren:

- Primaire scleroserende cholangitis (PSC) – indicatie voor jaarlijks MRI+MRCP
- Specifiek voor iCCA: cirrose, hepatitis B en C
- Hepatolithiase
- Lifestyle-gerelateerd: alcohol, roken, obesitas, diabetes, mogelijks hormonale anticonceptie

- in Azië: hepatobiliary flukes

## 2. Diagnose and staging

- Anamnese (alcohol, roken) en klinisch onderzoek (stigmata van chronise leverlijden)
- Bloedname: standaard + TSH + CA19.9 + leverfunctie (INR en albumine), hepatobilar met virale serologie en auto-immuunserologie
- CT thorax + abdomen (tri-fasisch)
- Eventueel aanvullende MRI lever + MRCP (vooral voor p/dCCA)
- EUS +/- ERCP
  - Evaluatie locoregionale extent
  - Voor APO: brushing +/- biopsies van primaire tumor of metastatische lymfeklieren ifv ligging
  - Simultane stenting bij obstructieve letsels
- Percutane drainage (PTC) zo niet bereikbaar via ERCP.

### 3. TNM classificatie

Verschillende TNM-classificatie voor iCCA vs pCCA vs dCCA.

#### **Intra-hepatisch CCA**

AJCC Stage	Stage grouping	Stage description*
0	<b>Tis</b> <b>N0</b> <b>M0</b>	The cancer is only in the mucosa (the innermost layer of cells in the bile duct). It hasn't started growing into the deeper layers (Tis). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IA	<b>T1a</b> <b>N0</b> <b>M0</b>	The tumor is no more than 5 cm (about 2 inches) across and has not invaded nearby blood vessels (T1a). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IB	<b>T1b</b> <b>N0</b> <b>M0</b>	The tumor is more than 5 cm (about 2 inches) across but has not invaded nearby blood vessels (T1b). The cancer has not spread to nearby lymph nodes (N0) or to distant sites (M0).
II	<b>T2</b> <b>N0</b> <b>M0</b>	The tumor has grown into nearby blood vessels, <b>OR</b> there are 2 or more tumors, which may or may not have grown into nearby blood vessels (T2). The cancer has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIIA	<b>T3</b> <b>N0</b> <b>M0</b>	The cancer has grown through the visceral peritoneum (the outer lining of organs in the abdomen) (T3). The cancer has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIIB	<b>T4</b> <b>N0</b> <b>M0</b>	The cancer has grown directly into nearby structures outside of the liver (T4). The cancer has not spread to nearby lymph nodes (N0) or to distant sites (M0).
	OR	
	<b>Any T</b> <b>N1</b> <b>M0</b>	The cancer is any size and might or might not be growing outside the bile duct (Any T) and has spread to nearby lymph nodes (N1). It has not spread to distant sites (M0).
IV	<b>Any T</b> <b>Any N</b> <b>M1</b>	The cancer is any size and may or may not be growing outside the bile duct (Any T). It may or may not have spread to nearby lymph nodes (Any N). It has spread to distant organs such as the bones or lungs (M1).

\*The T categories are described in the table above, except for:

- **TX:** Main tumor cannot be assessed due to lack of information.
- **T0:** No sign of a primary tumor.

The N categories are described in the table above, except for:

- **NX:** Nearby lymph nodes cannot be assessed due to lack of information.

