Gallbladder cancer

F Sukhum Kobdej

Advisor : Dr Somkit Mingphreudhi

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Introduction

- Gallbladder cancer is an uncommon malignancy (1.2%)
  - Most common biliary tract malignancy
  - Incidence 2/10,000
  - Females : male = 2-3 : 1
- GB carcinoma arising from the epithelium
  - Adenocarcinoma (95.7%)
    - Mucinous adenocarcinoma; more aggressive
  - Squamous carcinoma (2.4%)
  - Adenosquamous carcinoma (1.9%)

  } More aggressiveness and worse prognoses than adenocarcinoma
- Precancerous lesions of GB adenocarcinoma
  - Intracholecystic papillary-tubular neoplasm
  - Biliary intraepithelial neoplasia

Okumura K et al. Gallbladder cancer: Historical treatment and new management options. World J Gastrointest Oncol 2021; 13(10): 1317-1335
Pavlidis ET, Galanis IN, Pavlidis TE. New trends in diagnosis and management of gallbladder carcinoma. *World J Gastrointest Oncol* 2024; 16(1): 13-29

Introduction

- Pathogenesis
  - Chronic irritation of gallbladder mucosa -> mucosal metaplasia, dysplasia and subsequently carcinoma
    - Chronic inflammation from gallstone, infection(salmonella infection)
  - Flat intraepithelial neoplasia (flat IN) pathway of carcinogenesis
    - Described as biliary intraepithelial neoplasia (BiiN)
  - The mutational profile of gallbladder adenocarcinoma most commonly involves K-*ras, TP53, CDKN2a,* and c-*erb*-b2 mutations

Ramachandran A, Srivastava DN, Madhusudhan KS. Gallbladder cancer revisited: the evolving role of a radiologist. Br J Radiol 2020; 94: 20200726
Menon G, Babiker HM. Gallbladder Carcinoma. [Updated 2024 Aug 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-

Introduction

Table 1 Risk factors for gallbladder cancer[35]

Patient predisposition	Environmental factors	Patient factors/conditions
Female sex	Chronic bacterial infections	Diabetes
Age	Aflatoxins	High body mass index
Race/ethnicity	Ochratoxin	Primary sclerosing cholangitis
Genetics (variants)	Arsenic	Porcelain gallbladder
	Liver fluke	Gallbladder polyps
	Geography	Crohn's disease
		Anomalous biliary ductal insertion
		Gallstones
		Sjogren's syndrome

Okumura K et al. Gallbladder cancer: Historical treatment and new management options. World J Gastrointest Oncol 2021; 13(10): 1317-1335

Introduction

American Joint Committee on Cancer (AJCC)
TNM Staging for Gallbladder Carcinoma (8th ed., 2017)

Table 3. **Definitions for T, N, M**

T	**Primary Tumor**
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 muscle 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 extension 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 extension 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 main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

Confine to gallbladder

N	**Regional Lymph Nodes**
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	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis

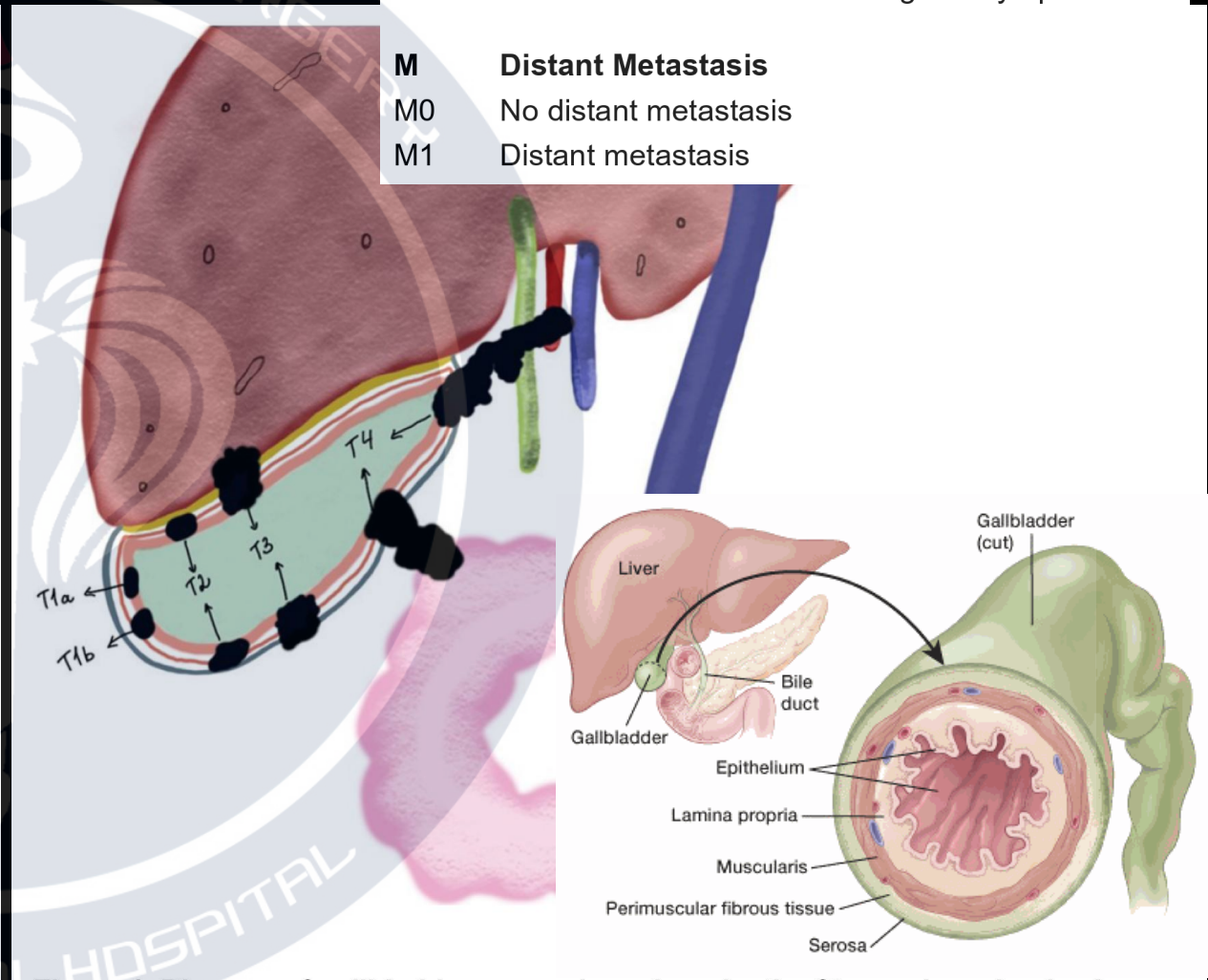

Figure 1 Diagram of gallbladder cancer based on depth of tumor invasion is shown.

Okumura K et al. Gallbladder cancer: Historical treatment and new management options. World J Gastrointest Oncol 2021; 13(10): 1317-1335
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Biliary Tract Cancers Version 6.2024 — January 10, 2025
American cancer society. Gallbladder Cancer Early Detection, Diagnosis, and Staging. cancer.org | 1.800.227.2345, 2023

Introduction

- Location of tumor
  - 60% in the fundus
  - 30% in the body and infundibulum
  - 10% in the cystic duct
- Pattern of spread
  - Lymphatic dissemination
    - Through lymphatic flow along glissonean pedicles
  - Hematogenous
    - Through cystic vein to portal vein or small veins directly drains to liver parenchyma
  - Local invasion -> liver and adjacent organ
  - Peritoneal spread

Ramachandran A, Srivastava DN, Madhusudhan KS. Gallbladder cancer revisited: the evolving role of a radiologist. Br J Radiol 2020; 94: 20200726

Introduction

- Pattern of LN metastasis
  - On the Right route, 95% of LNM
    - LN around CBD -> LN group 13a or the LN around PV -> LN around the aorta
  - On the left route, it could be seen in 50% of the LNM
    - Gallbladder LN around gallbladder triangle -> LN behind the head of the pancreas -> LN at hepatoduodenal ligament -> LN around the aorta
  - The portal route was seen in 20% of the LNM
    - Drained directly through the hilar LN -> peri-aortic lymph nodes

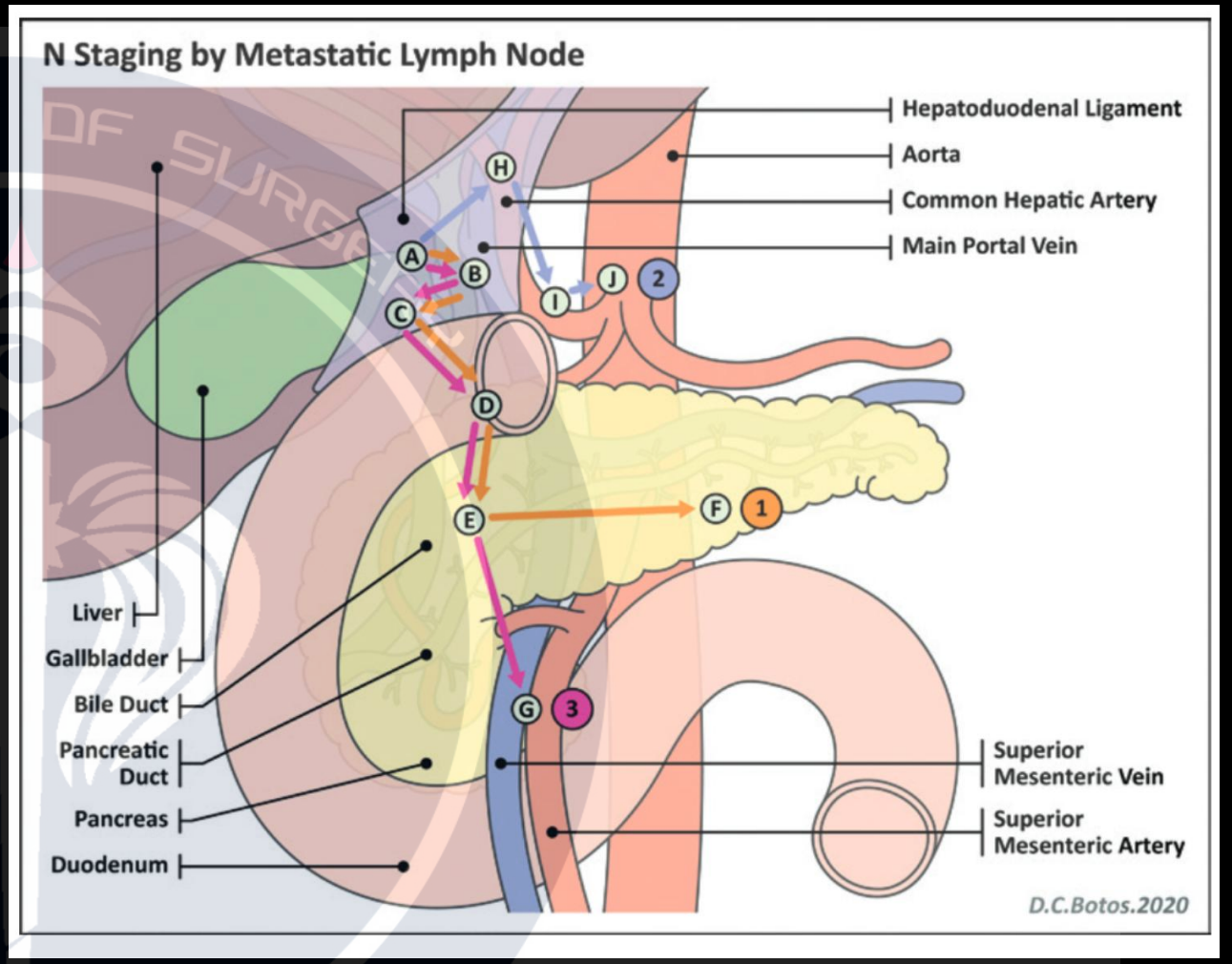

Figure 1. N staging is determined by the number of metastatic lymph nodes. 1 = cholecystoretropancreatic pathway (main pathway) (orange), 2 = cholecystoceliac pathway (blue), 3 =cholecystomesenteric pathway (pink), A = cysticduct node, B = porta hepatis node, C = node of foramen of Winslow, D = superior retropancreaticoduodenal node, E = posterior pancreaticoduodenal node (principal retroportal node), F =paraaortic lymph node, G = superior mesenteric lymph node, H = suprapyloric node, I = retroligamentous node, J = paraceliac node. (Courtesy of D. C. Botos.)

Li Y, Song Y, Zhang Y and Liu S (2022) Progress in gallbladder cancer with lymph node metastasis. Front. Oncol. 12:966835
Camila Lopes Vendrami, Michael J. Magnetta, Pardeep K. Mittal, Courtney C. Moreno, and Frank H. Miller. RadioGraphics 2021 41:1, 78-95

Introduction

- Risk of LN metastasis
  - Recurrence, extrahepatic metastasis and LNM are closely related to T stage, and among the metastases of GBC, LNM has the highest risk of recurrence.
  - The higher the T-stage of GBC is, the higher the probability of LNM
    - T1a stage : 0-2.5%
    - T1b stage : 5%-16%
    - T2 stage : 9%~~30%
    - T3 stage : 39%-72%
    - T4 stage : 67%-80%

Li Y, Song Y, Zhang Y and Liu S (2022) Progress in gallbladder cancer with lymph node metastasis. Front. Oncol. 12:966835

Presentation

- Relatively asymptomatic in its early stages
- Presentation of GBC has been divided into three common scenario
  - Identification by final pathology following a routine cholecystectomy
  - Discovery during the index surgery
  - Suspicion before surgery due to atypical symptomatology
- Malignancy identified during or after cholecystectomy for benign disease defines as “incidental gallbladder cancer”
- Clinical presentation
  - Abdominal pain, symptoms consistent with biliary colic
  - More advanced stage : jaundice, malaise, weight loss, palpable mass

Sukhumura K et al. Gallbladder cancer: Historical treatment and new management options. World J Gastrointest Oncol 2021; 13(10): 1317-1335
BLUMGART’S Surgery *of the* Liver, Biliary Tract and Pancreas. 7th ed. 2023

Presentation

- Laboratory findings
  - Lab values consistent with chronic disease
    - Anemia, hypoalbuminemia, leukocytosis
    - Advanced stage : hyperbilirubinemia, ↑ ALP
  - Tumor markers
    - Not helpful for diagnosis
    - CEA and CA 19-9 may be elevated -> useful for detection of disease recurrence
      - Increased CA 19-9 may suggest underlying occult disease

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Imaging of Gallbladder Cancer

- 3 morphologic types on imaging
  1. Mass replacing the GB, most common type (40–60%)
     - Nearly fills or replaces the lumen
     - Often directly invading the surrounding liver parenchyma

Figure 2. Mass replacing the gallbladder. (a) USG of a patient of GBC showing a heteroechoic mass replacing the GB (asterisk) with a large calculus within (arrow). (b, c) Axial CT scans in arterial (b) and venous (c) phases showing a large heterogeneously enhancing mass (asterisk) completely replacing the GB and infiltrating the liver parenchyma. GBC, gall bladder cancer; USG, Ultrasonography.

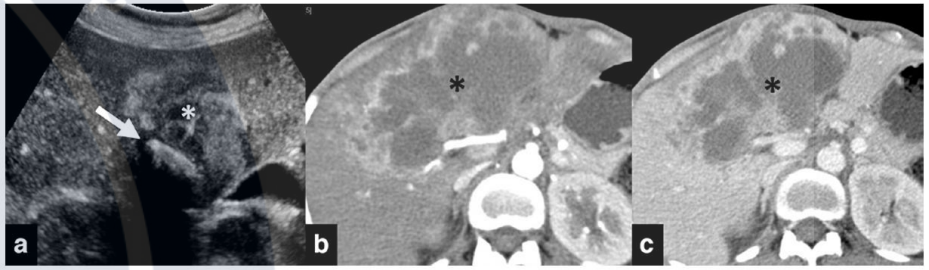
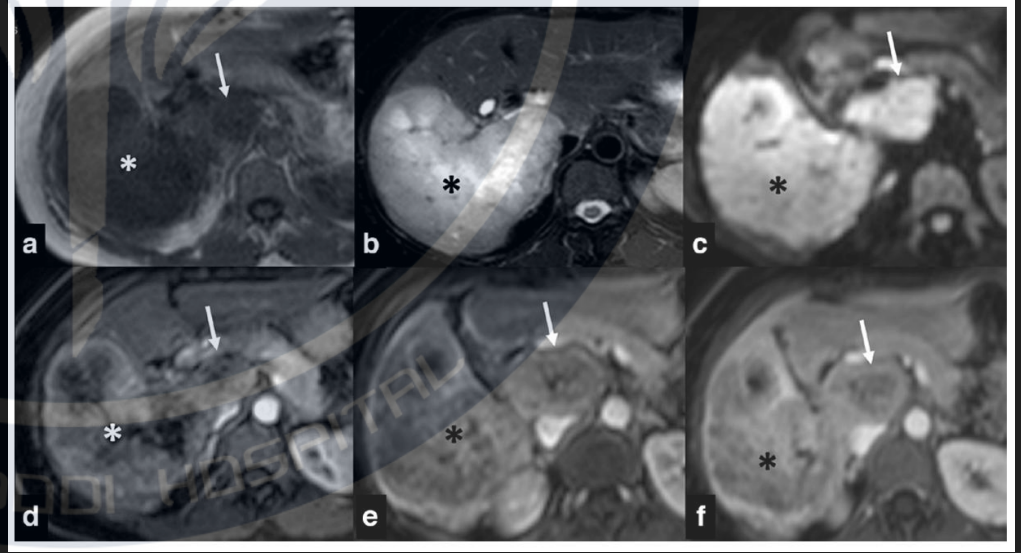


Figure 3. MRI of mass rep
T_2W fat saturated (b), di
enhanced arterial (d), ve
images showing a large ga
liver and appearing hypoi
and showing restriction c
trast enhancement. A large portocaval lymph node is noted (arrow).



