

# Patient Journey

Approccio personalizzato al  
paziente e esperienze a  
confronto:  
Epatocarcinoma e  
Colangiocarcinoma

**01 Febbraio 2024**

**VERONA**

**CROWNE PLAZA**

**Via Belgio, 16**

**Colangiocarcinoma**

**Il ruolo del chirurgo**

**Prof. Alfredo Guglielmi**

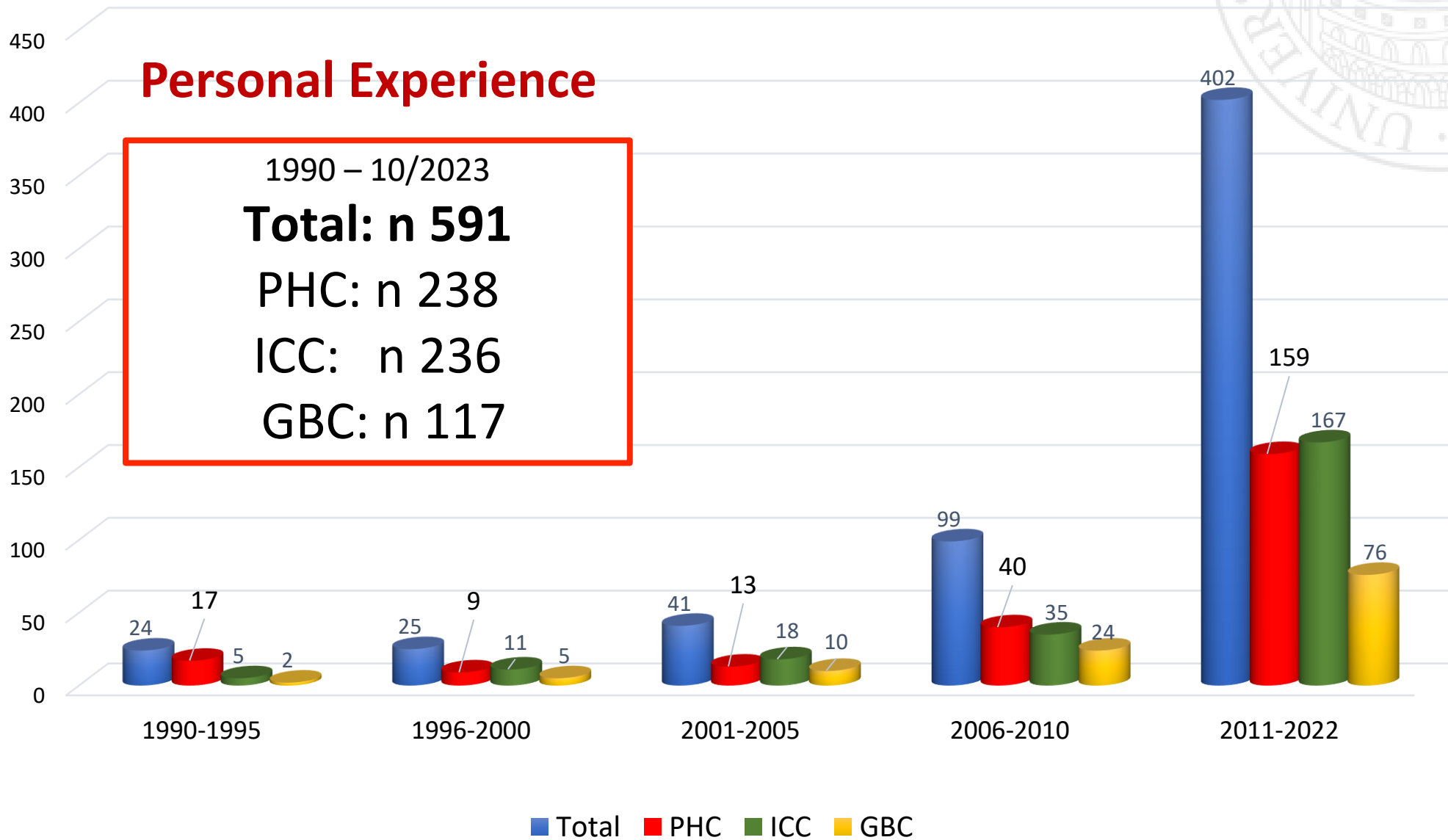
**AIGOM**

ASSOCIAZIONE ITALIANA  
GRUPPI ONCOLOGICI MULTIDISCIPLINARI

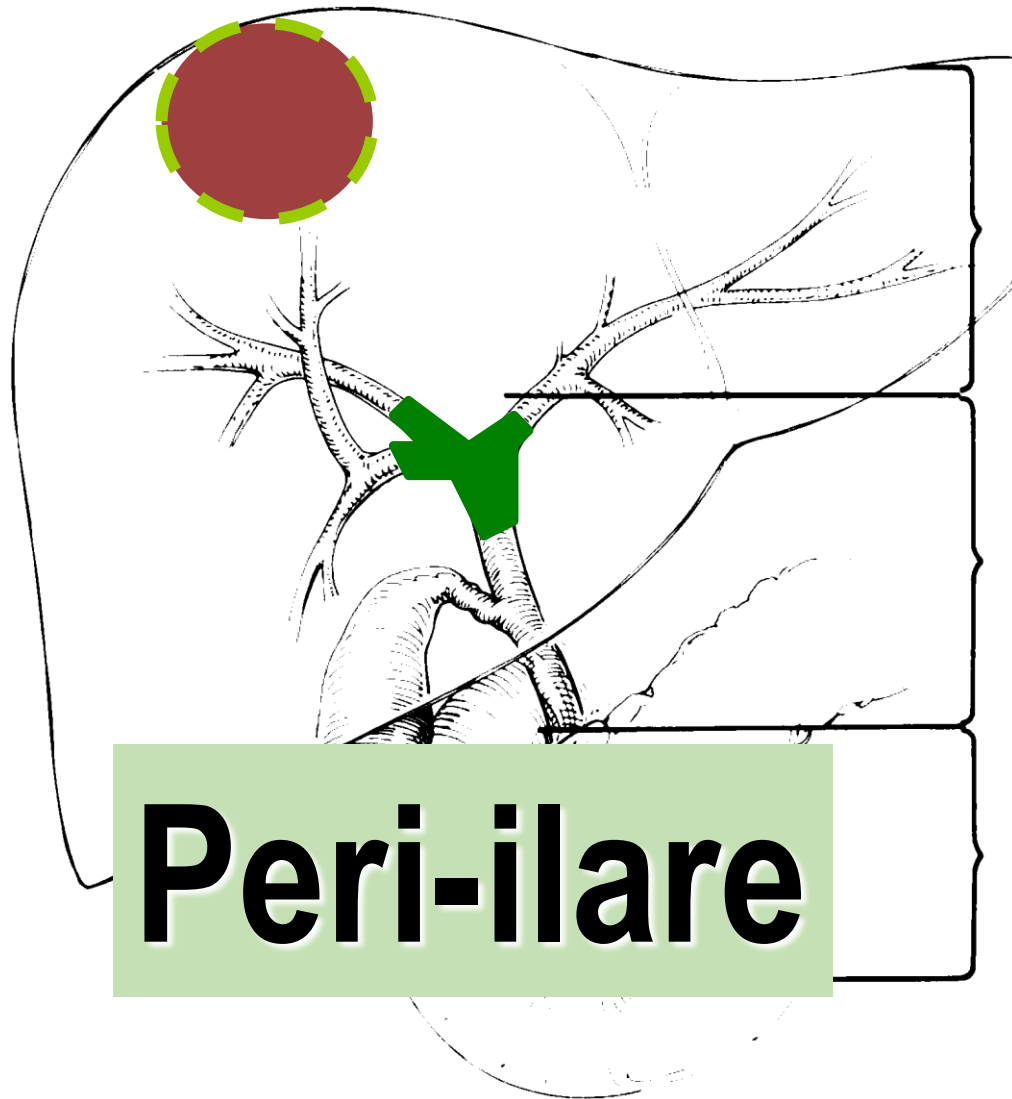


University of Verona  
Department of Surgery  
General and Hepatobiliary Surgery  
GB Rossi Hospital  
Prof. Alfredo Guglielmi

# SURGERY OF CHOLANGIOCARCINOMA



# Definizione



**Intraepatico**

**Ilare**

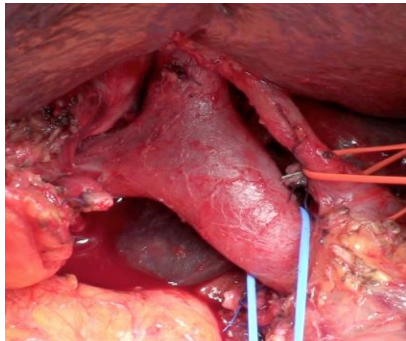
**Distale**

Nakeeb AnnSurg 1996;224(6):463-75

Khan Gut 2002; 51(suppl VI):vi1-vi9

Sandhu CurrGastroenterolRep 2008;10:43-52

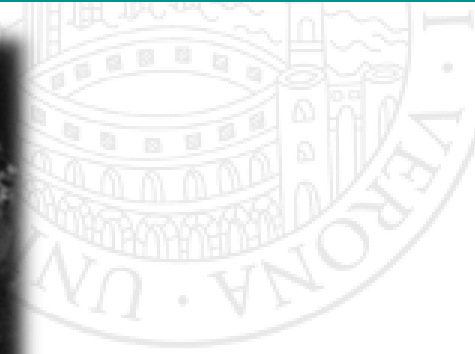
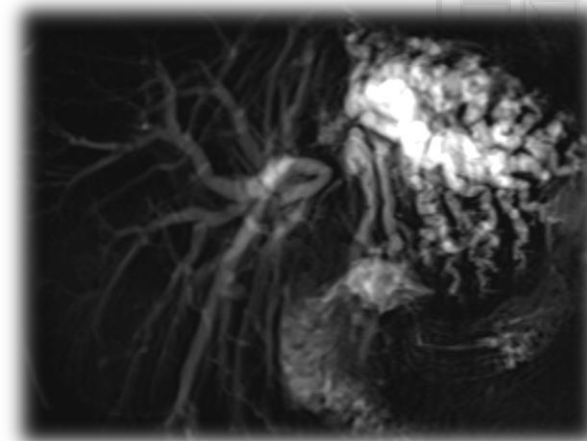
# Surgery of Cholangiocarcinoma



	INTRAHEPATIC	PERIHILAR
Major hepatectomy	60-80%	<b>85-97%</b>
Bile duct resection	0-10%	<b>95-100%</b>
Pancreatic resection	0%	0-5%
Vascular resection	V.cava 2-17% Portal 9-15%	Artery 4-15% Portal <b>20-35%</b>

Nagino M, Ann Surg - 2013; Ercolani G, EJSO - 2015; Ruzzenente A, Eur Rev Pharm Sci – 2015; Reames BN, J Surg Onc 2017; Conci S, Eur J Surg Oncol 2017; Bartsch F, Int J Surg 2018

# Surgical Results of Cholangiocarcinoma



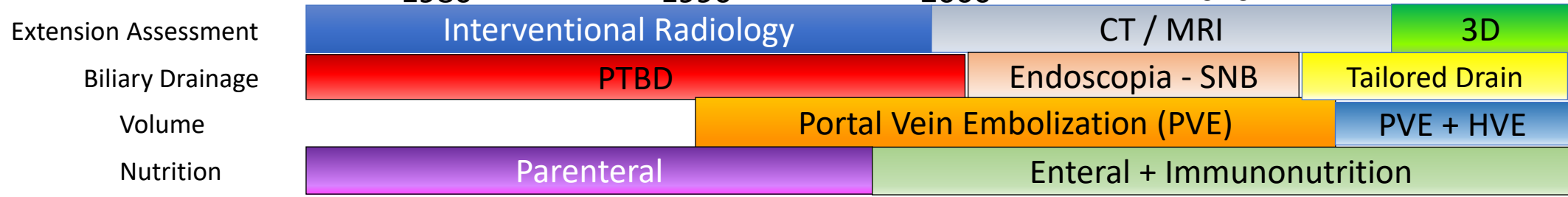
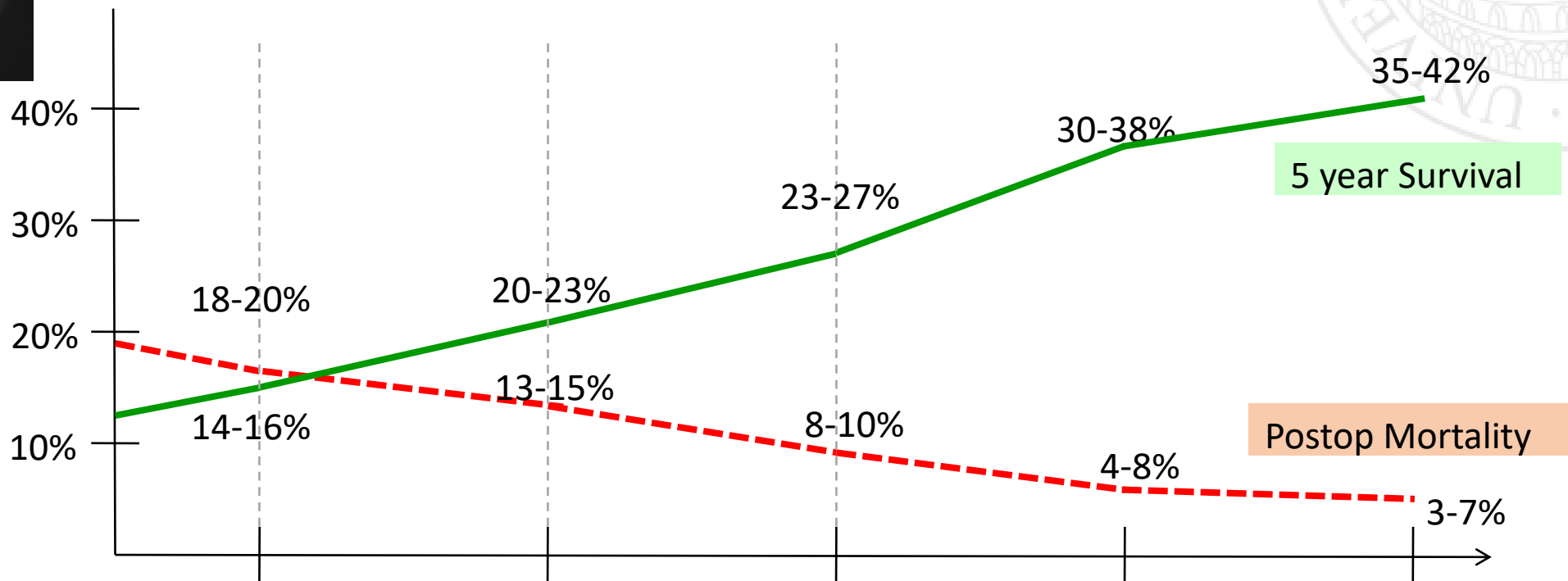
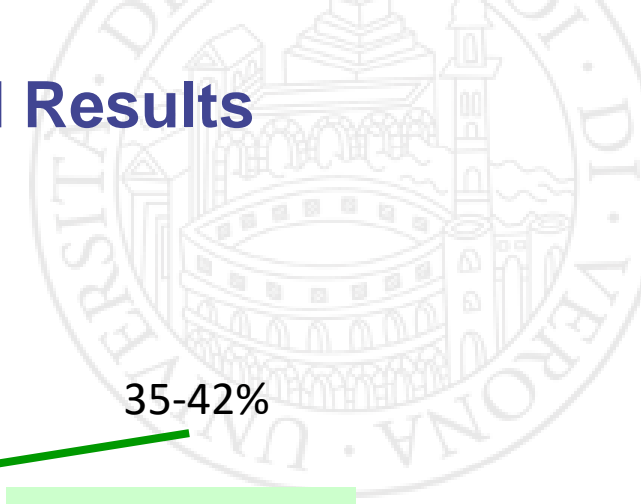
	Morbidity	Mortality	5y. Survival
<b>INTRAHEPATIC</b>	2 - 4%	1-2%	30-40%
<b>PERIHILAR</b>	40-70%	2-15%	20-38%

