Management of biliary malignancies Radiation oncology perspective including contouring

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ROADMAP

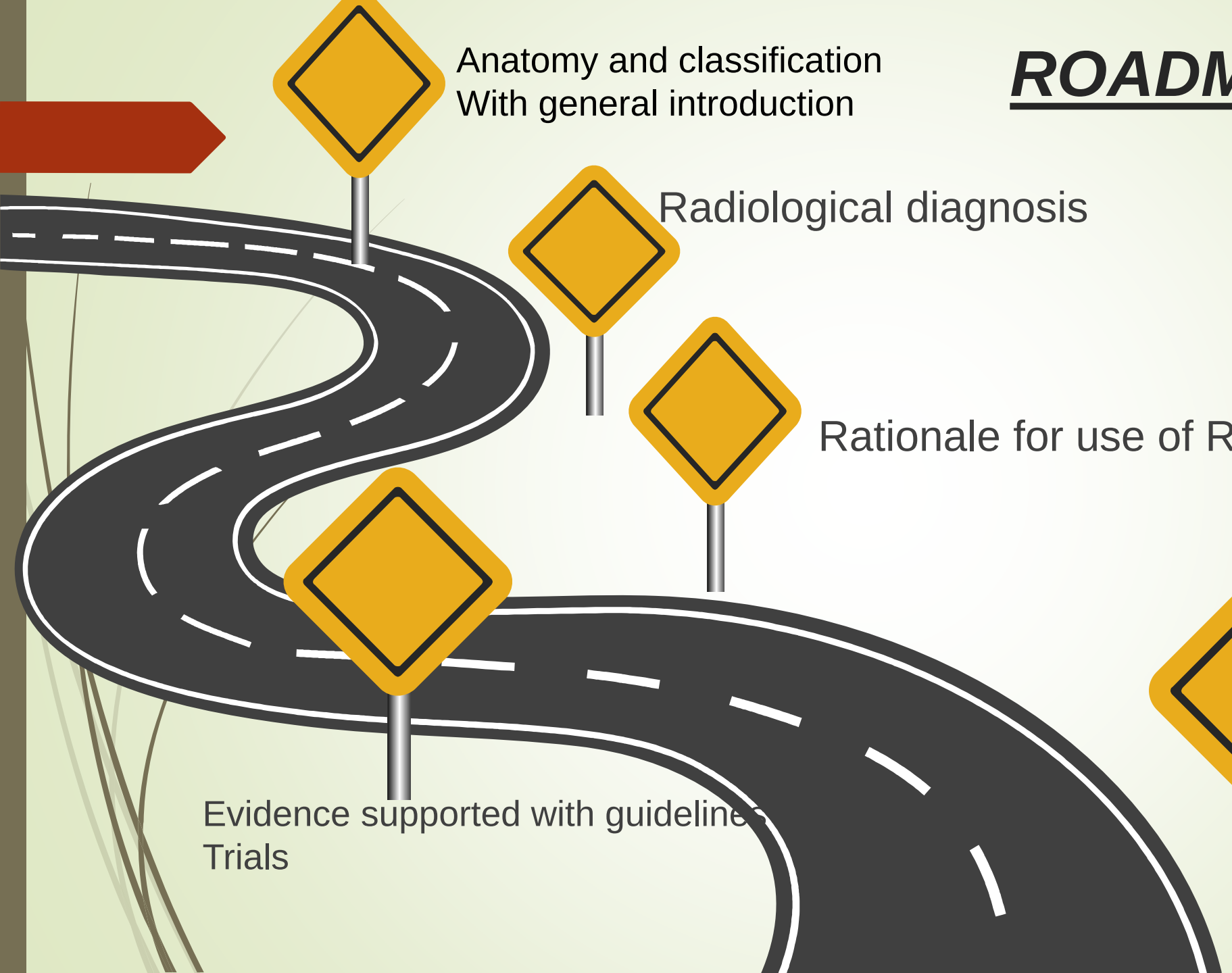
Anatomy and classification
With general introduction

Radiological diagnosis

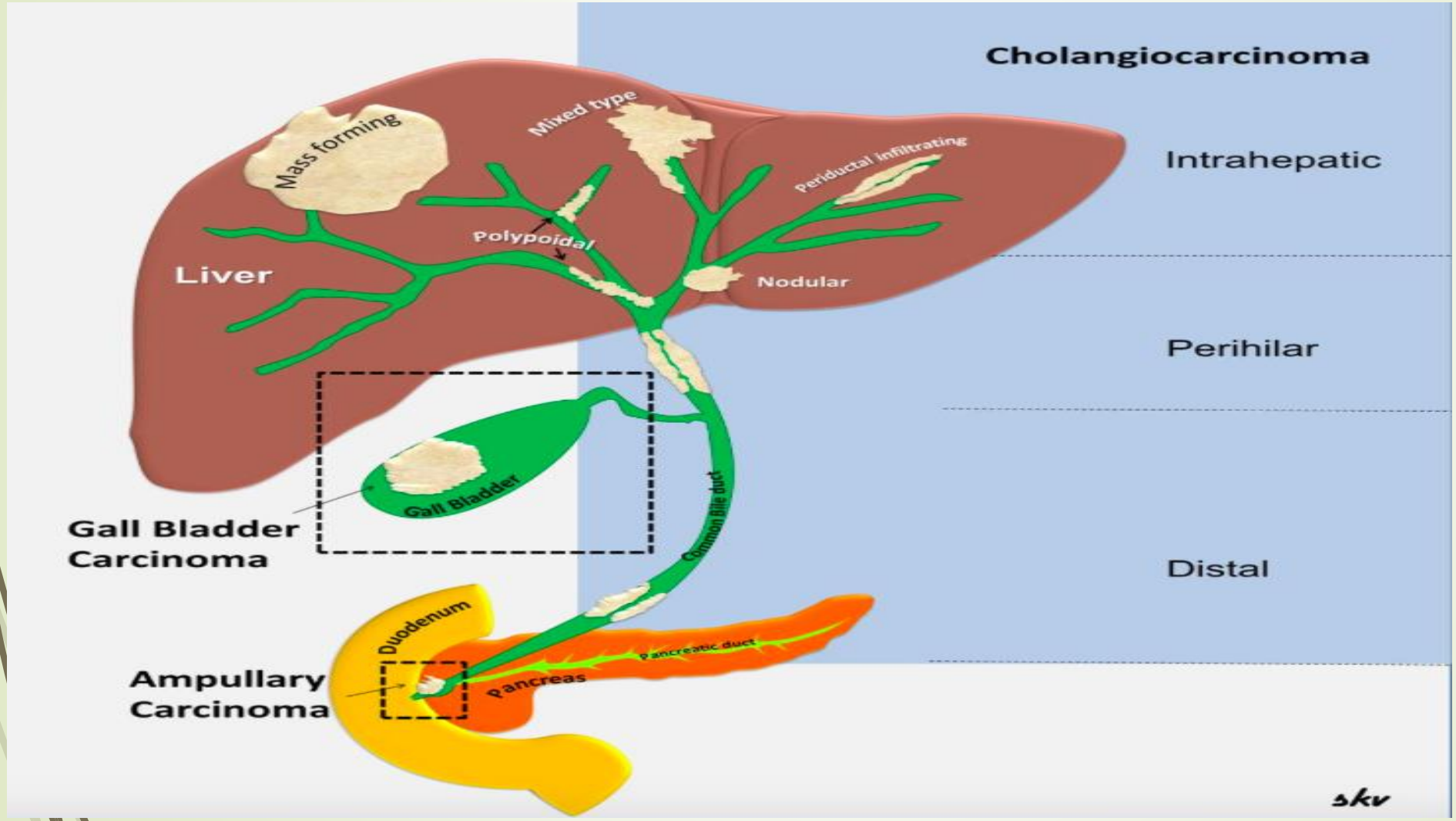
Rationale for use of RT

Evidence supported with guideline
Trials

Contouring
Guidelines.



Biliary Anatomy



Biliary malignancies

- Intrahepatic Cholangiocarcinomas
- Extrahepatic Cholangiocarcinomas
- Perihilar Bile-Duct carcinomas
- Gall Bladder carcinomas

Original Research Article

Gall bladder carcinoma (GBC): Rising incidences in the Malwa belt region of northern India a hospital based cancer registry

Sapna Marcus[1*], Jasmeet Kaur[2], H P Yadav[3]

Department of Radiation Oncology, Guru Gobind Singh Medical College and Hospital, Faridkot, Punjab, INDIA.
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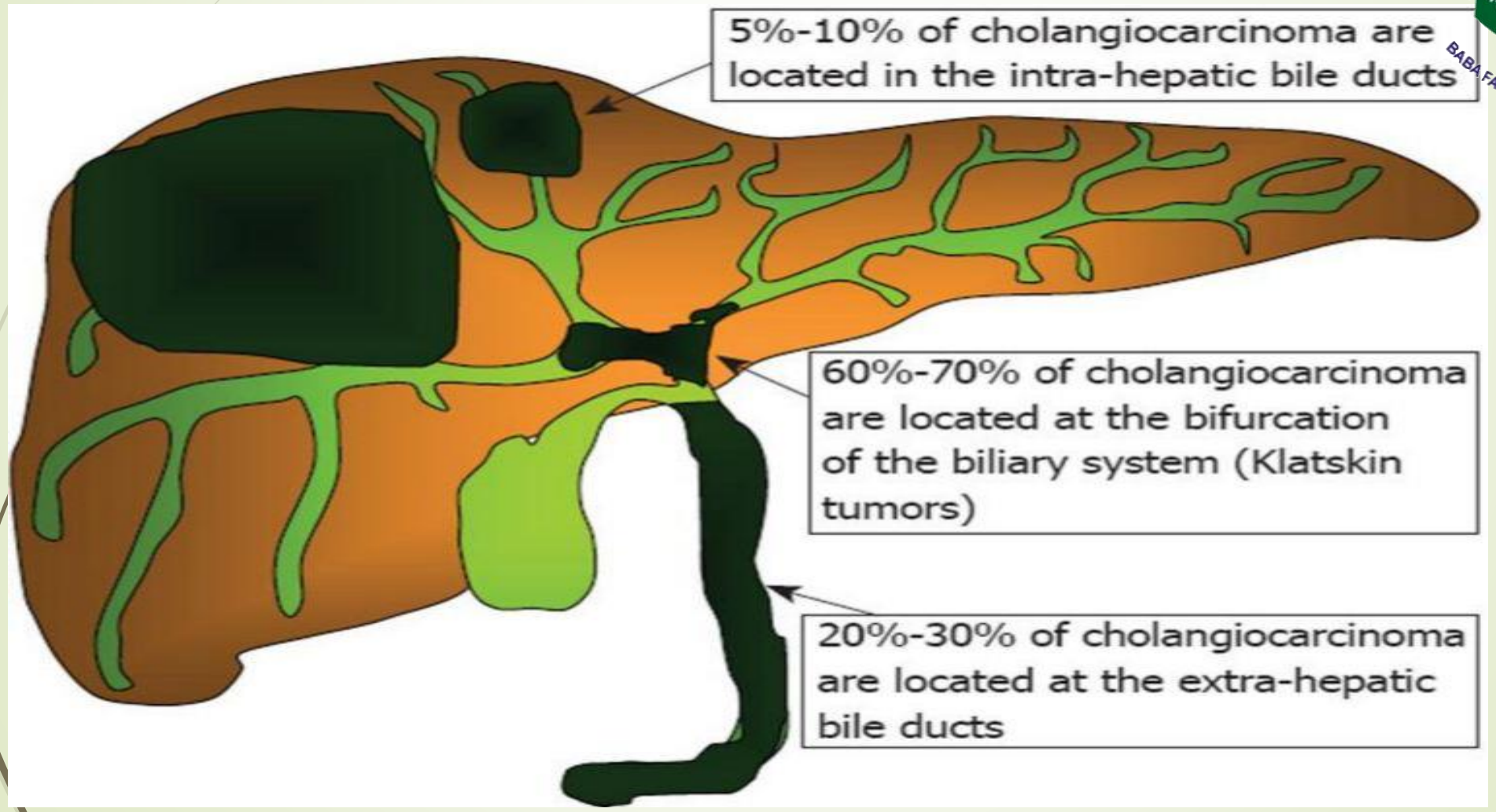
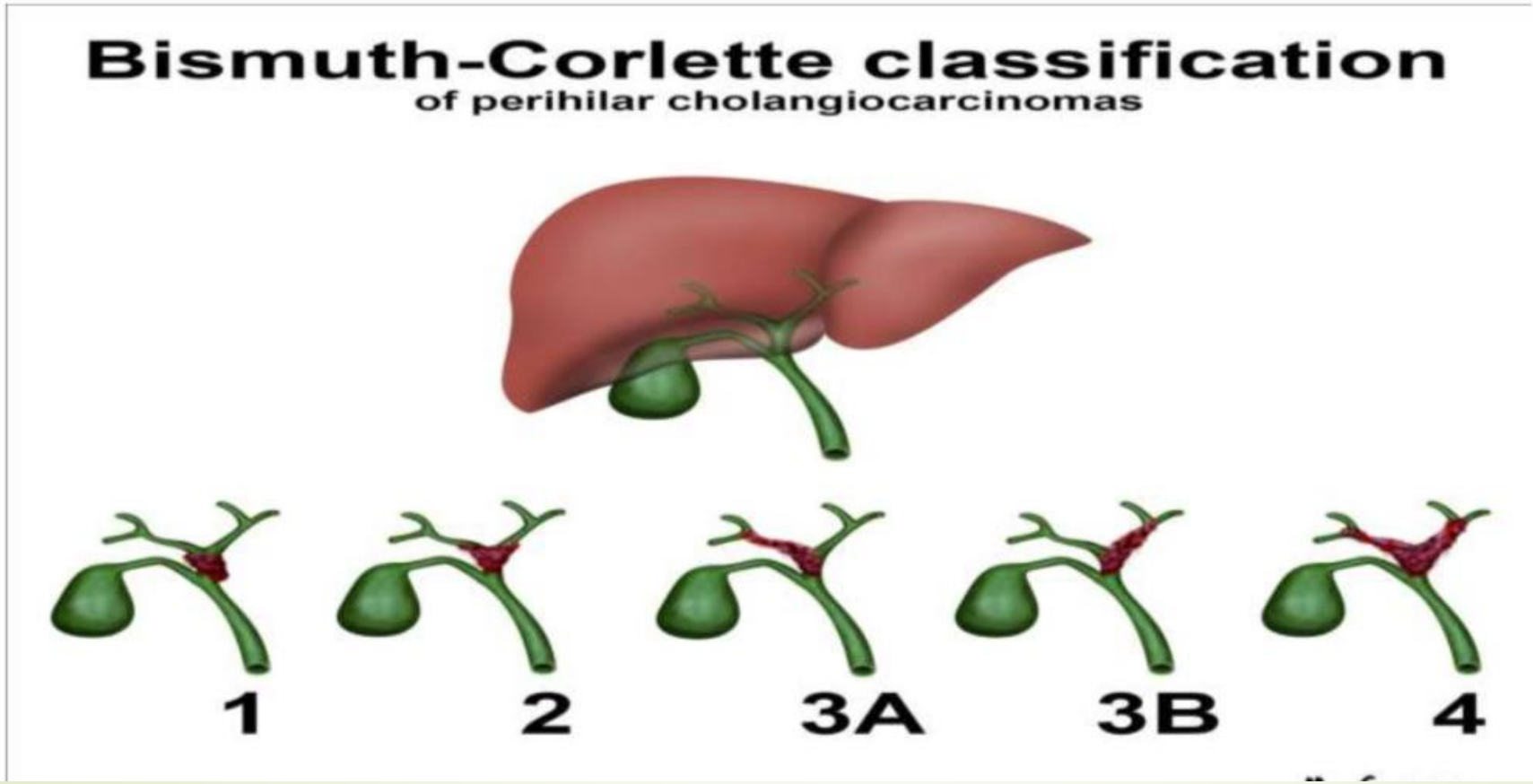
Classification of biliary tract tumors