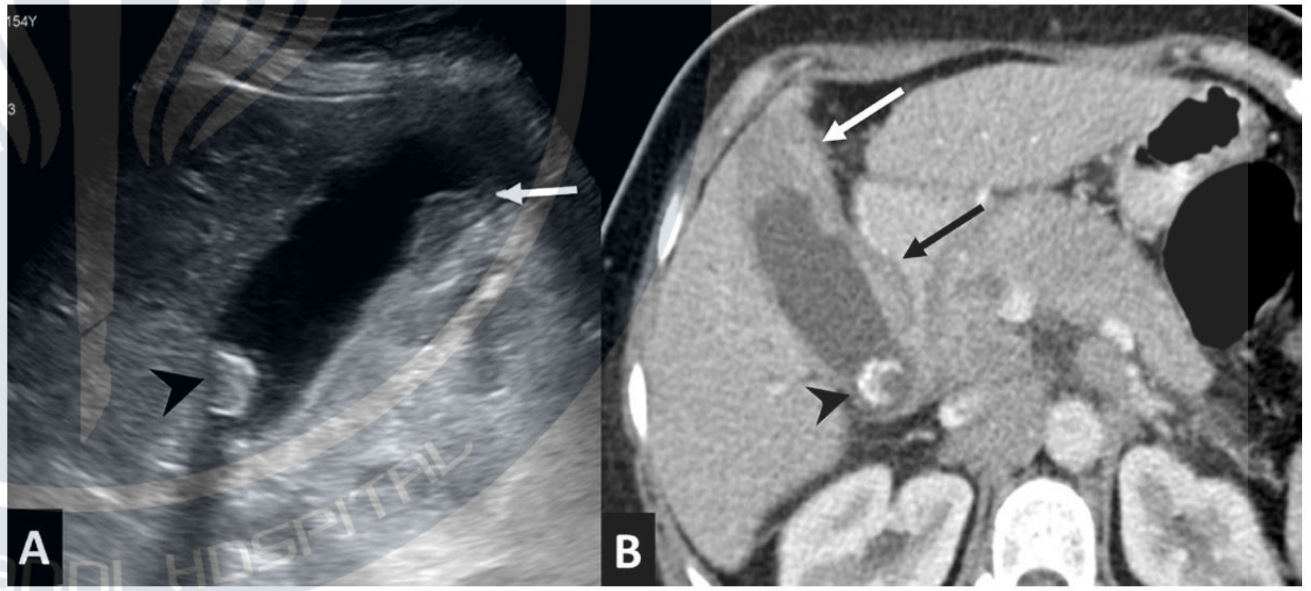
Ramachandran A, Srivastava DN, Madhusudhan KS. Gallbladder cancer revisited: the evolving role of a radiologist. Br J Radiol 2020; 94: 20200726

A. Furlan et al. AJR 2008; 191:1440–1447

Imaging of Gallbladder Cancer

- 3 morphologic types on imaging
  2. Focal wall thickening or asymmetric diffuse wall thickening (20–30%)
     - Asymmetric, irregular, or extensive thickening GB wall
     - Marked enhancement during the arterial phase that persists or becomes isodense or isointense to the liver during the portal venous phase

Figure 4. Asymmetric wall thickening: Ultrasonography (a) and CT scan (b) images showing asymmetric wall thickening in the fundus (white arrow) and body (black arrow) of gallbladder. Calculus is seen in the neck region (arrow head). Thickening which is asymmetric, nodular and >1 cm thick suggests malignancy.



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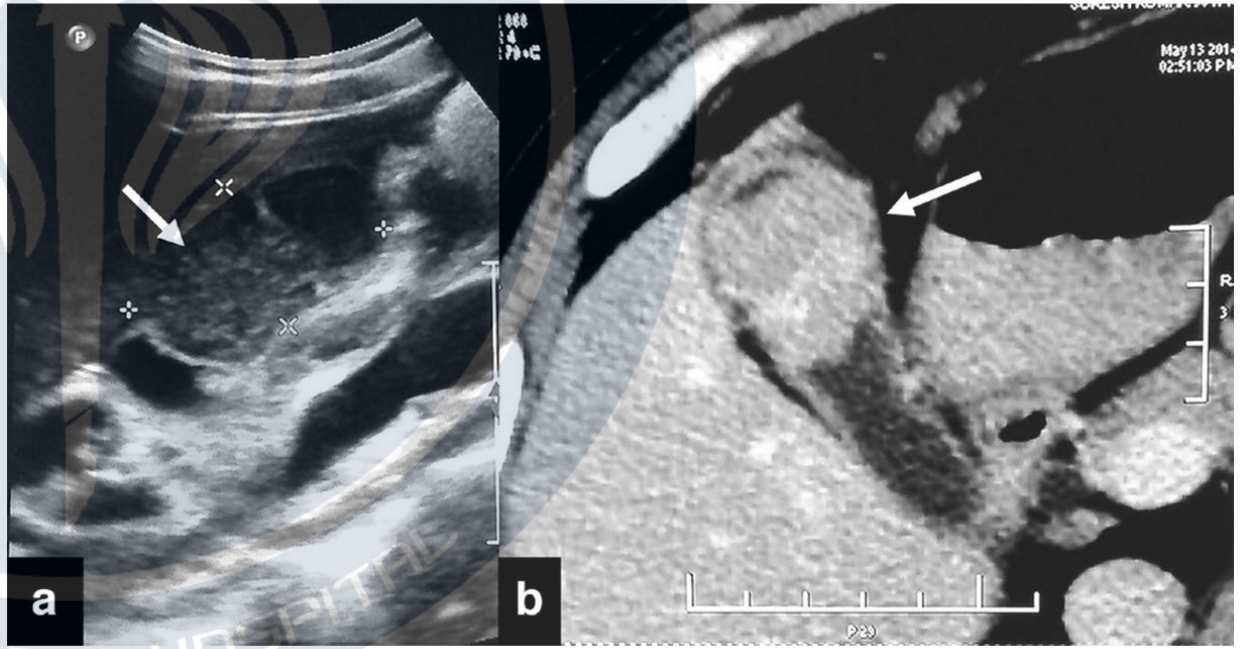
A. Furlan et al. AJR 2008; 191:1440–1447

Imaging of Gallbladder Cancer

- 3 morphologic types on imaging
  3. Intraluminal growth or polyp (15–25%)
     - Better differentiated histologically, better prognosis
     - The wall adjacent to the polyp should be normal, and irregularity or focal thickening > 3 mm can be a hint towards malignancy

Figure 5. Intraluminal polypoidal mass. Ultrasonography (a) and CT scan (b) showing a hypoechoic and enhancing polypoidal mass (arrow) in the lumen of gallbladder. This variety has the best prognosis.



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Investigation

- U/S
  - First-line modality for the evaluation of GB diseases
  - Asymmetric and irregular wall thickening and thickness of more than one cm should raise a suspicion of GBC
  - GB polyps -> malignancy is usually associated with larger polyps
  - Limited utility in differentiation of mural thickening resulting from chronic cholecystitis, subtle flat lesion,
- CEUS
  - Irregularly tortuous extension arterial branches and tortuous-type tumor vessels
  - Destruction of intactness of GB wall

Kalra et al. Journal of Clinical and Experimental Hepatology | May-June 2019 | Vol. 9 | No. 3 | 334–344
Ramachandran A, Srivastava DN, Madhusudhan KS. Gallbladder cancer revisited: the evolving role of a radiologist. Br J Radiol 2020; 94: 20200726

Investigation

- Cross sectional imaging
- CT
  - Imaging modality of choice for detect and staging of gallbladder cancer, evaluate FLR, anatomical variation
  - Inferior to USG in depicting mucosal irregularity, mural thickening, and cholelithiasis
    - Superior for evaluating the areas of the GB wall that are obscured by gallstones or mural calcification
- MRI
  - Better depict biliary anatomy and availability of diffusion- weighted sequences
  - Better definition of the level and extent of hilar involvement by GBC in MRCP
  - Diffusion- weighted imaging (DWI) : High sensitivity in the detection of liver and lymph node metastases, although specificity is poor
    - Helps in differentiating tumefactive biliary sludge from a solid tumor

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Investigation

- Cross sectional imaging
  - Mass replacing gallbladder
    - CT : Typically hypodense, 40% has hypervascular foci
    - MRI : Hypo to isointense signal in T1, Moderately hyperintense signal in T2
    - Enhancement pattern : intense irregular enhancement at periphery in arterial phase with persistent delayed enhancement
  - Focal wall thickening type
    - Asymmetric, irregular, or extensive thickening which may have marked enhancement during the arterial phase that persists or isodense during the portal venous phase
    - May arise as a nidus in preexisting background chronic cholecystitis -> obscure or delay the diagnosis of cancer
  - Polypoid lesion
    - Usually size > 1 cm, thickened implantation base

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A. Furlan et al. AJR 2008; 191:1440–1447

Investigation

- PET-CT
  - High sensitivity in detecting primary and metastatic lesions
    - Can detect occult metastasis
  - Helpful in equivocal primary lesions
  - Detect residual tumor after incidental cholecystectomy
  - Limitation for benign inflammatory lesion -> can accumulate FDG and result in false-positive interpretations

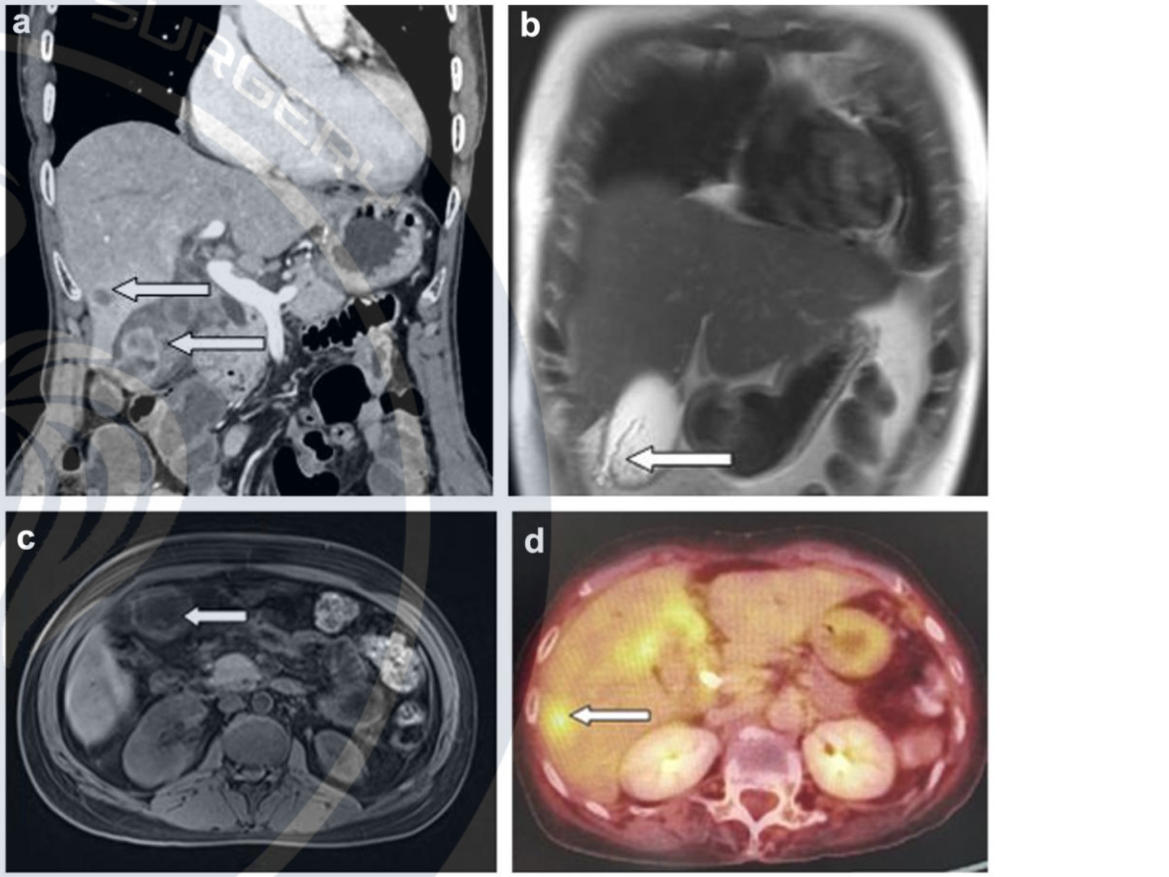


Fig. 3 (Clockwise) Coronal CECT image shows a heterogeneously enhancing advanced GBC with hepatic metastasis (**a**); coronal T2-weighted MRI image and axial fat-suppressed image show acute cholecystitis mimicking GBC (**b**, **c**); FDG PET image shows increased uptake in the GB fossa as well as in the hepatic metastasis (**d**)

Ramachandran A, Srivastava DN, Madhusudhan KS. Gallbladder cancer revisited: the evolving role of a radiologist. Br J Radiol 2020; 94: 20200726

Prasad and Sen Egyptian Journal of Radiology and Nuclear Medicine (2021) 52:1

Investigation

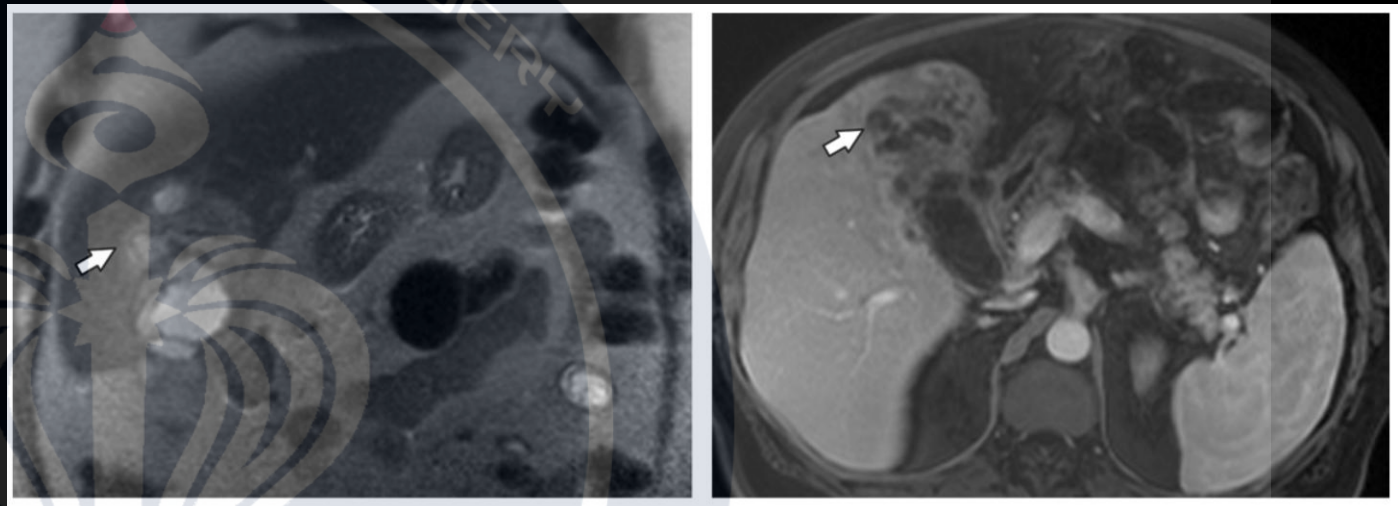
- EUS
  - Can help differentiate gallbladder cancer from other lesions
    - Assess of tumor depth of invasion; but T1 and T2 cannot easily differentiated using EUS
  - Improves the characterization of local extension and regional LN involvement
  - Tissue diagnosis from FNA/ FNB
    - Sensitivity of 80–100%, specificity of 100%, and accuracy of 83–100%
    - Risk of bile leakage and peritoneal dissemination of tumor
    - Preoperative tissue diagnosis is not routinely recommended for resectable gallbladder cancer
      - Consider in some cases when it is difficult to categorize a lesion as benign or malignant, or when the surgery is extremely invasive

S. Hijioka et al. Diagnostics 2021, 11, 1586

Mimics of gallbladder cancer

Gallbladder mass

- Pericholecystic abscess
  - Related to perforated acute or chronic cholecystitis
  - Clinical manifestation : acute/ subacute RUQ pain with sepsis, fever
  - Imaging
    - Cluster sign : multiple small adjacent abscess
    - Focal wall discontinuity, particularly in contrast enhanced
    - May contain gas in abscess
    - Fluid collection, perihepatic inflammatory changes



a. b.