Guglielmi A, World J Surg – 2009; Ercolani G, Eur J Surg Oncol – 2015;  
Conci S, Eur J Surg Oncol 2017; Conci S – Ann Surg Oncol – 2018



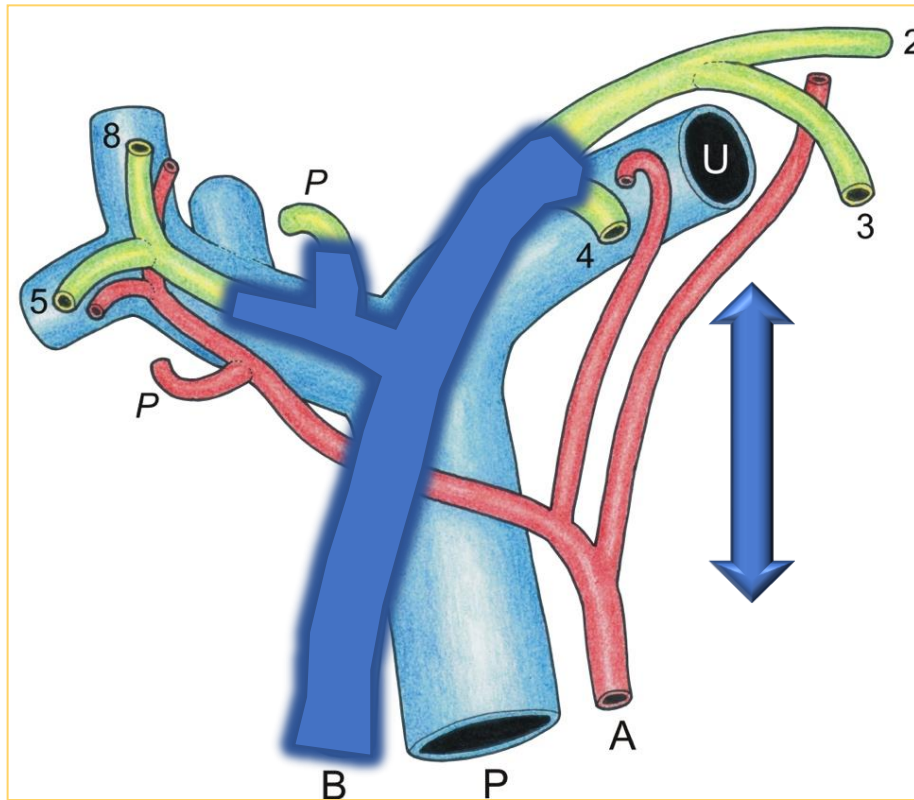


# Evolution of Preoperative Management and Results of Perihilar Cholangiocarcinoma

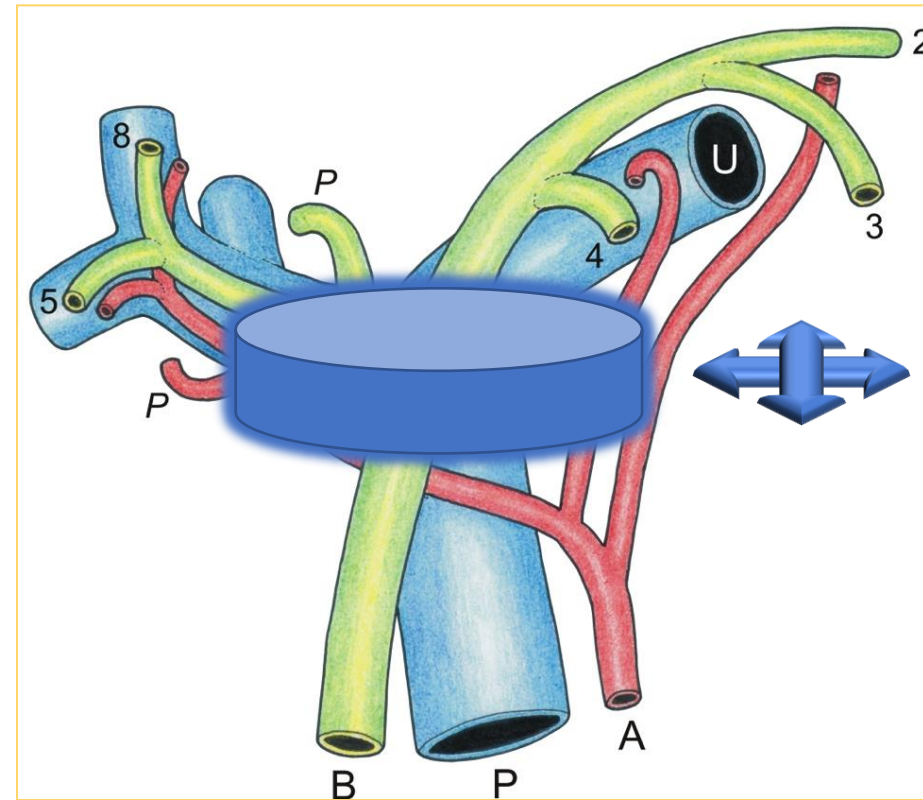


# Evaluation of tumour extension

## Biliary Extension (longitudinal)



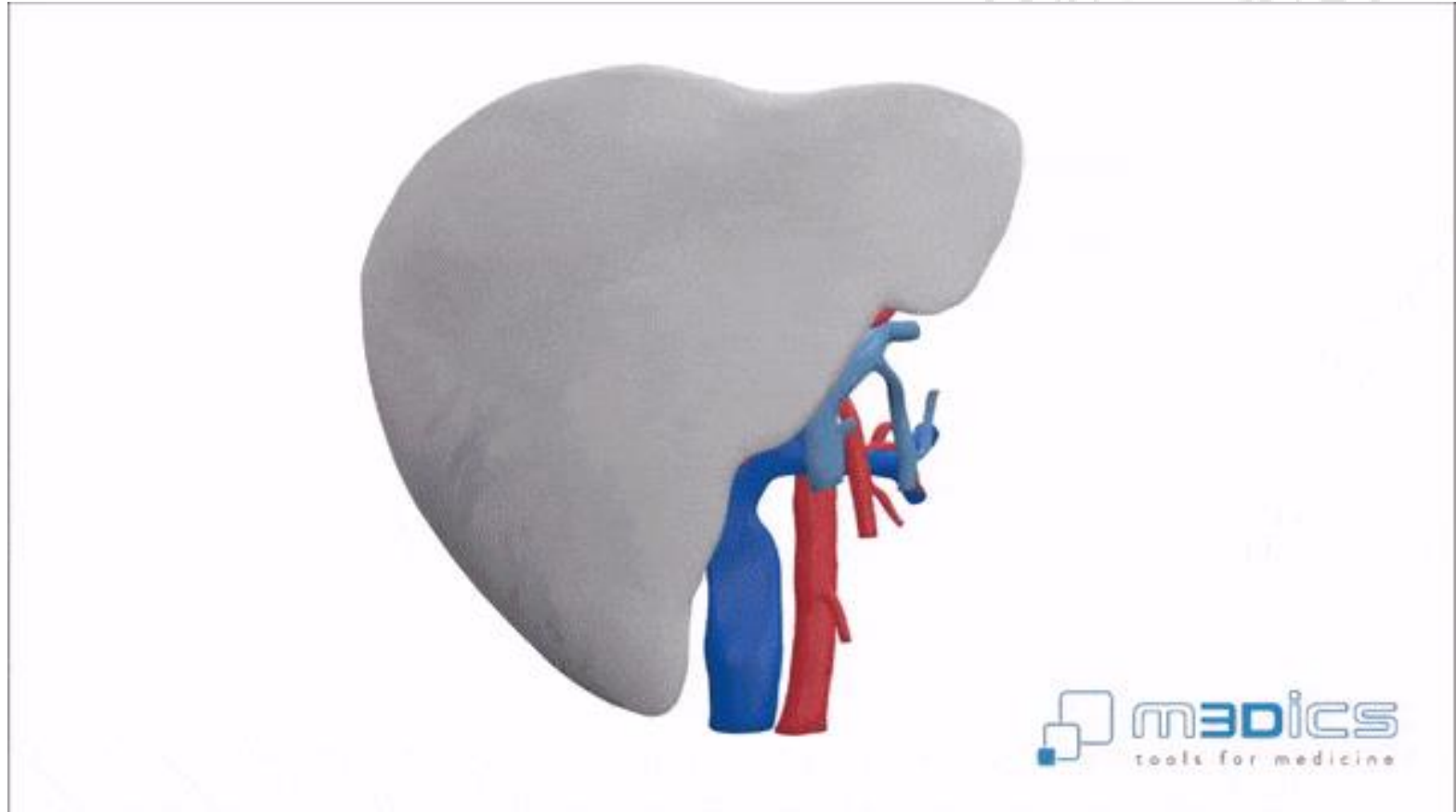
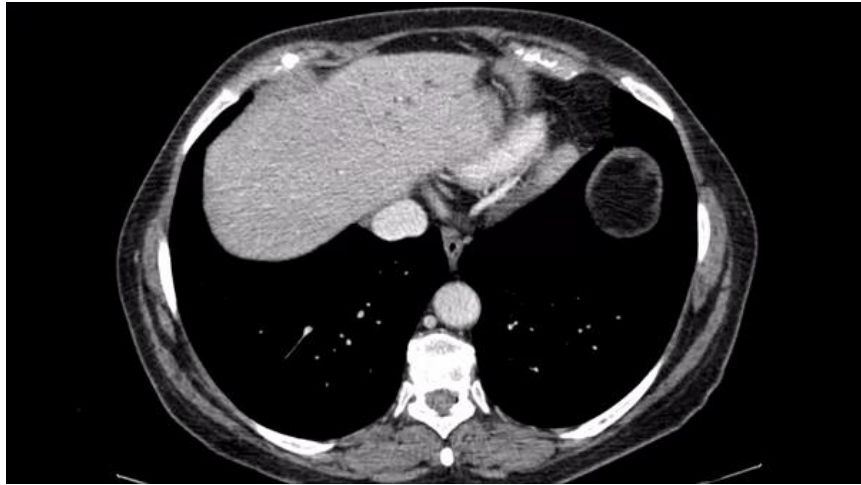
## Vascular Invasion (radial)



