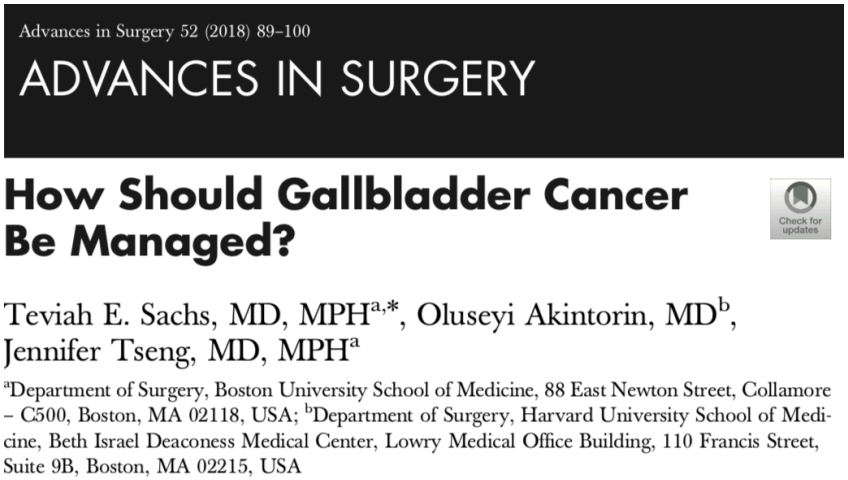
Gallbladder cancer : Incidental gallbladder cancer : how to manage ?

Bert Van den Bossche (ASZ Aalst)

BSHBPS XIXth Post Graduate Course

Epidemiology

- Gallbladder cancer : highly malignant and rarely curable
- 5000 newly diagnosed/ y in US
- very bad overall survival
- eventhough :


Advances in Surgery 52 (2018) 89–100
ADVANCES IN SURGERY

How Should Gallbladder Cancer Be Managed?

Teviah E. Sachs, MD, MPH[a,*], Oluseyi Akintorin, MD[b], Jennifer Tseng, MD, MPH[a]

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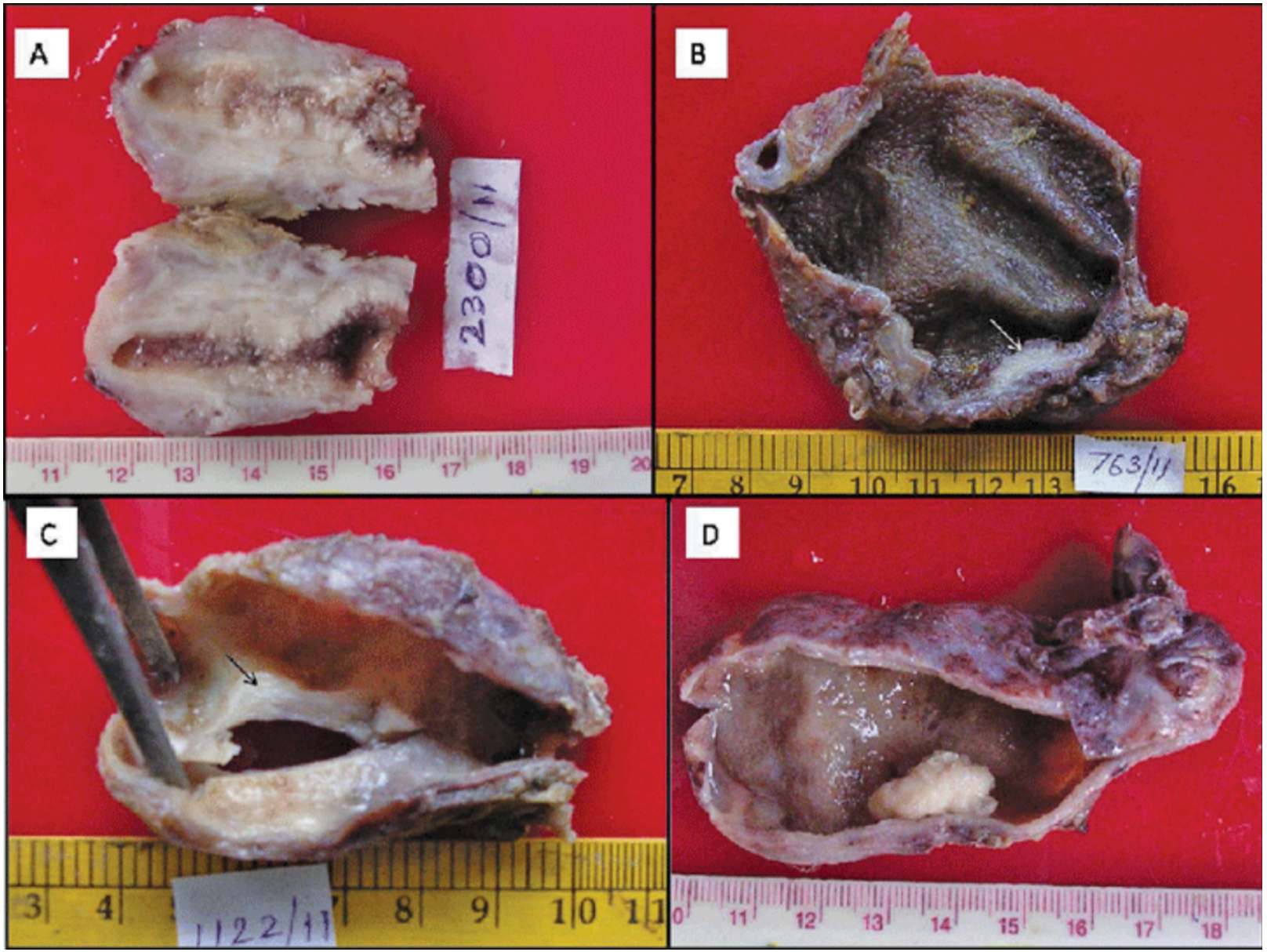
✓ for incidental gallbladder cancer - mostly found on laparoscopic resection - cure is possible and survival rates are far better



Incidental Gall Bladder Carcinoma in Patients Undergoing Cholecystectomy : A Report of 7 Cases

Ramesh S Waghmare1, Rima N Kamat2

1Assistant Professor, 2Associate Professor, Department of Pathology, Topiwala National Medical College and BYL Nair Ch. Hospital, Dr. A.L. Nair Road, Mumbai Central,

Epidemiology

- diagnosis is incidental in 50 - 70 % of cases, either during or subsequent to cholecystectomy
- incidence: 0,35 - 1,5% of cholecystectomies worldwide
- more commonly in acute cholecystitis (present in 57% of Ca cases)
- sex ratio : 2 / 4 (m / f)
- mostly in the 7th decade, with a ‘long’ history of cholelithiasis

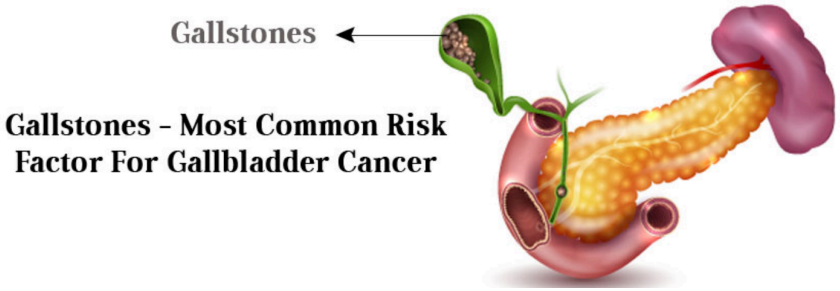
REVIEW

Incidentally-discovered gallbladder cancer: When, why and which reoperation?

M. Isambert[a,*], C. Leux[b], S. Métairie[b], J. Paineau[c]

Journal of Visceral Surgery (2011) **148**, e77—e84

Epidemiology

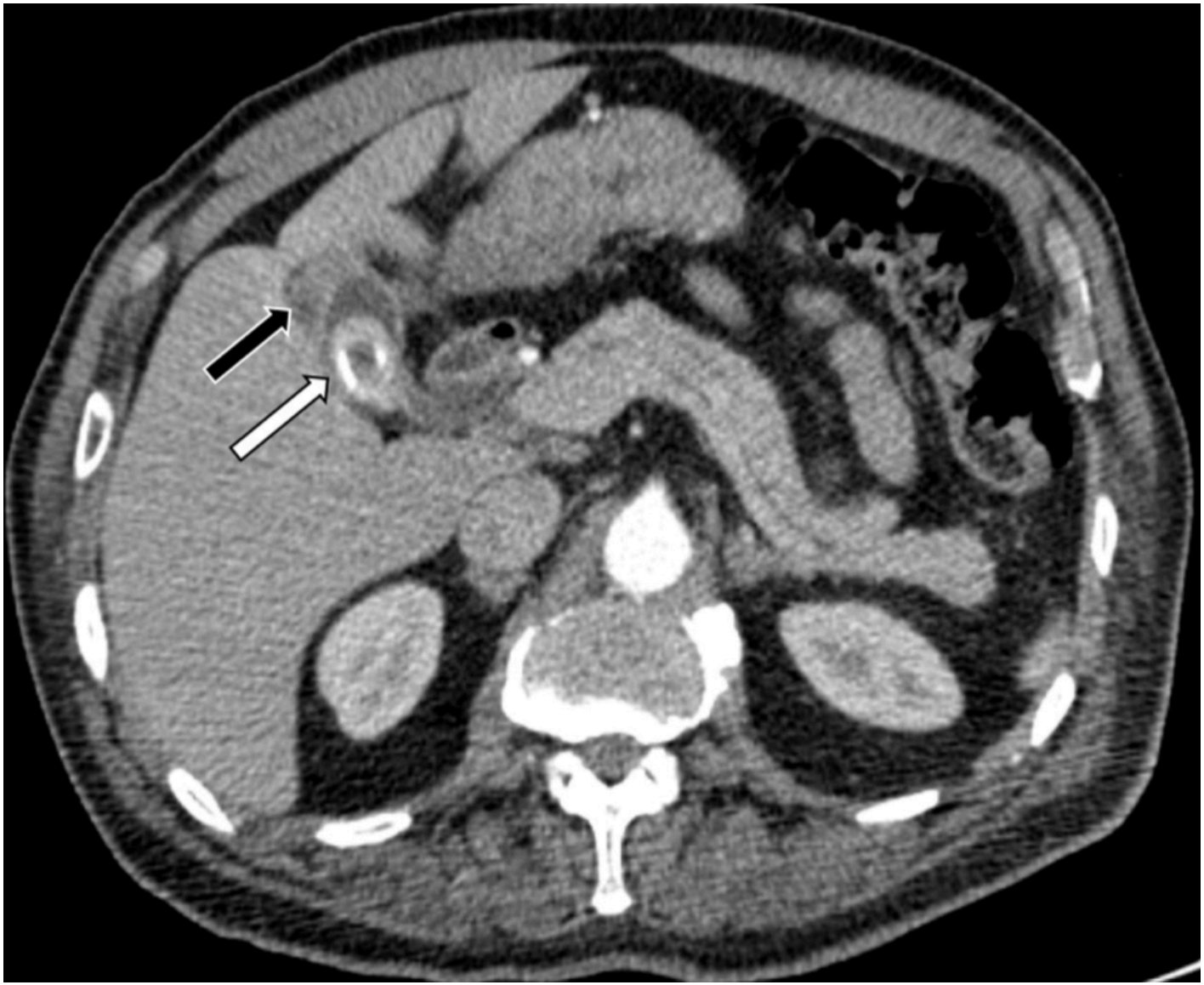


- Lithiasis and chronic cholecystitis most common risk factors for gallbladder cancer
- Chronic irritation / inflammation < gallbladderCa in a dysplasia to carcinoma sequence
  - ✳ gallstones (and those >2-3 cm) risk factor for Ca

Misra S, Chaturvedi A, Misra NC, et al. Carcinoma of the gallbladder. Lancet Oncol 2003;4(3):167–76.