Anatomically, biliary tree is divided into 3 parts, upper 3rd-55%, middle 3rd 15% and lower 3rd 10%.Of these tumours, 10% are diffuse



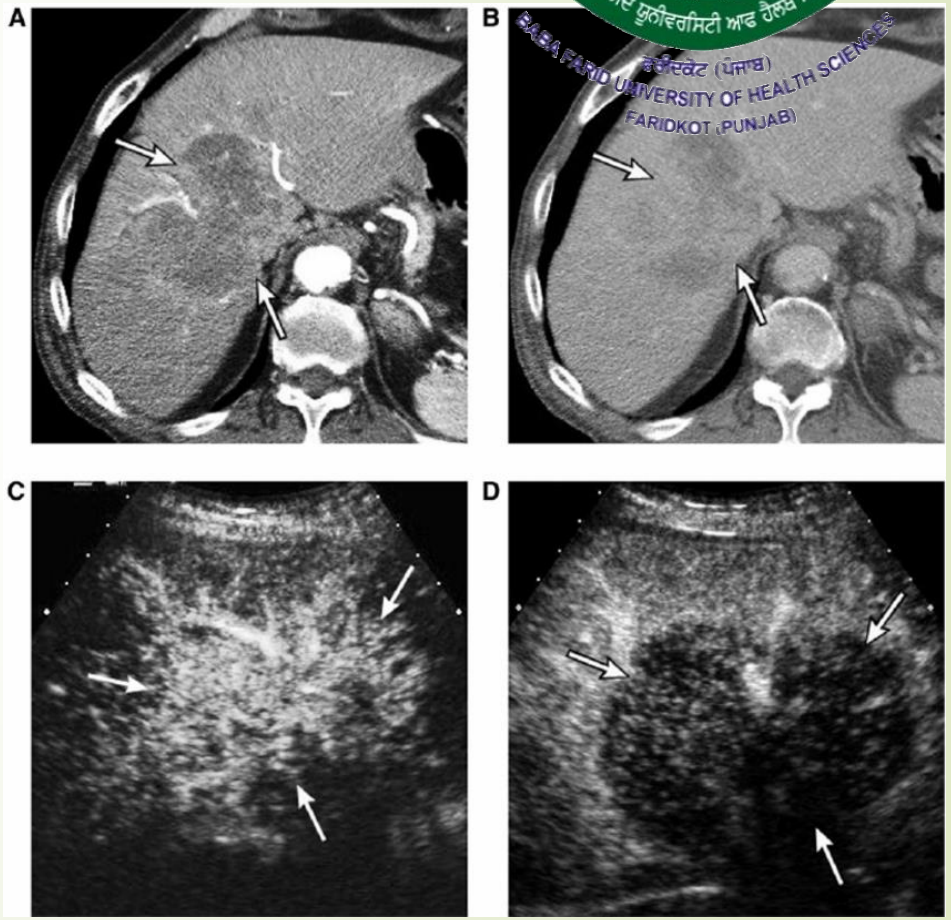
Radiological Appearance of IHCC

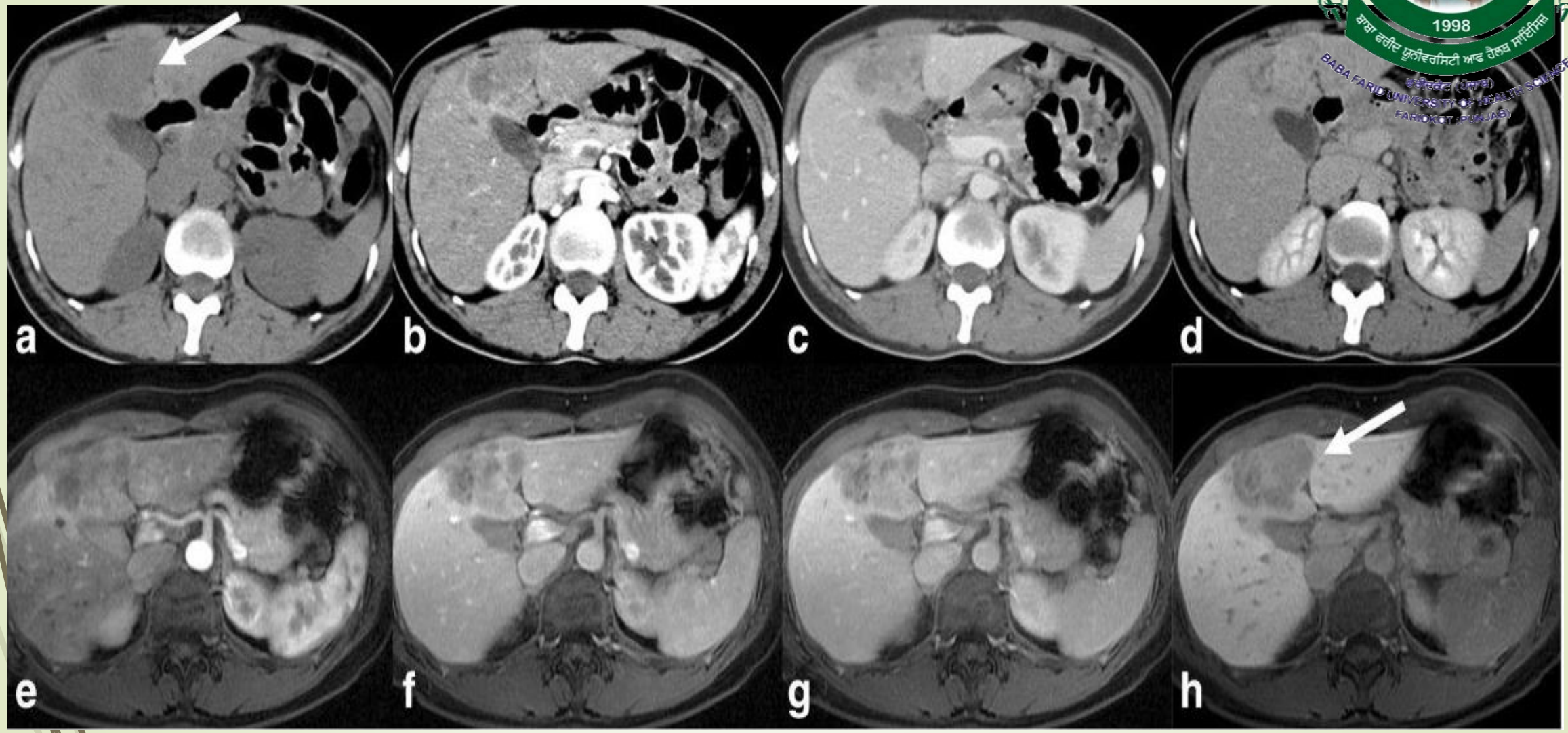
(A) Arterial phase CT scan shows a large mass (arrows) with irregular peripheral enhancement.

(B) Three-minute delay phase CT scan shows progression of enhancement within the mass (arrows).

(C) Contrast-enhanced sonogram at 19 s delay shows hypervascularity of the mass (arrows).

D) Contrast-enhanced sonogram at 34 s delay shows early complete washout of enhancement of the mass (arrows),