# Preoperative Management: Diagnosis from 2D to 3D

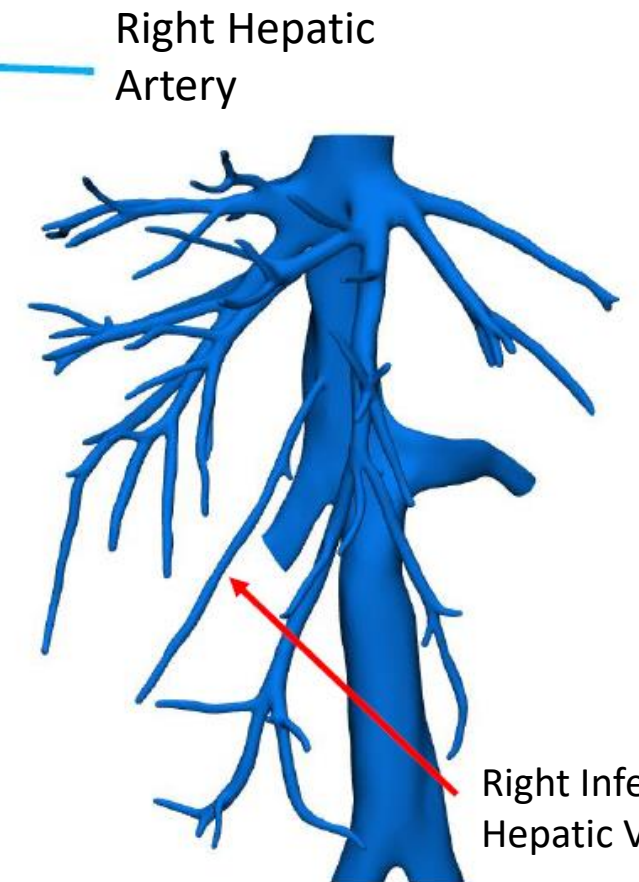
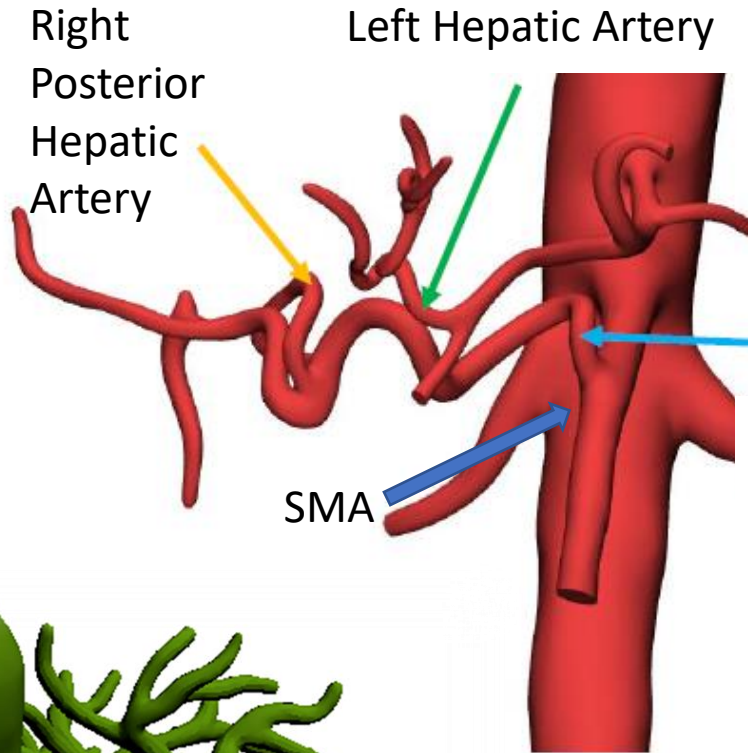
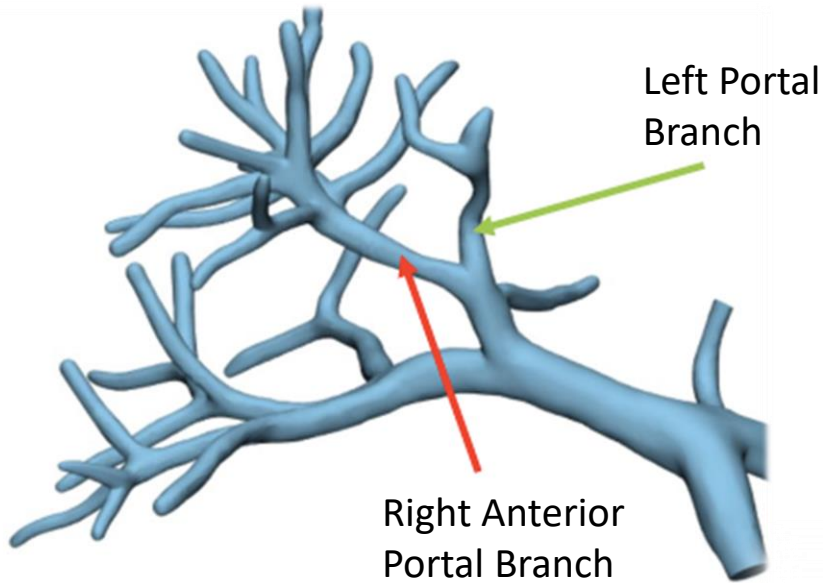
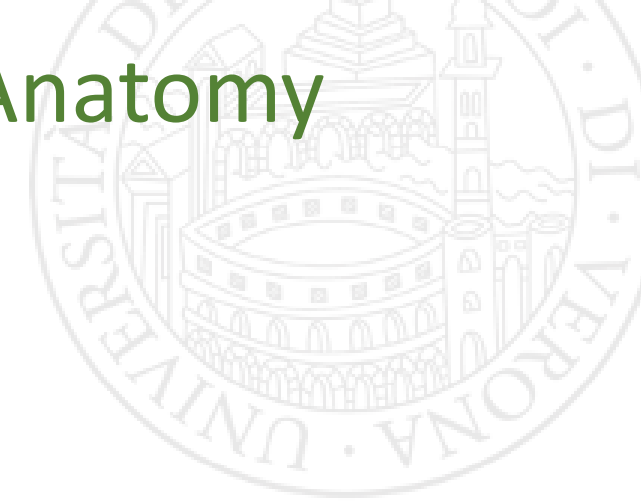


**CT Scan before biliary drainage**

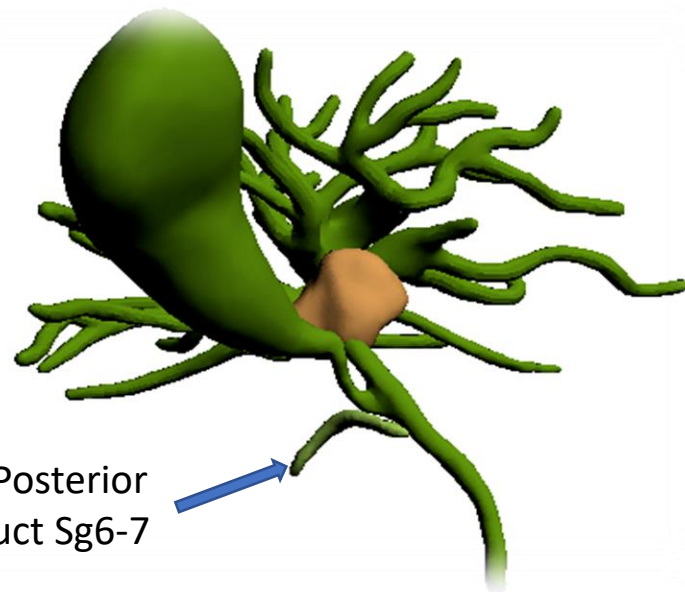




# 3D Rendering: Vascular and Biliary Anatomy



*Anatomical Variants*

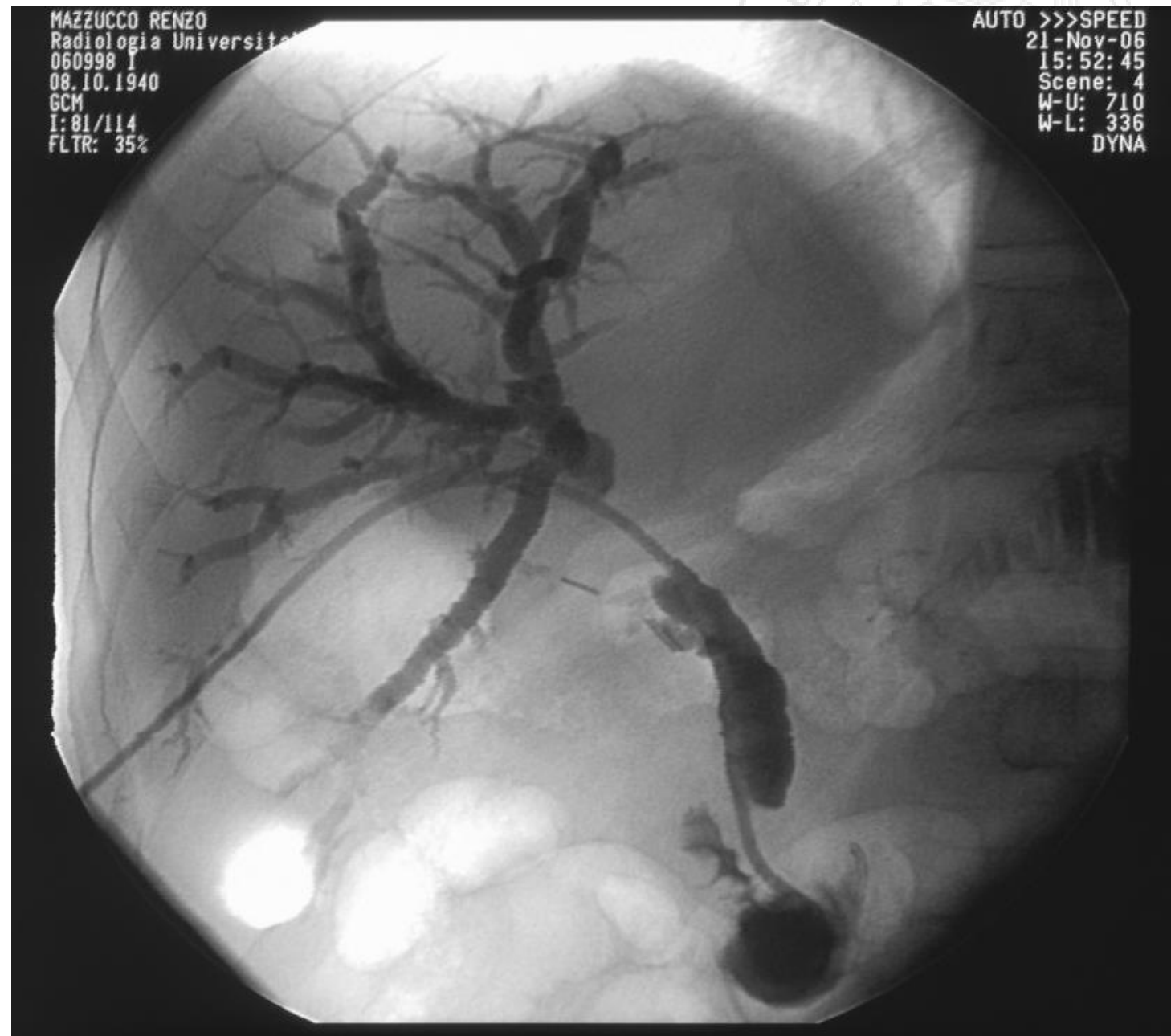


Right Posterior Bile Duct Sg6-7

Right Inferior Hepatic Vein

# Il Drenaggio Biliare

- Percutaneo
- Endoscopico
- Naso-biliare





# Role of Preoperative Biliary Drainage in Jaundiced Patients Who Are Candidates for Pancreatoduodenectomy or Hepatic Resection

## Highlights and Drawbacks

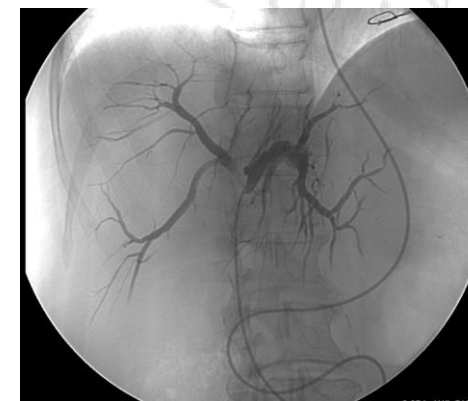
*Calogero Iacono, MD, Andrea Ruzzenente, MD, PhD, Tommaso Campagnaro, MD, Luca Bortolasi, MD, Alessandro Valdegamberi, MD, and Alfredo Guglielmi, MD*