Figure 8. Acute and chronic cholecystitis with suspected perforation in a 67-year-old man with abdominal pain and malaise. Cholecystitis is difficult to distinguish from gallbladder cancer at imaging. **(a)** Coronal T2-weighted image shows an abnormal gallbladder with an intermediate-signal-intensity lesion (arrow) arising from the gallbladder fundus. **(b)** Axial contrast-enhanced T1-weighted image shows heterogeneous soft tissue (arrow) arising from the gallbladder fundus, from cholecystitis mimicking gallbladder cancer. Acute and chronic cholecystititis were confirmed at surgery.

Lopes Vendrami et al.RadioGraphics 2021; 41:78–95

Mimics of gallbladder cancer

Gallbladder mass

- Primary or secondary malignancy
    - HCC invading gallbladder
    - Cholangiocarcinoma invading gallbladder
  - In large tumor evaluation of tumor origin is helpful
    - Uncertain of origin : enhancement pattern, patient characteristics
  - Biopsy is often necessary to histologically confirm the diagnosis of large tumors

Lopes Vendrami et al.RadioGraphics 2021; 41:78–95

Mimics of gallbladder cancer

Focal or diffused wall thickening

- Acute cholecystitis
  - Smooth symmetrical GB wall thickening
  - Pericholecystic edema
  - Reactive liver parenchymal enhancement
  - Early enhancement
- Chronic cholecystitis
  - Chronic intermittent obstruction of cystic duct
  - Diffused GB wall thickening
  - Mild restricted diffusion
  - Smooth delayed enhancement
- Gangrenous cholecystitis
  - Irregular arterial enhancement due to focal tissue necrosis

Gallbladder cancer :
irregular wall, focal arterial enhancement

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Mimics of gallbladder cancer

Focal or diffused wall thickening

- Xanthogranulomatous cholecystitis
  - Rare form of chronic cholecystitis with intramural nodules
  - Focal/ diffused wall thickening with preservation of inner mucosa
    - Intermediate to mild high signal intensity on T2-weighted images
    - Areas of slight enhancement on early-phase images and persistent enhancement on late-phase images -> fibrosis related to the xanthogranulomas
  - Intramural nodule -> fatty content; loss intensity in opposed phase

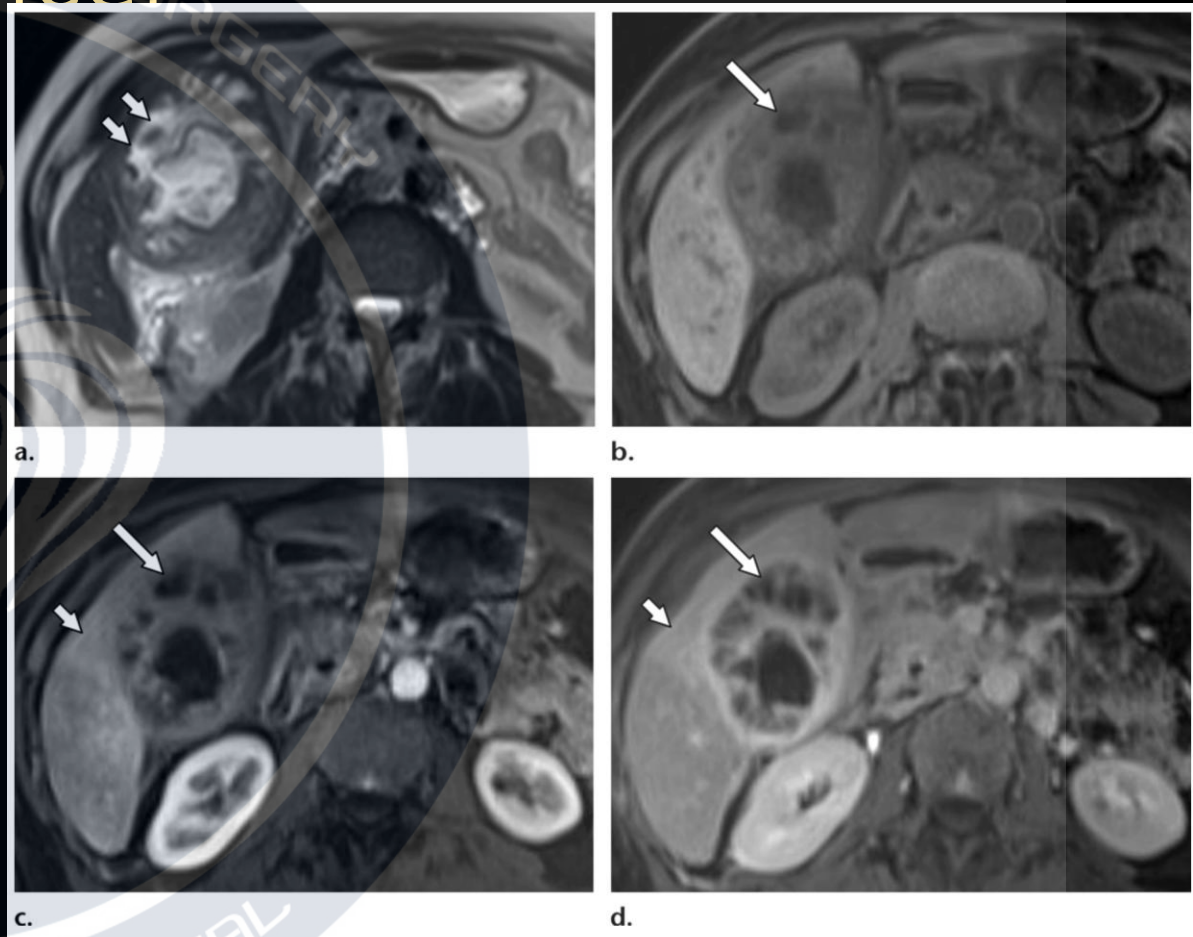

Figure 9. Xanthogranulomatous cholecystitis in a 68-year-old woman. **(a)** Axial T2-weighted image shows a heterogeneously thickened gallbladder wall with multiple intramural lesions (arrows), which are iso- or hyperintense. **(b)** Axial T1-weighted image shows hypointense cystic foci (arrow). **(c, d)** Axial early **(c)** and delayed **(d)** contrast-enhanced T1-weighted images show mild arterial and marked delayed enhancement surrounding the cystic foci (long arrow). There is mild surrounding hepatic parenchymal enhancement (short arrow), which is likely reactive.

Lopes Vendrami et al.RadioGraphics 2021; 41:78–95

Mimics of gallbladder cancer

Focal or diffused wall thickening

- Gallbladder adenomyomatosis
  - Hyperplastic changes of the gallbladder wall
  - Mucosal overgrowth, thickening of the muscular wall
  - Presence of intramural diver-ticula or sinus tracts (Rokitansky-Aschoff sinuses)
  - “pearl necklace”or “string of beads” sign (presence of Rokitansky-Aschoff sinuses within the thickened gallbladder wall
    - Better seen in MRI than in CT
  - No evidence of pericholecystic infiltration or invasion of adjacent structures

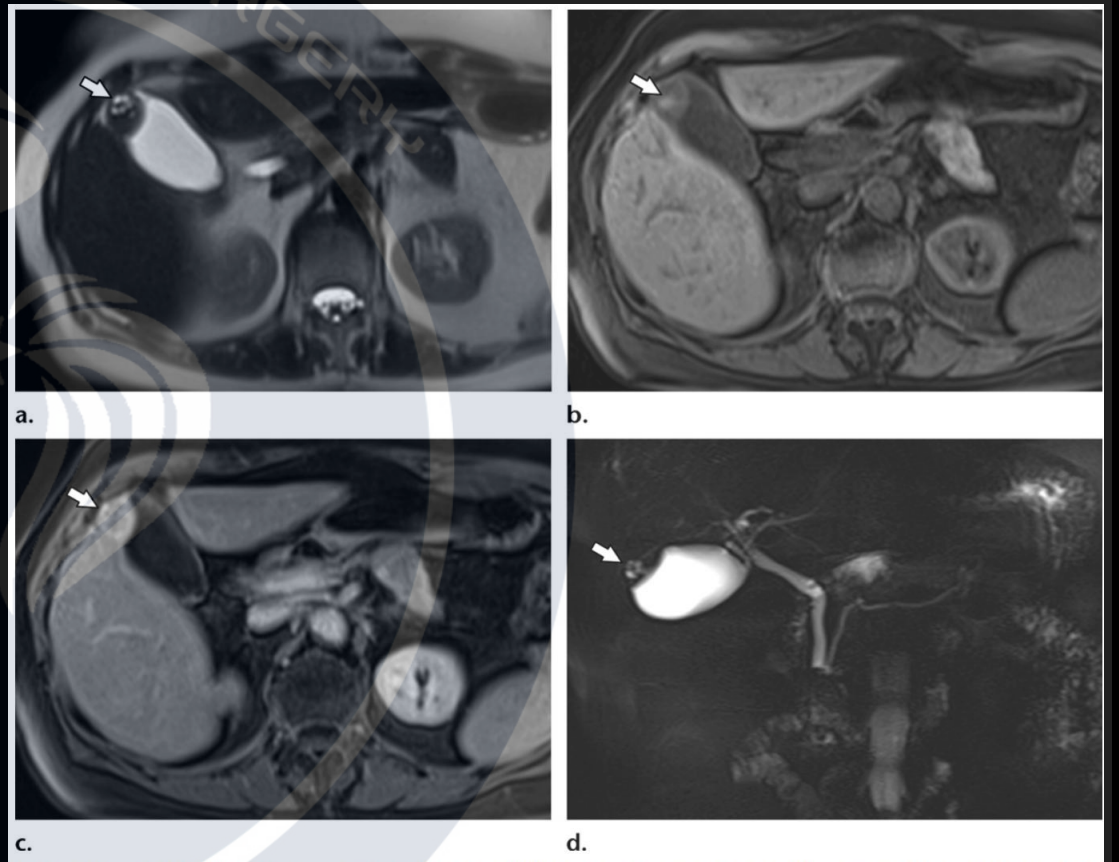

Figure 11. Gallbladder adenomyoma mimicking gallbladder cancer in a 53-year-old woman. **(a)** Axial T2-weighted image shows a focal mass (arrow) in the fundus that is hypointense with areas of high signal intensity from dilated Rokitansky-Aschoff sinuses. **(b)** Axial fat-suppressed T1-weighted image shows that the mass (arrow) has a focus of higher signal intensity. **(c)** Axial contrast-enhanced fat-suppressed T1-weighted image shows that the mass (arrow) has fairly homogeneous enhancement, from hypervascular focal fundal adenomyomatosis mimicking gallbladder cancer. **(d)** Image from MR cholangiopancreatography shows the characteristic outpouchings from dilated Rokitansky-Aschoff sinuses (arrow), which distinguish the lesion from cancer.

Lopes Vendrami et al.RadioGraphics 2021; 41:78–95

Mimics of gallbladder cancer

Focal or diffused wall thickening

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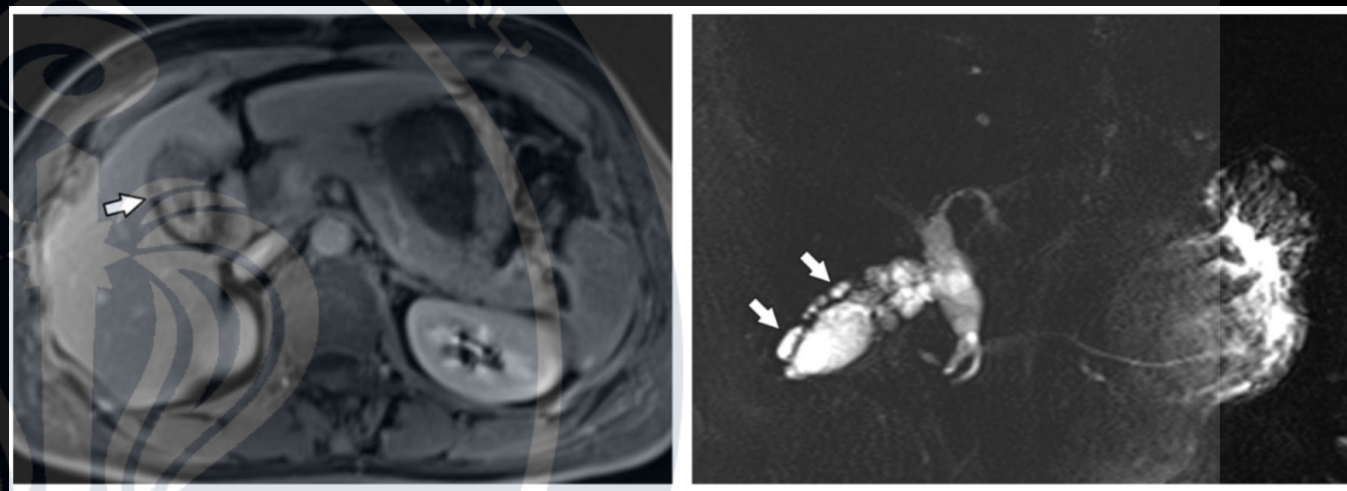

Figure 12. Adenomyomatosis in a 71-year-old woman. **(a)** Axial contrast-enhanced T1-weighted image shows apparent gallbladder wall thickening (arrow). **(b)** Image from MR cholangiopancreatography shows the “pearl necklace” sign (arrows), which refers to the characteristically curvilinear arrangement of multiple round hyperintense outpouchings.

Lopes Vendrami et al.RadioGraphics 2021; 41:78–95

Mimics of gallbladder cancer

Polypoid gallbladder lesion

- Benign polyps
  - Adenomatous polyp
  - Cholesterol polyp
  - Tumefactive sludge
- Malignant polyps
  - Metastasis to gallbladder : melanoma

- Gall bladder polyps with higher risk of malignancy
  - Size > 10 mm
  - Sessile types
  - Wall adjacent to the polyp should be normal, and irregularity or focal thickening > 3 mm

Lopes Vendrami et al.RadioGraphics 2021; 41:78–95

Management and Follow-up of Gallbladder Polyps

(detected on transabdominal ultrasound; excluding definite pseudo-polyp)

≥ 10 mm

Cholecystectomy † is suggested if no alternative cause for the patient's symptoms is demonstrated and the patient is fit for, and accepts, surgery. The patient should be counselled regarding the benefit of cholecystectomy versus the risk of persistent symptoms.

< 10 mm

Does the patient have symptoms that are attributable to the gallbladder?

Yes

Cholecystectomy † is recommended providing the patient is fit for, and accepts, surgery. Multidisciplinary discussion may be employed to assess perceived individual risk of malignancy.

No

Does patient have one or more risk factors for malignancy? #

- Age > 60 years
- Primary sclerosing cholangitis (PSC)
- Asian ethnicity
- Sessile polypoid lesion (incl. focal gallbladder wall thickening > 4 mm)

No

Yes

Polyp ≤ 5 mm:

Follow-up not required

Polyp 6-9 mm:

Follow-up ultrasound * of the gallbladder is recommended at 6 months, 1 year and 2 years.

Follow-up should be discontinued after 2 years in the absence of growth.

Polyp ≤ 5 mm:

Follow-up ultrasound * of the gallbladder is recommended at 6 months, 1 year and 2 years.

Follow-up should be discontinued after 2 years in the absence of growth.

Polyp 6-9 mm:

Cholecystectomy † is recommended if the patient is fit for, and accepts, surgery.