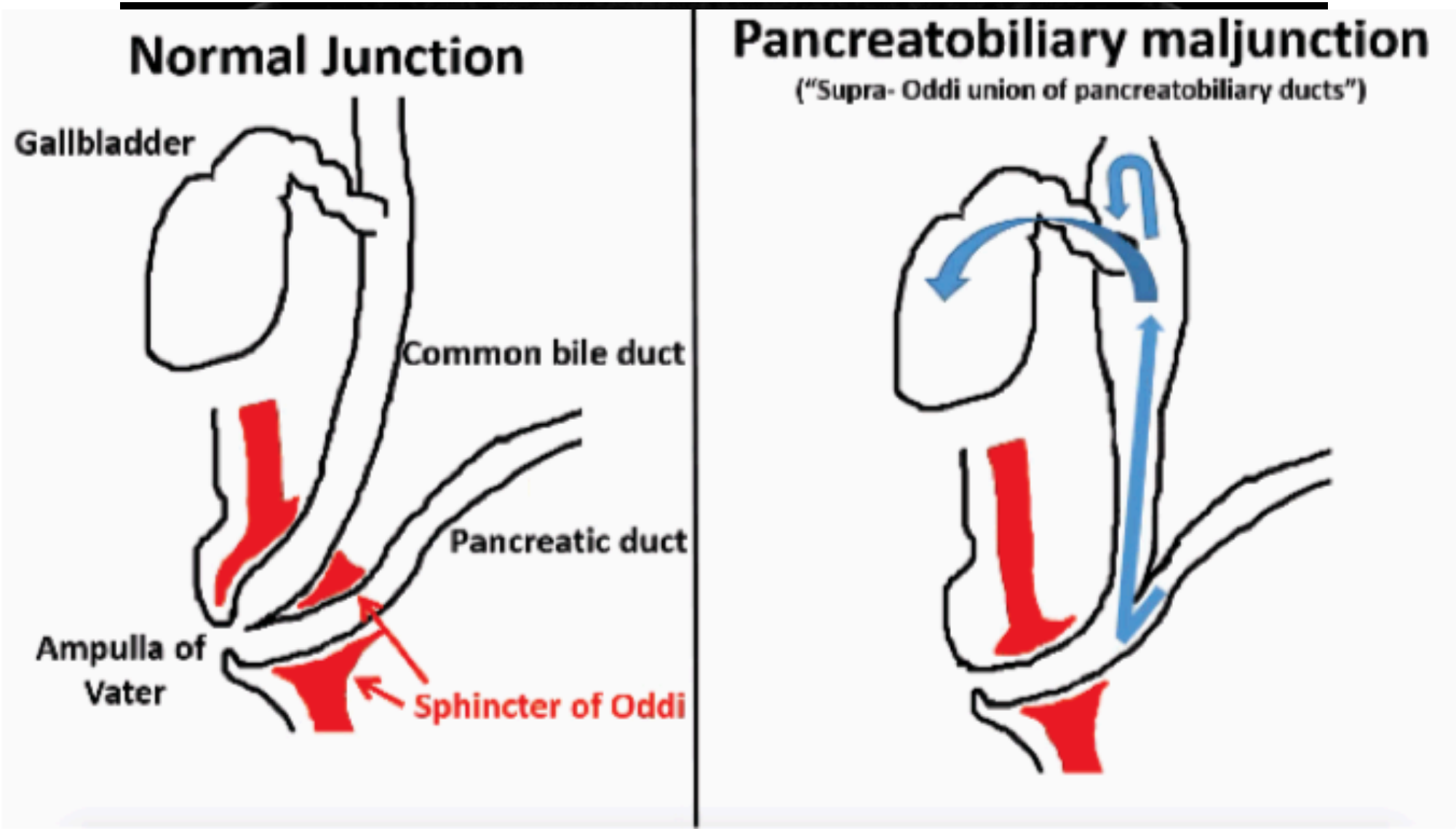
Lewis JT, Talwalkar JA, Rosen CB, et al. Prevalence and risk factors for gallbladder neoplasia in patients with primary sclerosing cholangitis: evidence for a metaplasia-dysplasia-carcinoma sequence. Am J Surg Pathol 2007;31(6):907–13.

Diehl AK. Gallstone size and the risk of gallbladder cancer. JAMA 1983;250(17):2323–6.

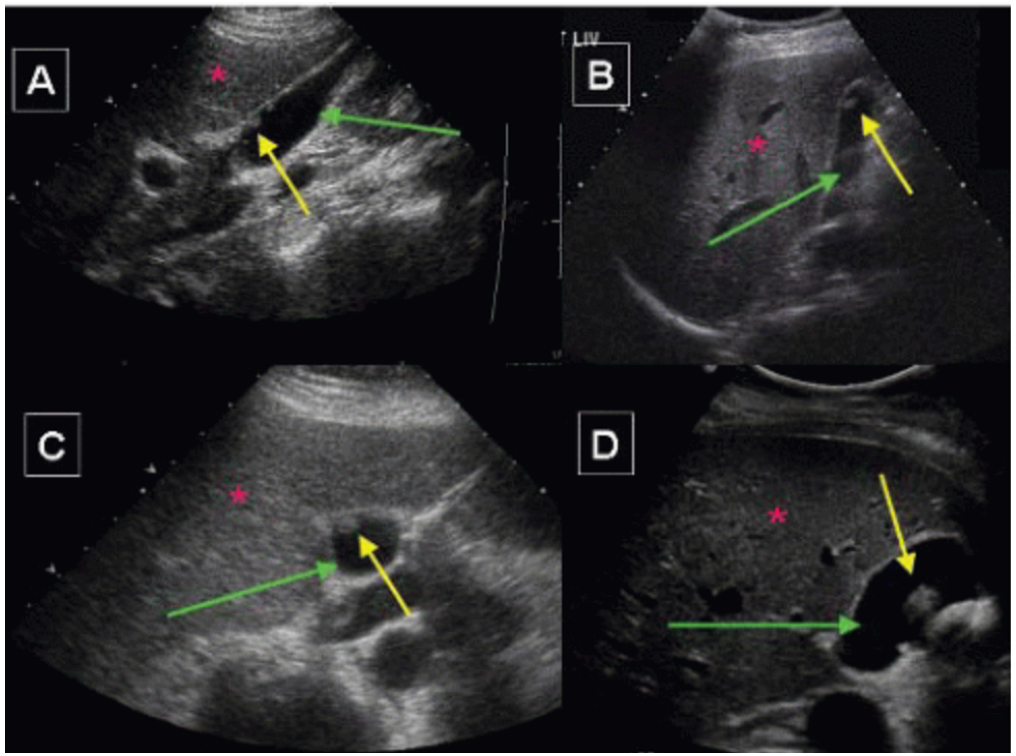


Further risk factors

- Chronic bacterial infection (Helicobacter and Salmonella species)
- Aflatoxine (< mostly associated with HCC, < aspergillum sp.)
- Porcelain gallbladder
- PSC : Primary Sclerosing Cholangitis
- Anomaly in pancreaticobiliary duct junction
  - joining is more proximal
  - elongated common channel
  - more risk for all biliary tract cancers, including gallbladderCa
  - < reflux of pancreatic fluid ?

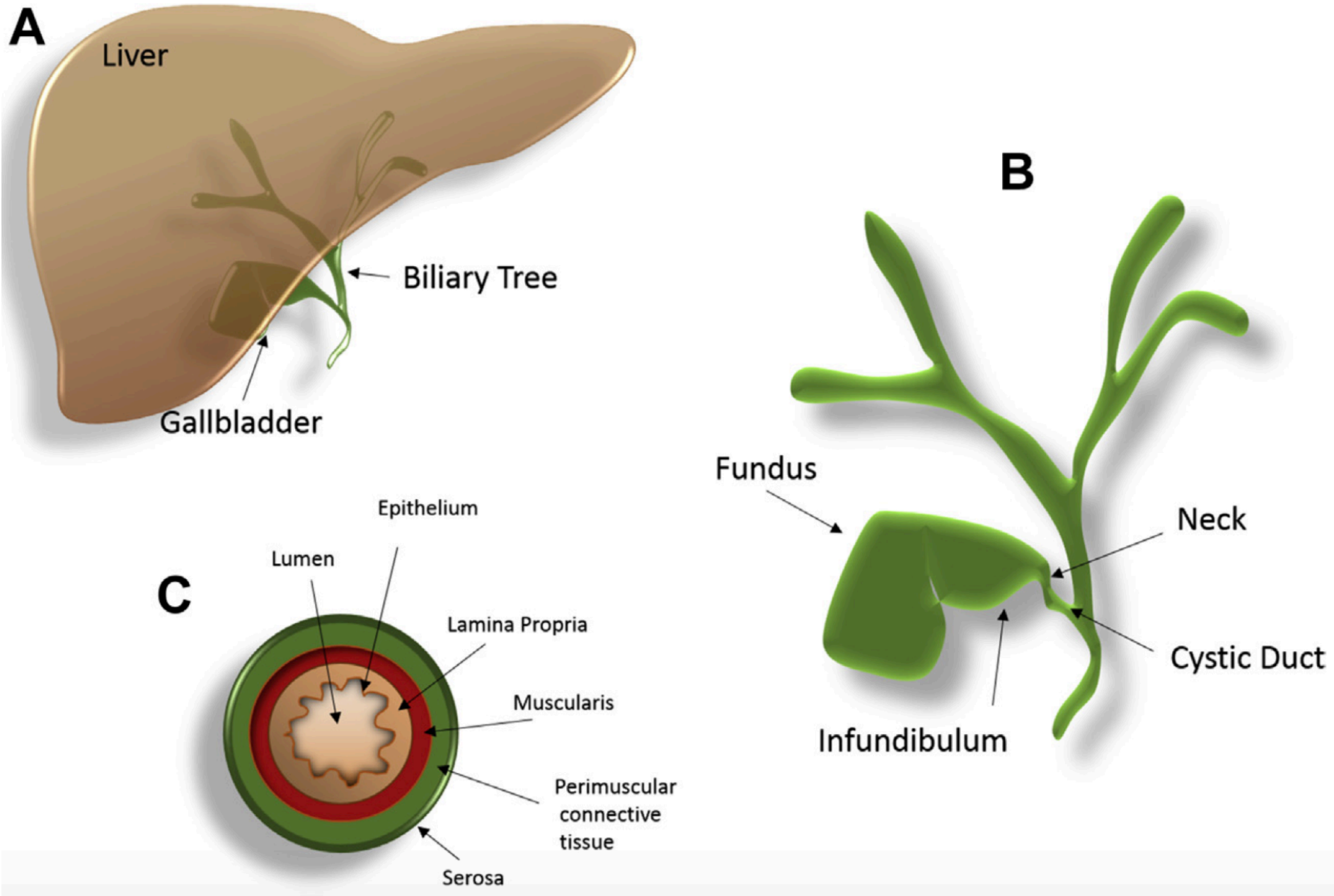

Normal Junction
Gallbladder
Common bile duct
Pancreatic duct
Ampulla of Vater
Sphincter of Oddi
Pancreatobiliary maljunction
("Supra- Oddi union of pancreatobiliary ducts")

Risk factors



- Polyps, most commonly adenomatous polyps, believed to be a precursor (adenoma to carcinoma sequence as in colonic polyps)

  ✳ Adenomas larger than 1cm or growing in time or have suspicious features need cholecystectomy (25 times greater risk of developing malignancy then <1cm)


A
Liver
Biliary Tree
Gallbladder
B
Fundus
Neck
Cystic Duct
Infundibulum
C
Epithelium
Lumen
Lamina Propria
Muscularis
Perimuscular connective tissue
Serosa

Presentation

- rarely identified early, mostly incidentally
- symptoms sometimes similar to cholelithiasis,-itis, colics
- advanced tumors : weight loss, right upper quadrant fullness, jaundice, duodenal obstruction
- gallbladderCa incidentally found on cholecystectomy account for less than 1% of cholecystectomies

Dorobisz T, Dorobisz K, Chabowski M, et al. Incidental gallbladder cancer after cholecystectomy: 1990 to 2014. Onco Targets Ther 2016;9:4913–6.
Choi SB, Han HJ, Kim CY, et al. Incidental gallbladder cancer diagnosed following laparoscopic cholecystectomy. World J Surg 2009;33(12):2657–63.

What to do then ?

- if very early stage - stage 1a or less - cholecystectomy is considered curative

- if discovered intraoperatively :

  ✓ (open) resection

  ✓ stop operation and referral to an expert center

    ➡ minimizing the risk of inadequate resection/ peritoneal/port-site seeding

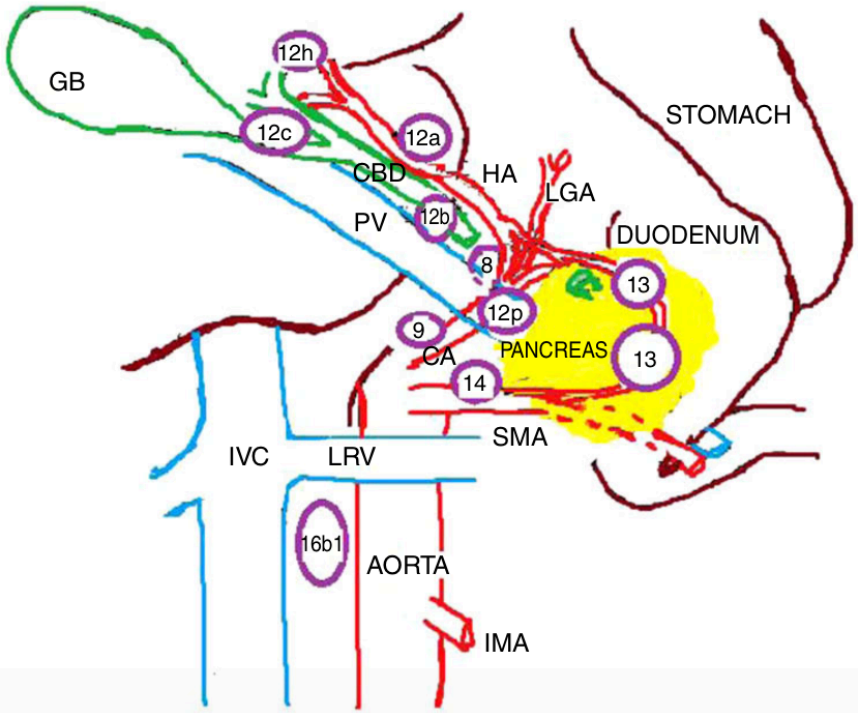
- later stage cancers should be appropriately staged prior to resection

Type and modes of spread

- Type : adenocarcinoma
- Characteristics of spread :
  - ✓ extremely lymphophilic
  - ✓ extensive subserosal lymphatic network
  - ✓ dissection plane between gallbladder and liver common site of spread after cholecystectomy
  - ✓ lymphatics drain to :
    - hepatic pedicle and celiac axis
    - directly into the gallbladder
  - ✓ direct hematogenous spread to the liver (venous drainage)
  - ✓ endoluminal spread into the biliary ducts
  - ✓ peritoneal spread (highly adjacent to inert material -graspers)

Lundberg O. Port site metastases after laparoscopic cholecystectomy. Eur J Surg Suppl 2000:27–30.