Percutaneous



Endoscopic



Naso-biliary Tube

### Minor Complications

*Cholangitis, Obstruction, Displacement*

**9-31%**

**48-65%**

**5-38%**

### Major Complications

*Bleeding, Perforation, Pancreatitis*

**5-15%**

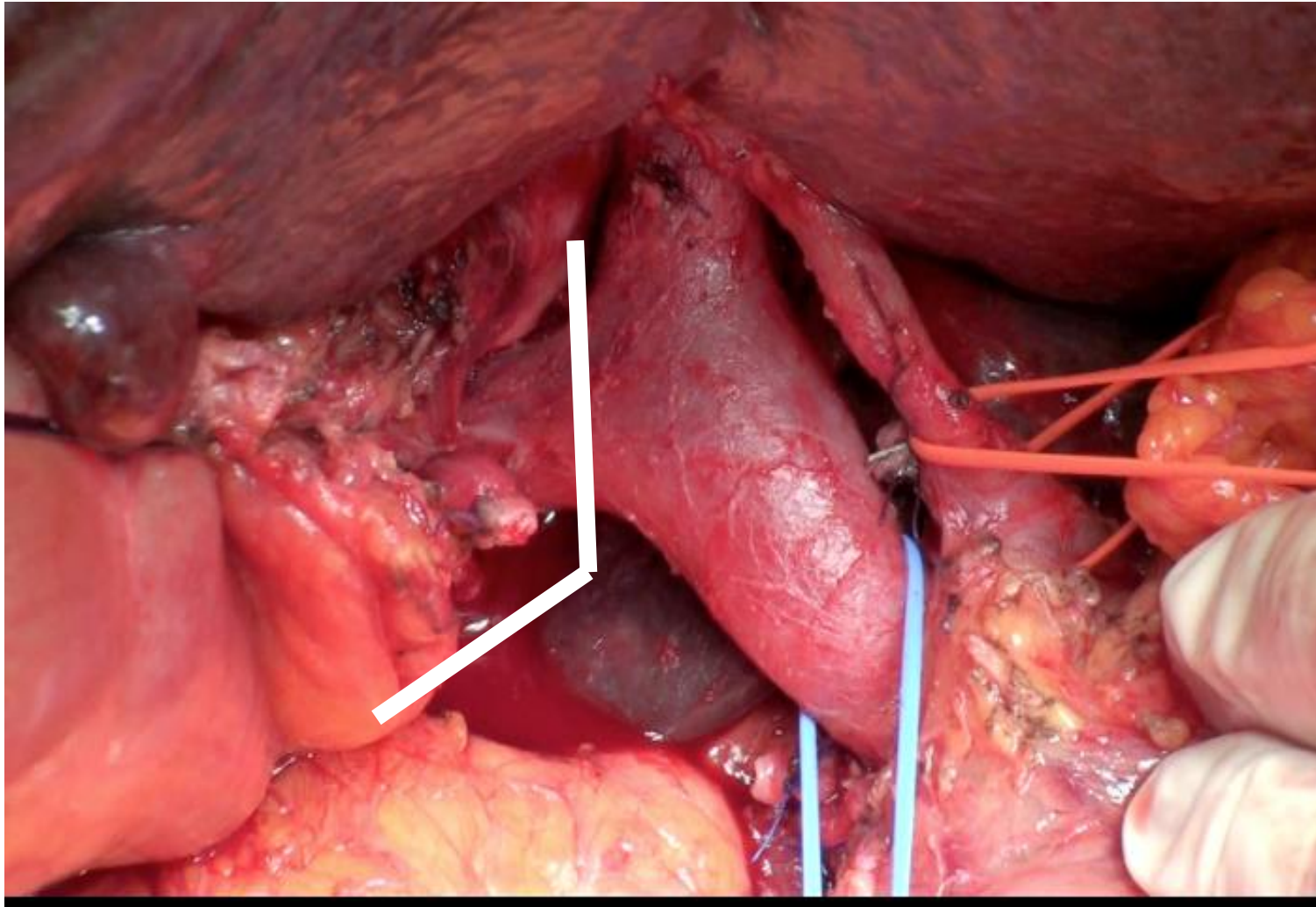
**0-5%**

**2-7%**



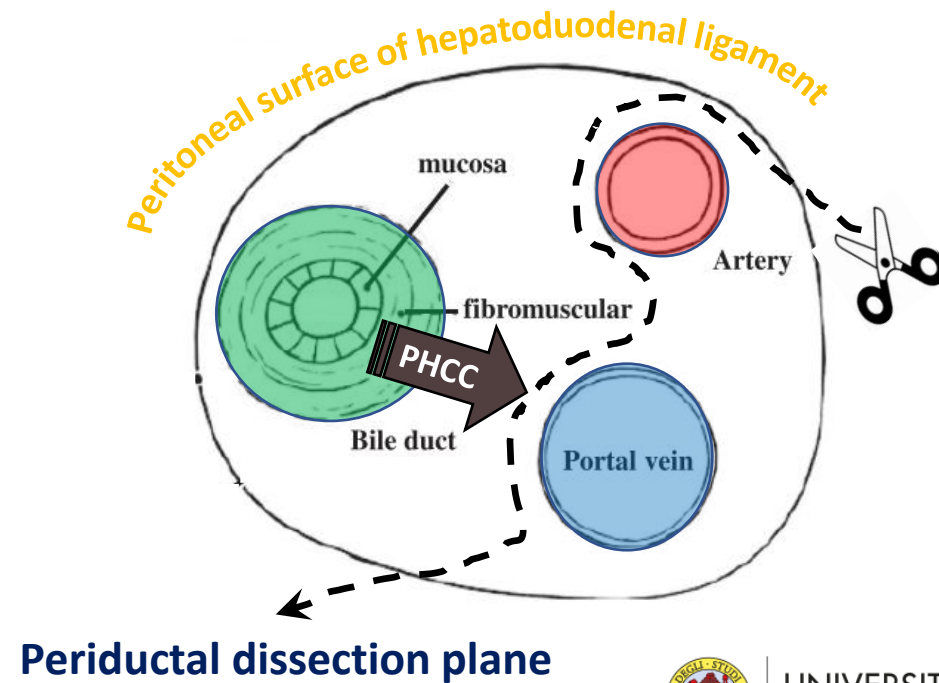
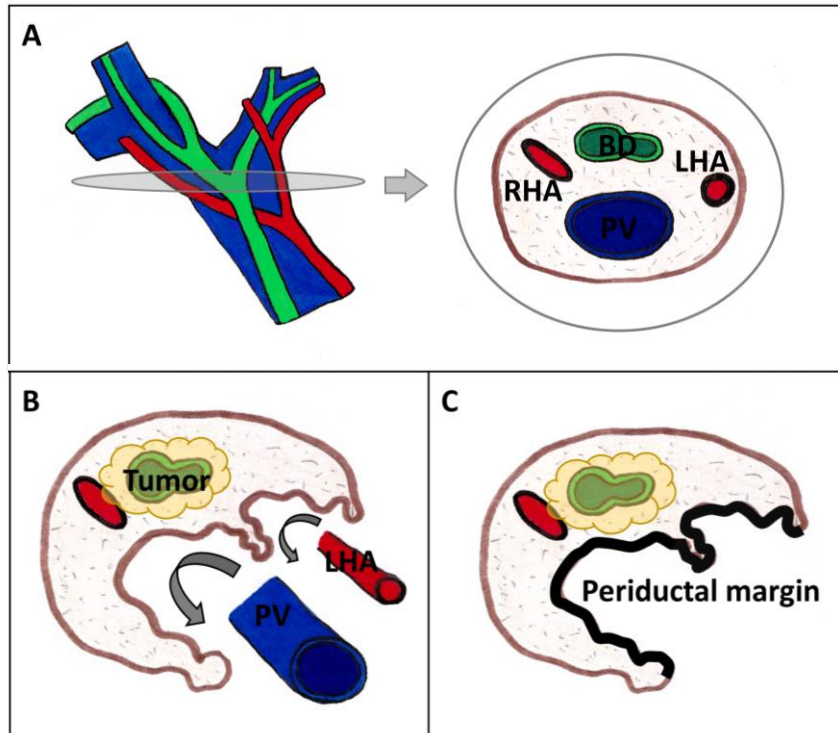
**Which technique of surgery ?**

**No Touch Technique**



# Toward R0 surgery...Identification of Radial Margin

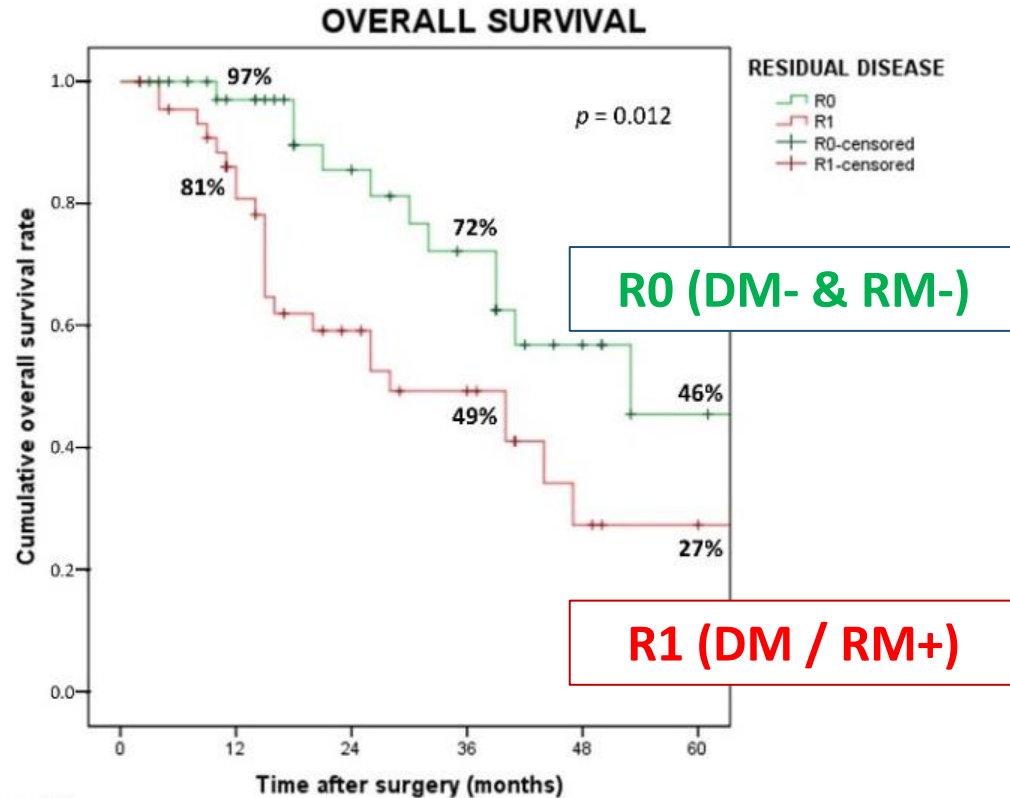
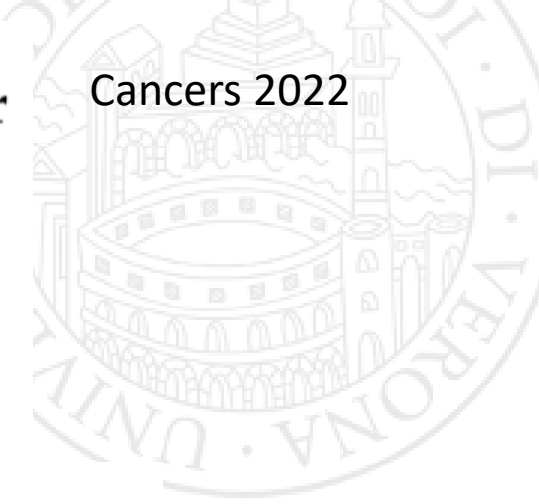
The assessment of RM status is a challenging issue





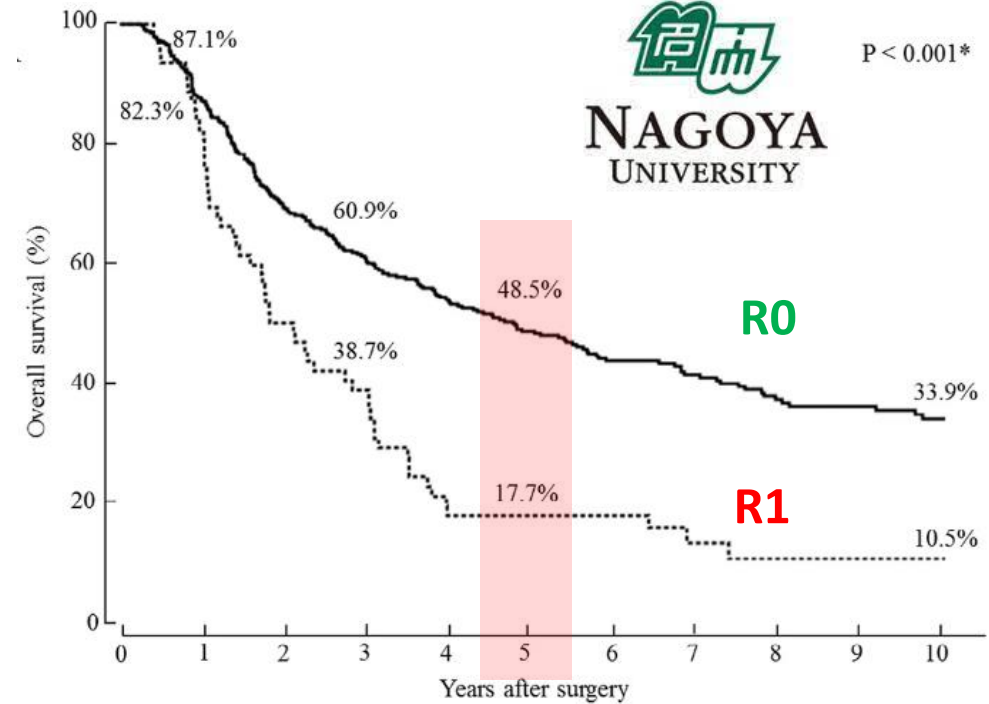
# The Prognostic Role of True Radical Resection in Perihilar Cholangiocarcinoma after Improved Evaluation of Radial Margin Status

Mario De Bellis <sup>1</sup>, Maria Gaia Mastrosimini <sup>2</sup>, Simone Conci <sup>1</sup>, Sara Pecori <sup>2</sup>, Tommaso Campagnaro <sup>1</sup>, Claudia Castelli <sup>2</sup>, Paola Capelli <sup>2</sup>, Aldo Scarpa <sup>2</sup>, Alfredo Guglielmi <sup>1,†</sup> and Andrea Ruzzenente <sup>1,\*,†</sup>