K. G. Foley et al. Management and follow-up of gallbladder polyps: updated joint guidelines between the ESGAR, EAES, EFISDS and ESGE. European Radiology (2022) 32:3358–3368

Table 3. Radiological differential diagnoses of GBC

Morphologic type of GBC	Imaging differential diagnosis	Remarks
Focal or diffuse wall thickening	Xanthogranulomatous cholecystitis (XGC)	A chronic inflammatory condition with focal or diffuse infiltration of foamy macrophages in the GB wall; may have pericholecystic inflammation with formation of adhesions and lymphadenopathy. Imaging characteristics: USG : Hypoechoic nodules (representing xanthogranulomas or abscesses) in the thickened GB wall[74] CT: Hypodense intramural nodules, continuity of the mucosa is maintained MRI: T1 and T2 hyperintense foci in the wall
	Adenomyomatosis	Characterised by epithelial and smooth muscle proliferation secondary to chronic obstruction. Show prominent Rokitansky Aschoff sinuses containing cholesterol, bile and sludge. No malignant potential Imaging characteristics: USG: ring down reverberation artefact due to cholesterol crystals MRI: "pearl - necklace sign" on T_2 weighted images
	Acute cholecystitis complicated by pericholecystsic abscess, fistula formation with bowel	Mimics Stage 3A tumor
Intraluminal Polypoid mass	Adenomatous polyp (neoplastic), Hyperplastic, cholesterol polyp (non-neoplastic)	Size is the most important predictor of malignancy in neoplastic polyp; Multiple numbers suggest benignity; Comet tail artefact suggests cholesterol polyp
	Carcinoid tumor	Rare tumor constituting 0.2% of all neuroendocrine tumors[75]
	Metastatic melanoma	50–60% of metastases to GB are from melanoma[76]
Mass replacing GB	Hepatocellular carcinoma (HCC)	Characteristic enhancement of HCC helps in differentiation
	Metastases to Gall bladder	

GB, gall bladder; USG, ultrasonography; XGC, xanthogranulomatous cholecystitis.

Gallb

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Diagnosis

- Preoperative tissue diagnosis is generally not recommended
  - Tendency to seed the peritoneum, biopsy tracts and surgical wound
  - Biopsy is recommended only in the case of unresectable disease
  - FNA : Acceptable sensitivity for preoperative diagnosis of gallbladder cancer of 88%
- Cholecystectomy in the known case of gallbladder cancer to provide preoperative diagnosis is also not recommended
  - Risk of disruption of the gallbladder and tumor dissemination
- In resectable disease -> Proceed to definitive resection
  - Prepared for the possibility of a resection being performed for benign disease
  - Due to dismal prognosis of gallbladder cancer -> acceptable risk when a high degree of suspicion for malignancy is present based on preoperative imaging

Qadan and Kingham. Surg Clin North Am. 2016 April ; 96(2): 229–245
BLUMGART'S Surgery *of the* Liver, Biliary Tract and Pancreas. 7th ed. 2023

Management of gallbladder cancer

- Surgery remains the first-choice basic treatment for long-sustained oncological outcomes even in elderly patients
  - Usually inoperable at presentation
  - Curative resection may be performed in only 15%-35% of cases and is associated with high recurrence
  - Extent of surgery is determined by extent of disease and location

Pavlidis ET, Galanis IN, Pavlidis TE. New trends in diagnosis and management of gallbladder carcinoma. *World J Gastrointest Oncol* 2024; 16(1): 13-29
BLUMGART'S Surgery *of the* Liver, Biliary Tract and Pancreas. 7th ed. 2023

Incidental gallbladder cancer

- Gallbladder cancer diagnosed during or after cholecystectomy for benign disease
  - 0.2 -3 % of all cholecystectomy specimen
  - 27% up to 70% of all gallbladder cancers discovered during cholecystectomy or on pathologic review
  - Mostly early stage; pathologic T1 or T2 -> potential for cure
  - Residual disease following attempted resection -> reduces disease-free interval and disease-specific survival
    - Survival comparable to stage 4 gallbladder cancer
- Incidence of residual disease : varies by the T-stage classification of the primary tumor

Residual tumor at any site	
T stage	%
T1	37.5%
T2	56.7%
T3	77.3%

Qadan and Kingham. Surg Clin North Am. 2015 April ; 95(2): 229–245
BLUMGART'S Surgery *of the* Liver, Biliary Tract and Pancreas. 7th ed. 2023
Thomas A. Aloia et al. Gallbladder Cancer: expert consensus statement. HPB 2015, 17, 681–690

Ann Surg Oncol (2020) 27:1132–1142
https://doi.org/10.1245/s10434-019-08074-4

Annals of
SURGICAL ONCOLOGY
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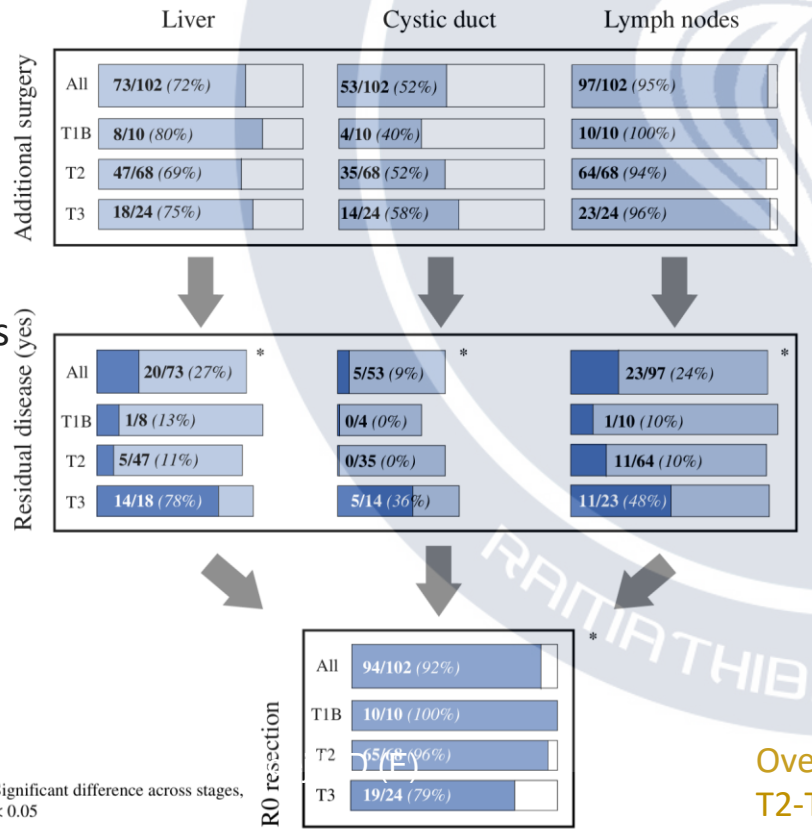
ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Re-resection in Incidental Gallbladder Cancer: Survival and the Incidence of Residual Disease

Elise A. J. de Savornin Lohman, MD, PhD[1], Lydia G. van der Geest, PhD[2], Tessa J. J. de Bitter, MSc[3], Iris D. Nagtegaal, MD, PhD[3], Cornelis J. H. M. van Laarhoven, MD, PhD[1], Peter van den Boezem, MD, PhD[1], Chella S. van der Post, MD, PhD[3], and Philip R. de Reuver, MD, PhD[1]

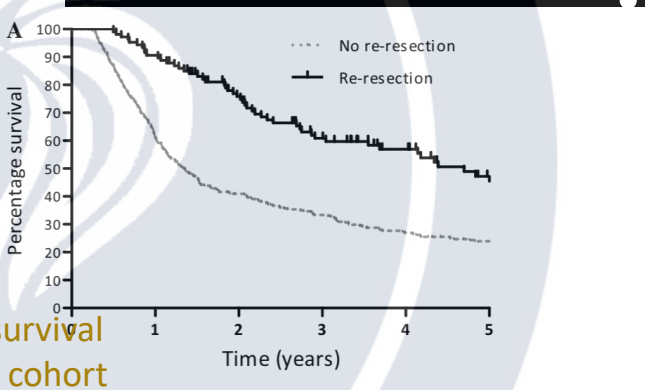
[1]Department of Surgery, Route 618, Radboudumc, Nijmegen, The Netherlands; [2]Netherlands Comprehensive Cancer Organization, Utrecht, The Netherlands; [3]Department of Pathology, Radboudumc, Nijmegen, The Neth

FIG. 2 Extent of resection and incidence of residual disease according to T stage



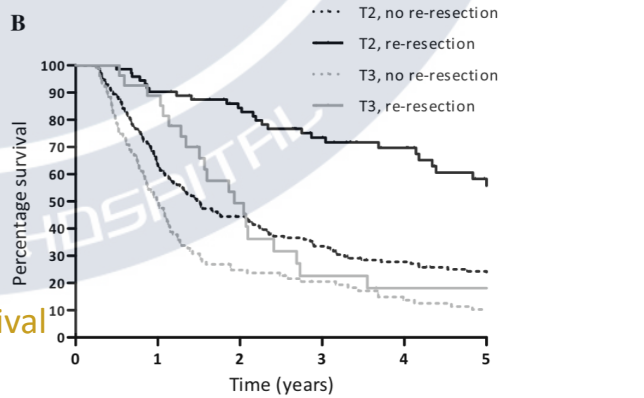
- T3 -> more presented with residual disease
- R0 re-resection was achieved in 92% of patients across the re-resected cohort
  - Only 72% of patients with T3 disease (p<0.001)

- Annals of Surgical Oncology, 2020
- Retrospective study
  - 463 Patients with iGBC
    - Netherlands Cancer Registry, and pathology reports of reresected patients
- Survival and prognostic factors were analyzed



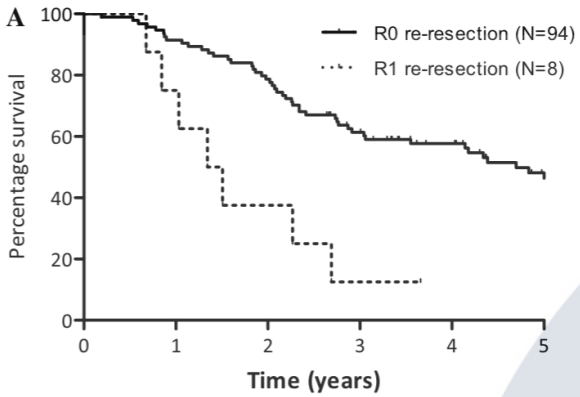
Overall survival
In entire cohort

No re-resection	N	316	195	127	99	75	62
Re-resection	N	107	98	74	56	41	27

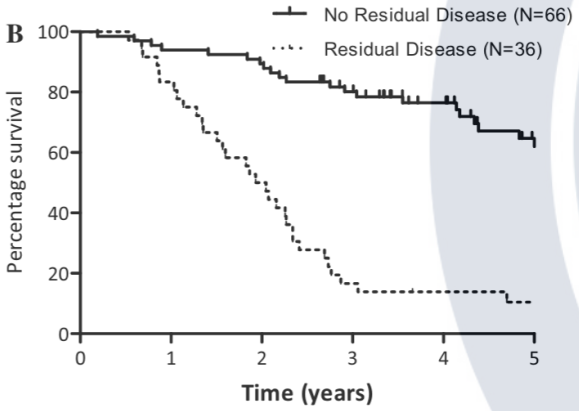


Overall survival
T2-T3

- Re-resection : better overall survival
  - Median survival was 16.1 mo in no resection vs 56.3 mo in re-resection (p<0.001)
  - Re-resection in T1b iGBC was not significantly associated with longer survival



R0	N	94	87	75	55	42	28
R1	N	8	7	4	2	1	1



RD -	N	66	63	60	50	38	25
RD +	N	36	31	19	7	5	4

- Overall survival of patients with iGBC after re-resection (N=102), by margin status and residual disease.

TABLE 2 Prognostic factors for survival after re-resection in patients with incidental gallbladder cancer (N = 102)

Characteristic	Univariable cox regression			Multivariable cox regression		
	HR	95% CI	p value	HR	95% CI	p value
Age, years	1.02	0.99–1.05	0.156			
Pathological N stage						
N0	1					
N1/N2	0.72	0.38–1.35	0.303			
N*x*	1.38	0.80–2.37	0.247			
Pathological T stage						
T1	1			[c]		
T2	1.42	0.50–4.01	0.512	[c]		
T3/T*x*	4.09	1.39–12.04	0.011	[c]		
Radicality re-resection						
R0	1			[c]		
R1/R2	3.93	1.74–8.88	0.001	[c]		
Tumor differentiation grade						
Well	1					
Moderate	0.81	0.37–1.78	0.606			
Poor	1.20	0.52–2.80	0.668			
Unknown	0.82	0.34–1.95	0.648			
Residual disease, lymph node (yes)	3.18	1.84–5.52	< 0.001	**2.35**	**1.30–4.23**	**0.005**
Residual disease, liver (yes)	7.08	3.57–14.05	< 0.001	**5.54**	**2.70–11.37**	**< 0.001**
Residual disease, cystic duct (yes)	5.82	2.17–15.57	< 0.001	[c]		
Lymphovascular invasion (yes)[a]	2.31	1.36–3.91	0.002	[c]		
Perineural invasion (yes)[b]	1.86	1.06–3.27	0.031	[c]		

All variables with $p < 0.10$ on univariable analysis were entered into the multivariable model

Bolded values indicate statistical significance ($P < 0.005$)

HR hazard ratio, *CI* confidence interval

[a]Missing values in 10 cases

[b]Missing values in 13 cases

[c]Not significant during forward selection

- Re-resection is associated with improved survival in T2 and T3 iGBC
- Presence of RD is the main prognostic factor for survival after re-resection and can be predicted by pT and pN stage

Incidental gallbladder cancer

- High-resolution imaging is uniformly utilized to evaluate for residual disease, nodal metastases, and identification of distant metastatic disease
  - CT, MRI for metastatic workup
  - Role of PET-CT is not established
    - Can detect occult metastasis
- Selection for re-operation is based on surgical staging
  - M1 disease is considered unresectable -> no role of surgical intervention

Qadan and Kingham. Surg Clin North Am. 2016 April ; 96(2): 229–245

Incidental gallbladder cancer

- Timing of Re-operation
  - Delaying re-resection of incidental gallbladder cancer may improve patient selection
    - Permit careful evaluation for residual disease and extrahepatic spread, as well as observation of the biologic behavior of the tumor
    - Avoidance of unnecessary laparotomy in patients who may not have benefited from surgical resection
  - No consensus on the ideal time for completion radical cholecystectomy
    - 4-8 wk window has the best outcome from large multicentre study
    - Urgent re-resection(<4 wk) associated with inflammation from previous surgery and complicate further resection

K. Søreide,et al. Management of incidental gallbladder cancer after cholecystectomy. BJS 2019; 106:32–45
J Palepu et al. 'IHPBA-APHPBA clinical practice guidelines': international Delphi consensus recommendations for gallbladder cancer. HPB 2024, 26, 1311–1326

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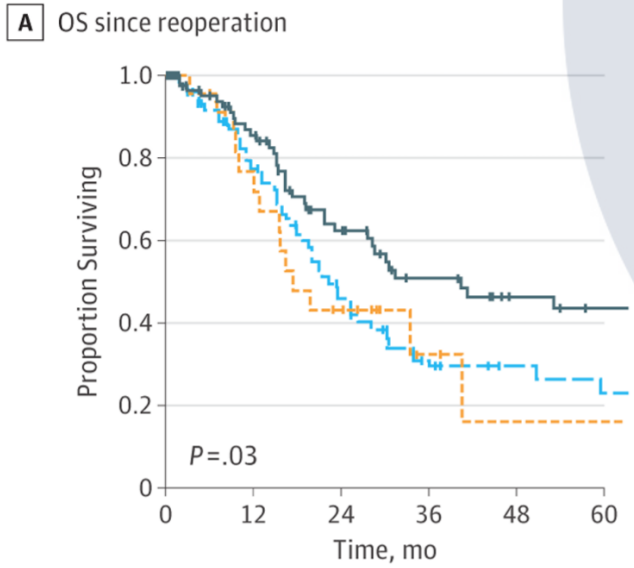
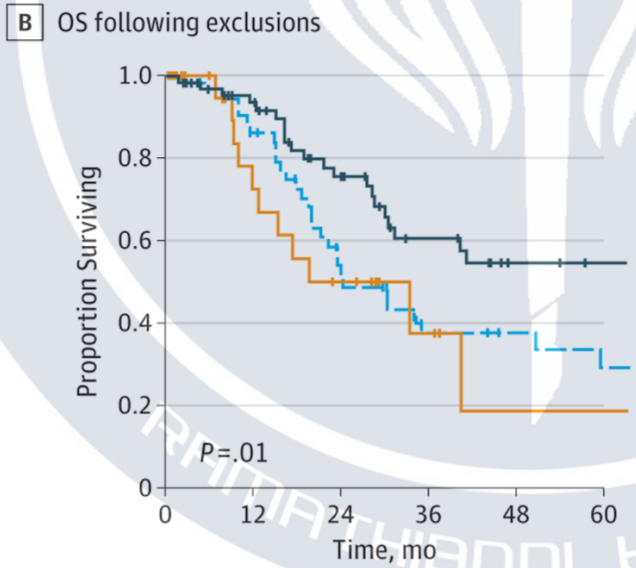
Association of Optimal Time Interval to Re-resection for Incidental Gallbladder Cancer With Overall Survival:

