Pitfalls στη Χειρουργική Θεραπεία του Χολαγγειοκαρκινώματος

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Cholangiocarcinoma

EPIDEMIOLOGY

Relatively uncommon malignancy
More common outside the United States, particularly in South America and Eastern/Central Europe

Less common than gallbladder cancer

Incidence per 100,000 in U.S.: 1.0 in females
1.5 in males

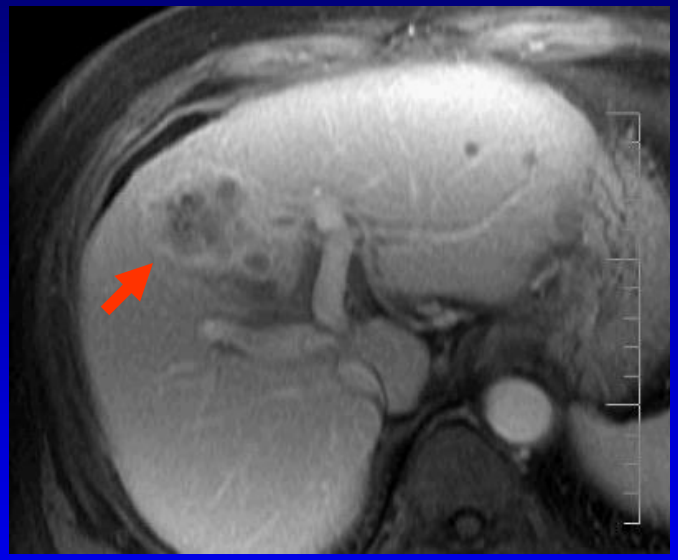
Increasing incidence with age
70% of cases in over 65 years

Hilar location most common

Cholangiocarcinoma

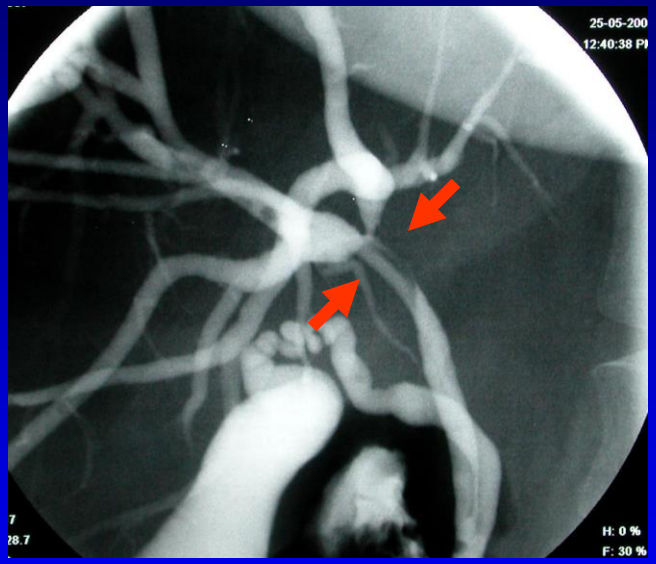
Location

Peripheral



- 7-20%
- Intrahepatic mass
- Cirrhosis uncommon
- Etiology unknown

Hilar



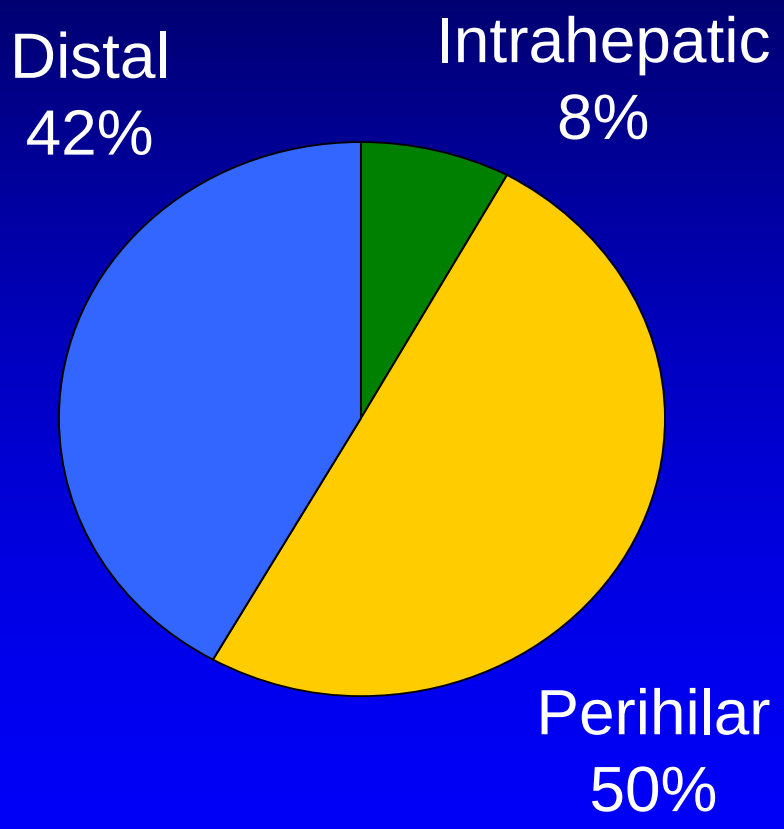
- 40-60%
- Biliary confluence
- Most common

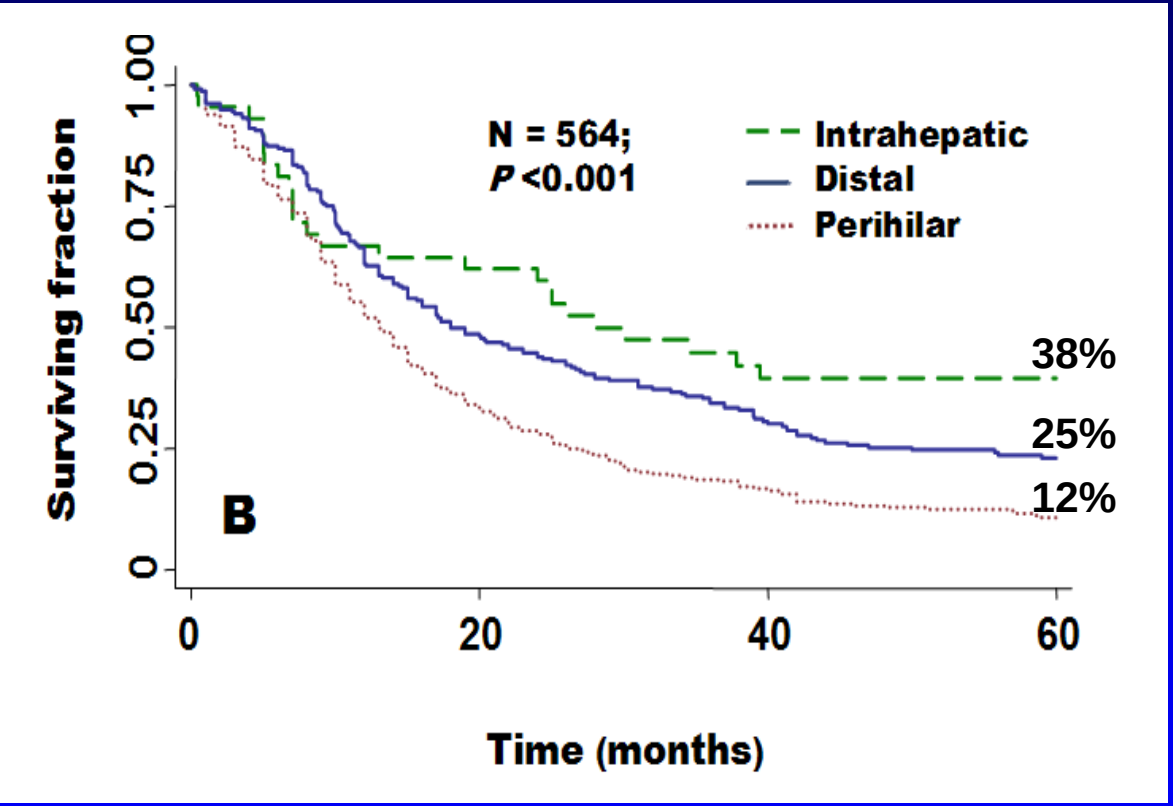
Distal

- 20-30%
- 10-15% of peripancreatic tumors

Cholangiocarcinoma

Johns Hopkins Experience (1973-2004)





De Oliviera et al. Ann Surg (2007)

Hilar Cholangiocarcinoma

Treatment

- Complete resection is the only effective therapy.
- Outcomes after R0 resection:
  - 5-year overall survival of 25-40%
  - DFS of 15-25%
- Few patients are resectable.
- R1/2 resections are not uncommon.

Questions to Ask When Considering Surgery?

1. Is complete (R0) resection possible?
2. Can it be done with enough remaining liver, adequate blood supply and good biliary drainage?
    - Extent of disease
    - Vascular involvement
    - Lobar atrophy
    - Metastatic disease
    - Underlying liver disease
    - Other comorbidities

Hilar Cholangiocarcinoma

CRITERIA OF UNRESECTABILITY

Patient-Related Factors

- Medical contraindication to major abdominal surgery
- Cirrhosis or insufficient remnant hepatic volume

Metastatic Disease

- N2 lymphadenopathy
- Distant metastases

Hilar Cholangiocarcinoma

CRITERIA OF UNRESECTABILITY

Local Tumor-Related Factors

- Tumor extension to secondary biliary radicles bilaterally
- Encasement or occlusion of the main portal vein proximal to its bifurcation
- Unilateral tumor extension to secondary bile ducts with contralateral vascular encasement or occlusion
- Atrophy of one hepatic lobe with contralateral portal vein encasement or secondary biliary extension

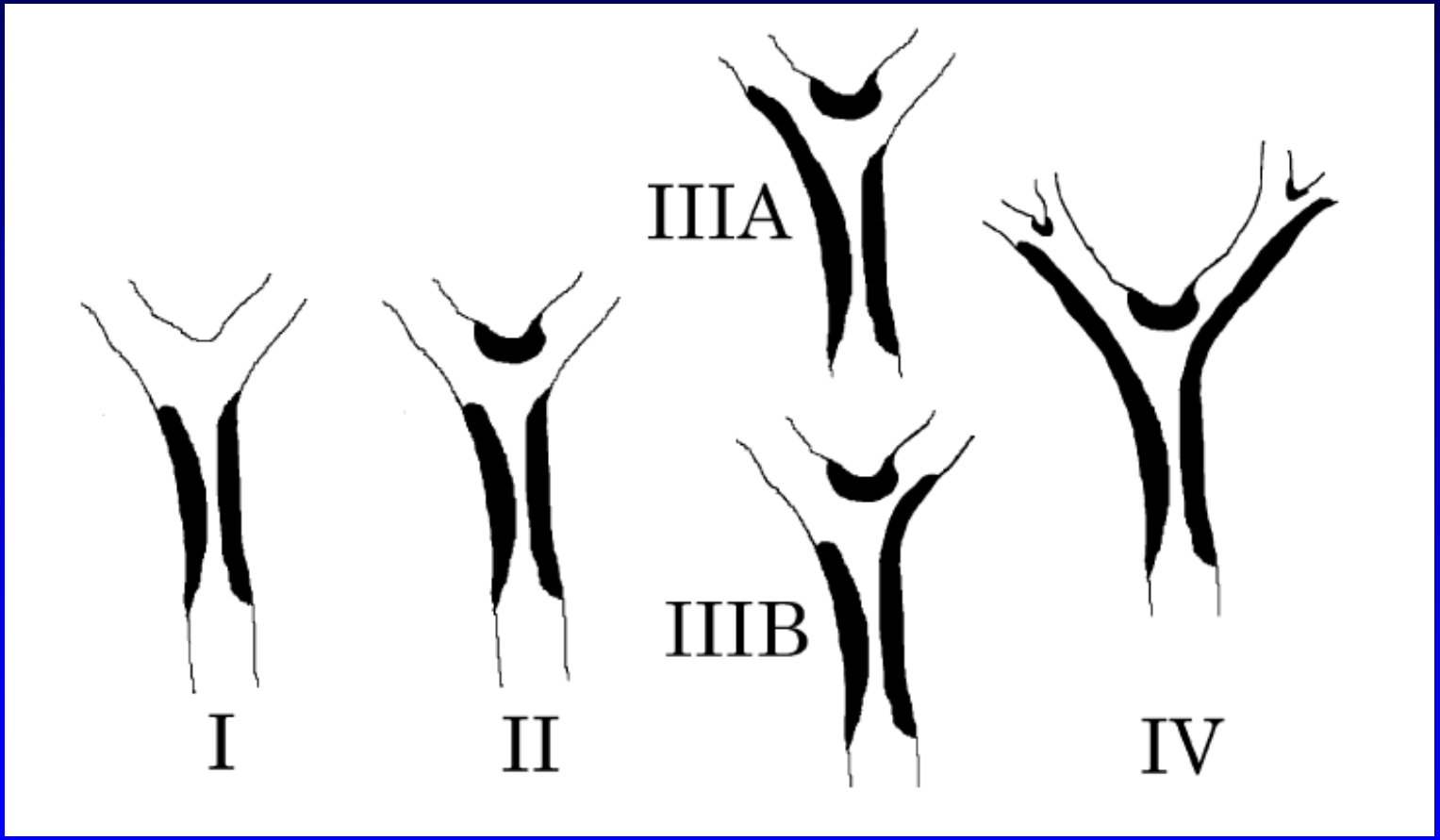
Aggressive Surgical Treatment

- True resectability is defined at surgery
- Pre-operative evaluation of resectability is often difficult
- No histologic confirmation is usually needed
- Surgical exploration!!!

Sue CW, et al. Ann Surg 1996

Neuhaus O, et al. J Hepatobiliary Pancrat Surg 2000

Bismuth-Corlette Classification of Biliary Extent of Hilar Cholangiocarcinoma

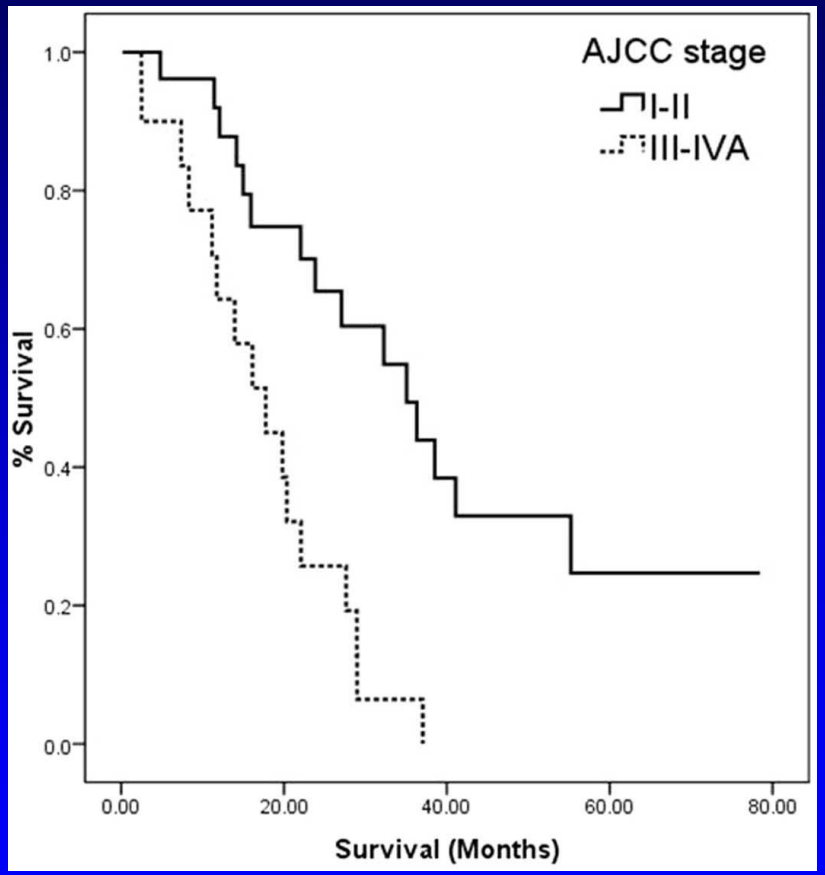


Bismuth H. Ann Surg 1992

TNM Classification 7th Ed

Table 2 Perihilar bile duct tumors (American Joint Commission on Cancer Staging 7th edition)

T1	Tumor confined to bile duct histologically
T2a	Tumor beyond the wall of bile duct into adjacent fat
T2b	Tumor beyond the wall of bile duct into liver parenchyma
T3	Tumor invades ipsilateral portal vein (R or L) or hepatic artery (R or L)
T4	Tumor invades (1) Main portal vein or its branches bilaterally (or) (2) Common hepatic artery (or) (3) The second-order biliary radicals bilaterally (4) Unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement
Node	
Nx	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery, and portal vein)
N2	Metastasis to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes
Metastasis	
M0	No distant metastasis
M1	Distant metastasis
Tumor stage AJCC staging 6th edition	
0	Tis, N0, M0
I	T1, N0, M0
II	T2a-b, N0, M0
IIIa	T3, N0, M0
IIIb	T1 or T2 T3, N1, M0
IVa	T4, N0 N1, M0
IVb	Any T, N2, M0 Any T, any N, M1

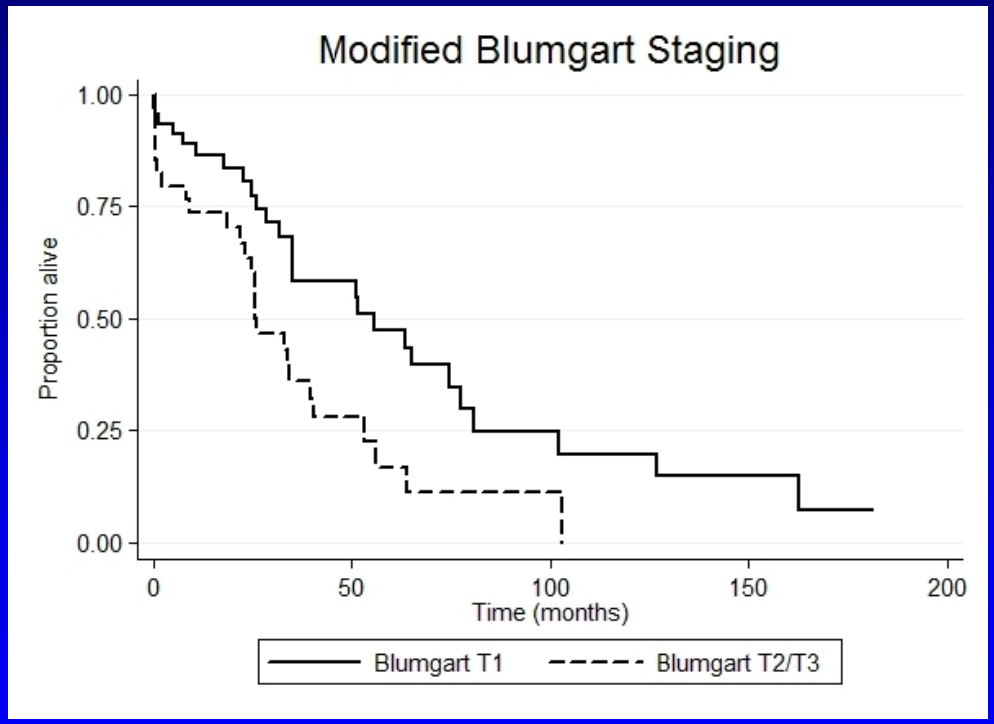


American Joint Committee on Cancer. AJCC cancer staging manual. 7th ed. Springer, 2011

MSKCC Classification of HCC

Summary of the T classification of the AJCC (seventh edition) and MSKCC staging systems

	AJCC	MSKCC
T1	Confined to the bile duct	Involves biliary confluence; ± unilateral extension to second-order biliary radicals
T2	Invades beyond the wall of the bile duct to adjacent adipose (a) or hepatic parenchyma (b)	T1 ± ipsilateral PV involvement ± ipsilateral hepatic lobar atrophy
T3	Invades unilateral branches of PV or HA	Involves biliary confluence with bilateral extension to second-order radicles; or unilateral extension to second-order radicles with contralateral PV involvement or contralateral lobar atrophy; or main or bilateral PV involvement
T4	Invades main PV or its branches bilaterally; or CHA; or second-order biliary radicles bilaterally; or unilateral second-order biliary radicles with contralateral PV or HA	—

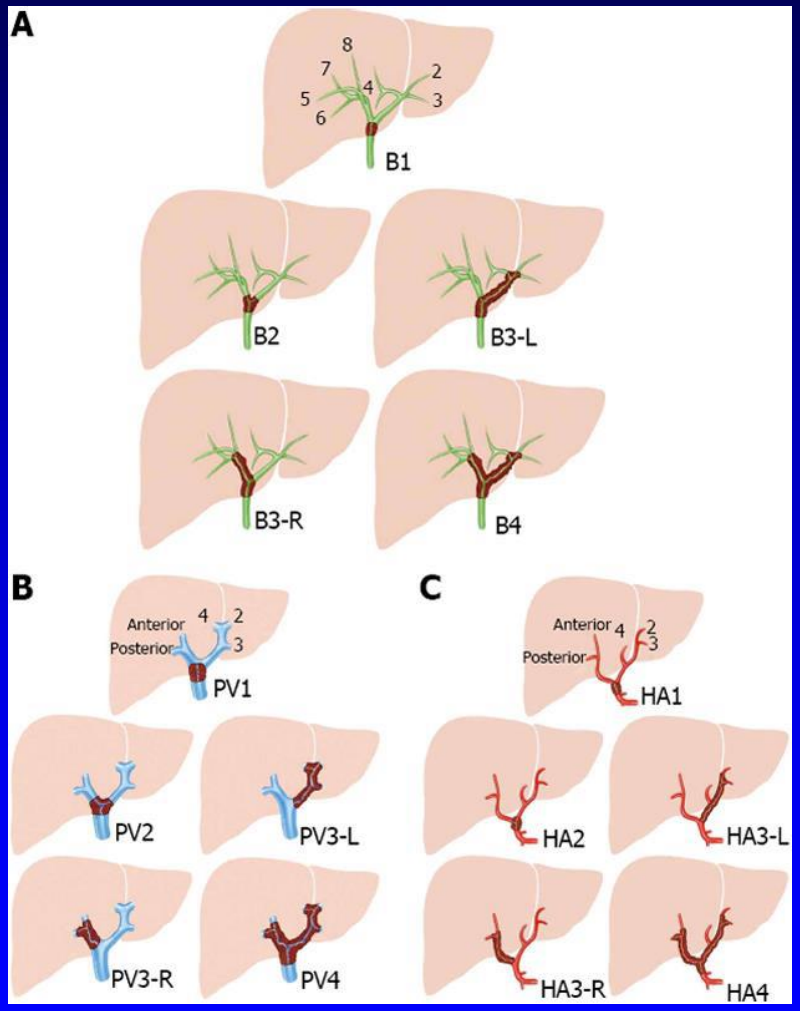


Jarnagin WR, et al. Ann Surg 2001

EHPBA Consensus Classification

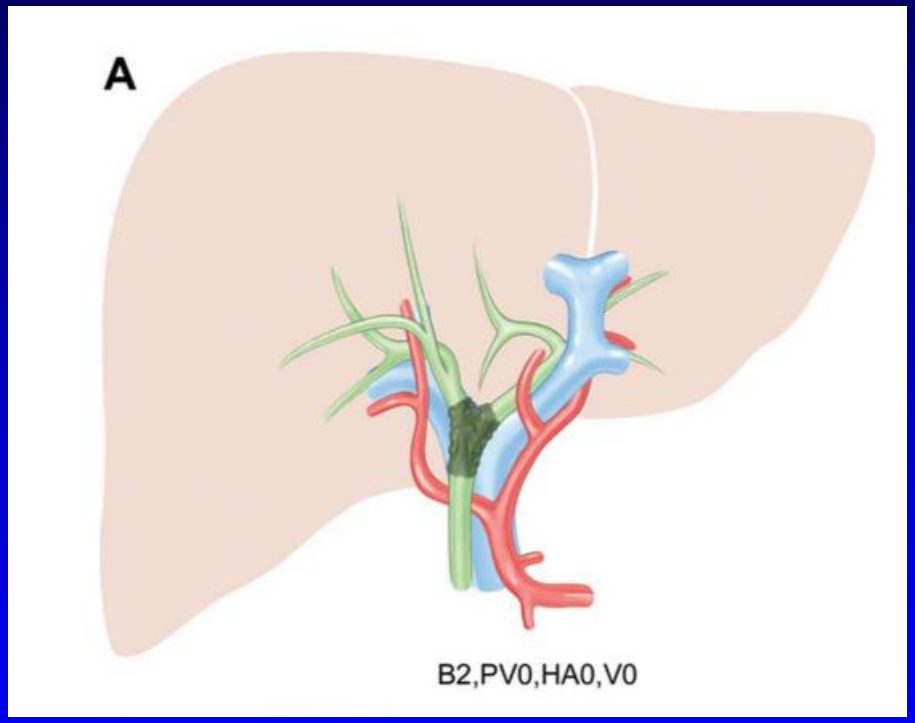
Table 3 Consensus classification (European Hepato-Pancreato-Biliary Association)

