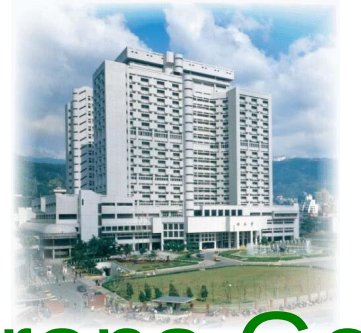

Taipei Veterans General Hospital Practices Guidelines for

Biliary tract cancer

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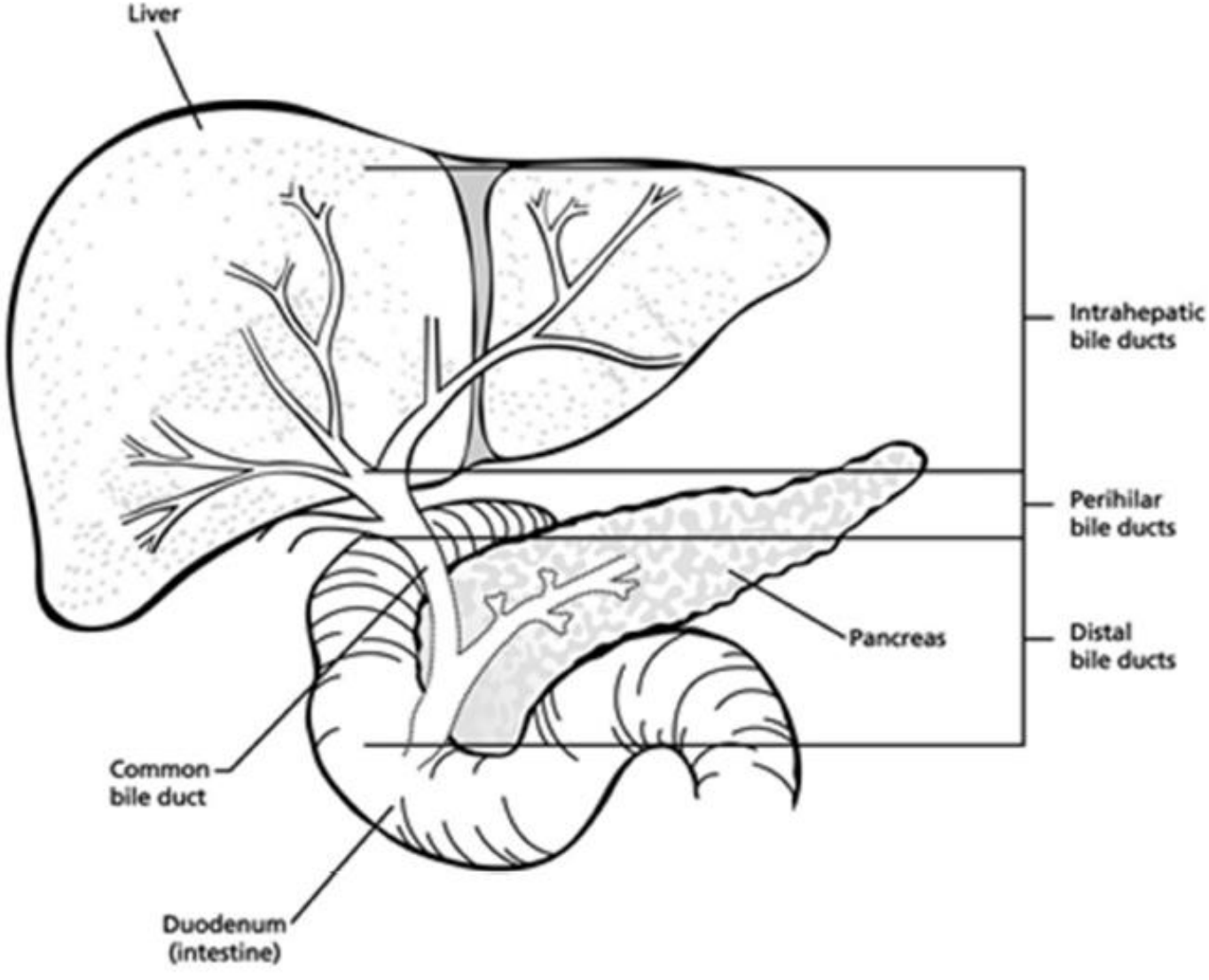
Biliary tract cancer

Biliary tract cancers by location



Multidisciplinary Team

- **Surgical Oncologist**
- **Gastroenterologist**
- **Medical Oncologist**
- **Radiation Oncologist**
- **Pathologist**
- **Diagnostic Radiologist**
- **Nurses (for specialized)**
- **Social Workers**
- **Dietitian (for Nutrition Support)**

Biliary tract cancer

膽道癌 多專科醫療團隊

團隊召集人：陳明晃醫師　　團隊副召集人：　雷浩然醫師

核心成員	非核心成員
專科（或次專科）別或領域別名稱	專科（或次專科）別或領域別名稱
胃腸科 黃怡翔主任、蘇建維醫師、李懿宬醫師、李沛璋醫師	家醫部 林明慧醫師、楊宛伶護理師
一般外科 周嘉揚主任、雷浩然醫師、周書正醫師、高義筑醫師 移植外科 劉君恕主任、夏振源醫師	一般外科 石宜銘醫師、王心儀醫師、石博威醫師、陳世欽醫師 移植外科 林釀呈醫師、陳正彥醫師
腫瘤醫學部(藥物治療科) 趙毅部長、陳明晃醫師、洪逸平醫師、陳三奇醫師、姜乃榕醫師	腫瘤醫學部(放射腫瘤) 藍耿立醫師、黃品逸醫師
腫瘤醫學部(放射腫瘤科) 賴宜君醫師、吳元宏醫師、康鈺玫醫師	放射線部 黃宣恩醫師、陳蓉萱醫師
放射線部 李潤川主任、柳建安醫師、邱乃祈醫師	藥劑部 趙凡琇藥師
病理科 楊清越醫師	營養部 吳家蕙營養師
個案管理師 林宜演、陳怡岑護理師	社工室 蕭美華社會工作師
	家醫科 張心慧 安寧共照師

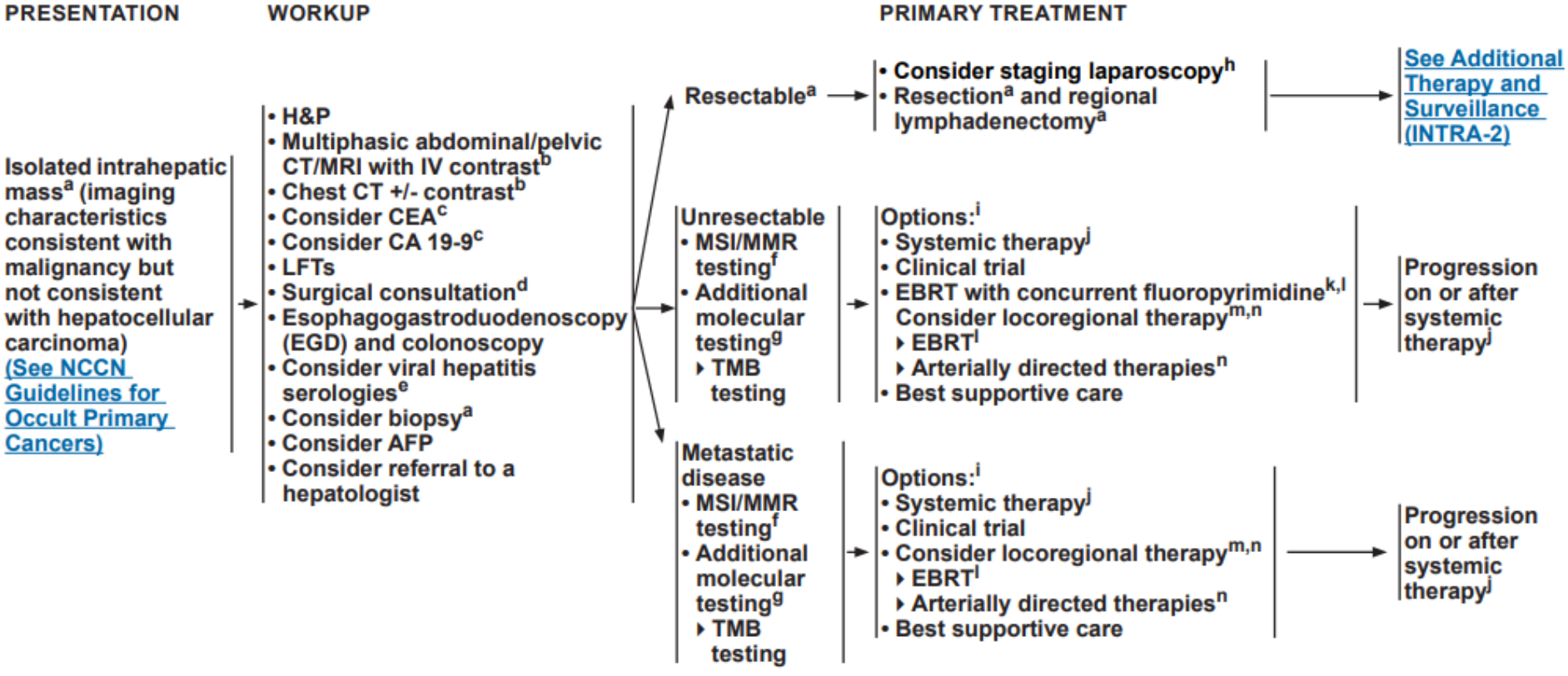
Intrahepatic Cholangiocarcinoma

Pretreatment work-ups-Intrahepatic cholangiocarcinoma

- **History and physical exam**
- **CBC, PT/APTT and chemistry profile**
- **Abdominal CT/MRI (with contrast dynamic study)**
- **Chest CT**
- **Tumor markers: CEA, CA199, AFP**
- **Hepatitis markers (HBV and HCV)**
- **Optional studies**
  - Whole body bone scan (if with symptom or advanced stage)
  - Cholangiography, including MRCP and ERCP with spy glass for biopsy
  - Cardiac function (cardiac ultrasound and/or ejection fraction + wall motion)
  - Pulmonary function test (if age > 65 and prepare for surgery)
  - Liver function test
  - Assessment of hepatic reserve (ICG test, 3D CT reconstruction)
  - UGI endoscopy and colonoscopy
  - PET CT (Emerging evidence indicates that may be useful to detect regional LN and distant metastasis)