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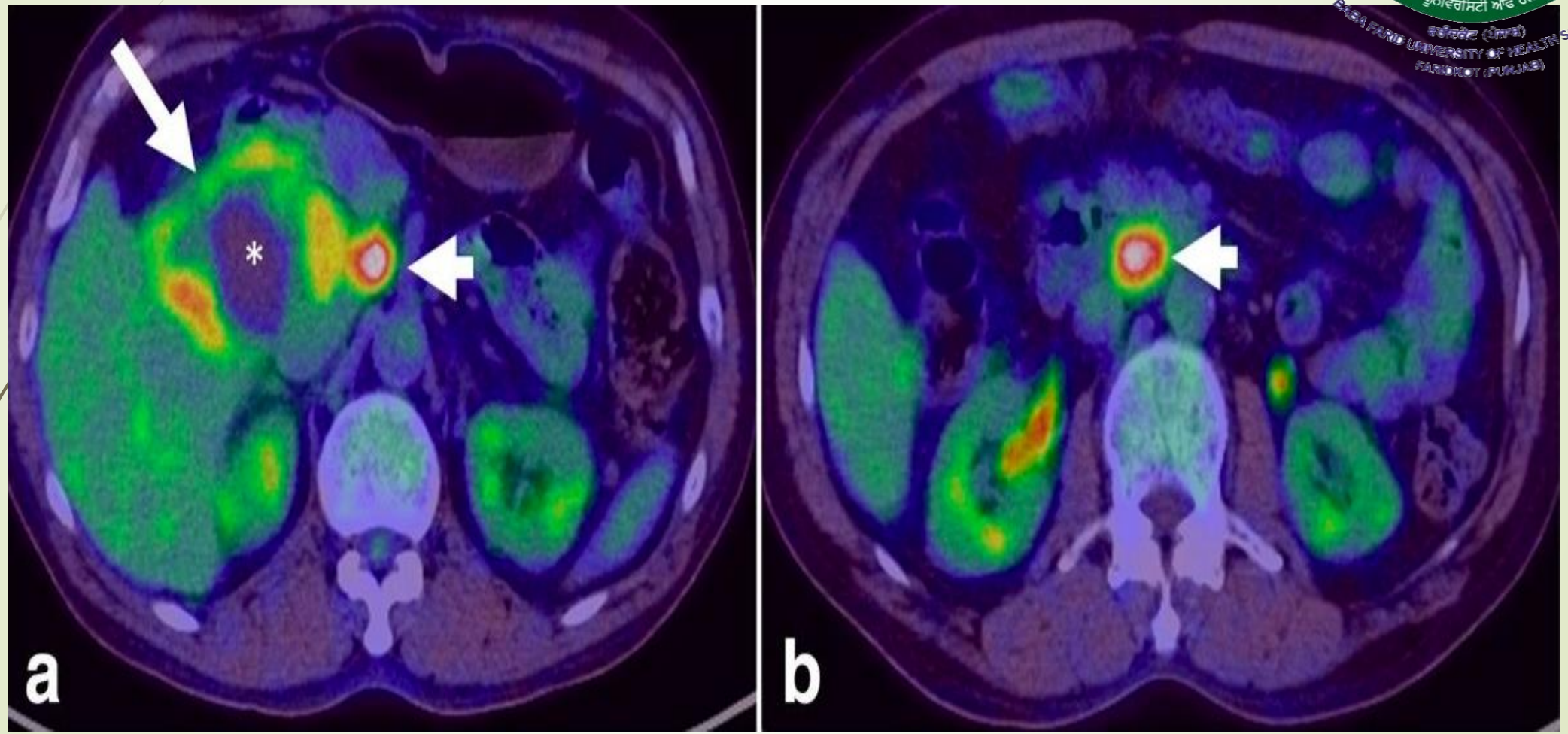
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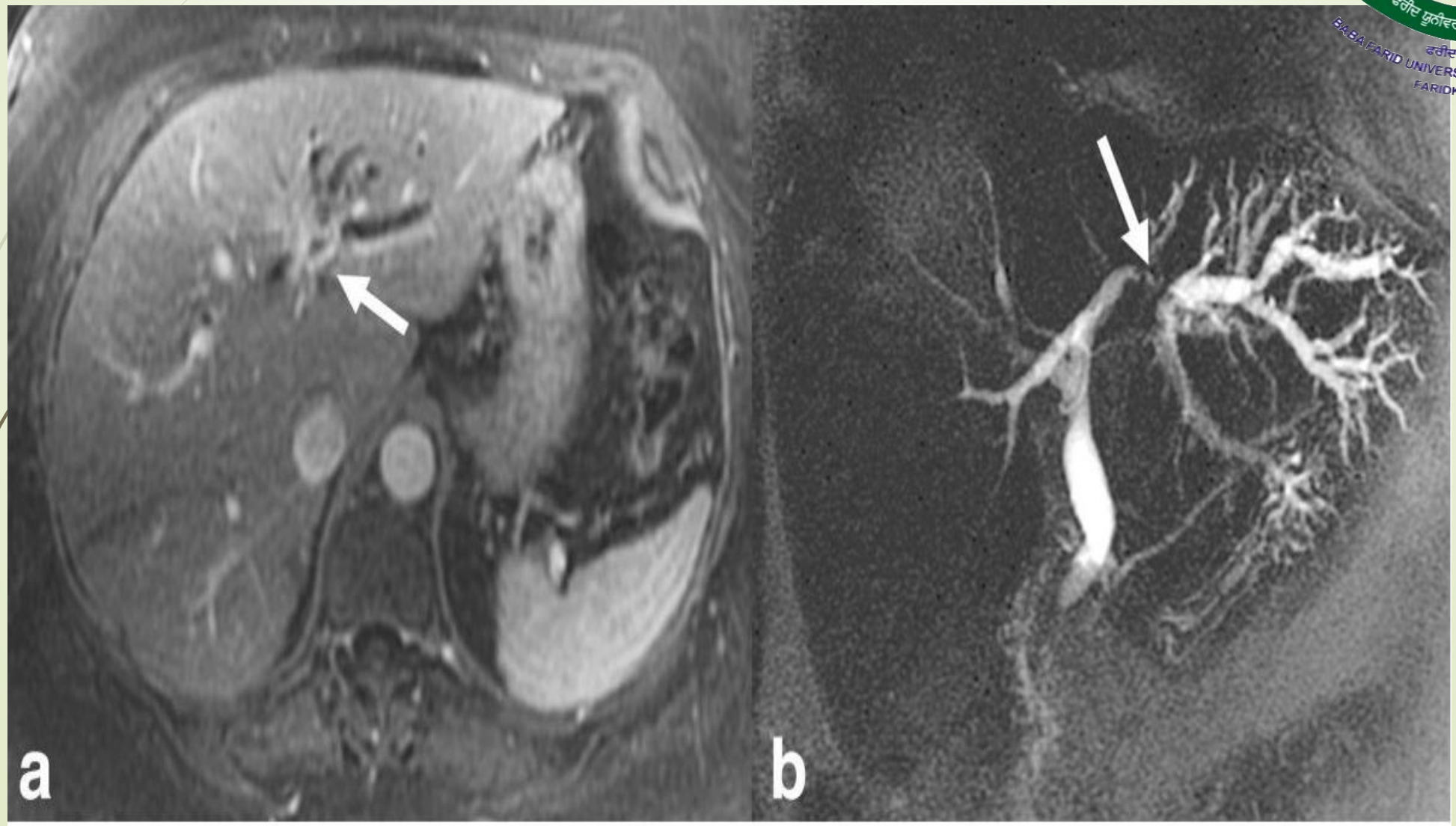
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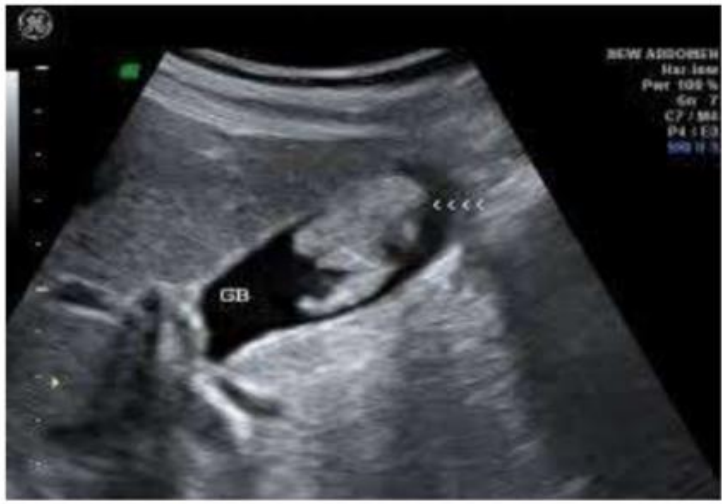
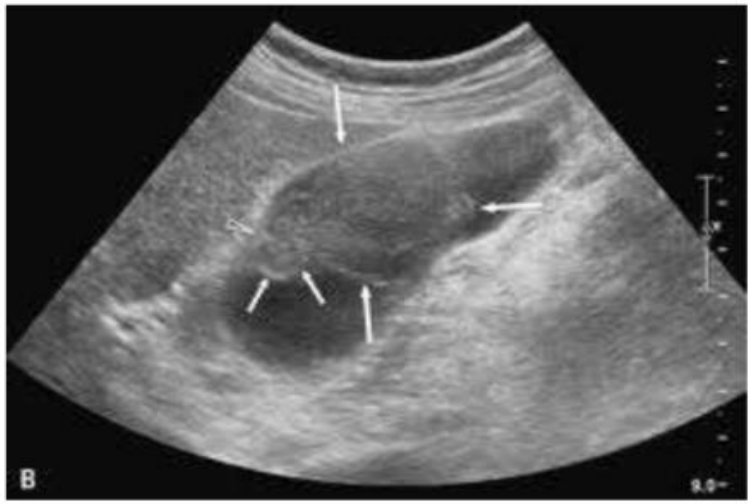
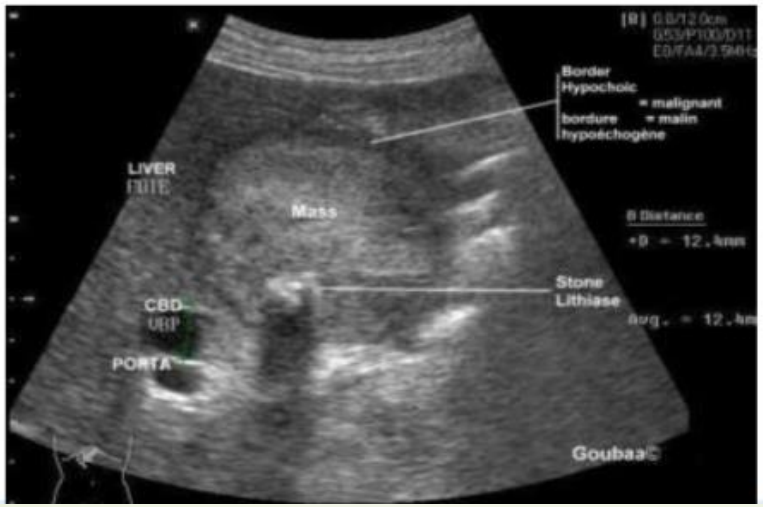
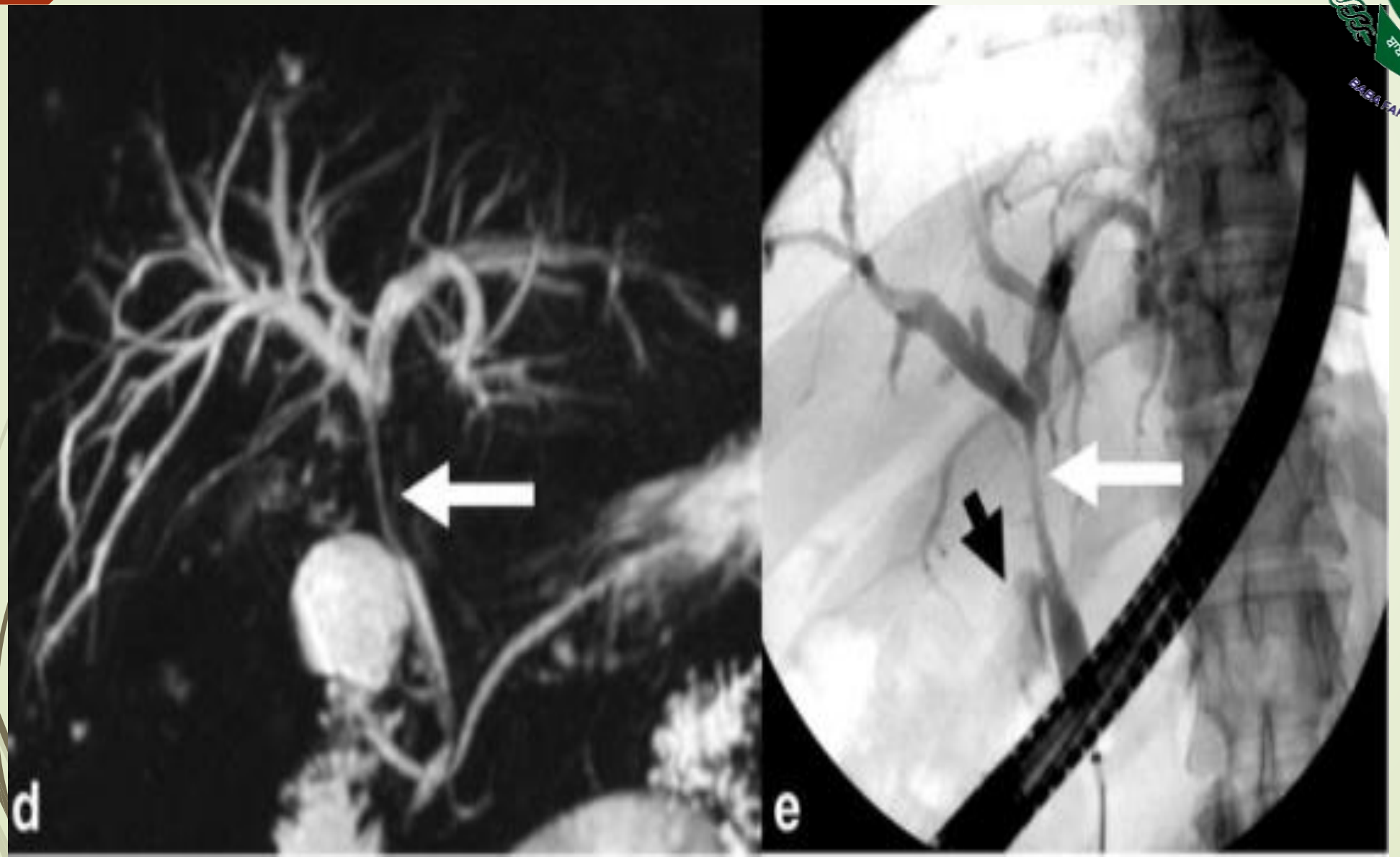
Ultrasonographic Appearance of GBC