Patients at risk

	0	12	24	36	48	60
R0	40	31	15	3		
R1	45	31	13	1		

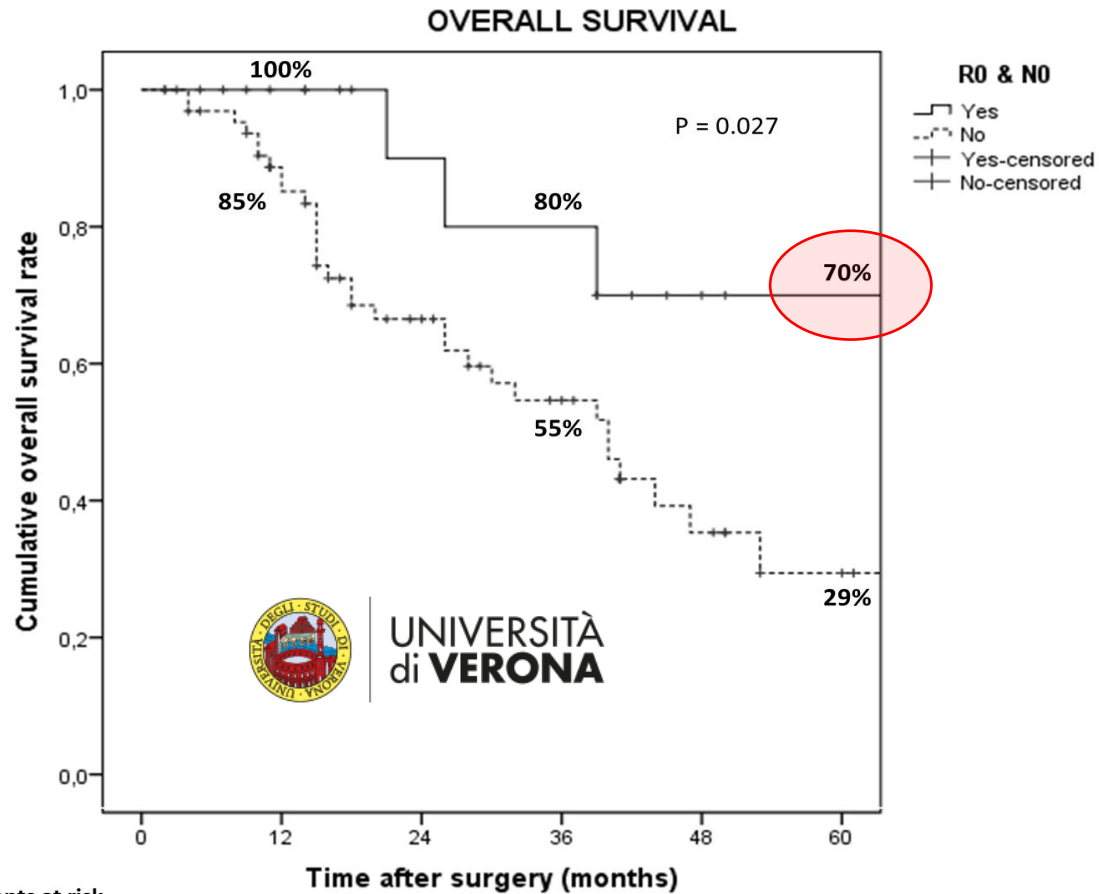


No. at risk

	0	1	2	3	4	5	6	7	8	9	10
A	340	296	205	143	68	41					
B	62	51	24	9	4	1					

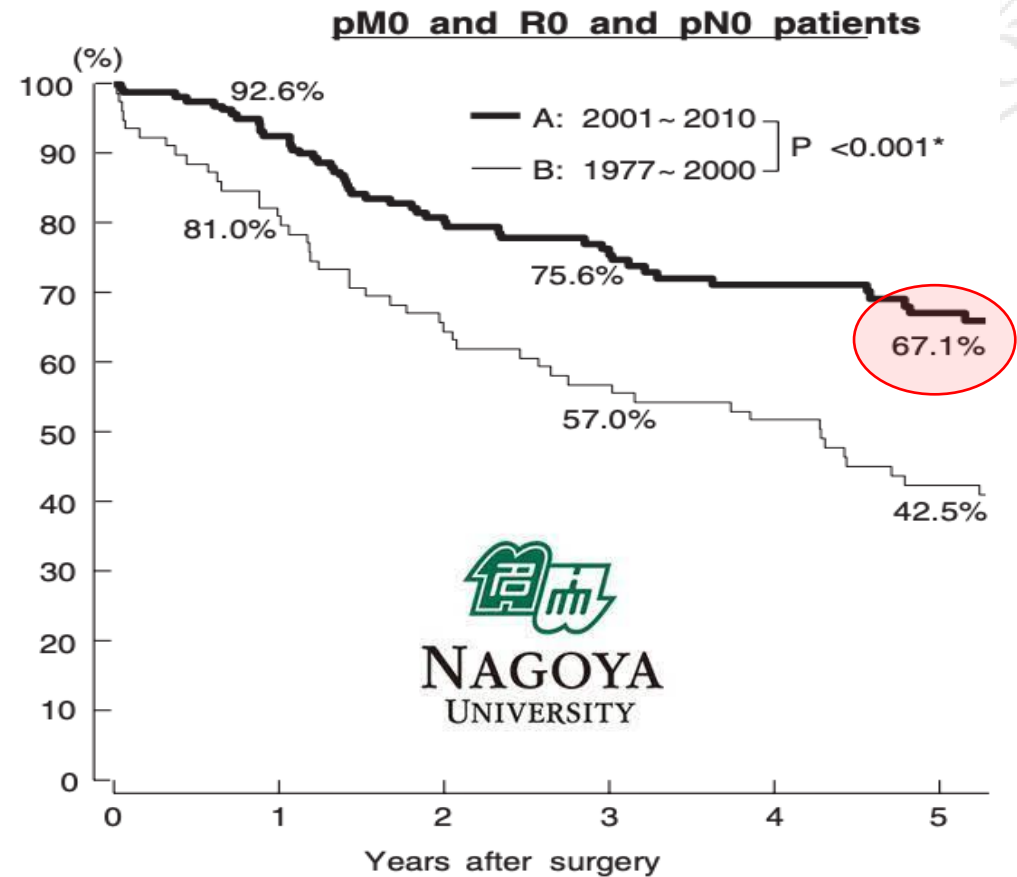
# The prognostic role of true radical resection in perihilar cholangiocarcinoma after improved evaluation of radial margin status

De Bellis M, Mastrosimini MG, Conci S, Campagnaro T, Pecori S, Capelli P, Scarpa A, Guglielmi A, Ruzzenente A. *Cancers*, 2022



Patients at risk

	0	12	24	36	48	60
R0 & N0 – Yes	19	14	8	8	1	1
R0 & N0 – No	66	48	20	20	3	3



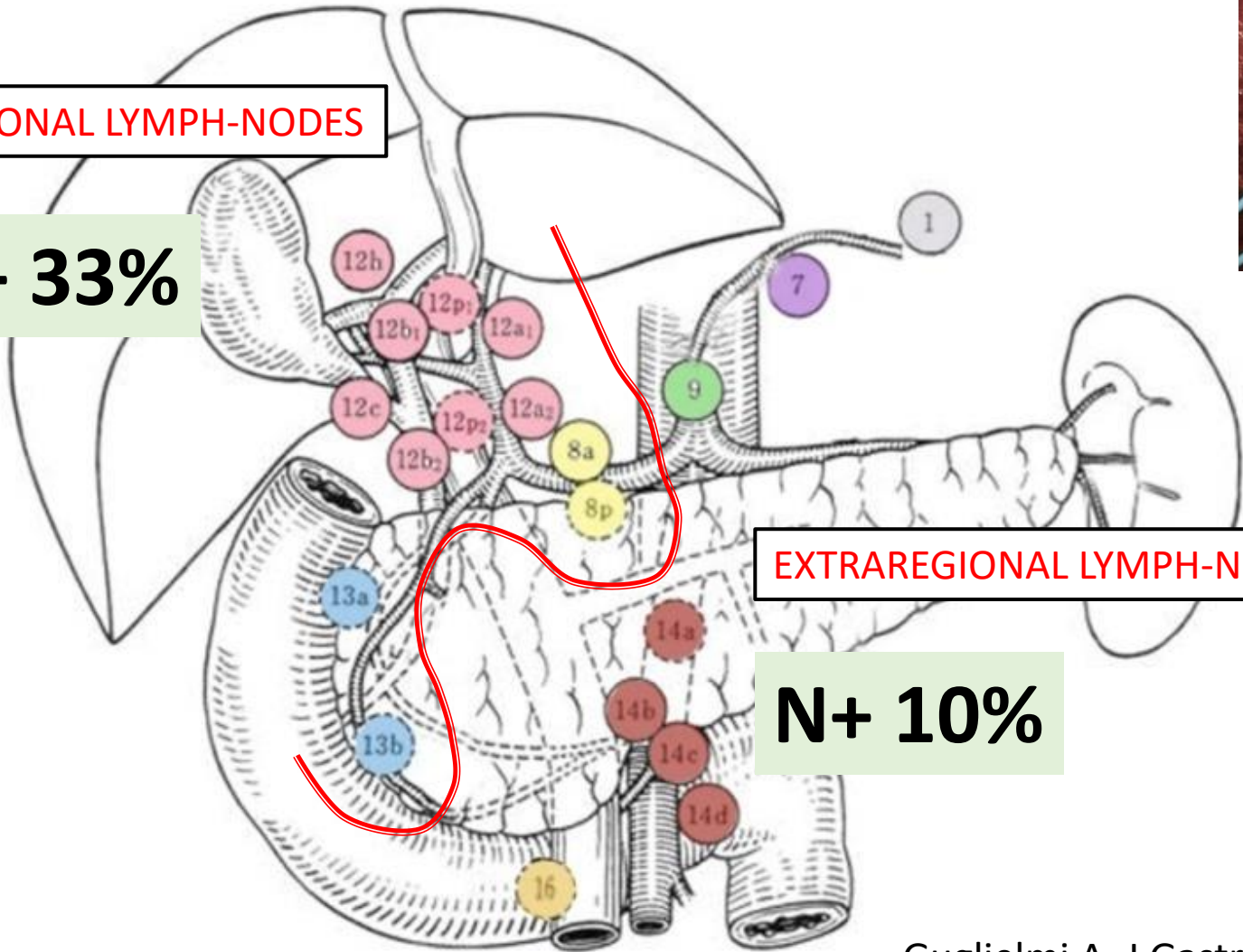
No. at risk

	0	1	2	3	4	5
A: 164	164	147	93	93	59	59
B: 79	79	64	45	45	32	32

# Lymph-nodes Metastases

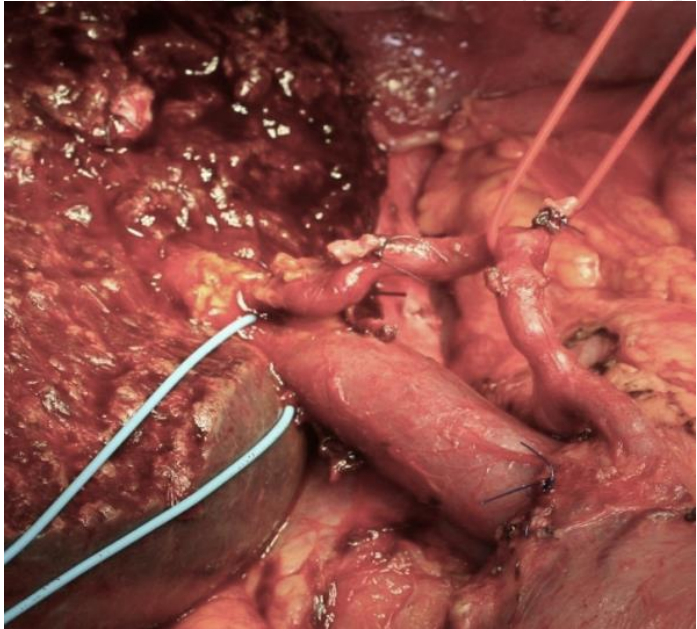
REGIONAL LYMPH-NODES

**N+ 33%**



EXTRAREGIONAL LYMPH-NODES

**N+ 10%**



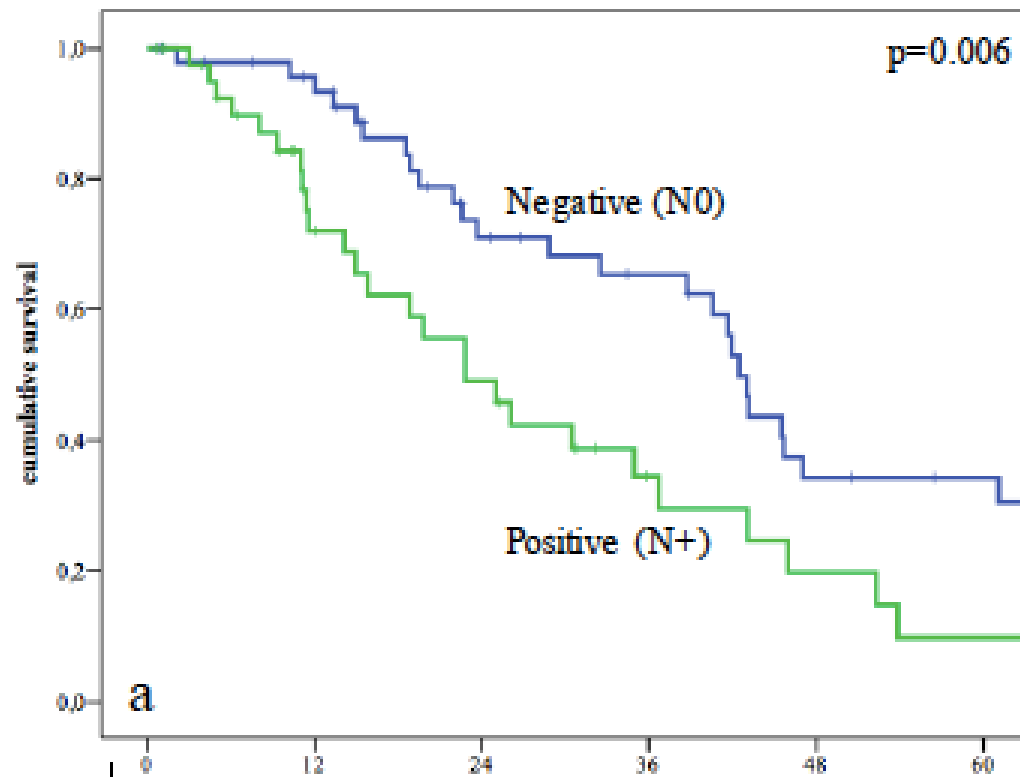
# What is the most accurate lymph node staging method for perihilar cholangiocarcinoma? Comparison of UICC/AJCC pN stage, number of metastatic lymph nodes, lymph node ratio, and log odds of metastatic lymph nodes

