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ONCOLOGIA EPATO-BILIO-PANCREATICA

Carcinoma della colecisti: clinical management

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Gallbladder carcinoma

The most aggressive of the biliary cancers

Usually advanced at diagnosis

< 10% of cases amenable of resection

High recurrence rate after R0 resection

GBC: survival by stage

Stage	5-y surv
Localized	40%
Regional	15%
Distant	< 10%

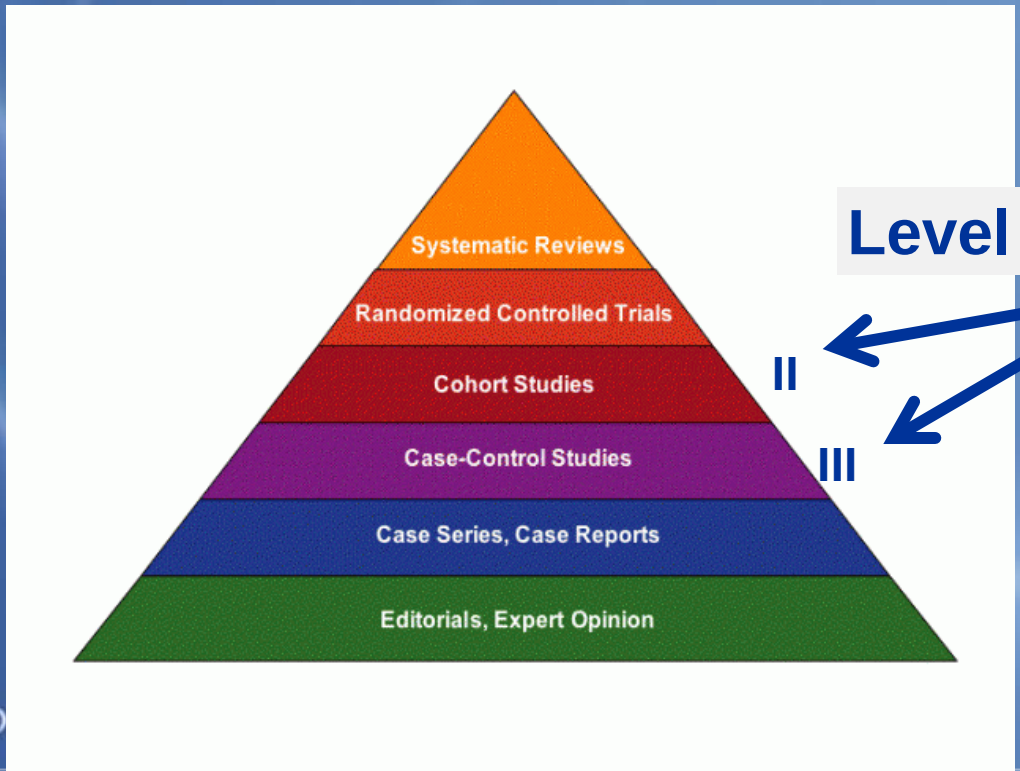
SEER registry from 1995-2001

Gallbladder carcinoma: What is the main therapeutic goal?

Radical and adequate resection

Gallbladder carcinoma: evidence based medicine

Very few randomized phase III trials



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Gallbladder carcinoma: Integrated therapeutical approach

Incidental finding during laparoscopic cholecystectomy for benign disease

Resection of gallbladder with a suspected carcinoma

Potentially resectable locally-advanced carcinoma

Incidental finding during laparoscopic cholecystectomy for benign disease

In three large series combined, incidental GBC was found in 31 of 9497 patients undergoing laparoscopic cholecystectomy (0.33 %)

Yamaguchi, Anna Surg 1996
The southern surgeons group. NEJM 1991
Konstantidinis, Arch Surg 2009