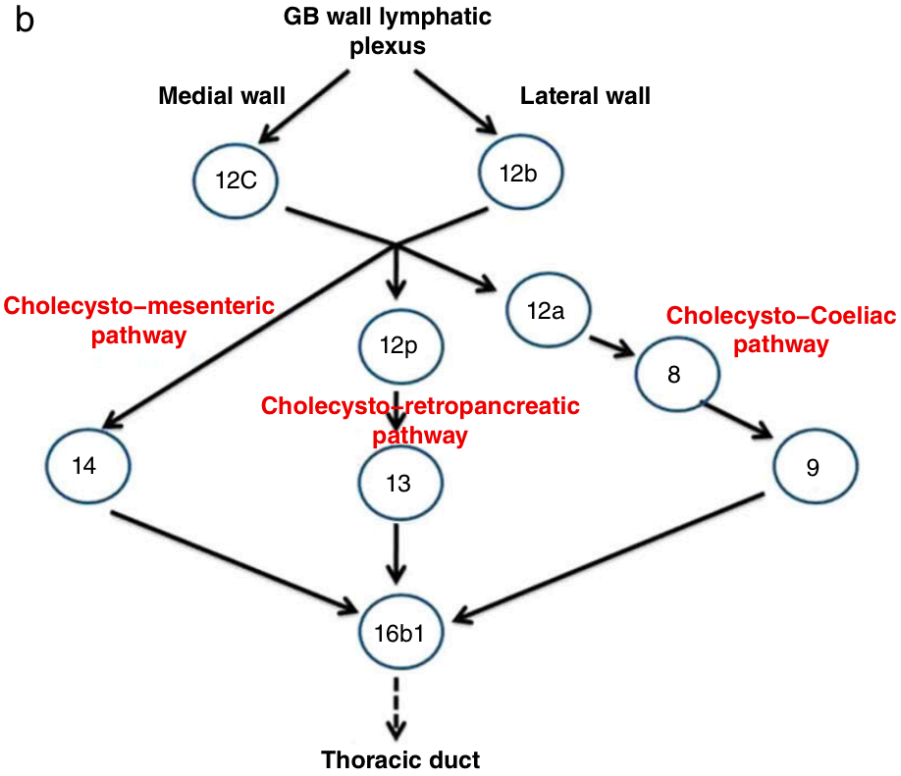
a



Abbreviations

GB – Gallbladder
CBD – Common bile duct
PV – Portal vein
HA – Hepatic artery
LGA – Left gastric artery
CA – Coeliac artery
SMA – Superior mesenteric artery
IMA – Inferior mesenteric artery
LRV – Left renal vein
IVC – Inferior vena cava

b



Lymph node (LN) stations

8 – Common hepatic artery LN
9 – Coeliac LN
12 – Along hepatoduodenal ligament
12a – Proper hepatic artery LN
12b – Pericholedochal LN
12c – Cystic LN
12p – Retroportal LN
12h – Hilar LN
13 – Posterior superior pancreaticoduodenal LN
14 – Superior mesenteric artery LN
16b1 – Para-aortic LN between left renal vein and inferior mesenteric artery

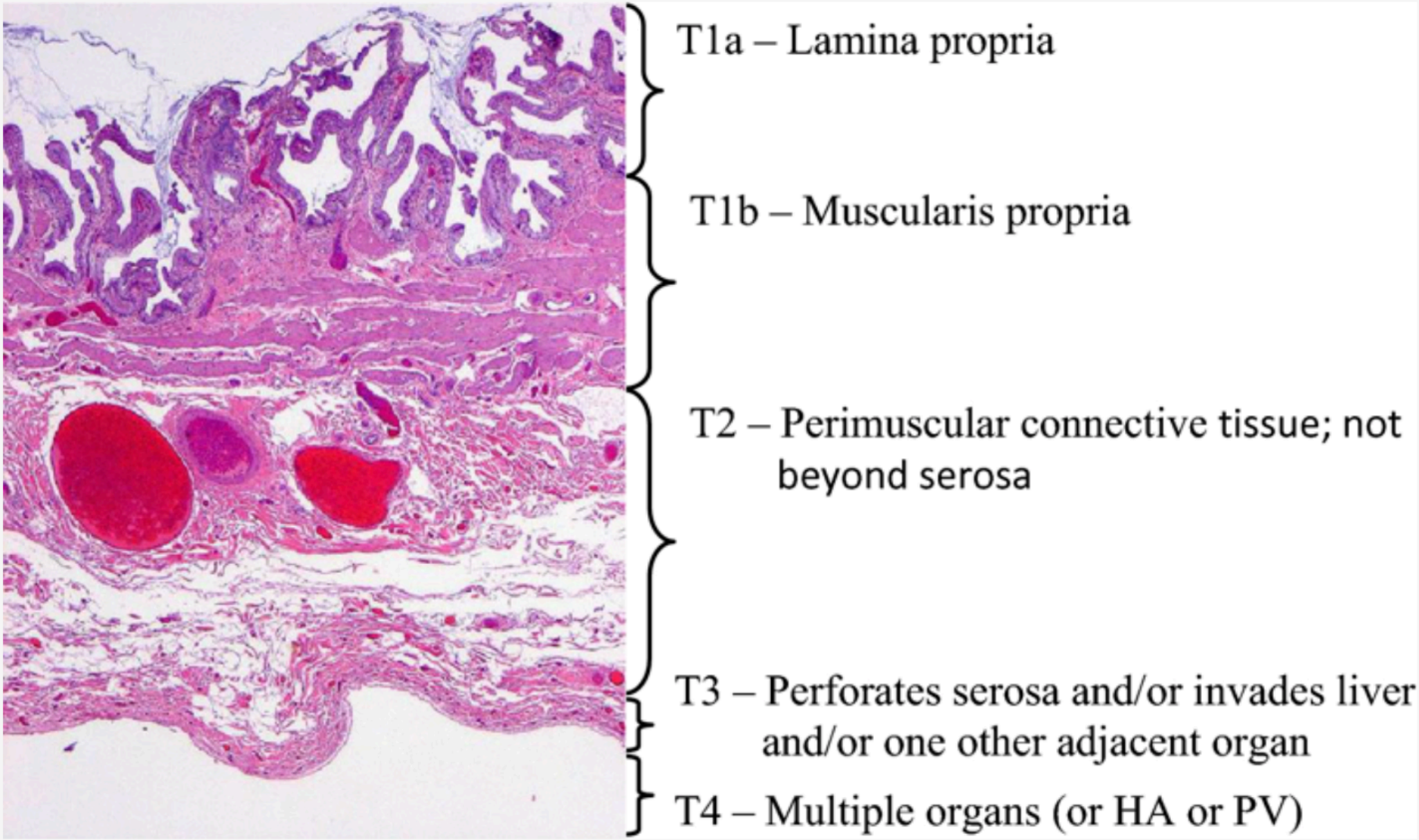


Fig. 2

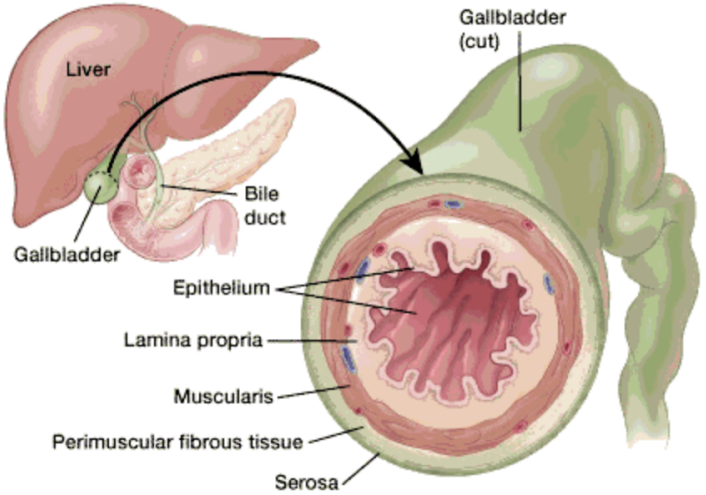
T-staging system for gallbladder cancer

Staging

T,N,M Staging of gallbladder cancer, adapted from the AJCC 8th edition

Stage Grouping	T Stage	N Stage	M Stage
Not stageable	X Cant be assessed	X Cant be assessed	X Cant be assessed
	0 No evidence of primary tumor		
0	is Carcinoma in situ		
I	1a Tumor invades lamina propria		
	1b Tumor invades muscular layer		
II	2a Tumor invades into perimuscular tissue on the visceral peritoneal side, but not through serosa	0 No regional lymph nodes involved	0 No distant metastatic disease
	2b Tumor invades into perimuscular tissue on the hepatic side, but not through serosa		
IIIA IIIB	3 Tumor invades through serosa either into liver parchnyma or	1 Metastatic disease involving 1-3 lymph nodes	
IVA[a] IVB[b]	4 Tumor invades main portal vein, hepatic artery or invades two or more adjacent organs	2 Metastatic disease involving >4 lymph nodes	1 Distant metastatic disease

[a]Stage IVA disease T4N0 or T4N1.
[b]Stage IVB disease is any T stage, with either N2 or M1 disease present.
From Zhu AX, Pawlik TM, Kooby DA, et al. Gallbladder. In: Amin MB, editor. AJCC Cancer Staging Manual. 8th edition. Chicago; AJCC; 2017. p. 303; with permission.



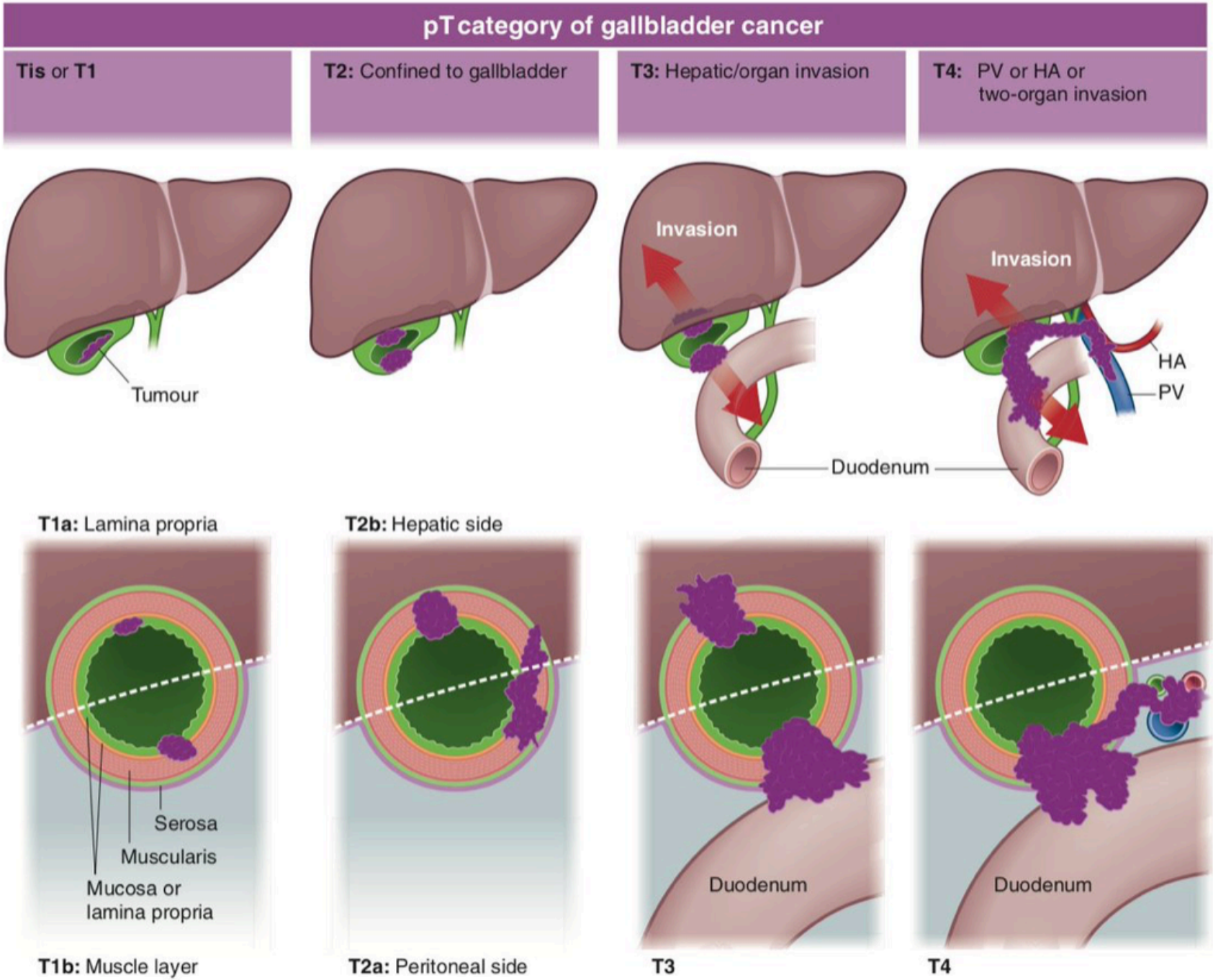
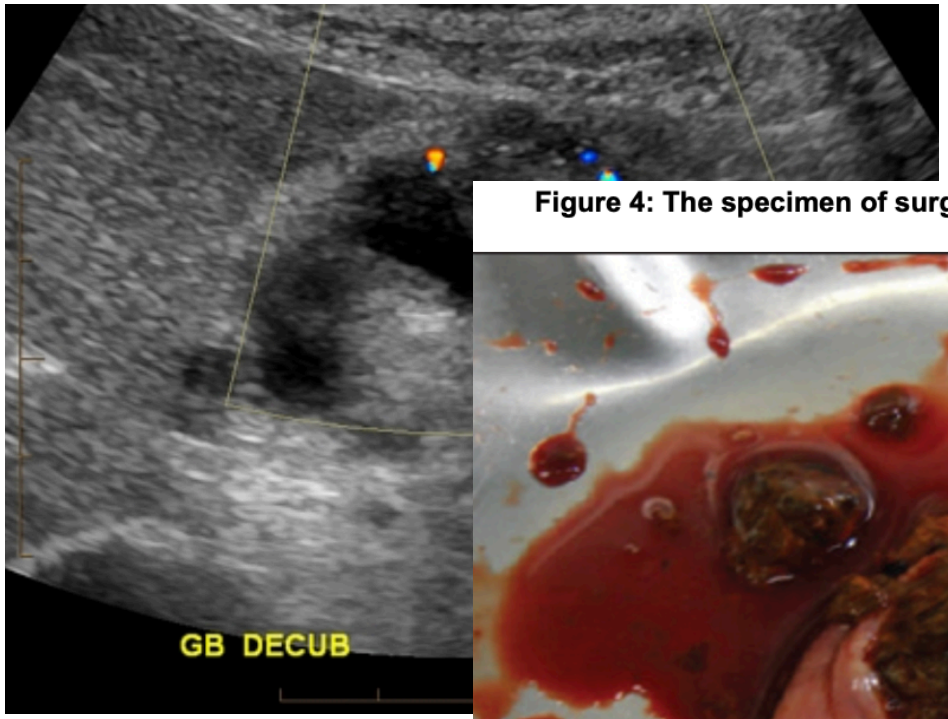


Fig. 1 Illustration of pT categories of the TNM system for gallbladder cancer. Based on the AJCC eighth edition. PV, portal vein; HA, hepatic artery

Work up

- **Preoperatively** suspected :
  - ✓ EUS right upper quadrant
  - ✓ CT or MRI
  - ✓ PET (may be of use in select cases of suspected M+)
  - ✓ labo :
    - ✓ CA 19.9 (sensitivity 72%, specificity 96%)
    - ✓ CEA , CA 242 (less sensitive, more specific)
  - ✓ Endoscopic EUS : depth of invasion, FNA of suspected lesion

Sadamoto Y, Kubo H, Harada N, et al. Preoperative diagnosis and staging of gallbladder carcinoma by EUS. Gastrointest Endosc 2003;58(4):536–41.
Costache M, Iordache S, Karstensen J, et al. Endoscopic ultrasound-guided fine needle aspiration: from the past to the future. Endosc Ultrasound 2013;2(2):77–85.