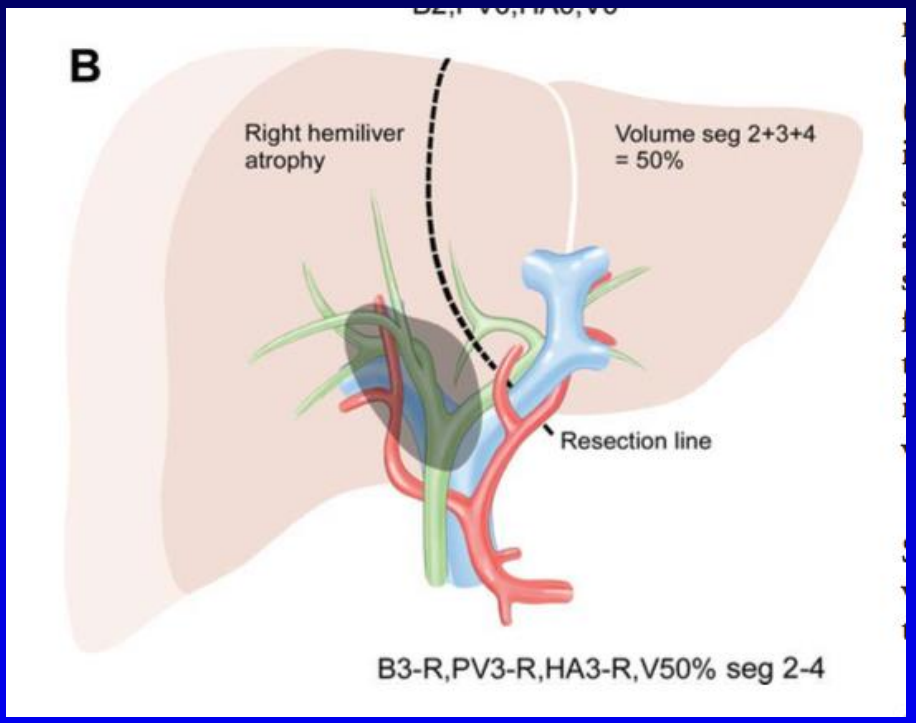
Label	Side location	Description
Bile duct (B)		
B1		Common bile duct
B2		Hepatic duct confluence
B3	R	Right hepatic duct
B3	L	Left hepatic duct
B4		Right and left hepatic duct
Tumor size (T)		
T1		< 1 cm
T2		1-3 cm
T3		⩾ 3 cm
Tumor form (F)		
Sclerosing		Sclerosing (or periductal)
Mass		Mass-forming (or nodular)
Mixed		Sclerosing and mass-forming
Polypoid		Polypoid (or intraductal)
Involvement (> 180°) of the portal vein (PV)		
PV0		No portal involvement
PV1		Main portal vein
PV2		Portal vein bifurcation
PV3	R	Right portal vein
PV3	L	Left portal vein
PV4		Right and left portal veins
Involvement (> 180°) of the hepatic artery (HA)		
HA0		No portal involvement
HA1		Proper hepatic artery
HA2		Hepatic artery bifurcation
HA3	R	Right hepatic artery
HA3	L	Left hepatic artery
HA4		Right and left hepatic artery
Liver remnant volume (V)		
V0		No information on the volume needed (liver resection not foreseen)
V%	Indicate segments	Percentage of the total volume of a putative remnant liver after resection
Underlying liver disease (D)		Fibrosis
		Nonalcoholic steatohepatitis
		Primary sclerosing cholangitis
Lymph nodes (N)		
N0		No lymph node involvement
N1		Hilar and/or hepatic artery lymph node involvement
N2		Periaortic lymph node involvement
Metastases (M)		
M0		No distant metastases
M1		Distant metastases (including liver and peritoneal metastases)



Toouli J, et al. Oxford: HPB, 2008

EHPBA Classification





2.5 cm tumor involving the bile duct confluence

a larger tumor involving the right biliary system, hepatic artery, and portal vein that is associated with right hemiliver atrophy

Hilar Cholangiocarcinoma

Goal of Resection:
Complete Tumor Excision with Negative Margins

Recommended

ESTABLISHED:

- Excision of supraduodenal bile duct
- Cholecystectomy
- Restore bilioenteric continuity

LESS CONTROVERSIAL:

- Routine hepatectomy/caudate
- Portal lymphadenectomy
- Selected major vascular reconstruction

MORE CONTROVERSIAL:

- Routine PV resection (Neuhaus)

Hilar Cholangiocarcinoma

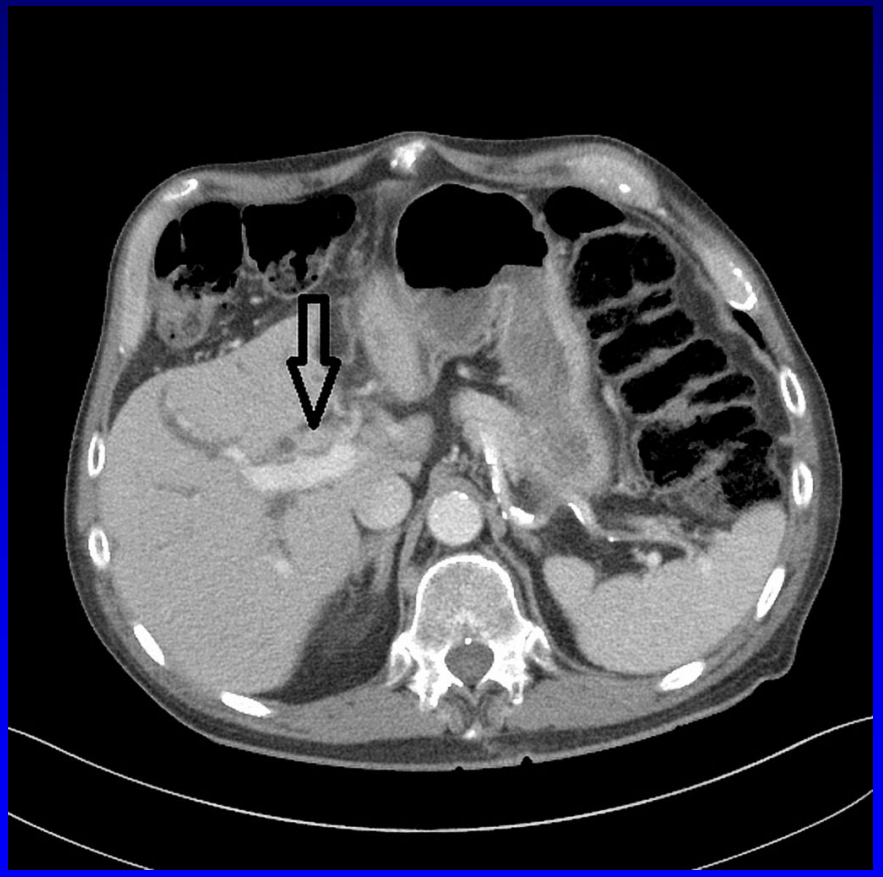
PREOPERATIVE EVALUATION

1. Cholangiography
   - Assessment of extent of biliary ductal involvement
   - ERCP vs MRCP vs PTC
2. Cross-sectional imaging
   - Soft tissue extent, lobar atrophy, vascular involvement, remnant volume, metastases
   - CT vs MRI

Controversies:

- Role of preoperative stenting
- FDG-PET
- Staging laparoscopy

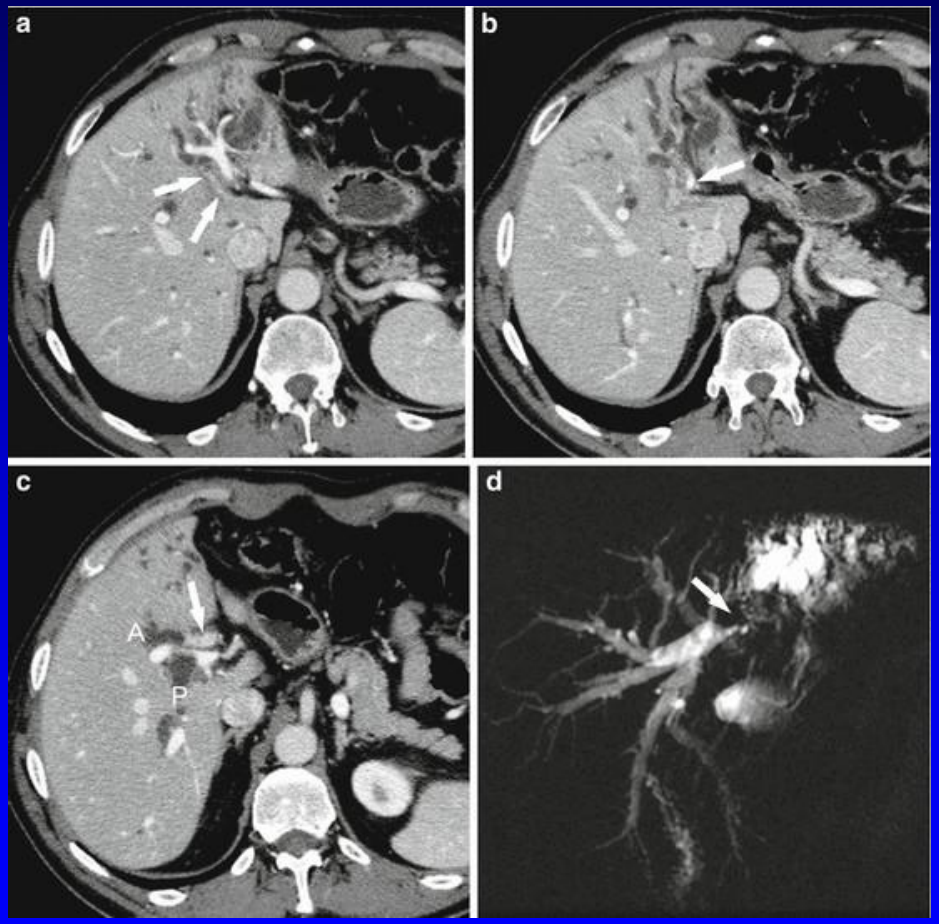
Triple-phase Liver CT scan



”…High quality helical multi-slice MDCT scan with I.V. contrast and appropriately time scans remains the best single test to identify and stage HCC…”

AHPBA/SSAT/SSO/ASCO Consensus Conference on the Multidisciplinary Management of Bile Duct Cancer 2014

Triple-phase Liver CT scan



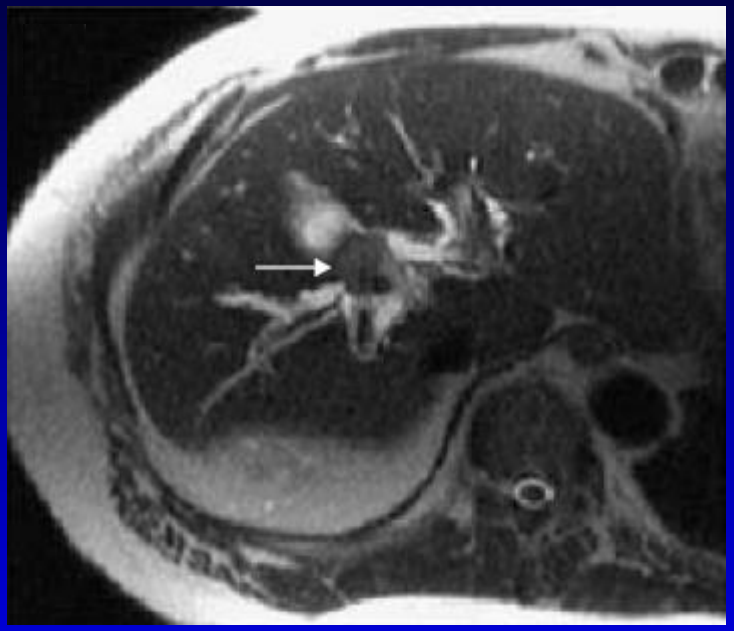
- PV invasion
  - sensitivity 96.3%
  - specificity 92.6%
  - accuracy 94%
- HA invasion >90%
- Bile Duct extension 96%
- Resectability 60-90%

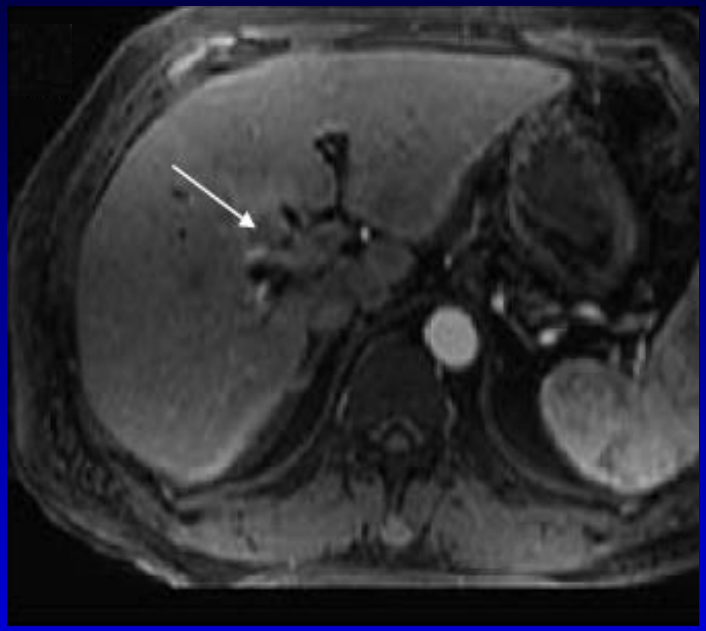
- RHA in Left-sided tumors!!!

- Best before biliary drainage and stents

Nagino M. J Gastroenterol 2012

Non-Invasive Imaging: MRI/MRCP





- High quality images of the biliary tree - as good as cholangioscopy for assessing biliary tumor extent*.
- Provides additional data regarding metastases, vascular involvement, lobar atrophy.
- Predicts overall resectability in 80% of cases

Masselli et al Eu J Radiol (2008)
**Lee et al. Gastrointest Endosc 2002;56:25*

Hilar Cholangiocarcinoma

Role of FDG-PET

	GC	Nodular CC (Mass 1 cm)	Infiltrating CC (No mass)	Total CC
Total patients	14	22	14	36
True positive	7	17	2	19
False negative	2	3	9	12
True negative	4	1	3	4
False positive	1	1	0	1
Sensitivity	78% (7/9)	85% (17/20)	18% (2/11)	61% (19/31)
Specificity	80% (4/5)	50% (1/2)	100% (3/3)	80% (4/5)
PPV	88% (7/8)	94% (17/18)	100% (2/2)	95% (19/20)
NPV	67% (4/6)	25% (1/4)	25% (3/12)	25% (4/16)

- Not useful for infiltrating cholangiocarcinoma
- Extensive desmoplastic reaction – poor vascularity
- False negatives due to low volume metastases
- False positives due to stents or recent cholecystectomy
- FDG-PET is NOT recommended as a routine staging procedure

Anderson et al. J Gastrointest Surg 8:90 (2010)
Blechacz B, et al. Nat Rev Gastroenterol Hepatol. 2011

Pathological Confirmation is NOT required before Surgical Resection in Suspected HCC!!!

- ERCP
  brush cytology<50%
- PTC
- Intraductal US: op dependent
- EUS – FNAB: LNs<30%
- Peroral Cholangioscopy Spyglass
- FISH analysis!!!

Consider benign causes:

-IgG4 related biliary strictures
-Mirrizi's syndrome
-PSC
-Previous biliary surgery

Forsmark CE, et al. HPB 2015
AHPBA/SSAT/SSO/ASCO Consensus Conference on the Multidisciplinary Management of Bile Duct Cancer

STAGING LAPAROSCOPY

100 patients with potentially resectable biliary cancer
- hilar cholangioca = 56
- gallbladder ca = 44

All underwent staging laparoscopy prior to surgical exploration

RESULTS:

Overall 69% were unresectable (HC = 59%, GB = 82%)

Laparoscopy yield: 48% in patients with gallbladder cancer
(56% in those w/o previous cholecystectomy)
25% in patients with hilar cholangiocarcinoma

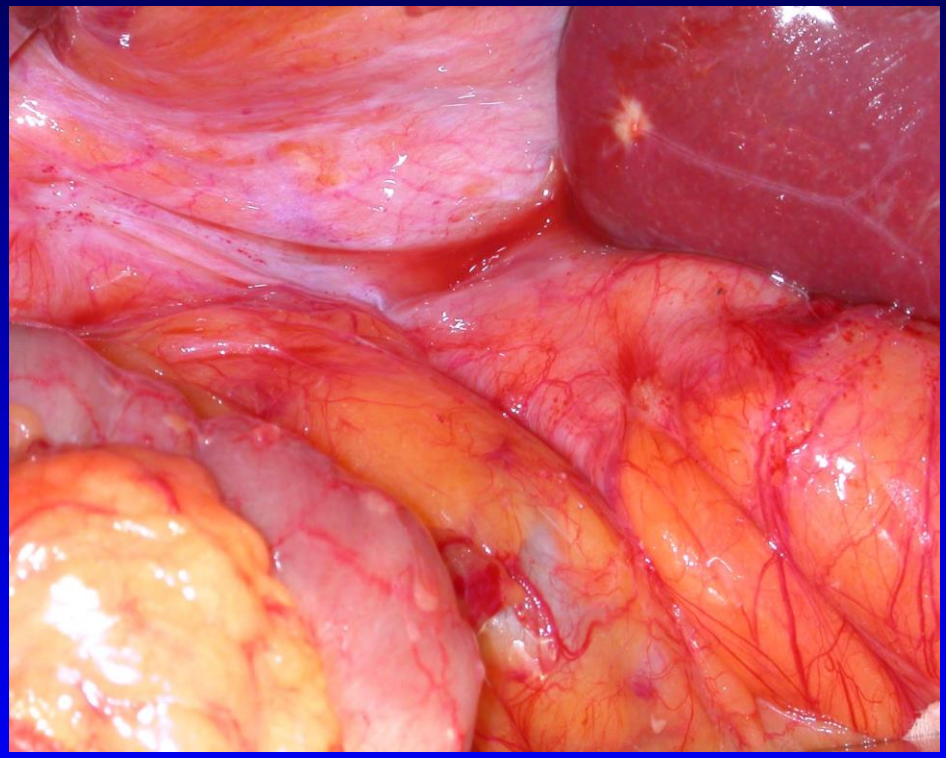
Most useful at detecting peritoneal or liver metastases.

Weber et al. Ann Surg 235:392 (2002)

Staging Laparoscopy

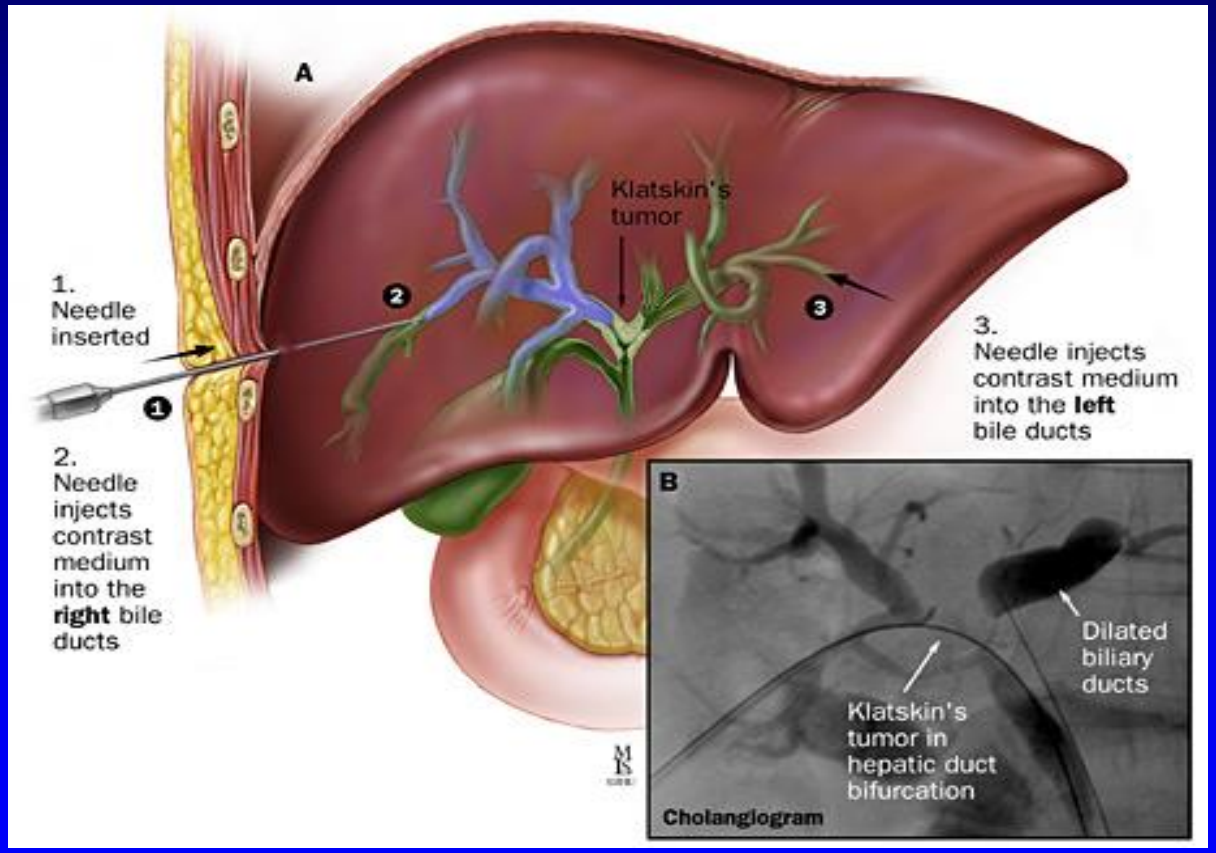
Study	No. of patients	Yield (%)	Accuracy (%)
Tilleman[a]	110	41	72
Connor	84	24	53
Goere	20	25	45
Ruys	175	14	32
Barlow	100	45	71

- Most useful to detect liver and/or peritoneal metastasis
- In locally advanced tumors T2/T3
- Increased levels of CA19.9> 1000
- Combined with LapUS
- Fewer nontherapeutic laparotomies
- Shorter LOS



Ruys AT, et al. Ann Surg Oncol 2011
Barlow AD, et al. Langenbeck's Arch Surg 2013

Biliary Stents for the Management of HCC



Preoperative Biliary Drainage
Pros

Treatment

- **Pre-operative biliary drainage**
  - Cholestasis, liver dysfunction, biliary cirrhosis develop rapidly with un-relieved obstruction.
    - Hyperbilirubinemia impairs liver regeneration
  - Liver dysfunction increases post-operative mortality and morbidity
    - Reduces resistance to systemic infection
  - S.Bili > 10 mg% - Pre-operative biliary drainage to bring down to 2.5-3.0 mg%

Roger et al. Surg Clin N Am 2008; 1409-28

- Preoperative biliary drainage may not reduce the peri-operative risk in pts undergoing Whipple's procedure
- But for hilar cholangiocarcinoma, to undergo safe hepatic resection, biliary drainage is mandatory

Nimura et al. HPB, 2008; 10: 130-133

- Endoscopically or percutaneously placed stent for decompression in obstructive jaundice – controversial

Laurent A et al. HPB (Oxford) 2008; 10:126-128

- Jaundice predisposes to mortality 36%vs16%
  morbidity 50%vs15%
  after hepatectomy

Roger et al. Surg Clin N Am 2008

Preoperative Biliary Drainage Cons

Preoperative Biliary Drainage Before Resection for Hilar Cholangiocarcinoma: Whether or Not? A Systematic Review

- Meta-analysis of eleven studies;
  - No difference in death rate or length of post-operative stay
  - Infectious complication rates is adversely affected
  - In absence of evidence of clinical benefit, pre-operative biliary decompression in hilar tumor + jaundice shouldn't be performed.

