

Cholangiocarcinoma

UPDATE MANAGEMENT

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Cholangiocarcinoma

- Definition
- Epidemiology
- Risk factors
- Pathological classification
- Clinical presentation, Laboratory findings, Imaging studies and Diagnosis
- Staging
- Therapy
- Prognosis



Definition

Cholangiocarcinoma

An adenocarcinoma arising from the epithelial lining of biliary tree including both intra and extrahepatic portions. But those from the gall bladder and the ampulla of Vater are excluded.

T.Uttaravichien. 1985.



Epidemiology

World incidence 1-2 per 100,000

Annual incidence in Khonkaen

Male 135.4 per 100,000

Female 43.0 per 100,000

Green A, Uttaravichien T, Bhudhisawasdi V, et al 1991.



Peak age group 40 -60

Very, very rare below 30

M : F ~ 3:1

Nearly all of the cases is “ Native of Isan”

Two common presentation

‘Malignant Obstructive Jaundice’

‘Liver Mass’

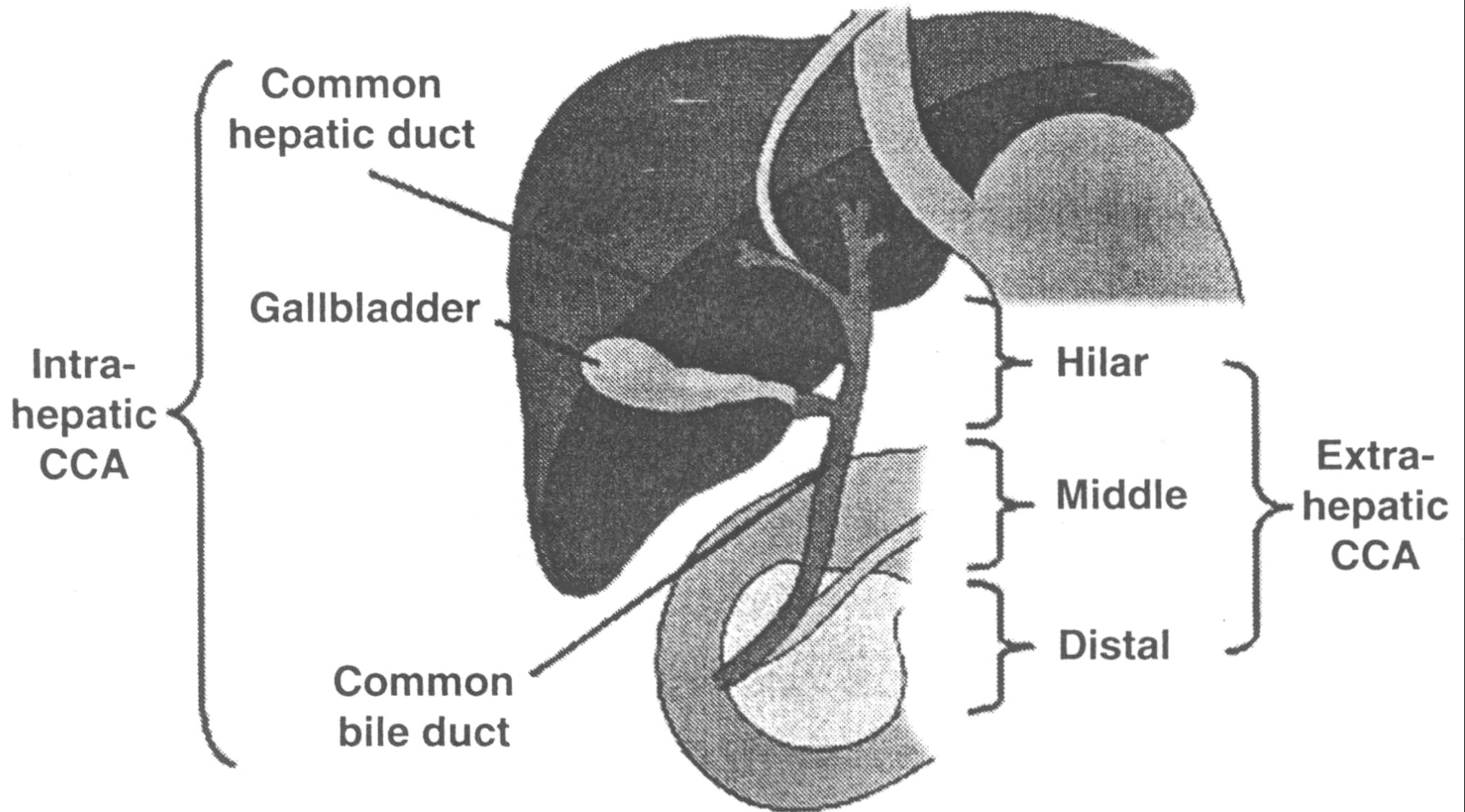


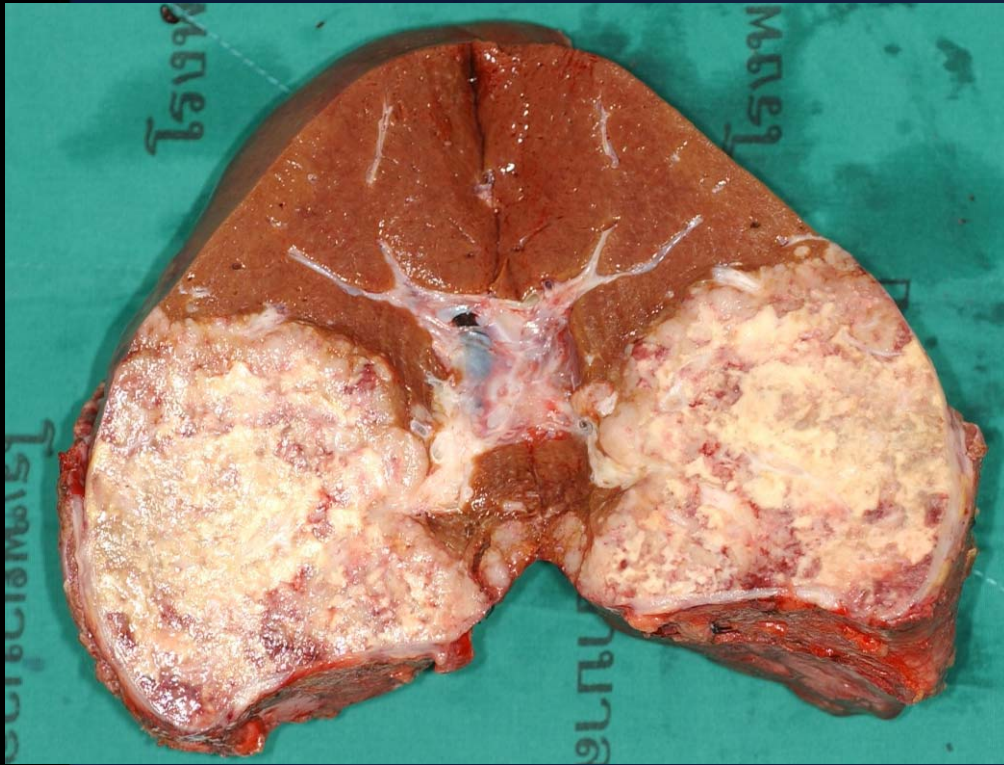
Pathological classification

1. Intrahepatic cholangiocarcinoma
2. Extrahepatic cholangiocarcinoma



Classification of Cholangiocarcinoma





Spiral CT scan and surgical pathology of intrahepatic cholangiocarcinoma

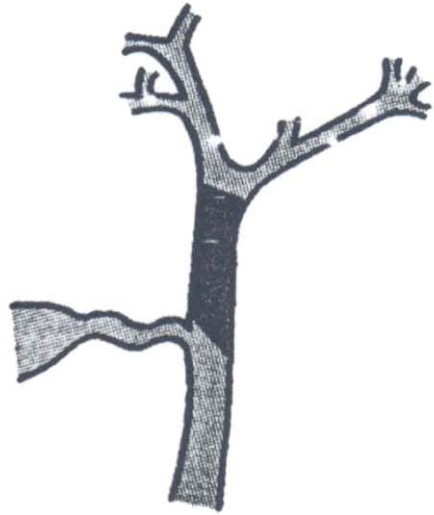


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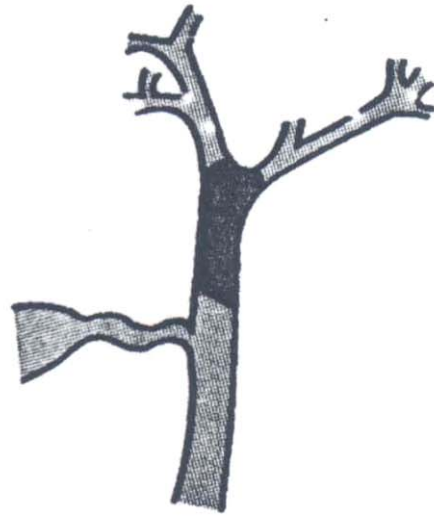
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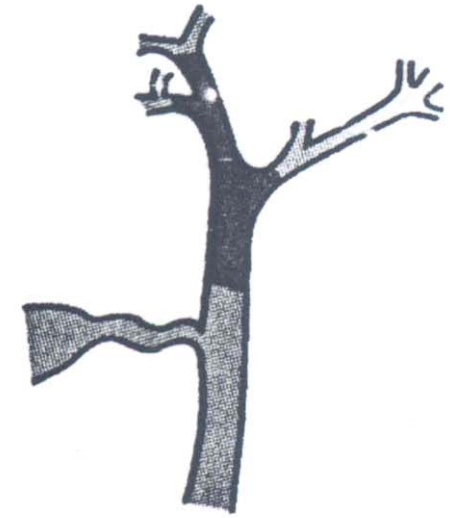
Type I