## Perihilair CCA

AJCC Stage	Stage grouping	Stage description*
0	<b>Tis</b> <b>N0</b> <b>M0</b>	The cancer is only in the mucosa (the innermost layer of cells in the bile duct). It hasn't started growing into the deeper layers (Tis). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
I	<b>T1</b> <b>N0</b> <b>M0</b>	The cancer has grown into deeper layers of the bile duct wall, such as the muscle layer or fibrous tissue layer (T1). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
II	<b>T2a or T2b</b> <b>N0</b> <b>M0</b>	The tumor has grown through the bile duct wall and into the nearby fatty tissue (T2a) or into the nearby liver tissue (T2b). The cancer has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIIA	<b>T3</b> <b>N0</b> <b>M0</b>	The cancer is growing into branches of the main blood vessels of the liver (the portal vein and/or the hepatic artery) on one side (left or right) (T3). The cancer has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIIB	<b>T4</b> <b>N0</b> <b>M0</b>	The cancer is growing into the main blood vessels of the liver (the portal vein and/or the common hepatic artery) or into branches of these vessels on both sides (left and right), <b>OR</b> the cancer is growing into other bile ducts on one side (left or right) and a main blood vessel on the other side (T4). The cancer has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIIC	<b>Any T</b> <b>N1</b> <b>M0</b>	The cancer is any size and may or may not be growing outside the bile duct or into nearby blood vessels (Any T) and has spread to 1 to 3 nearby lymph nodes (N1). It has not spread to distant sites (M0).
IVA	<b>Any T</b> <b>N2</b> <b>M0</b>	The cancer is any size and may or may not be growing outside the bile duct or into nearby blood vessels (Any T). It has also spread to 4 or more nearby lymph nodes (N2). It has not spread to distant sites (M0).
IVB	<b>Any T</b> <b>Any N</b> <b>M1</b>	The cancer is any size and may or may not be growing outside the bile duct or into nearby blood vessels (Any T). It may or may not have spread to nearby lymph nodes (Any N). It has spread to distant organs such as the bones, lungs, or distant parts of the liver (M1).

\*The T categories are described in the table above, except for:

- **TX**: Main tumor cannot be assessed due to lack of information.
- **T0**: No sign of a primary tumor.

The N categories are described in the table above, except for:

- **NX**: Nearby lymph nodes cannot be assessed due to lack of information.

## Distaal CCA

AJCC Stage	Stage grouping	Stage description*
0	Tis N0 M0	The cancer is only in the mucosa (the innermost layer of cells in the bile duct). It hasn't started growing into the deeper layers (Tis). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
I	T1 N0 M0	The cancer has grown less than 5 mm (about 1/5 of an inch) into the bile duct wall (T1). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIA	T2 N0 M0	The cancer has grown between 5 mm (about 1/5 of an inch) and 12 mm (about 1/2 inch) into the bile duct wall (T2). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
	OR	
	T1 N1 M0	The cancer has grown less than 5 mm (about 1/5 of an inch) into the bile duct wall (T1) and has spread to 1 to 3 nearby lymph nodes (N1). It has not spread to distant sites (M0).

<b>IIB</b>	<b>T3 N0 M0</b>	The cancer has grown more than 12 mm (about ½ inch) into the bile duct wall (T3). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
	OR	
	<b>T2 or T3 N1 M0</b>	The cancer has grown 5 mm (about 1/5 of an inch) or more into the bile duct wall (T2 or T3) and has spread to 1 to 3 nearby lymph nodes (N1). It has not spread to distant sites (M0).
<b>IIIA</b>	<b>T1, T2, or T3 N2 M0</b>	The cancer has grown to any depth into the bile duct wall (T1, T2, or T3) and to 4 or more nearby lymph nodes (N2). It has not spread to distant sites (M0).
<b>IIIB</b>	<b>T4 Any N M0</b>	The cancer is growing into nearby blood vessels (the celiac artery or its branches, the superior mesenteric artery, and/or the common hepatic artery) (T4). The cancer may or may not have spread to nearby lymph nodes (Any N). It has not spread to distant sites (M0).
<b>IV</b>	<b>Any T Any N M1</b>	The cancer has grown to any depth within the bile duct wall and may or may not be growing into nearby blood vessels (Any T). It may or may not have spread to nearby lymph nodes (any N). It has spread to distant organs such as the liver, lungs, or peritoneum (inner lining of the abdomen [belly]) (M1).

\*The T categories are described in the table above, except for:

- TX: Main tumor cannot be assessed due to lack of information.

The N categories are described in the table above, except for:

- NX: Nearby lymph nodes cannot be assessed due to lack of information.

## 4. Behandeling

Steeds te bespreken in multidisciplinair overleg.