Liu F et al. Dig Dis Sci 2011; 56:663

- PTBD only when:

1. Cholangitis
2. Renal dysfunction
3. Possible vascular invasion on the side of the FLR
4. PVE

Liu F, et al. Dig Sci 2011
Cherqui D, et al Arch Surg 2000

Preoperative Biliary Drainage

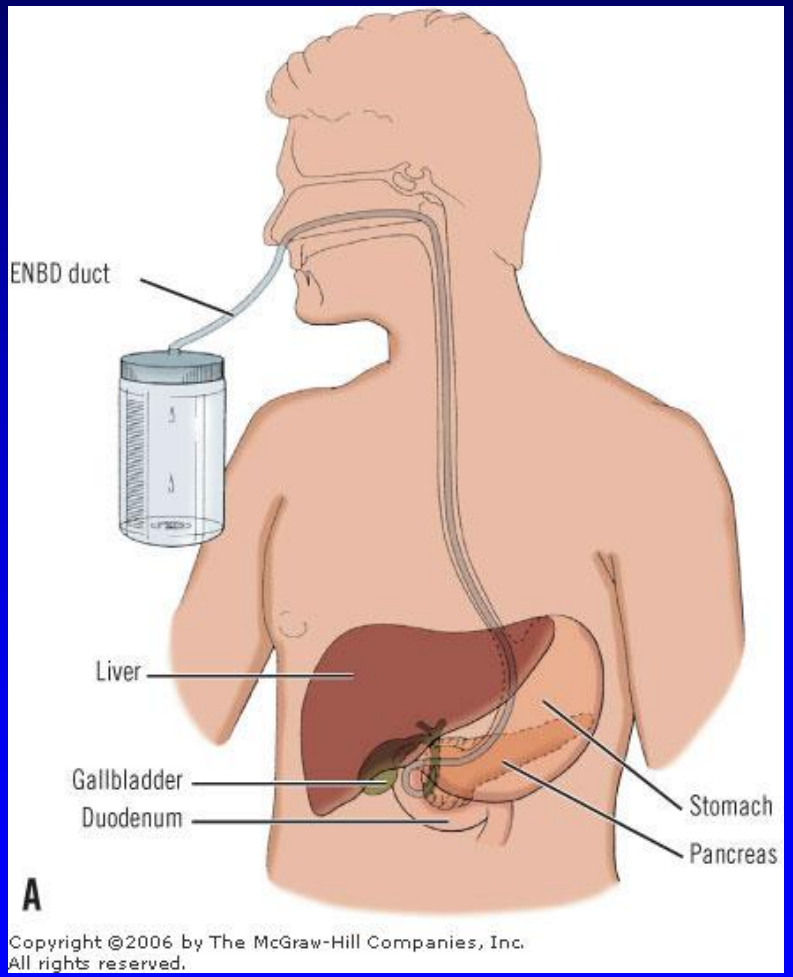
	HCCA by Bismuth classification, n[a]
EBD	I – 48
	II – 87
	III – 139
	IV – 106
PTBD	I – 9
	II – 41
	III – 77
	IV – 62

Table 3 Post-procedure complications and post-operative results by type of PBD[a]

	EBD, total (%)	PTBD, total (%)	Studies explicitly reported in, n
Post-procedure complications			
Cholangitis	153/557 (27)	51/380 (13)	6 (EBD); 7 (PTBD)
Pancreatitis	51/562 (9)	3/42 (7)	7 (EBD); 1 (PTBD)
Catheter dislocation/dislodgment	21/90 (23)	7/156 (4)	1 (EBD); 3 (PTBD)
Haemobilia/Bleeding	1/87 (1)	14/277 (5)	1 (EBD); 6 (PTBD)
Portal vein injury and/or thrombosis	–	15/248 (6)	3 (PTBD)
Retroperitoneal or duodenal perforation	4/257 (2)	–	3 (EBD)
Cancer seeding (tract)	–	10/248 (4)[b]	3 (PTBD)
Failure to proceed to surgery	27/164 (16)	9/72 (13)	1 (EBD); 2 (PTBD)[e]
Others			
Biliary perforation/intra-peritoneal bile leak or peritonitis	2	1	2 (EBD); 1 (PTBD)
External bile leak	–	6	1 (PTBD)
AV shunt formation	–	2	1 (PTBD)
Post-operative results			
Mortality[c]	6/281 (2)	23/416 (6)	
Morbidity[c]			
Hepatic failure	22/194 (11)	56/432 (13)	
Sepsis/abscess/cholangitis	17/120 (14)	44/262 (17)	
Bile leak	NR	21/166 (13)	
Anastomotic leak	NR	25/205 (12)	
Survival, %[d]			
1-year, median (range)	91 (89–92)	73 (67–90)	2 (EBD); 6 (PTBD)
5-year, median (range)	46 (41–51)	30 (11–60)	2 (EBD); 5 (PTBD)

Kennedy TJ, et al. HPB(Oxford) 2009
Hameed A, et al HPB 2016

Endoscopic Naso-biliary Drainage



- Multiple PTBDs
  - Hemorrhage 15%
  - Sepsis 10%
  - Biliary injury 9%
  - Seeding meta 5%
- EBDs
  - Dislocation-Recurrent cholangitis 60%
- ENBD Unilateral in Future Remnant Lobe

Kawakamy H, et al. J Gastroenterol 2011
Kawashima H, et al. Ann Surg 2012
Takahashi Y, et al. Br J Surg 2012

Preoperative Biliary Drainage

- EBD and PTBD are equally effective
- PTBD should be THE STANDARD!!!
- Unilateral drainage of the FLR
- Single and temporary PBD
- Drainage of contralateral liver only when persistent jaundice/ sepsis
- PBD always when PVE is performed
- PBD when FLR <30 - 40%
- PBD when vascular reconstruction is anticipated

Hameed A, et al HPB 2016

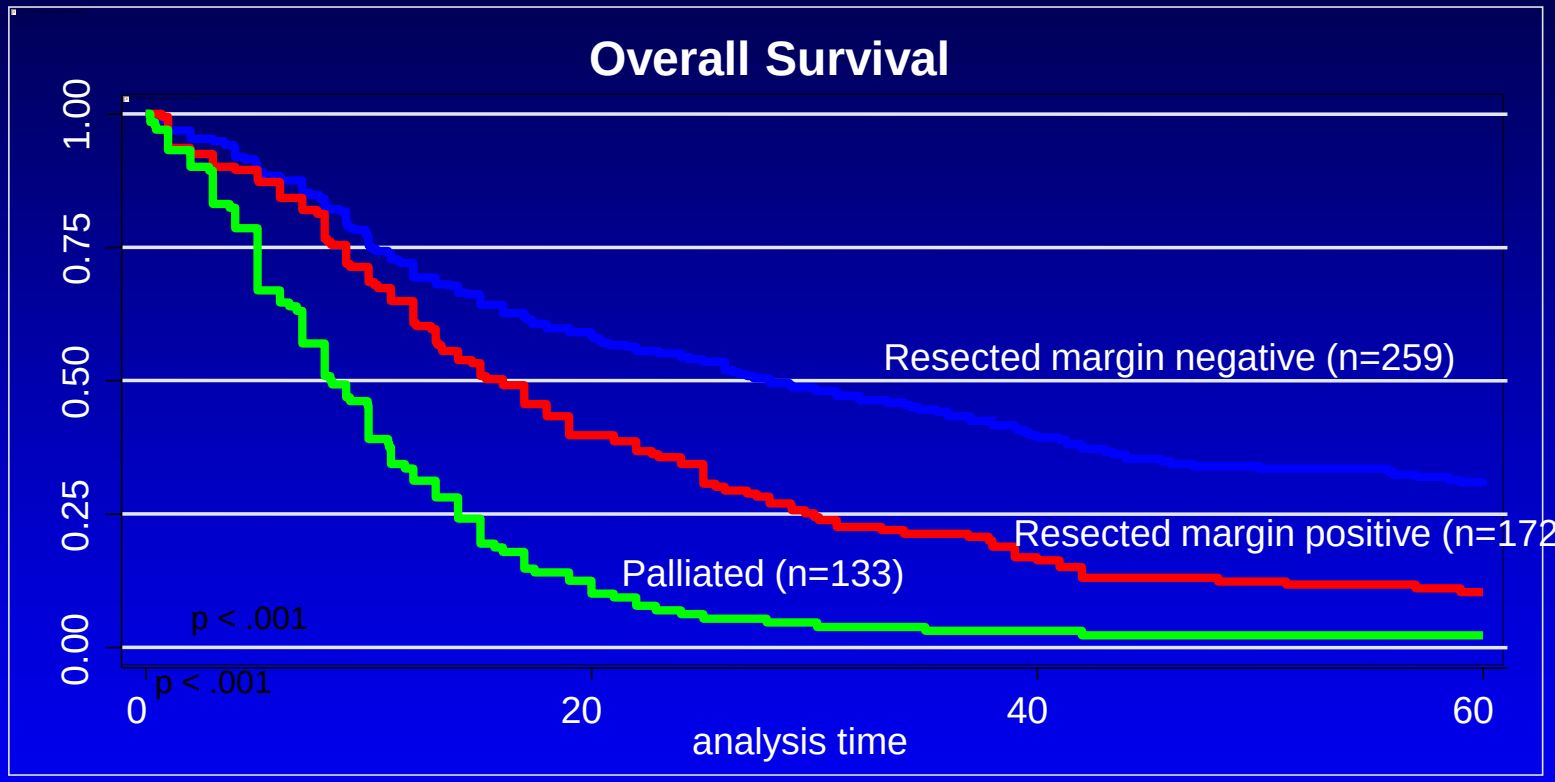
Tumor-free Resection

Difficult to achieve a wide/long resectional margin with curative intent.

1. HCC is located in the liver hilum surrounded by vital structures
2. Vertical and longitudinal spread up to 2 cm
3. Cannot predict exact length and width of microscopic Tu extension
4. IntraOp frozen-section examination of margins is inaccurate in 10-15% of pts

Endo I , et al. Ann Surg Oncol 2008
Xiang S, et al Int J Colorectal Dis 2015
Okazaki Y, et al. Hepatogastroenterology 2002

Cholangiocarcinoma: Johns Hopkins Series



	Resected Margin neg (n = 259)	Resected Margin pos (n = 172)	Palliated (n = 133)
5-year Survival	30 %	10 %	2 %
Median Survival	28 mo	16 mo	8 mo

Tumor-free Resection

West

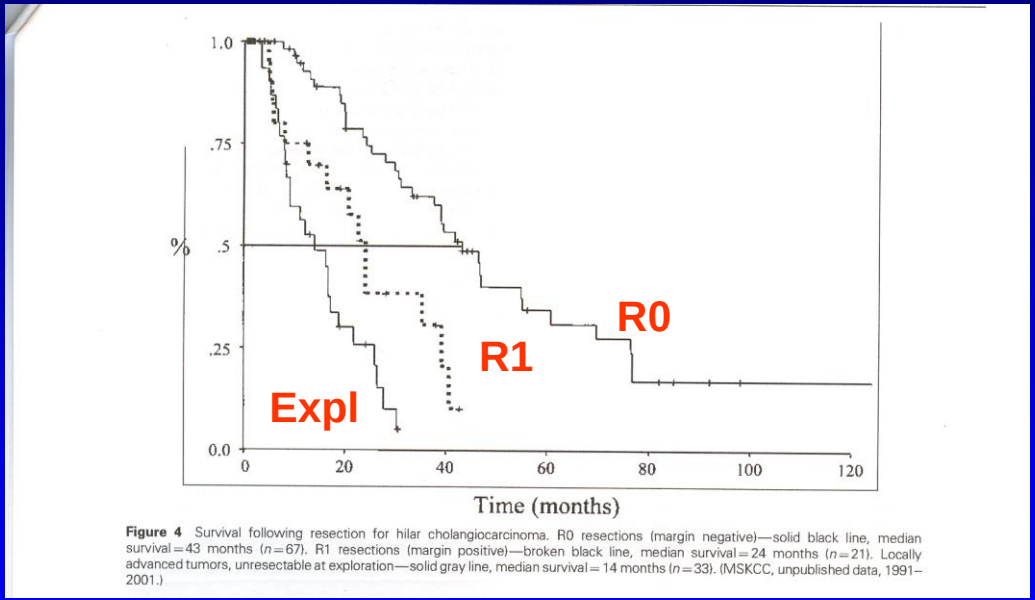
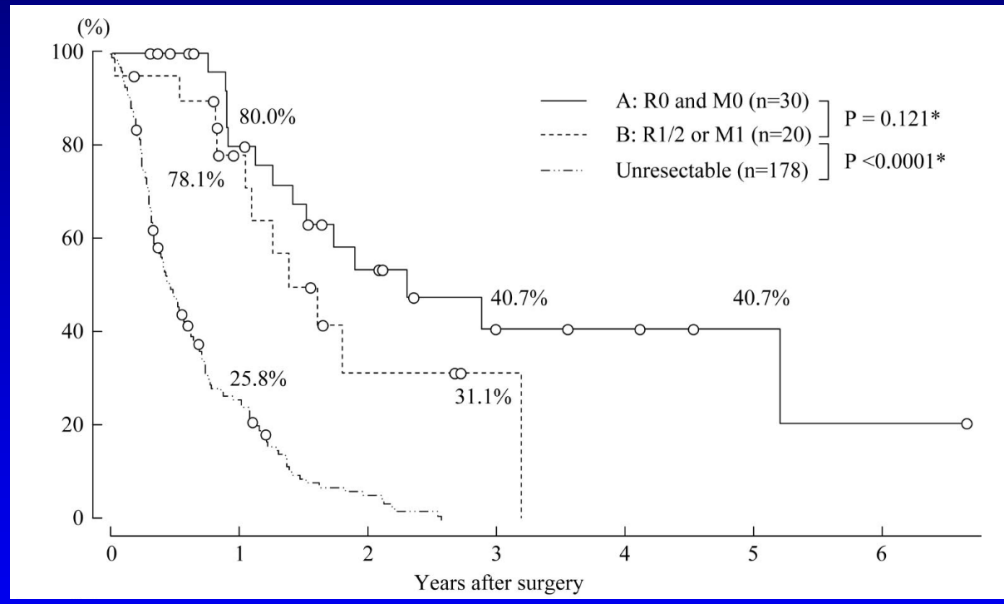


Figure 4 Survival following resection for hilar cholangiocarcinoma. R0 resections (margin negative)—solid black line, median survival = 43 months ($n = 67$). R1 resections (margin positive)—broken black line, median survival = 24 months ($n = 21$). Locally advanced tumors, unresectable at exploration—solid gray line, median survival = 14 months ($n = 33$). (MSKCC, unpublished data, 1991–2001.)

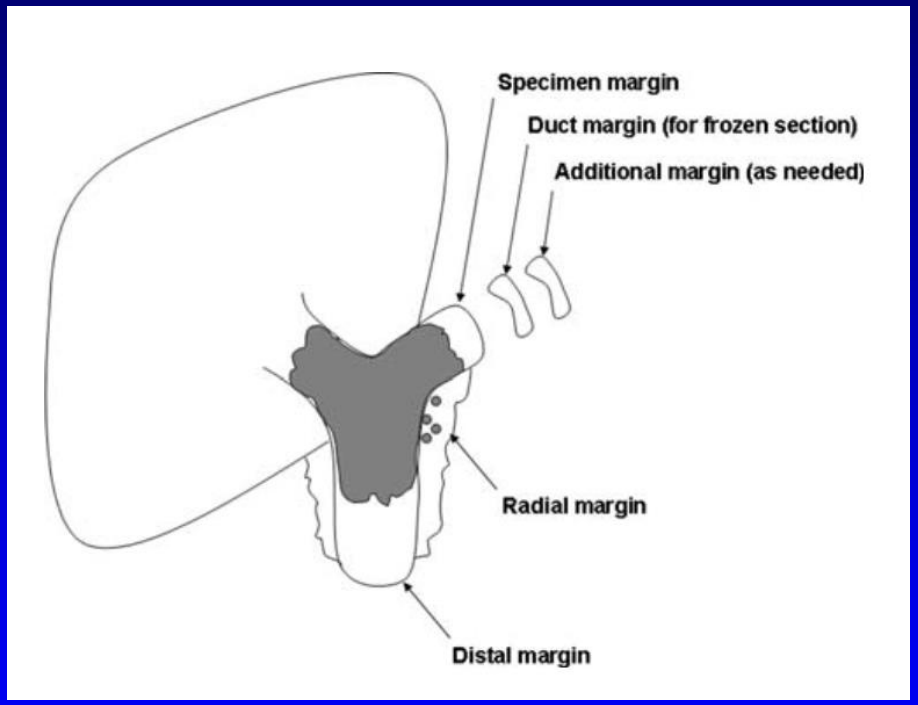
East

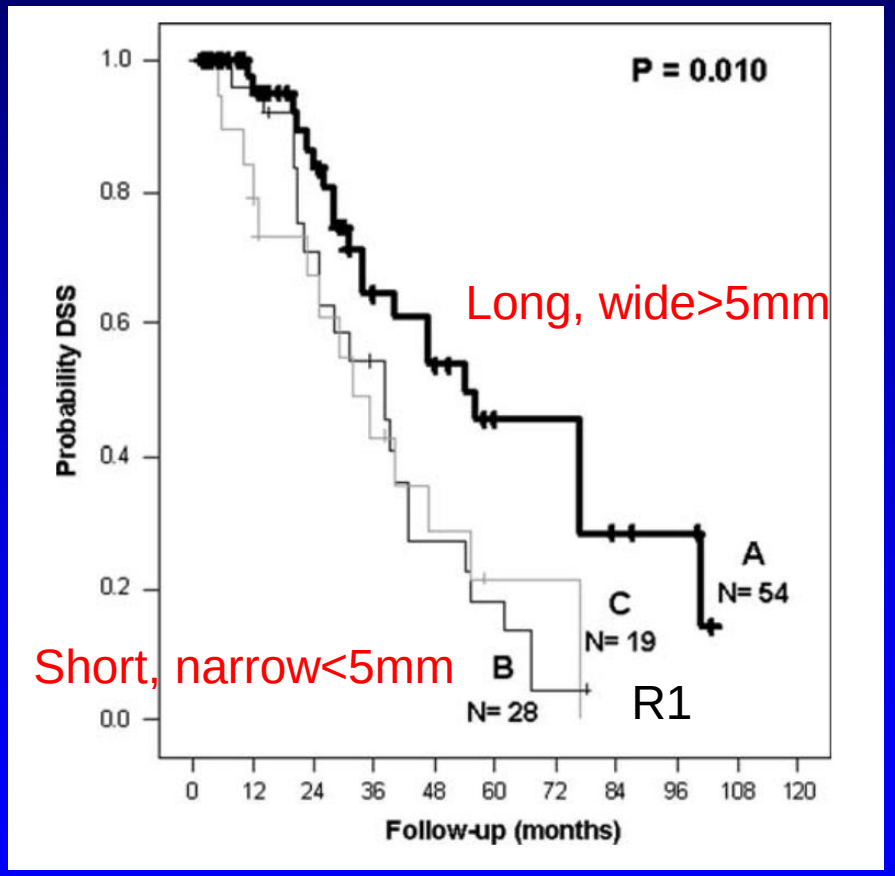


R0 resection: median survival 43 mo
R1 resection: 24 mo
Exploration: 14 mo

Nagino M, et al. Ann Surg 2010
Jarnagin M, et al. Ann Surg 2004

Tumor-free Resection





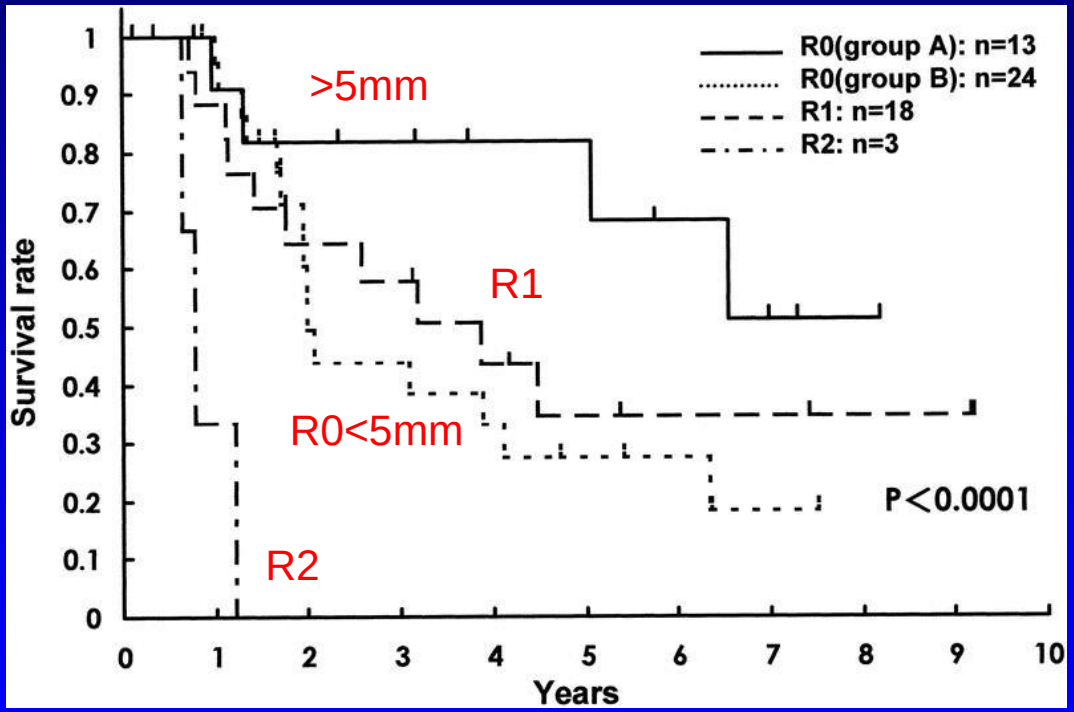
Endo I, et al. Ann Surg Oncol 2008

Tumor-free Resection

Pts with a secondary R0 resection margin after additional resection have an equivalent survival to those with a primary R0 resection

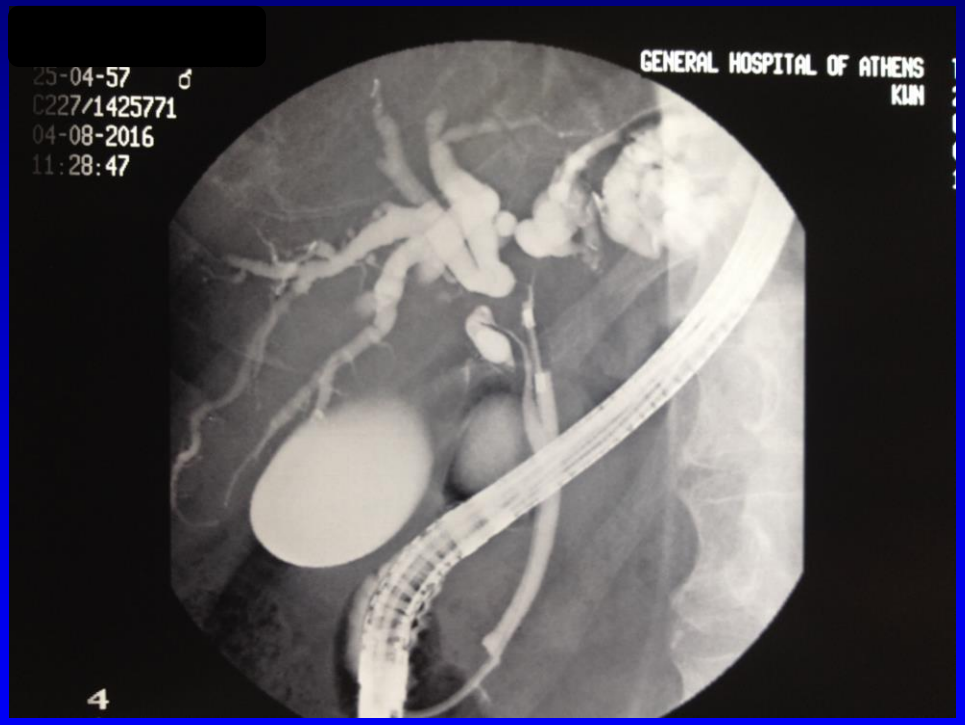
Increased incidence of biliary fistula, vascular injury, pseudoaneurysm

Dysplasia at the margin NOT associated with worse prognosis!!!