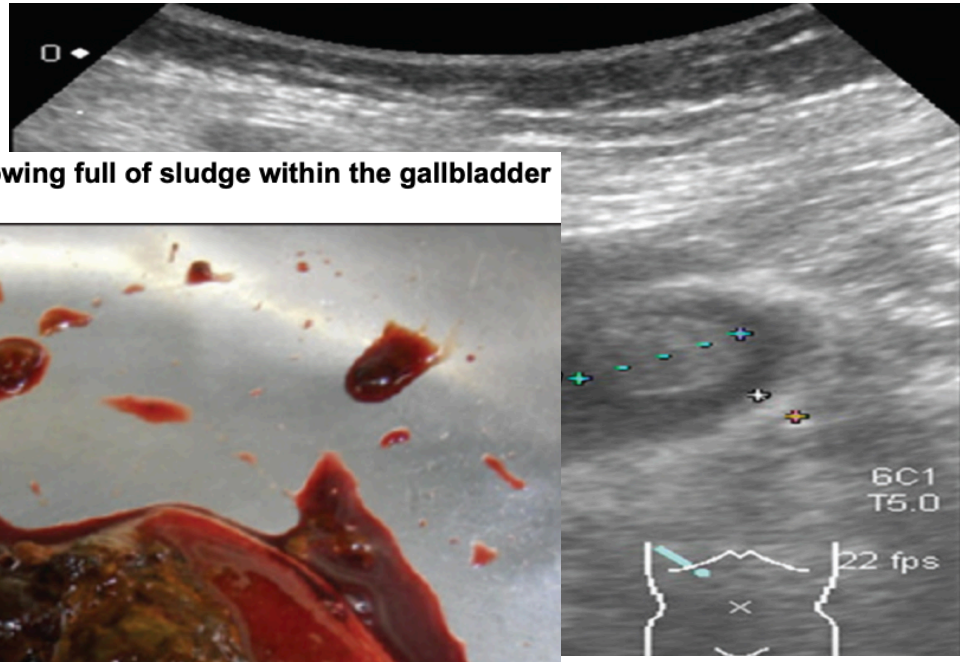
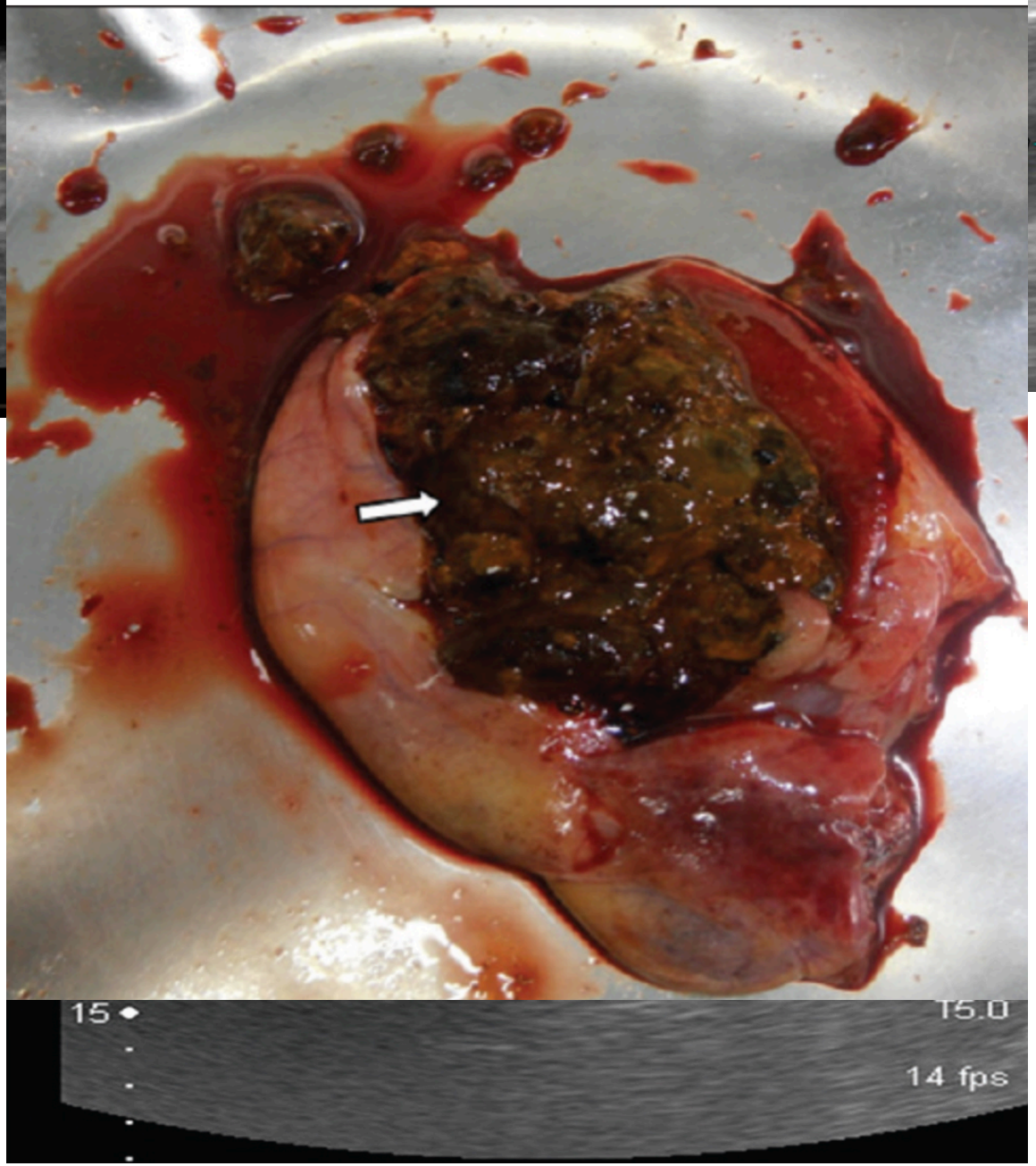
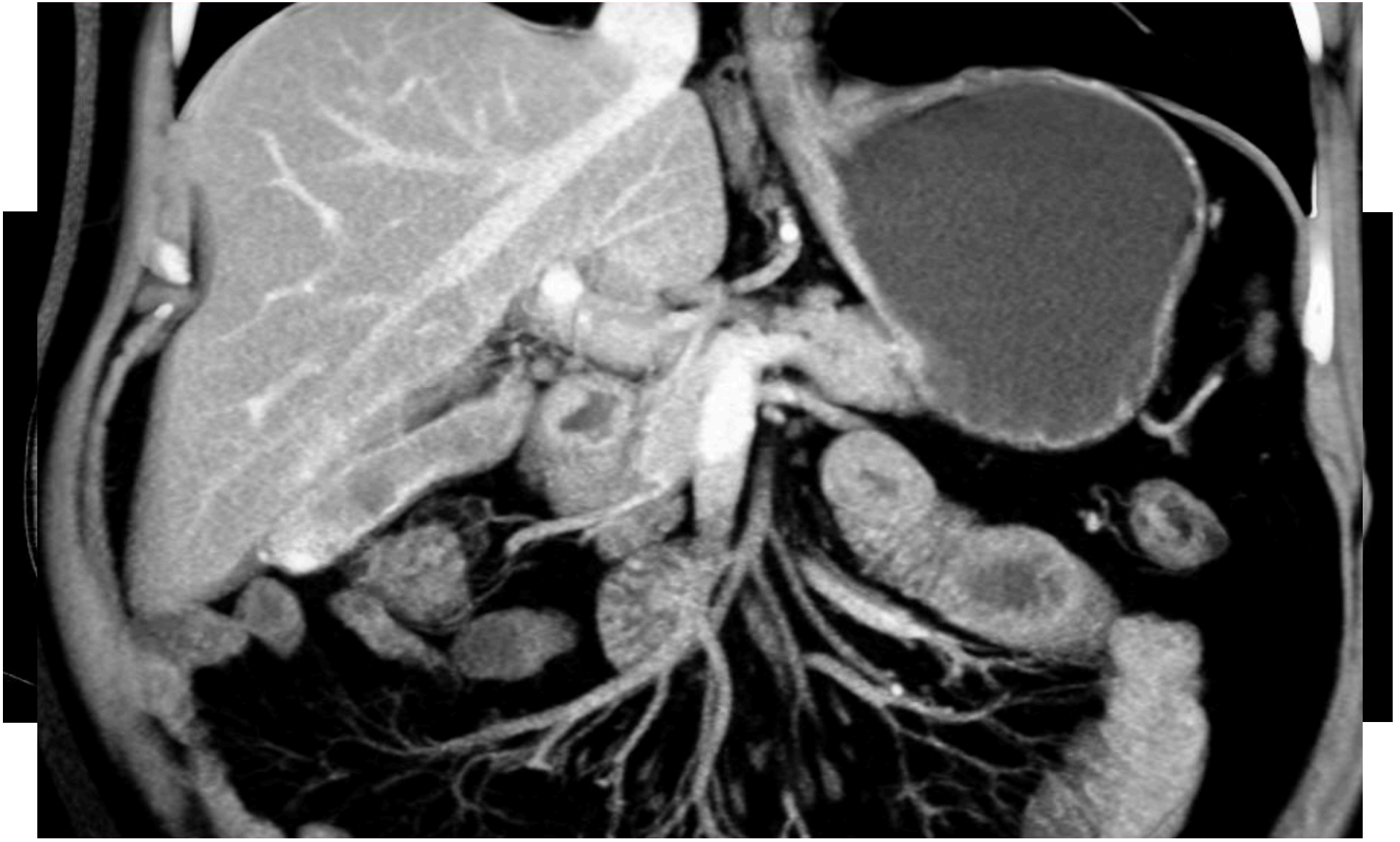
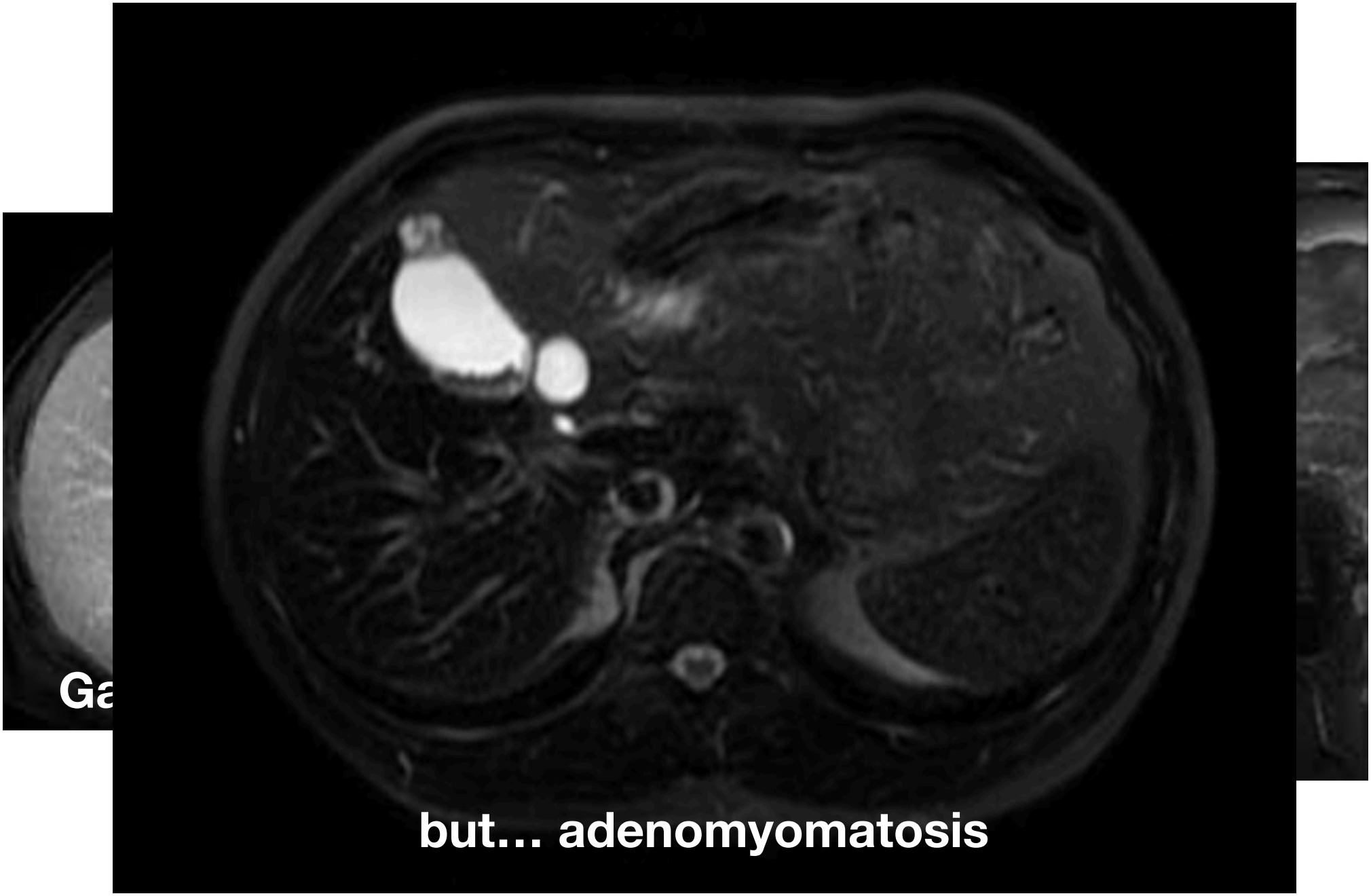