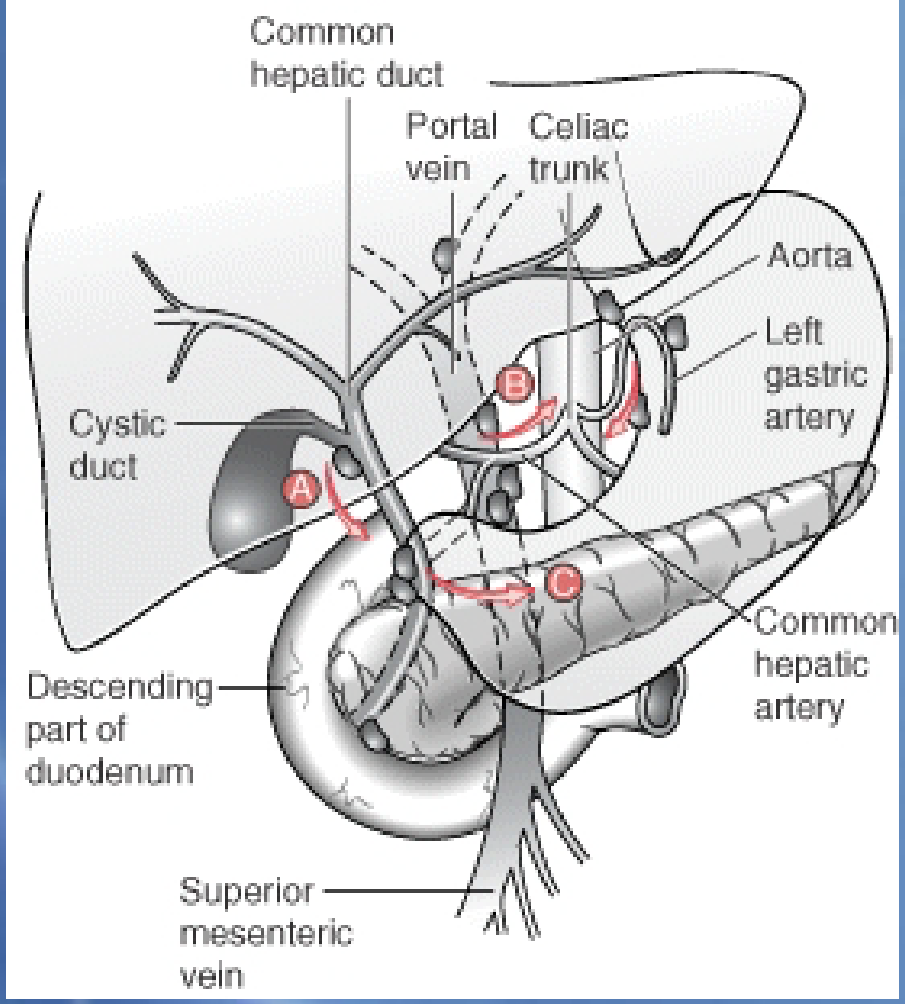
“….approximately half the patients have undergone cholecystectomy prior to referral to a surgeon with expertise in hepatobiliary surgery….”

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or muscular layer
T1a	Tumor invades lamina propria
T1b	Tumor invades muscular layer
T2	Tumor invades perimuscular connective tissue; no extension beyond serosa or into 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 main portal vein or hepatic artery or invades two or more extrahepatic organs or structures
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein
N2	Metastases to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1-3	N1	M0
Stage IVA	T4	N0–1	M0
Stage IVB	Any T	N2	M0
	Any T	Any N	M1

AJCC TNM, VII Ed.

The recently updated AJCC staging criteria distinguishes regional hilar nodal metastases (stage III) from peripancreatic, periduodenal, celiac and SMA locations which are considered as distant metastatic disease (stage IV).