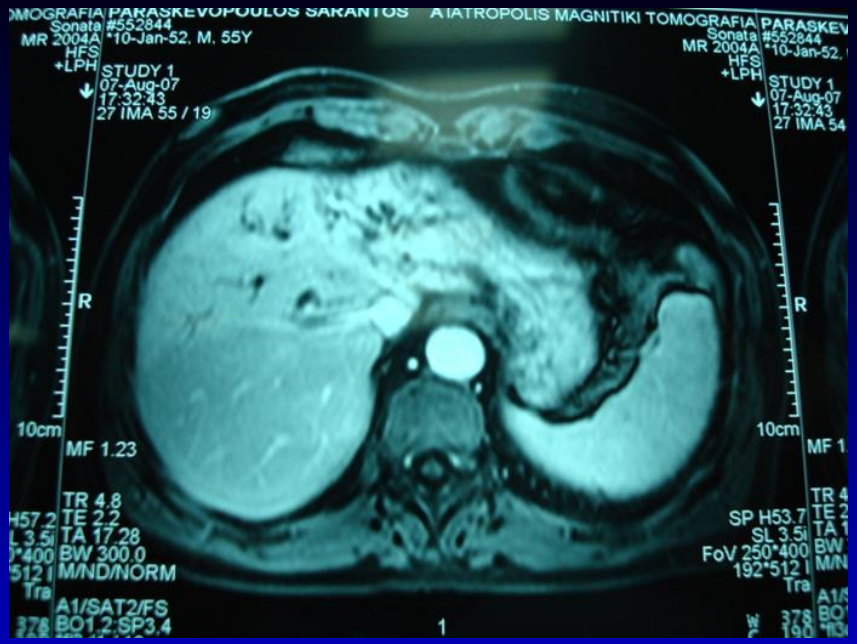


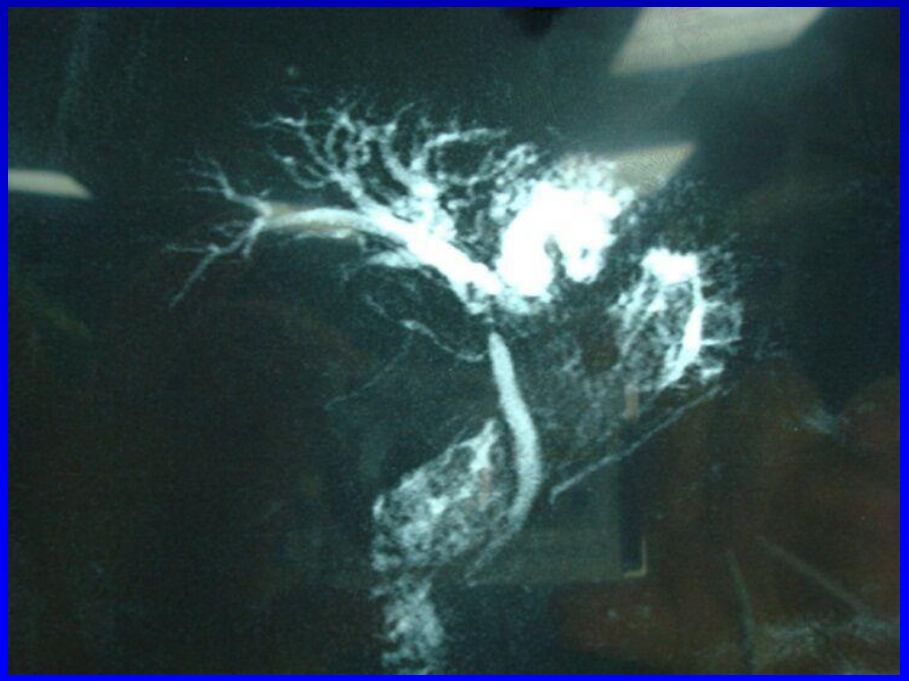
Seyama Y, et al. Ann Surg 2003
Ribero D, et al. Ann Surg 2011

Tumor-free Resection

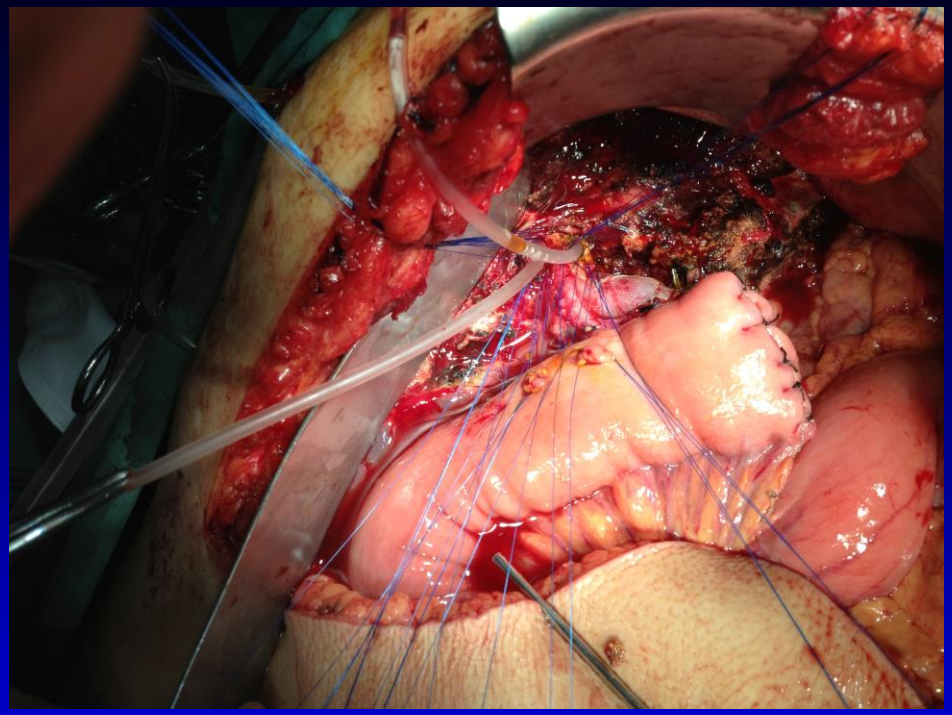


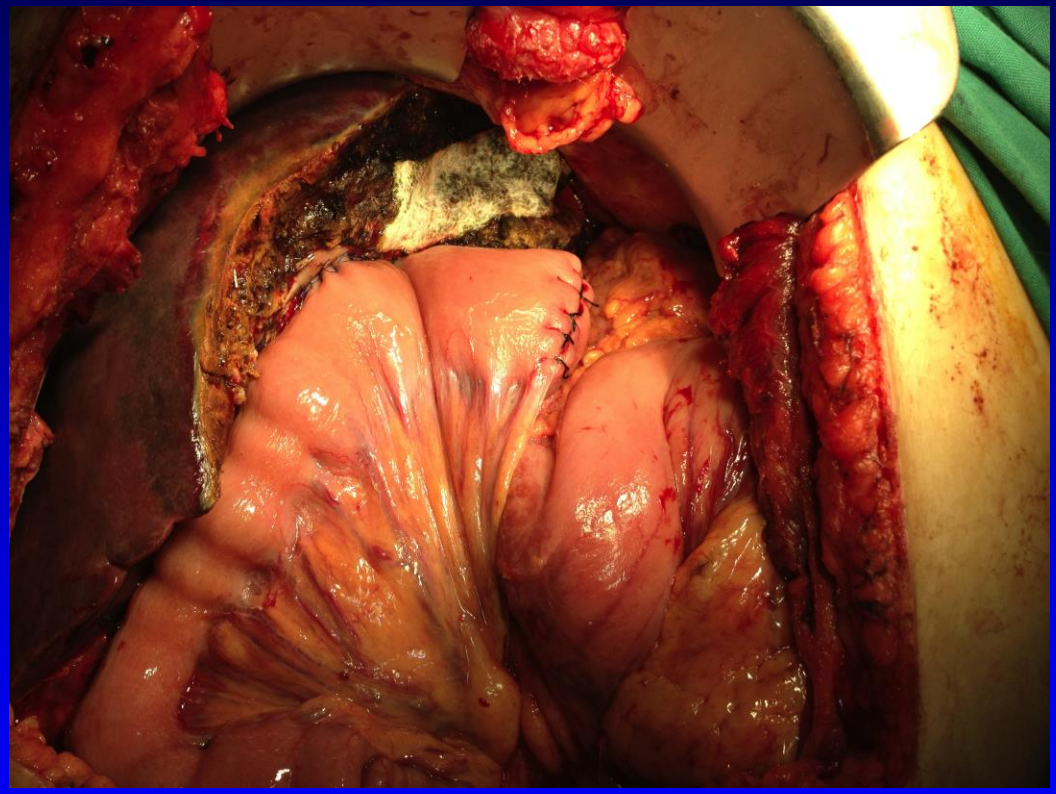
by Dimitris P. Korkolis, MD, PhD

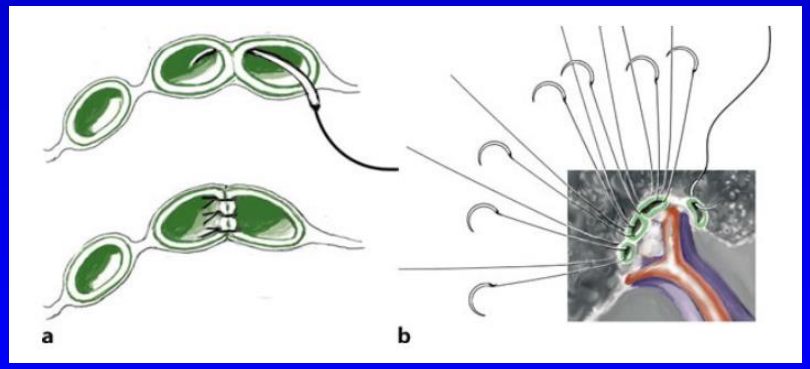




by Dimitris P. Korkolis, MD, PhD

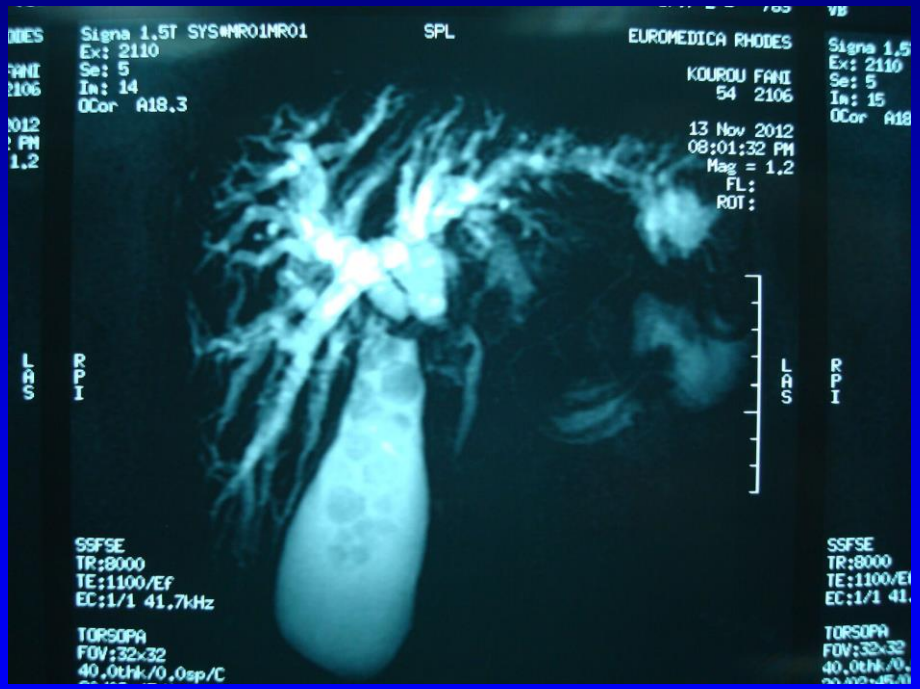


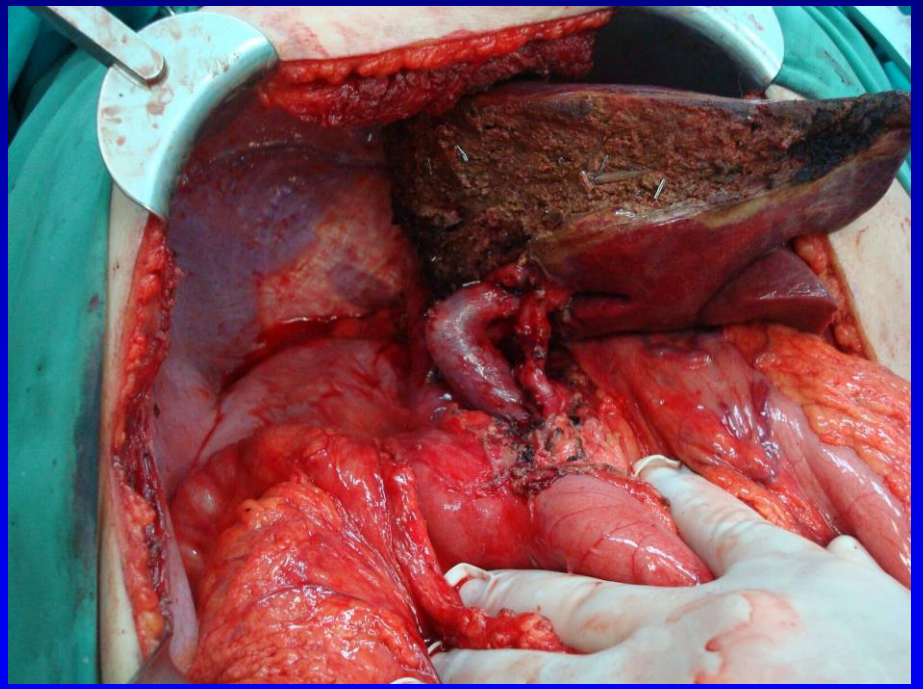




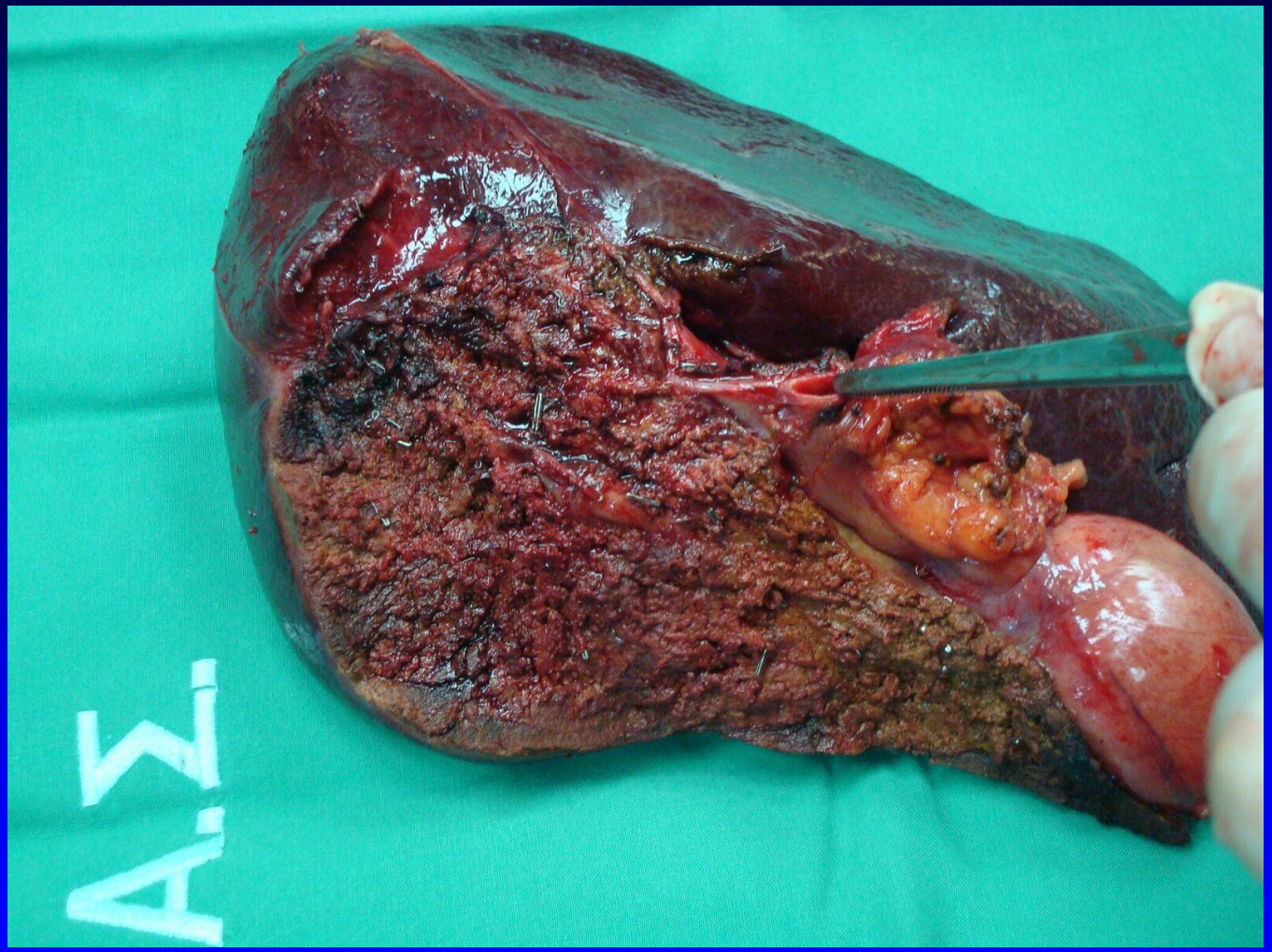
by Dimitris P. Korkolis, MD, PhD

Resection Margins





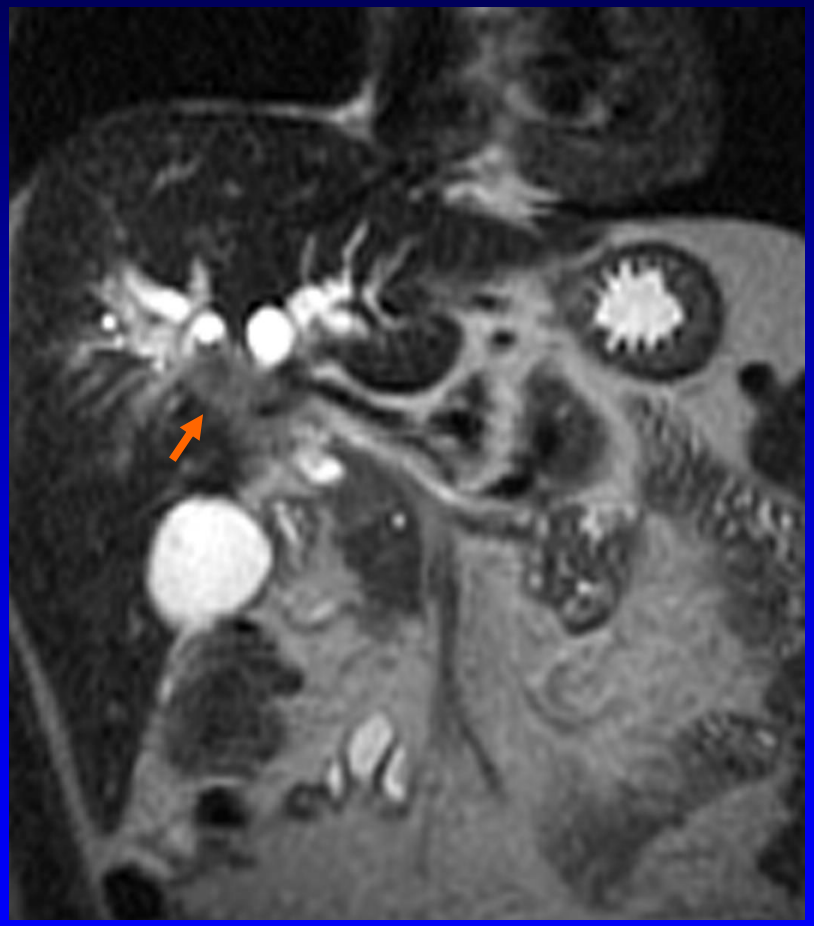
by Dimitris P. Korkolis, MD, PhD



by Dimitris P. Korkolis, MD, PhD

Hilar Cholangiocarcinoma

Anatomical Considerations



- Frequent submucosal tumor extension beyond gross margin (5 – 20 mm)
- Often unilateral extension to 2^{o} biliary radicles and beyond
- Hepatic resection required

Shimada et al. Int Surg 1988;73:87

Hepatic Resection

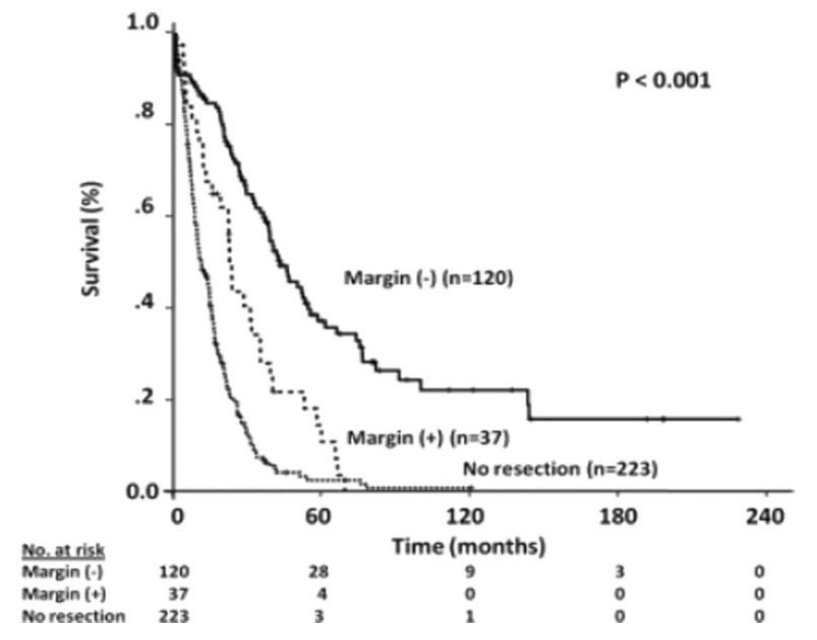
Authors	Published year	Time period		Resections	R0 (%)	PH (%)	Mortality (%)	Morbidity (%)	5-year survival (%)
Gerhards et al.	2000	1983	–1987	42	5	36	19	66	NA
		1988	–1992	45	13	9	20	73	NA
		1993	–1997	25	32	52	12	52	NA
Kawarada et al.	2002	1976	–1993	62	55	65	2	31	20
		1994	–2000	25	88	100	4	20	50
Dinant et al.	2006	1988	–1993	45	13	9	20	73	22
		1993	–1998	25	32	52	12	52	35
		1998	–2003	29	59	72	10	68	59
Gulik et al.	2010	1988	–1993	45	13	9	NA	NA	20
		1993	–1998	25	32	52	NA	NA	
		1998	–2003	29	59	72	10	68	33
Nagino et al.	2012	1977	–1990	72	75	92	11	76	23
		1991	–2000	116		93	10	80	
		2001	–2005	168	78	98	3	52	38
		2006	–2010	218		99	1	43	
Furusawa et al.	2014	1990	–2000	70	70	99	1.4	85.7	33
		2001	–2012	74	78	100	0	61	35

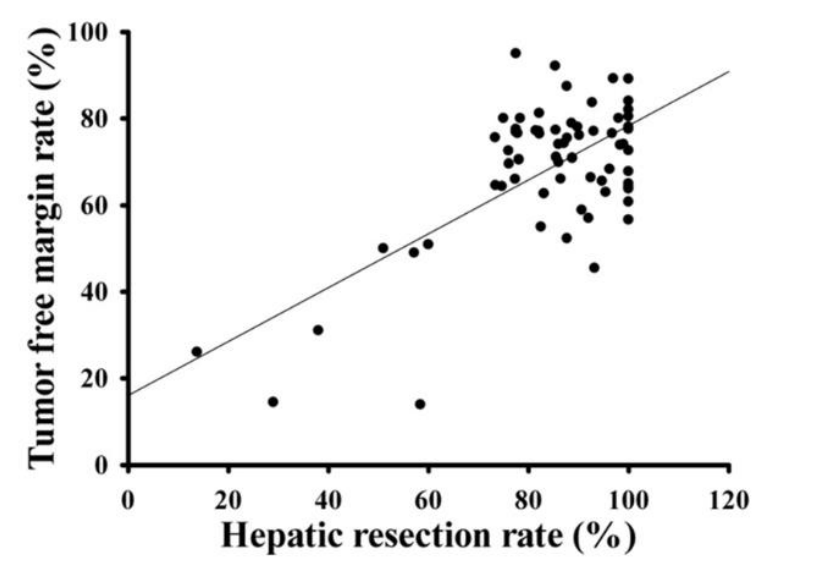
Concomitant Liver Resection

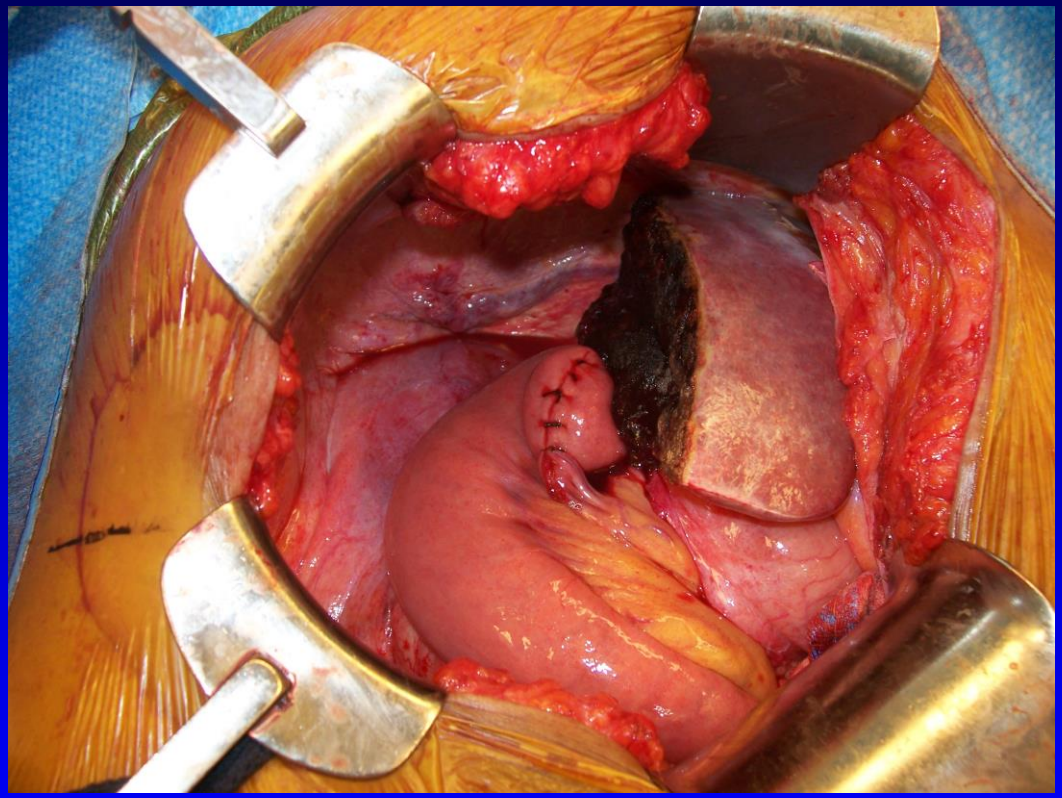
Study	Year	Total Number	Liver resections	R0 resections		30-day mortality		5-Year survival	
				Liver resection (%)	Bile duct resection only (%)	Liver resection (%)	Bile duct resection only (%)	Liver resection (%)	Bile duct resection only (%)
Capussotti	2002	36	32	91	75	NR	NR	39.5	0
Ito	2008	38	20	85	39	0[a]	0[a]	50	0
Lee	2010	302	268	76.5	26.4	1.7	0	35.5	17.5
Song	2012	230	177	86.4	49	NR	NR	45	18
Nuzzo	2012	440	376	79.2	65.6	NR	NR	26.6	0
De Jong	2012	355	224	66.5	54.3	6.7	1.2	22	10
Matsuo	2012	157	129	83.7	42.9	8.5	3.6	37.5	8
Lim	2013	52	26	100	27	0	0	87.4*	76.1*

Nuzzo G, et al. Arch Surg 2012
Capussoti L, et al. J Am Coll Surg 2002
Van Gulik TM, et al. Dig Surg 2012

Hepatic Resection







De Jong MC, et al. Arch Surg 2011
Matsuo K, et al. J Am Coll Surg 2012

Is Hepatic Resection Necessary for type I and II HCC?