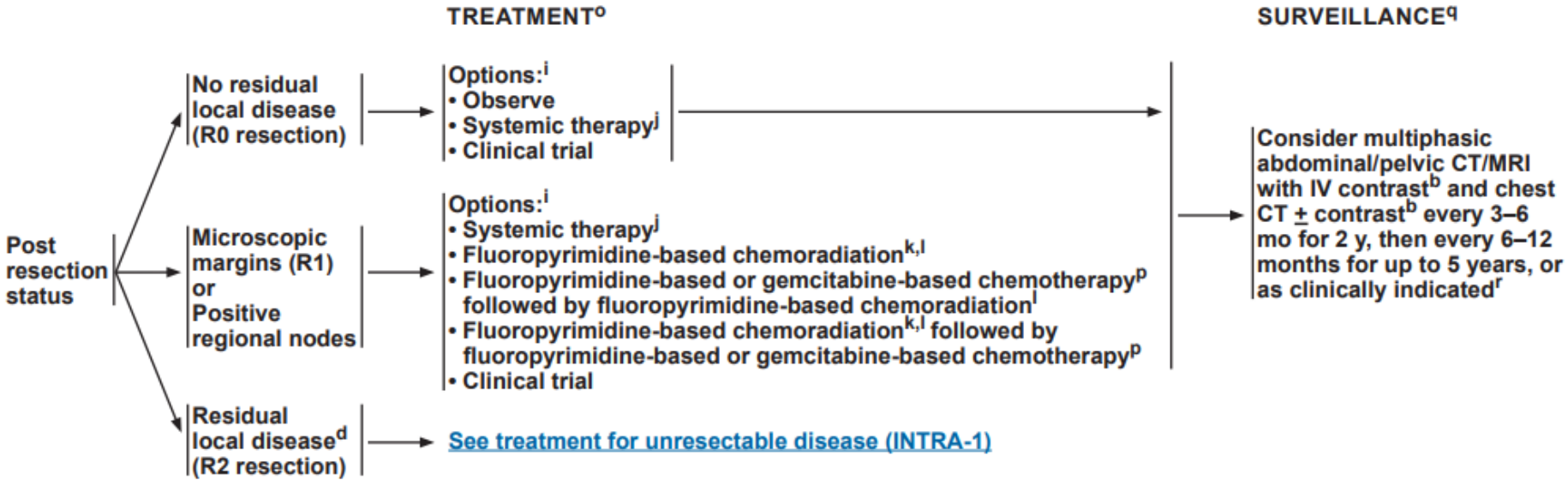
Intrahepatic Cholangiocarcinoma

Treatment Stratification of intrahepatic cholangiocarcinoma(IHCC)



Local regional therapy includes RFA, TACE, DEB-TACE, yttrium-90 microspheres and photodynamic therapy (PDT).

Intrahepatic Cholangiocarcinoma



Adjuvant Therapy[b,2]

Preferred Regimens

- Capecitabine[c,3] (category 1)

Other Recommended Regimens

- 5-fluorouracil + oxaliplatin
- Capecitabine + oxaliplatin
- Gemcitabine + capecitabine
- Gemcitabine + cisplatin
- Capecitabine + cisplatin (category 3)
- Single agents:
  - 5-fluorouracil
  - Gemcitabine

Useful in Certain Circumstances

- None

Intrahepatic Cholangiocarcinoma

Guidelines for surgical apporach

PS 0-2, CTP class A-B
without extrahepatic metastasis
Without lymph node metastasis beyond porta hepatis

Single tumor

Resection

Multiple tumors

Unilateral lobe location

Bilateral lobe location with limited distribution

Child A, PS 0 ,Consider resectable

Evaluate resectability

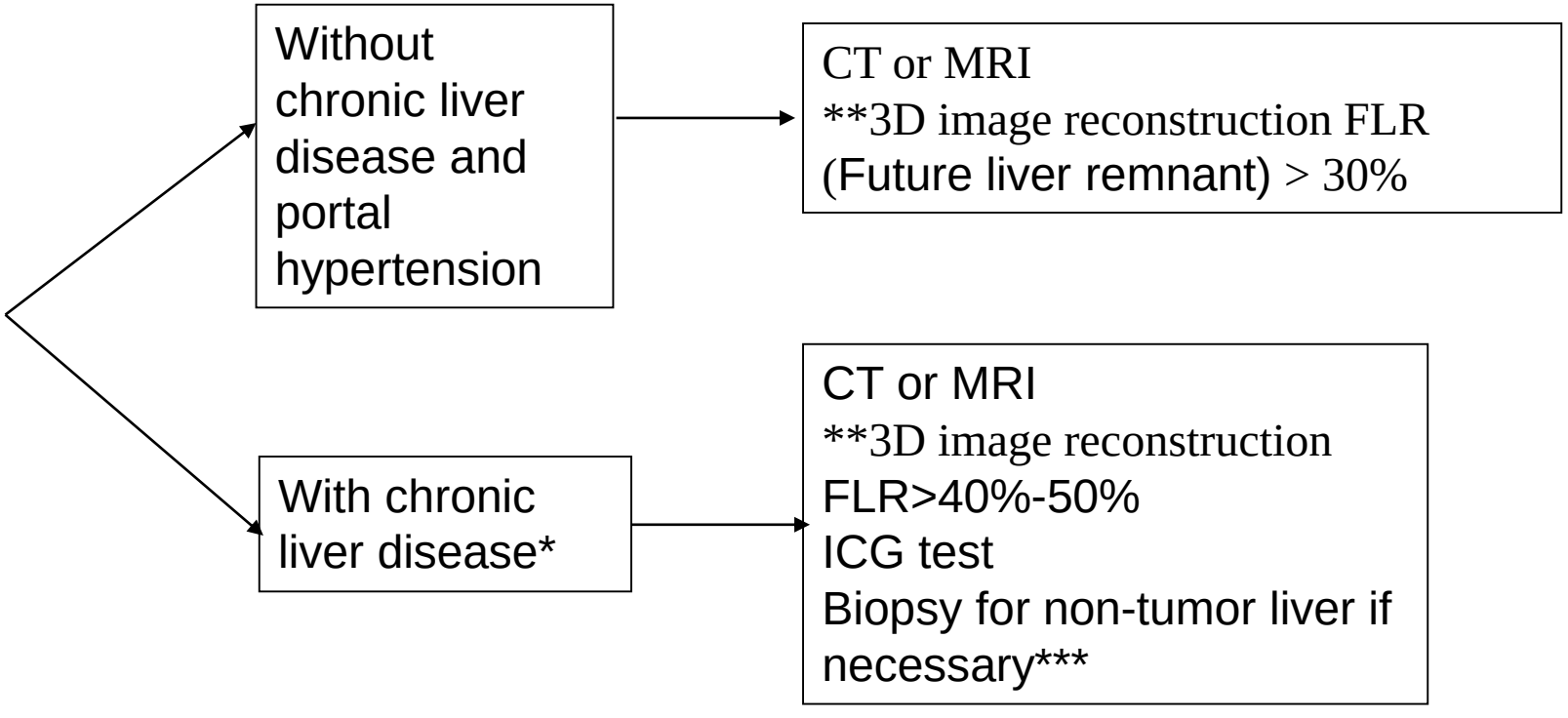
Portal invasion

Unilateral side portal invasion, without extrahepatic metastasis, tumors are confined to single lobe

Child A, PS 0, Consider resectable

Evaluate resectability

Evaluate Resectability of Intrahepatic Cholangiocarcinoma



Consider portal vein embolization if future liver remnant volume is not sufficient

* Chronic liver disease refers to HBV infection, HCV infection, cirrhosis or alcoholic liver disease

** Optional in some major resection cases to evaluate remnant liver volume

** If severe steatosis or steatohepatitis was suspected, serum AST or ALT level > 2X upper normal limit, or major liver resection is planed

Recommend for liver hilum lymph node dissection

- **Liver hilum lymph node dissection for accurate staging is recommend.**
- **Patients with following clinical characteristics are strongly suggested for hilum lymph node dissection.**
  - Enlarged lymph node on pre-operative image study
  - Multiple tumors
  - Central location
  - Elevated serum CEA or CA19-9 level
  - Tumor larger than 5cm
  - Periductal infiltrative type on gross

TNM Staging System: UICC/AJCC 2010 8th Edition of Intrahepatic cholangiocarcinoma

T category

- Tx: primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ (intraductal tumor)
- T1: Solitary tumor without vascular invasion
- T1a: Solitary tumor ≤ 5 cm without vascular invasion
- T1b: Solitary tumor > 5 cm without vascular invasion
- T2: Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion
- T3: tumor perforating the visceral peritoneum
- T4: Tumor involving local extrahepatic structures by direct invasion

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis present

T	N	M	Stage
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2	N0	M0	II
T3	N0	M0	IIIA
T4	N0	M0	IIIB
Any T	N1	M0	IIIB
Any T	Any N	M1	IV

Intrahepatic Cholangiocarcinoma

Principle of surgery-1

- **Pre-operative liver biopsy is not always necessary before proceeding with a definitive potentially curative resection. A suspicious mass on imaging in the proper clinical setting should be treated as malignant.**
- **Diagnostic laparoscopy to ruled out unresectable disseminated disease should be considered.**
- **Initial exploration should assess for multi-focal hepatic disease, lymph node metastases and distant metastases. Lymph node beyond the porta hepatis and distant metastatic disease contraindicate resection.**
- **Hepatic resection with negative margin is the goal of surgical therapy. While major resections are often necessary, wedge resections and segmental resections are all appropriate given that a negative margin can be achieved.**
- **A portal lymphadenectomy is reasonable as this provides relevant staging information**
- **Multi-focal liver disease is generally representative of metastatic disease and is a contraindication to resection, In highly selected cases with limited multi-focal disease resection can be considered .**
- **Gross lymph node metastases to the porta hepatis portend a poor prognosis and resection should only be considered in highly selected cases.**
-