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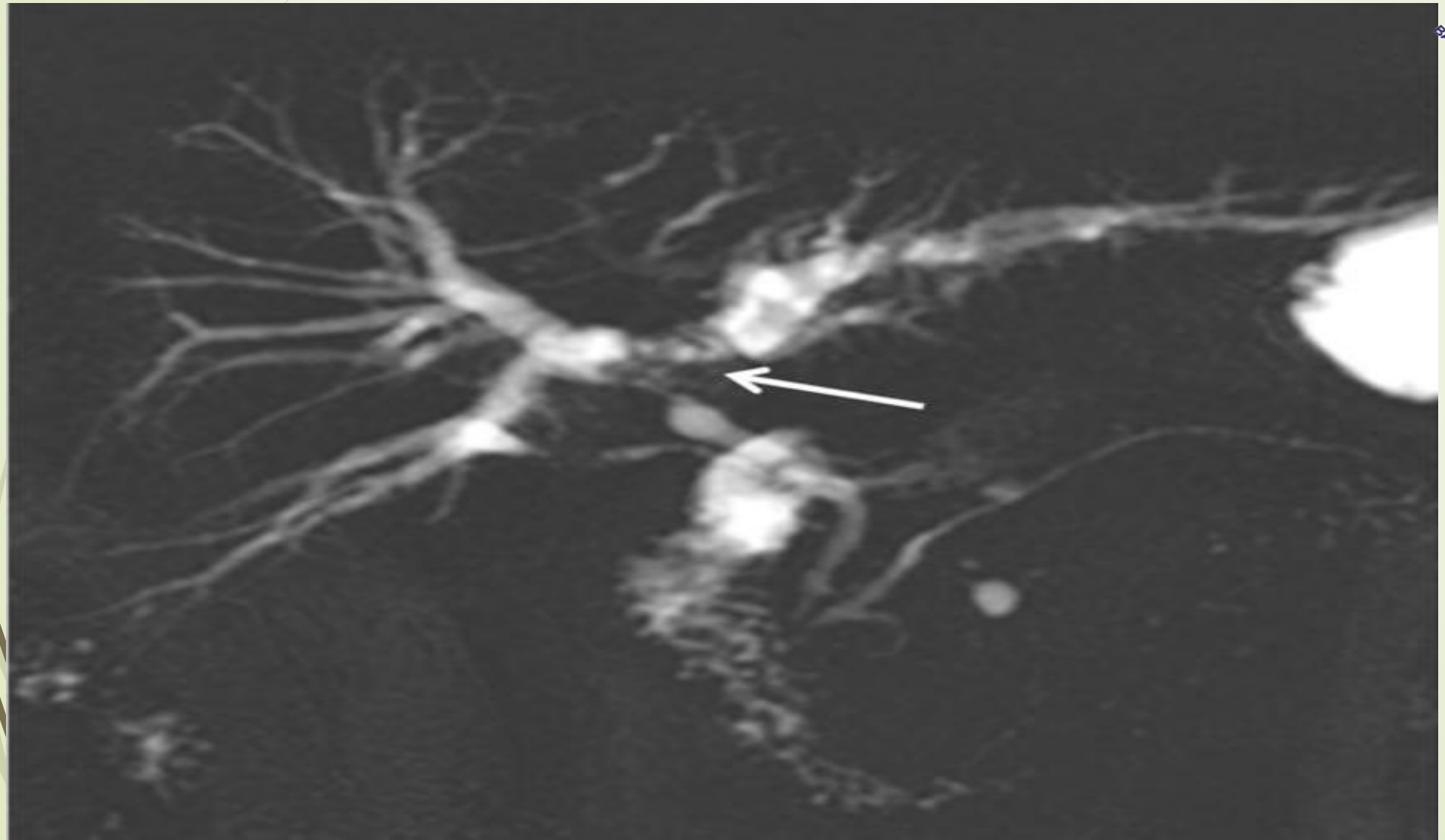

Usual presentation

- Fever- 20%
- Diarrhoea, anorexia,
- Changes in urine & stool colour and weight loss.
- Liver may be enlarged and smooth-25-40%
- Distended and non tender gallbladder 10%
- Epigastric tenderness.

Which patient group are we going to offer radiotherapy to?

Rationale for using RT in biliary carcinomas

- Neoadjuvant radio- therapy reduced risk of implantation metastases after endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography
- Palliative for symptom relief (metastatic ds OR CPS C)

High Risk Group for Adjuvant RT

- Poor histologic differentiation.
- Lymph Node metastasis
- Positive RM status
- Higher primary tumor stage

Where does radiation fit in ??

- Adjuvant setting
- Neoadjuvant setting
- Definitive setting
- Palliative setting

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NCCN Guidelines Version 2.2019
Intrahepatic Cholangiocarcinoma

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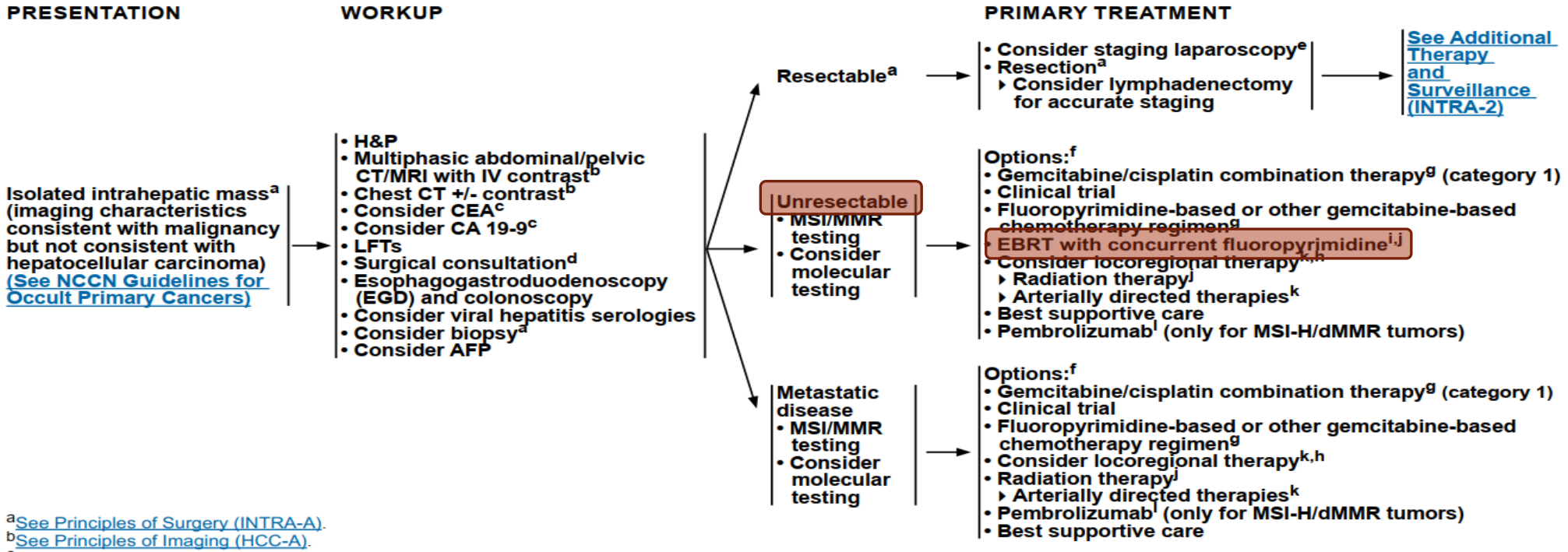

[a] See Principles of Surgery (INTRA-A).
[b] See Principles of Imaging (HCC-A).
[c] CEA and CA 19-9 are baseline tests and should not be done to confirm diagnosis.
[d] Consult with multidisciplinary team.
[e] Laparoscopy may be done in conjunction with surgery if no distant metastases are found.
[f] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilities.
[g] A phase III trial supporting gemcitabine/cisplatin has been reported for patients with advanced or metastatic billiary tract cancer. (Valle JW, Wasan HS, Palmer DD, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Eng J Med 2010;362:1273-1281.) Clinical trial participation is encouraged. There are phase II trials that support the following combinations: gemcitabine/oxaliplatin, gemcitabine/capecitabine, gemcitabine/albumin-bound paclitaxel, capecitabine/cisplatin, capecitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin, and the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting.
[h] Intra-arterial chemotherapy (with or without systemic chemotherapy) may be used in a clinical trial or at experienced centers.
[i] There are limited clinical trial data to define a standard regimen or definitive benefit. Participation in clinical trials is encouraged. (Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in billiary tract cancer. Surg Oncol Clin N Am 2002;11:941-954).
[j] See Principles of Radiation Therapy (GALL-C).
[k] Principles of Locoregional Therapy (HCC-E).
[l] There are limited clinical trial data to support pembrolizumab in this setting. Personalized, molecularly matched combination therapies for treatment-naïve, lethal malignancies: the I-PREDICT Study. Sicklick JK, Leyland-Jones B, Kato S, et al. J Clin Oncol 2017;35:2512.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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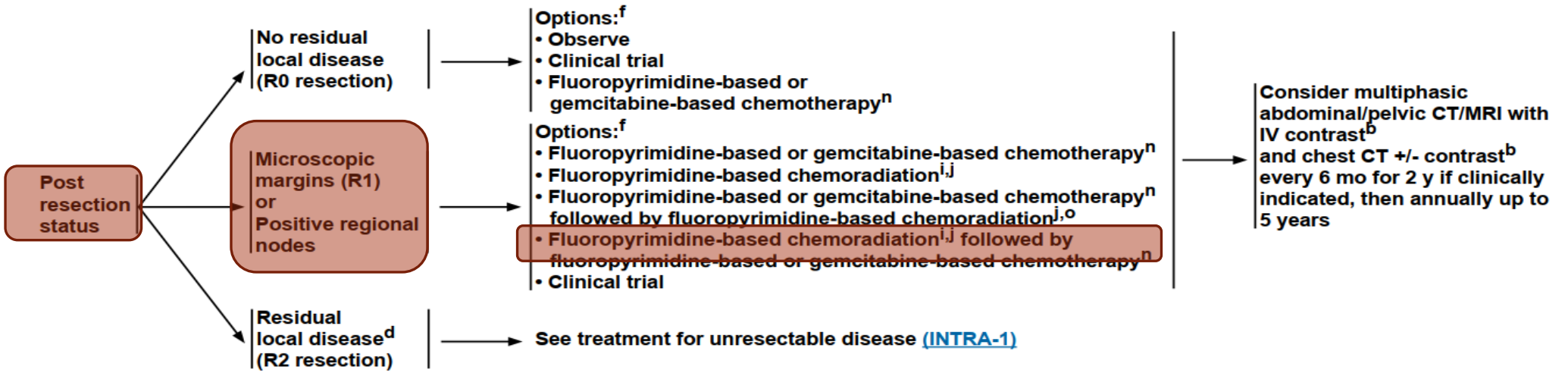

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[j] See Principles of Radiation Therapy (GALL-C).
[m] Adjuvant chemotherapy or chemoradiation has been associated with survival benefit in patients with biliary tract cancer (BTC), especially in patients with lymph node-positive disease (Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systemic review and meta-analysis. J Clin Oncol 2012;30:1934-1940).
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[o] Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG S0809: A phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. J Clin Oncol 2015;33:2617-2622.
[p] There are no data to support a specific surveillance schedule or tests for monitoring. Physicians should discuss appropriate follow-up schedules/imaging with patients.

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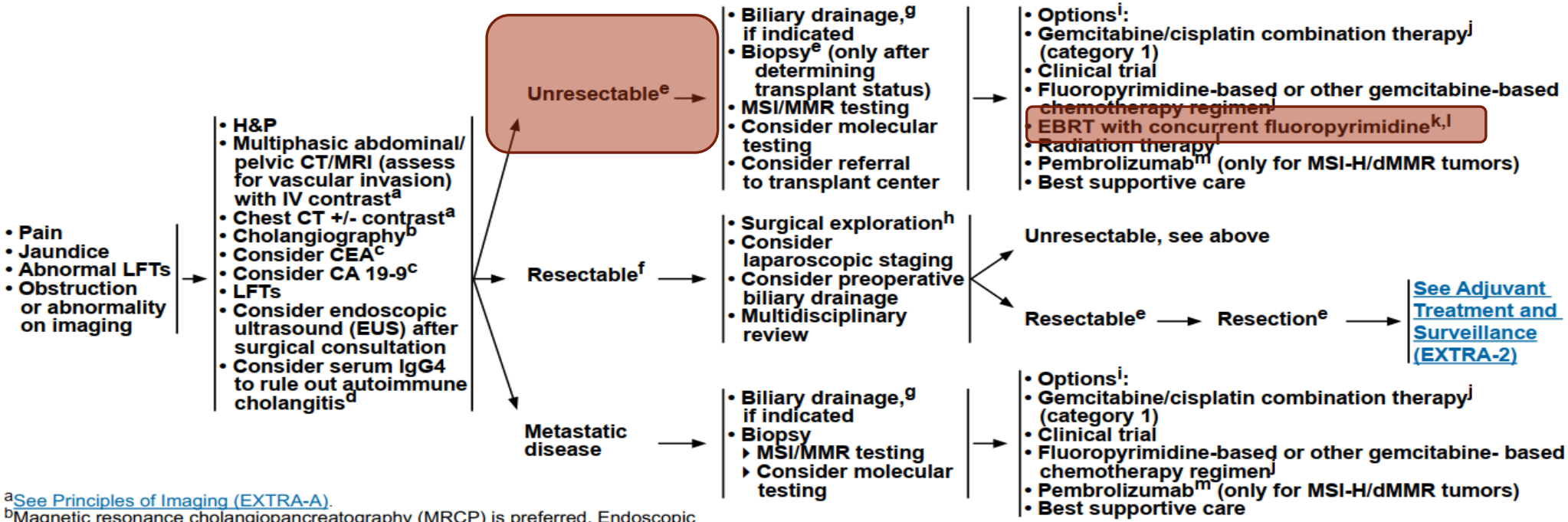
Extrahepatic Cholangiocarcinoma