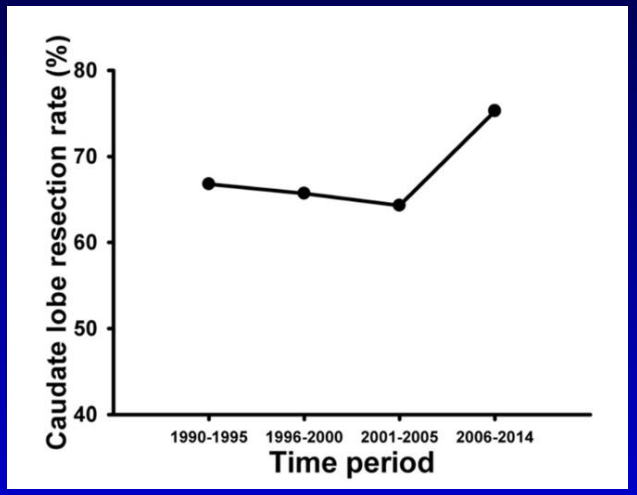
- Local Hilar Resection:
  - Bismuth type I-II
  - Tis – T2
  - Papillary tumor type

- Concomitant liver resections should be considered in all pts with type I-II HCC
  - higher curability
  - lower local recurrence rate
  - better OS
  - similar postop M&M

Lim GH, et al. World J Surg 2013
Chen XP, et al. Br J Surg 2009
Otani K, et al. Hepatogastroenterology 2012

Caudate Lobe Resection

- Nagoya University Medical Center, Japan
- 91 pts with HCC
- R0 resection in 86% with resection pf segment I
- Median Survival: 33 μήνες



Nimura Y, et al. J Hepatobiliary Pancreat Surg 1995

- 75 pts with HCC stage II-IV
- With caudate lobe resection: 5ετής επιβίωση=25%
- Without caudate lobe resection: 2ετής επιβίωση=0%

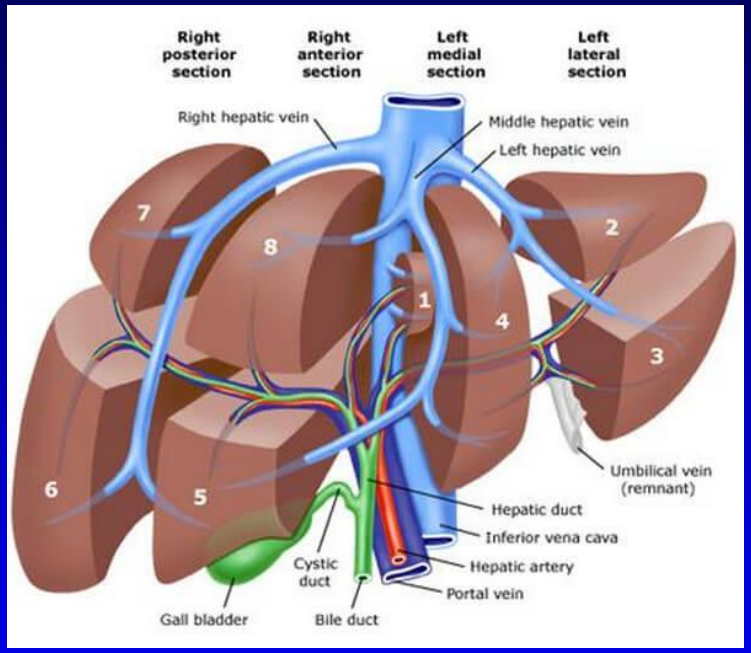
Gazzaniga GM, et al. J Hepatobiliary Pancreat Surg 2000

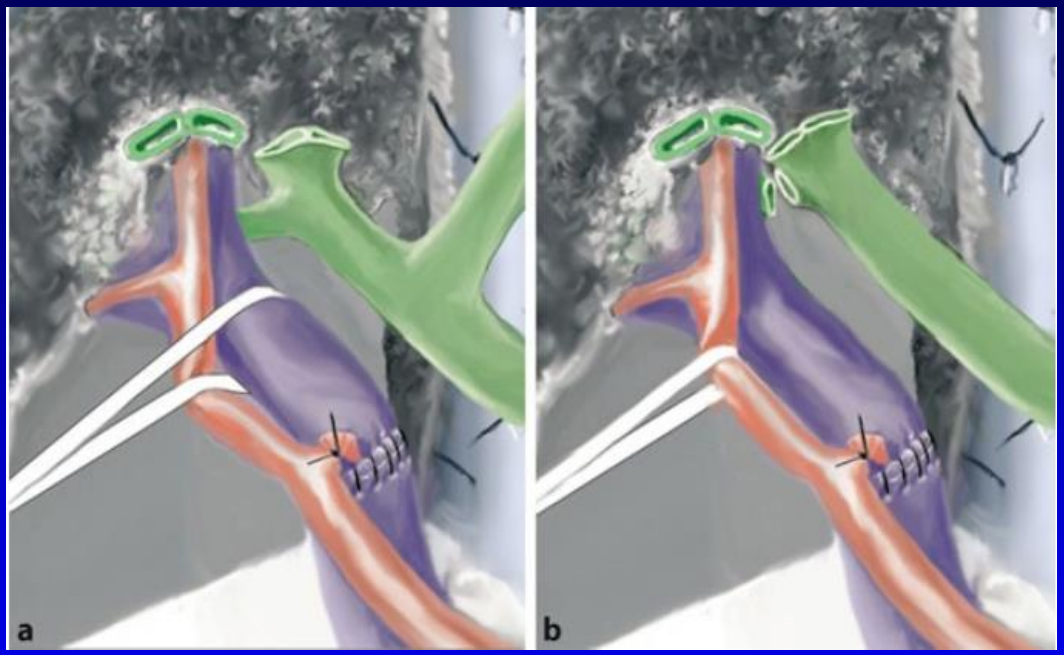
Caudate Lobe Resection

	N	Εκτομή	Εγχειρητικό Bypass	Stent	5ετής επιβίωση	10ετής επιβίωση	Εκτομή Κερκοφόρου Λοβού
Lahey Clinic USA	100	25	53	22	7%	0%	8%
Nagoya University Hospital Japan	155	122	10	23	16%	18%	89%

Dugan JM, et al. Ann Surg 2000

Caudate Lobe Resection



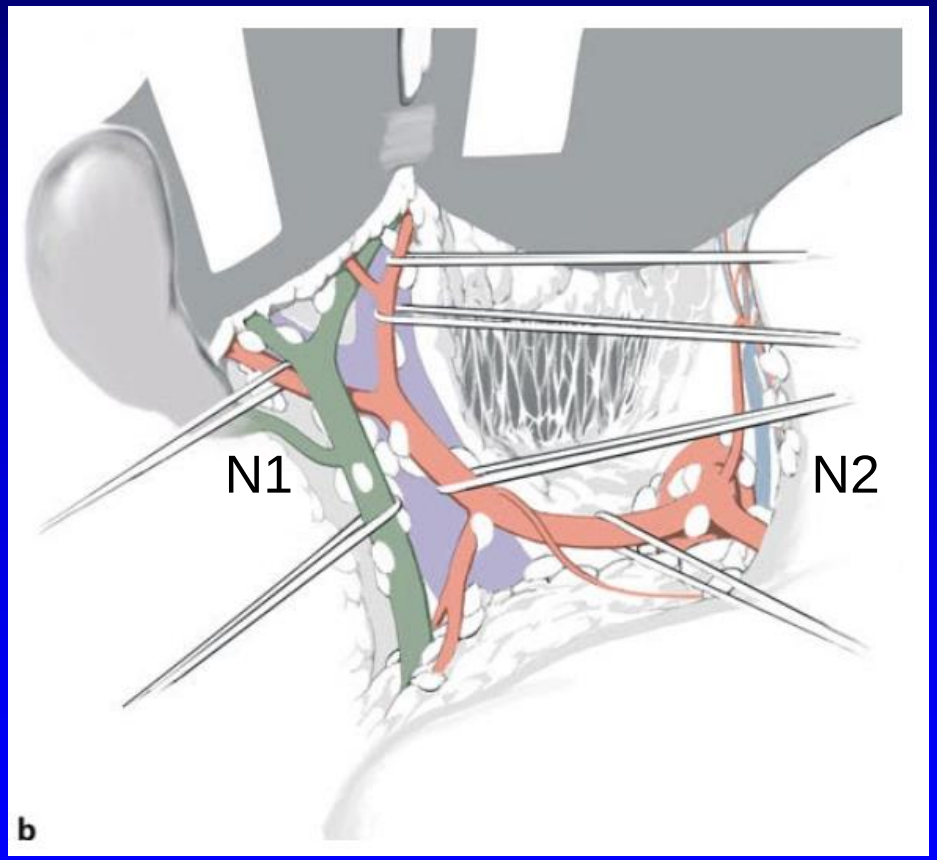


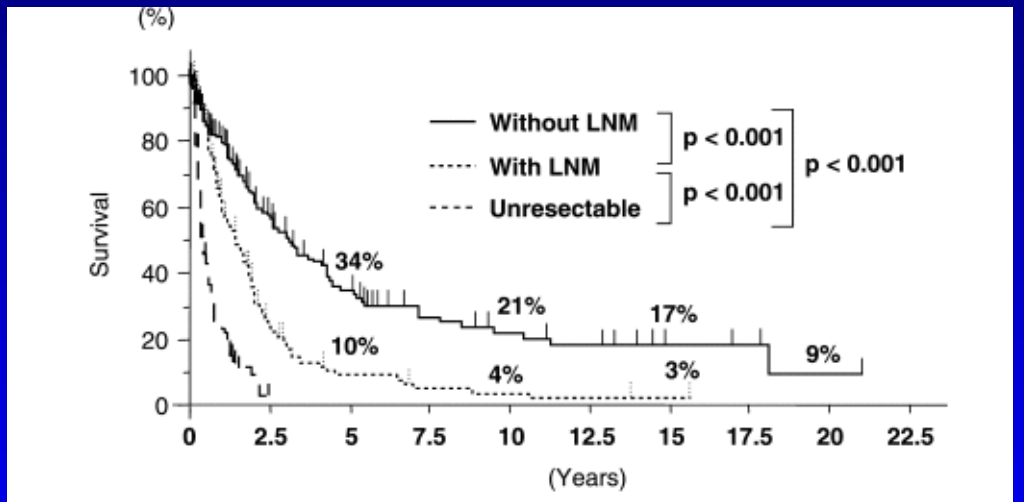
- Segment I involvement in 40-58%
- Biliary communications
- Frequent direct invasion

- Site of tumor recurrence
- Postop bile leak

Cheng QB, et al. Eur J Surg Oncol 2012
Dumitrascou T, et al. J Gastrointest Surg 2012

Lymphadenectomy in HCC

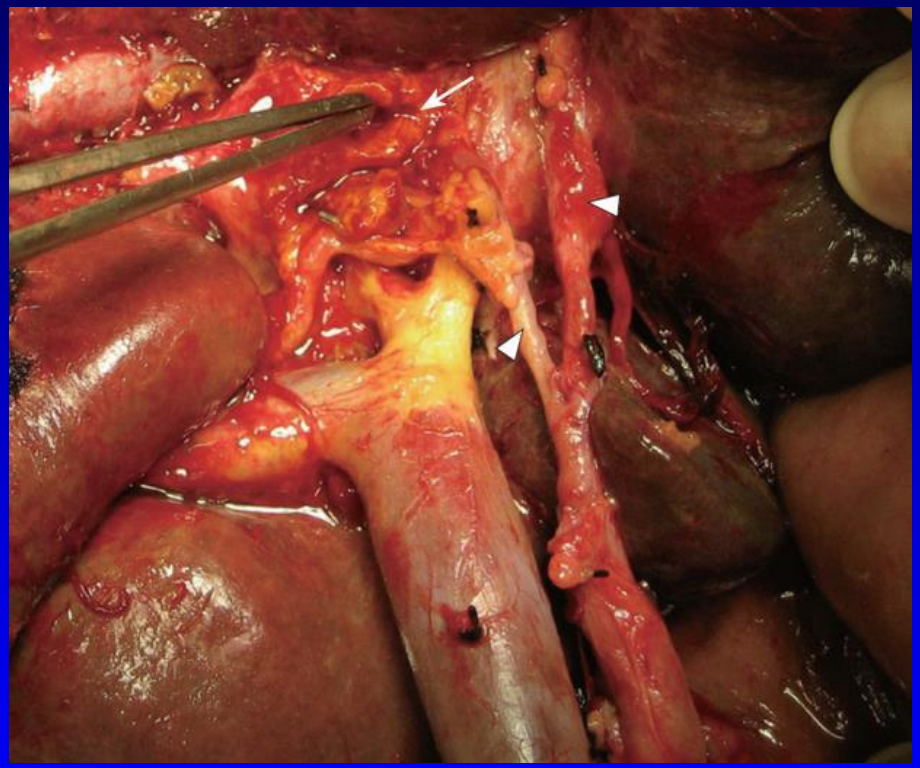




No. at risk					MST
Without LNM 152	31	12	4	1	3.0 Y
With LNM 149	8	3	1	-	1.5 Y
Unresectable 99	-				0.4 Y

DeOliveira ML, et al. Curr Opinion in Gastroenterol 2013

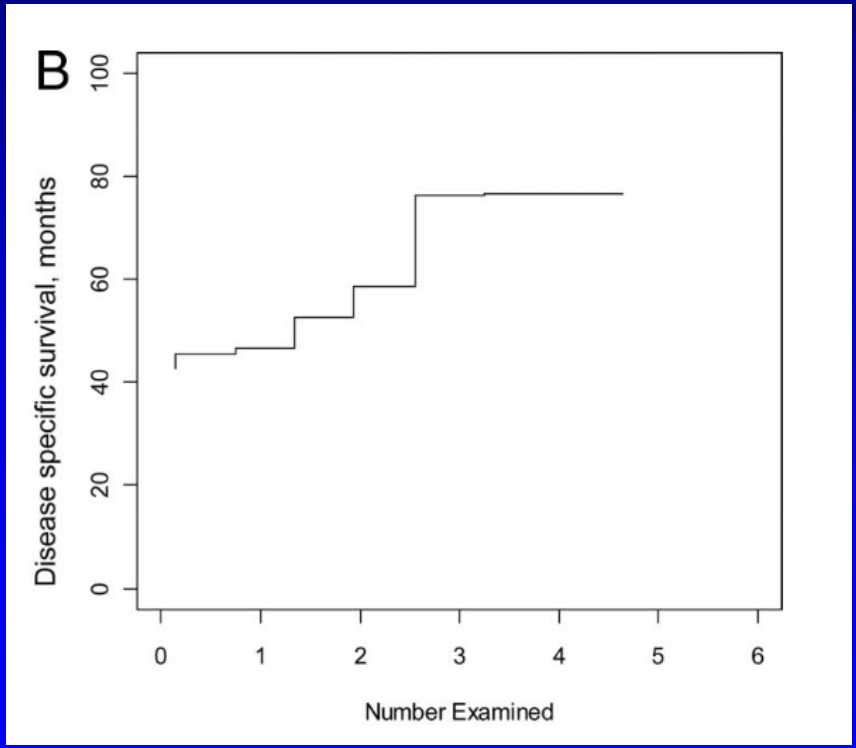
Lymphadenectomy in HCC

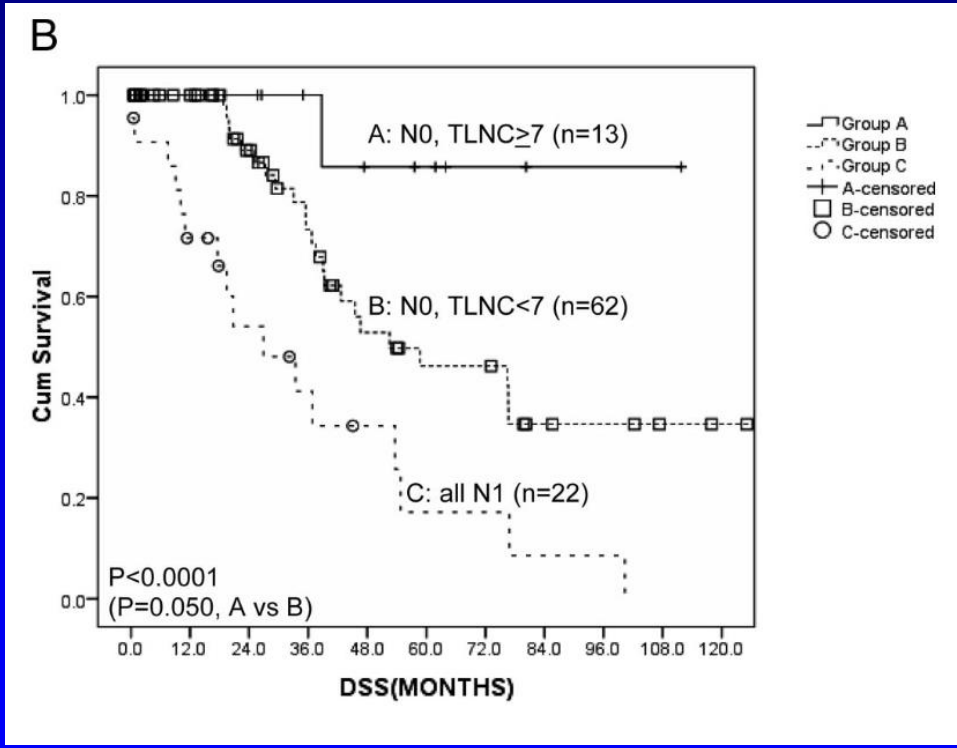


by Dimitris P. Korkolis, MD, PhD

Adequate Lymph Node Assessment for Extrahepatic Bile Duct Adenocarcinoma

Kaori Ito, MD, Hiromichi Ito, MD,* Peter J. Allen, MD, FACS,* Mithat Gonen, PhD,† David Klimstra, MD,‡ Michael I. D'Angelica, MD, FACS,* Yuman Fong, MD, FACS,* Ronald P. DeMatteo, MD, FACS,* Murray F. Brennan, MD, FACS, FRCS,* Leslie H. Blumgart, MD, FACS, FRCS,* and William R. Jarnagin, MD, FACS**





Ito K, et al. Ann Surg 2010

Lymph node dissection in resectable Perihilar Cholangiocarcinoma – a Systematic Review

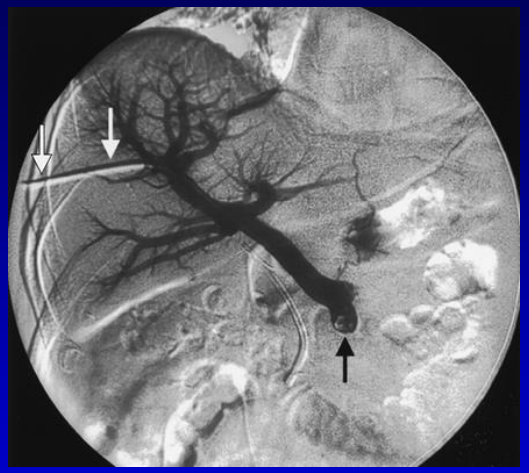
Author	Type of LAD	Lymph node station***	Median LNC	Min LNC	Max LNC	Median Positive	Recommended LNC
Kitagawa[17]	Ext	8a/p, 9, 12a/b/c/h/p, 13a, 14+16 in ext. LAD	24*	-	-	3.4*	-
Schwarz[18]	Reg. + Ext.	-	5	1	37	0	10
Ito[12]	Reg.	12a/b/h/p	3	0	16	1	7
Kawai[19]	Reg.	12a/b/h/p, 14	12	5	38	-	12
Raviaoli[20]	Reg.	8a,8p,12a/b/h/p	7	4	26	-	-
Rocha[21]	Reg.	-	3	0	16	-	7
Guglielmi[22]	Reg.	-	7	1	25	-	3
Murakami **[23]	Ext	-	21	4	107	-	-
Murakami**[24]	Reg. + Ext.	8a/p, 12a/b/h/p, 13a +16 in ext. LAD	16	1	64	3	-
Oshiro**[25]	Reg.	8a/p, 12a/b/h/p, 13a	13	0	57	-	12
Patel[26]	Reg.	-	3	0	24	0	-
Ruys[27]	Reg. + Ext.	-	5	-	-	-	2
De Jong[28]	Reg.	-	3	1	22	3	-
Kow[29]	Reg.	8a/p, 9, 12a/b/h/p	11	0	42	0	-
Noji[30]	Reg.	8a/p, 9, 12a/b/h/p	2	1	8		
Aoba[13]	Reg. + Ext.	8a/p, 12a/b/h/p, 13a + 16 in ext. LAD	11	1	59	-	5
Guglielmi[14]	Reg.	8a/p, 12a/b/h/p, 13a	7	1	25	-	7
Ocuin[31]	Reg.	-	3	1	16	-	7
Hakeem[15]	Reg. + Ext.	8a/p, 9, 12a/b/c/h/p, 13a, 14 + 16 in ext. LAD	9	0	58	2	20
Nari[32]	-	-	9	4	27	1	-
Cumulative	Median (IQR)		7 (3-11)	1 (0-1)	27 (23-53)	1 (0-2.5)	7 (6-11)

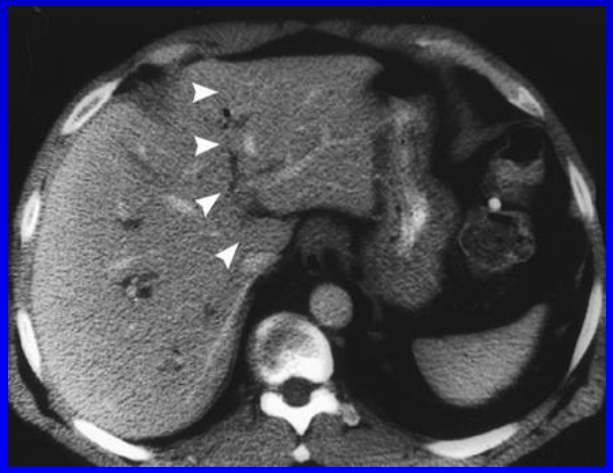
Subgroup	LNC 0-2 (n=110)	LNC 3-6 (n=1160)	LNC 7-9 (n=257)	LNC 10-14 (n=489)	LNC ≥15 (n=185)	P value
LNC	1.5 (1.0-2.0)	3.0 (3.0-5.0)	7.0 (7.0-9.0)	11.5 (11.0-12.8)	21.0 (16.0-24.1)	P<0.001
Positive LN	-	1.0 (0.0-2.5)	1.5 (1.0-2.0)	0.5 (0.0-1.0)	-	P=0.554
Rate of N+	35.5 (35.0-36.0)	36.0 (32.8-43.8)	49.5 (37.3-56.5)	41.0 (33.0-45.3)	40.0 (40.0-53.0)	P=0.265
Rate of N0	64.5 (64.0-65.0)	64.0 (56.3-67.2)	48.5 (43.5-61.8)	59.0 (55.0-61.0)	60.0 (47.0-60.0)	P=0.008*
Rate of T3/T4	58.5 (58.0-59.5)	44.0 (29.5-53.3)	50. 5 (47.0-54.0)	27.5 (25.3-53.)	62.0 (62.0-63.0)	P=0.344
Survival (months)	-	22.0 (17.0-25.0)	22.0 (22.0-31.0	-	22.0 (21.5-22.5)	P=0.319
5 year Survival rate	39.0 (38.0-41.0)	21.0 (10.3-31.3)	21.0 (15.0-25.0)	39.5 (24.9-48.8)	37.0 (19.0-40.0)	P=0.729