### **Early**

- Heelkunde gevolgd door adjuvant Capecitabine

### **Locally-advanced**

- Neo-adjuvant cisplatinum-gemcitabine + durvalumab gevolgd door heelkunde

- Voor liver-limited iCCA: locoregionale modaliteiten te overwegen. Zo goede respons, herevaluatie voor heekkunde

### Advanced of metastatic

! Molecular profiling !

- NGS: IDH1, HER2/neu, BRAF
- RNA-seq: FGFR2, NTRK
- MSI

Eerste lijn: cisplatinum-gemcitabine + durvalumab

Tweede lijn:

- Targetted therapie op basis van moleculaire kenmerken (cfr. Schema).
- Zo geen druggable target: mFolfox

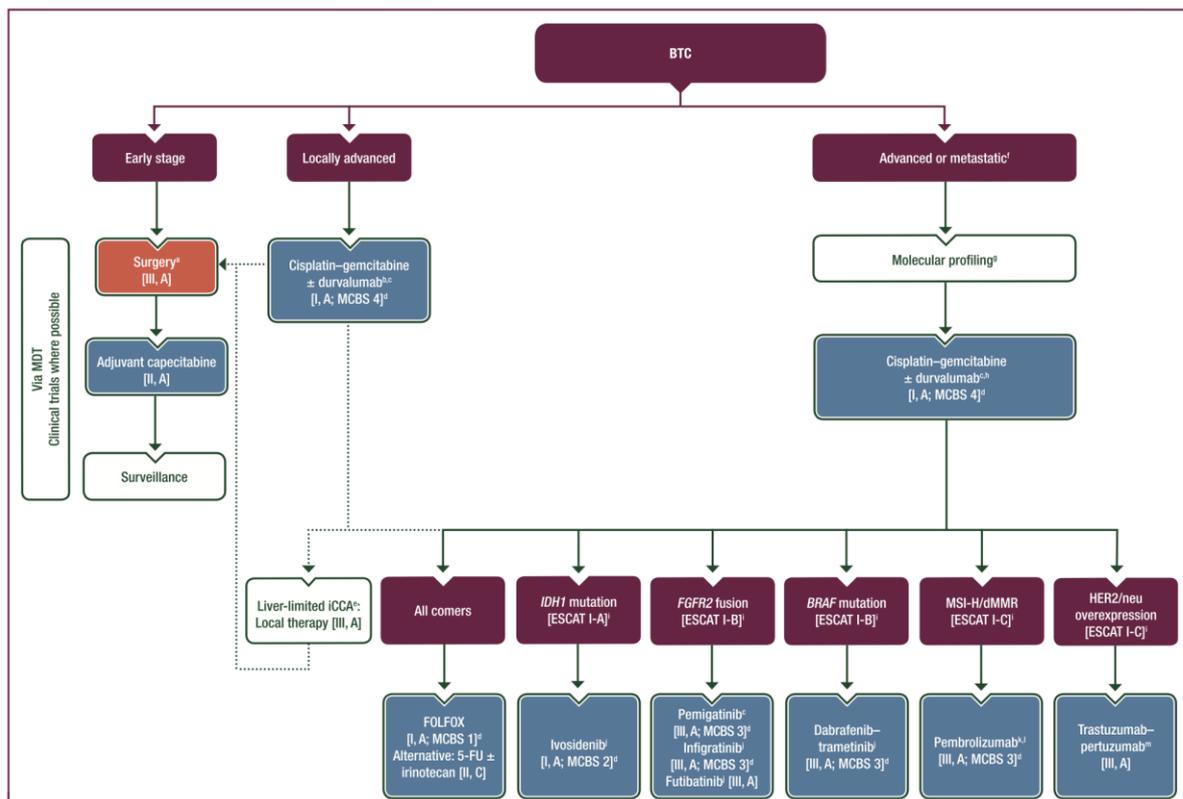


Figure 1. Treatment algorithm for BTC.

# Galblaascarcinoom

# 1. Definitie en risicofactoren

Meestal adenocarcinomen.

Vaak toevallige vondst op APO na cholecystectomie.