Intrahepatic Cholangiocarcinoma

Principle of surgery-2

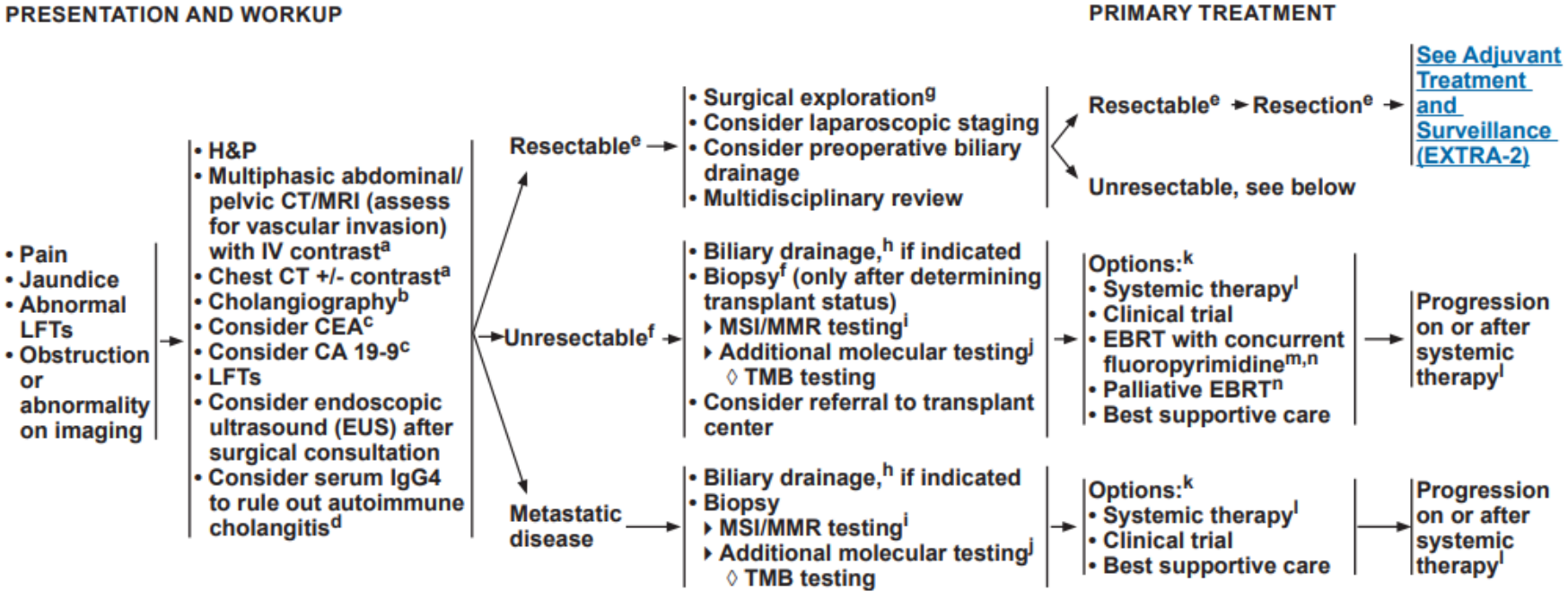
- There was no evidence of effective pre-operative neoadjuvant chemotherapy.
- If initially unresectable disease is converted to resectable disease by chemotherapy, liver resection can be considered.
- No evidence of standard adjuvant chemotherapy regiment, but patients should be encouraged to enroll on randomized trials.
- For recurrence after resection, re-resection for resecatble tumor should be considered.
- Liver transplant is not a standard treatment for intrahepatic cholangiocarcinoma. In early stage disease without lymph node, vascular and bile duct involvement but unresectable due to liver cirrhosis, patients may benefit from liver transplant.
- Currently, the criteria should be limited to the tumor within Milan criteria.

Extrahepatic Cholangiocarcinoma

Pretreatment work-ups-Extrahepatic cholangiocarcinoma

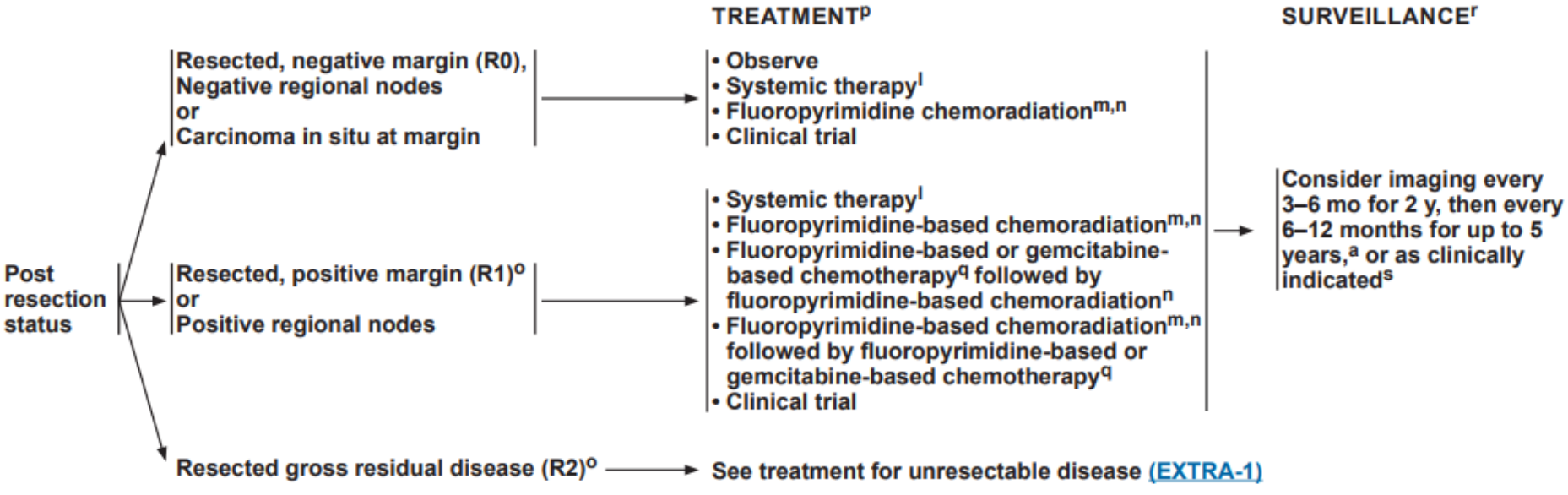
- **History and physical exam**
- **CBC, PT/APTT and chemistry profile**
- **Abdominal CT/MRI (with contrast dynamic study)**
- **Chest CT**
- **Tumor markers: CEA, CA199**
- **Hepatitis markers (HBV and HCV)**
- **Optional studies**
  - Whole body bone scan (if with symptom or advanced stage)
  - Cholangiography, including MRCP and ERCP with spy glass for biopsy
  - Cardiac function (cardiac ultrasound and/or ejection fraction + wall motion)
  - Pulmonary function test (if age > 65 and prepare for surgery)
  - Liver function test
  - Assessment of hepatic reserve (ICG test, 3D CT reconstruction)
  - UGI endoscopy and colonoscopy
  - PET CT (Emerging evidence indicates that may be useful to detect regional LN and distant metastasis)

Treatment Stratification of Extrahepatic cholangiocarcinoma



Extrahepatic Cholangiocarcinoma

Additional Tx and Surveillance



Adjuvant Therapy[b,2]

Preferred Regimens

- Capecitabine[c,3] (category 1)

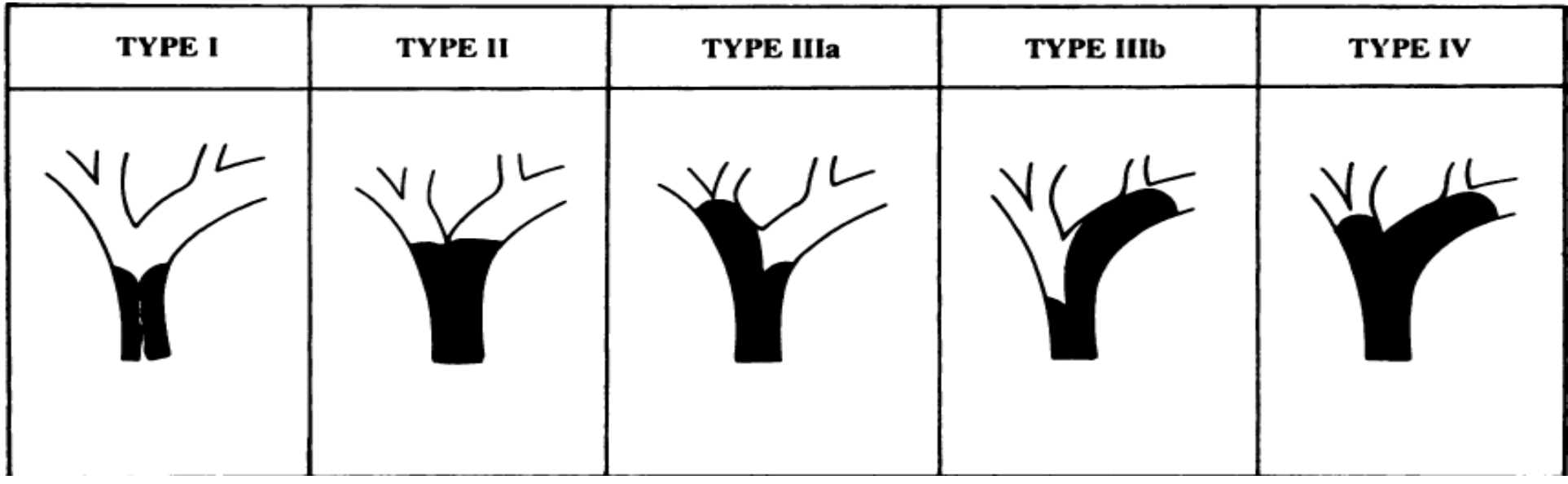
Other Recommended Regimens

- 5-fluorouracil + oxaliplatin
- Capecitabine + oxaliplatin
- Gemcitabine + capecitabine
- Gemcitabine + cisplatin
- Capecitabine + cisplatin (category 3)
- Single agents:
  - 5-fluorouracil
  - Gemcitabine