[a] See Principles of Imaging (EXTRA-A).
[b] Magnetic resonance cholangiopancreatography (MRCP) is preferred. Endoscopic retrograde cholangiopancreatography/percutaneous transhepatic cholangiography (ERCP/PTC) are used more for therapeutic intervention.
[c] CEA and CA 19-9 are baseline tests and should not be done to confirm diagnosis.
[d] Patients with IgG-4–related cholangiopathy should be referred to an expert center.
[e] Before biopsy, evaluate if patient is a resection or transplant candidate. If patient is a potential transplant candidate, consider referral to transplant center before biopsy. Unresectable perihilar or hilar cholangiocarcinomas that measure ≤3 cm in radial diameter, with the absence of intrahepatic or extrahepatic metastases and without nodal disease, may be considered for liver transplantation at a transplant center that has an UNOS-approved protocol for transplantation of cholangiocarcinoma.
[f] See Principles of Surgery (EXTRA-B).
[g] Consider biliary drainage for patients with jaundice prior to instituting chemotherapy. Consider baseline CA 19-9 after biliary decompression.
[h] Surgery may be performed when index of suspicion is high; biopsy is not required.
[i] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilities.
[j] A phase III trial supporting gemcitabine/cisplatin has been reported for patients with advanced or metastatic billiary tract cancer. (Valle JW, Wasan HS, Palmer DD, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Eng J Med 2010;362:1273-1281.) Clinical trial participation is encouraged. There are phase II trials that support the following combinations: gemcitabine/oxaliplatin, gemcitabine/capecitabine, gemcitabine/albumin-bound paclitaxel, capecitabine/cisplatin, capecitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin, and the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting.
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Extrahepatic Cholangiocarcinoma

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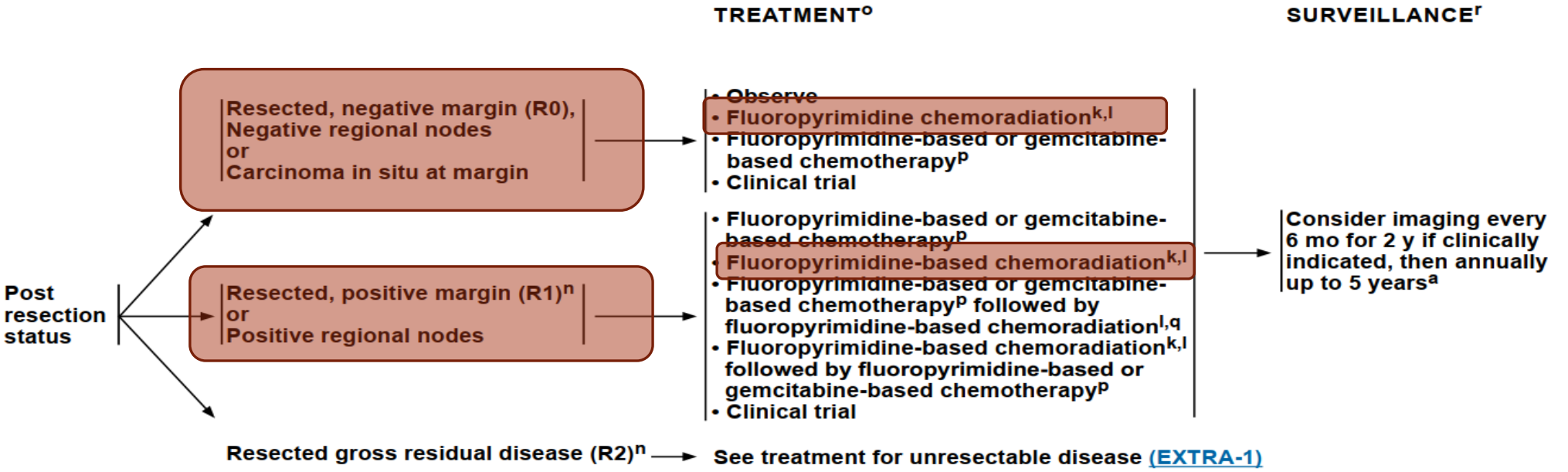

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[l] See Principles of Radiation Therapy (GALL-C).

[n] Management of patients with R1 or R2 resections should be evaluated by a multidisciplinary team.

[o] Adjuvant chemotherapy or chemoradiation has been associated with survival benefit in patients with biliary tract cancers, especially in patients with lymph node-positive disease (Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systemic review and meta-analysis. J Clin Oncol 2012;30:1934-1940).

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[q] Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG S0809: A phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. J Clin Oncol 2015;33:2617-2622.

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Evidence Supporting Role of Radiotherapy in Biliary Tract Carcinomas

SEER Database
Adjuvant RT for Extrahepatic Cholangiocarcinoma

- 1988-2003 (4758 patients): Significant difference in overall survival between Surgery +RT vs Surgery alone ($p<0.001$) & between RT/Surgery/both vs none ($p<0.001$)

  Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 4, pp. 1191–1198, 2009

- 1973-2003 (2323 patients): Adjuvant RT is not associated with any improvement in OS/DFS.

  Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 1, pp. 189–198, 2011

European Journal of Surgical Oncology (EJSO)
Volume 33, Issue 2, March 2007, Pages 202-207

Predictive factors for prognosis of hilar cholangiocarcinoma: Postresection radiotherapy improves survival

Q. Cheng [1], X. Luo [1], B. Zhang, X. Jiang, B. Yi, M. Wu

Show more

https://doi.org/10.1016/j.ejso.2006.09.033

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Abstract

Aims

Several studies have analyzed the determinants of long-term survival in hilar cholangiocarcinoma (HCCA) patients, but the majority of these have not speculated adjuvant therapy on prognosis. We conduct this study to identify potential predictive factors for prognosis of HCCA focusing on aspects dealing with adjuvant therapy.

Patients and methods

Data from 75 consecutive HCCA patients undergoing surgical resection with curative intent were recorded prospectively. The survivals of patients were comparable with respect to different factors followed by a univariate and multivariate analysis.

J Natl Compr Canc Netw. 2018 Jan;16(1):59-65. doi: 10.6004/jnccn.2017.7067.

Chemoradiotherapy Versus Chemotherapy Alone for Unresected Nonmetastatic Gallbladder Cancer: National Practice Patterns and Outcomes.

Verma V[1], Surkar SM[2], Brooks ED[3], Simone CB 2nd[4], Lin C[1].

⊕ Author information

Abstract

Purpose: Current guidelines recommend chemotherapy (CT) with or without radiotherapy for unresected nonmetastatic gallbladder cancer (GC), with little consensus. However, several small-volume, single-institution studies have documented the efficacy of local therapy for this population. This is the largest study to date evaluating outcomes of chemoradiotherapy (CRT) versus CT alone in unresected nonmetastatic GC. **Methods:** The National Cancer Database was queried for primary GC cases (2004-2013) receiving CT alone or CRT. Patients receiving resection or lack of CT were excluded, as were those with metastatic disease or unknown M classification. Logistic regression analysis ascertained factors associated with CRT delivery. Kaplan-Meier analysis evaluated overall survival (OS) between both cohorts. Cox proportional hazards modeling determined variables associated with OS. **Results:** In total, 1,199 patients were analyzed (CRT: n=327, 27%; CT: n=872, 73%). Groups were evenly balanced, with no factor on multivariate logistic regression analysis statistically predicting for receipt of a particular paradigm. Median OS in the CRT and CT groups was 12.9 versus 7.8 months, respectively (*P*=.001). On multivariate analysis, OS was associated with age and years of treatment (*P*=.001 each). Notably, receipt of CRT independently predicted for improved OS (*P*=.001). **Conclusions:** CRT, compared with CT alone, was independently associated with improved survival in unresected nonmetastatic GC. Although causation is not implied, these results support the necessity for prospective CRT evaluation.

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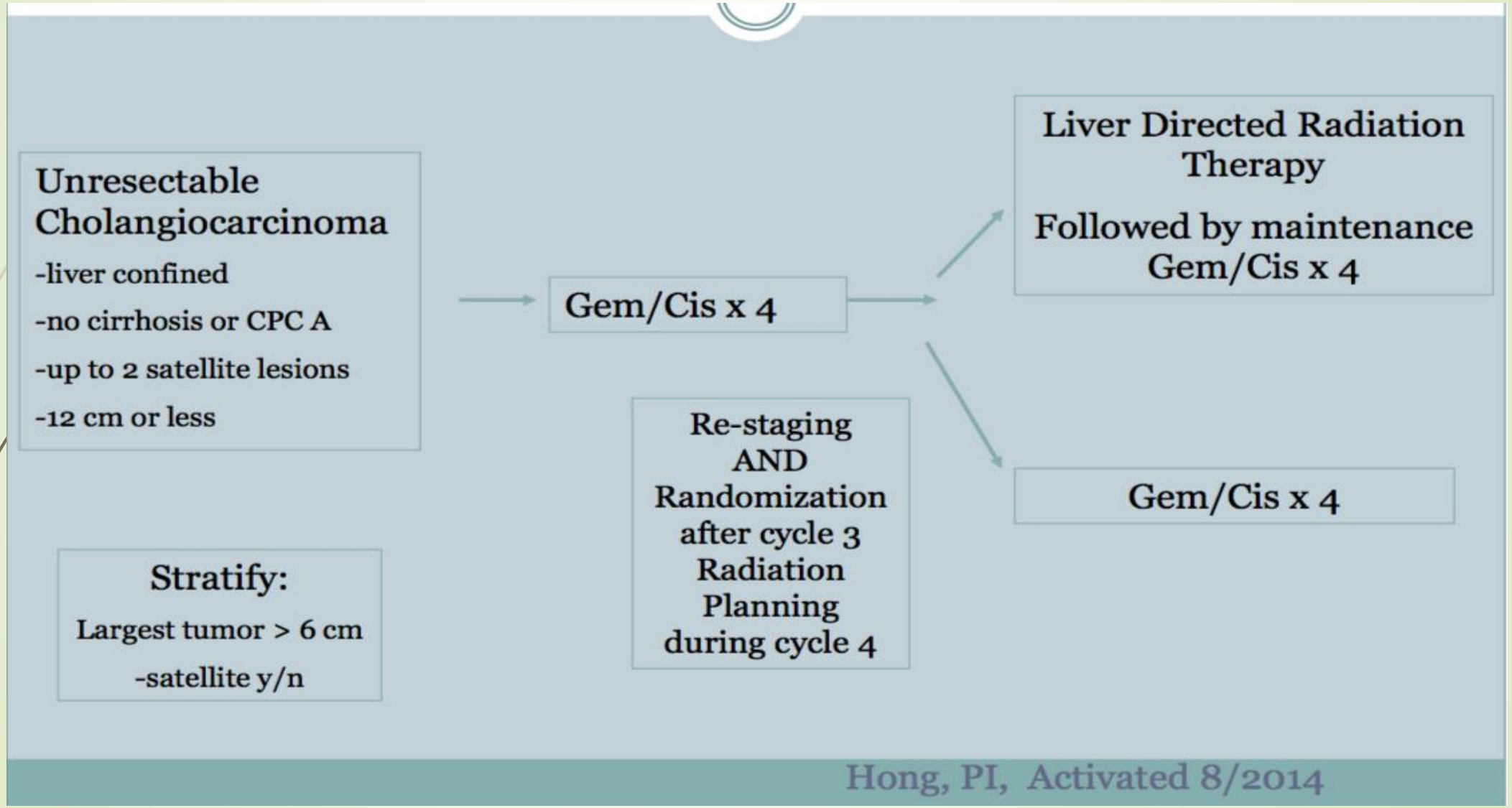
Adjuvant external-beam radiotherapy with concurrent chemotherapy after resection of primary gallbladder carcinoma: a 23-year experience.

Czito BG[1], Hurwitz HI, Clough RW, Tyler DS, Morse MA, Clary BM, Pappas TN, Fernando NH, Willett CG.

- **PURPOSE:** Primary adenocarcinoma of the gallbladder is a rare malignancy. To better define the role of adjuvant radiation therapy and chemotherapy, a retrospective analysis of the outcome of patients undergoing surgery and adjuvant therapy was undertaken.
- **METHODS AND MATERIALS:** Twenty-two patients with primary and nonmetastatic gallbladder cancer were treated with radiation therapy after surgical resection. Median radiation dose was 45 Gy. Eighteen patients received concurrent 5-fluorouracil (5-FU) chemotherapy. Median follow-up was 1.7 years in all patients and 3.9 years in survivors.
- **RESULTS:** The 5-year actuarial overall survival, disease-free survival, metastases-free survival, and local-regional control of all 22 patients were 37%, 33%, 36%, and 59%, respectively. Median survival for all patients was 1.9 years.
- **CONCLUSION:** Our series suggests that an approach of radical resection followed by external-beam radiation therapy with radiosensitizing 5-FU in patients with locally advanced, nonmetastatic carcinoma of the gallbladder **may improve survival. This regimen should be considered in patients with resectable gallbladder carcinoma**.

NRG GI-001 Phase III Trial (unresectable CC)



CONTOURING

RT Contouring Guidelines in Hepatic Cholangiocarcinoma

- Conventional radiotherapy for unresectable cases covers the gross tumour volume (GTV) with a 1.0-cm margin for CTV.
- Niska et al, assessed if the GTV varies between various phases of multiphasic CT imaging in the case of IHCC. The results showed that the IHCC lesions were best identified on the **portal venous phase in 64% and the arterial phase in 29% of the cases.**

Practice Radiat Oncol 2016 Jan-Feb;6(1):e9-16.