S. Conci <sup>a,c</sup>, A. Ruzzenente <sup>a,c</sup>, M. Sandri <sup>b</sup>, F. Bertuzzo <sup>a</sup>,  
T. Campagnaro <sup>a</sup>, F. Bagante <sup>a</sup>, P. Capelli <sup>c</sup>, M. D'Onofrio <sup>d</sup>,  
M. Piccino <sup>a</sup>, A.E. Dorna <sup>a</sup>, C. Pedrazzani <sup>a</sup>, C. Iacono <sup>a,\*f</sup>,  
A. Guglielmi <sup>a,f</sup>

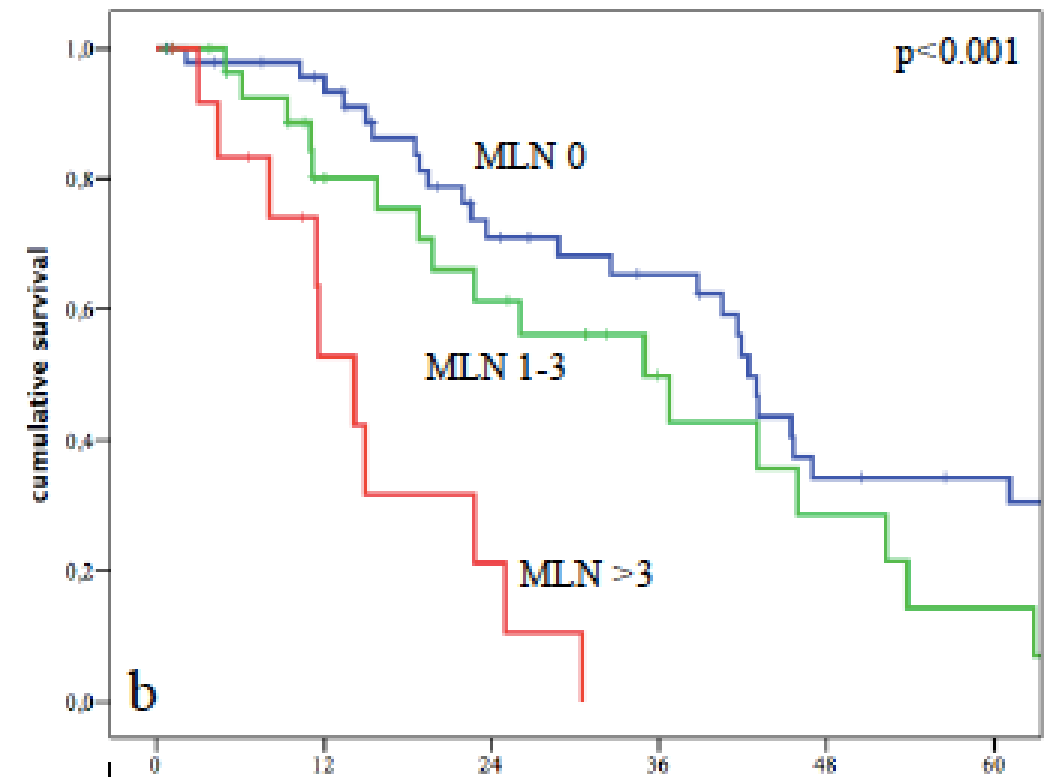
*Eur J Surg Oncol* - 2018

Lymphadenectomy in 93% (100% period 2006-2016)  
Mean number of LN : 8 (3-27)

## LN Status



## Number of metastatic LN (MLN)



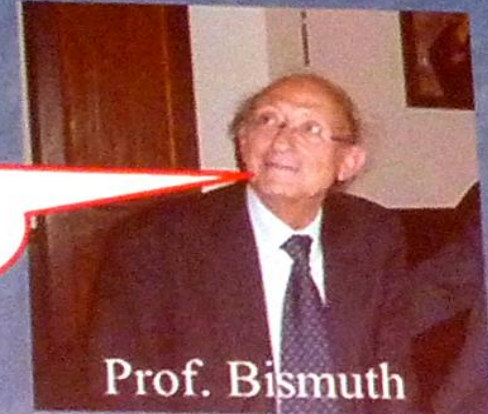




# Classification of Hilar Cholangiocarcinoma

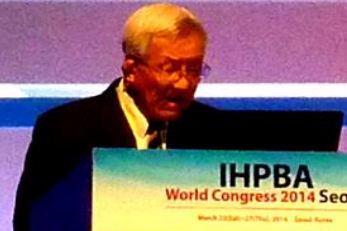
Bismuth H et al. *Ann Surg* 1992;215:31-38

Type IV is unresectable!



Prof. Bismuth

TYPE I	TYPE II	TYPE IIIa	TYPE IIIb	TYPE IV



IHPBA  
World Congress 2014 Seoul  
March 22-26, 2014, Seoul, Korea

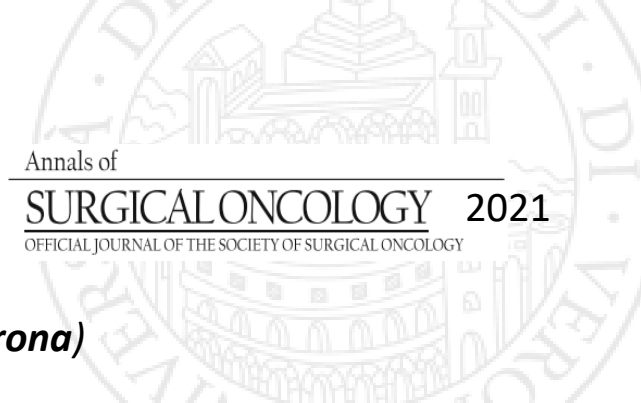




# Surgery for Bismuth-Corlette Type IV Perihilar Cholangiocarcinoma: Results from a Western Multicenter Collaborative Group

Ruzzenente A. Guglielmi A. Lang H. Van Guglik T. et al

Perihilar Cholangiocarcinoma Collaboration Group (coordinating centers: **Amsterdam, Mainz, Verona**)

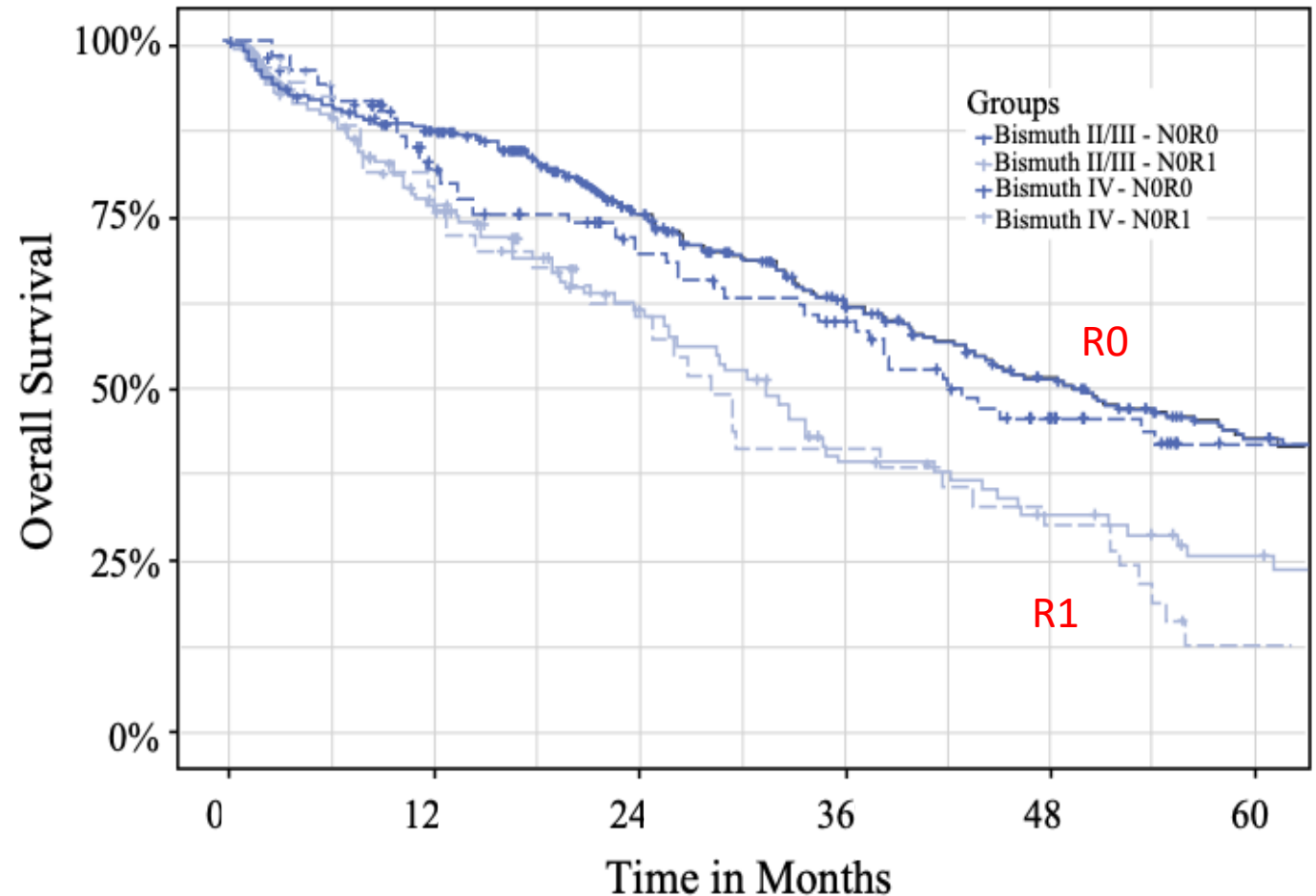


## Resected PHC between 2000 and 2017

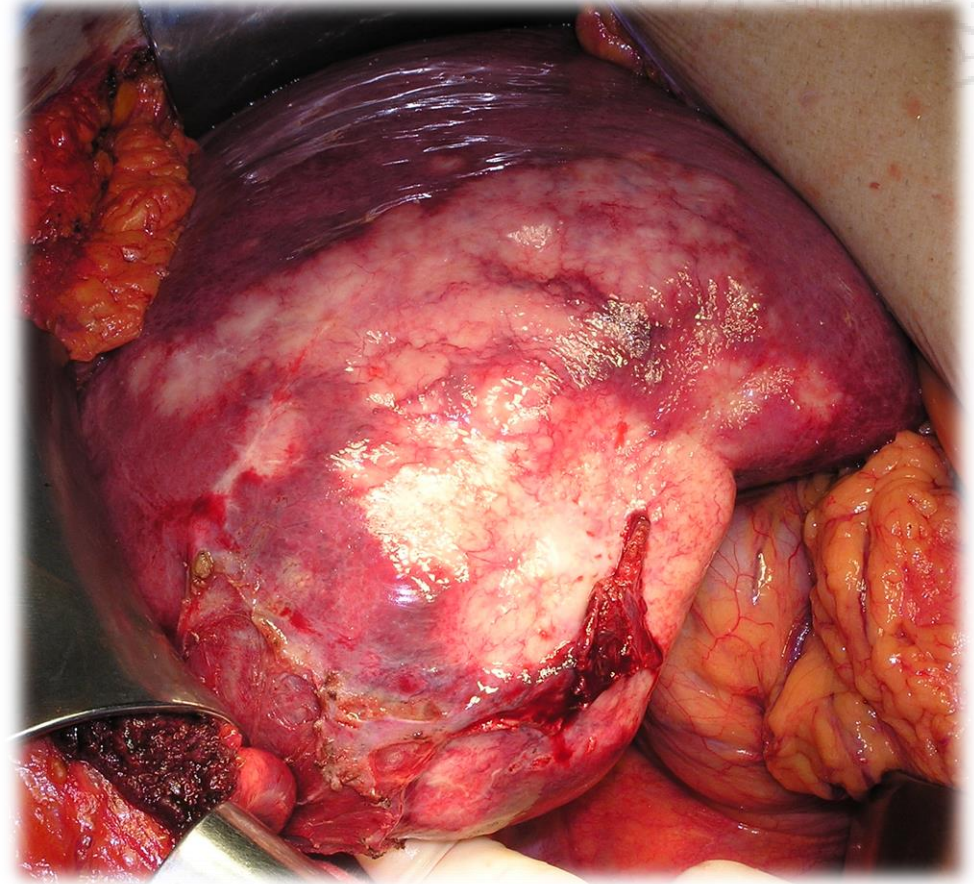
Bismuth type II or III = 826 (73%)

Bismuth type IV = 312 (27%)

	Bismuth II-III	Bismuth IV
<b>R0</b>	<b>68%</b>	<b>61%</b>
<b>MORTALITY</b>	<b>13%</b>	<b>12%</b>
<b>CLAVIEN DINDO <math>\geq 3</math></b>	<b>46%</b>	<b>51%</b>