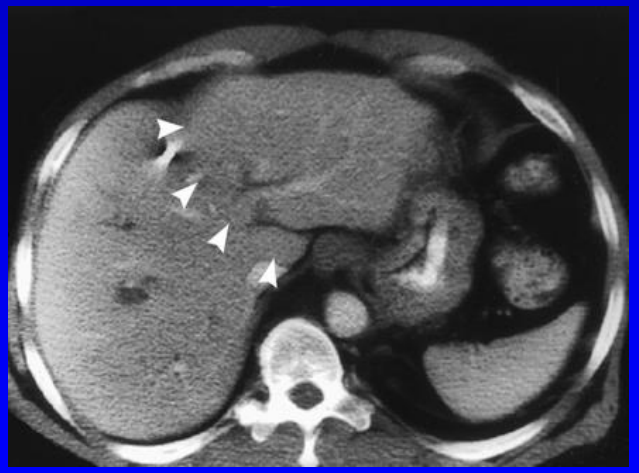
ACCEPTED MANUSCRIPT

ML DeOliveira, et al. Am J Surg 2015

PVE







Kawasaki S, et al. Ann Surg 2003

PVE

	Pts with HCC	Negative Resection Margins	5year Survival
PVE	51	75%	40%
Non-PVE	18	45% p<0.0178	6% p<0.0001

– Benefits
  - Post-resection morbidity is diminished, as evidenced by minimal changes in liver function
  - Subclinical disease or rapid progression may be detected prior to definitive surgery, thus avoiding an unnecessary operation
    - Abdalla EK et al. Br J Surg 2001; 88:165
- Reduces risk of postop liver insufficiency
- Increases rate of R0 resection

- No RCTs
- When FLR: 25-30%
- In cirrhotic livers
- Before any major hepatectomy
- Always with PTBD

Abdalla EK, et al. Surgery 2004
Van Gulik, et al. Dig Surg 2011
Hemming AW, et al. Ann Surg 2005

PVE

Preoperative Portal Vein Embolization for Major Liver Resection

- In a meta-analysis of data from 37 published series
  - Total 1088 pts underwent PVE prior to liver resection
  - 4 weeks after PVE, overall increase in liver volume of between 10 %- 12%
  - 85% pts underwent laparotomy for attempted major hepatectomy
  - Of who underwent laparotomy, resection was not possible in 27 pts, because of advanced, unresectable disease
  - Following resection, 23 patients had transient liver failure and 7 pts died of acute liver failure

Abulkhir A et al. Ann Surg 2008; 247:49

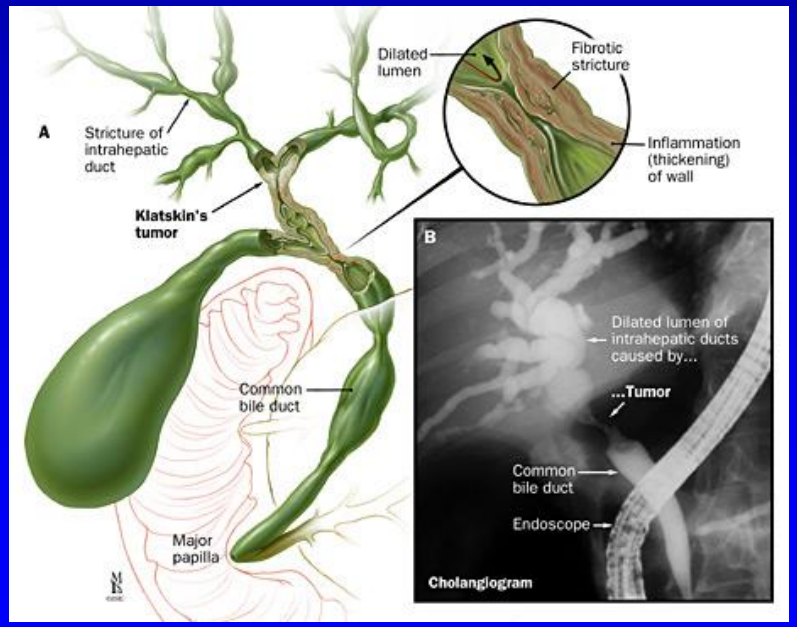
PVE Disadvantages:

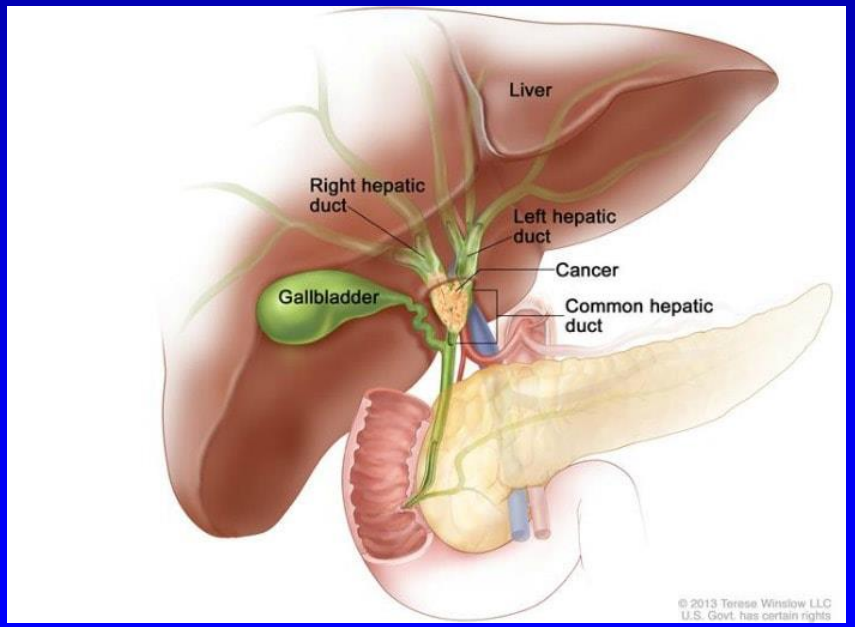
- Waiting time for FLR to hypertrophy
- Preoperative difficulty in deciding whether a Right or Left Hemihepatectomy is necessary in centrally placed HCC
- No evidence to support routine use

Abulkhir A, et al. Ann Surg 2008

Left- or Right- Sided Hepatectomy?

- According to the predominant site of the lesion
- RH for type I-II-IIIA-IV LH for type IIIB-IV
- Extended Right Hemihepatectomy: The most radical for centrally located HCC





Anatomical Considerations in HCC

1.The extrahepatic part of left hepatic duct is longer

2.The hepatic duct confluence lies on the right side of the hepatic hilum

3.Bile duct confluence lies at the base of segment IV

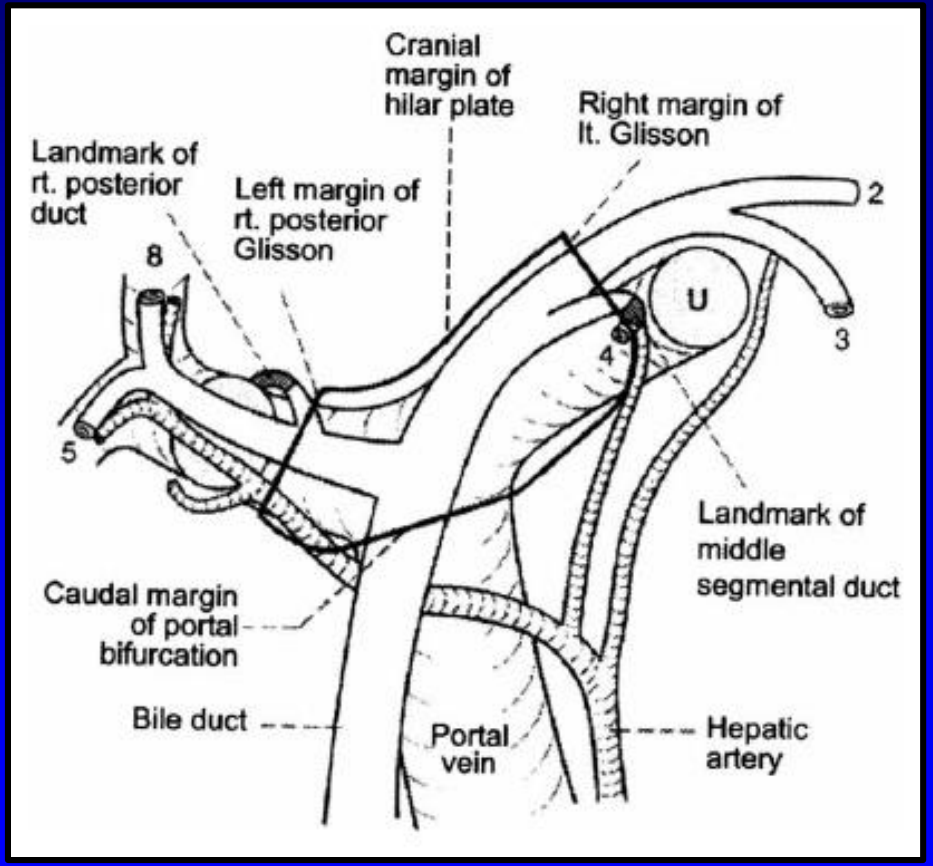
4.The right hepatic artery runs behind the CBD

5.The left portal vein is longer than the RPV

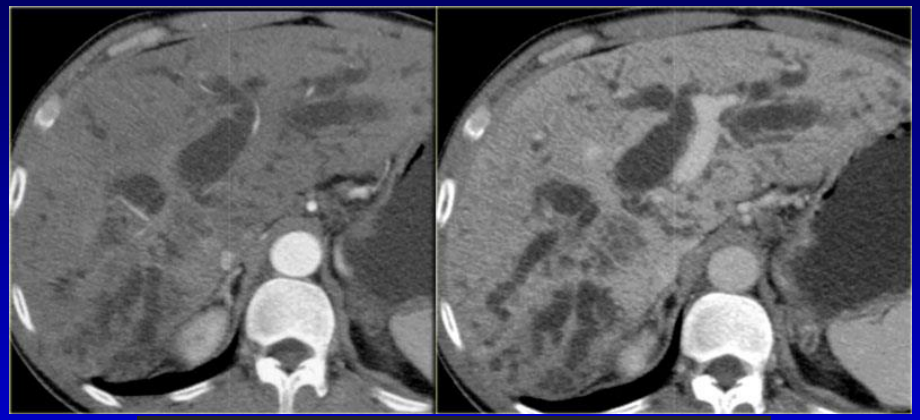
6.Many anatomic variations jeopardize a left-sided hemihepatectomy

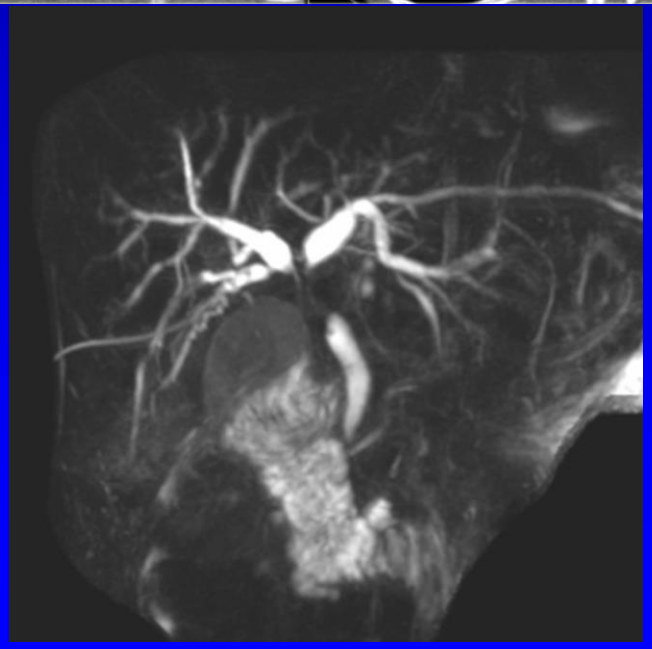
7.Enables en-block PV bifurcation (non-touch technique)

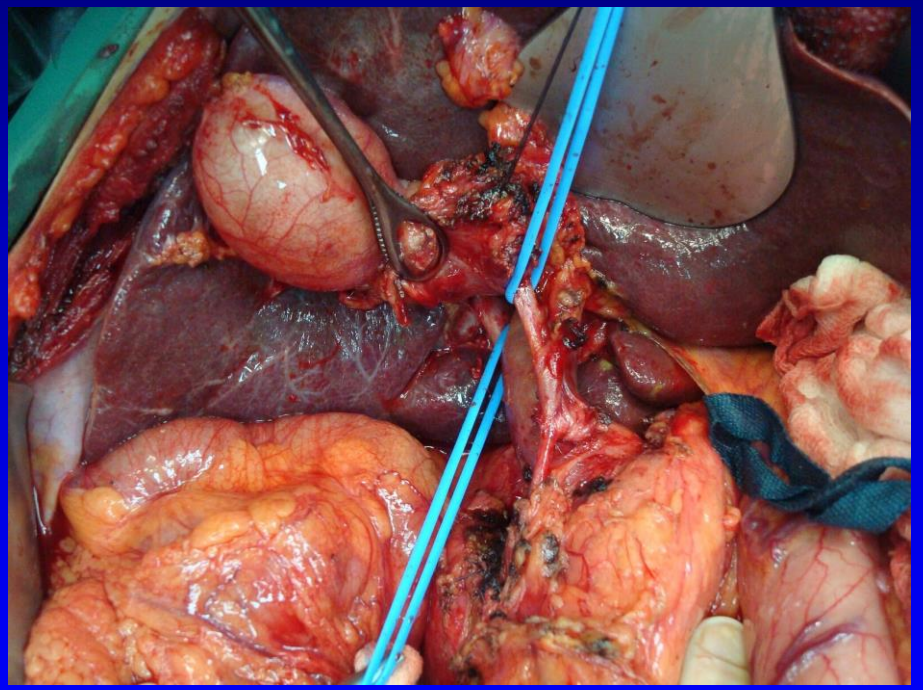
8.Enables en-block resection of ductal confluence and structures



Type IIIA HCC

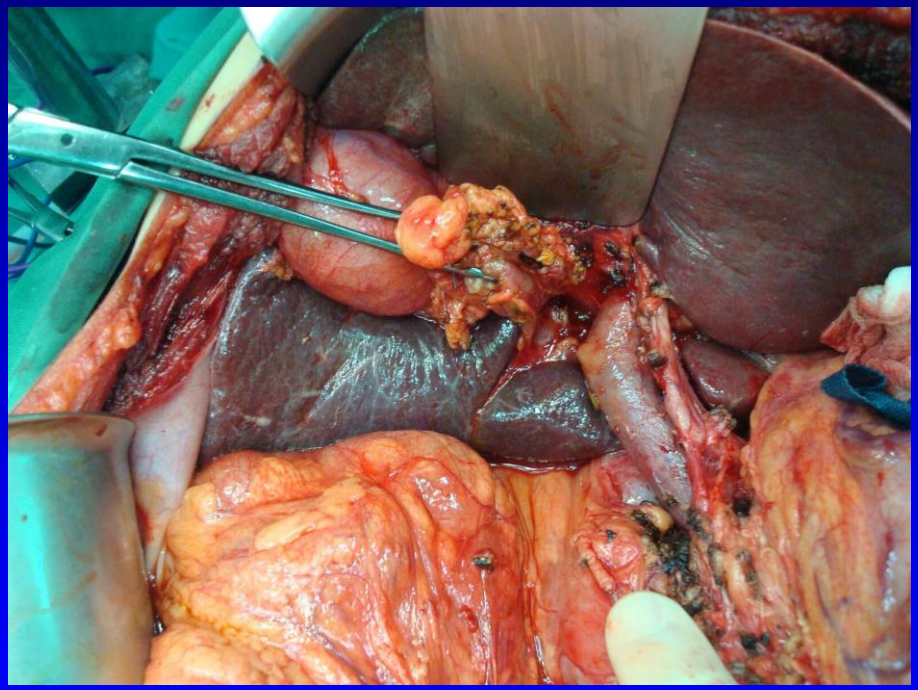


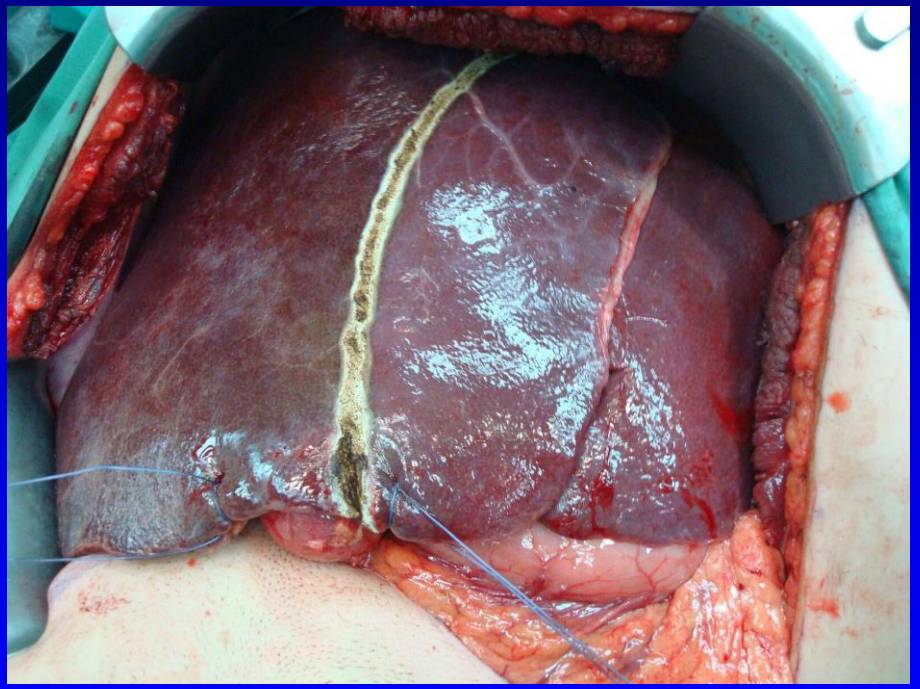




by Dimitris P. Korkolis, MD, PhD

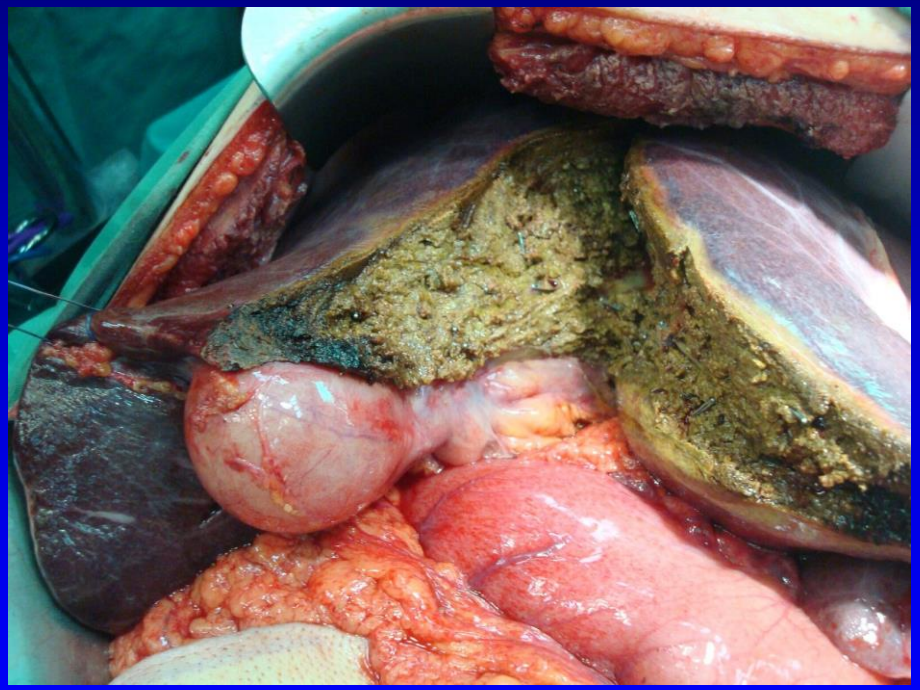
Type IIIA HCC





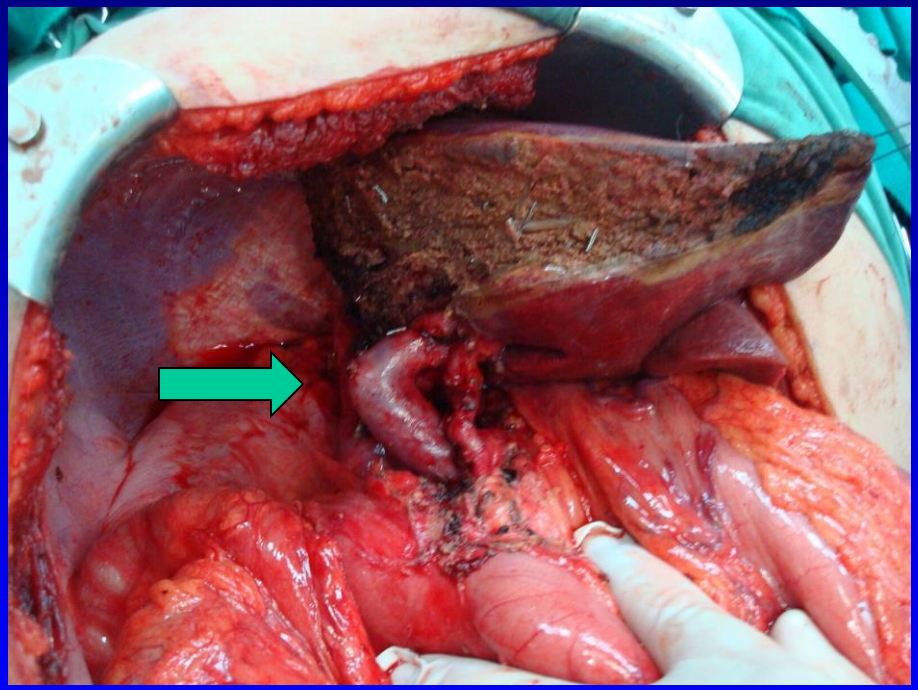
by Dimitris P. Korkolis, MD, PhD

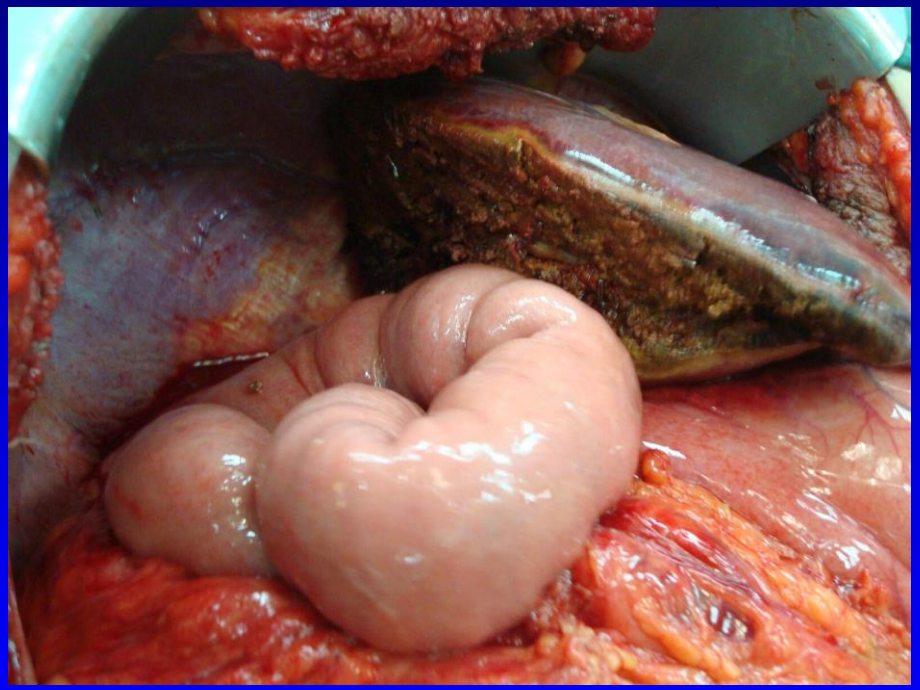
Type IIIA HCC



by Dimitris P. Korkolis, MD, PhD

Type IIIA HCC





by Dimitris P. Korkolis, MD, PhD

Minor Liver Resections

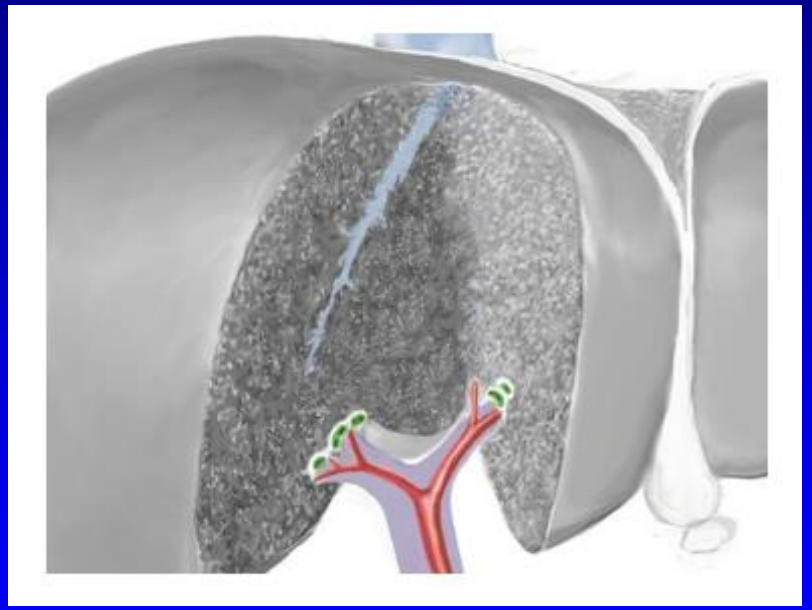
- In selected pts with limited disease extension
- When PVE is not available
- To avoid complications such as PV injury
- When concerns exist about liver hypertrophy
- In pts with insufficient residual liver function
- S4a + S5 + S1 minor hepatectomy (Taj-Mahal)
- May provide comparable results