Figure 4: The specimen of surgery showing full of sludge within the gallbladder



<— be careful




Ga
but… adenomyomatosis

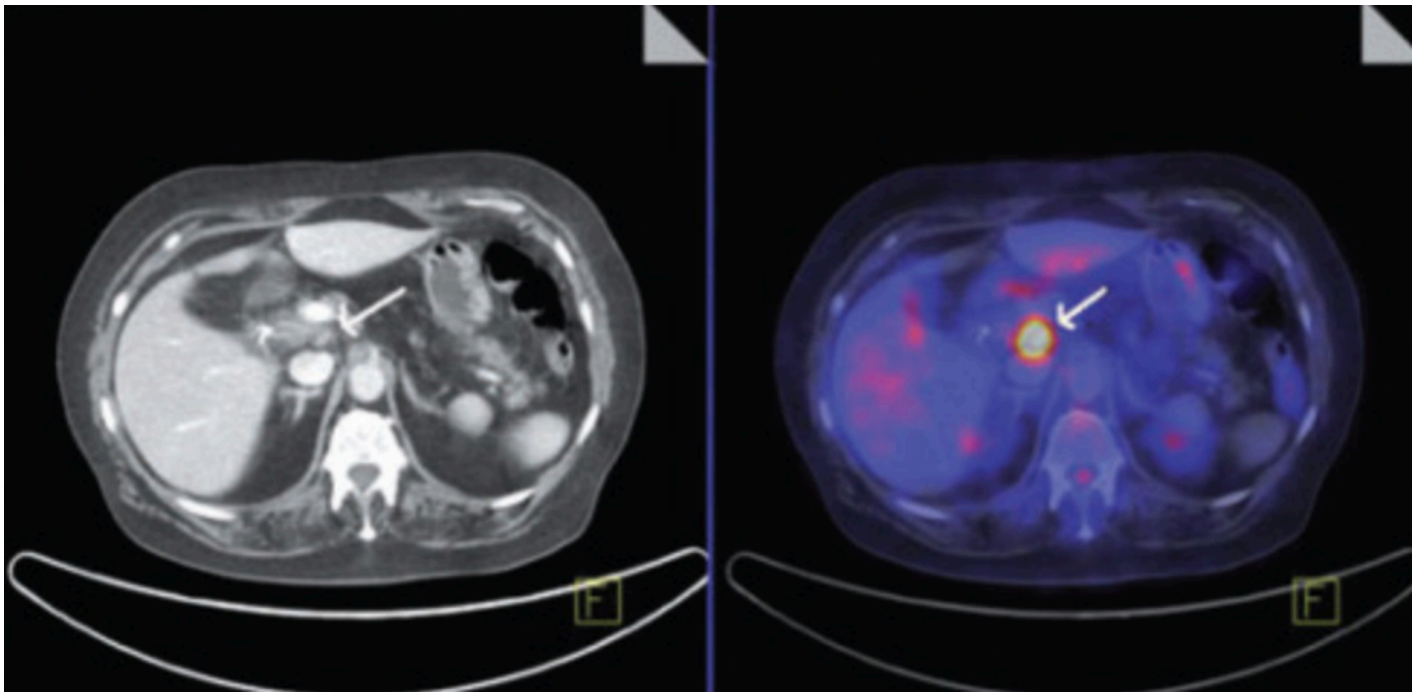


Figure 2. An example of a ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}FDG PET-CT) which showed evidence (positive finding) of localized disease (arrow) in a patient who was diagnosed with an incidental gallbladder carcinoma aftercholecystectomy

Preoperative warning signs

Localized or irregular thickening of the gallbladder wall is a major sign : it is important for the surgeon to actually view the ultrasound images and not rely on the radiology report alone. CT may give false reassurance ; ultrasound, especially with Doppler exam, is the best study to assess the gallbladder wall

A polyp > 10 mm is considered a precancerous lesion, particularly if it is iso- or hypo-echoic, sessile, shows increased vascularisation on doppler exam, is enhanced on CT, or shows signs of growth on two successive studies. Such findings demand complementary imaging and prompt cholecystectomy

Non-visualization of the gallbladder on ultrasound is very suspicious, especially if it is replaced by a sub-hepatic tissue mass which enhances on CT with IV contrast

Lymphadenopathy either in the pedicle or at a distance, especially if there are numerous enlarged nodes or when there is little clinical evidence of inflammation

An atypical peri-cholecystic or hepatic abscess

Rarely seen, a porcelain gallbladder: calcification of the wall makes ultrasound difficult and underlying cancer is present in 20% of cases

Questions before surgery

- If preoperatively suspected cholecystectomy should be performed by laparotomy
- laparoscopy seems to aggravate the risk of peritoneal dissemination (risk of bile leakage, pneumoperitoneum, passage of instruments, abdominal positive pressure and tumor manipulation)
- most authors feel that laparoscopy is CI for gallbladder cancer for fear of turning T1a or T1b into a T3 or M1 disease

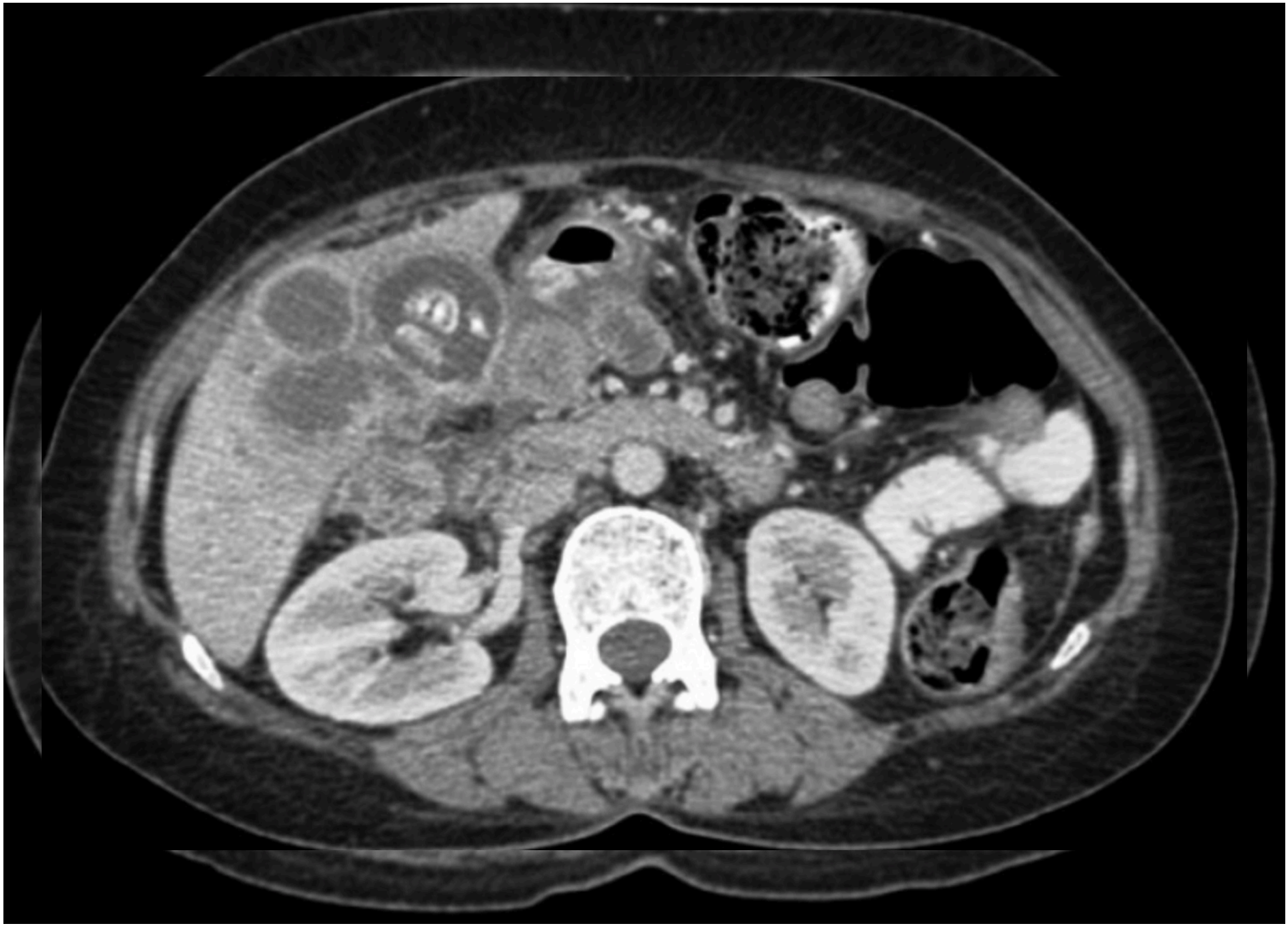
Work up

- Perioperatively or postoperatively diagnosed :
  - ✓ incidentally diagnosed AFTER resection
    - ➡ adequate laboratory testing and staging in case further resection is warranted
  - ✓ INTRAoperatively suspected for gallbladderCa
    - ➡ conversion to open (=minimizing the risk of peritoneal seeding)
    - ➡ if advanced disease : biopsy of M+lesions , stop cholecystectomy if possible (<adjuvant therapy)
    - ➡ if not comfortable, referral to expert center

Table 4 Intra-operative macroscopic signs of gallbladder [1,5,32,33].

A gallbladder mass or an infiltrated or thickened appearance of the wall (often difficult to distinguish from empyema of the gallbladder)
Gross appearance suggesting acute cholecystitis in the absence of any clinical signs of infection or inflammation
Macroscopically evident lymphadenopathy in the pedicle or at a distance
Hilar infiltration: this is difficult to assess when there is pedicular inflammation due to cholecystitis or cholangitis
Hepatic masses or metastases

Incidentally discovered gallbladder cancer:when, why and which reoperation ?
M Isambert et al. J of Visceral surgery April 2011, p77-84



Intraoperative diagnosis

- absolute prevention of bile leakage , because of the risk of peritoneal M+
- frozen section examination if possible or urgent definitive histological result
- if radical surgery is decided upon conversion to laparotomy is advised
- gallbladder is not removed when :
  - ✓ to much inflammation and risk of bile spillage or damage to gallbladder
  - ✓ general condition of patient does not allow radical surgery
  - ✓ performing extended cholecystectomy with a lymph node dissection can not be done (technical, day clinic,..)
- two stage resection when radical resection can not be done immediately, BUT with a minimal delay
- no difference in survival between initial curative resection and two stage resection

Horkoff MJ, Ahmed Z, Xu Y et al (2019) Adverse outcomes after bile spillage in incidental gallbladder cancers: a population-based study. Ann Surg. https://doi.org/10.1097/SLA.0000000000000332

S.P. Shih, R.D. Schulick, J.L. Cameron, *et al.*
Gallbladder cancer: the role of laparoscopy and radical resection
Ann Surg, 245 (2007), pp. 893-901

Risk of residual disease at re-operation

Table 5. Risk of residual disease at re-operation (%) [5], [19], [23].