Useful in Certain Circumstances

- None

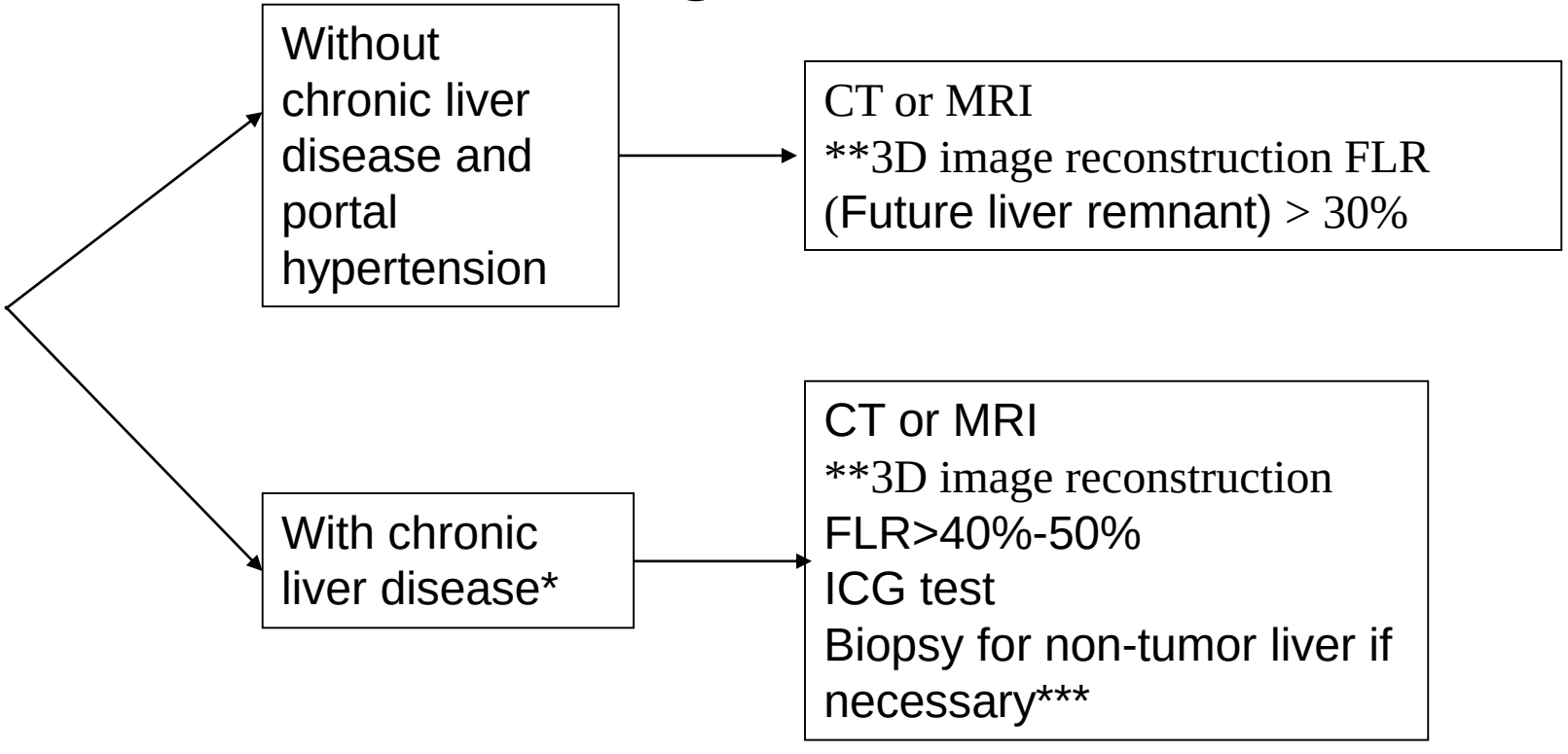
Perihilum cholangiocarcinoma



Bismuth , Ann Surg. 1992

- **Type I : local excision**
- **Type II: local excision plus resection of segment 1 for type II**
- **Type IIIa,b: local excision, resection of segment 1, and right or left hepatectomy**
- **Type IV: initially unresectable, consider neoadjuvant CCRT and subsequent surgery in selected case.**

Evaluate Resectability of extrahepatic Cholangiocarcinoma



Consider portal vein embolization if future liver remnant volume is not sufficient

* Chronic liver disease refers to HBV infection, HCV infection, cirrhosis or alcoholic liver disease

** Optional in some major resection cases to evaluate remnant liver volume

** If severe steatosis or steatohepatitis was suspected, serum AST or ALT level > 2X upper normal limit, or major liver resection is planed

Principle of surgery

- **Complete resection with negative margins and regional lymphadenopathy, surgery may involve major hepatectomy or pancreaticoduodenectomy.**
- **Diagnostic laparoscopy could be considered in selected cases**
- **Perihilum cholangiocarcinoma**
  - Tumor will need to be resected along with the involved biliary tree and the involved hemi-liver with a reasonable change of margin-negative resection. The contralateral liver requires intact arterial and portal inflow as well as biliary drainage.
  - In case with small future liver remnant, pre-operative biliary drainage and contralateral portal vein embolization should be considered.
  - Initial exploration rules out distant metastatic disease or lymph node metastasis beyond liver hilum.
  - Caudate resection is generally required
  - Resection and reconstruction of the portal vein and hepatic artery may be necessary and require expertise
  - Frozen section to assess the proximal and disctal bile duct margins is recommended

TNM Staging System: UICC/AJCC 2010 8th Edition of Perihilum cholangiocarcinoma

- **T category**
- Tx: primary tumor cannot be assessed
- T0:no evidence of primary tumor
- Tis: Carcinoma in situ/high grade dysplasia
- T1: Tumor confined to the bile duct, with extention up to the muscle layer or fibrous tissue
- T2: Tumor invades beyond the wall of the bile duct to surrounding adipose tissue or tumor invades adjacent hepatic parenchyma
- T2a: Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
- T2b: Tumor invades adjacent hepatic parenchyma
- T3: Tumor invades unilateral branches of the portal vein or hepatic artery
- T4: Tumor invades the main portal vein or its branches bilaterally, or the common hepatic artery; or unilateral second order biliary radicals with contralateral potal vein or hepatic artery involvement
- **N category**
- Nx: regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: One to three positive lymph node typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes
- N2: four or more lymph nodes from the sites described for N1
- **M category**
- M0: no distant metastasis
- M1: Distant metastasis

T	N	M	Stage
Tis	N0	M0	0
T1	N0	M0	I
T2a-b	N0	M0	II
T3	N0	M0	IIIA
T4	N0	M0	IIIB
Any T	N1	M0	IIIC
Any T	N2	M0	IVA
Any T	Any N	M1	IVB

TNM Staging System: UICC/AJCC 2010 8th Edition of Distal bile duct cholangiocarcinoma

- **T category**
- Tx: primary tumor cannot be assessed
- Tis: Carcinoma in situ/high grade dysplasia
- T1: Tumor invades the bile duct wall with a depth less than 5mm
- T2: Tumor invades the bile duct wall with a depth of 5-12 mm
- T3: Tumor invades the bile duct wall with a depth greater than 12 mm
- T4: Tumor invades the celiac axis, superior mesenteric artery, and/or common hepatic artery
- **N category**
- Nx: regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastases in one to three regional lymph nodes
- N2: Metastases in four or more regional lymph nodes
- **M category**
- M0: no distant metastasis
- M1: distant metstasis

T	N	M	Stage
Tis	N0	M0	0
T1	N0	M0	I
T1	N1	M0	IIA
T1	N2	M0	IIIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T2	N2	M0	IIIA
T3	N0	M0	IIB
T3	N1	M0	IIB
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	Any N	M1	IV

Gallbladder Cancer

Pretreatment work-ups- Gallbladder cancer

- **History and physical exam**
- **CBC, PT/APTT and chemistry profile**
- **Abdominal CT/MRI (with contrast dynamic study)**
- **Tumor markers: CEA, CA199**
- **Hepatitis markers (HBV and HCV)**
- **Optional studies**
  - Whole body bone scan (if with symptom or advanced stage)
  - Cholangiography, including MRCP and ERCP with spy glass for biopsy
  - Chest CT
  - Cardiac function (cardiac ultrasound and/or ejection fraction + wall motion)
  - Pulmonary function test (if age > 65 and prepare for surgery)
  - Liver function test
  - Assessment of hepatic reserve (ICG test, 3D CT reconstruction)
  - UGI endoscopy and colonoscopy
  - PET CT (Emerging evidence indicates that may be useful to detect regional LN and distant metastasis)

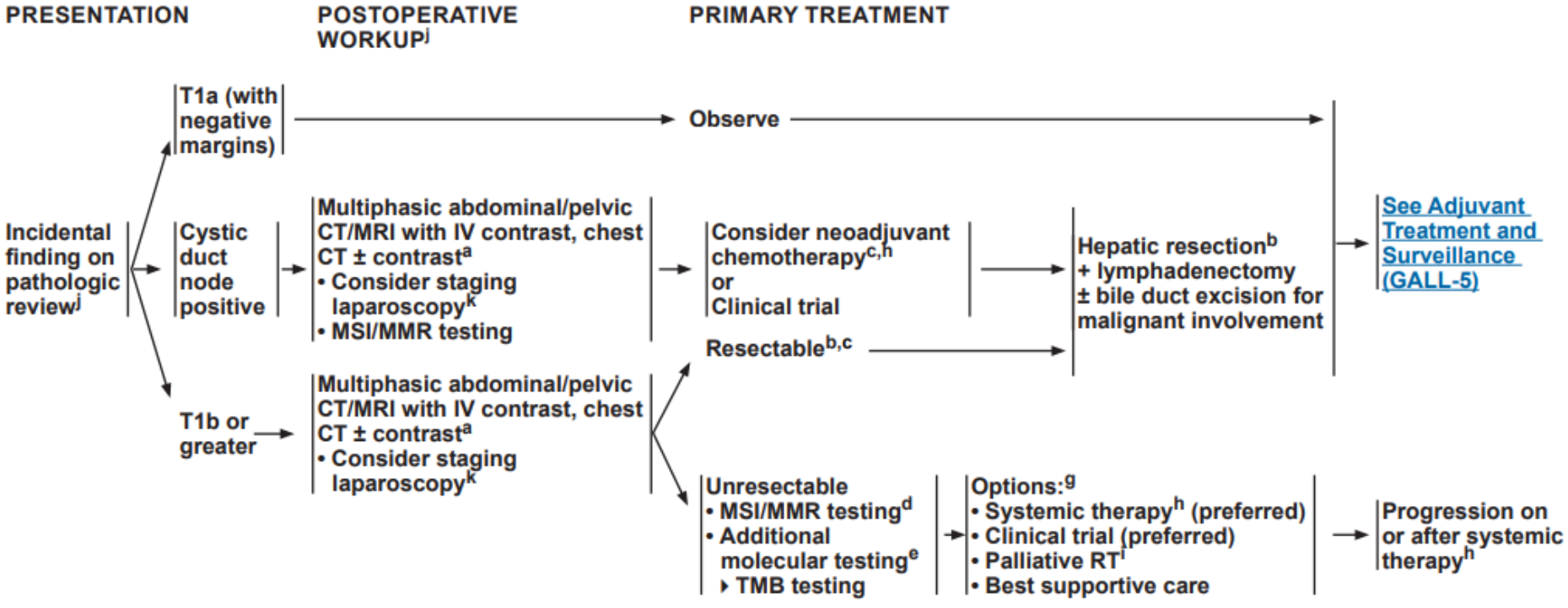
TNM Staging System: UICC/AJCC 2010 8th Edition of Gallbladder cancer

- **T category**
- Tx: primary tumor cannot be assessed
- T0: no evidence of primary tumor
- T1:Tumor invades the lamina propria or muscular layer
- T1a: Tumor invades the lamina propria
- T1b: Tumor invades the muscular layer
- T2: Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum) Or tumor invades the perimuscular connective tissue on the hepatic side, with no extention into the liver.
- T2a: Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum)
- T2b: tumor invades the perimuscular connective tissue on the hepatic side, with no extention into the liver
- T3:Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon pancreas, omentum or extrahepatic bile ducts
- T4: Tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures.