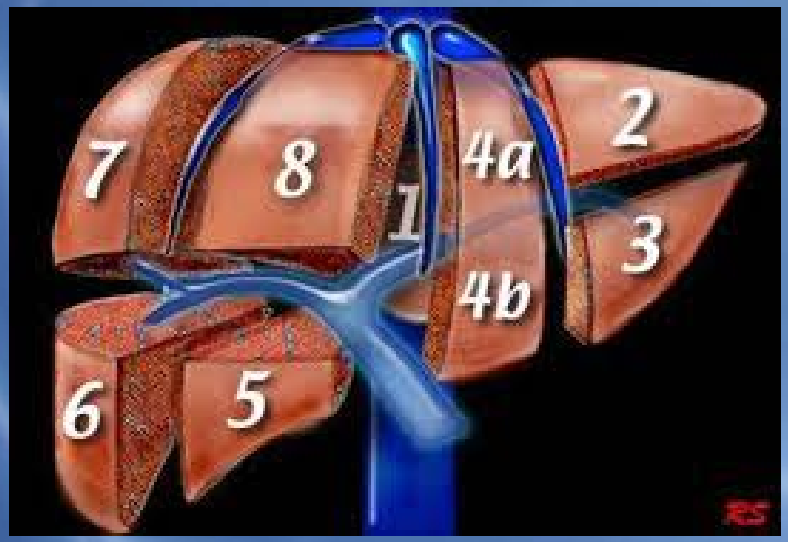


A, The main pathway of lymphatic drainage and, thus, lymph node metastasis from gallbladder cancer, is to the **cholecysto-retropancreatic nodes**. This pathway drains from the gallbladder to nodes along the cystic duct and common bile duct and then to nodes posterior to the duodenum and pancreatic head. ***B,*** The cholecysto-celiac pathway courses from the gallbladder through the gastrohepatic ligament to **celiac nodes**. ***C,*** The third lymphatic drainage route is the cholecysto-mesenteric pathway, coursing from the gallbladder posterior to the **pancreas to aortocaval lymph nodes.**

T1 and T2 tumors are the primary targets of surgical therapy

Resectable GBC: < 10% of cases

pT1a	simple cholecystectomy
pT1b	radical cholecystectomy
	(liver segments 5 and 4b, nodal dissection)



Unexpected tumor during laparoscopy choclecystectomy for benign disease

→ **pT1b** or **pT2**

→ staging negative

→ **radicalization** (partial hepatic resection and regional lymphadenectomy: porta hepatis, gastrohepatic ligament, and retroduodenal lymph nodes)

115 cases of re-resection for pT1b

46% of pts : residual disease

Pawlik, J Gastroint Surg 2007

98 pts with GBC after routine cholecystectomy
48 pts pT2
Survival:

- 40% simple cholecystectomy
- 90% radical resection

Shirai, Ann Surg 1992
Chijjjwa, J Am Coll Surg 2001
Foster, Ann Surg Oncol 2007
Suzuki, World J Surg 2004

T3 → resectable (but possible high morbidity)
T4 → unresectable

French retrospective analysis
724 cases (85% T3-4)
OS = 2-8 months

Cubertafond, Ann Surg 1994

Japan retrospective analysis
Stage III
5-y surv 44%

Cubertafond, Ann Surg 1994

Simple vs radical cholecystectomy

No prospective randomi

In a Japanese series ics from 172 major hospitals,

984 patients section compared to 702 patients with simp

urv rate 66 % vs 14 %,
-y surv rate 51 % vs 6 %

Surgeon expertise, patient characteristics, surgical morbidity/mortality

Laparoscopically removed GB: Important questions for surgeons

Was the GB torn or ruptured?

Was a protective bag used?

Was the cystic duct involved?

If a cancer is identified incidentally in a cholecystectomy specimen, the pathologist should report on T stage, location of the tumor with respect to the liver bed or peritoneal surface, and histology of the cystic duct margin.

2010 ESMO guidelines

treatment after incidental finding of gallbladder cancer on pathological review

A radical re-resection (after a complete staging including laparoscopy demonstrating resectability) is highly recommended for patients with incidental gallbladder carcinoma stage T1b (tumour invades muscle layer) or greater. Patients with T1a tumours (tumour invades lamina propria) do not further benefit from re-resection if the gallbladder was removed intact and should be observed only [III, B].

treatment after incidental finding of gallbladder cancer at surgery

After incidental finding of gallbladder cancer at surgery staging has to be performed intraoperatively and extended cholecystecomy including *en bloc* hepatic resection and lymphadenectomy with or without bile duct excision has to be considered depending on resectability and expertise of the surgeon.