T1b	38–40
T2	57–70
T3	77–91
All stages	61–70
Clear cystic duct margin	4
Cystic duct invasion	42

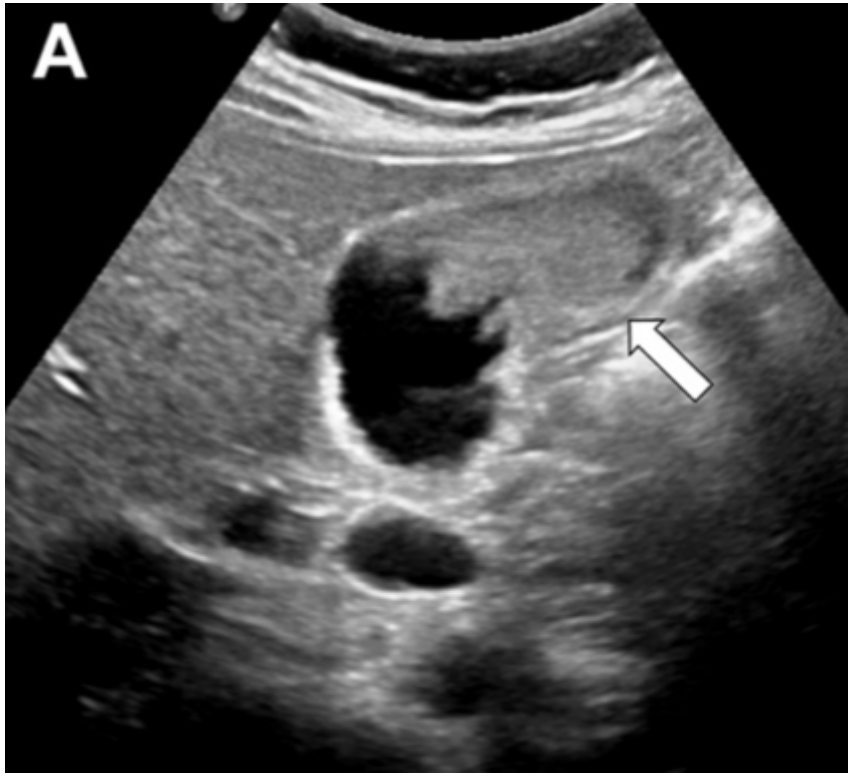
T.M. Pawlik, A.L. Gleisner, L. Vigano, *et al.*
Incidence of finding residual disease for incidental gallbladder carcinoma: implications for re-resection
J Gastrointest Surg, 11 (2007), pp. 1478-1486

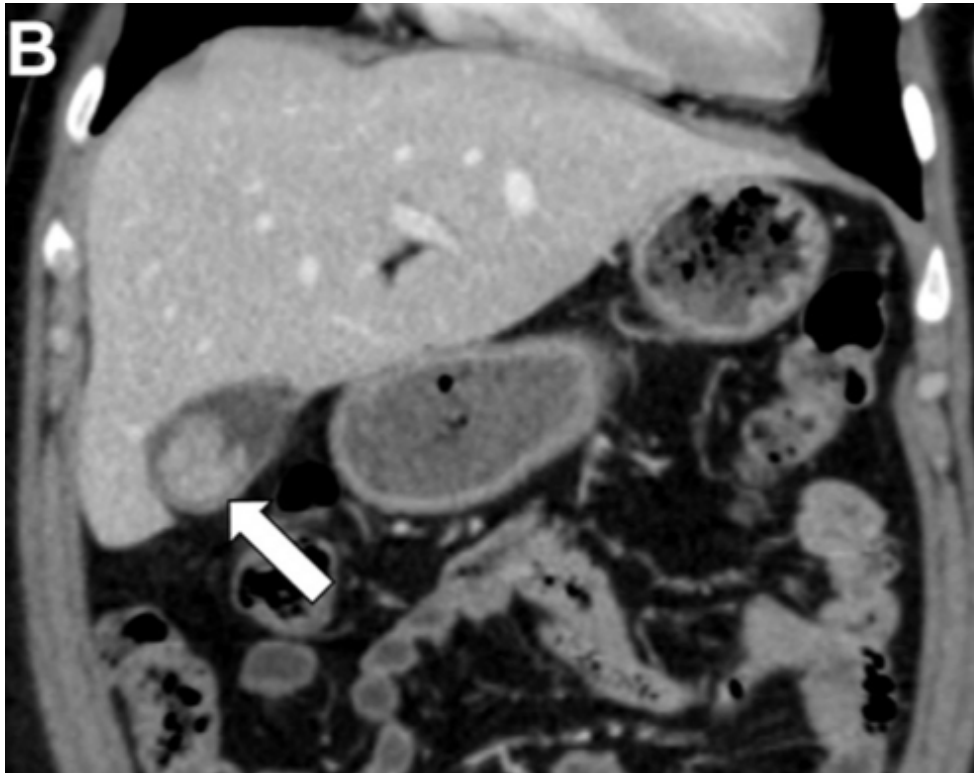
Operative considerations

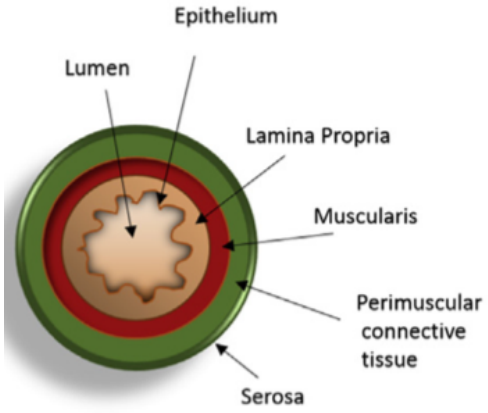
- **Early-stage disease :**
  - ✳ Cancers incidentally diagnosed on pathology of the gallbladder
    - T1a or in situ disease (CIS)
    - cystic duct margin is negative  no further surgery
    - ➡ appropriate work up for staging and rule out distant M+

Kasumova GG, Tabatabaie O, Najarian RM, et al. Surgical management of gallbladder cancer simple versus extended cholecystectomy and the role of adjuvant therapy. Ann Surg 2017;266:625–31.

T1a lesion : tumor invades the lamina propria but not muscular layer







Staging before re-operation

- CT thorax - CT abdomen and pelvis:
  - ✓ to detect M+
  - ✓ to asses locoregional extension
  - ✓ sensitivity for peritoneal M+ and lln invasion is low
- MRI with MRCP :
  - ✓ detecting common bile duct or vascular invasion
- PET : few benefit at this moment

Gallbladder Cancer
Managing the Incidental Diagnosis
Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065 USA
Leonid Cherkassky, MD, Michael D'Angelica, MD*
Surg Oncol Clin N Am 28 (2019) 619–630

Staging Laparoscopy

Although these results suggest a low threshold for the use of laparoscopy in gallbladder cancer overall, in the authors' experience, the utility significantly decreases in the case of IGBC. This is not surprising because these patients have already undergone laparoscopic exploration at the time of initial cholecystectomy and because the presentation is typically at earlier stages. In the authors'

subjects (yield 4.3%, accuracy 20%). The authors, therefore, selectively perform laparoscopy for those patients at highest risk for disseminated disease as identified in the authors' analysis: positive margin at initial cholecystectomy, poorly differentiated tumor, T3 disease, or imaging studies suggesting RD. Other high-risk factors associated with higher risk of occult metastatic disease that may indicate SL are node-positive disease (typically found in cystic duct lymph node if removed) and occurrence of bile spillage at initial cholecystectomy, which risks peritoneal dissemination.30, 31

When re-operation ?

- within 10 days (before post-operative adhesions become too developed) for patients with early diagnosis and no initial severe inflammation;
- otherwise, at three to four weeks, to allow for partial regression of pre- or post-operative inflammation;
- in all cases, before six weeks.

but ..

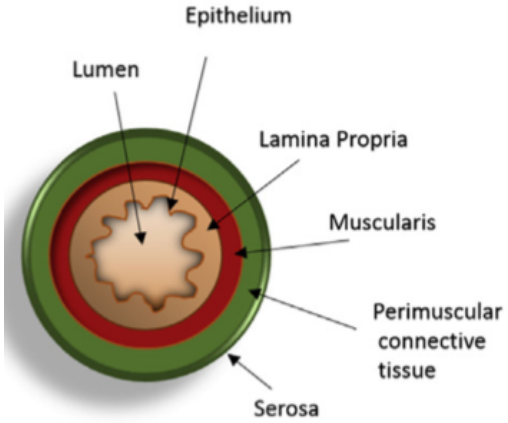
Management of incidental gallbladder cancer in a national cohort

British Journal of Surgery (IF 5.586) **Pub Date : 2019-07-01** , *DOI: 10.1002/bjs.11205*

L. Lundgren, C. Muszynska, A. Ros, G. Persson, O. Gimm, B. Andersson, P. Sandström

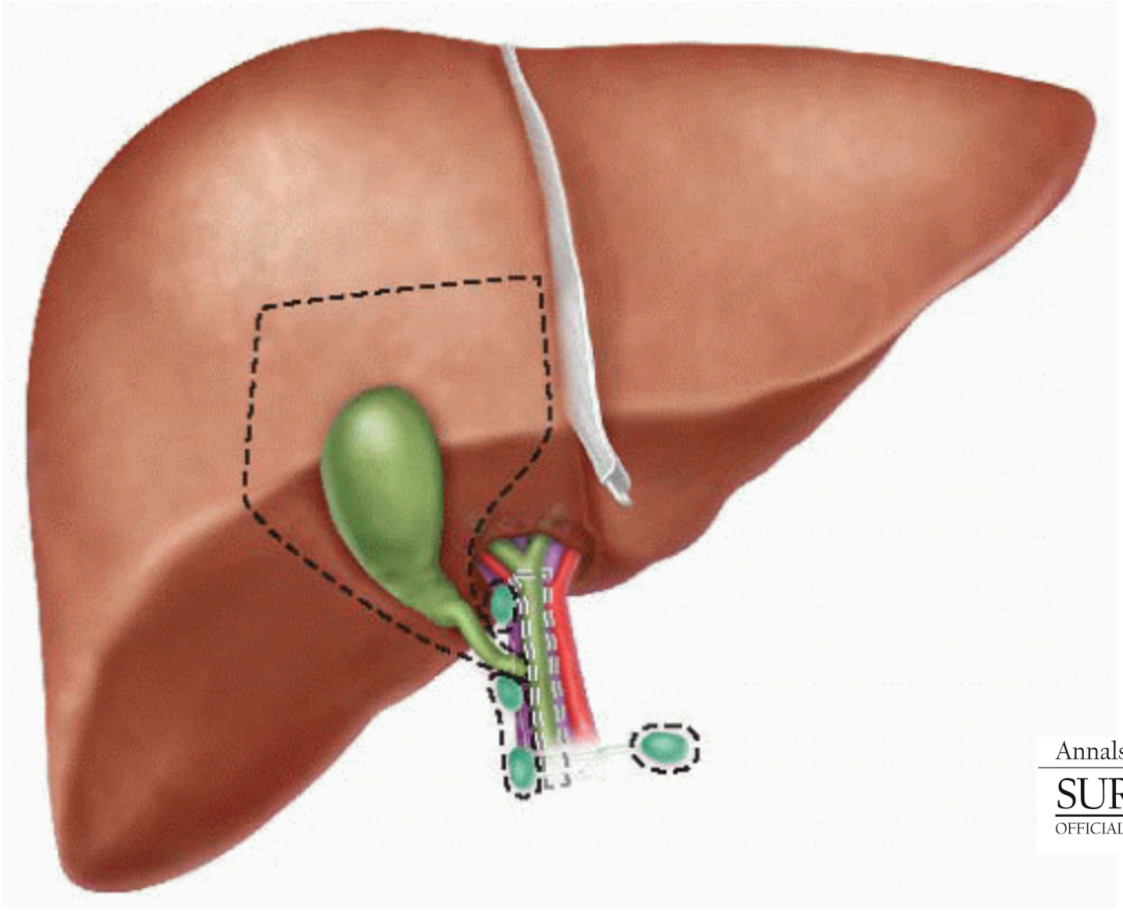
resection within 60d or after 60d post cholecystectomy showed NO difference in likelihood of completing re-resection with curative intent

Operative considerations



- **Locally advanced disease :**
  - ✳ non metastatic and no invasion beyond the serosa
    - T1b, 2 or 3 ? (invasion muscularis or beyond, but not through serosa)
    - ➡ en bloc liverresection (extended cholecystectomy) with portal lymfadenectomy
    - ➡ sometimes common bile duct resection to obtain negative margins (when cystic duct margin is positive)
    - ➡ adjuvant chemotherapy because of improved survival (median survival > 50% better than surgery alone)

How to re-operate ?



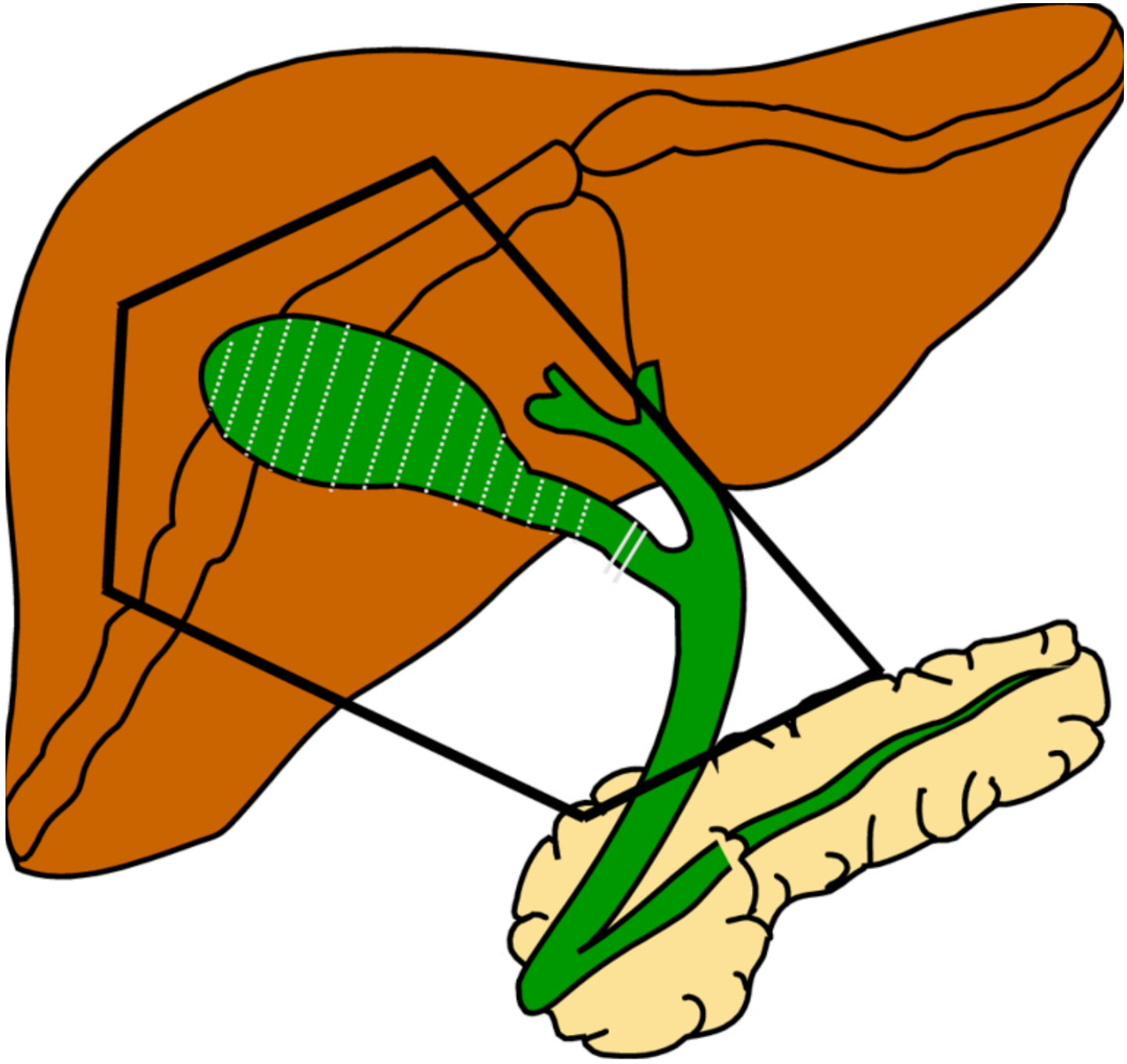
Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