- **N category**
- Nx: regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastases to one to three regional lymph nodes
- N2: Metastases to four or more regional lymph nodes
- **M category**
- M0: no distant metastasis
- M1: distant metstasis

T	N	M	Stage
Tis	N0	M0	0
T1	N0	M0	I
T2a	N0	M0	IIA
T2b	N0	M0	IIB
T3	N0	M0	IIIA
T1-3	N1	M0	IIIB
T4	N0-1	M0	IVA
Any T	N2	M0	IVB
Any T	Any N	M1	IVB

Treatment Stratification of Gallbladder cancer



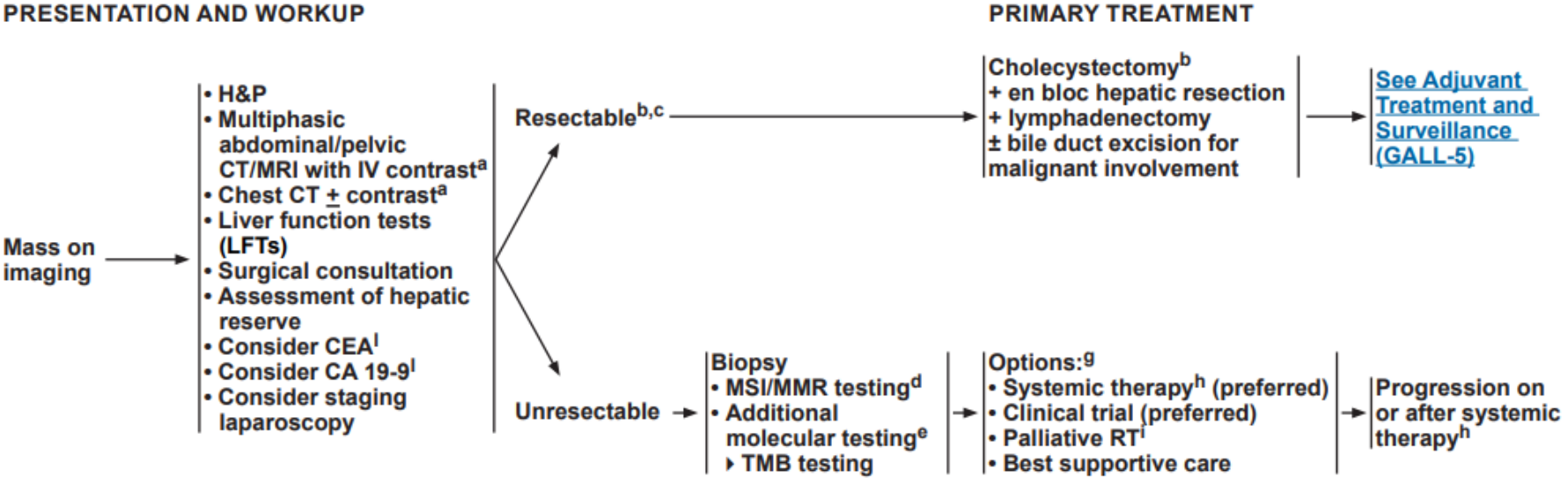
Neoadjuvant Therapy[a]

Preferred Regimens
- None

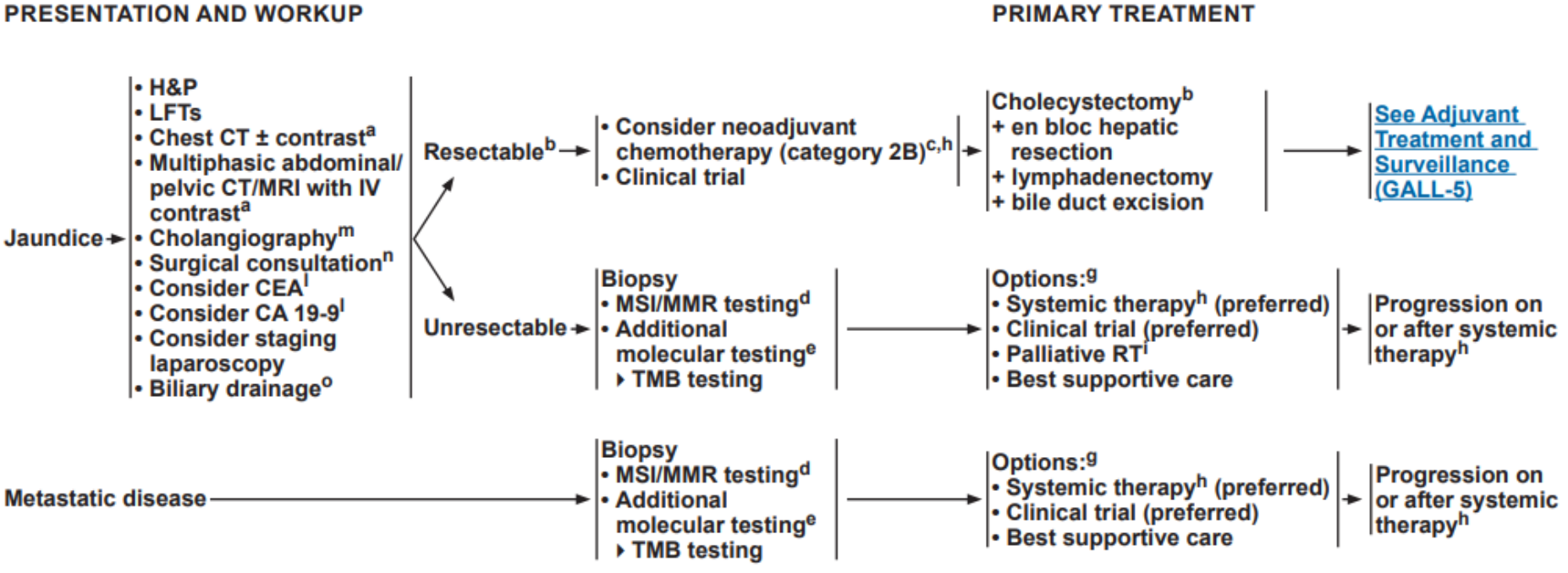
Other Recommended Regimens
- 5-fluorouracil + oxaliplatin
- Capecitabine + oxaliplatin
- Gemcitabine + capecitabine
- Gemcitabine + cisplatin
- Gemcitabine + cisplatin + albumin-bound paclitaxel[1] (category 2B)
- Gemcitabine + oxaliplatin (category 2B)
- Single agents:
  - 5-fluorouracil
  - Capecitabine
  - Gemcitabine

Useful in Certain Circumstances
- None

Treatment Stratification of Gallbladder cancer



Treatment Stratification of Gallbladder cancer

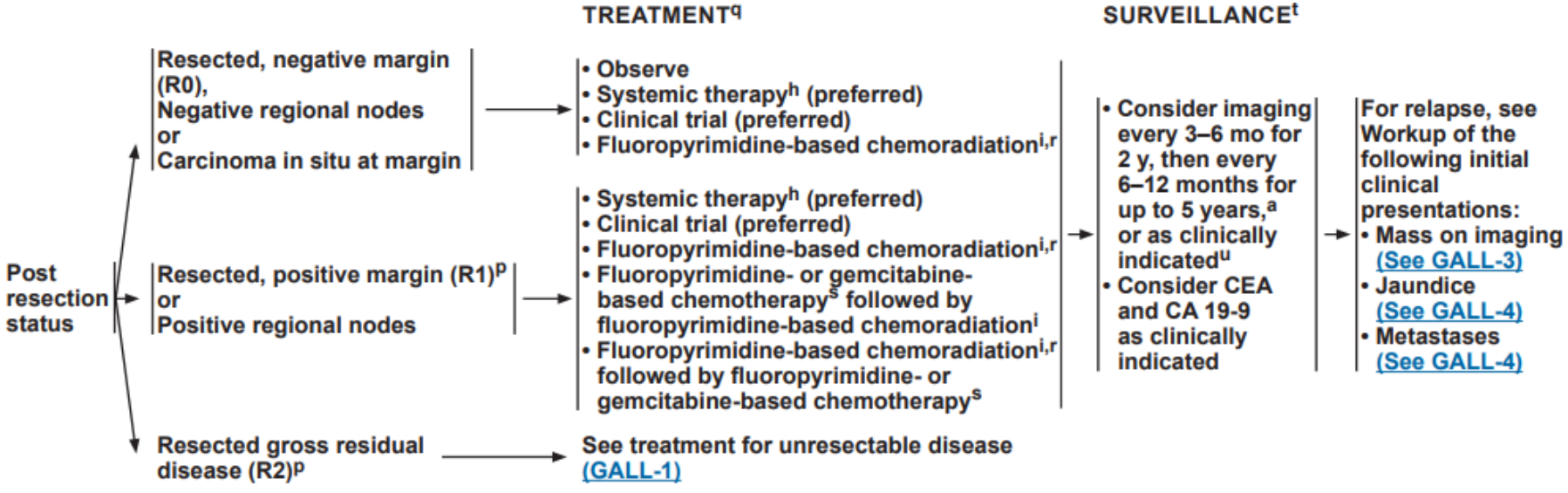


Neoadjuvant Therapy[a]

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• None	• 5-fluorouracil + oxaliplatin • Capecitabine + oxaliplatin • Gemcitabine + capecitabine • Gemcitabine + cisplatin • Gemcitabine + cisplatin + albumin-bound paclitaxel[1] (category 2B) • Gemcitabine + oxaliplatin (category 2B) • Single agents: ‣ 5-fluorouracil ‣ Capecitabine ‣ Gemcitabine	• None