Risicofactoren: cfr. cholangiocarcinomen

## 2. Diagnose and staging

- Anamnese (alcohol, roken) en klinisch onderzoek (stigmata van chronise leverlijden)
- Bloedname: standaard + CA19.9 + leverfunctie (INR en albumine), hepatobilar met virale serologie en auto-immuunserologie
- CT thorax + abdomen (tri-fasisch)
- EUS +/- ERCP
  - Evaluatie locoregionale extent
  - Voor APO: brushing +/- biopsies van primaire tumor of metastatische lymfeklieren ifv ligging.

### 3. TNM classificatie

AJCC Stage	Stage grouping	Stage description*
0	<b>Tis</b> <b>N0</b> <b>M0</b>	Cancer is only in the epithelium (the inner layer of the gallbladder) and has not grown into deeper layers of the gallbladder (Tis). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
I	<b>T1</b> <b>N0</b> <b>M0</b>	The tumor has grown into the lamina propria or the muscle layer (muscularis) (T1). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIA	<b>T2a</b> <b>N0</b> <b>M0</b>	The cancer has grown through the muscle layer into the fibrous tissue on the side of the peritoneum (the lining of the abdominal cavity) (T2a). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIB	<b>T2b</b> <b>N0</b> <b>M0</b>	The cancer has grown through the muscle layer into the fibrous tissue on the side of the liver, but has not invaded the liver (T2b). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIIA	<b>T3</b> <b>N0</b> <b>M0</b>	The cancer has grown through the serosa (the outermost covering of the gallbladder) and/or it has grown directly into the liver and/or one nearby structure like the stomach, duodenum (first part of the small intestine), colon, pancreas, or bile ducts outside the liver (T3). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).

IIIB	<b>T1-3</b> <b>N1</b> <b>M0</b>	The cancer may or may not have grown outside of the gallbladder into the liver and/or one other nearby structure, but it has not grown into the main blood vessels leading into the liver (portal vein or hepatic artery) (T1 to T3). It has spread to no more than 3 nearby lymph nodes (N1). It has not spread to distant sites (M0).
IVA	<b>T4</b> <b>N0 or N1</b> <b>M0</b>	The tumor has grown into one of the main blood vessels leading into the liver (portal vein or hepatic artery) or it has grown into 2 or more structures outside of the liver (T4). It may or may not have spread to no more than 3 nearby lymph nodes (N0 or N1). It has not spread to distant sites (M0).
IVB	<b>Any T</b> <b>N2</b> <b>M0</b>	The primary tumor may or may not have grown outside the gallbladder. The cancer has spread to 4 or more nearby lymph nodes (N2). It has not spread to distant sites (M0).
		OR
	<b>Any T</b> <b>Any N</b> <b>M1</b>	The primary tumor may or may not have grown outside the gallbladder. The cancer may or may not have spread to nearby lymph nodes. It has spread to distant sites such as the liver, peritoneum (the lining of the abdomen [belly]), or the lungs (M1).

\* The following additional categories are not listed on the table above:

- **TX:** Main tumor cannot be assessed due to lack of information.
- **T0:** No sign of a primary tumor.
- **NX:** Regional lymph nodes cannot be assessed due to lack of information.

## 4. Behandeling

Steeds te bespreken in multidisciplinair overleg.

### **Early**

**Curatieve resectie** zo mogelijk! Gevolgd door **adjuvant Capecitabine**.

Bij toevallige vondst na cholecystectomie: alle stadium  $\geq T1b$  = bijkomende **oncologische resectie** met lymphadenectomie + resectie eversegment IVb/V en het hepatoduodenaal ligament.

Ook grote T4 tumoren gelocaliseerd in galblaas fundus zijn potentieel curatief resecabel met partiële hepatectomie +/- resectie (deel van) colon transversum.

Infundibulaire T4 tumoren zijn moeilijker curatief te reseceren: noodzaak tot resectie van galwegen, duodenale bulbus, soms ook pancreas kop.

### **Locally-advanced of metastatic**

Cfr. Cholangiocarcinoom