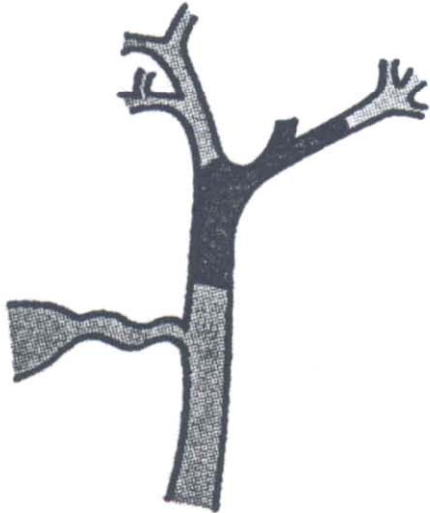
Type II



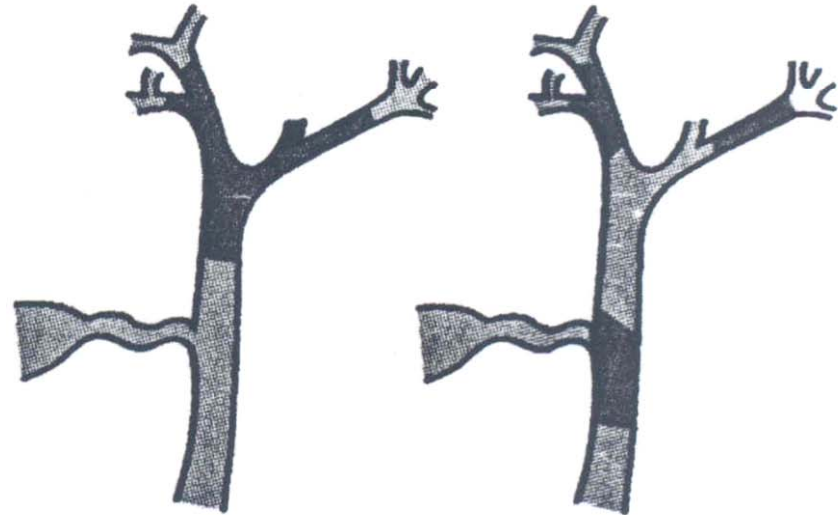
Type IIIa



Type IIIb

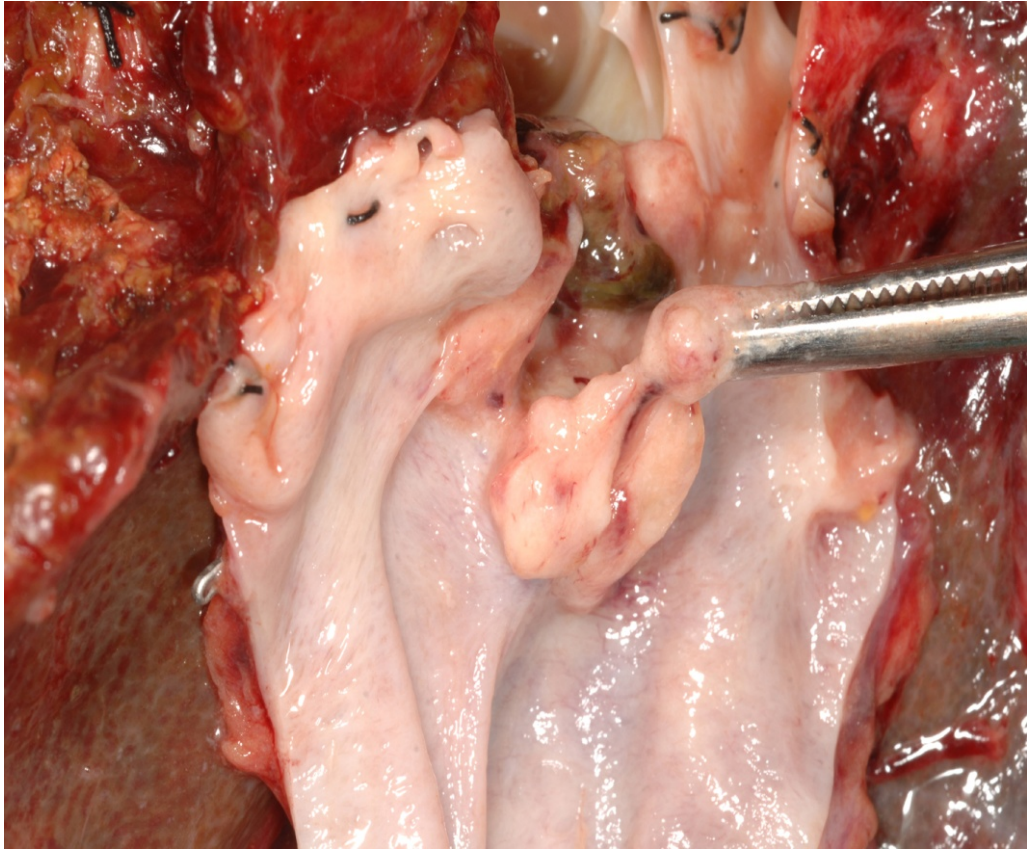


Type IV

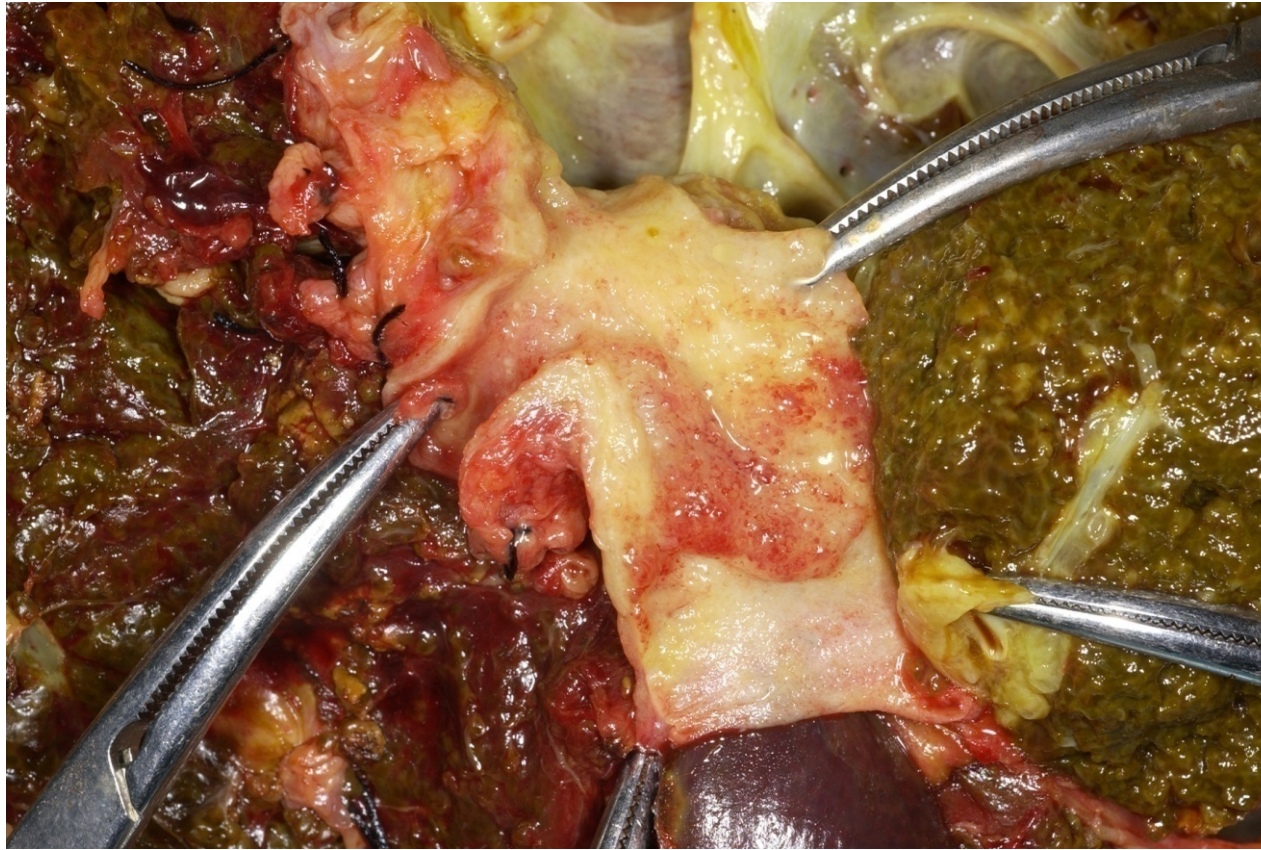


Bismuth-Corlette classification of hilar cholangiocarcinoma

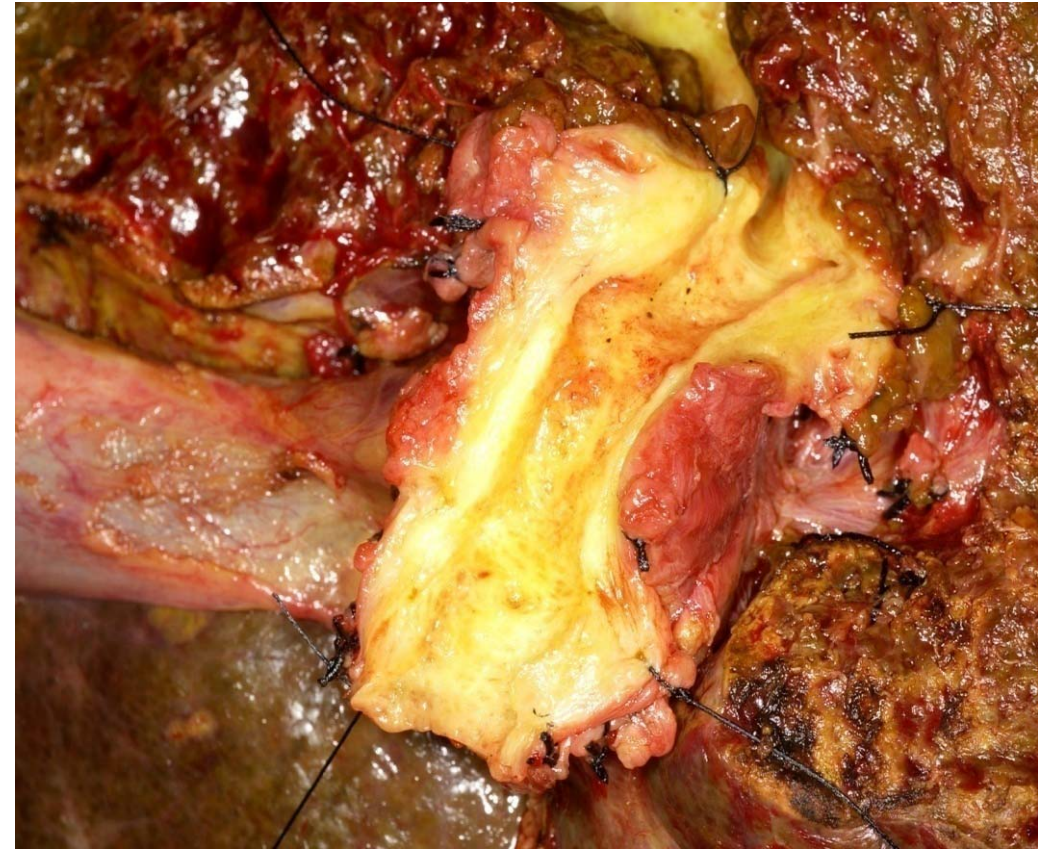
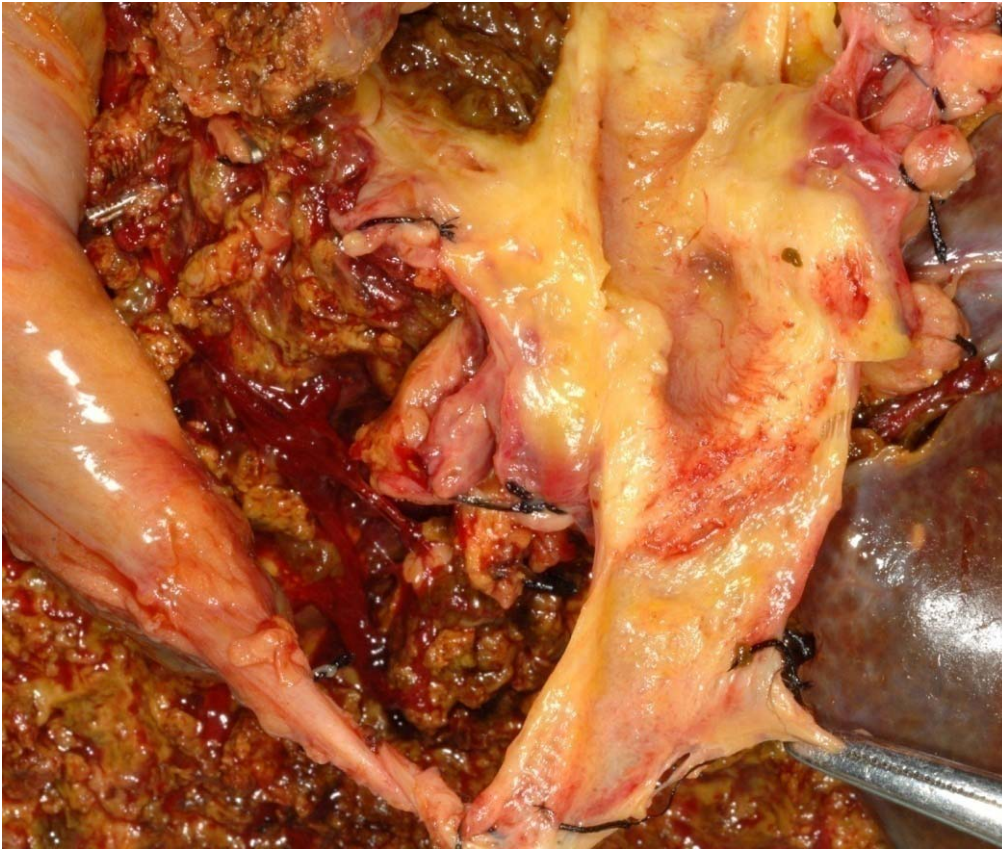
Papillary type