FIG 1 • Schematic representation of radical cholecystectomy by resection of hepatic segments IV/V *(black dotted lines)* and the gallbladder. Optional resection of the extrahepatic biliary tree is also shown *(gray dotted lines)*.

extending resection as a wedge to include the gallbladder fossa). The performance of a major hepatectomy or a common bile duct (CBD) excision was not associated with other clinicopathologic variables or long-term survival[39]; instead, the variables that

Analysis of the Extent of Resection for Adenocarcinoma of the Gallbladder

Ann Surg Oncol (2009) 16:806–816 **Michael D'Angelica, Kimberly Moore Dalal, Ronald P. DeMatteo, Yuman Fong, Leslie H. Blumgart**

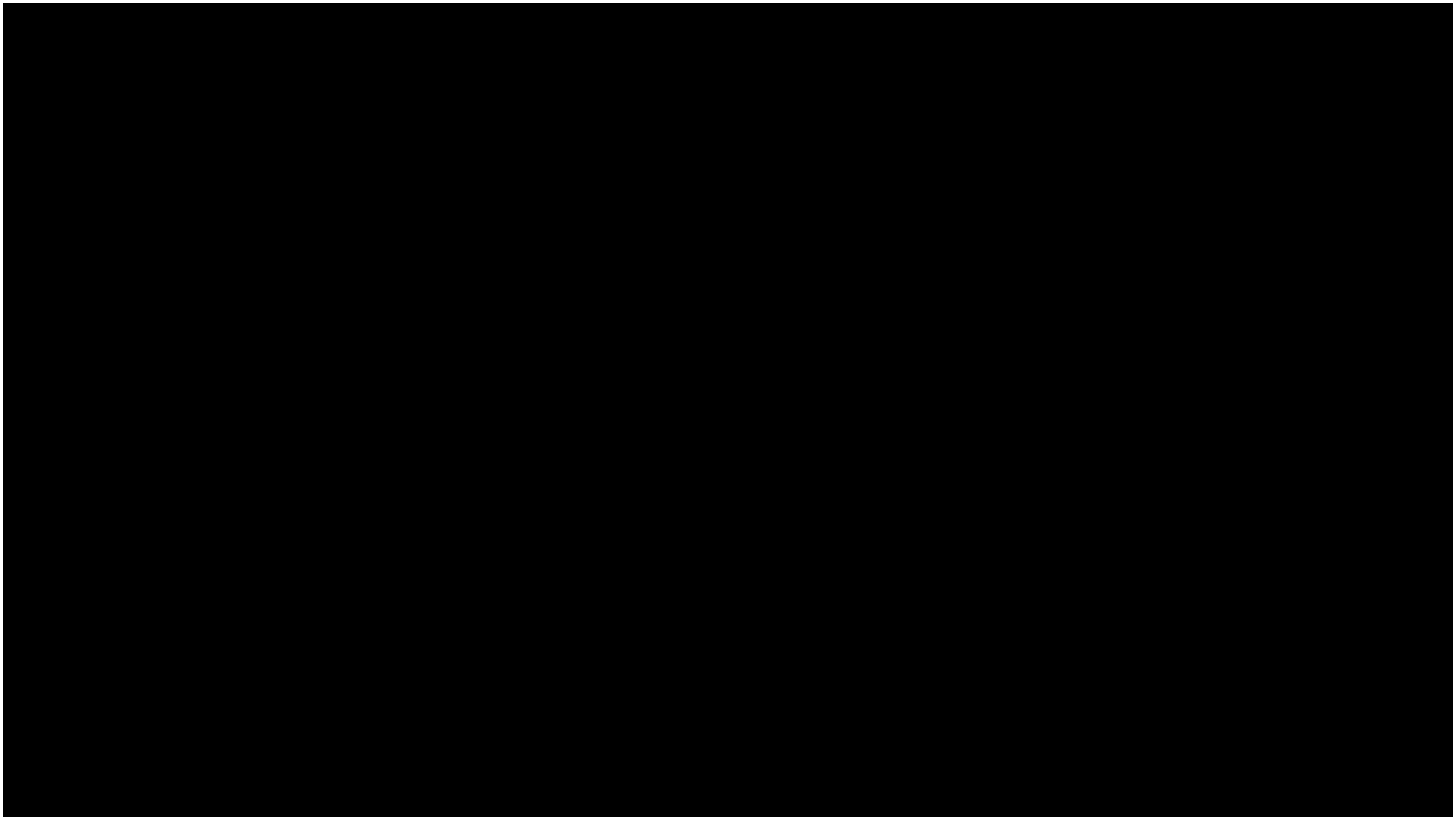


The goal of re-operation and definitive resection for incidental gallbladder cancer is to clear disease from the liver and porta hepatis. The most common approach involves removal of liver tissue around the gallbladder fossa (segmentectomy 4/5) and porta hepatis lymphadenectomy

Selecting treatment sequence for patients with incidental gallbladder cancer: a neoadjuvant approach versus upfront surgery

Leonid Cherkassky[2] · William Jarnagin[1]

Updates in Surgery (2019) 71:217–225



Courtesy to : Surgical oncology

Why re-operate ?

- T1a : no benefit for OS (5y OS 95-100%)
- T1b : clear benefit for extended cholecystectomy (5y OS with surgery is 79% vs 42% without)
- T2 : benefit for extended cholecystectomy (5y OS with surgery 55-90% versus 0-40% without surgery)
- T3 - T4 : limited indications for re-operation, in selected cases if R0, N0 can be achieved

M. Kai, K. Chijiiwa, J. Ohuchida, M. Nagano, M. Hiyoshi, K. Kondo
A curative resection improves the postoperative survival rate even in patients with advanced gallbladder carcinoma
J Gastrointest Surg, 11 (2007), pp. 1025-1032

Goetze TO, Paolucci V. Immediate re-resection of T1 incidental gallbladder carcinomas: a survival analysis of the German Registry. Surg Endosc 2008.

Gallbladder Cancer

Managing the Incidental Diagnosis

Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065 USA
Leonid Cherkassky, MD, Michael D'Angelica, MD*

Surg Oncol Clin N Am 28 (2019) 619–630

Table 1
Selected series of reresection for incidentally diagnosed gallbladder cancer

Reference, Year	Number of Subjects	Procedure	5-y OS (%)	Comments
Shirai et al,[6] 1992, Japan single-institution	10 35	EC (reresection) SC	90[a] 41	T2 subjects summarized, low number of T3 or T4 subjects
Fong et al,[7] 2000, MSKCC	37 16	EC SC	61[a] 19	16 subjects either refused or were not offered reresection (comparison made for only T2 tumors)
Ouchi et al,[13] 2002, multicenter Japan	153 (T2), 30 (T3) 48 (T2), 10 (T3)	EC SC	70% for T2, 20%[a] for T3	$P<.05$ for T3, $P = .051$ for T2, no difference for T1 or T4
Foster et al,[11] 2007, Roswell	13 25	EC SC	62[a] 16	T2 and T3 subjects
Shih et al,[17] 2007, Hopkins	29 5	EC SC	49[a] 0	T3 subjects
Goetze & Paolucci,[12] 2010, multicenter German	231 393	EC SC	41[a] 25	—
Fuks et al,[9] 2011, multicenter French	148 70	EC SC	41[a] 15	—

Abbreviations: EC, extended cholecystectomy; MSKCC, Memorial Sloan-Kettering Cancer Center; SC, simple cholecystectomy.

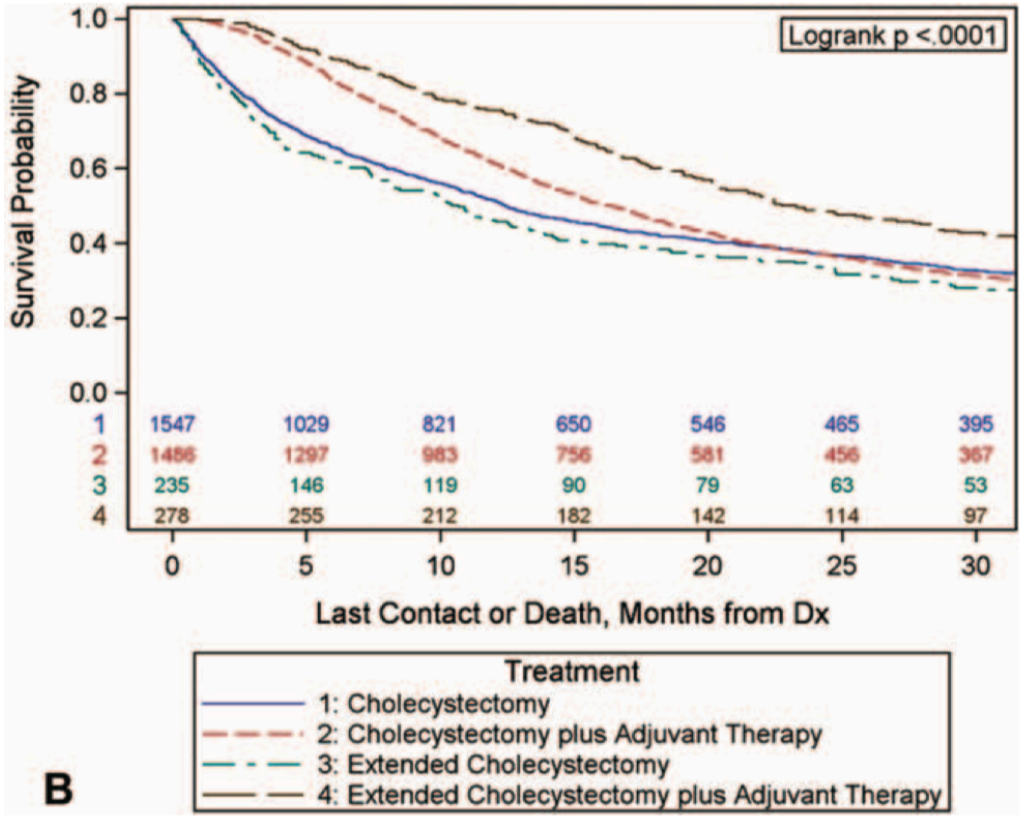
ALTHOUGH ?

Annals of Surgery • Volume 266, Number 4, October 2017

Surgical Management of Gallbladder Cancer

Simple Versus Extended Cholecystectomy and the Role of Adjuvant Therapy

Gyulnara G. Kasumova, MD, Omidreza Tabatabaie, MD, MPH,* Robert M. Najarian, MD,† Mark P. Callery, MD,‡ Sing Chau Ng, MS,* Andrea J. Bullock, MD,§ Robert A. Fisher, MD,¶ and Jennifer F. Tseng, MD, MPH**



Conclusions: Adjuvant therapy prolongs survival after resection of T2/T3 tumors. Simple cholecystectomy with adjuvant therapy appears to be superior to extended resection alone in the short term and may serve as a potential alternative to re-resection in select high-risk individuals.

Principal prognostic factor

- Loco regional lymph node involvement
- If lymph nodes are involved, survival rate is decreased by half or even 2/3 (N0 : 61% versus N1 : 18%)
- N status is no CI for surgery (better survival if R0 and surgery than no surgery)
- Para-aortic, mesenteric, celiac lln = M+ , abort resection ?
- R0 resection is a very important prognostic factor
  - ➡ DFS when R1 11m versus R0 with 93m in case of incidental gallbladder carcinoma after cholecystectomy (R1 meaning residual disease found in the re-resection specimen)

Butte JM, Kingham TP, Gonen M et al (2014) Residual disease predicts outcomes after definitive resection for incidental gallbladder cancer. J Am Coll Surg 219:416–429

Bad prognostic factors

- Histologic grade (poorly differentiated or not)
- Lymphovascular invasion
- Total lymph node count (>6 for good staging)
- Common bile duct involvement
- Presence of residual disease after re-resection (>T status)
- Jaundice
- Port site biopsy + / peritoneal seeding
- Bile spillage during cholecystectomy

Residual Disease Predicts Outcomes after Definitive Resection for Incidental Gallbladder Cancer

Jean M Butte, MD[1], T Peter Kingham, MD, FACS[1], Mithat Gönen, PhD[2], Michael I D'Angelica, MD, FACS[1], Peter J Allen, MD, FACS[1], Yuman Fong, MD, FACS[1], Ronald P DeMatteo, MD, FACS[1], and William R Jarnagin, MD, FACS[1]

J Am Coll Surg. 2014 September ; 219(3): 416–429. doi:10.1016/j.jamcollsurg.2014.01.069.