Gall bladder cancer

Additional Tx and Surveillance



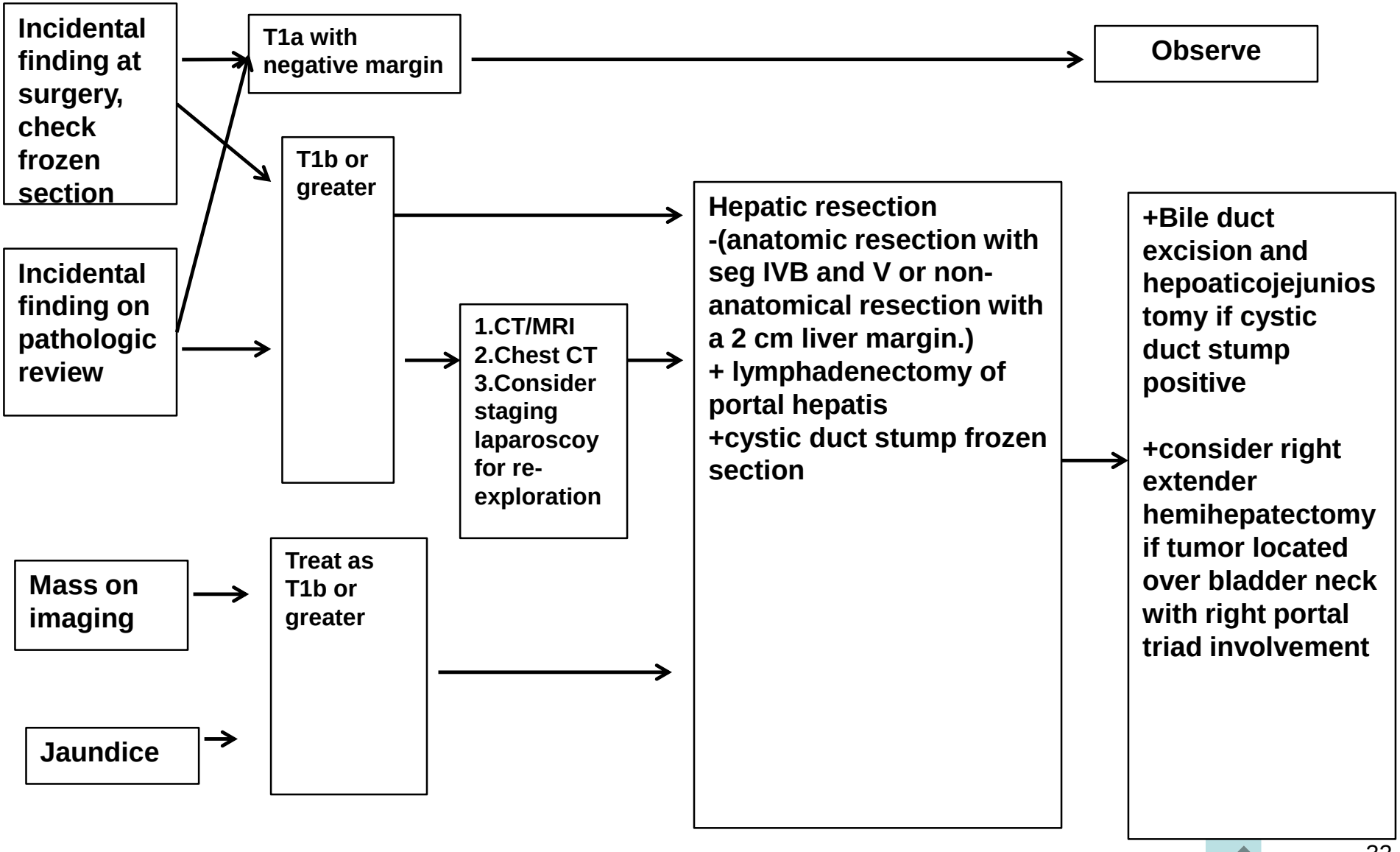
Adjuvant Therapy[b,2]

Preferred Regimens
- Capecitabine[c,3] (category 1)

Other Recommended Regimens
- 5-fluorouracil + oxaliplatin
- Capecitabine + oxaliplatin
- Gemcitabine + capecitabine
- Gemcitabine + cisplatin
- Capecitabine + cisplatin (category 3)
- Single agents:
  - 5-fluorouracil
  - Gemcitabine

Useful in Certain Circumstances
- None

Principle of surgical approach for resectable GB caner



Gallbladder cancer

Principle of surgery-for incidental finding at surgery

- **If there is convincing clinical evidence of cancer but definitive resection can't be performed due to expertise is unavailable, a biopsy is not necessary to avoid peritoneal dissemination.**
- **A definitive resection should be performed for the convincing clinical evidence of gall bladder cancer.**
- **In selected cases with unclear diagnosis, frozen section biopsies can be performed carefully followed by definitive resection to avoid peritoneal dissemination.**
- **For T1a lesion, simple cholecystectomy is sufficient while other stages should receive radical cholcystectomy including segments IVB and V and lymphadenectomy and extended hepatic and biliary resection as necessary to obtain a negative margin.**

Principle of surgery-for incidental finding on pathologic review

- **Review operative record and check the completeness of cholecystectomy, signs of disseminated disease, tumor location and other pertinent information.**
- **Review pathologic report of T stage and cystic duct margin status and other margins.**
- **Diagnostic laparoscopy can be performed but is of relative low yield. Higher yield may be seen in patients with T3 or higher tumors, poorly differentiated tumors or with a margin positive cholecystectomy. Diagnostic laparoscopy should also be considered in patients with any suspicious of metastatic disease on imaging that is not amenable to percutaneous biopsy**
- **Repeat cross-section imaging of the chest , abdomen and pelvis should be performed before definitive resection.**
- **Initial exploration should rule out distant lymph node metastases in the celiac axis or aorto-caval groove as there contraindicate further resection**
- **Hepatic resection should be performed to obtain clear margins which usually consist of segments IVB and V may be needed in some patients to obtain negative margins**
- **Lymphadenopathy should be performed to clear all lymph node in the porta hepatis**
- **Resection of the bile duct may be needed to obtain negative margins. Routine resection of the bile duct for lymphadenectomy has been shown to increase morbidity without convincing evidence for improved survival.**
- **Port site resection has not been shown to be effective as the presence of a port site implant is a surrogate marker of underlying disseminated disease and has not been shown to improve outcome**

Gallbladder cancer

Principle of surgery-Mass on image with suspicious of GB cancer

- Staging should be carried out with cross-sectional imaging of the chest, abdomen and pelvis
- If there is a suspicious mass, a biopsy is not necessary and a definitive resection should be carried out.
- Diagnostic laparoscopy can be considered before definitive resection
- In selected cases with unclear diagnosis, it may be reasonable to perform a cholcystectomy(including intra-operative frozen section) followed by the definitive resection during the same operation if pathology confirmed cancer.
- The resection is carried out as per the principles described above.

Principle of surgery-Gallbladder cancer and jaundice

- **The presence of jaundice in gallbladder cancer usually portends a poor prognosis. These patients need careful surgical evaluation.**
- **Although a relative contraindication, in select patients curative intent resection can be attempted for resectable disease in centers with available expertise.**

Recommended regimens of chemoradiotherapy and adjuvant chemotherapy

Standard chemoradiotherapy regimen

- Nil
- Capecitabine 1250mg/m^2 BID for 14 days every 3 week, total 24 weeks (8 cycles)[24]
- **S-1 80-120 mg/day BID for 4-week on/2-week off every 6 weeks, total 24 weeks (4 cycles)[49] or 2-week on/1-week off every 3 weeks if poor compliance, total 24 weeks (8 cycles)**

Alternative regimens

5-FU based based chemoradiotherapy

- Continues 5-FU 500 mg/m^2 for 3 days, every 2 week
- Capecitabine 825 mg/m^2 PO twice daily during radiation; following radiation, consider an additional 4 momths of therapy[22]

Gemcitibne based chemoradiotherapy

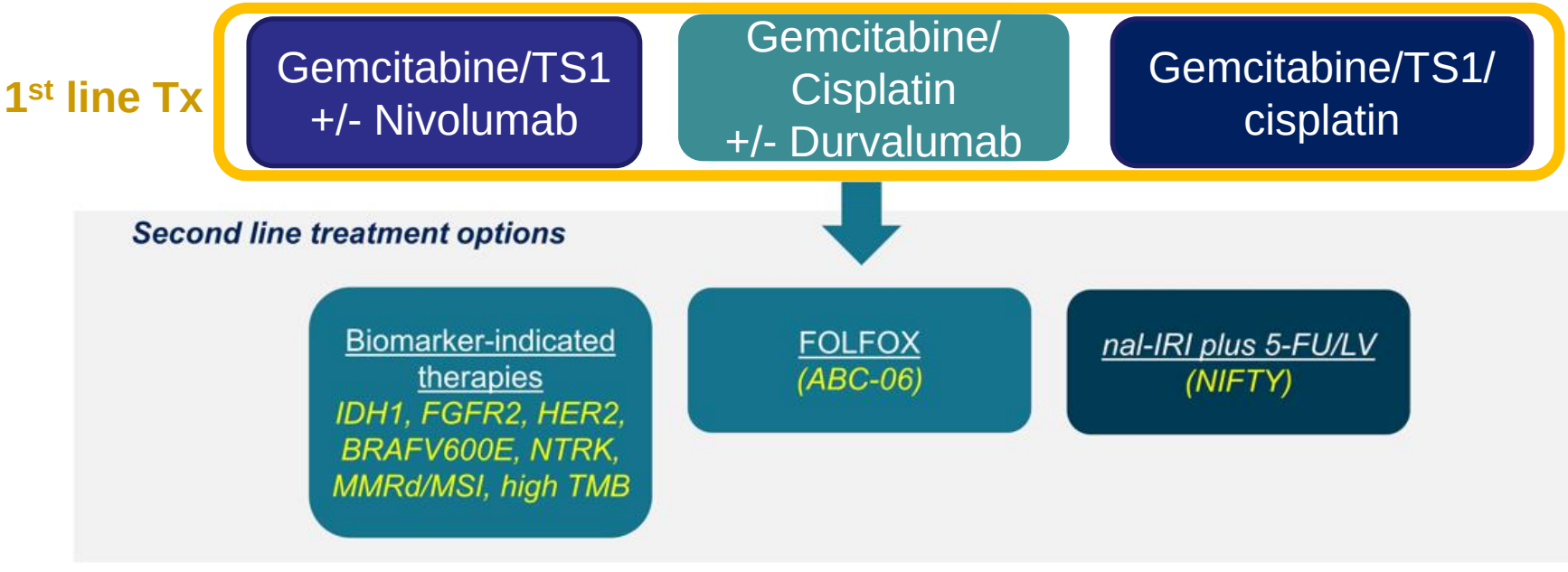
- Gemcitabine 400mg/m^2 every week.