Noji T, et al. J Gastrointest Surg 2014
Tsuchikawa T, et al. Exp Rev Gastroenterol Hepatol 2015

Central Hepatectomy for HCC

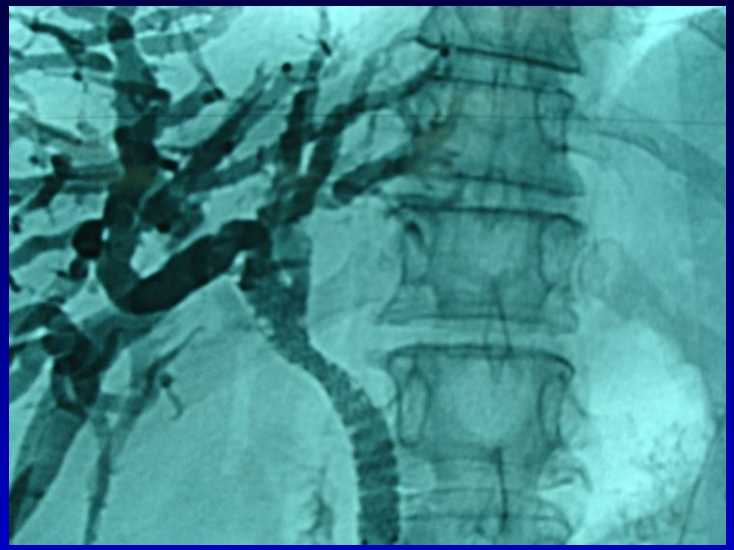
Central Lobe resection 4,5,8 and 1 technically difficult because:

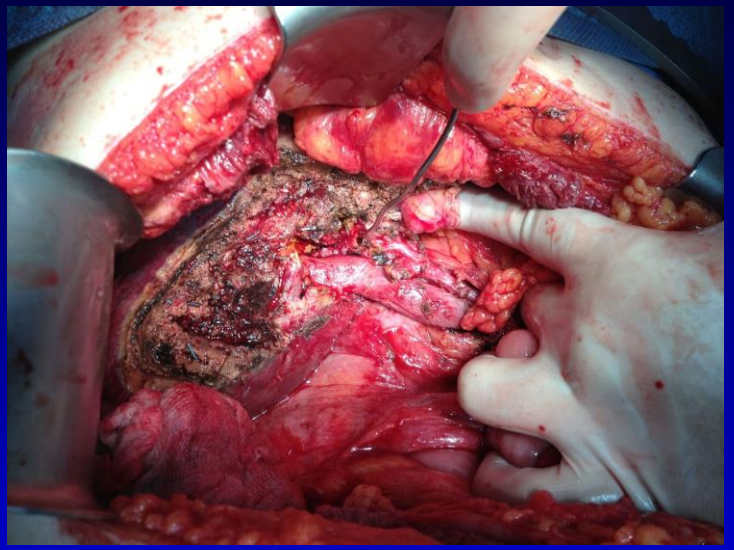
- The operation involves two liver transection lines
- Need to preserve blood supply to the outer liver segments
- Many intrahepatic ductal openings may be left in the liver remnant requiring multiple anastomoses

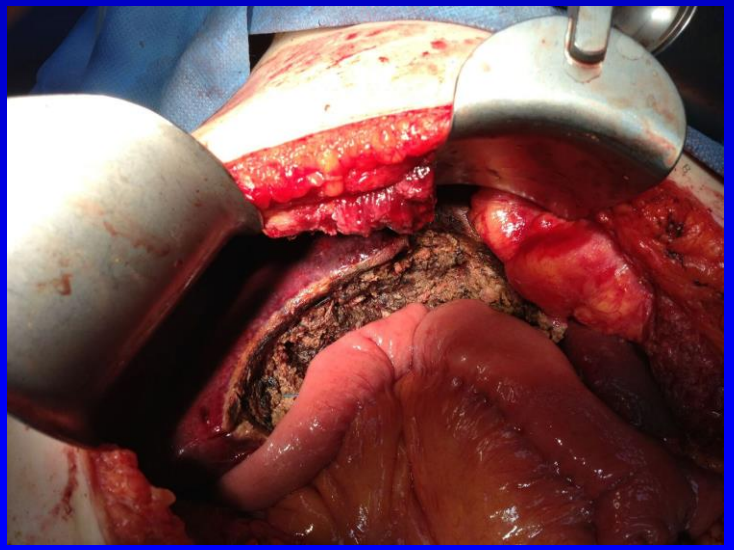


Chen XP, et al. Br J Surg 2009

Central Hepatectomy for HCC







by Dimitris P. Korkolis, MD, PhD

Combined Vascular Resection

- Indications:

    1. Intraoperative suspicion of gross invasion to vessels

    2. Tight adherence of tumor during vessel skeletonization

    3. Routine resection of PV in systematic radical surgery??

Dumitraskou T, et al. J Gastrointest Surg 2013
Young AL, et al. J Hepato-Biliary-Pancreat Sci 2010
De Jong, et al. Cancer 2012

Portal Vein Resection for HCC

Study	Year	No. of patients	Portal vein resection	Morbidity		Mortality		5-Year survival	
				With resection (%)	Without resection (%)	With resection (%)	Without resection (%)	With resection (%)	Without resection (%)
Ebata	2003	188	54	Nr	Nr	9.6	9.3	9.9	36.8
Miyazaki	2007	161	34	NR	NR	8.8	4.2	14	30
Hirano[a]	2008	64	43	28.5	57.1	4.8	4.8	NR	NR
Song	2009	259	51	Nr	Nr	9.8	NR	22.8	30.9
Young	2010	51	21	78	NR	8	NR	20	NR
Nagino	2010	50	50	54	NA	2	NA	30.3	NA
Igami	2010	293	111	NR	NR	NR	NR	23	51
Lee	2010	302	40	NR	NR	0	1.7	31.5	41.3
Hemming	2011	95	42	NR	NR	2	8	38	38
Nuzzo	2012	376	42	NR	NR	19	9	22.8	25.5
De Jong	2012	305	51	NR	NR	11.8	6.7	24	30
Tamoto	2013	49	36	58	76	2	7	59	51

Maddern GJ, et al. World J Surgery 2015

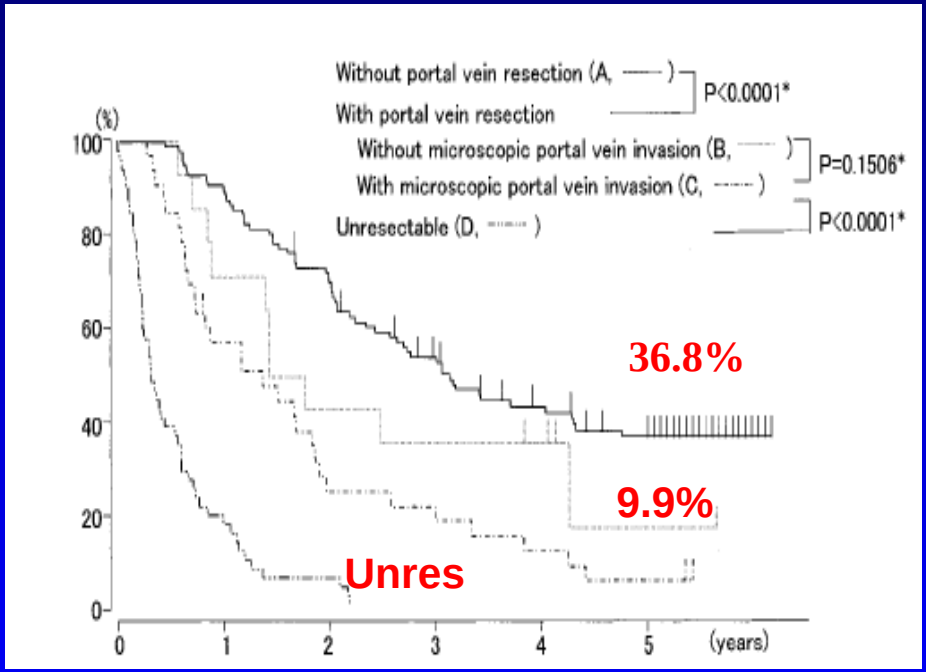
Hepatectomy With Portal Vein Resection for Hilar Cholangiocarcinoma

Audit of 52 Consecutive Cases

Tomoki Ebata, MD, Masato Nagino, MD,* Junichi Kamiya, MD,* Katsuhiko Uesaka, MD,* Tetsuro Nagasaka, MD,† and Yuji Nimura, MD**

TABLE 5. Multivariate Cox Regression Analysis of Prognostic Factors

Variable	Relative Risk	95% Confidence Interval	*P*
Histologic differentiation (moderate/poor)	2.57	1.44–4.61	0.0015
Lymph node metastasis (present)	1.89	1.16–3.07	0.0101
Macroscopic portal vein invasion (present)	2.18	1.09–4.35	0.0278



	3-year	5-year survival
PV (-)	53.6%	36.8%
PV (+)	26.4%	9.9%

Ebata T, et al. Ann Surg 2003

Surgical treatment of hilar cholangiocarcinoma in the "new era": the Nagoya University experience

Tsuyoshi Igami · Hideki Nishio · Tomoki Ebata · Yukihiro Yokoyama · Gen Sugawara · Yuji Nimura · Masato Nagino

- 2001 – 2008 428 pts with HCC
- 298 (70%) pts operated for cure
  - R0 n = 220 (74%)
  - R1 n = 70 (23%)
  - R2 n = 8 (3%)

- PVR (+): 111 (37%) pts
  - Mortality: 0%
  - PV thrombosis: 5 (2%) → re-laparotomy and thrombectomy

- HA (+): 53 (18%) pts
  - Mortality: 1 / 53 2 / 53 survived > 5 έτη

Igami T, et al. J Hepatobiliary Pancret Surg 2009

PORTAL VEIN RESECTION IN HCC

- Overall Mortality 6.8% (161 pts)
- Mortality:

PVR (+)	8.8%	
PVR (-)	4.2%	NS

- PVR (+) Poor prognostic factor
- Survival

	1 yr	3 yr	5 yr
PVR (-)	63%	39%	30%
PVR (+)	42%	17%	14%
Unres	15%	0%	0%

p<0.001

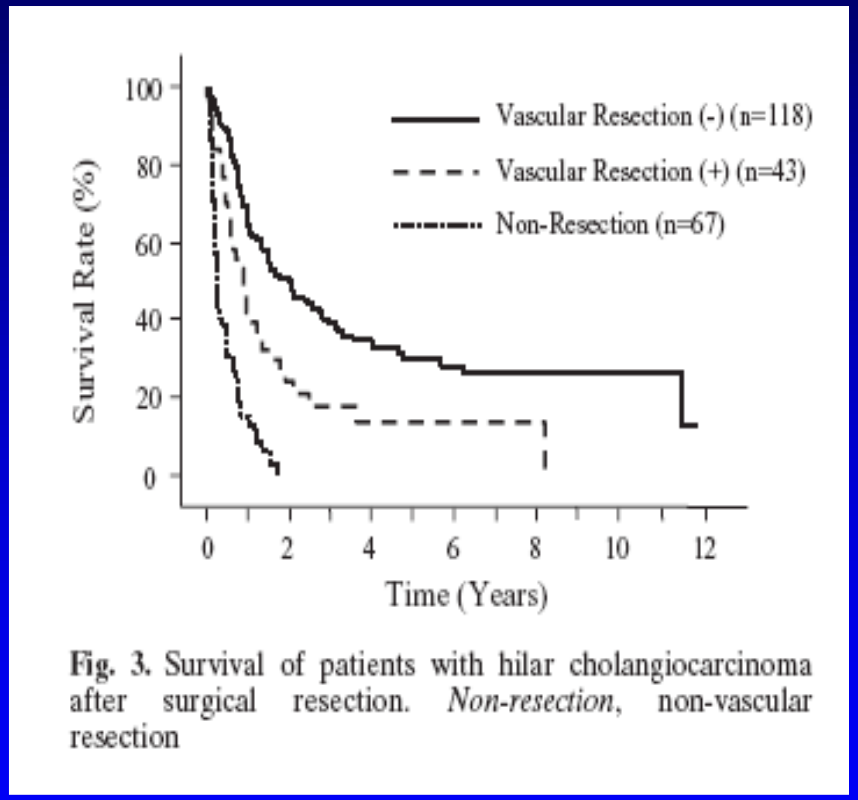
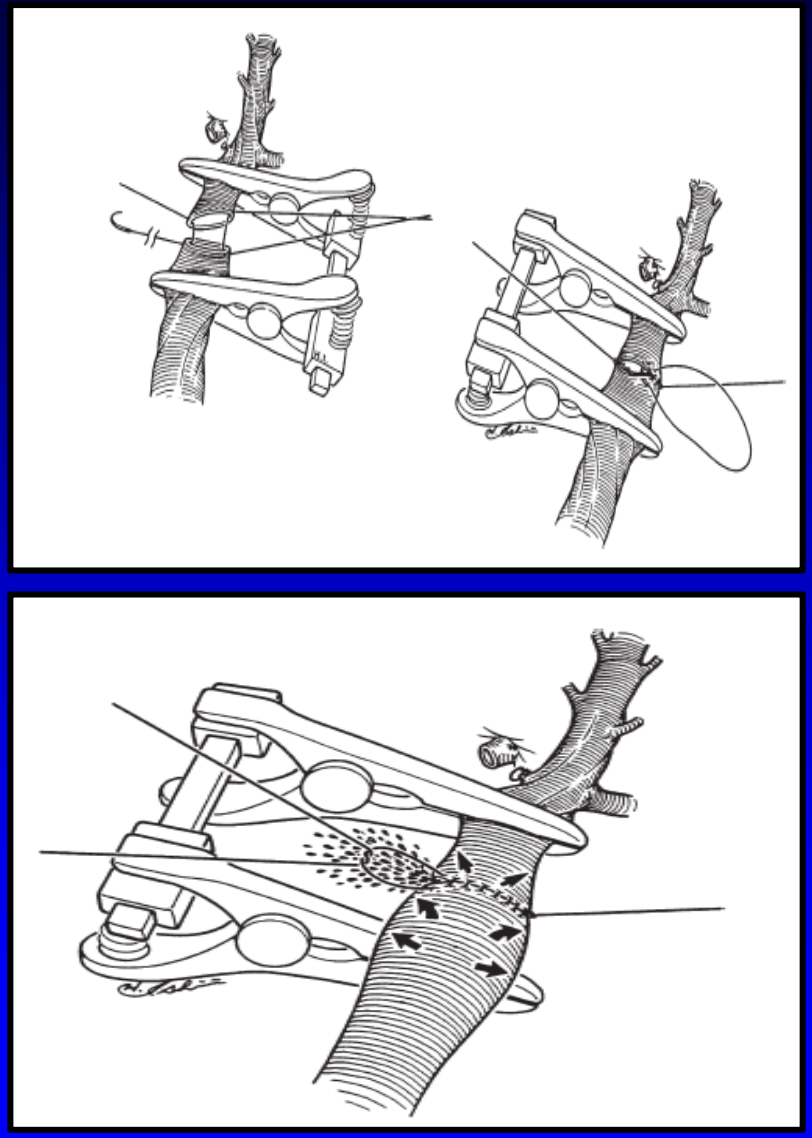


Fig. 3. Survival of patients with hilar cholangiocarcinoma after surgical resection. *Non-resection*, non-vascular resection

Miyazaki M, et al. Surgery 2007

PORTAL VEIN RESECTION IN HCC

- Before or After Hepatectomy
- End-to-end Anastomosis
- Autologous Vein graft
- Continuous 6-0 Prolene
- No growth factors
- No prostaglandin E1
- No iv heparin

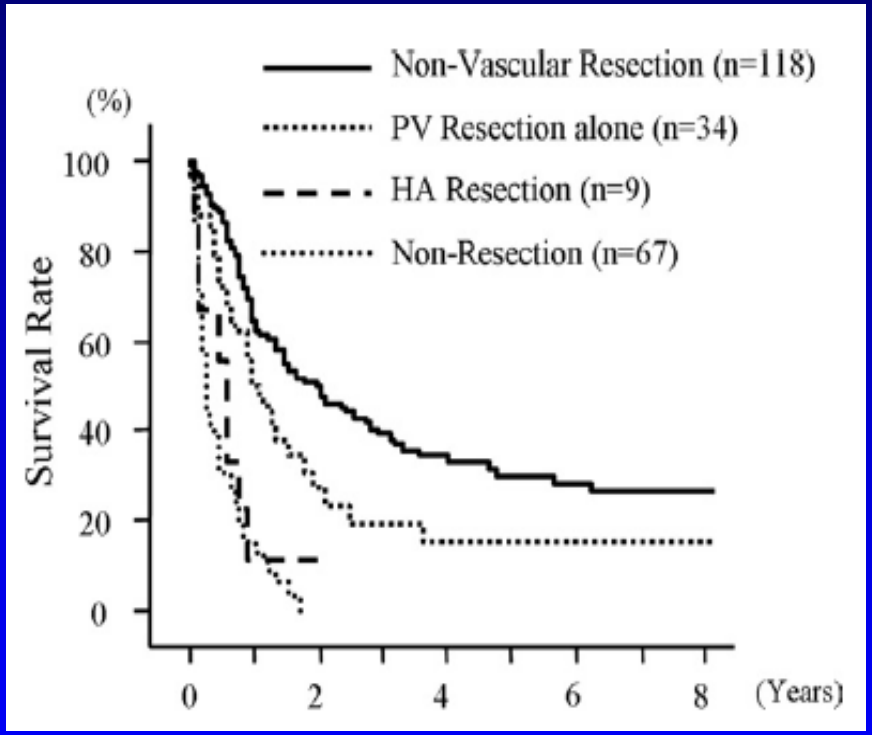


Nagino M, et al. Ann Surg 2012

HEPATIC ARTERY RESECTION IN HCC

- Mortality rates

Madariaga 1998: *55%*
Gerhards 2000: *56%*
Miyazaki 2007: *33%*
Nagino 2010: *5%*



Nagino M, et al. Ann Surg 2010
Miyazaki M, et al. J Hepatobiliary Pancreat Surg 2007

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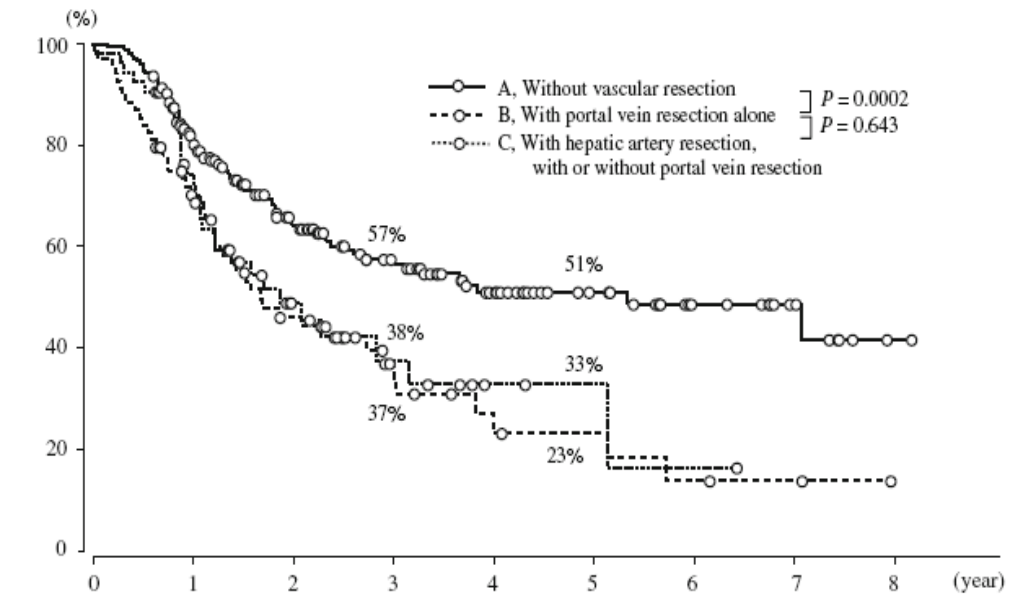
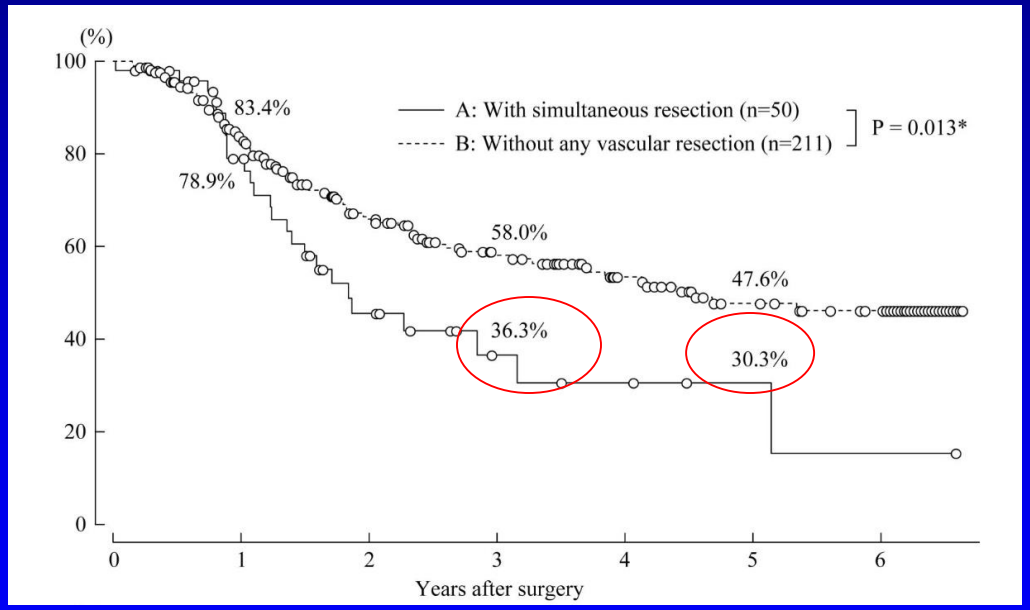


Igami T, et al. J Hepatobiliary Pancret Surg 2009

Hepatectomy With Simultaneous Resection of the Portal Vein and Hepatic Artery for Advanced Perihilar Cholangiocarcinoma

An Audit of 50 Consecutive Cases



Nagino M, et al. Ann Surg 2010

HEPATIC ARTERY RESECTION IN HCC

- End-to-end anastomosis
- Graft: GDA
  Gastroepiploic v and/or artery
- PV Arterialization
- Thrombosis!!!
  - Liver Ischemia
  - Abscess
  - Hepatico-J rupture
- PV + HA resection/reconstruction