Gallbladder Cancer

Managing the Incidental Diagnosis

Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065 USA
Leonid Cherkassky, MD, Michael D'Angelica, MD*

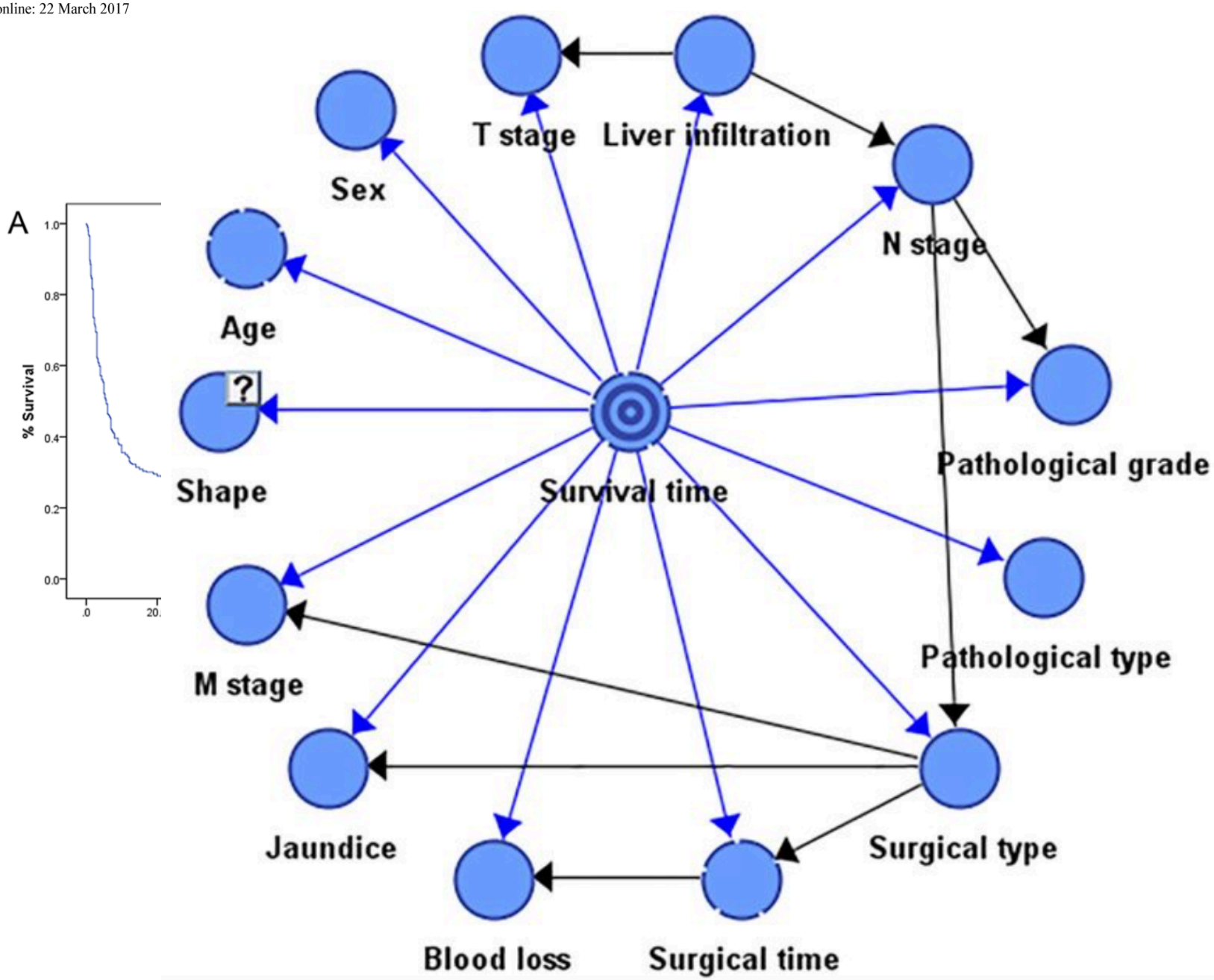
Surg Oncol Clin N Am 28 (2019) 619–630

Analysis of prognostic factors for survival after surgery for gallbladder cancer based on a Bayesian network

www.nature.com/scientificreports

Published online: 22 March 2017

Prognostic factors



different TNM
section.

Operative considerations

- Port-site recurrence after initial cholecystectomy predicts peritoneal spread of gallbladder cancer

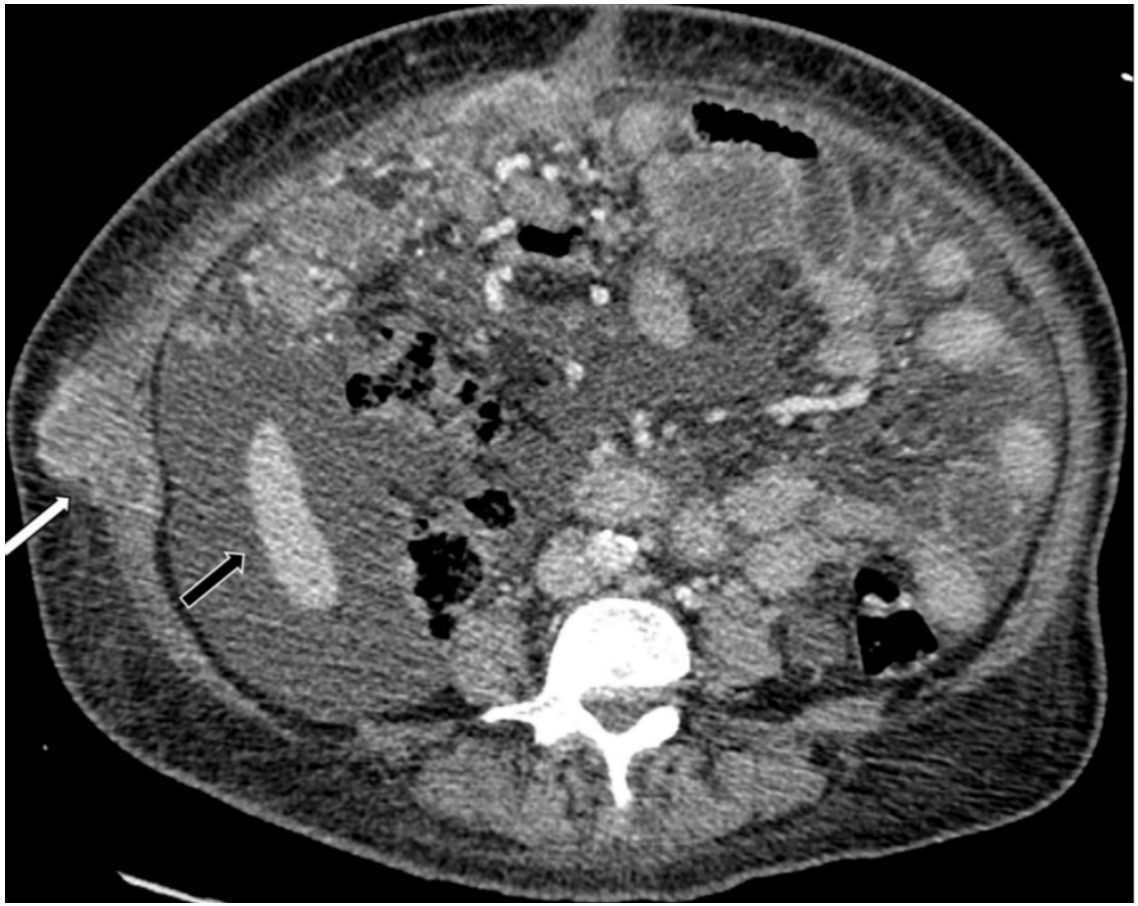
  ✓ resection of port-site at the time of definitive resection is not mandatory and does not improve survival

  ✓ if recurrence at the port-site after definite resection

  ➡ radiation and chemotherapy (pain relief and clinical response)

  ➡ palliative

Maker AV, Butte JM, Oxenberg J, et al. Is port site resection necessary in the surgical management of gallbladder cancer? Ann Surg Oncol 2012;19(2):409–17.
Fuks D, Regimbeau JM, Pessaux P, et al. Is port-site resection necessary in the surgical management of gallbladder cancer? J Visc Surg 2013;150(4):277–84.



Metastatic or locally unresectable disease has a median survival of 6 months

Treatment should focus on the patient's wishes

Surgical intervention should be avoided

If jaundice occurs biliary drainage via endoscopic or percutaneous routes is appropriate

Chemotherapy, radiation or both show improved survival and palliation of symptoms

Adjuvant therapy

in T1b, T2, T3

- chemotherapy : (after EC)
  - ✓ most commonly gemcitabine based
  - ✓ or 5-FU or capecitabine based
  - ✓ in combination with a platinum agent (cis- or oxaliplatinum)
- for R1 or R2 resections : radiation therapy to control the disease
- radiation therapy in R0 ?
  - ✓ data less clear but combination therapy can be considered

Wang SJ, Lemieux A, Kalpathy-Cramer J, et al. Nomogram for predicting the benefit of adjuvant chemoradiotherapy for resected gallbladder cancer. J Clin Oncol 2011;29(35):4627.

Neoadjuvant systemic therapy

Selecting treatment sequence for patients with incidental gallbladder cancer: a neoadjuvant approach versus upfront surgery

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Updates in Surgery (2019) 71:217–225

- **Rationale :**

  - ✓ in some patients outcome is characterized by poor tumor biology with early and frequent distant recurrence (as in pancreatic, gastric Ca,..)
  - ✓ early recurrence : median time is 11 months (all stages)
  - ✓ immediate treatment of micrometastatic disease
  - ✓ optimize patient selection for surgery
  - ✓ favor treatment compliance (avoid complication that postpone adjuvant chemotherapy)
  - ✓ in vivo assessment of tumor chemosensitivity (<future management decisions)
  - ✓ downstage the primary tumor
  - ✓ in patients with incidental GBCa and R1 before reoperation

Neoadjuvant systemic therapy

- NO current Level 1 evidence that supports neoadjuvant chemotherapy in management of Incidental GallbladderCa(IGBC)
- Systemic chemotherapy for IGBC is not as effective as chemotherapy for other GI malignancies (adjuvant and neoadjuvant)
- Mostly gemcitabine/cisplatinum doublet therapy

ing liver mass or clinically positive nodes. At MSKCC, those patients with evidence of T3, node-positive, poor differentiation or residual disease would be candidates for neoadjuvant chemotherapy. This theoretically provides immediate treatment of any micrometastatic disease in these high-risk patients and incorporates time as a selection strategy to identify those patients who will quickly progress to distant disease and, therefore, cannot benefit from surgery. Certain cases require major hepatectomy or

Carefull use in selected patients - risk of treating patients that need surgery first

Follow up

- Close follow up is necessary
- 3 to 6 months intervals for at least 5 years
- Long term survivors, yearly follow up
- Follow up by :
  - ✓ clinical evaluation
  - ✓ CA19.9, CA242 and CEA (if elevated preoperatively)
  - ✓ CT abdomen, pelvis and thorax

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Gallbladder Cancer: Diagnosis, Surgical Management, and Adjuvant Therapies

Laura Hickman MD, Carlo Contreras MD

Table 4
Five-year survival for GBC by American Joint Committee on Cancer T-classification and stage

	5 Year OS[97] (%)		5-Year OS[57] (%)
T1a	85.9	Stage I	62.5
T1b		Stage IIA	50.2
T2	56.1	Stage IIB	
T3	19.2	Stage IIIA	25.7
T4	14.1	Stage IIIB	22.1
		Stage IVA	15.7
		Stage IVB	6.7

Advances in Surgery 52 (2018) 89–100

ADVANCES IN SURGERY

How Should Gallbladder Cancer Be Managed?

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Table 3
Survival of patients with gallbladder cancer based on stage at presentation

Stage	Five-year survival (%)
0/in situ	80
I	50
II	28
IIIA	8
IIIB	7
IVA	4
IVB	2

Future directions

- Extended cholecystectomy + portal lymphadenectomy with adjuvant therapy in well selected patients offers the best long-term survival
- New trails need to be developed, up till now no dramatic change in OS
- Molecular targeted therapy in its infancy, but promising trails

Valle JW, Borbath I, Khan S, et al. On behalf of the ESMO Guidelines Committee Biliary cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27(Suppl 5):v28–37.

Surgical Clinics of North America
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Table 3
Targetable genetic mutations in gallbladder cancer

Targetable Mutations	Prevalence (%)	Potential Therapeutics
EGFR	4–13	Afatinib, Erlotinib, Cetuximab
HER2/neu amplification	10–16	Trastuzumab, Lapatinib, Pertuzumab
TP53	4–47	Bevacizumab
ERBB3	0–12	Seribantumab, Pertuzumab, Trastuzumab
PTEN *PIK3CA*	0–4 6–14	mTOR inhibitors (everolimus)
KRAS	4–13	Trametinib, Selumetinib
AR1D1A	15	mTOR inhibitor (everolimus), anti-PD-L1 (Pembrolizumab) for tumors with microsatellite instability
CDKN2A/B loss	6–19	Palbociclib

Data from Jain A, Javle M. Molecular profiling of biliary tract cancer: a target rich disease. J Gastrointest Oncol 2016;7(5):797–803; and Sicklick JK, Fanta PT, Shimabukuro K, et al. Genomics of gallbladder cancer: the case for biomarker-driven clinical trial design. Cancer Metastasis Rev 2016;35(2):263–75.

Summary

- Gallbladder cancer terrible disease, survival is poor in all but the earliest stage
- OS not much changed despite progress in diagnosis
- Multidisciplinary approach, patient selection is critical
- Clinical trails should be offered to patients to advance the understanding of this disease
- Neoadjuvant regimes : gemcitabine based +/- platinum for 3 months (in which time is also a selection strategy)


THANK
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