Chemotherapy followed by CCRT (for gall bladder cancer and extrahepatic CCA)[23]

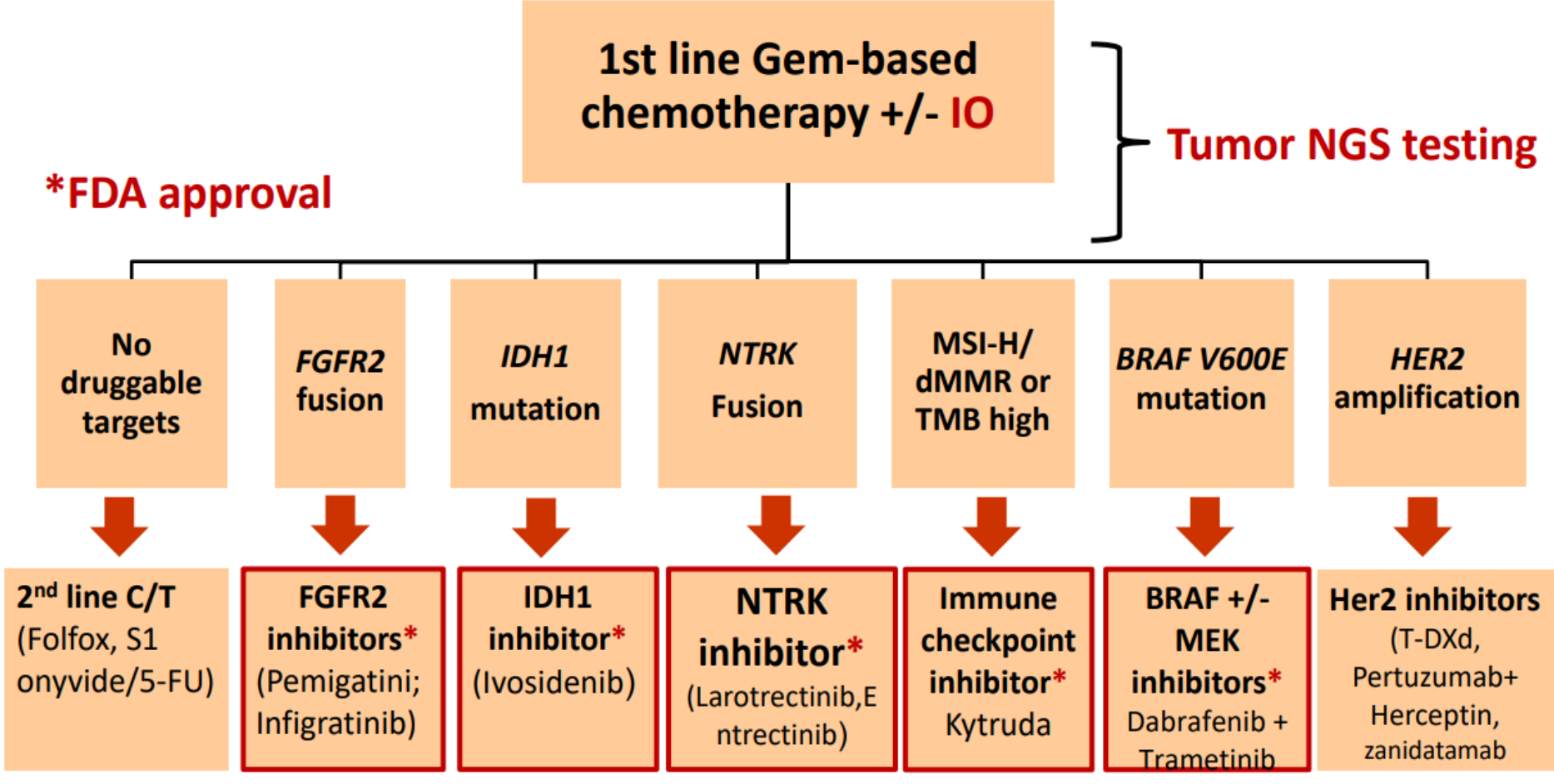
- Four cycles of gemcitabine (1,000 mg/m2 intravenously on days 1 and 8) and capecitabine (1,500 mg/m2 per day on days 1 to 14) every 21 days followed by concurrent capecitabine (1,330 mg/m2 per day) and radiotherapy (45 Gy to regional lymphatics; 54 to 59.4 Gy to tumor bed).

Biliary Tract Cancer

Current Treatment Landscape in BTC



Treatment Algorithm in Advanced Biliary Tract Cancers



Recommended regimens of biliary tract cancer

Standard regimen

- **Gemcitabine + cisplatin (Category 1)[1]**

  Cisplatin (25 mg/m^2) followed by Gemcitabine (1000 mg mg/m^2) on days 1 and 8, every 3 weeks for eight cycle

- **Gemcitabine + cisplatin + Durvalumab (Category 1)[50]**

  Cisplatin (25 mg/m^2) followed by Gemcitabine (1000 mg mg/m^2) on days 1 and 8, plus Durvalumab 1500 mg on days1 every 3 weeks, for eight cycle, then Durvalumab 1500 mg on days1 every 4 weeks

- **Gemcitabine + TS-1 (Category 1)[18]**

  Gemcitabine 1000 mg/m^2 on Day 1 and 8, S1:60-100 mg on Day1-14, every 3 weeks

- **Gemcitabine + TS-1+cisplatin (Category 1)[25]**

  Gemcitabine (1000 mg/m2) and cisplatin (25 mg/m2) on Day 1 and TS-1 80mg/m2 day 1-7, every 2 weeks

Alternative regimens

Gemcitabine + Oxaliplatin[2]

Gemcitabine 1000 mg/m^2 on day 1, followed by Oxaliplatin 100 mg/m^2 on day 2.

Gemcitabine +5-FU[3]

Gemcitabine 1000 mg/m2 on Days 1, 8, and LV 25mg/m^2 followed by 5-FU 600 mg/m^2 on Days 1, 8, and 15 every 4 week

Gemcitabine + capecitabine[4]

Capecitabine 650 mg/m^2 twice daily on D1 to D14 and Gemcitabine 1,000 mg/m^2 on days 1 and 8 every 3 weeks

5-FU + cisplatin[5]

Leucovorin 200 mg/m^2 and 400 mg/m^2 bolus of 5-FU followed by a 22-h continuous infusion of 600 mg/m^2 5-FU for 2 days and Cisplatin 50 mg/m^2 on Day 2.

Recommended regimens of biliary tract cancer

Alternative regimens (cont)

Modified Gemcitabine + TS-1[35]

Gemcitabine (800 mg/m2) on Day 1 and TS-1 80-120mg day 1-10, every 2 weeks

Nivolumab + modified Gemcitabine + TS-1 (NGS)[51]

Nivolumab 240 mg on Day 1 plus Gemcitabine (800 mg/m^2) on Day 1 and TS-1 80-120mg day 1-10, every 2 weeks

FOLFOX [19]

Leucovorin 400 mg/m2 iv over 2 hrs before 5-FU on Day 1
5-FU 400 mg/m2 iv bolus on D1 followed by 2400 mg/m2 iv over 40 hrs
Oxaliplatin 100 mg/m2 iv over 2 hours on D1, every 2 weeks

5-FU+Cisplatin[20]

Leucovorin 400 mg/m2 iv before 5-FU on Day 1-4
5-FU 400 mg/m^2/d CIVD on Day1-4
Cisplatin (CDDP) 80 mg/m^2 iv on D1, every 3 weeks

Erbitux + Gemcitabine + oxaliplatin[21]

Erbitux 500mg /m2 on D1
Gemcitabine 800 mg/m^2 on D 1
Oxaliplatin 85 mg/m^2 on D 1, every 2 weeks.

Biliary tract cancer

Subsequent-line Therapy for Biliary Tract Cancers if Disease Progression

Preferred Regimens
- FOLFOX[36]
- Onyvide+5-FU

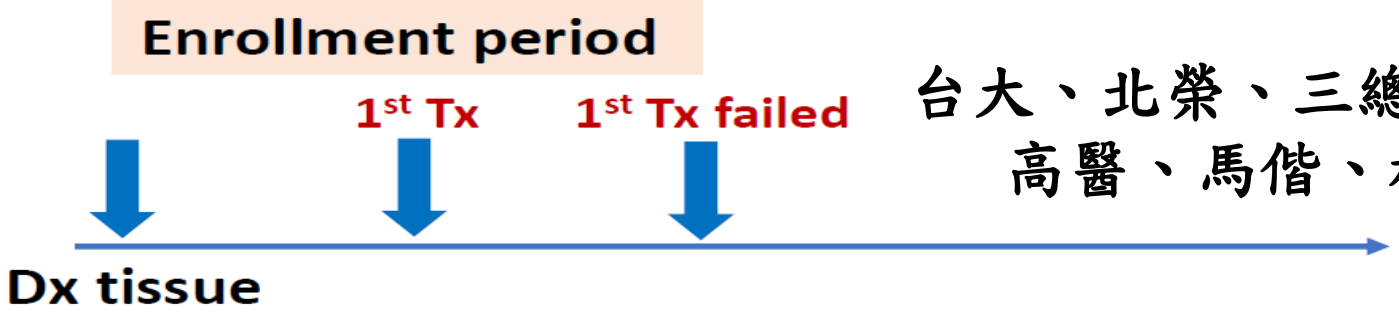
Other Recommended Regimens
- Regorafenib[38]
- FOLFIRI[39]

Useful in Certain Circumstances
- For *NTRK* gene fusion-positive tumors:
  Entrectinib[40]
  Larotrectinib[41]
- For MSI-H/dMMR tumors:
  Pembrolizumab[42]
- For cholangiocarcinoma with *FGFR2* fusions or rearrangements:
  Pemigatinib[43], Infigratinib[44]
- For cholangiocarcinoma with *IDH1* mutations
  Ivosidenib[45]
- For BRAF-V600E mutated tumors
  Dabrafenib + trametinib[46]
- Nivolumab[47]
- Lenvatinib + pembrolizumab[48]

TCOG T3221 台灣膽道癌精準醫療研究合作計畫 (100 cases per year)

6.1. Inclusion Criteria

1. Ages 20 and above
2. Pathological reported showed adenocarcinoma or adenosquamous carcinoma for patients with BTC (include IHCC, EHCC, GBC or AVC) or hepatocholangiocarcinoma as locally advanced or metastatic status.
3. Willingness to provide the residual biopsy/operative slides.
4. Life expectancy more than 3 months.
5. Patients fully understand the protocol with the willingness to have regular follow-up.
6. Patients are ready to have 1st systemic treatment or under 1st line therapy



台大、北榮、三總、中國、成大
高醫、馬偕、林長、高長

Follow up

Physical examination and radiologic imaging:

- Every 3 mo for 5 y

CBC and chemistry profile:

As indicated

Tumor marker:

CEA, CA199

Reference

1. Valle J, Wasan H, Palmer DH et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362(14):1273-81.
2. André T, Tournigand C, Rosmorduc O et al. Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. Ann Oncol. 2004;15(9):1339-43.
3. Alberts SR, Al-Khatib H, Mahoney MR, et al. Gemcitabine, 5-fluorouracil, and leucovorin in advanced biliary tract and gallbladder carcinoma: a North Central Cancer Treatment Group phase II trial. Cancer.2005 ;103(1):111-8.
4. Koeberle D, Saletti P, Borner M, et al. Patient-reported outcomes of patients with advanced biliary tract cancers receiving gemcitabine plus capecitabine: a multicenter, phase II trial of the Swiss Group for Clinical Cancer Research. J Clin Oncol. 2008;26(22):3702-8
5. Taïeb J, Mitry E, Boige V et al. Optimization of 5-fluorouracil (5-FU)/cisplatin combination chemotherapy with a new schedule of leucovorin, 5 -FU and cisplatin (LV5FU2-P regimen) in patients with biliary tract carcinoma. Ann Oncol. 2002;13(8):1192-6.
6. Butte, J.M., et al., *The role of laparoscopic staging in patients with incidental gallbladder cancer.* HPB (Oxford), 2011. **13**(7): p. 463-72.