Resection of gallbladder with a suspected carcinoma

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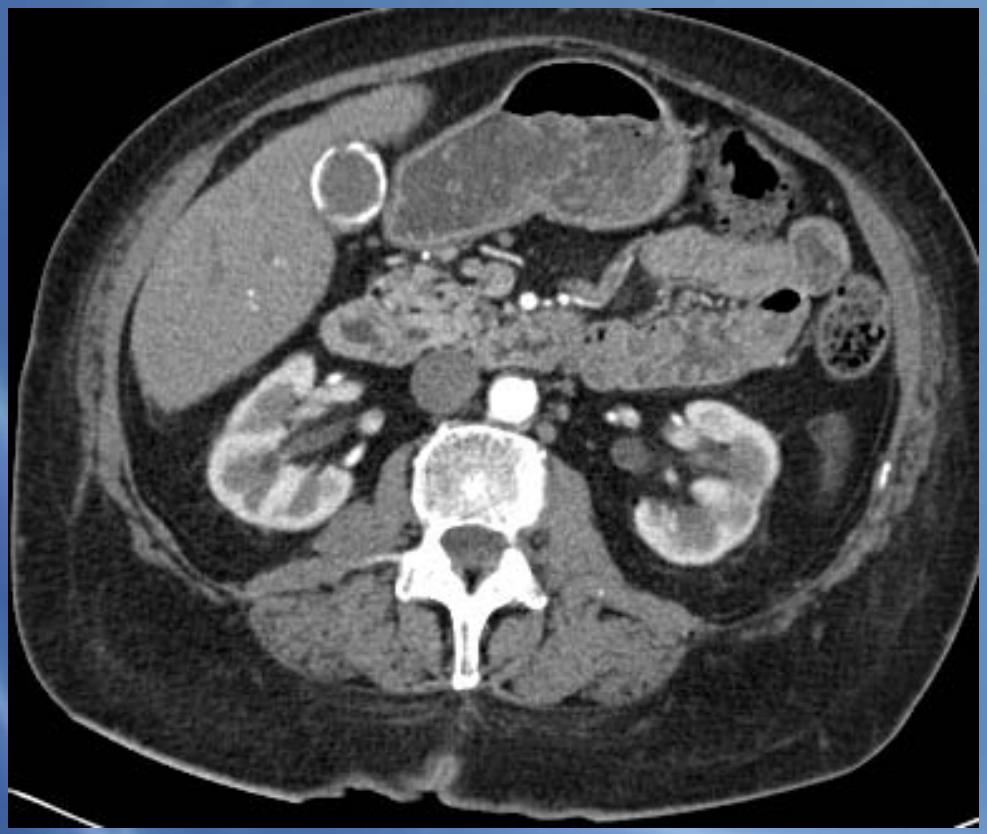
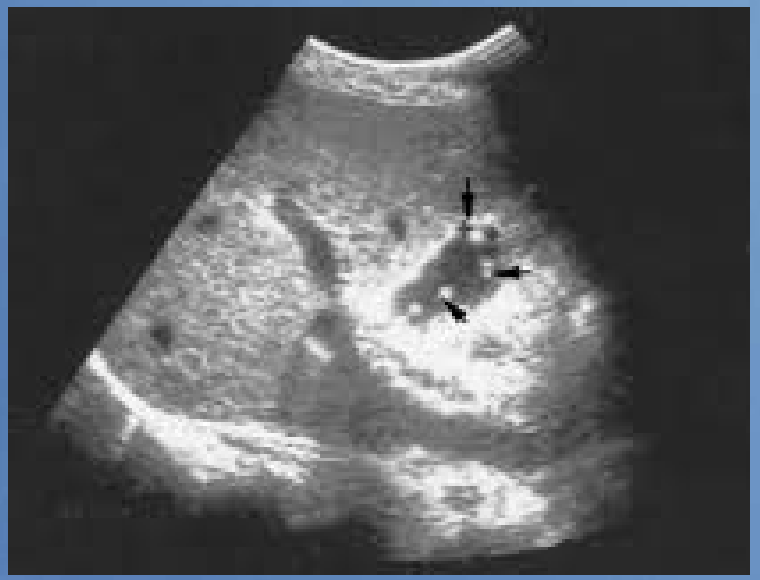
Porcelain gallbladder



Gallbladder poplyps



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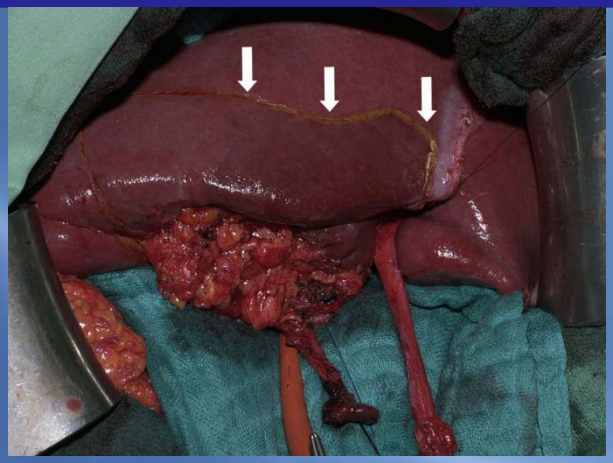
If GBC is strongly suspected preoperatively, an open rather than laparoscopic procedure is generally recommended

For a GB mass or polyp >1 cm → EUS (with FNA for cytology of the gallbladder and lymph nodes)

If benign → laparoscopy
If malignant → open

Potentially resectable locally-advanced carcinoma



LA GBC:
diagnostic laparoscopy may be useful

Prospective analysis of 100 pts with biliary cancers staged by laparoscopy
→ unresectable or metastatic disease in 50% of patients

Weber, Ann surg 2002

Locally advanced GBC

Adjuvant or neoadjuvant therapy?