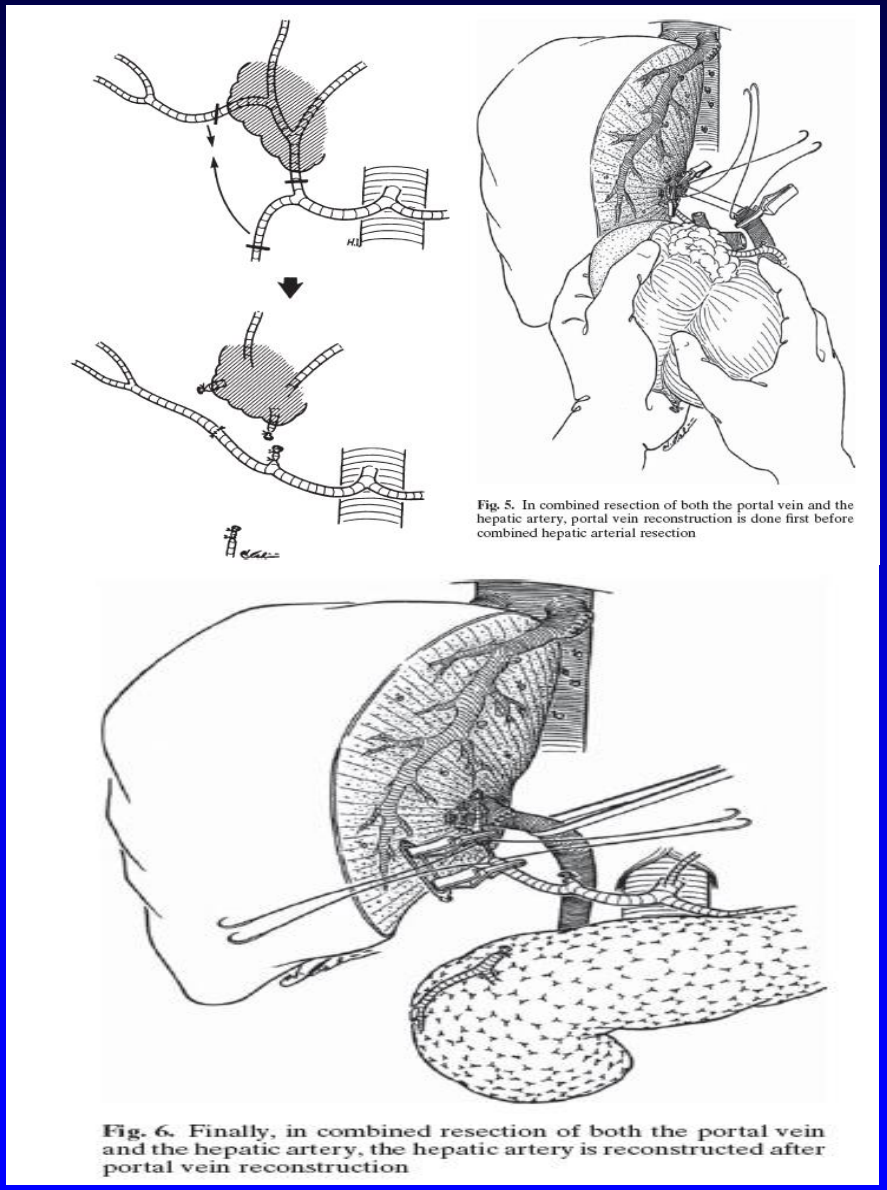
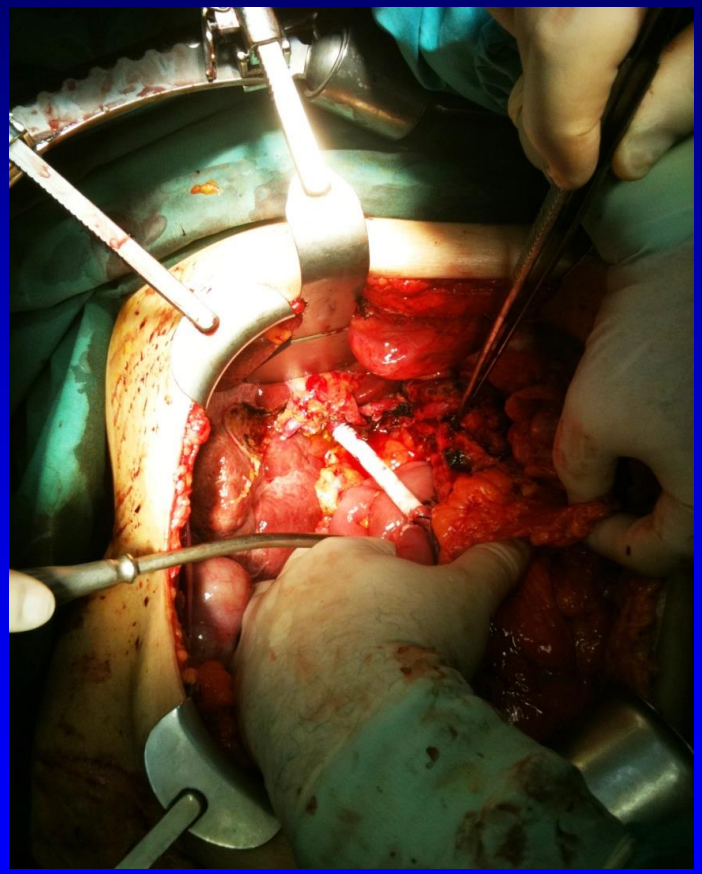


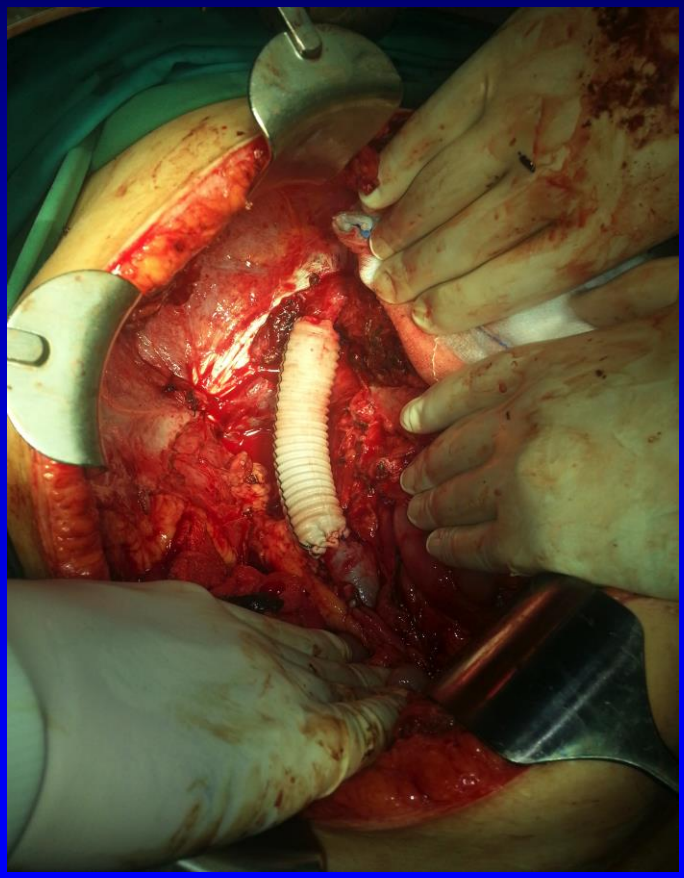
Fig. 5. In combined resection of both the portal vein and the hepatic artery, portal vein reconstruction is done first before combined hepatic arterial resection

Fig. 6. Finally, in combined resection of both the portal vein and the hepatic artery, the hepatic artery is reconstructed after portal vein reconstruction

Miyazaki M, et al. J Hepatobiliary Pancreat Surg 2007

PV – IVC Resection for the treatment of HCC





by Dimitris P. Korkolis, MD, PhD

“BERLIN’S CONCEPT”

- Strongest determinant of Survival: *Surgical Radicality!!!*
- R0 resection after Right trisectionectomy: 65% p<0.05
- R0 resection: 1-yr 5-yr survival:
  PV(-): 85% 0%
  PV(+): 100% 65% p<0.001
- R0 resection: 5-yr survival
  Right trisegm and PV(-): 52%
  Right trisegm and PV(+): 72% p<0.05
- Mortality: 17%!!!

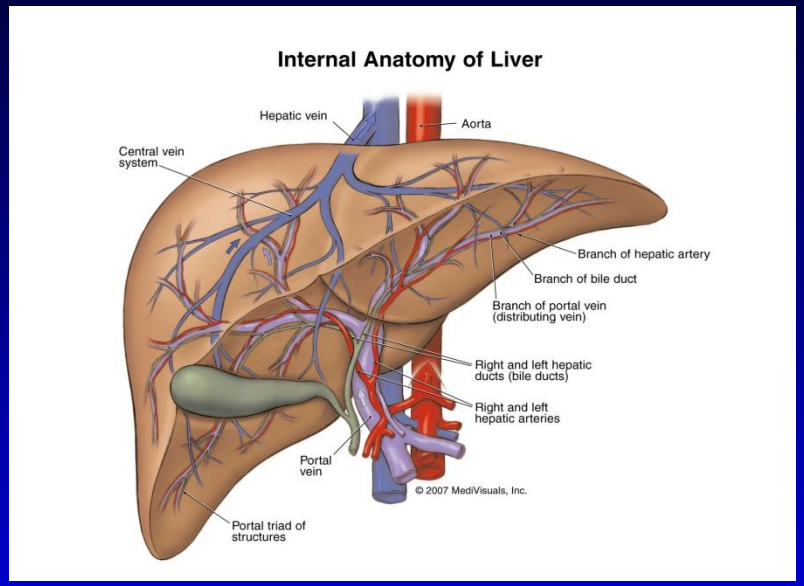
Peter Neuhaus, et al. Ann Surg 2008
Peter Neuhaus, et al. Langenbecks Arch Surg 2003

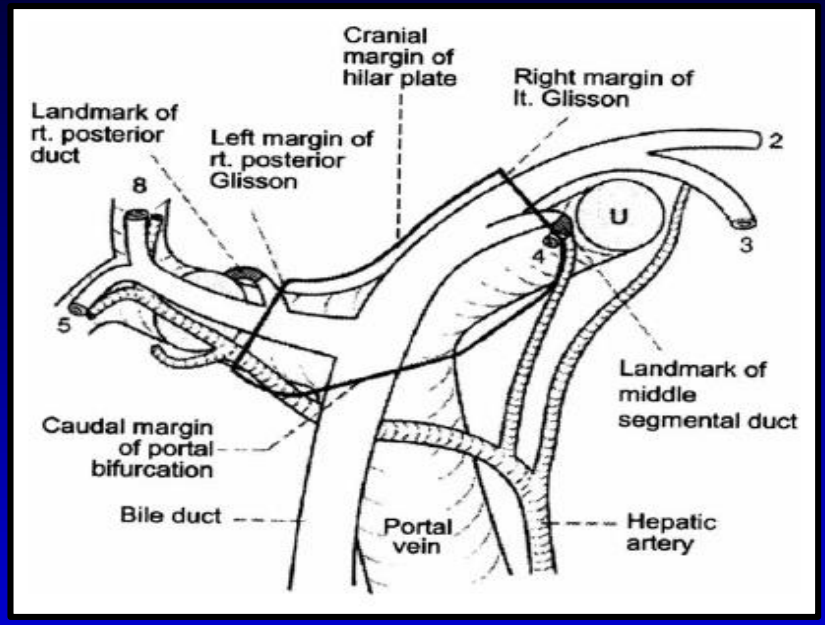
“NO – TOUCH TECHNIQUE”

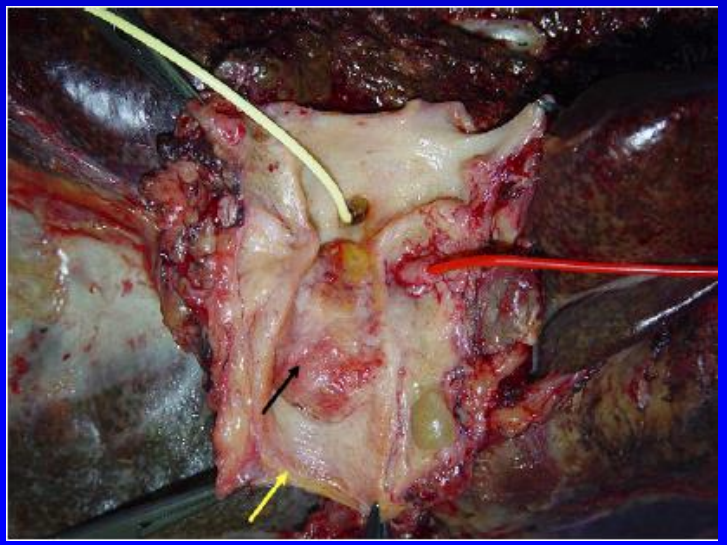
- Right Trisectionectomy with en-block portal vein and bile duct resection
- Wide negative resection margins> 2 cm
- No manipulation between the tumor, RHA and RPV
- No microscopic tumor dissemination
- Stable surgical anatomy of segments II - III
- Avoids vascular kinking after R Trisectionectomy and caudate lobectomy
- Prerequisites: PTC – PTBD of the remnant liver
  PVE

P. Neuhaus. HPB 2008

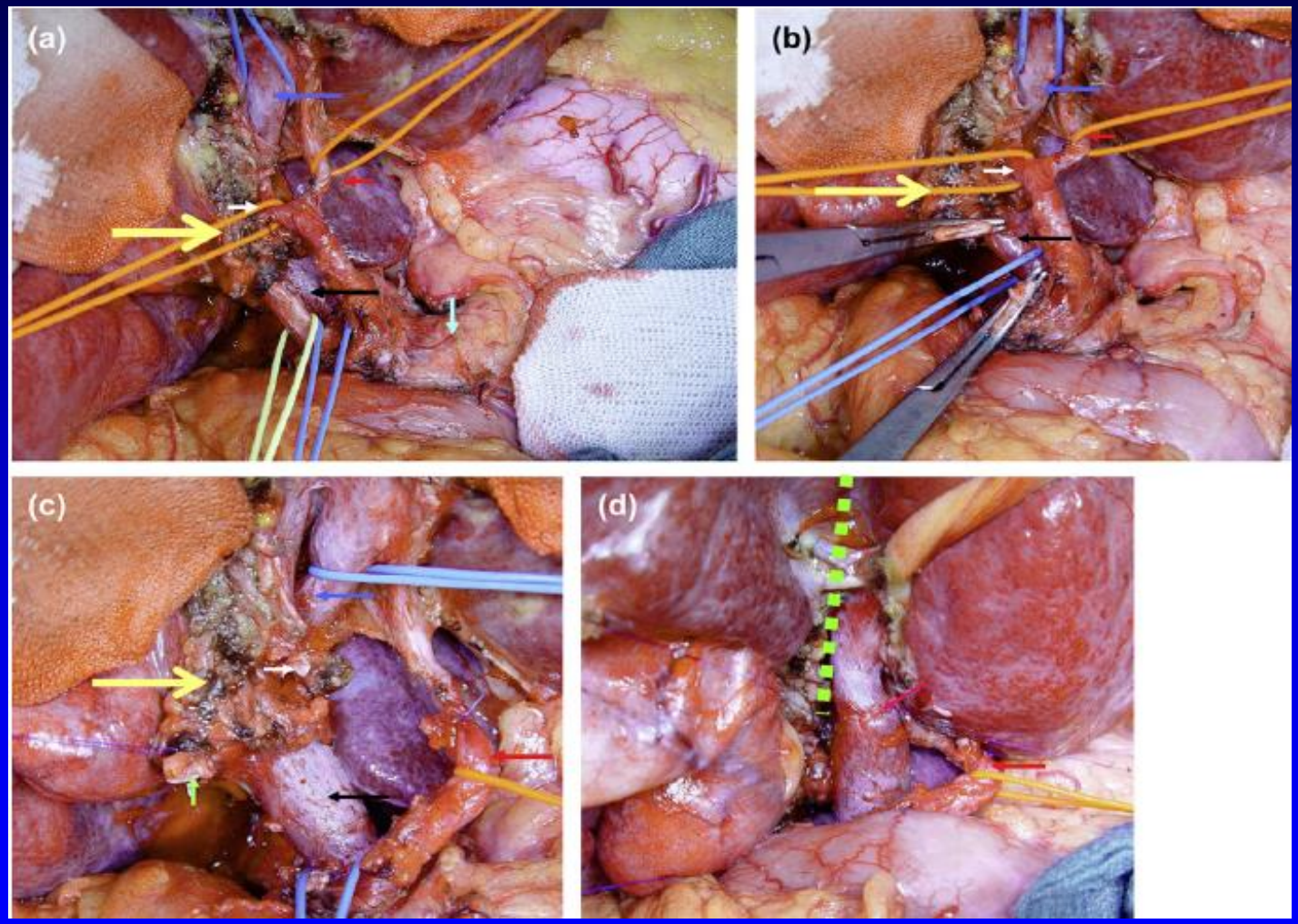
“NO – TOUCH TECHNIQUE”







“NO – TOUCH TECHNIQUE”



P. Neuhaus. HPB 2008

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EJSO 34 (2008) 263–271
www.ejso.com

Review

Radical surgery for hilar cholangiocarcinoma

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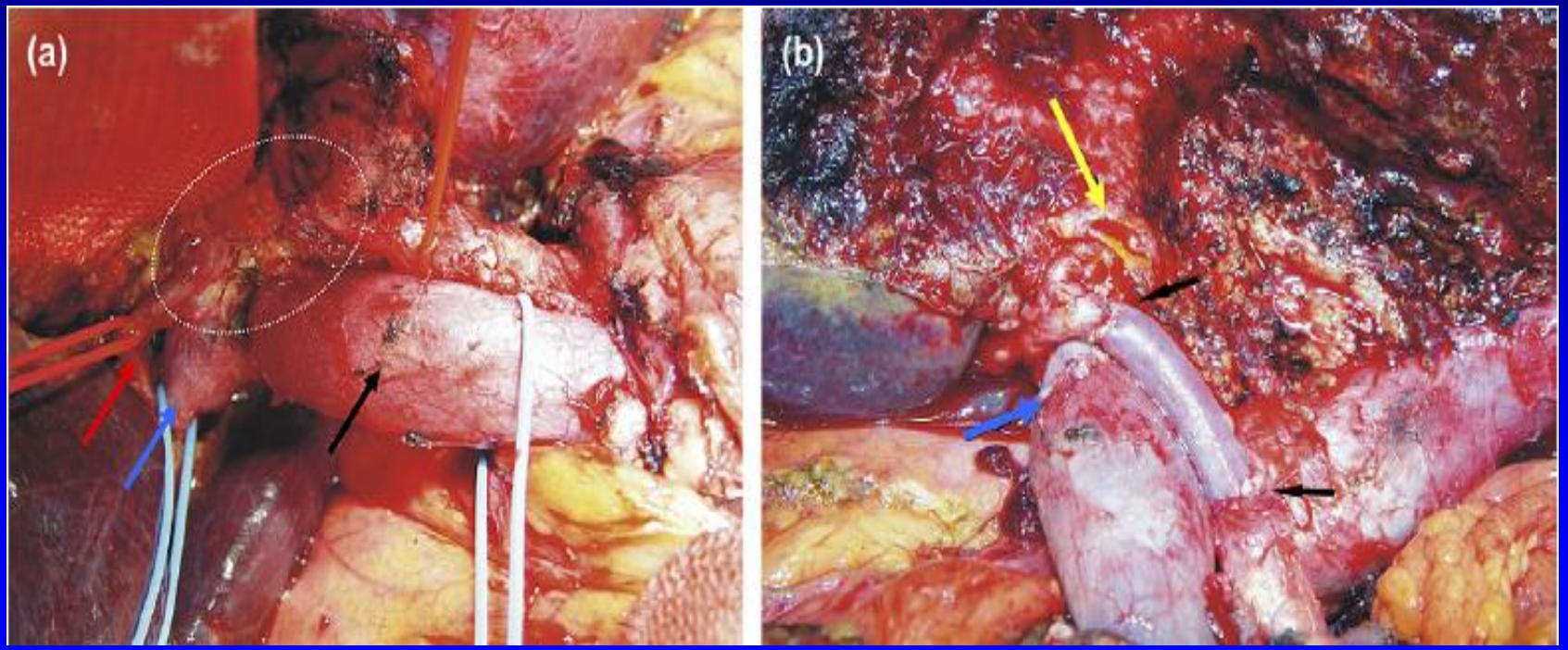
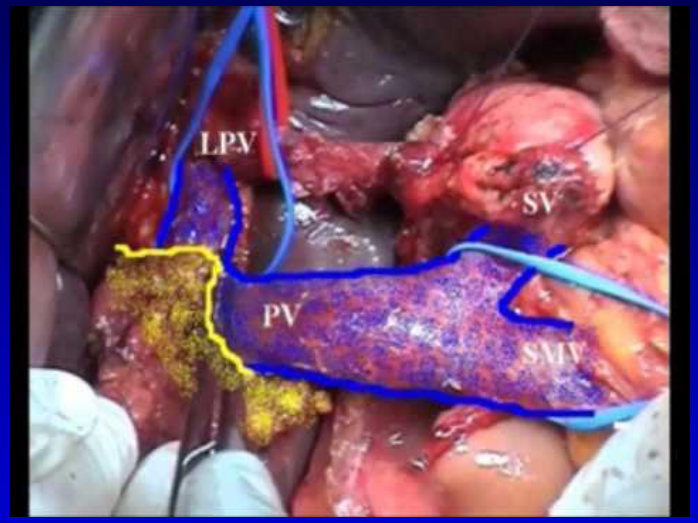
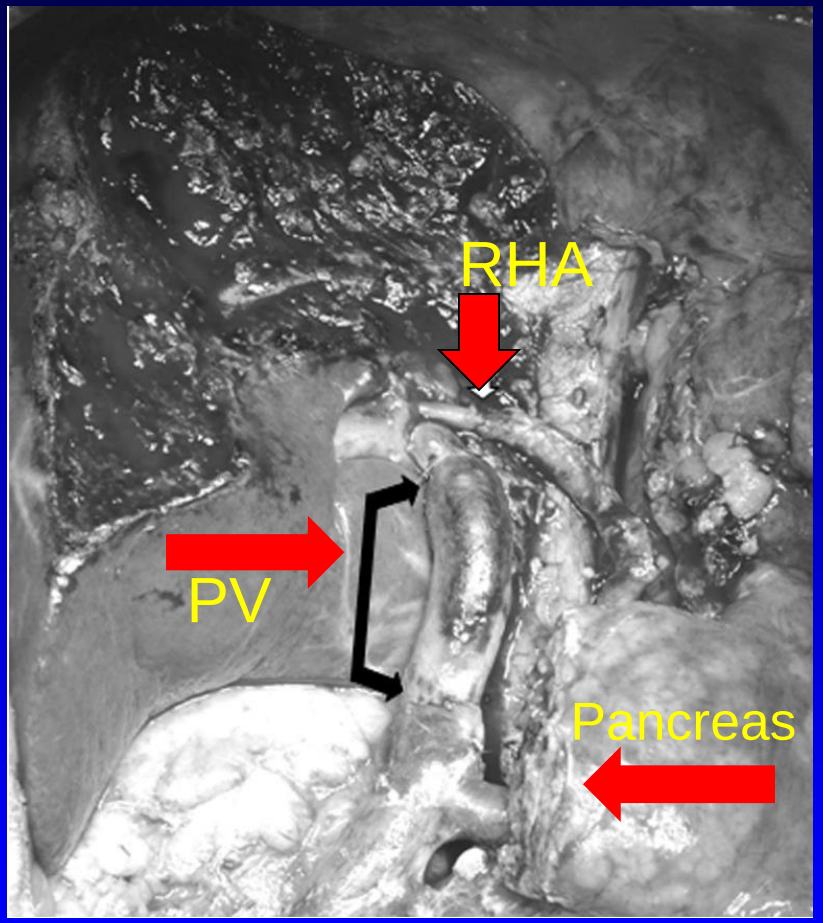


Jonas S, et al. EJSO 2008

Hepatopancreatoduodenectomy



- Diffusely infiltrating tumors of the whole extrahepatic bile ducts
- Downward superficial spreading
- Bulky nodal metastases of the pancreatoduodenal region
- Mortality <5%



Matsumoto N, et al. Br J Surg 2014

Kaneoka Y, et al. World J Surg 2010

Hemming AW, et al. J Am Coll Surg 2012

Conclusions

- Treatment of HCC remains challenging
- Strategy of surgical resection has improved over years
- Some consensus have been reached:
    a. R0 margin achievement
    b. Combination of partial hepatectomy
    c. Routine caudate lobe resection
    d. Portal vein resection when involved by tumor
- Controversial issues
- Improvement of imaging technology
- RCTs