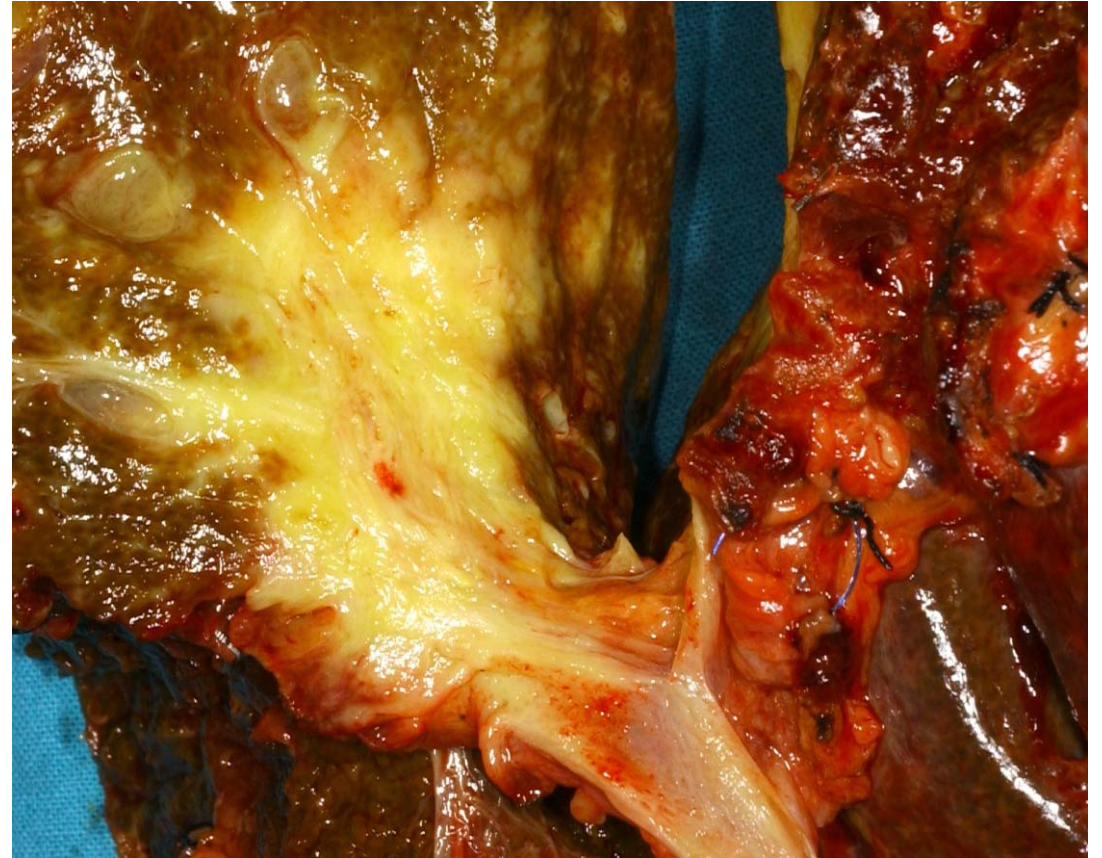
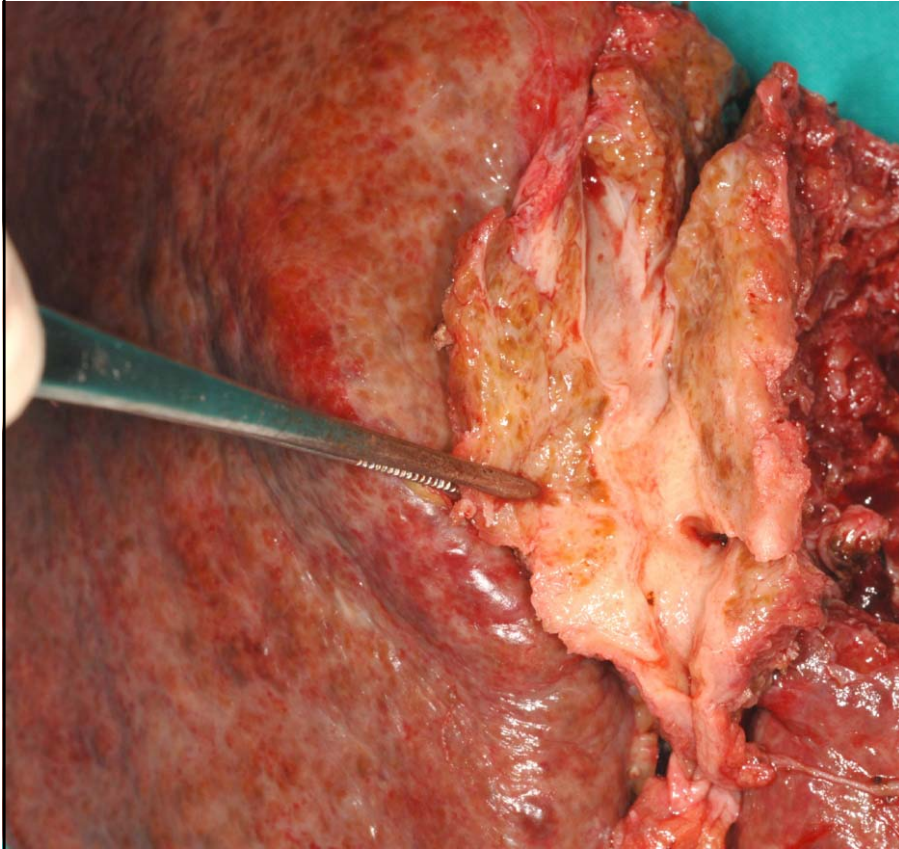
Nodular type



Nodular infiltrating type



Diffuse infiltrating



Clinical presentation, Laboratory findings, Imaging studies and Diagnosis



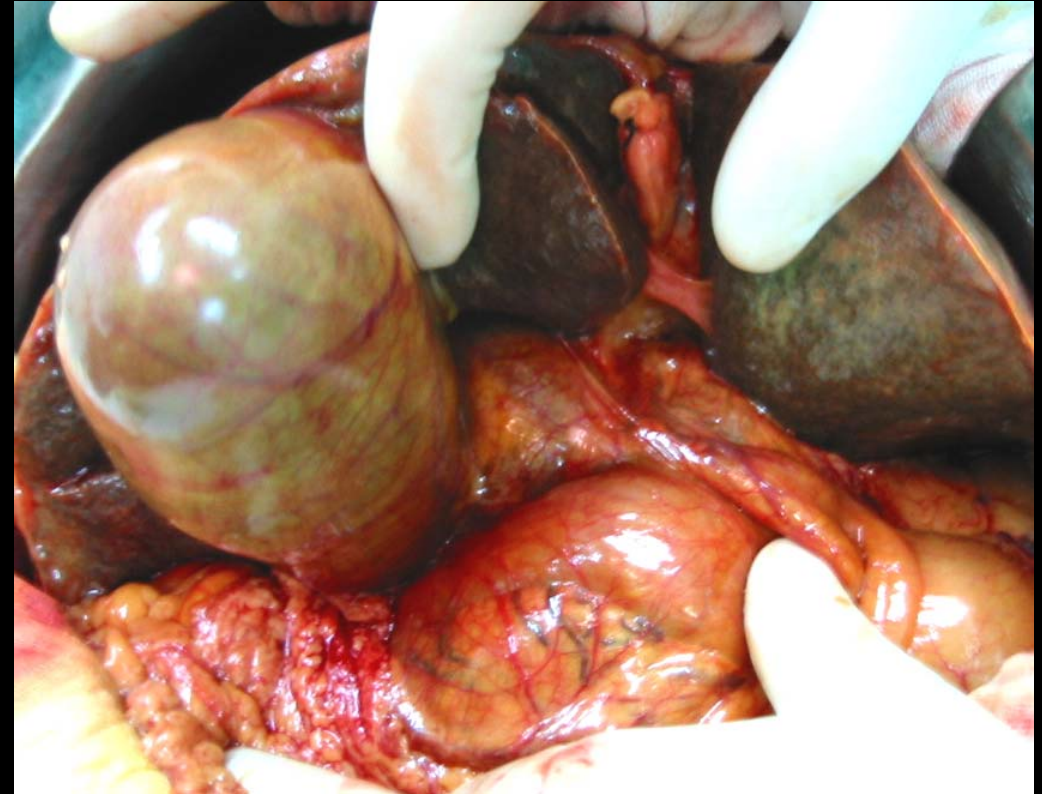
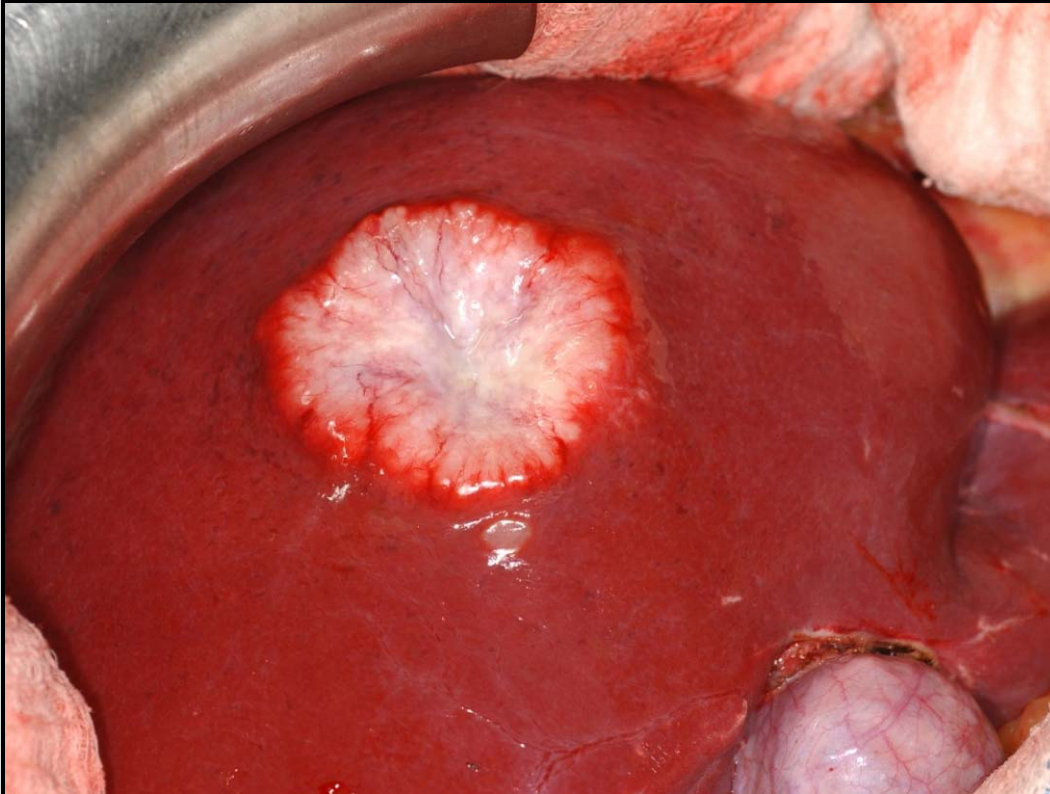
Clinical presentation