An atlas for clinical target volume definition, including elec[illegible] nodal irradiation in definitive radiotherapy of biliary cancer

SILVIA BISELLO[1], MATTEO RENZULLI[2], MILLY BUWENGE[1], LUCIA CALCULLI[2], GIUSEPPINA SALLUSTIO[3], GABRIELLA MACCHIA[4], FRANCESCO DEODATO[4], GIANCARLO MATTIUCCI[5], SILVIA CAMMELLI[1], ALESSANDRA ARCELLI[1], LUCIA GIACCHERINI[1], FRANCESCO CELLINI[5], GIOVANNI BRANDI[6], SARA GUERRI[2], SAVINO CILLA[7], RITA GOLFIERI[2], LORENZO FUCCIO[8], ALESSIO G. MORGANTI[1*] and ALESSANDRA GUIDO[1*]

[1]Radiation Oncology Unit, Department of Experimental, Diagnostic and Specialty Medicine, S. Orsola-Malpighi Hospital; [2]Radiology Unit, Department of Diagnostic and Preventive Medicine, S. Orsola-Malpighi Hospital, I-40138 Bologna; [3]Radiology Unit; [4]Radiation Oncology Unit, Catholic University of The Sacred Heart, I-86100 Campobasso; [5]Radiation Oncology Department, Sacred Heart Catholic University, I-00168 Rome; [6]Department of Experimental, Diagnostic and Specialty Medicine, 'L. e. A. Seragnoli' Institute of Hematology and Medical Oncology, S. Orsola-Malpighi Hospital, I-40138 Bologna; [7]Medical Physics Unit 'Giovanni Paolo II' Foundation, Catholic University of the Sacred Heart, I-86100 Campobasso; [8]Department of Medical and Surgical Sciences, University of Bologna, I-40138 Bologna, Italy

Received June 7, 2018; Accepted October 31, 2018

RTOG contouring guidelines for adjuvant RT

CTV must include:

1. **Post-operative bed**
   - Based on location of initial tumor from pre-operative imaging and pathology reports
2. **Anastomoses**
   - Pancreaticojejunostomy(PJ)
   - Choledochal or hepaticojunostomy
3. **Abdominal nodal regions**
   - Peripancreatic
   - Celiac
   - Superior mesenteric
   - Porta hepatis
   - Para-aortic

Table I. CTV for intrahepatic cholangiocarcinoma.

Delineation type	JSHBPS classification	Recommended margins
Tumor delineation		
Intrahepatic cholangiocarcinoma	-	GTV + 10 mm radially
Lymph node group, nodes delineation		
Hepatoduodenal ligament lymph nodes	12	10 mm margin around the segment of portal vein from the confluence between the right and left hepatic ducts and the upper border of the pancreas
Common hepatic artery lymph nodes	8	10 mm margin around the common hepatic artery
Para-aortic lymph nodes	16	10 mm margin around the abdominal aorta, from the diaphragmatic aortic hiatus to the upper border of the origin of the inferior mesenteric artery
Posterior pancreaticoduodenal lymph nodes	13	10 mm around the posterior pancreaticoduodenal artery
Left gastric artery lymph nodes	7	10 mm around the trunk of the left gastric artery
Lesser gastric curvature lymph nodes	3	The area around the lesser curvature of the stomach
Right paracardial lymph nodes	1	The narrowed anatomic space identified between gastric cardia and the liver, extending posteriorly to the aorta and inferiorly to the lesser curvature LNs
Left paracardial lymph nodes	2	The anatomic space defined medially by the gastric fundus, anteromedially by the visceral peritoneum, posteriorly by the spleen, superiorly by the hemi diaphragm, and inferiorly by the great curvature LNs

Lymph node nomenclature is based on the 3rd English Edition of Classification of biliary tract cancers established by the JSHBPS. The anatomical structures of interest and the abdominal vessels of reference were identified for each lymph node region. JSHBPS, Japanese Society of Hepato-Biliary-Pancreatic Surgery; CTV, clinical target volume; GTV, gross tumor volume.

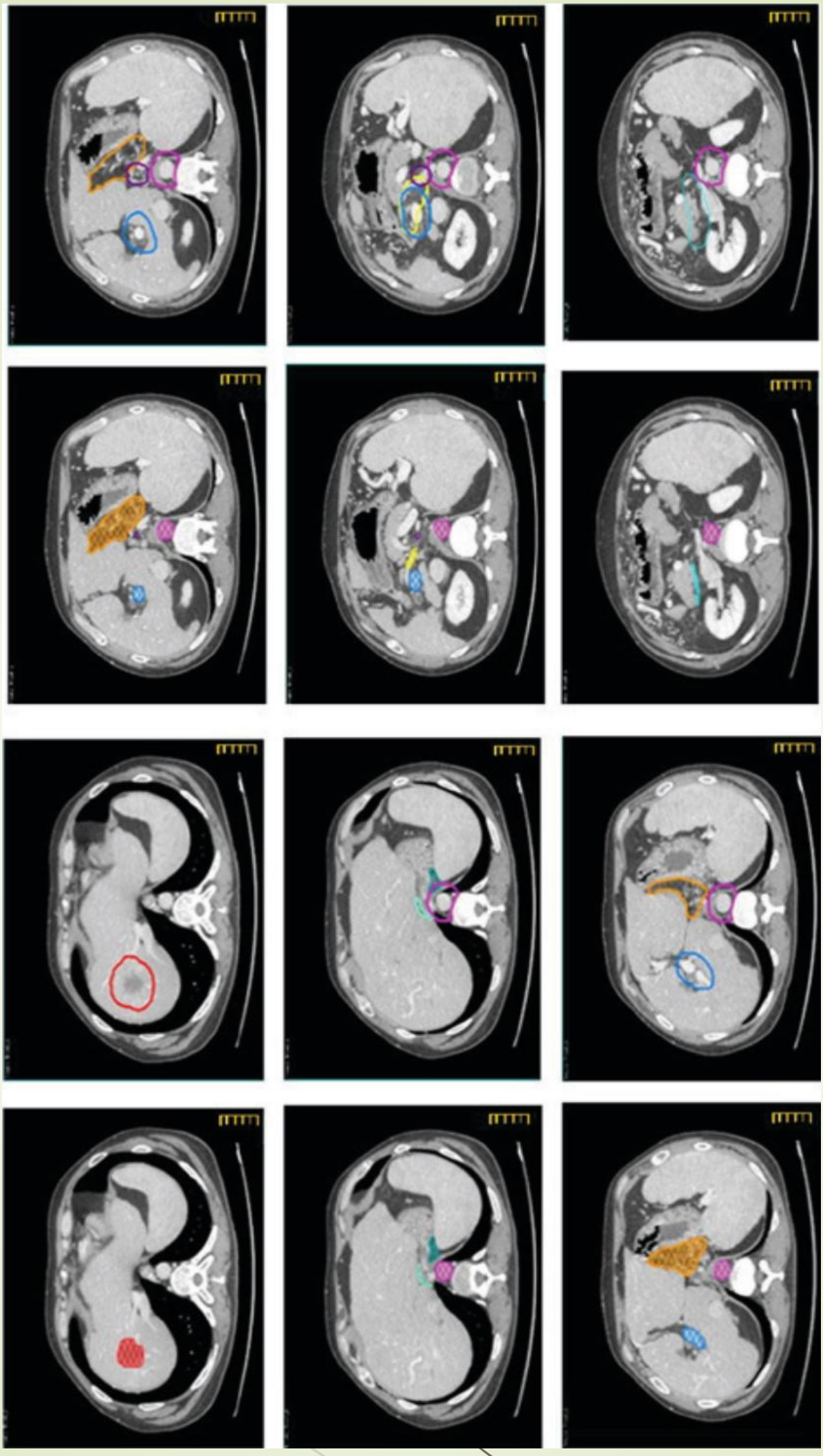


Table II. CTV for extrahepatic cholangiocarcinoma.

Delineation type	JSHBPS classification	Recommended margins
Tumor delineation		
Extrahepatic cholangiocarcinoma	-	GTV + 25 mm on the proximal direction of the bile duct + 20 mm on the distal direction + 15 mm radially in all directions
Lymph node group, nodes delineation		
Hepatoduodenal ligament lymph nodes	12	10 mm margin around the segment of portal vein from the confluence between the right and left hepatic ducts and the upper border of the pancreas
Left gastric artery lymph nodes	7	10 mm around the trunk of the left gastric artery
Common hepatic artery lymph nodes	8	10 mm margin around the common hepatic artery
Para-aortic lymph nodes	16	10 mm margin around the abdominal aorta, from the diaphragmatic aortic hiatus to the upper border of the origin of the inferior mesenteric artery
Posterior pancreaticoduodenal lymph nodes	13	10 mm around the posterior pancreaticoduodenal artery
Anterior pancreaticoduodenal lymph nodes	17	10 mm margin around the anterior pancreaticoduo denal artery
Peri-choledochal nodes	12b2	10 mm margin around the choledochal duct

Lymph node nomenclature is based on the 3rd English Edition of Classification of biliary tract cancers established by the JSHBPS. The anatomical structures of interest and the abdominal vessels of reference were identified for each lymph node region. JSHBPS, Japanese Society of Hepato-Biliary-Pancreatic Surgery; CTV, clinical target volume; GTV, gross tumor volume.

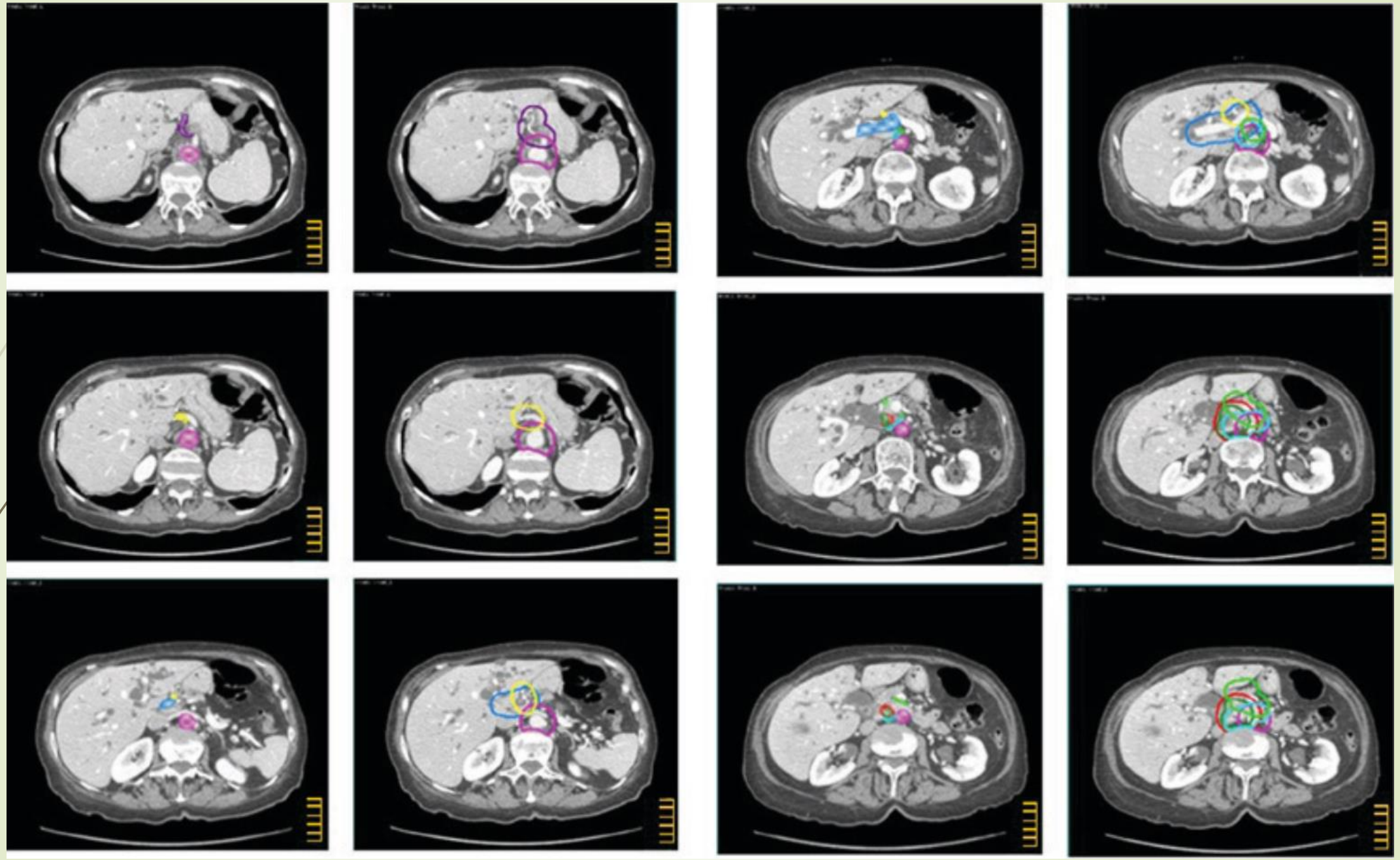
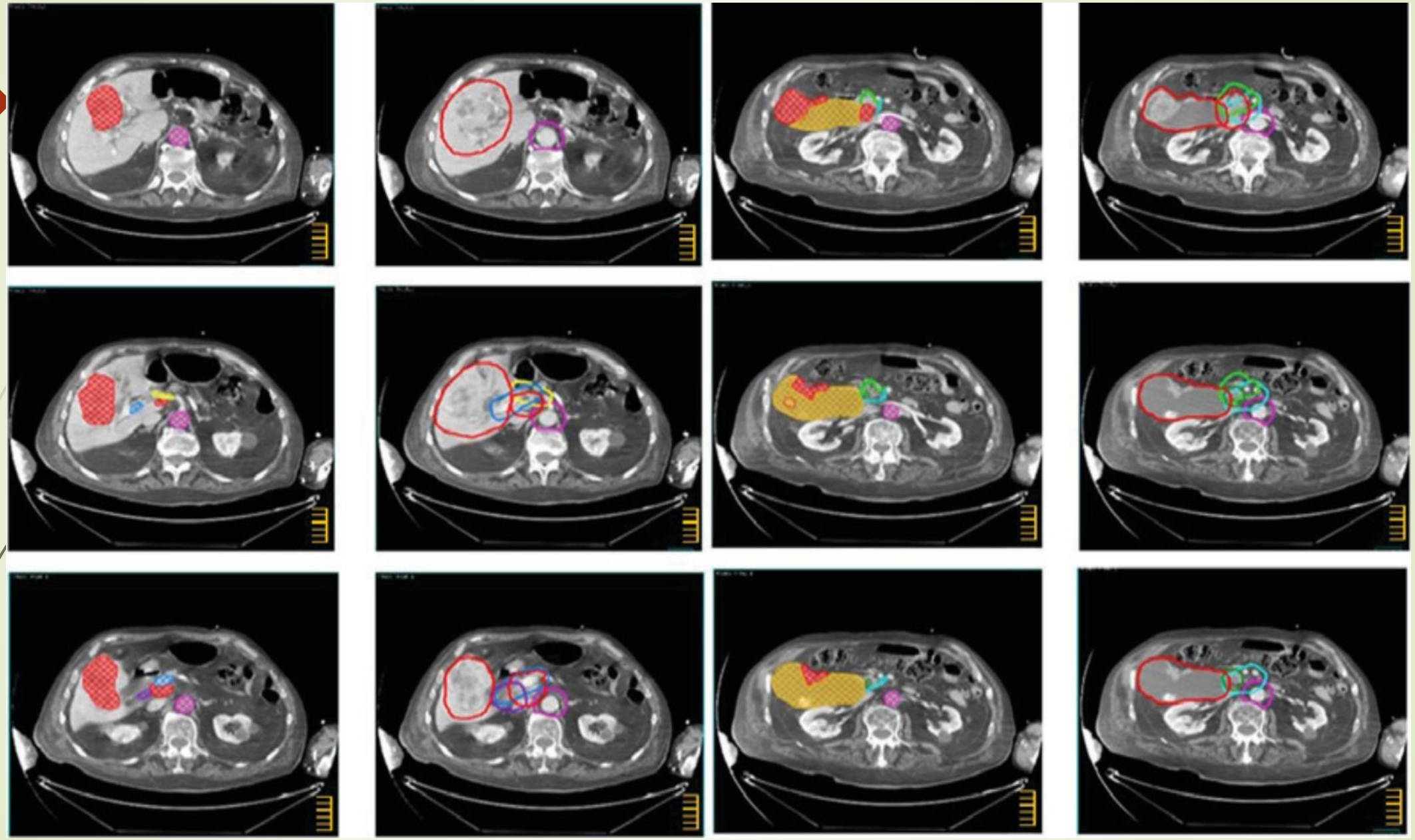