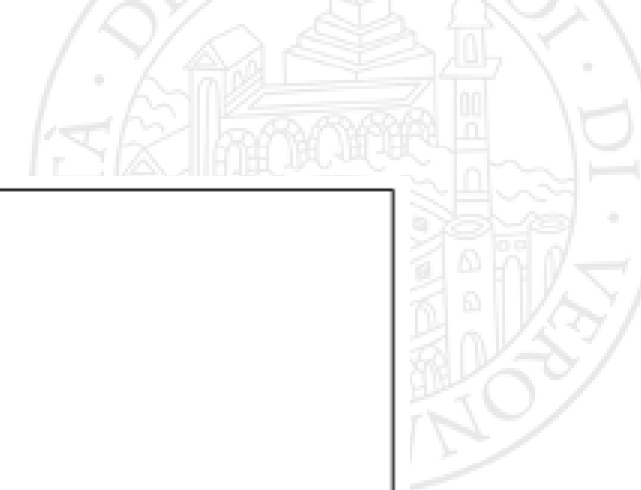


# SURGERY OF INTRAHEPATIC CHOLANGIOCARCINOMA

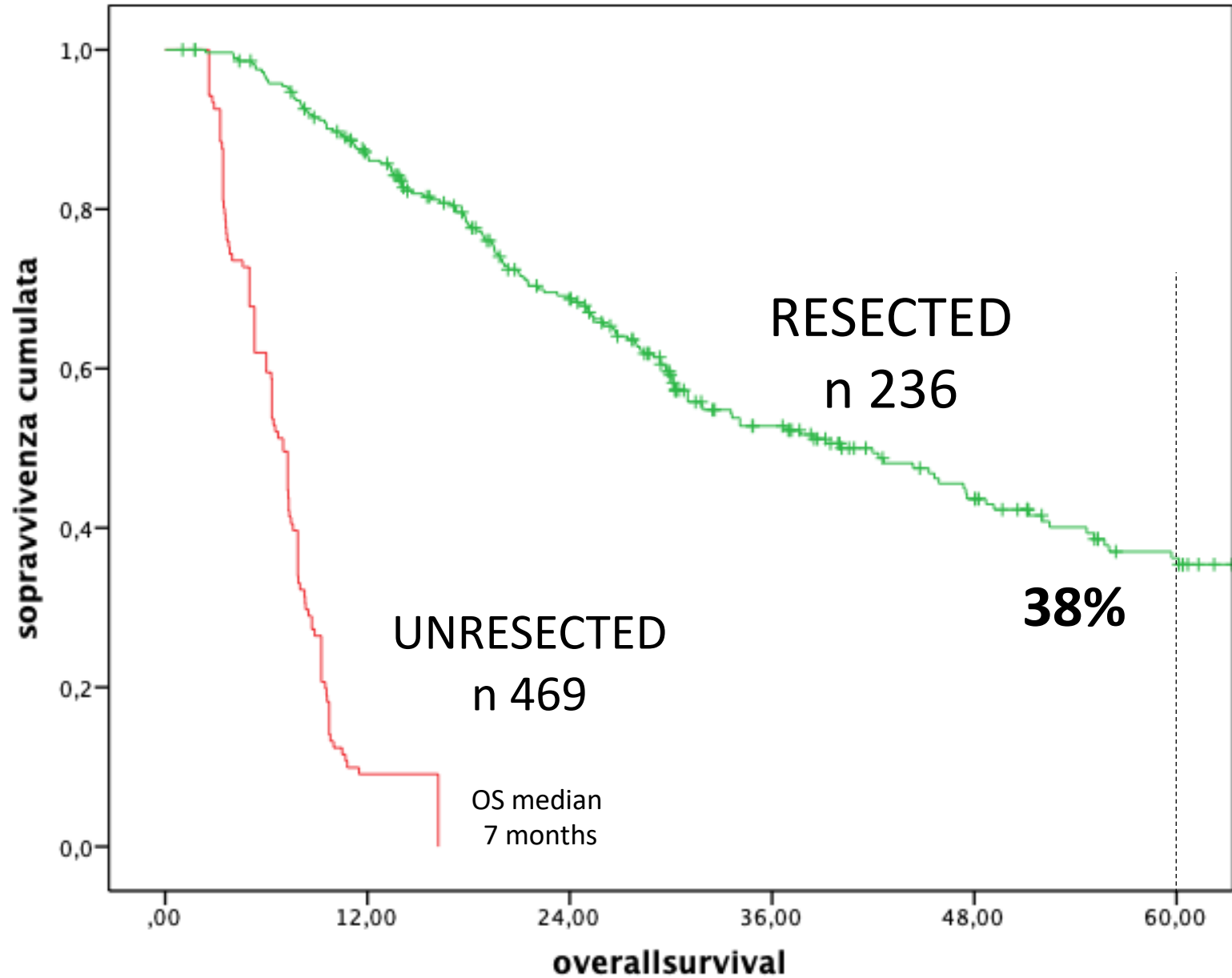




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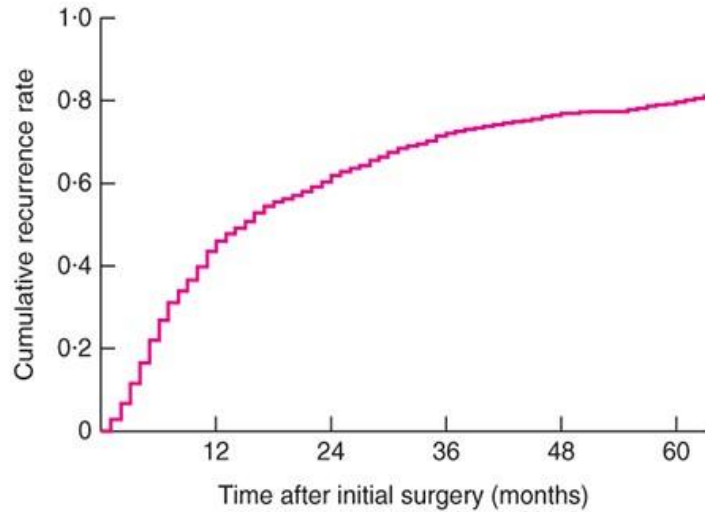
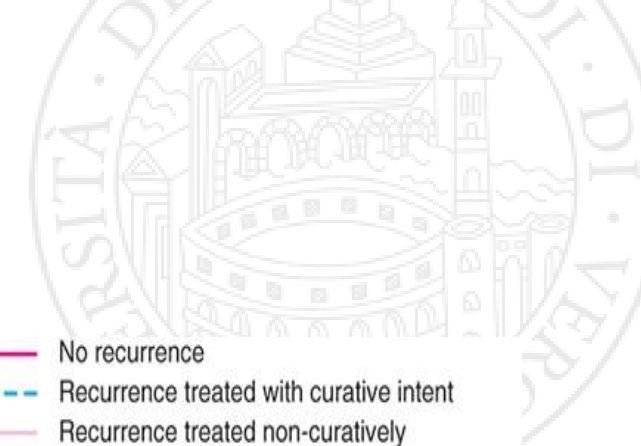
**1990-2023**  
**715 ICC**  
**OBSERVED**



# Early versus late recurrence of intrahepatic cholangiocarcinoma after resection with curative intent

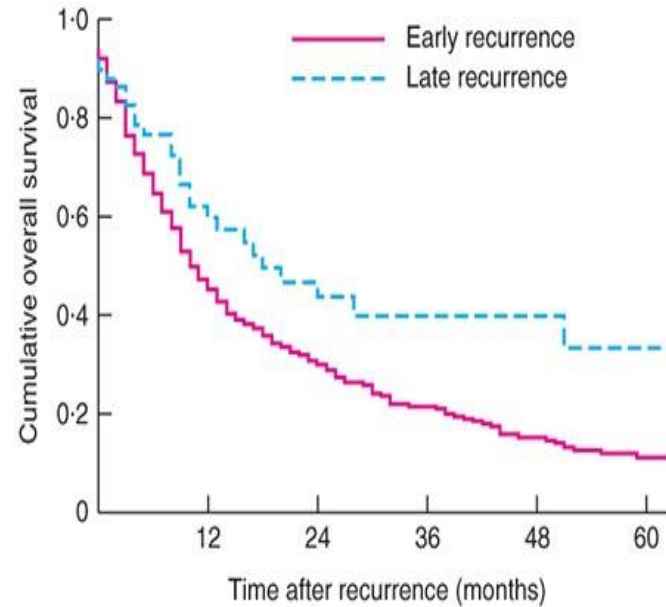
X.-F. Zhang<sup>1,3</sup>, E. W. Beal<sup>3</sup>, F. Bagante<sup>6</sup>, J. Chakedis<sup>3</sup>, M. Weiss<sup>3</sup>, I. Popescu<sup>10</sup>, H. P. Marques<sup>11</sup>, L. Aldrighetti<sup>1</sup>, S. K. Maithel<sup>3</sup>, C. Pulitano<sup>12</sup>, T. W. Bauer<sup>6</sup>, F. Shen<sup>2</sup>, G. A. Poultsides<sup>3</sup>, O. Soubrane<sup>13</sup>, G. Martel<sup>14</sup>, B. G. Koerkamp<sup>15</sup>, E. Itaru<sup>16</sup> and T. M. Pawlik<sup>3</sup>

BJS 2018



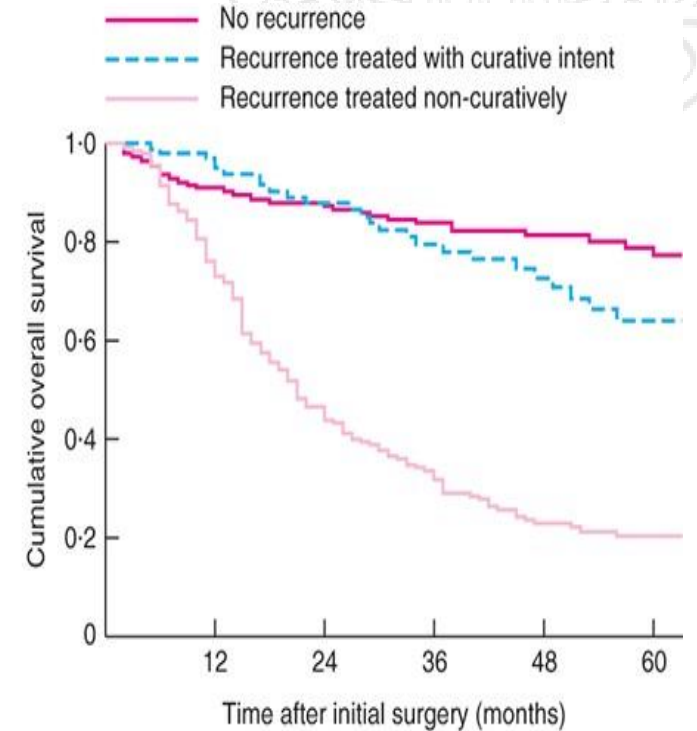
No. at risk 933 485 288 187 124 89

**a** Recurrence, all patients



No. at risk		0	12	24	36	48	60
Early	540	190	101	51	25	14	
Late	145	27	15	10	7	3	

**a** Overall survival after diagnosis of recurrence



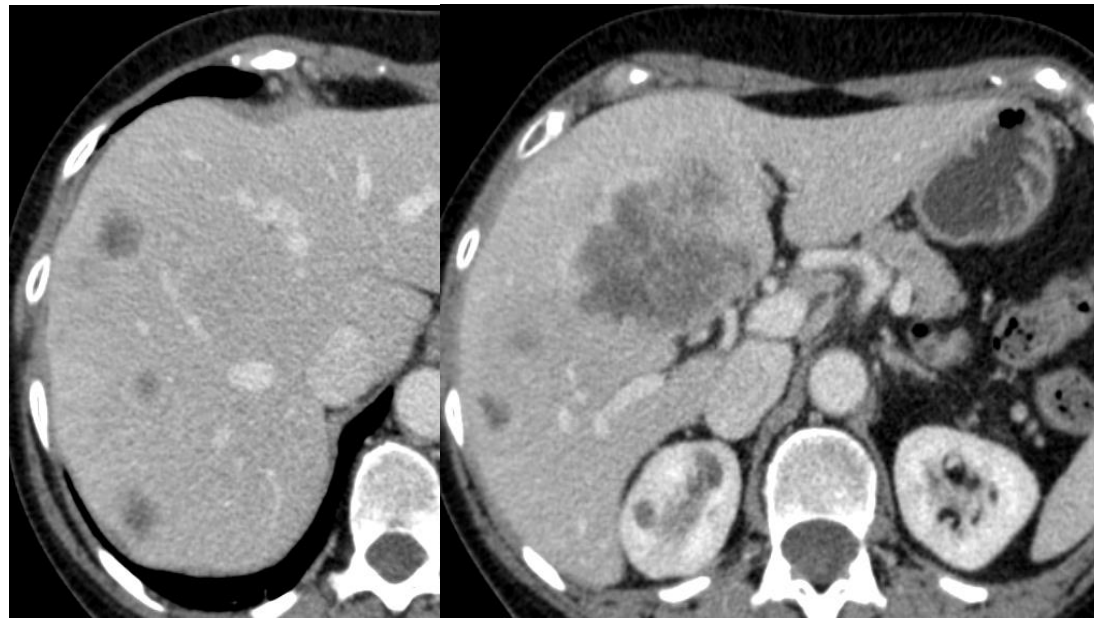
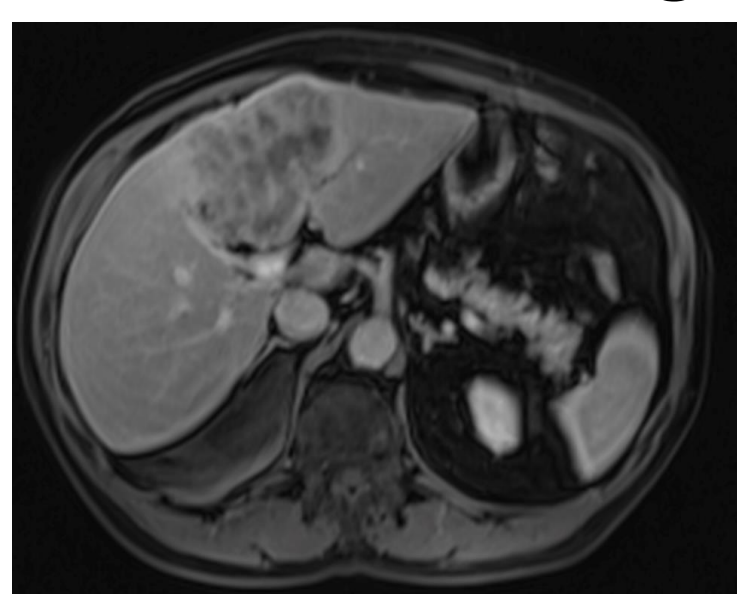
No. at risk		0	12	24	36	48	60
No recurrence	248	193	132	109	76	54	
Curative	103	91	68	54	36	24	
Non-curative	224	160	87	54	30	23	