Non-jaundice

50%

Obstructive jaundice

50%



Intrahepatic / Extrahepatic Tumor

Clinical presentations

Intrahepatic type

- Palpable mass : RUQ / EPG ; Hepatomegaly
- Asymptomatic
- Pain : Shoulder pain / Back pain
- Dyspepsia / Anorexia / Weight loss
- Fever of Unknown origin

Dyspepsia = Most common nonspecific symptom
Incidental finding during check-up, common



Extrahepatic cholangiocarcinoma

- Obstructive Jaundice
- Palpable mass : RUQ / EPG ; Hepatomegaly
- Palpable mass : RUQ ; Hydrop gall bladder
- Acute acalculous cholecystitis

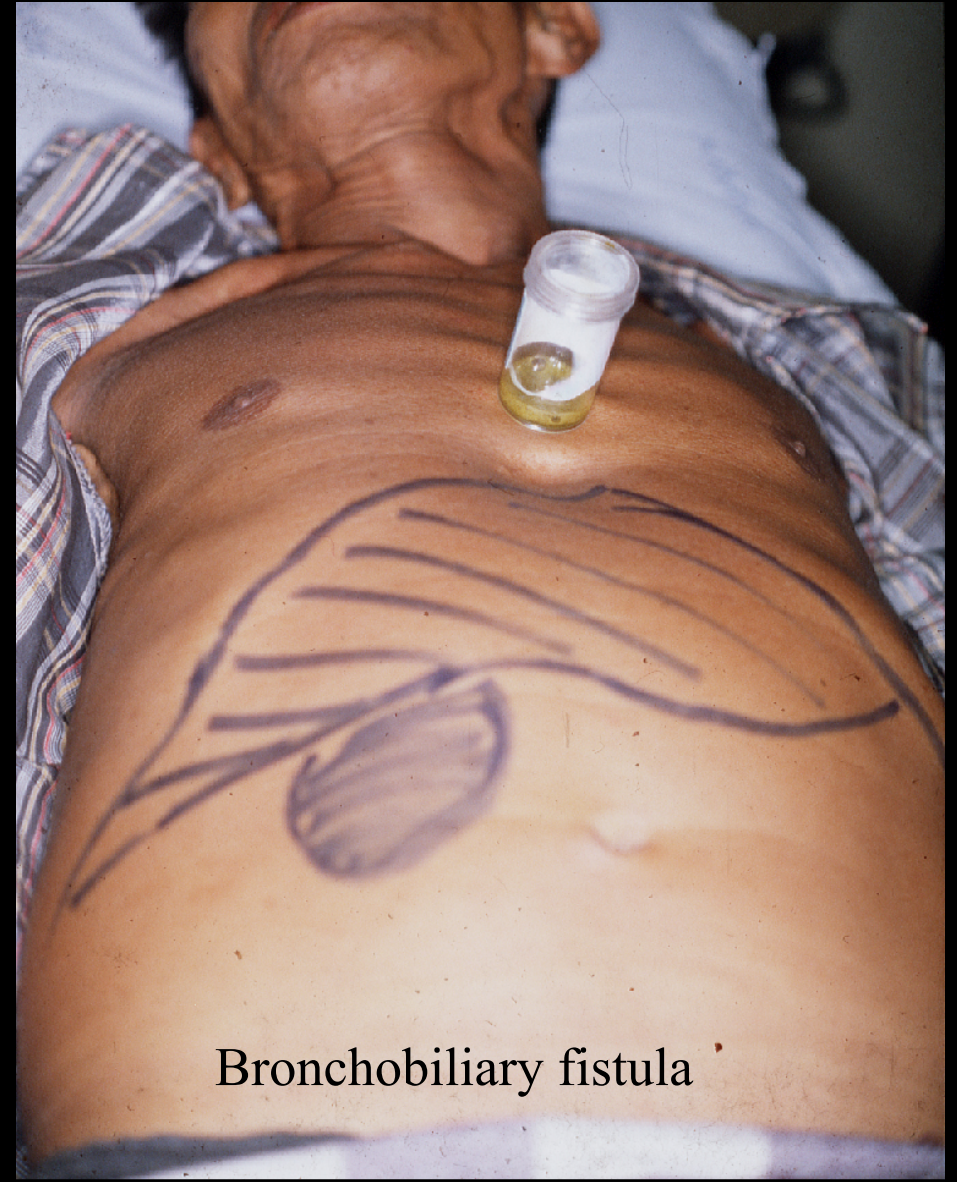
Dyspepsia = Most common nonspecific symptom

Pruritus = Most distressing symptom

**Obstructive Jaundice
from
Extrahepatic CHCA**



Classic Case



Bronchobiliary fistula



Investigation

Ultrasound and CT scan:
Mass, Location, Number,
Ductal dilatation, Nodes
Vascular involvement



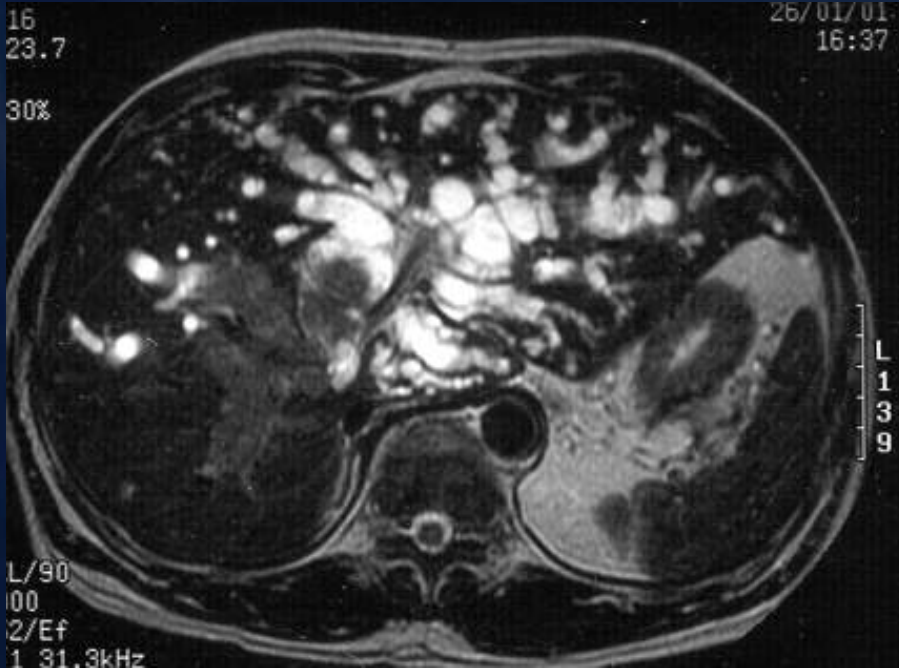
Ultrasound / CT scan / MRI (MRCP) :

Mass, Location, Number, Ductal dilatation, Nodes

Color Doppler, Angiography :

Vascular involvement





Investigation

MRI and MRCP:

Mass, Location, Number,
Ductal dilatation, Nodes
Vascular involvement



Investigation : Tumour Markers

Alkaline phosphatase 95 %

CEA 90 %

CA 19-9 40 %

is non-specific / no use for screening test



Staging



AJ CC Clinical staging

TNM Pathologic Classification of Intrahepatic CCA

| Stage | Tumor | Node | Metastasis |
|-------|-------|-------|------------|
| I | T1 | N0 | M0 |
| II | T2 | N0 | M0 |
| IIIA | T3 | N0 | M0 |
| IIIB | T4 | N0 | M0 |
| IIIC | Any T | N1 | M0 |
| IV | Any T | Any N | M1 |

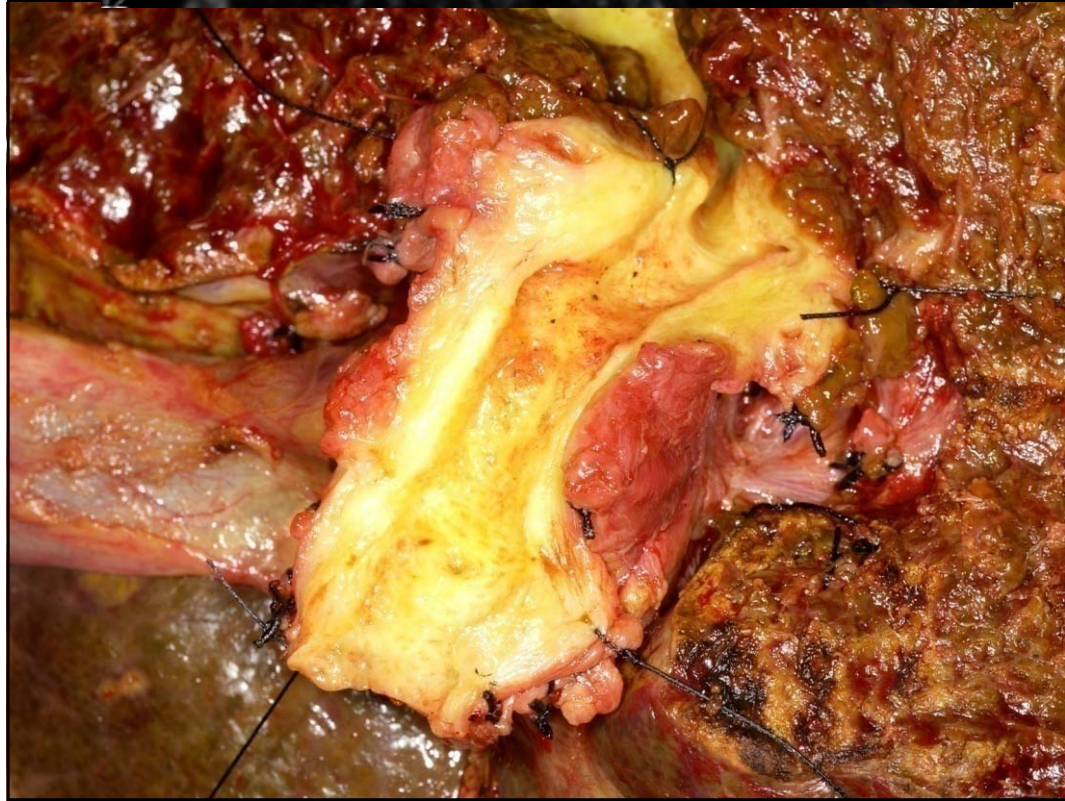
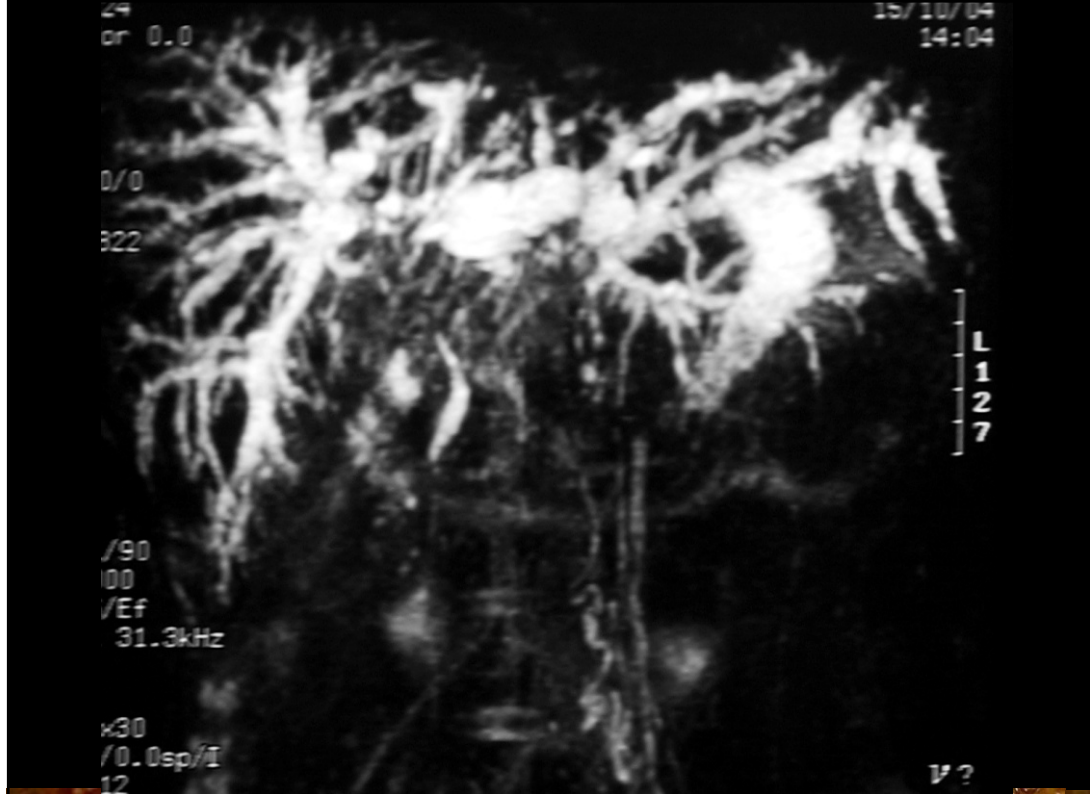
T1, solitary tumor without vascular invasion; T2, solitary tumor with vascular invasion or multiple tumors, none >5 cm; T3, multiple tumors >5 cm or tumor involving a major branch of the portal or hepatic vein(s); T4, tumor(s) with direct invasion of adjacent organs other than gallbladder or with perforation of visceral peritoneum; N0, no regional lymph node metastasis; N1, regional lymph node metastasis; M0, no distant metastasis; M1, distant metastasis.