Chemotherapy, Radiotherapy or Chemoradiation?

Locally advanced GBC: “adjuvant “chemotherapy

After a radical surgery?

After a non radical surgery?

LA pancreaticobiliary tract carcinoma: Adjuvant chemotherapy

Pts tot		508 (Pancreas 173, Chol 139, **GB 140**, AV 56)		
GB		MMC + 5-FU	SURG	
Pts tot		69	43	
Stage II		14 (20%)	3 (7%)	
Stage III		23 (33%)	14 (33%)	
Stage IV		**32 (46%)**	**26 (60%)**	
5-y Surv	tot	26 %	14 %	p = 0.03
	radical	46 %	31 %	p = 0.15
	not rad.	**9 %**	**0 %**	**p = 0.02**
5-y DFS	tot	20 %	12 %	p = 0.02
	rad.	35 %	25 %	p = 0.11
	not rad.	**8 %**	**0 %**	**p = 0.02**

Takada et al., Cancer 2002

GBC:
Hepatic arterial infusion chemotherapy

Up to 60% PR
Duration of response = 3 months
Median OS = < 1 year

HAI not clearly better than systemic

LA GBC:
Adjuvant radiotherapy

Concerns:

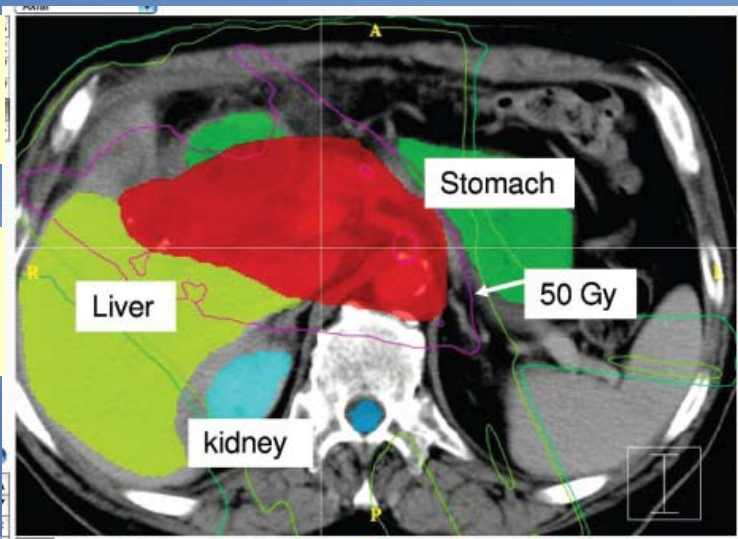
- Very small retrospective series

- Mix of CC and GBC

- Mix of curative and palliative surgery

IMRT (Intensity-Modulated Radiation Therapy)

Dose: 50.4 Gy in 1.8 Gy per fraction (+ 5-FU)



LA GBC:
Adjuvant radiotherapy

SEER: 3,187 GBC cases from 1992-2002

73% → surgery (77% simple cholecyst.)

20% received RT

RT vs non RT: 14 vs 8 months surv ($p < 0.0001$)

N+ pts = greatest benefit

Weber, Ann surg 2002

Some favourable results exist also for 5-FU combined with RT

It is entirely possible that the apparent survival prolongation from RT seen in this series was ***attributable to tumor biology and not RT.***

LA GBC:
Adjuvant chemoradiotherapy

"..The use of adjuvant therapy cannot compensate for inadequate surgery.."

Zhu, The Oncologist 2010

2010 ESMO guidelines

adjuvant (and additive) therapy

As both gallbladder and biliary tract neoplasms present a high incidence of local failure after surgical resection reaching 52%, a locoregional adjuvant treatment may be considered. Several retrospective reports on adjuvant and recently also on neoadjuvant (chemo)radiotherapy suggest survival benefit in both gallbladder and biliary duct cancer and postoperative chemoirradiation may be considered as an option. Fluorouracil was mostly used for chemoradiotherapy in biliary cancers. Recently concomitant gemcitabine with or without oxaliplatin has shown feasibility with radiotherapy in this disease.

Conclusions

No standard medical treatment exists in locally advanced GBC

No standard regimen exists for adjuvant chemotherapy

A personalized medical treatment with the goal of a radical resection can be shared with the patient