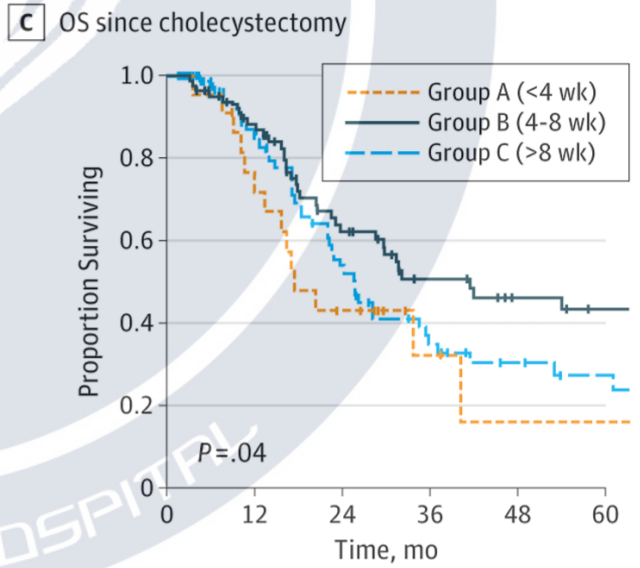
A Multi-Institution Analysis From the US Extrahepatic Biliary Malignancy Consortium

Cecilia G. Ethun, MD, Lauren M. Postlewait, MD, Nina Le, BS, Timothy M. Pawlik, MD, MPH, PhD, Stefan Buettner, MD, George Poultsides, MD, Thuy Tran, MD, Kamran Idrees, MD, Chelsea A. Isom, MD, Ryan C. Fields, MD, Linda X. Jin, MD, Sharon M. Weber, MD, Ahmed Salem, MD, Robert C. G. Martin, MD, PhD, Charles Scoggins, MD, Perry Shen, MD, Harveshp D. Mogal, MD, Carl Schmidt, MD, Eliza Beal, MD, Ioannis Hatzaras, MD, Rivfka Shenoy, MD, David A. Kooby, MD, and **Shishir K. Maithel, MD**

- Retrospective study in multicenter
- Comparing time interval from cholecystectomy to re-operation
  - Group A : <4 wk
  - Group B : 4-8 wk
  - Group C : > 8 wk
- Overall survival from date of reoperation for all patients
  - Group B was associated with improved OS (40.4 months, n = 89) compared with groups A (17.4 months, n = 25) and C (22.4 months, n = 89) (P = 0.03)







Surgical treatment of gallbladder cancer

- Staging laparoscopy
  - May avoid non-therapeutic laparotomy in about a half in patients with disseminated disease
  - Lowest yield in early stage
  - Considered in poorly-differentiated, higher T-stage(T3) with a greater risk of disseminated disease

K. Søreide,et al. Management of incidental gallbladder cancer after cholecystectomy. BJS 2019; 106:32–45

Surgical treatment of gallbladder cancer

- Extent of primary resection is based on T staging

American Joint Committee on Cancer (AJCC)
TNM Staging for Gallbladder Carcinoma (8th ed., 2017)

Table 3. **Definitions for T, N, M**

T	**Primary Tumor**
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 muscle 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 extension 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 extension 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 main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

- T1a -> simple cholecystectomy
  - Rare and mostly found on pathological review for cholecystectomy in benign disease
  - Cure rate 85-100%
- T1B, T2 -> risk of LN metastasis
  - Cholecystectomy + en-bloc liver segment 4b/5
  - Lymphadenectomy of periportal LN

Qadan and Kingham. Surg Clin North Am. 2016 April ; 96(2): 229–245

Surgical treatment of gallbladder cancer

- Extent of primary resection is based on T staging

American Joint Committee on Cancer (AJCC)
TNM Staging for Gallbladder Carcinoma (8th ed., 2017)

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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

- T3, T4; Locally advanced
  - Radical cholecystectomy including segments IVb and V + Lymphadenectomy
  - Extended hepatic or biliary resection as necessary to obtain a negative margin
  - Role of extensive vascular reconstructions -> not shown to provide a durable survival benefit
  - En-bloc adjacent organ resection is permissible but has not been associated with improved longterm survival

Qadan and Kingham. Surg Clin North Am. 2016 April ; 96(2): 229–245
Thomas A. Aloia et al. Gallbladder Cancer: expert consensus statement. HPB 2015, 17, 681–690

Table 4 Surgical procedures performed for gallbladder cancer

Procedure	Description	Indications
Curative procedures		
Simple cholecystectomy	Dissection, ligation, and transection of cystic duct and artery at the level of Calot triangle and dissection of the cystic plate	Benign gallbladder conditions, gallbladder polyps, porcelain gallbladder, GBC (T0, Tis, and T1a)
Extended cholecystectomy	Simple cholecystectomy + hepatic wedge resection at the level of gallbladder fossa (2-3 cm in depth)	T1b and higher GBC
IVb/V hepatic bisegmentectomy	Resection of liver segments IVb and V *en bloc* with the gallbladder with intra-parenchymal transection of the middle hepatic vein	GBC invading liver parenchyma
Extended liver resections	Most commonly right hepatectomy, rarely left hepatectomy	GBC invading structures of porta hepatis
Bile duct resection	Resection of the extrahepatic bile duct + Roux-en-Y hepaticojejunostomy	GBC invading extrahepatic bile ducts or positive cystic duct margin at frozen section pathology
Lymphadenectomy	Removal of lymph nodes from N1 and N2 zones	T1b and higher GBC, N+ GBC
Multivisceral resection	May involve right colectomy, pancreaticoduodenectomy, resection of abdominal wall, *etc.*	Locally advanced GBC
Palliative procedures		
Biliodigestive anastomoses	Roux-en-Y hepaticojejunostomy	Locally advanced unresectable GBC presenting with jaundice
Digestive anastomoses	Gastro-enteric anastomosis, ileo-transverse colon anastomosis	Locally advanced unresectable GBC presenting with intestinal obstruction

Okumura K et al. Gallbladder cancer: Historical treatment and new management options. World J Gastrointest Oncol 2021; 13(10): 1317-1335

Surgical treatment of gallbladder cancer

- Surgical treatment of extrahepatic bile duct
  - Positive cystic duct margin to warrant additional re-excision, bile duct resection can be avoided
    - Intra-operative frozen section of the cystic duct stump margin can help determine the need for extended duct resection
    - Bile duct resection + reconstruction(Roux-en-Y hepaticojejunostomy anastomosis)
  - Routine bile duct resection is not recommended
    - No improve outcome, increase morbidity

Qadan and Kingham. Surg Clin North Am. 2016 April ; 96(2): 229–245
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Surgical treatment of gallbladder cancer

- Hepatic margin and extended liver resection
  - Recommendations varied from limited 2 cm margin of segment4b/5 to formal anatomical segment 4b/5 resection
  - Retrospective studies showed parenchymal sparing with achieving R0 resection give no difference in OS to formal anatomical resection

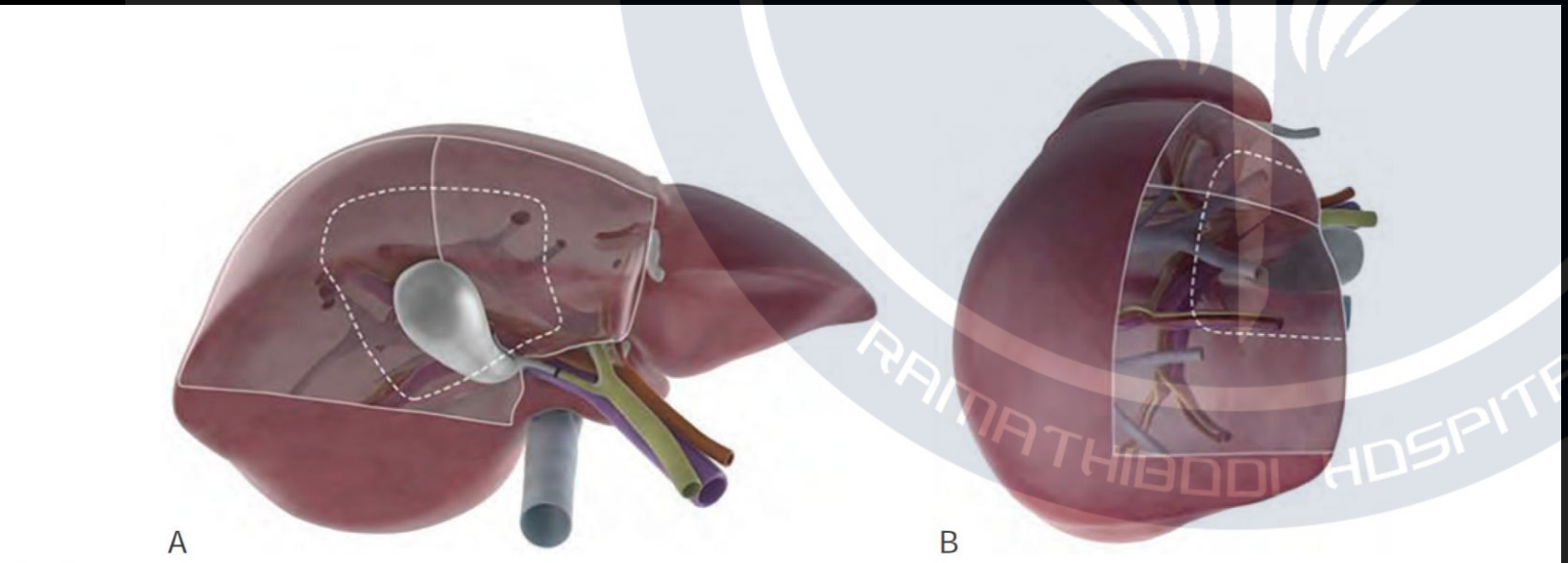

FIGURE 49.6 Anatomic IVb/V segmentectomy *(solid white line)* compared with nonanatomic wedge resection *(dotted white line)* of the liver for radical resection of gallbladder cancer in two views (see Chapter 119).

- Major hepatectomy : Rt hepatectomy or extended Rt hepatectomy
  - Only performed if necessary to achieved negative margins
  - Tumor invade inflow vascular structures

Qadan and Kingham. Surg Clin North Am. 2016 April ; 96(2): 229–245
BLUMGART'S Surgery *of the* Liver, Biliary Tract and Pancreas. 7th ed. 2023

Surgical treatment of gallbladder cancer

- Lymphadenectomy
  - Independently associated with poor prognosis
  - LN resection showed improved survival
  - Multiple studies showed cutoff of harvested LN 6 or greater associated with improved DFS
  - Standard lymphadenectomy (D2) : Dissection of LN level 1 and 2
    - Level 1 (nodes along cystic duct or the common bile duct)
    - Level 2 (nodes located posterosuperior to the head of the pancreas and around the portal vein/hepatic arteries) lymph nodes

Qadan and Kingham. Surg Clin North Am. 2016 April ; 96(2): 229–245

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J Palepu et al. 'IHPBA-APHPBA clinical practice guidelines': international Delphi consensus recommendations for gallbladder cancer. HPB 2024, 26, 1311–1326

Surgical treatment of gallbladder cancer

- Lymphadenectomy
  - LN stations 8, 12c, 12b, 12a, 12p, and 13a
  - Any LN dissection beyond this template should be labelled as ‘extended’ resection

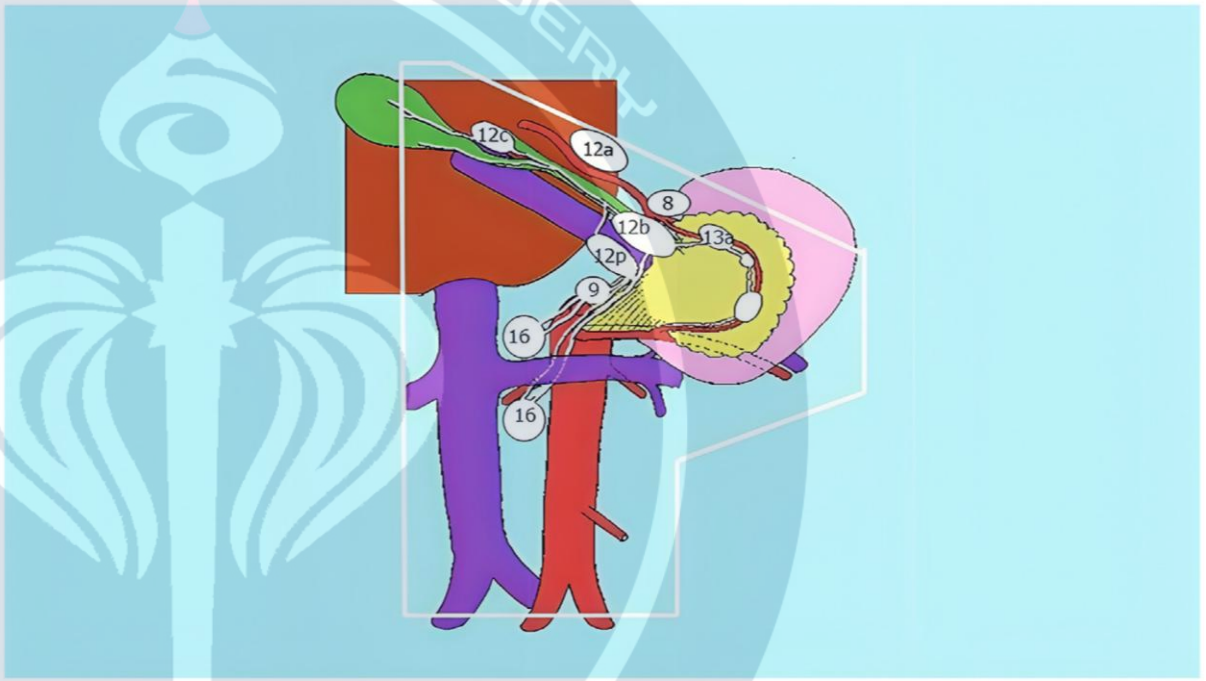

Figure 1 Standard lymph node dissection for gallbladder carcinoma. The standard dissection involves the lymph nodes in the hepatoduodenal ligament (12c, 12b, 12a, and 12p), the lymph nodes along the common hepatic artery (8), and the posterior pancreatoduodenal lymph nodes (13). 8: lymph nodes around the common hepatic artery; 9: lymph nodes around the celiac trunk; 12c: the cystic lymph nodes; 12b: the pericholedochal lymph nodes; 12a: lymph nodes around the proper hepatic artery; 12p: lymph nodes around the portal vein; 13: the posterior superior pancreaticoduodenal lymph nodes; 14: lymph nodes around the superior mesenteric artery; 16: the paraaortic lymph nodes

J Palepu et al. ‘IHPBA-APHPBA clinical practice guidelines’: international Delphi consensus recommendations for gallbladder cancer. HPB 2024, 26, 1311–1326

Surgical treatment of gallbladder cancer

- Port site resection
  - Incidence of port site metastasis 10%
    - Increase incidence with perforation of gallbladder during cholecystectomy
    - Highest at extraction port
  - Port site metastasis patients have poorer OS than patients w/o port sire involvement
    - Port site resection was not associated with improve OS or RFS
  - Not in the standard of care, increase rate of incisional hernia
- Gallbladder perforation at the index surgery
  - Higher recurrence in perforated gallbladder
    - Once perforated, use of retrieval bag cannot reduce the recurrence rate

Qadan and Kingham. Surg Clin North Am. 2016 April ; 96(2): 229–245
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Surgical treatment of gallbladder cancer

- Minimally invasive surgery
  - Surgical access : laparoscopic, laparocopic converted to open
    - No negative influence on survival
  - No clear adverse outcomes comparing open vs laparoscopic
  - Some might concern about reduced LN yield in laparoscopic approach
  - MIS (laparoscopic/robotic) can be offered in early GBC and should be performed by HPB surgeons/centers experienced in MIS

K. Søreide,et al. Management of incidental gallbladder cancer after cholecystectomy. BJS 2019; 106:32–45
J Palepu et al. 'IHPBA-APHPBA clinical practice guidelines': international Delphi consensus recommendations for gallbladder cancer. HPB 2024, 26, 1311–1326

Nonincidental gallbladder cancer

- Patient usually presents with symptoms in advanced stage
  - Less likely to undergo resection
- Jaundice as the presenting symptoms
  - Invasion of biliary tree
  - More likely to have advanced disease
- Outcomes are significantly worse compared with incidentally-discovered disease, even when matched for disease stage
- The principle in surgery of nonincidental gallbladder cancer and incidental cancer are similar
  - Due to increased risk of both dissemination of disease and locally advanced disease : Staging laparoscopy is recommended for evaluation of resectability

Qadan and Kingham. Surg Clin North Am. 2016 April ; 96(2): 229–245
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Intraoperative frozen section