AJ CC Clinical staging

TNM classification of Extrahepatic CCA

| Stage | Tumor | Node | Metastasis |
|-------|----------|-------|------------|
| 0 | Tis | N0 | M0 |
| IA | T1 | N0 | M0 |
| IB | T2 | N0 | M0 |
| IIA | T3 | N0 | M0 |
| IIB | T1 to T3 | N1 | M0 |
| III | T4 | Any N | M0 |
| IV | Any T | Any N | M1 |

Tis, carcinoma *in situ*; T1, tumor confined to the bile duct histologically; T2, tumor invades beyond the wall of the bile duct; T3, tumor invades the liver, gallbladder, pancreas, and/or unilateral branches of the portal vein (right or left) or hepatic artery (right or left); T4, tumor invades any of the following: main portal vein or its branches bilaterally, common hepatic artery, or other adjacent structures, such as the colon, stomach, duodenum, or abdominal wall; N0, no regional lymph node metastasis; N1, regional lymph node metastasis; M0, no distant metastasis; M1, distant metastasis.



MRCP and Surgical Pathology of extrahepatic (hilar) cholangiocarcinoma

Treatment options



Intrahepatic cholangiocarcinoma

Treatment Options

1. NO Surgical resection
2. Surgical resection

R_0 = No macro / microscopic residual

R_1 = microscopic tumor residual

R_2 = macroscopic residual



Intrahepatic cholangiocarcinoma

Surgical resection

Should be extensive

Radical and attempt for cure

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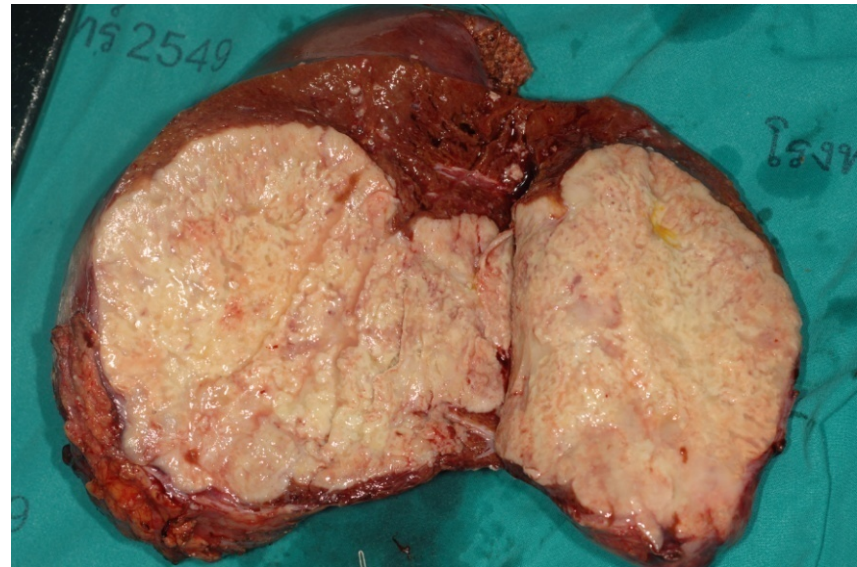
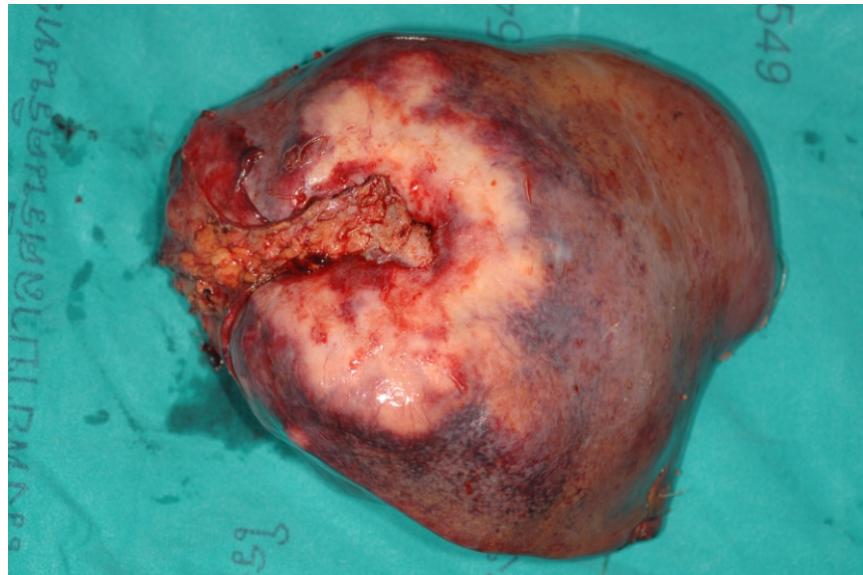
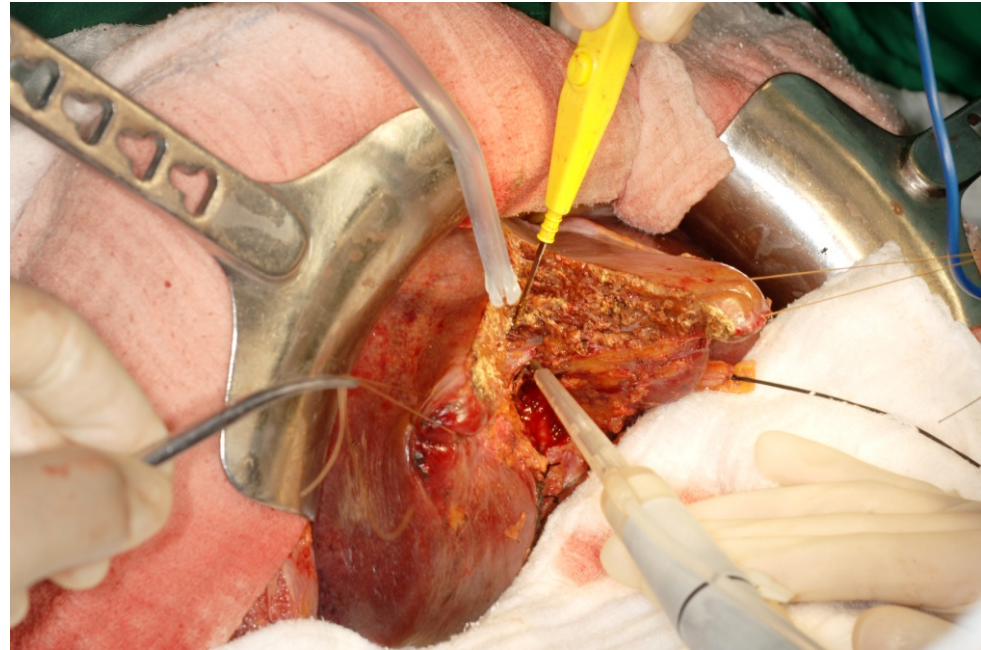
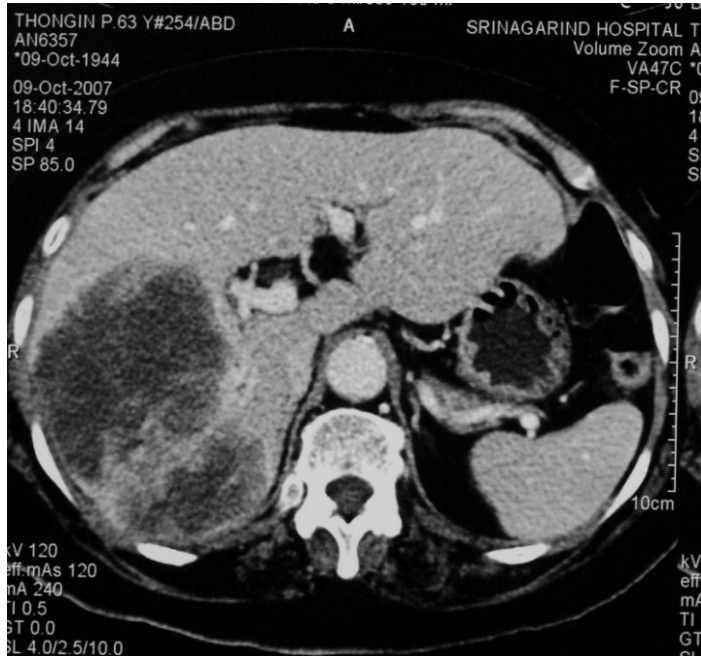


Intrahepatic cholangiocarcinoma

Surgical resection

- Complete (anatomical) resection whenever possible
- Removal of all regional nodes
- Skeletonization hepatoduodenal and hepatogastric ligament
- Reconstruction entero-biliary continuity indicated





Intrahepatic cholangiocarcinoma

Prognostic factors

- Surgical resection (RO>RI>RZ)
- Tumor free margin
- Hilar lymph nodes involvement
- Intraductal growth type
- Tumor staging