Table III. CTV for gallbladder carcinoma.

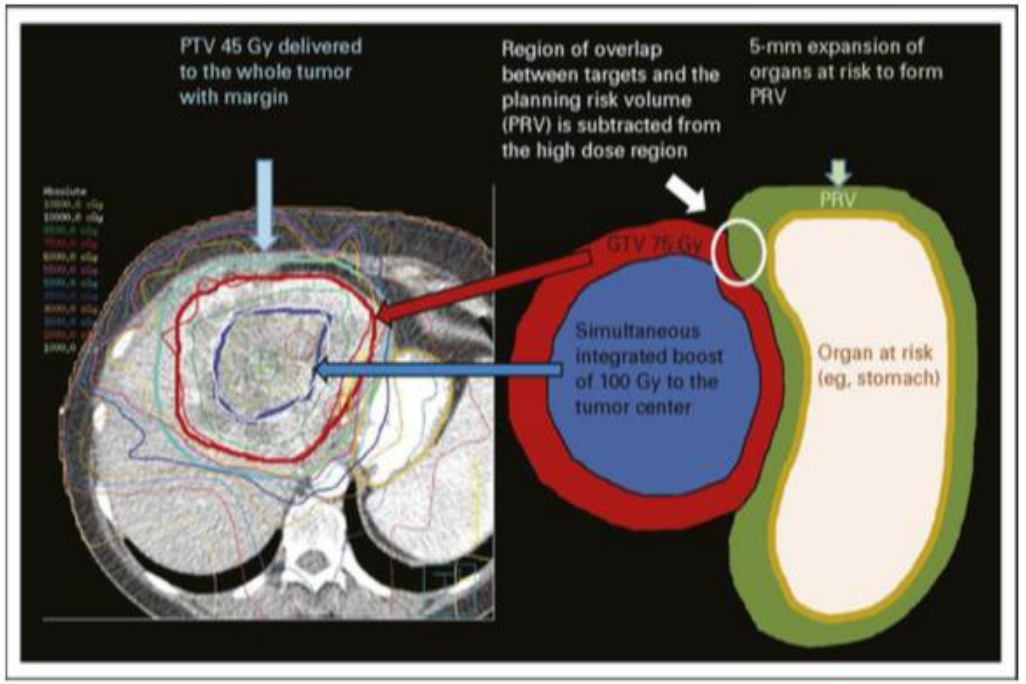
Delineation type	JSHBPS classification	Recommended margins
Tumor delineation		
Gallbladder carcinoma	-	GTV + 25 mm radially in hepatic direction + gallbladder residual volume
Lymph node group, nodes delineation		
Hepatoduodenal ligament lymph nodes	12	10 mm margin around the segment of portal vein from the confluence between the right and left hepatic ducts and the upper border of the pancreas
Common hepatic artery lymph nodes	8	10 mm margin around the common hepatic artery
Para-aortic lymph nodes	16	10 mm margin around the abdominal aorta, from the diaphragmatic aortic hiatus to the upper border of the origin of the inferior mesenteric artery
Posterior pancreaticoduodenal lymph nodes	13	10 mm around the posterior pancreaticoduodenal artery
Anterior pancreaticoduodenal lymph nodes	17	10 mm margin around the anterior pancreaticoduodenal artery
Peri-choledochal nodes	12b2	10 mm margin around the choledochal duct
Cystic duct lymph nodes	12c	10 mm around the cystic duct

Lymph node nomenclature is based on the 3rd English Edition of Classification of biliary tract cancers established by the JSHBPS. The anatomical structures of interest and the abdominal vessels of reference were identified for each lymph node region. JSHBPS, Japanese Society of Hepato-Biliary-Pancreatic Surgery; CTV, clinical target volume; GTV, gross tumor volume.



Contouring

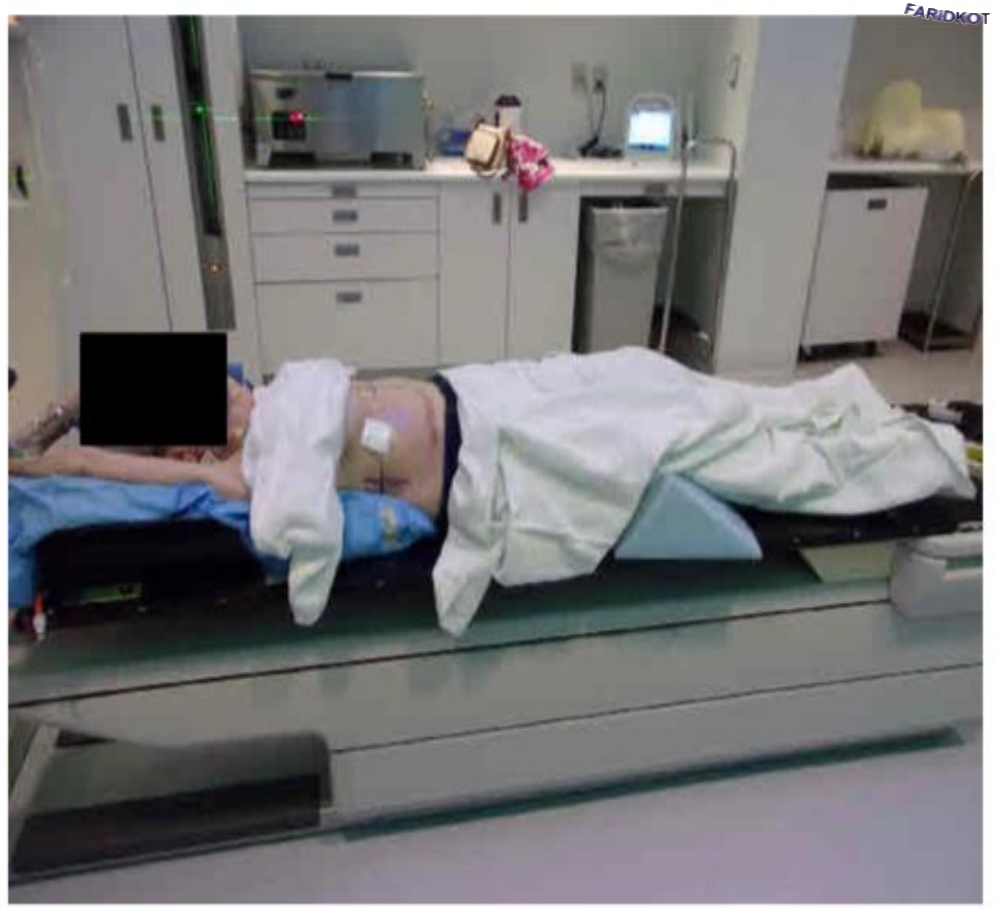
- Contour both target and normal structures on EACH breath hold scan; As you flip through scans, add but do NOT subtract from your volume. The goal is to cover everywhere the tumor or normal structures might be.
- If dose escalating, will contour avoidance structure (PRV) subtracted from high dose region (Right).



Tao et al; 2016

Radiation Simulation

- Fiducials placed for daily imaging
- Upper Vaclock with arms overhead
- NPO 3 hours prior to simulation and treatment (to standardize duodenal and gastric filling)
- Multi-phase contrast-enhanced 4DCT simulation with 2-3mm slices; Free breathing scan and 3-5 Breath hold scans during contrast administration

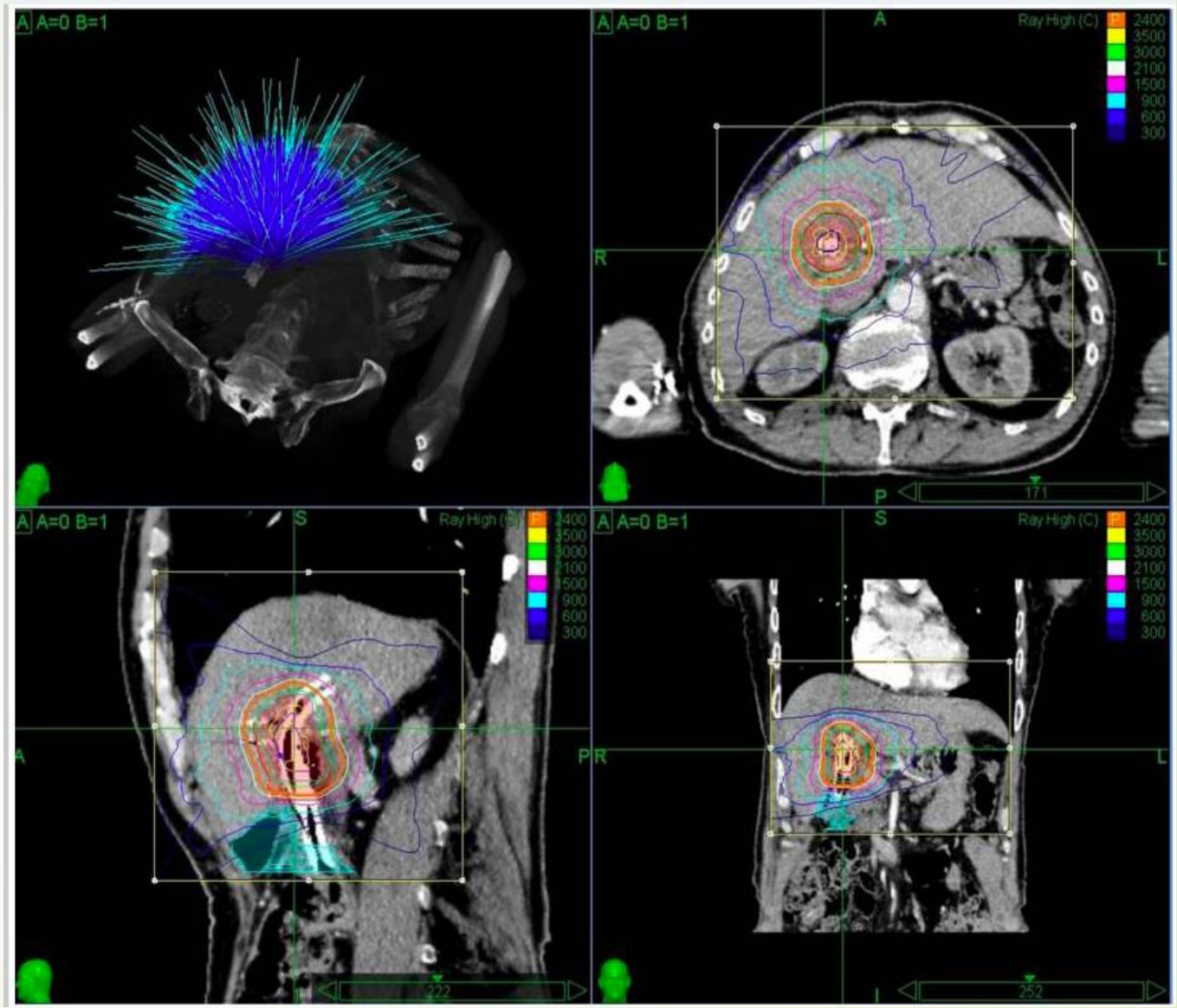


SBRT Plan

DVH constraints to these structures: bowel: 24 Gy in three fractions to no more than a third of the circumference of the bowel with a maximum point dose of 30 Gy in 3 fractions;

Liver: at least 750 cc of healthy Liver V21 = <30% and V15 < 50%.