- The intraoperative frozen tissue diagnosis is fairly reliable as to whether lesions are malignant or benign
- Accuracy is low in patients with polypoid lesions of the gallbladder
- Not reliably measure the depth of invasion of gallbladder carcinoma
- Some guideline suggest intraoperative CNBx with frozen section before radical resection in the absence of a preoperative diagnosis

Yamaguchi et al. Accuracy of Frozen Section Diagnosis of Gallbladder Tumor. Journal of Surgical Oncology 1997;65:132–136
Thomas A. Aloia et al. Gallbladder Cancer: expert consensus statement. HPB 2015, 17, 681–690

RESEARCH ARTICLE

Journal of SURGICAL ONCOLOGY WILEY

Surgical management of suspected gallbladder cancer: The role of intraoperative frozen section for diagnostic confirmation

Benjamin K. Y. Chan[1,2] | Lucia Carrion-Alvarez[1,3] | Rebecca Telfer[1] | Adeeb H. Rehman[1,2] | Nicholas Bird[1] | Kulbir Mann[4] | Robert P. Jones[1] | Hassan Z. Malik[1] | Stephen W. Fenwick[1] | Rafael Diaz-Nieto[1]

- J Surg Oncol. 2022
- Retrospective review of 454 complex gallbladder cases
- Patients were reviewed in MDT discussion
- Patients with suspected cancer, considered to have resectable disease
  - Operation with surgeon's intraoperative assessment
  - Frozen section -> Entire gallbladder was submitted to pathologist to evaluate cystic duct margin and area of concern

- None of the patients deemed to have benign disease following MDT evaluation had incidental gallbladder cancer on final pathology

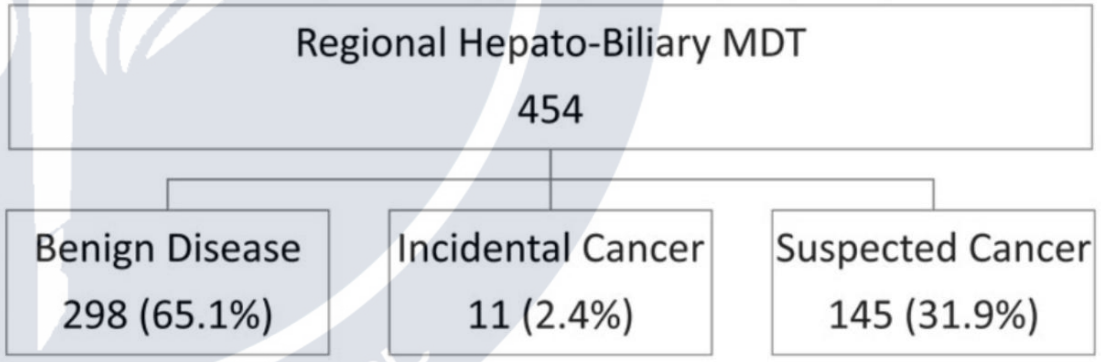

FIGURE 1 Regional hepato-biliary MDT patient outcome flow diagram. MDT, multidisciplinary team

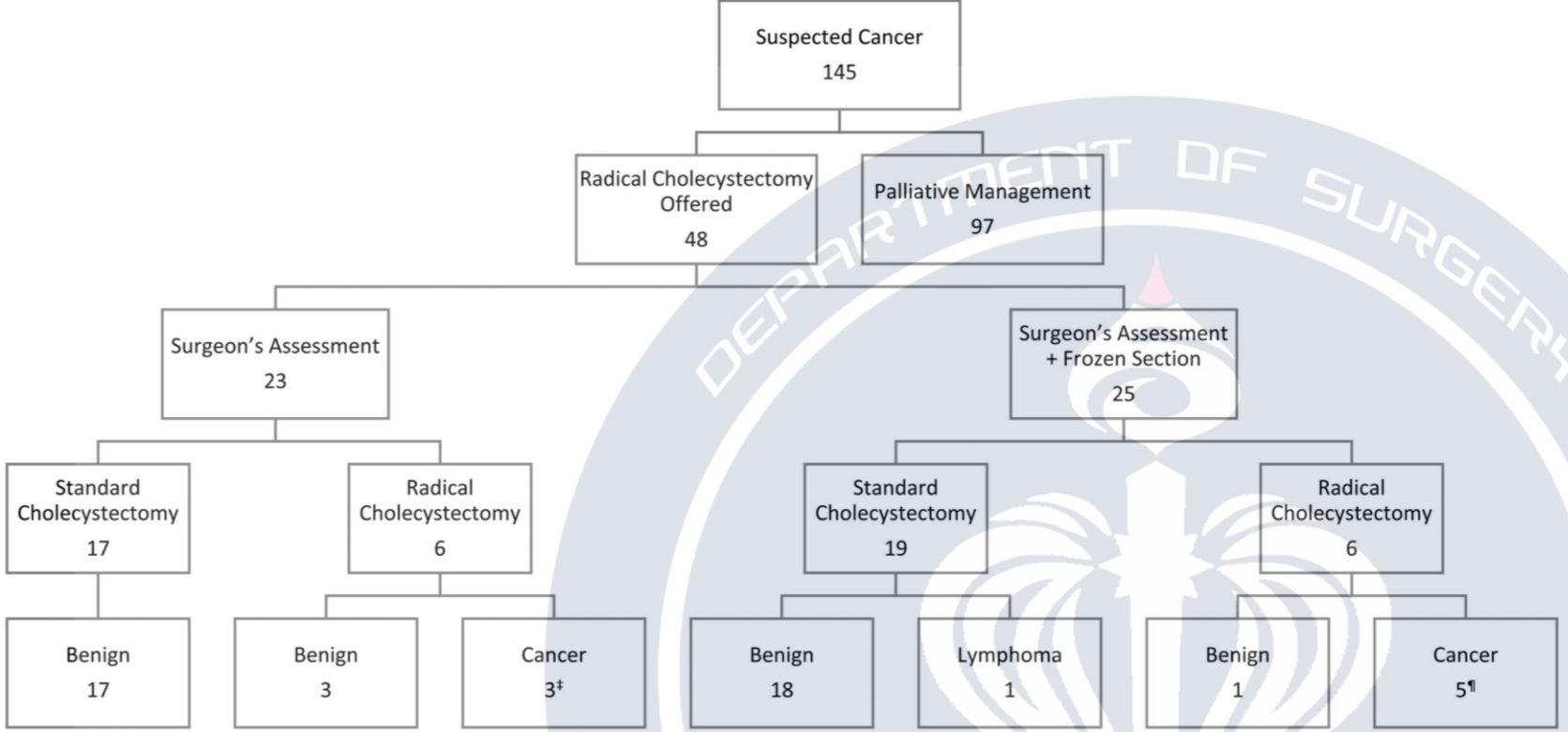

FIGURE 2 Potentially resectable gallbladder cancer patient flow diagram. Included one patient with ‡melanoma and ¶squamous cell carcinoma

- 48 patients -> offered a radical cholecystectomy had an intraoperative assessment for malignancy by the operating surgeon
- Traditional approach in 23 patients (47.9%)
  - 17 (74.0%) underwent a standard cholecystectomy -> all were benign
- 25 patients (52.1%) that underwent additional frozen section analysis
  - 19 (76.0%) underwent a standard cholecystectomy including a case of lymphoma

- MDT process is highly sensitive in identifying gallbladder cancersbut lacks specificity
- Surgeon's intraoperative assessment remains paramount in differentiating benign disease
- Intraoperative frozen section analysis was found to be a safe and viable adjunct to the surgeon's assessment

ORIGINAL ARTICLE

Utility and limitations of intraoperative frozen section diagnosis to determine optimal surgical strategy in suspected gallbladder malignancy

Shraddha Patkar[1*], Kaival Gundavda[2,*], Vikram Chaudhari[1], Subhash Yadav[3], Kedar Deodhar[3], Mukta Ramadwar[3] & Mahesh Goel[1]

[1]Department of Gastrointestinal and Hepatobiliary Surgery, Department of Surgical Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, Maharashtra, India, [2]Department of Surgical Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, Maharashtra, India, and [3]Department of Pathology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, Maharashtra, India

- HPB, 2022
- Retrospective analysis of suspected gallbladder cancer patients underwent upfront surgical resection
- Surgeon perform a surgical staging and clinically assess the gallbladder intraoperatively
  - Low suspicion : A cystic plate 'simple' cholecystectomy
    - Specimen was sent for frozen section
    - Radical cholecystectomy was performed when FS showed invasive carcinoma or dysplasia
  - High suspicion : anticipatory extended cholecystectomy
- 491 FS guided resections

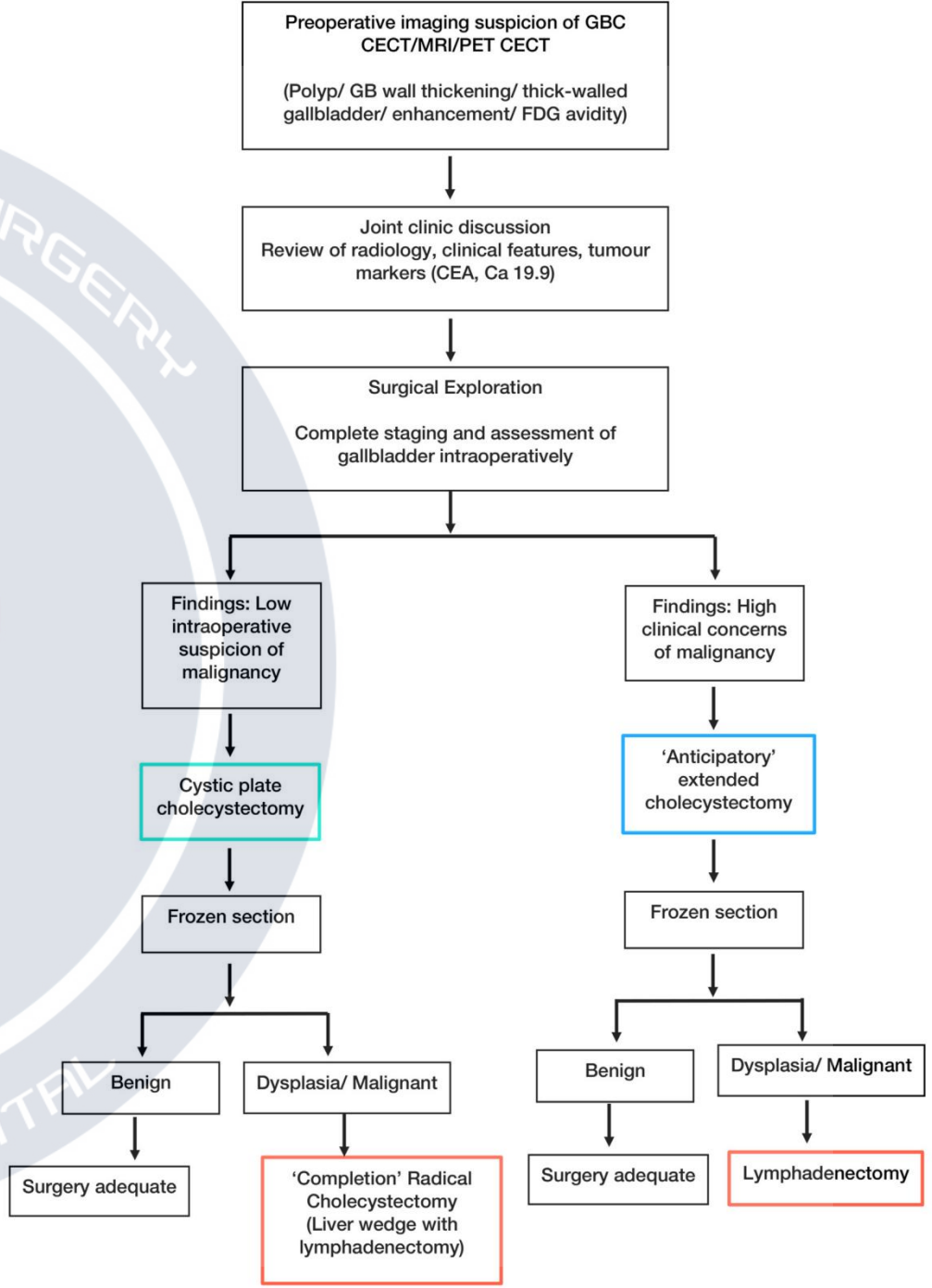

Figure 1 Suggested evaluation and treatment algorithm for suspected GBC (GB: gallbladder, FS: Frozen Section).

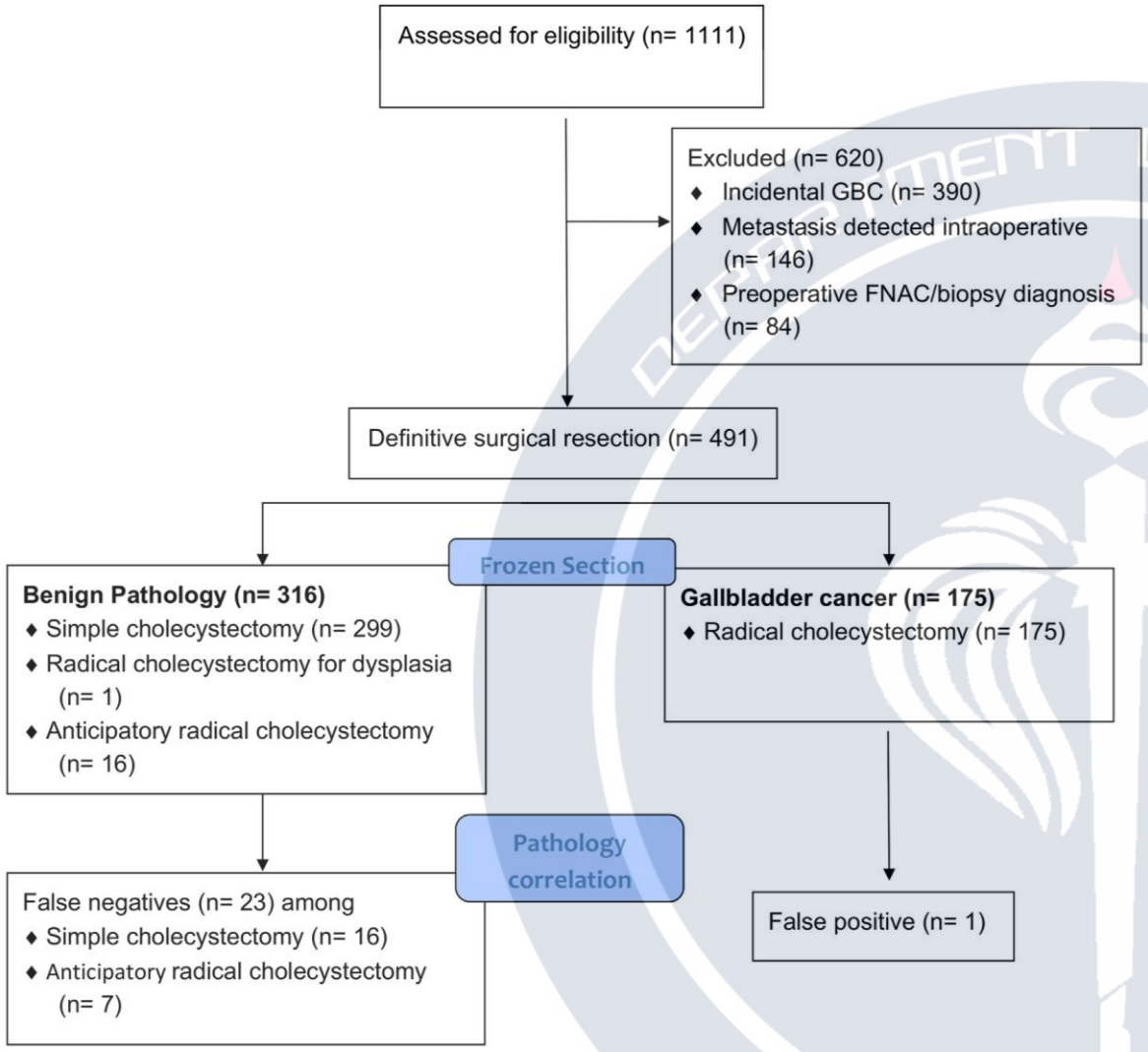

Figure 2 Frozen section and pathology correlation in patients undergoing definitive surgical resection (GBC: gallbladder cancer.