Treatment of extrahepatic cholangiocarcinoma

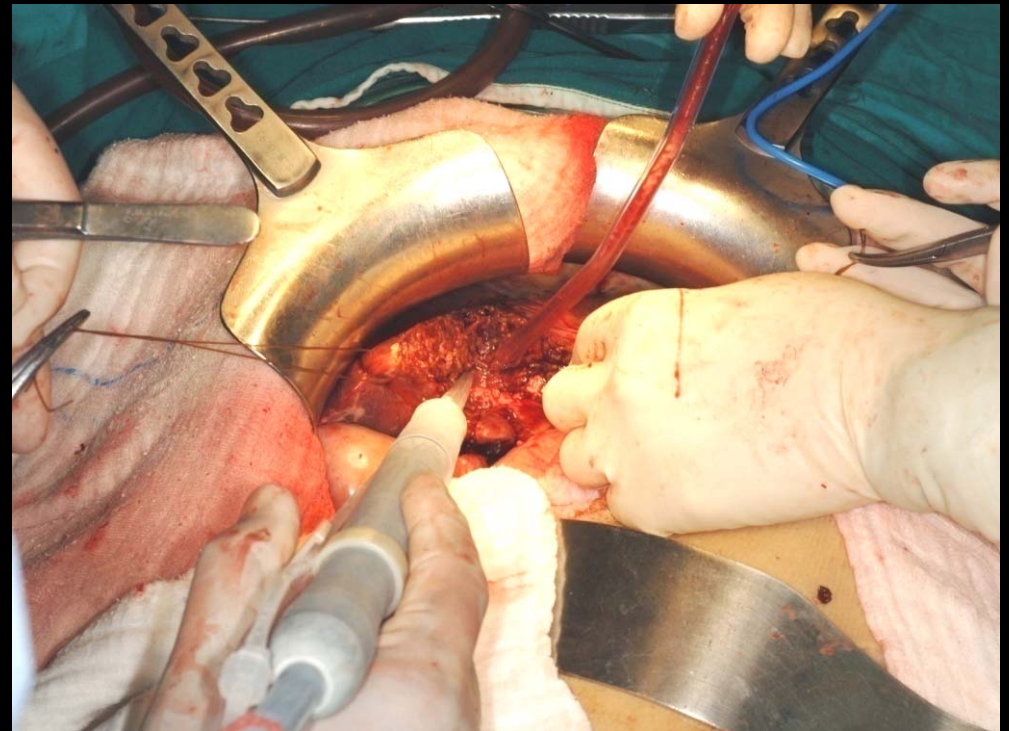
- curative
- palliative

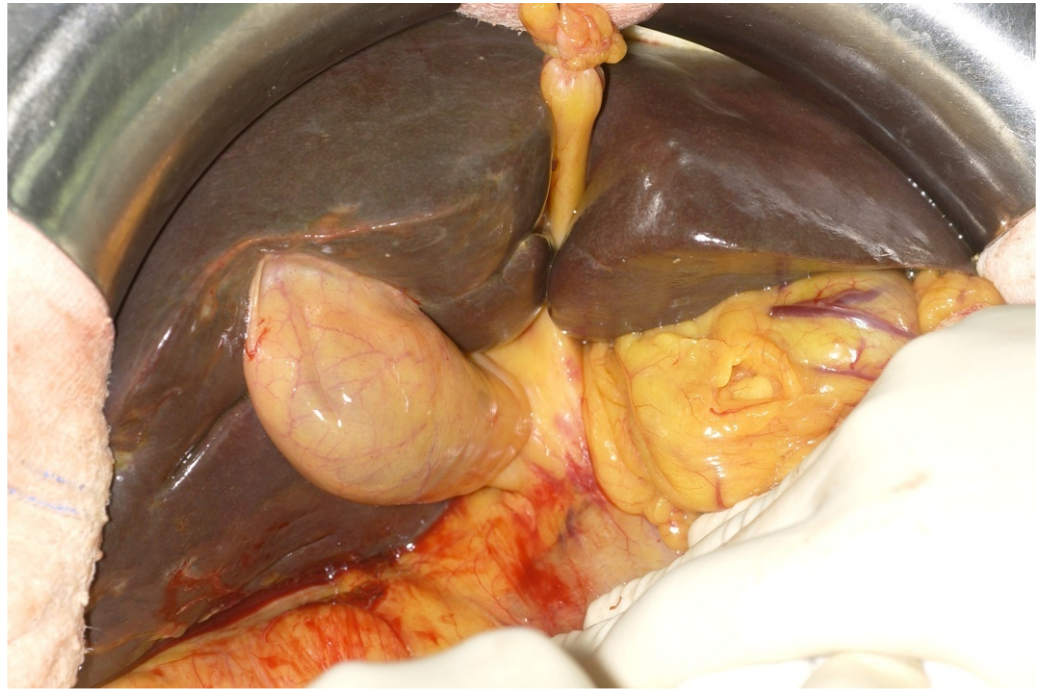
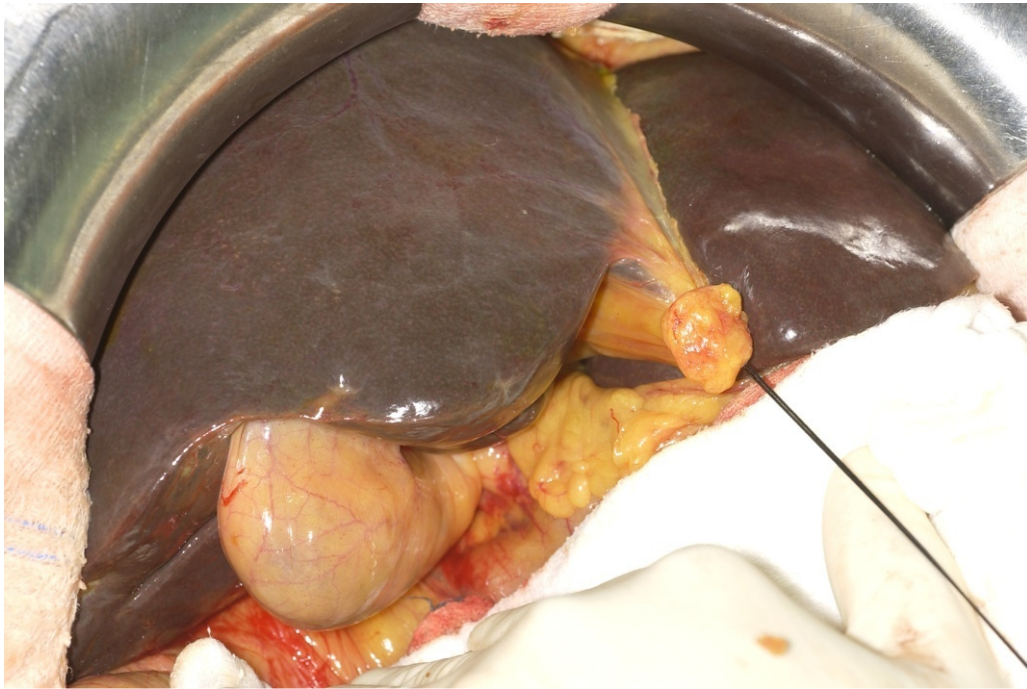
Hilar cholangiocarcinoma

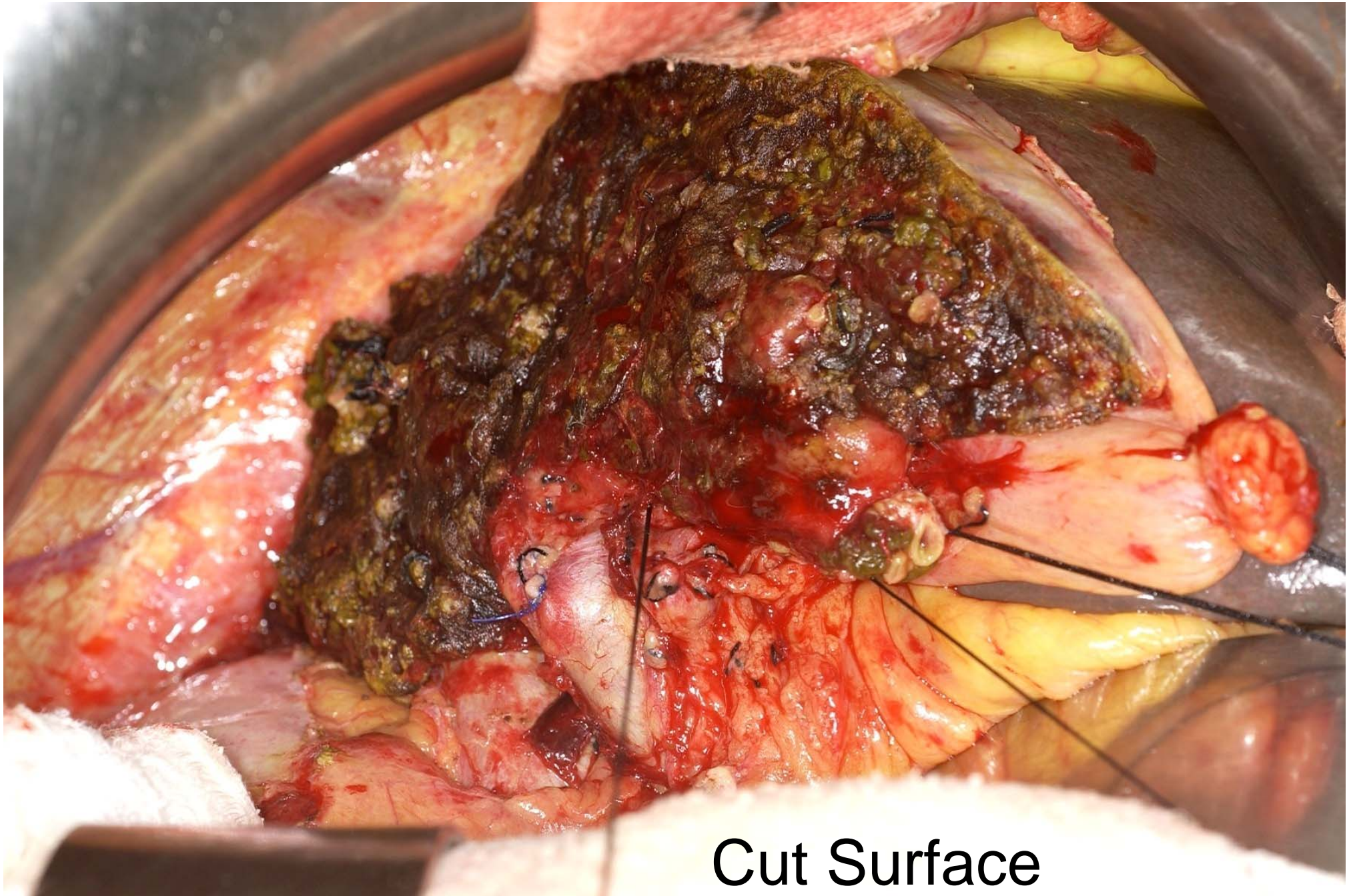
- hilar resection
- liver resection
- hepatoduodenal lymph node dissection
- caudate lobe resection
- vascular resection and reconstruction