Reference

7. D'Angelica, M., et al., *Analysis of the extent of resection for adenocarcinoma of the gallbladder.* Ann Surg Oncol, 2009. **16**(4): p. 806-16.
8. Fuks, D., et al., *Incidental gallbladder cancer by the AFC-GBC-2009 Study Group.* World J Surg, 2011. **35**(8): p. 1887-97.
9. Hawkins, W.G., et al., *Jaundice predicts advanced disease and early mortality in patients with gallbladder cancer.* Ann Surg Oncol, 2004. **11**(3): p. 310-5.
10. Maker, A.V., et al., *Is port site resection necessary in the surgical management of gallbladder cancer?* Ann Surg Oncol, 2012. **19**(2): p. 409-17.
11. Regimbeau, J.M., et al., *Prognostic value of jaundice in patients with gallbladder cancer by the AFC-GBC-2009 study group.* Eur J Surg Oncol, 2011. **37**(6): p. 505-12.
12. De Jong, M.C., et al., Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. J Clin Oncol, 2011. 29(23): p. 3140-5.
13. Endo, I., et al., Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. Ann Surg, 2008. 248(1): p. 84-96.

Reference

14. Fu, B.S., et al., The role of liver transplantation for intrahepatic cholangiocarcinoma: a single-center experience. Eur Surg Res, 2011. 47(4): p. 218-21.
15. Lang, H., et al. Operations for intrahepatic cholangiocarcinoma: single-institution experience of 158 patients. J Am Coll Surg, 2009. 208(2): p. 218-28.
16. Rana, A. and J.C. Hong, Orthotopic liver transplantation in combination with neoadjuvant therapy: a new paradigm in the treatment of unresectable intrahepatic cholangiocarcinoma. Curr Opin Gastroenterol, 2012. 28(3): p. 258-65.
17. Rafi S, Piduru SM, El-Rayes B, et al. Yttrium-90 radioembolization for unresectable standard-chemorefractory intrahepatic cholangiocarcinoma: survival, efficacy, and safety study. Cardiovasc Intervent Radiol. 2013 Apr;36(2):440-8.
18. Morizane C et al. Randomized phase II study of gemcitabine plus S-1 versus S-1 in advanced biliary tract cancer: a Japan Clinical Oncology Group trial (JCOG 0805). Cancer Sci. 2013 ;104:1211-6
19. Novarino AM, et al. FOLFOX-4 regimen or single-agent gemcitabine as first-line chemotherapy in advanced biliary tract cancer. Am J Clin Oncol. 2013 Oct;36(5):466-71
20. Ducreux, M et al. Effective treatment of advanced biliary tract carcinoma using 5-fluorouracil continuous infusion with cisplatin. Ann Oncol 1998; 9:653

Reference

21. Chen JS, Hsu C, Chiang NJ, et al. A KRAS mutation status-stratified randomized phase II trial of gemcitabine and oxaliplatin alone or in combination with cetuximab in advanced biliary tract cancer. Ann Oncol. 2015 ;26:943-9.
22. Lim K, Oh D, Chie E, et al. Which is better in patients with curatively resected extrahepatic biliary tract cancer? Adjuvant concurrent chemoradiation (CCRT) alone versus CCRT followed by maintenance chemotherapy. ASCO Meeting Abstracts. 2008;26:15659.
23. Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG S0809: A Phase II Intergroup Trial of Adjuvant Capecitabine and Gemcitabine Followed by Radiotherapy and Concurrent Capecitabine in Extrahepatic Cholangiocarcinoma and Gallbladder Carcinoma. J Clin Oncol. 2015;33:2617-22.
24. Primrose JN, Fox R, Palmer D, et al. Adjuvant capecitabine for biliary tract cancer: The BILCAP randomized study. J Clin Oncol 35, 2017 (suppl; abstr 4006)
25. Sakai D et al. Randomized phase III study of Gemcitabine, Cisplatin plus S-1 (GCS) versus Gemcitabine, Cisplatin (GC) for Advanced Biliary Tract Cancer. Annals of Oncology (2018) 29 (suppl_8): viii205-viii270. 10.1093/annonc/mdy282

Reference

25. Nai-Jung Chiang, Jen-Shi Chen, Ming-Huang Chen, Shih-Hung Yang, Chiun Hsu, Chia-Jui Yen, Hsiao-Hui Tsou, Shan Yanshen, and Li-Tzong Chen A phase II trial of modified gemcitabine plus S-1 combination as the first-line treatment in patients with advanced biliary tract cancer. Journal of Clinical Oncology 2017 35:4_suppl, 417-417
26. Chigusa Morizane, Takuji Okusaka, Junki Mizusawa, et al. Randomized phase III study of gemcitabine plus S-1 combination therapy versus gemcitabine plus cisplatin combination therapy in advanced biliary tract cancer: A Japan Clinical Oncology Group study (JCOG1113, FUGA-BT).Journal of Clinical Oncology 2018 36:4_suppl, 205-205
27. Demetri GD, Paz-Ares LG, Farago AF, et al. Efficacy and safety of entrectinib in patients with NTRK fusion-positive (NTRK-fp) tumors: pooled analysis of STARTRK-2, STARTRK-1 and ALKA-372-001. ESMO Congress 2018.
28. Drilon A, Siena S, Ou SI, et al. Safety and antitumor activity of the multitargeted pan-TRK, ROS1, and ALK inhibitor entrectinib: Combined results from two phase I trials (ALKA-372-001 and STARTRK-1). Cancer Discov. 2017 Apr;7(4):400-409.
29. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2019. [Epub ahead of print]

References

30. Lamarca A, Palmer DH, Wasan HS, et al. ABC-06 | A randomised phase III, multi-centre, open-label study of active symptom control (ASC) alone or ASC with oxaliplatin / 5-FU chemotherapy (ASC+mFOLFOX) for patients (pts) with locally advanced / metastatic biliary tract cancers (ABC) previously-treated with cisplatin/ gemcitabine (CisGem) chemotherapy [abstract]. J Clin Oncol 2019; 37(Suppl 15):Abstract 4003.
31. Caparica R, Lengele A, Bekolo W, Hendlisz A. FOLFIRI as second-line treatment of metastatic biliary tract cancer patients. Autops Case Rep 2019;9:e2019087.
32. Sun W, Patel A, Normolle D, et al. A phase 2 trial of regorafenib as a single agent in patients with chemotherapy-refractory, advanced, and metastatic biliary tract Adenocarcinoma. Cancer 2019;125:902-909.
33. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase2 study. Lancet Oncol 2020. [Epub ahead of print]
34. Abou-Alfa GK, Macarulla T, Javle MM, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, doubleblind, placebo-controlled, phase 3 study. Lancet Oncol 2020. [Epub ahead of print]
35. Chiang NJ, Chen MH, Yang SH, et al. Multicentre, phase II study of gemcitabine and S-1 in patients with advanced biliary tract cancer: TG1308 study Liver Int. 2020 Oct;40(10):2535-2543

References

36. Lamarca A, Palmer DH, Wasan HS, et al. ABC-06 | A randomised phase III, multi-centre, open-label study of active symptom control (ASC) alone or ASC with oxaliplatin / 5-FU chemotherapy (ASC+mFOLFOX) for patients (pts) with locally advanced / metastatic biliary tract cancers (ABC) previously-treated with cisplatin/gemcitabine (CisGem) chemotherapy [abstract]. J Clin Oncol 2019; 37(Suppl 15):Abstract 4003.
37. Changhoo Yoo, Kyu-Pyo Kim, Ilhwan Kim et al. Liposomal irinotecan (nal-IRI) in combination with fluorouracil (5-FU) and leucovorin (LV) for patients with metastatic biliary tract cancer (BTC) after progression on gemcitabine plus cisplatin (GemCis): Multicenter comparative randomized phase 2b study (NIFTY). *Journal of Clinical Oncology* 39, no. 15_suppl (May 20, 2021) 4006-4006.
38. Sun W, Patel A, Normolle D, et al. A phase 2 trial of regorafenib as a single agent in patients with chemotherapy-refractory, advanced, and metastatic biliary tract adenocarcinoma. Cancer 2019;125:902-909.
39. Caparica R, Lengele A, Bekolo W, Hendlisz A. FOLFIRI as second-line treatment of metastatic biliary tract cancer patients. Autops Case Rep 2019;9:e2019087.
40. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282.

References

41. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378:731-739.
42. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: Results from the phase II KEYNOTE-158 study. J Clin Oncol 2020;38:1-10.
43. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase2 study. Lancet Oncol 2020;21:671-684.
44. Javle M, Roychowdhury S, Kelley RK, et al. Final results from a phase II study of infigratinib (BGJ398), an FGFR-selective tyrosine kinase inhibitor, in patients with previously treated advanced cholangiocarcinoma harboring an FGFR2 gene fusion or rearrangement. J Clin Oncol 2021;39:265-265
45. Abou-Alfa GK, Macarulla T, Javle MM, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2020;21:796-807.
46. Subbiah V, Lassen U, Élez E, et al. Dabrafenib plus trametinib in patients with BRAFV600E-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm,multicentre basket trial. Lancet Oncol 2020;21:1234-1243.

References

47. Kim RD, Chung V, Alese OB, et al. A Phase 2 Multi-institutional Study of Nivolumab for Patients With Advanced Refractory Biliary Tract Cancer. JAMA Oncol. 2020;6:888-894.

48. Lwin, Z, Gomez-Roca, C, Saada-Bouzid E, et al. LEAP-005: Phase II study of lenvatinib (len) plus pembrolizumab (pembro) in patients (pts) with previously treated advanced solid tumors. Ann. Oncol. 2020;31:S1142-S1215.

49. Ikeda M, Nakachi K, Konishi M, et al. Journal of Clinical Oncology 2022 40:4_suppl, 382-382.

50. Oh DY, He AR, Qin S, et al. NEJM Evid 2022; 1(8).

51. Chiang NJ, Tan KT, Bai LY et al. Clin Cancer Res 2022; doi: 10.1158/1078-0432.CCR-22-1152.