Table 1 Pathology in FS reported negative for malignancy (n = 316)

	Surgical Procedure	Histopathology
FS negative for malignancy: 315	299 Simple Cholecystectomy	Benign: 283 Malignancy: 16
	16 'Anticipatory' Extended Cholecystectomy with lymphadenectomy	Benign: 9 Malignancy: 7
Dysplasia on FS: 1	Radical Cholecystectomy	Dysplasia: 1

Table 3 Data depicted as a 2 × 2 contingency table. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) and diagnostic accuracy of frozen section calculated

	HPR positive	HPR negative	
FS positive	174 True positives (A)	1 False positives (B)	175
FS negative	23 False negatives (C)	293 True negatives (D)	316
	197	294	Total: 491

Sensitivity: A/A + C = 88.32%.
Specificity: D/D + B = 99.6%.
PPV: A/A + B = 99.42%.
NPV: D/C + D = 92.7%.
Diagnostic Accuracy: A + D/A + B + C + D = 95.11%.

- For radiologically suspected GBC
  - Histologically confirmed diagnosis by intraoperative FS before undertaking radical resections is prudent
  - FS is safe and accurate as an adjunct for surgical strategy in suspected GBC
  - Frozen section -> less sensitive in 'polypoidal' tumours representing ICPN are encountered.

Surg Endosc
DOI 10.1007/s00464-015-4733-5

Determining the extent of cholecystectomy using intraoperative specimen ultrasonography in patients with suspected early gallbladder cancer

Ji Hoon Park[1,2] · Young Hoon Kim[1,2] · Haeryoung Kim[3] · Yoo-Seok Yoon[4] · Young Rok Choi[4] · Jai Young Cho[4] · Yoon Jin Lee[1,2] · Ho-Seong Han[4]

- Surgical Endoscopy 2015
- 45 patients underwent cholecystectomy for suspicious of gallbladder cancer
- Specimen ultrasound to determine the depth of invasion then specimen was sent for frozen section

- US alone
  - Sensitivity 81 % (54–96 %)
  - Specificity 85 % (65–96 %)
- Frozen section
  - Sensitivity 43 % (10–82 %)
  - Specificity 95 % (75–100 %)
- US was feasible to be incorporated in clinical practice
  - Combined use of specimen US and frozen section examination could help surgeons make correct decisions on the extent of cholecystectomy
  - Difficult to differentiate T1a vs T1b

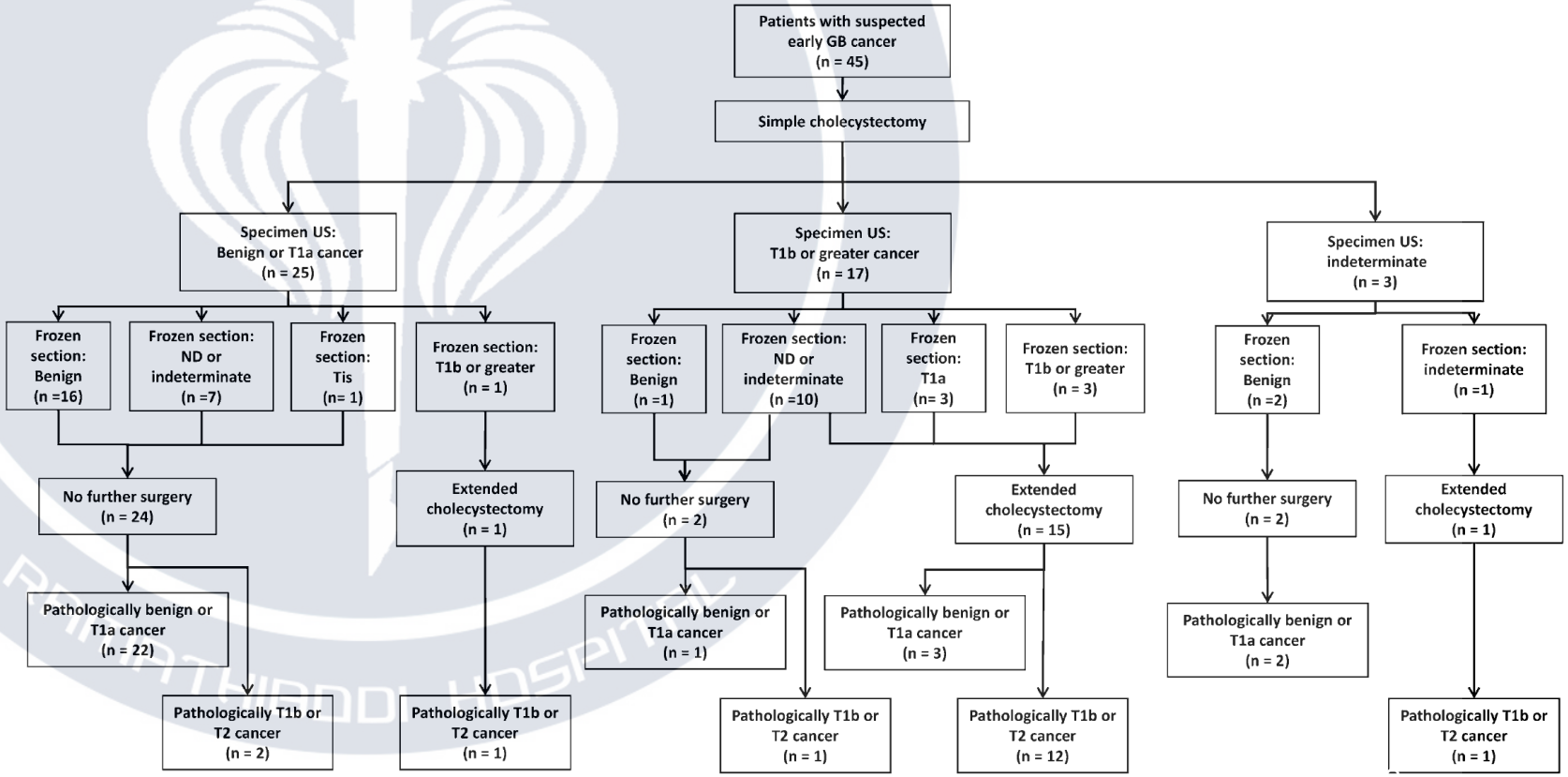

Fig. 1 Patient flow diagram. *GB* gallbladder, *ND* not done, *US* ultrasonography

Gallbladder cancer: Sukhum Kobdej,MD.(F)

Table 1 Imaging criteria for specimen ultrasonography for the assessment of the depth of invasion

Stage	Sonographic findings	
	Polypoid lesion	Flat lesion
Benign or T1a	Pedunculated mass with a thin base and preserved adjacent wall structures	Cholecystitis: intact or disrupted mucosal layer with or without mucosal thickening
		Adenomyomatosis: intramural cysts or echogenic foci in the thickened wall
		Adenocarcinoma: hypoechoic wall thickening not involving outer hyperechoic layer[a]
T1b	Sessile and/or broad-based mass with a preserved outer hyperechoic layer	Hypoechoic wall thickening not involving outer hyperechoic layer[a]
T2	Sessile and/or broad-based mass, but with a narrowed outer hyperechoic layer	Diffuse wall thickening with a narrowed outer hyperechoic layer

[a] Imaging characteristic differentiating T1a and T1b was not described in the literature

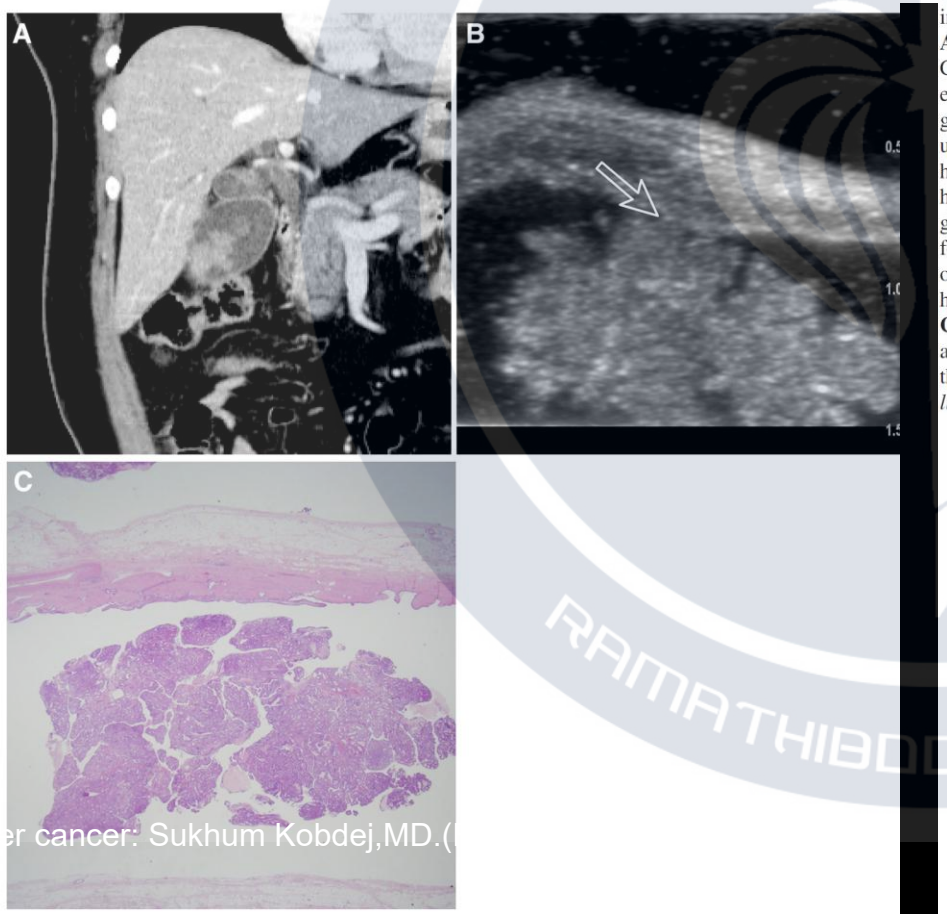

Fig. 2 T1a gallbladder cancer in a 76-year-old female. **A** A contrast-enhanced coronal CT image shows a enhancing mass in the gallbladder. **B** The specimen ultrasonography image shows a homogenous echoic mass with a lobulated margin in which the attachment was very thin (*arrow*). **C** The permanent pathology slide shows the well-differentiated adenocarcinoma. The mass was detached from the gallbladder wall during specimen preparation

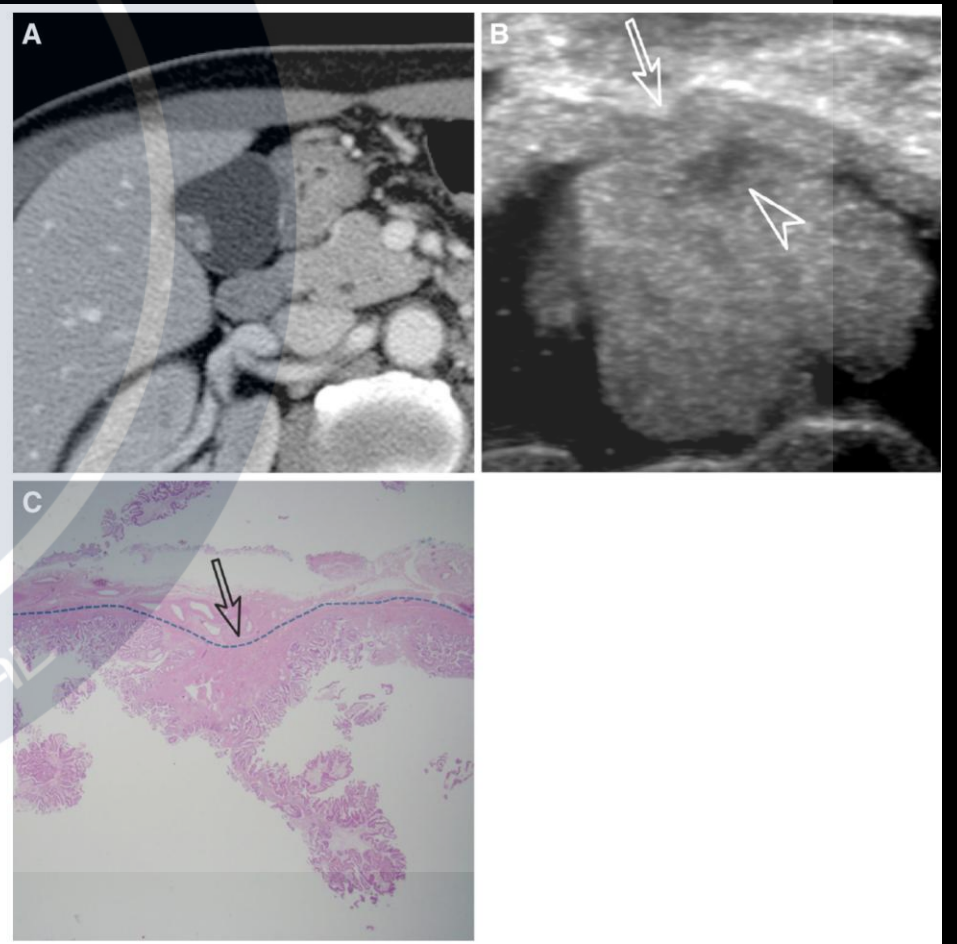

Fig. 3 T1b gallbladder cancer in a 71-year-old male. **A** Contrast-enhanced transverse CT image showing a 1.6-cm enhancing mass at the gallbladder. **B** The specimen ultrasonography image shows a homogenous echoic mass with a hypoechoic attachment to the gallbladder wall (*arrowhead*). A focal dimpling is visible at the outer margin of the inner hypoechoic layer (*arrow*). **C** Permanent pathology slide also shows the focal dimpling of the muscularis propria (*dotted line*)

Table 1 Imaging criteria for specimen ultrasonography for the assessment of the depth of invasion

Stage	Sonographic findings	
	Polypoid lesion	Flat lesion
Benign or T1a	Pedunculated mass with a thin base and preserved adjacent wall structures	Cholecystitis: intact or disrupted mucosal layer with or without mucosal thickening
		Adenomyomatosis: intramural cysts or echogenic foci in the thickened wall
		Adenocarcinoma: hypoechoic wall thickening not involving outer hyperechoic layer[a]
T1b	Sessile and/or broad-based mass with a preserved outer hyperechoic layer	Hypoechoic wall thickening not involving outer hyperechoic layer[a]
T2	Sessile and/or broad-based mass, but with a narrowed outer hyperechoic layer	Diffuse wall thickening with a narrowed outer hyperechoic layer

[a] Imaging characteristic differentiating T1a and T1b was not described in the literature

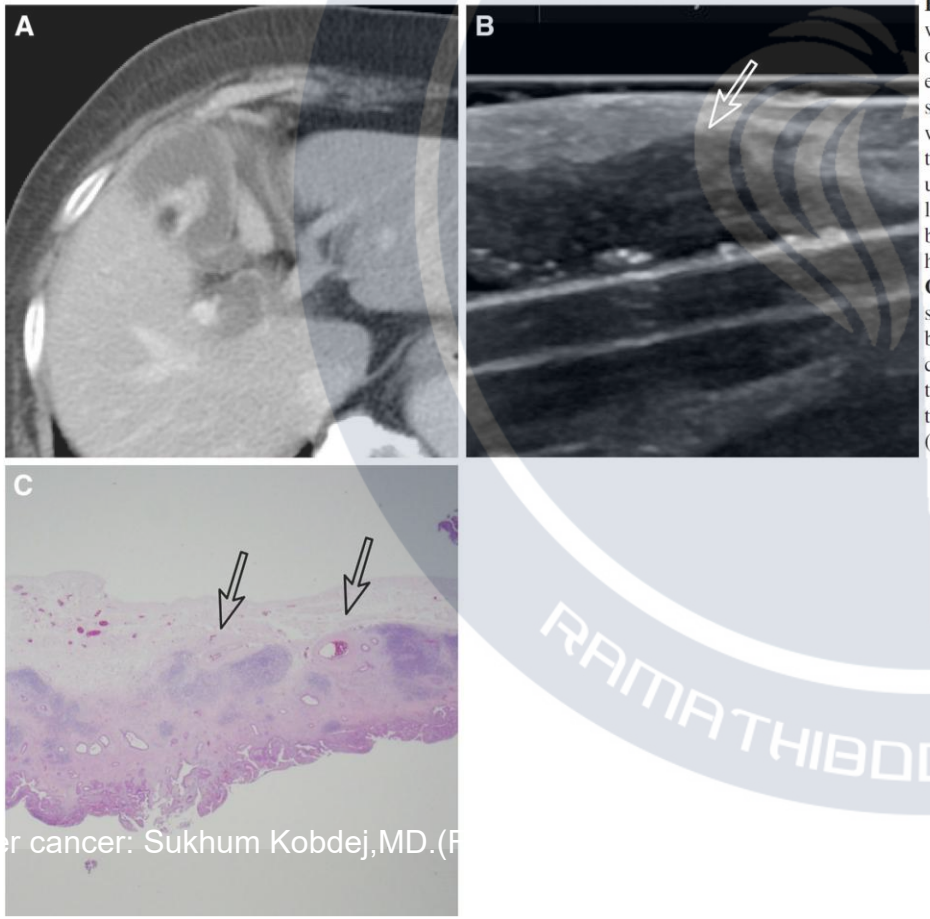

Fig. 4 T2 gallbladder cancer of a 79-year-old female. **A** A contrast-enhanced transverse CT image shows an asymmetric wall thickening in the gallbladder. **B** The specimen ultrasonography image shows a thickening of the inner hypoechoic layer invading the outer hyperechoic layer (*arrow*). **C** The permanent pathology slide shows tumor cells invading the perimuscular connective tissue layer (*arrows*)