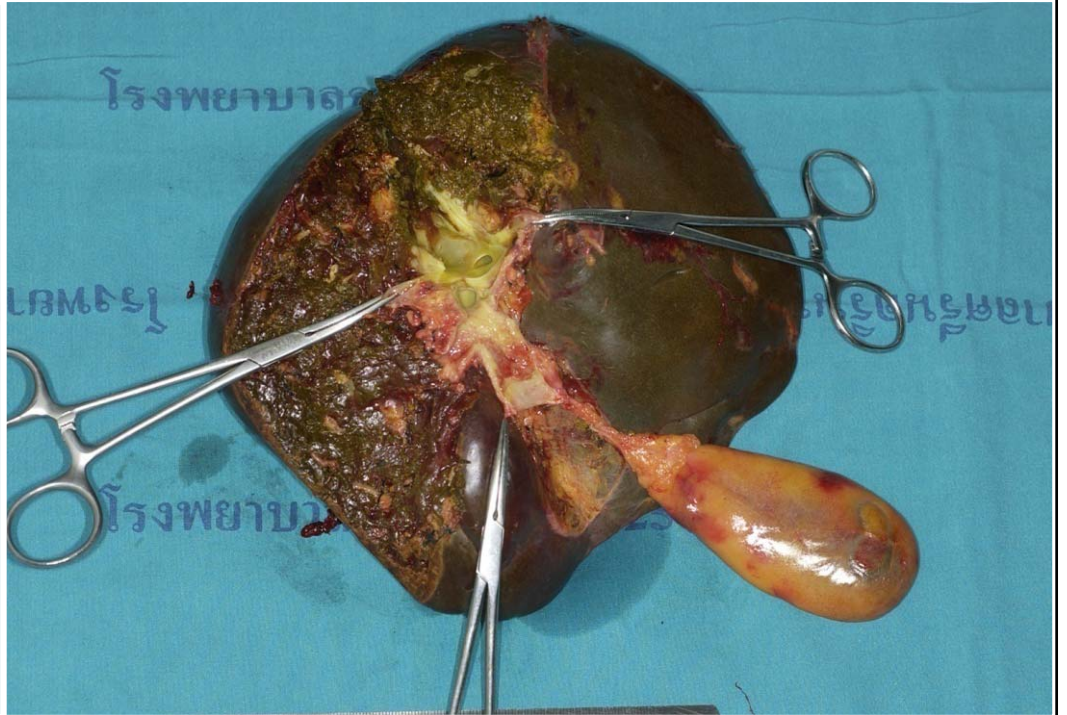
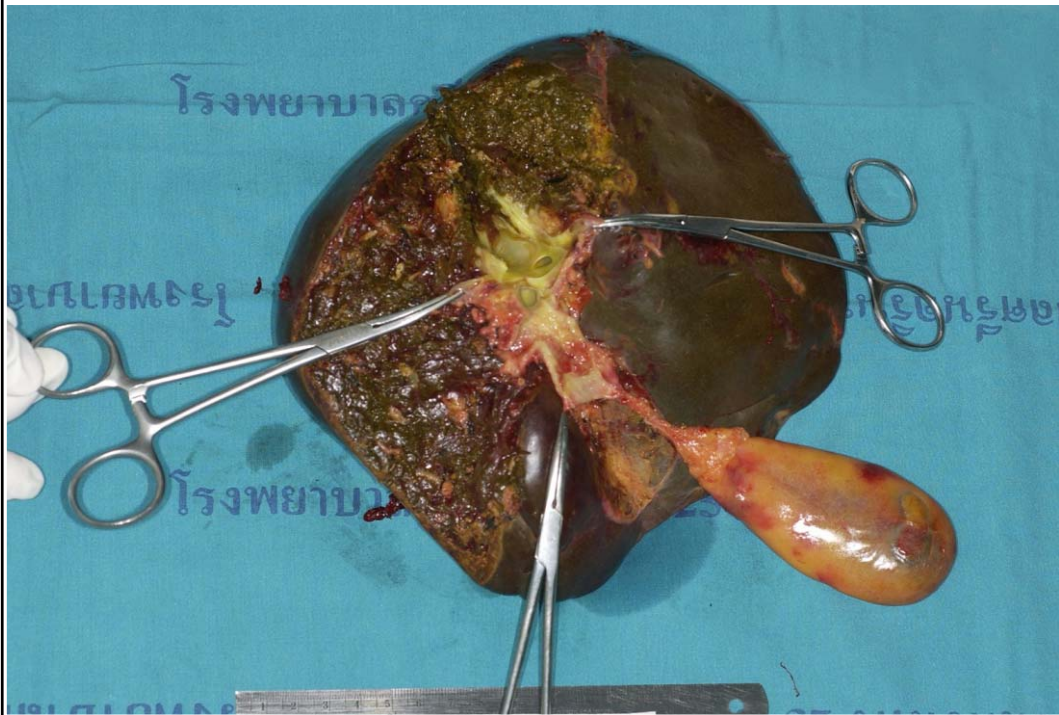
Exploration and potentially curative resection

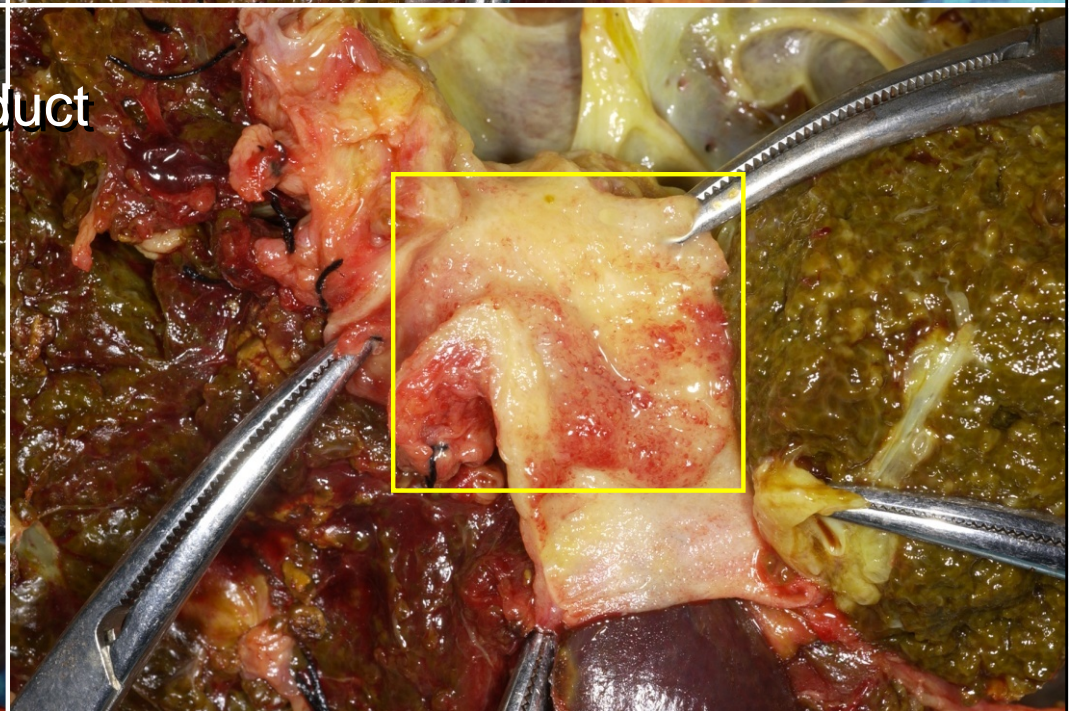
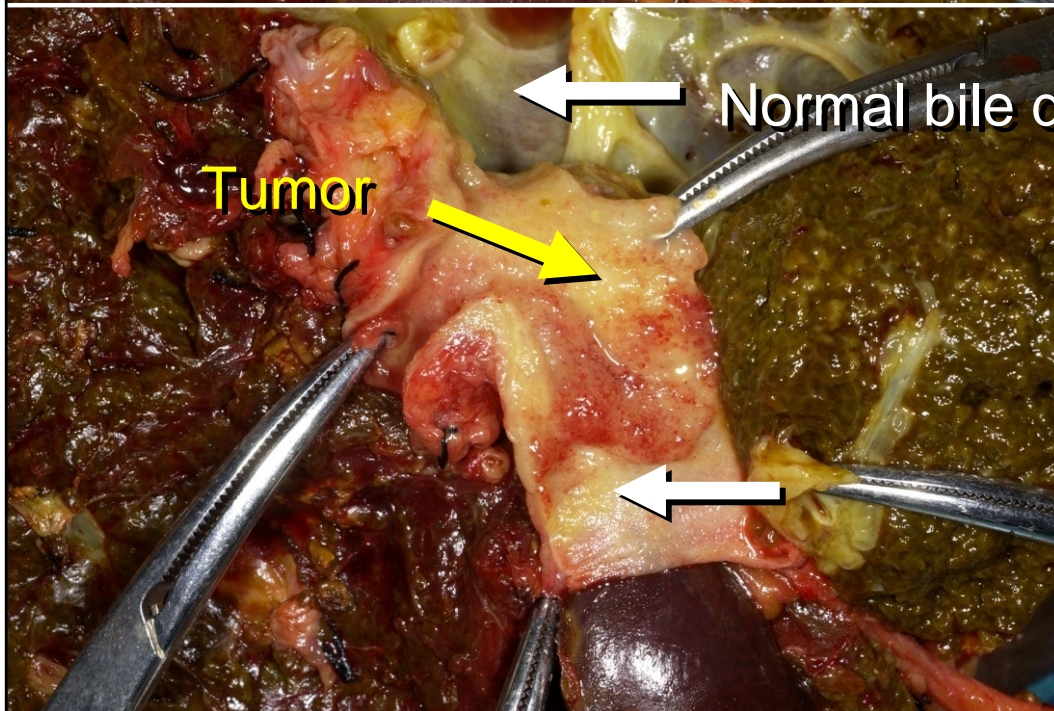
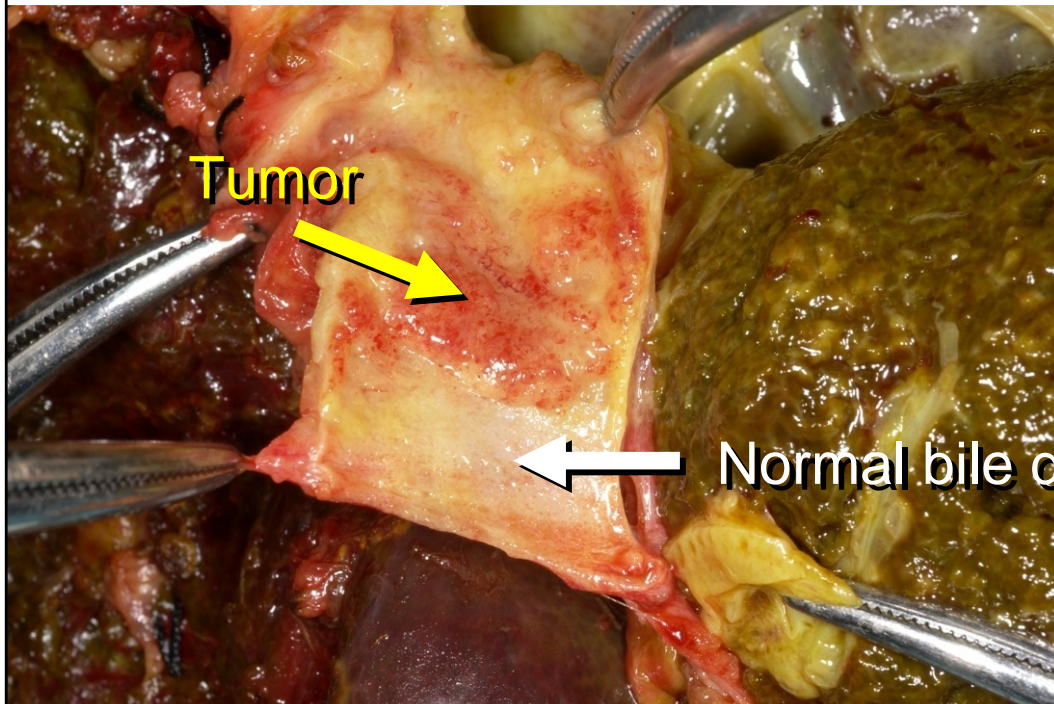






Cut Surface





Distal cholangiocarcinoma

- Pancreaticoduodenectomy
- Lymphadenectomy

Adjuvant therapy

- Chemotherapy
- Radiotherapy

Palliative treatment

- Surgery
- Endoscopic
- Chemotherapy
- Radiotherapy
- Ablative therapy

Modalities for palliative management

Biliary drainage procedures

- Surgical palliation
- Percutaneous biliary drainage
- Endoscopic stent

Adjuvant therapy

- Chemotherapy
- Radiotherapy
- Chemoradiotherapy
- Photodynamic therapy

Surgical palliation

- Biliary bypass
- Transtumoral tube placement
- Palliative resection

Endoscopic biliary drainage

Plastic stent

- Average duration 126 days
- Used when expected survival is 6 months or less

Metallic stent

- Used when expected survival more than 6 months

Complications: stent obstruction, cholangitis

1. Gerhards MF, et al. European Journal of Surgery 2001;167(4):274-80.
2. Davids PH, et al. Lancet 1992;340(8834-8835):1488-92.
3. Prat F, et al. Gastrointestinal Endoscopy 1998;47(1):1-7.