3 daily fractions were typically used,

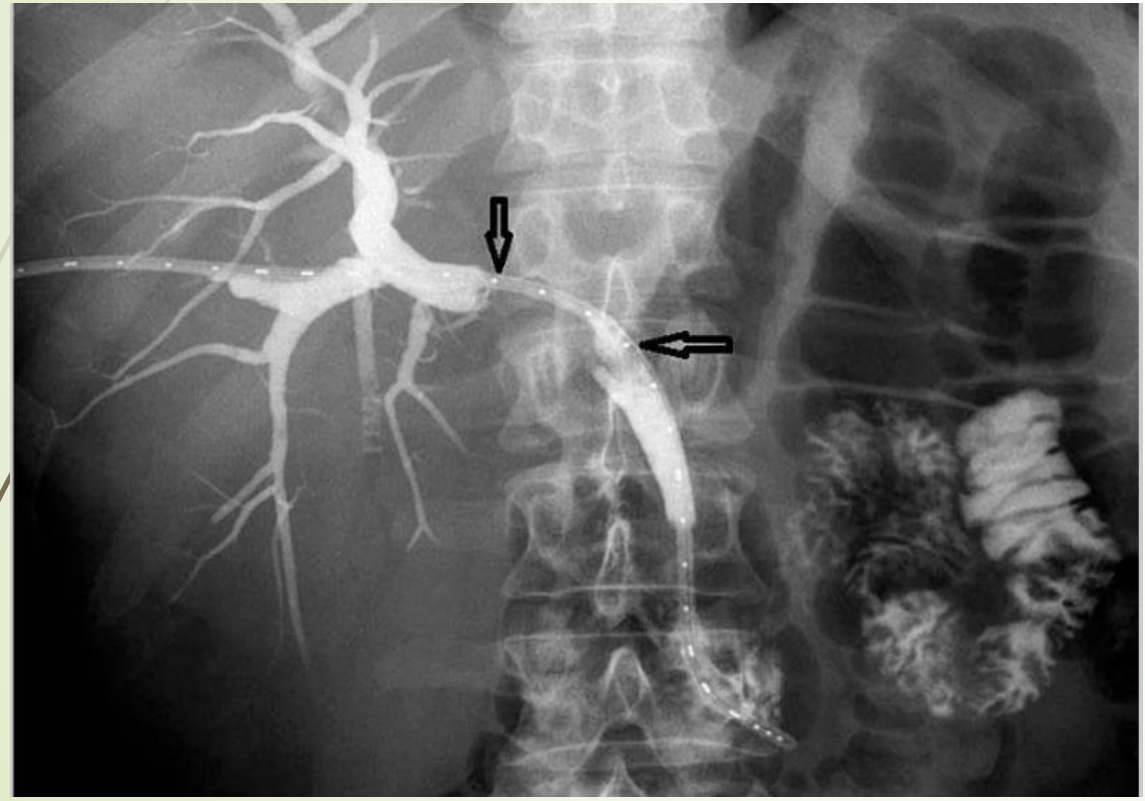


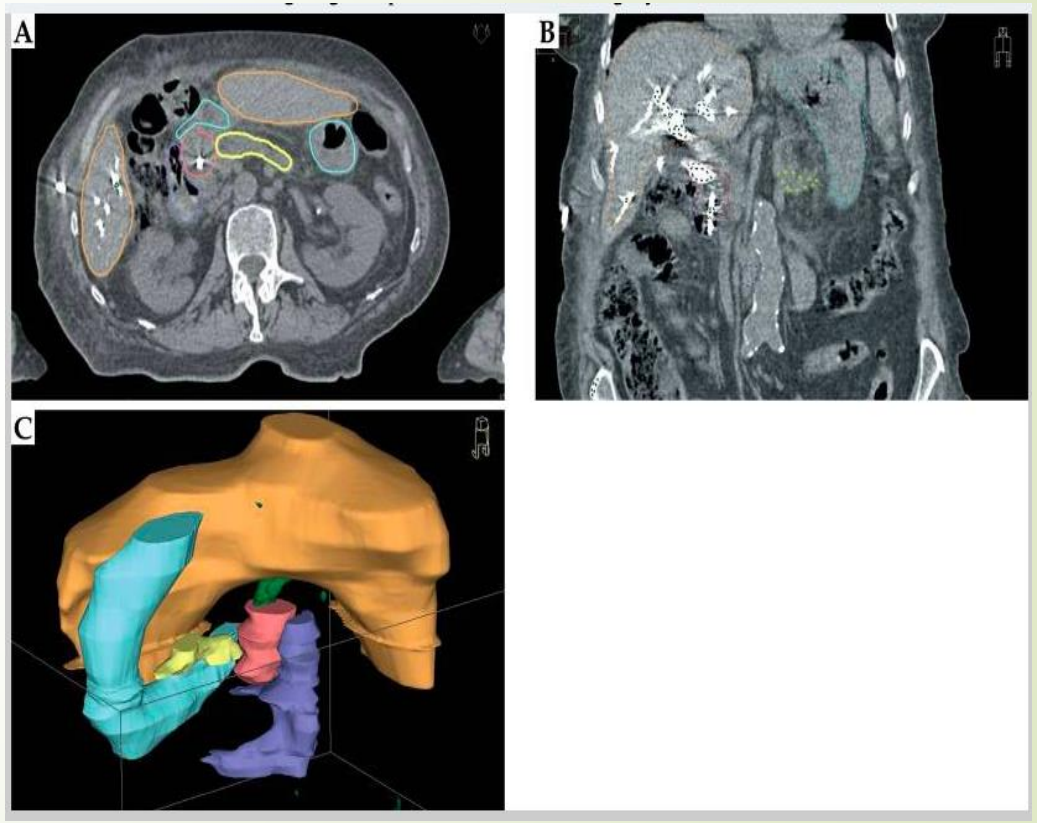
OAR Dose Constraints

Dose Constraints

Organ	Constraint
SpinalCord	Dmax < 30 Gy; Dmax < 45Gy
Heart	V40 Gy < 10%
Liver-GTV	700cc <24 Gy; Mean <24 Gy
Kidneys	V20 < 33% for each
Stomach	Dmax < 45 Gy
Duodenum	Dmax < 45 Gy
Esophagus	Dmax < 45 Gy
Common/ Main Bile duct	Dmax < 70Gy
Chest Wall	V40 < 150cc

2D and 3D Planning of ILBT





Contouring Guidelines in ILBT

- GTV is defined as any visible tumor by CT and/or MRI.
- CTV = 1-1.5 cm margin to the GTV, especially along the bile duct and to the target depth
- PTV = 0.5 to 1 cm to the CTV. 1 to 3 mm slice thickness is recommended, with contrast medium
- Not possible to treat nodes.
- PTV = defined by adding in the longitudinal direction a margin of 1 cm both, distally and proximally to the CTV.
- The dose-limiting surrounding organs (both for EBRT and BT) include the liver, pancreas, duodenum, small bowel, stomach, and spinal cord.

Evidence

Int J Radiat Oncol Biol Phys. 2014 Jul 15;89(4):822-9. doi: 10.1016/j.ijrobp.2014.04.020.

Impact of intraluminal brachytherapy on survival outcome for radiation therapy for unresectable biliary tract cancer: a propensity-score matched-pair analysis.

Yoshioka Y[1], Ogawa K[2], Oikawa H[3], Onishi H[4], Kanesaka N[5], Tamamoto T[6], Kosugi T[7], Hatano K[8], Kobayashi M[9], Ito Y[10], Takayama M[11], Takemoto M[12], Karasawa K[13], Nagakura H[14], Imai M[15], Kosaka Y[16], Yamazaki H[17], Isohashi F[1], Nemoto K[18], Nishimura Y[19]; Japanese Radiation Oncology Study Group (JROSG).

⊕ Author information

Abstract

PURPOSE: To determine whether adding intraluminal brachytherapy (ILBT) to definitive radiation therapy (RT) for unresectable biliary tract cancer has a positive impact on survival outcome.

METHODS AND MATERIALS: The original cohort comprised 209 patients, including 153 who underwent external beam RT (EBRT) alone and 56 who received both ILBT and EBRT. By matching propensity scores, 56 pairs (112 patients) consisting of 1 patient with and 1 patient without ILBT were selected. They were well balanced in terms of sex, age, performance status, clinical stage, jaundice, and addition of chemotherapy. The impact of ILBT on overall survival (OS), disease-specific survival (DSS), and local control (LC) was investigated.

RESULTS: The 2-year OS rates were 31% for the ILBT+ group and 40% for theILBT- group (P=.862). The 2-year DSS rates were 42% for the ILBT+ group and 41% for the ILBT- group (P=.288). The 2-year LC rates were 65% for the ILBT+ group and 35% for the ILBT- group (P=.094). Three of the 4 sensitivity analyses showed a significantly better LC for the ILBT+ group (P=.010, .025, .049), and another showed a marginally better LC (P=.068), and none of the sensitivity analyses showed any statistically significant differences in OS or DSS.

CONCLUSIONS: In the treatment for unresectable biliary tract cancer, the addition of ILBT to RT has no impact on OS or DSS but is associated with better LC. Therefore, the role of ILBT should be addressed by other measures than survival benefit, for example, by less toxicity, prolonged biliary tract patency decreasing the need for further palliative interventions, or patient quality of life.

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PMID: 24969796 DOI: 10.1016/j.ijrobp.2014.04.020

[Indexed for MEDLINE]

Can We Dose Escalate??

- How far is tumor from gastrointestinal mucosa? Would a 5mm expansion on gastrointestinal mucosa still allow you to cover >50% of the tumor in the high dose region?
- How big is tumor and how is patient's overall liver function, and therefore how much normal liver will you cover with high dose? Remember, a small volume of normal liver can tolerate a high dose, but a high volume of normal liver cannot tolerate even a low dose
- 700cc <24Gy; mean dose <24Gy for CP class A
- 700cc <20Gy; mean dose <20Gy for CP class B

The Aftermaths

Radiation Induced Liver Disease (RILD)

Classic RILD	Non-classic RILD
Occurs 2-3 months post-RT	Occurs 1wk-3 months post-RT
Associated with hepatomegaly,ascites +/- jaundice	Seen in cirrhotic livers
Due to veno-occlusive disease	Rise of SGOT/SGPT with worsening of liver function
Seen in healthy livers	Without features of classic RILD

Treatment: Once established, RILD is difficult to manage and is invariably fatal in the absence of transplant therapy. Medical management with diuretics, etc is only symptomatic

5 Year Survival of GBC and Cholangiocarcinoma

Table 5

Distribution and Survival for Each Stage (Nevin Stage of Gallbladder Cancer)

Stage	Percentage of Patients at Presentation	Survival (%) 1-Year	5-Year
I	6.5%	83%	59%
II	9%	71%	40%
III	18%	33%	9%
IV	11%	21%	7%
V	55.5%	3%	1%

Adapted from Gegner et al.[35]

INTRAHEPATIC

Stage	5-year relative survival
Localized	15%
Regional	6%
Distant	2%

EXTRAHEPATIC

Stage	5-year relative survival
Localized	30%
Regional	24%
Distant	2%

American Cancer Society. Bile Duct Cancer (Cholangiocarcinoma). 2014

Future Directions

- A Phase III trial aims to compare adjuvant CRT vs chemotherapy in EHCC and gall bladder cancer **(NCT02798510)** evaluating induction gemcitabine followed by 5-FU-based CCRT and maintenance capecitabine prior to LT.
- Need to test sequencing of adjuvant CCRT and chemotherapy in Phase III trials for EHCC and IHCC **(NCT02798510)**
- Cholangiocarcinoma - radiosensitization with oncolytic viral therapy **(NV1023 virus strain)**.

THANK-YOU


"You cannot hope to build
a better world without improving
the individuals. To that end,
each of us must work
for our own improvement."
Marie Curie
Goalcast