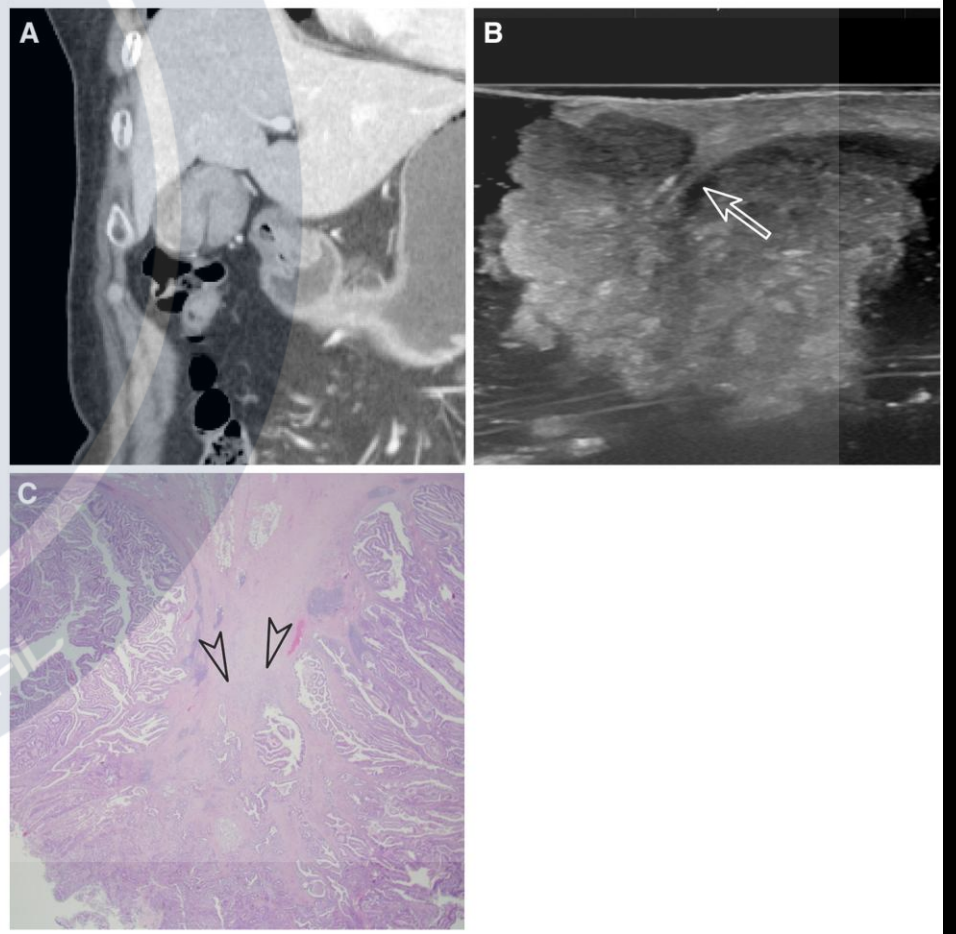

Fig. 5 T2 gallbladder cancer with a large stalk in a 58-year-old female. **A** A contrast-enhanced coronal CT image shows a 3.9-cm enhancing mass with a hypoattenuating stalk in the gallbladder. **B** The specimen ultrasonography image shows a large mixed echoic stalk budding from the outer hyperechoic layer (*arrow*). **C** The permanent pathology slide shows the stalk containing both smooth muscle and connective tissue. Note the tumor cells extending beyond the proper muscles (*arrowheads*)

Adjuvant therapy

- Adjuvant therapy may improve survival in patients with high-risk (T3–4, N1–2, positive margin) pathologic features
  - Patients with node-positive disease + negative margins -> Insufficient evidence at the current time to choose between adjuvant chemotherapy and chemoradiation
- SEER data support the use of adjuvant chemoradiation over chemotherapy alone, there is insufficient record of chemotherapy usage in the SEER database
  - Many experts will treat node-positive, margin-negative patients with adjuvant chemotherapy followed by consolidative chemoradiotherapy after restaging confirms an absence of distant metastasis
- Adjuvant chemoradiation is the treatment of choice in patients with R1/2 resection margins

Thomas A. Aloia et al. Gallbladder Cancer: expert consensus statement. HPB 2015, 17, 681–690

Adjuvant therapy

Adjuvant Therapy[c,1]

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances

• Capecitabine (category 1)[d,2]	• Gemcitabine + capecitabine[3]
	• Gemcitabine + cisplatin
	• Single agents:
	  ▸ 5-fluorouracil
	  ▸ Gemcitabine
		• None

Agents Used with Concurrent Radiation

- 5-fluorouracil
- Capecitabine

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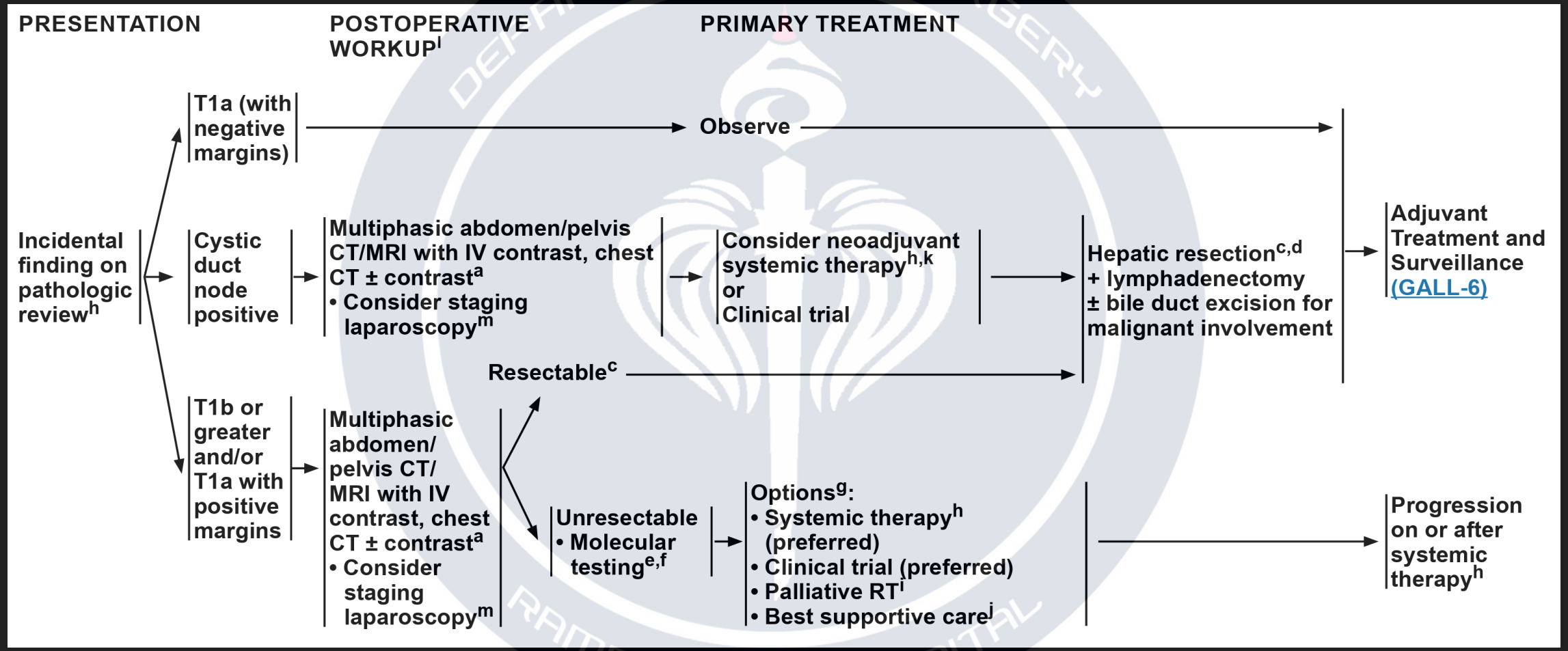
Neoadjuvant therapy

- Neoadjuvant therapy would be best applied to patients with clinical T3/T4/N1 disease on clinical trial or registry
  - Deserve further exploration
  - Gemcitabine and cisplatin -> most common agents used
    - Currently the best regimen to apply appropriately in the neoadjuvant setting

Thomas A. Aloia et al. Gallbladder Cancer: expert consensus statement. HPB 2015, 17, 681–690



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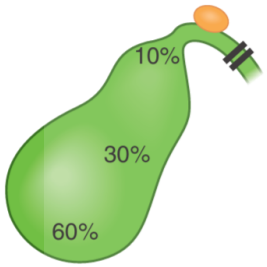
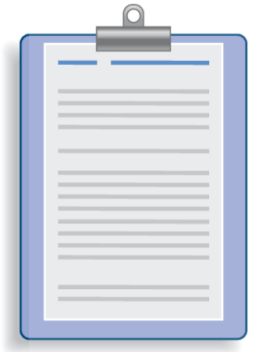
Pathology



- Cystic node? pN status
- Cystic duct? R status
- Complete sampling? T category
- Location? Hepatic or peritoneal side

>90% adenocarcinoma

Surgical note



Key information from index cholecystectomy

- Indication: stones/inflammation
- Urgency: emergency/elective
- Access: open, laparoscopic, converted
- Surgery: completed, partial or piecemeal; perforation? spillage?
- Specimen removal: port-site, use of bag
- Intraoperative findings: liver, peritoneum, other

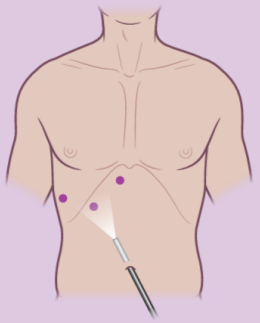
Staging

± Observation time

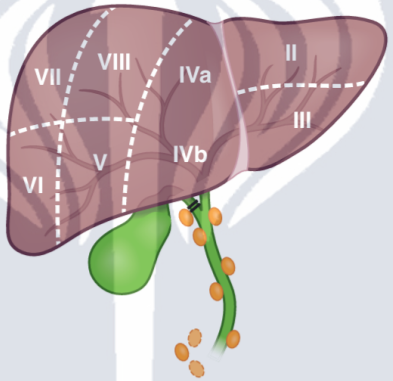
Imaging

- Multidetector CT: chest + abdomen
- MRI of liver
- PET–CT

± Staging laparoscopy



Surgical management



Redo surgery

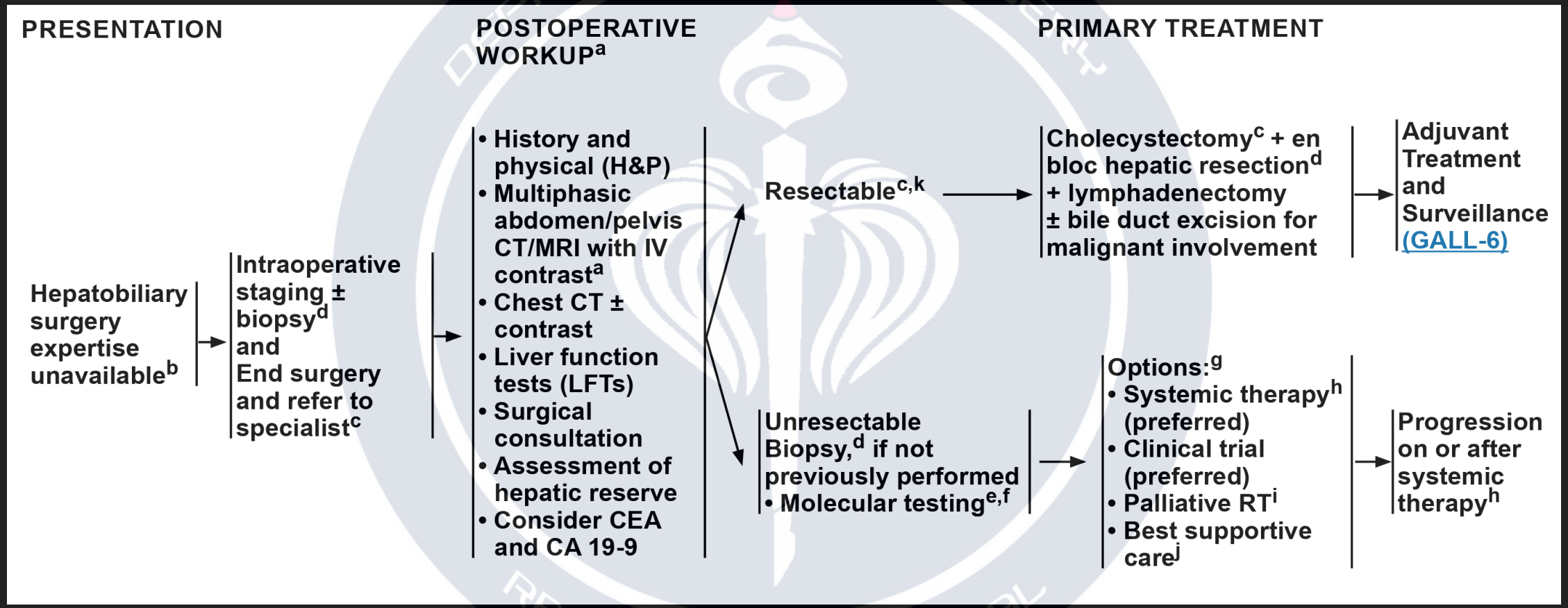
Extent of liver: liver bed or segments IVB+V

- ± Common bile duct excision
- ± Lymph node dissection
- ± Any wider excision or extended surgery

Adjuvant therapy

- Chemotherapy
- ± Radiotherapy
- ± Neoadjuvant?

K. Søreide,et al. Management of incidental gallbladder cancer after cholecystectomy. BJS 2019; 106:32–45



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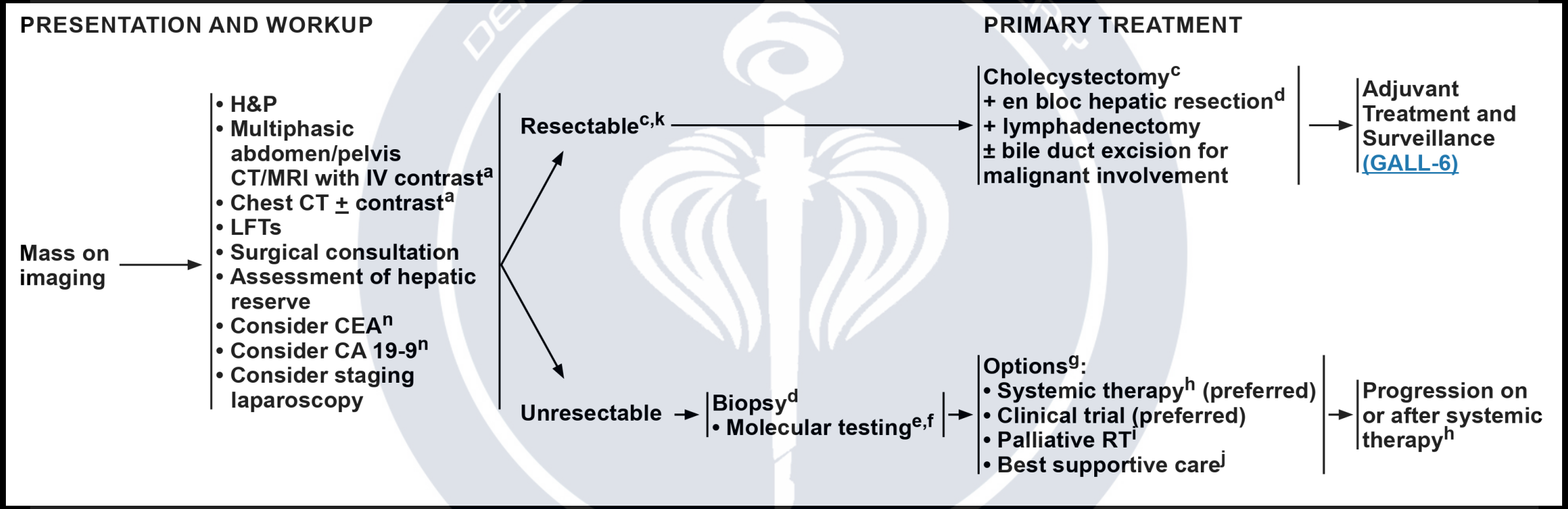

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Thank You