Additional therapy

- Radiotherapy
- Chemotherapy
- Chemoradiation
- Photodynamic therapy

Radiotherapy

- External beam radiotherapy (EBRT)
- ERBT with intraluminal brachytherapy
- ERBT with intraoperative radiotherapy (IORT)

Gerhards MF, van Gulik TM, Gonzalez GD, et al. Results of postoperative radiotherapy for resectable hilar cholangiocarcinoma. *World Journal of Surgery* 2003;27(2):173-9.

Pitt HA, Nakeeb A, Abrams RA, et al. Perihilar cholangiocarcinoma. Postoperative radiotherapy does not improve survival. *Annals of Surgery* 1995;221(6):788-97. .

External beam radiotherapy (EBRT)

- 42-50 Gy
- Neoadjuvant
- Adjuvant
- Controversial results

Pitt HA, et al. *Annals of Surgery* 1995;221(6):788-97.

Todoroki T, et al.. *International Journal of Radiation Oncology Biology Physics* 2000;46(3):581-7.

ERBT with intraluminal brachytherapy

Catheters loaded with Iridium 192

- across the hepaticojejunal anastomosis
- Percutaneous route

2-year survival 10-20%

EBRT

High complication ; stenosis, cholangitis
Failed to provide survival advantage

1. Gerhards MF, et al. World Journal of Surgery 2003;27(2):173-97.

2. Foo ML, et al. International Journal of Radiation Oncology Biology Physics 1997;39(4):929-35.

ERBT with intraoperative radiotherapy (IORT)

Single large dose of radiation (27.5-35 Gy)

Improvement of 5-year survival

| | |
|---------------------|--------|
| Resection alone | 10.5 % |
| Resection+EBRT&IORT | 33.9 % |

Chemotherapy

- Advanced hilar cholangiocarcinoma
- Phase II trials
- No large Phase III
- Retrospective nature
- Heterogeneous patient population
- Differing surgical management

1.Kubicka S, Rudolph KI, Tietze MK, et al. Phase II study of systemic gemcitabine chemotherapy for advanced unresectable hepatobiliary carcinomas. *Hepatogastroenterology* 2001;48(39):783-9.

2.Raderer M, Hejna MH, Valencak JB, et al. Two consecutive phase II studies of 5-fluouracil/ leucovorin / mitomycin C and of gemcitabine in patients with advanced biliary cancer. *Oncology* 1999;56(3):177-80.

Chemotherapy

5-FU+cisplatin

- response rate 20-40 %

Ellis P, et al. *Cancer* 1995;31A(10):1594-8.

Sanz-Altamira PM, et al. *Cancer* 1998;82(12):2321-5.

Taieb J, et al. *Annals of Oncology* 2002;13(8):1192-6.

Chemotherapy

Gemcitabine

- response rate 20-30 %

Kubicka S, et al. Hepatogastroenterology 2001;48(39):783-9.

Tsavaris N, et al. Investigational New Drugs 2004;22(2):193-8.

Raderer M, et al. Oncology 1999;56(3):177-80.

Chemoradiation

Brachytherapy and ERBT with 5-FU

Benefit

1. McMasters KM, Tuittle TM, Leach SD, et al. Neoadjuvant chemoradiation for extrahepatic cholangiocarcinoma. *American Journal of Surgery* 1997;174(6):605-8.

2. Morganti AG, Trodella L, Valentini V, et al. Combined modality treatment in unresectable extrahepatic biliary carcinoma. *International Journal of Radiation Oncology Biology Physics* 2000;46(4):913-9.

Photodynamic therapy

PDT

- Photosensitizer
- Oxygen derived free radical
- Cell death

Improved biliary drainage and quality of life

1.Gores GJ, et al. Gastroenterology 2003;(125):1536-8.

2.Wiedmann M, et al. Cancer 2003;97(11):2783-90.

3.Ortner ME, Caca K, Berr F, et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. Gastroenterology 2003;125(5):1355-63.

Results and survival



Surgical pathology type 138 case

| | |
|-------------|-----|
| Type I | 116 |
| Type II-III | 10 |
| Type IV | 12 |

T. Uttaravichien et al. Intrahepatic Cholangiocarcinoma in Thailand.
J Hepatobiliary Pancreat Surg 1999;6:128-135

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Staging

Intrahepatic cholangiocarcinoma

| | |
|-----------|----|
| Stage III | 10 |
| Stage IVA | 22 |
| Stage IVB | 84 |

T. Uttaravichien et al. Intrahepatic Cholangiocarcinoma in Thailand.
J Hepatobiliary Pancreat Surg 1999;6:128-135

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Prognosis

Intrahepatic Cholangiocarcinoma

Stage III (mean \pm SE, day) 1039 \pm 201

Stage IVA (mean \pm SE, day) 773 \pm 123

Stage IVB (mean \pm SE, day) 382 \pm 60

T. Uttaravichein et al. Intrahepatic Cholangiocarcinoma in Thailand. J Hepatobiliary Pancreat Surg 1999;6:128-135

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Results and long-term Survival after Resection of extrahepatic cholangiocarcinoma

| | |
|------------------|------------------|
| Morbidity | 30% - 50% |
| Mortality | < 10% |

M.I.D' Angolica et al:

Resectable Hilar Cholangiocarcinoma Surg Today 2004;34:885-890.

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Extrahepatic cholangiocarcinoma

5 – year survival Rates 9% - 28 %

- Margin - negative resection 24% - 43%
- Margin - positive resection 0% - 15%

M.I.D' Angolica et al:
Resectable Hilar Cholangiocarcinoma
Surg Today 2004;34:885-890.

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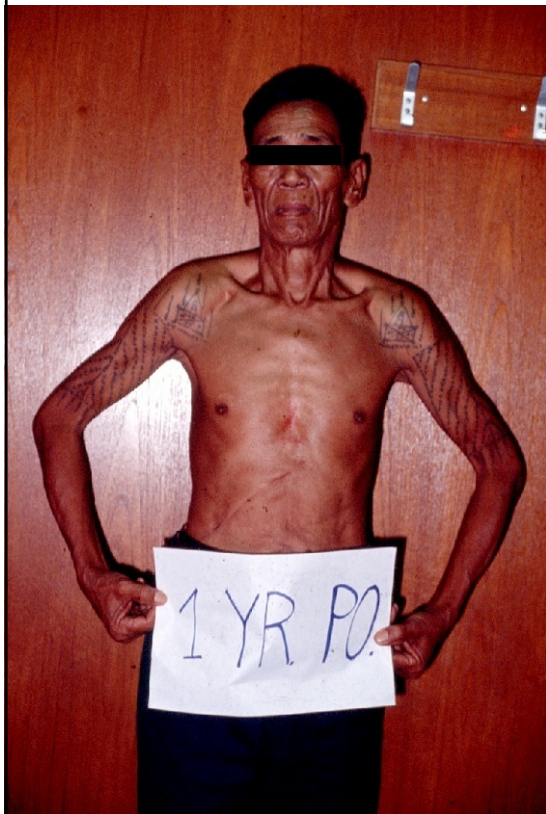
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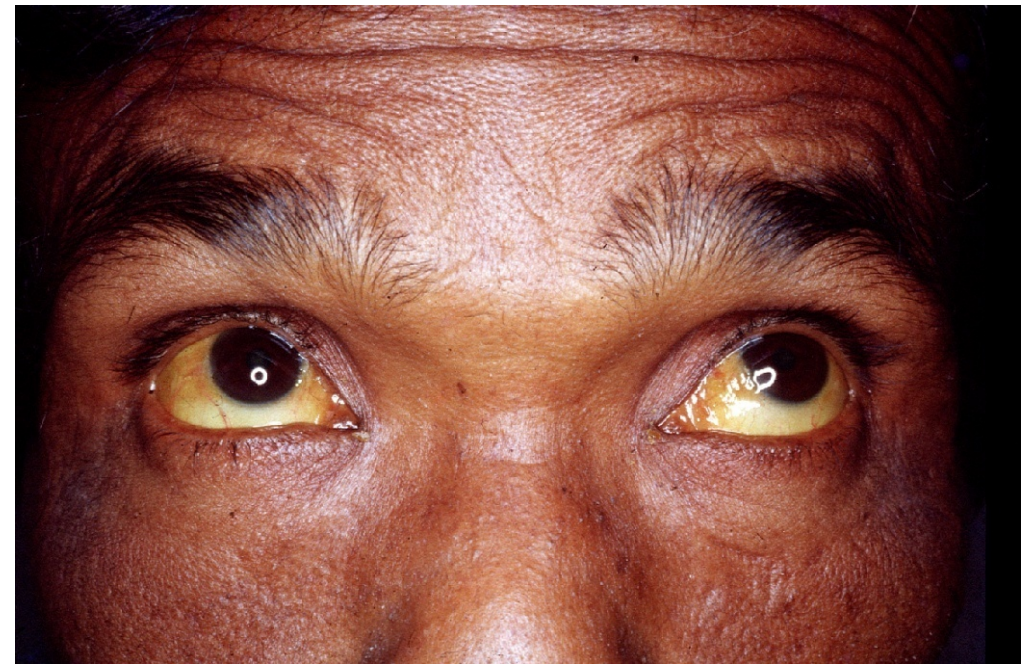
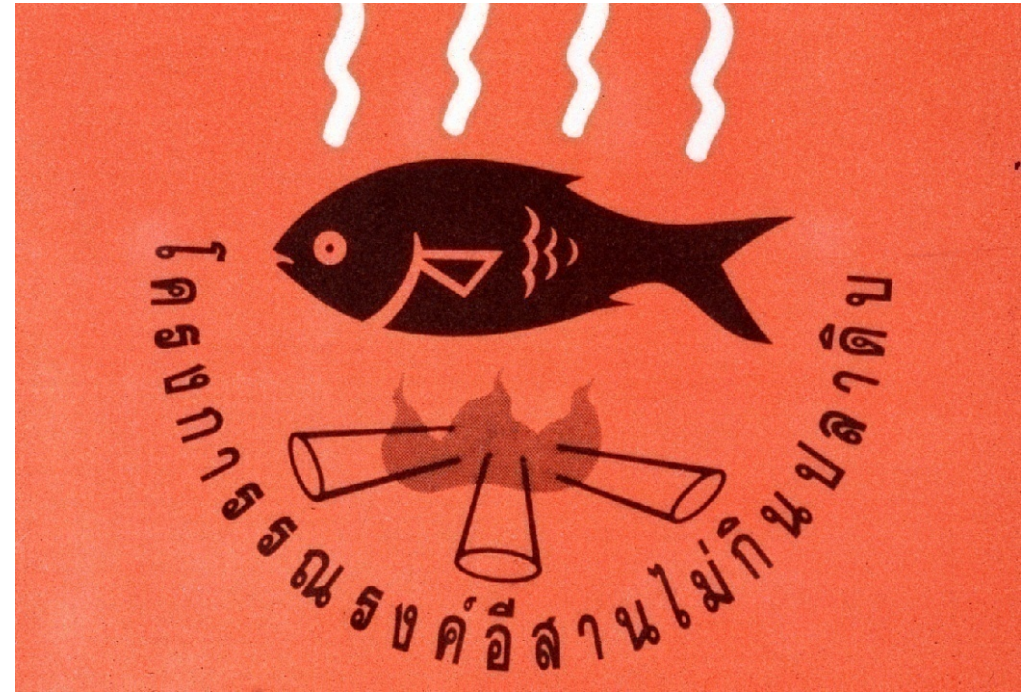


CONCLUSION

Surgery is the only chance to cure, but additional therapy must be investigated for improving the survival and quality of life.

Prevention and early detection campaign should be done along with the treatment strategy.







THANK YOU