**b** Overall survival according to treatment of recurrence



# Predictors of long-term Outcomes

- ✓ Tumor size
- ✓ Multifocality
- ✓ Margins
- ✓ Vascular invasion
- ✓ LN metastases
- ✓ Tumor markers



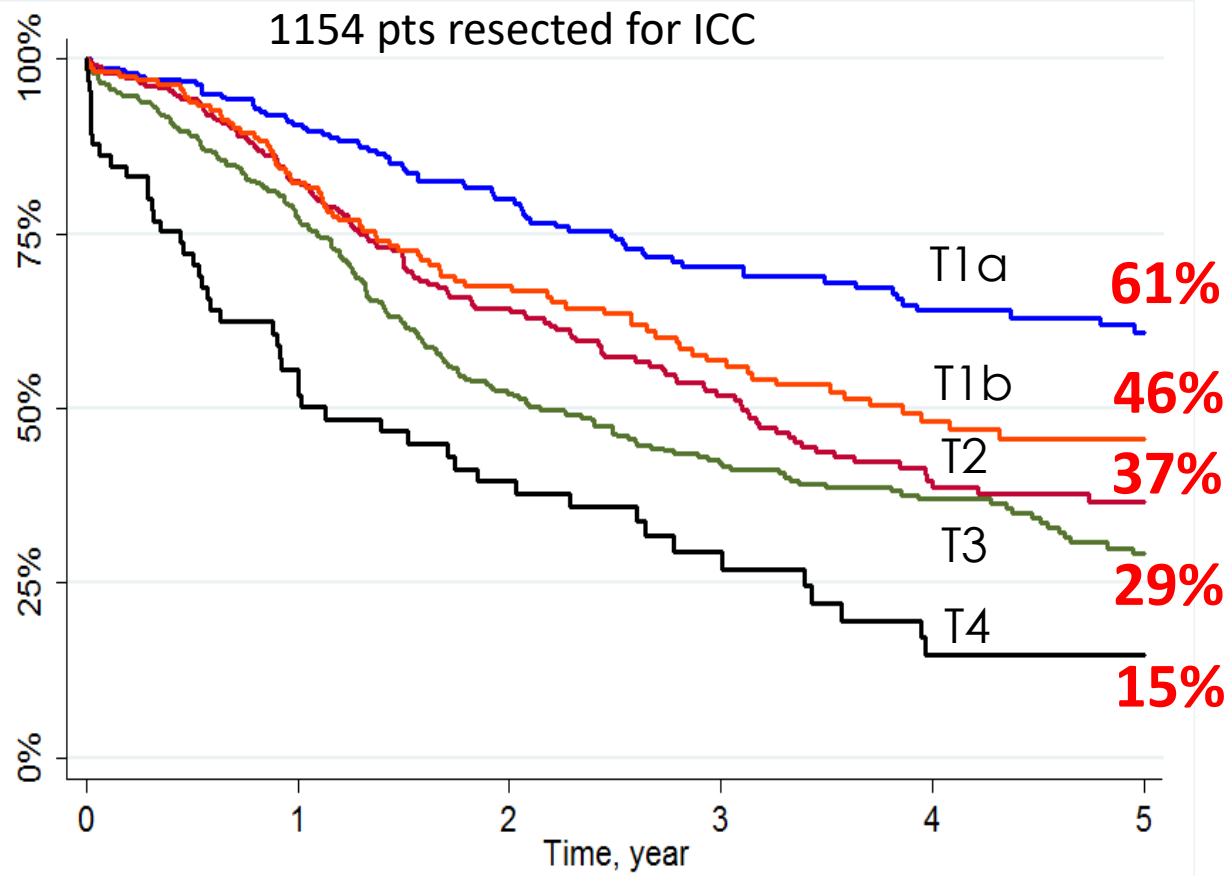


# Survival after Surgery for ICC

## According with T stages

**AJCC 8<sup>th</sup> ed.**

1154 pts resected for ICC

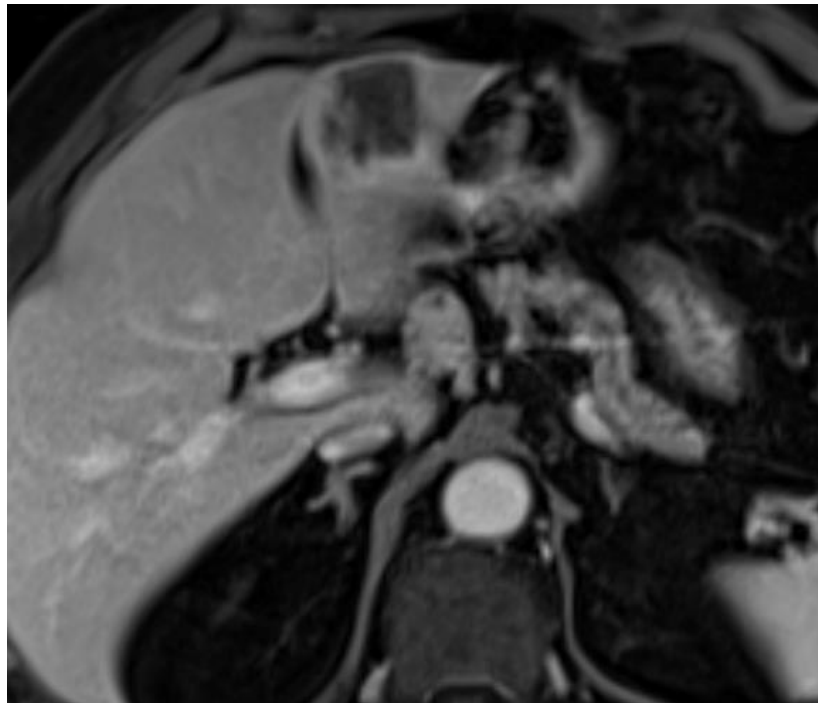


<b>T1a</b>	Solitary tumor ≤ 5cm
<b>T1b</b>	Solitary tumor > 5cm
<b>T2</b>	Vascular Invasion or Multiple tumors
<b>T3</b>	Perforation Visceral Peritoneum
<b>T4</b>	Involving local extrahepatic structures by direct invasion

Surgery is still controversial ?

# T2 → Multiple nodules

## SAME BIOLOGICAL BEHAVIOUR ?



Single  
T1a-b

solitary with different size  
 $\leq 5\text{cm}$   $> 5\text{cm}$



Single + satellites  
T2

multiple nodules in the same  
anatomical liver segment



Multifocal  
T2

multiple nodules in different  
anatomical liver segment

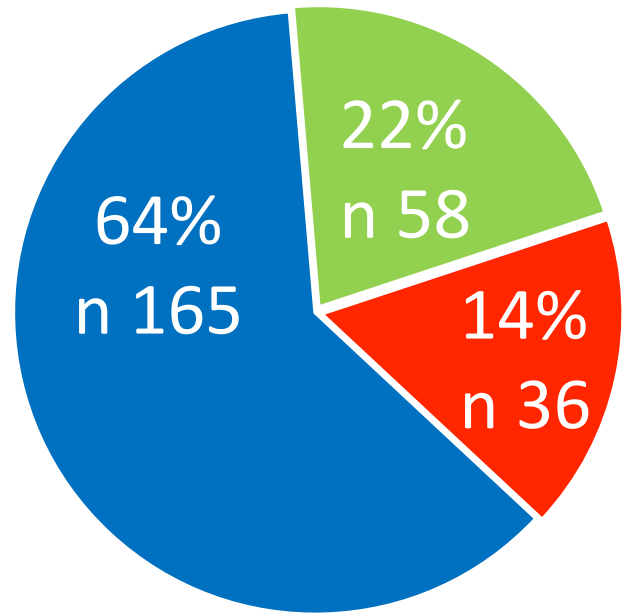
# Patterns of Distribution of Hepatic Nodules (Single, Satellites or Multifocal) in Intrahepatic Cholangiocarcinoma: Prognostic Impact After Surgery

Simone Conci, MD<sup>1</sup>, Andrea Ruzzenente, MD, PhD<sup>1</sup>, Luca Viganò, MD, PhD<sup>2</sup>, Giorgio Ercolani, MD, PhD<sup>3</sup>, Andrea Fontana, MD<sup>2</sup>, Fabio Bagante, MD<sup>1</sup>, Francesca Bertuzzo, MD<sup>1</sup>, Andrea Dore, MD<sup>1</sup>, Antonio Daniele Pinna, MD<sup>3</sup>, Guido Torzilli, MD<sup>2</sup>, Calogero Iacono, MD<sup>1</sup>, and Alfredo Guglielmi, MD<sup>1</sup>

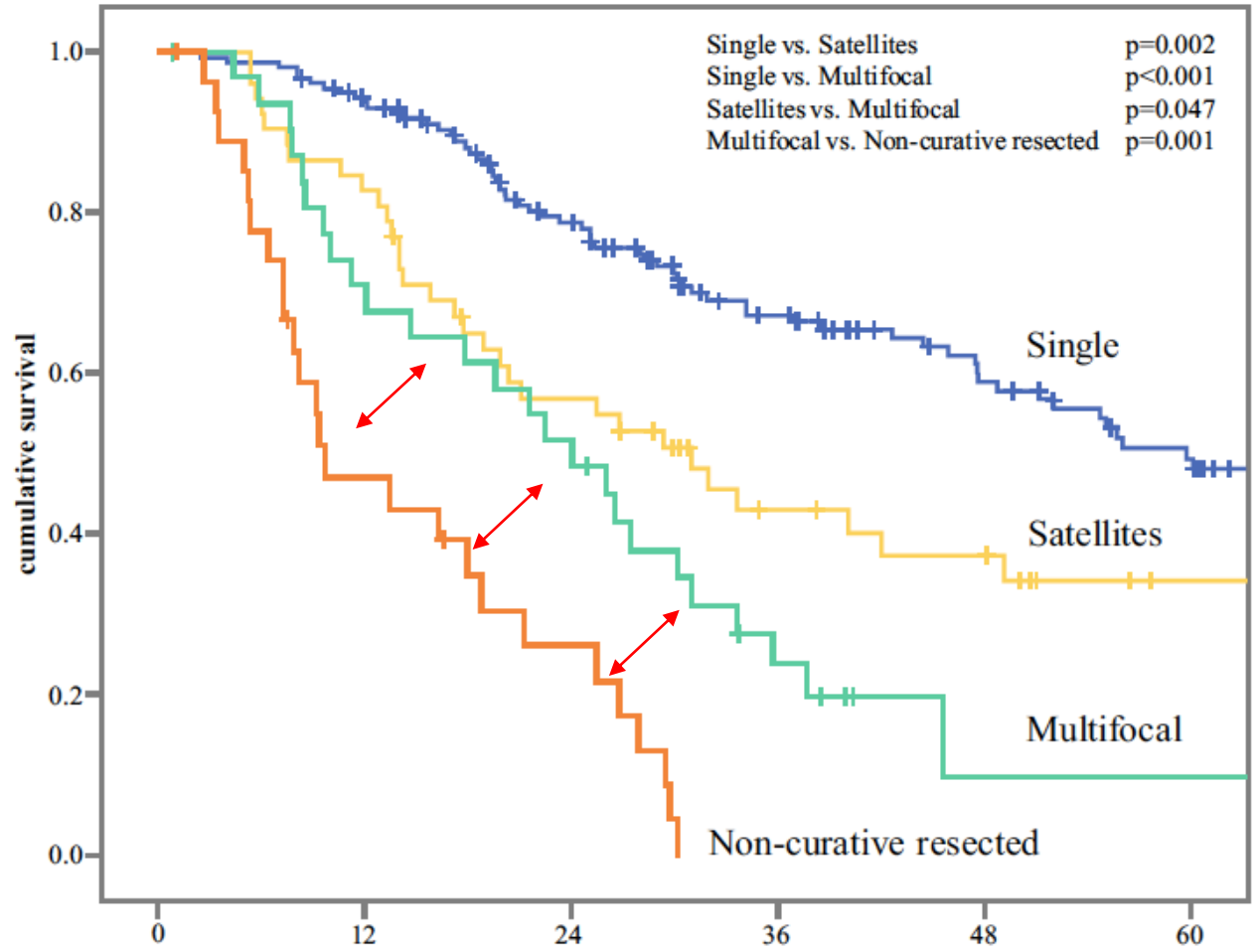
Ann Surg Oncol 2018



251 patients resected

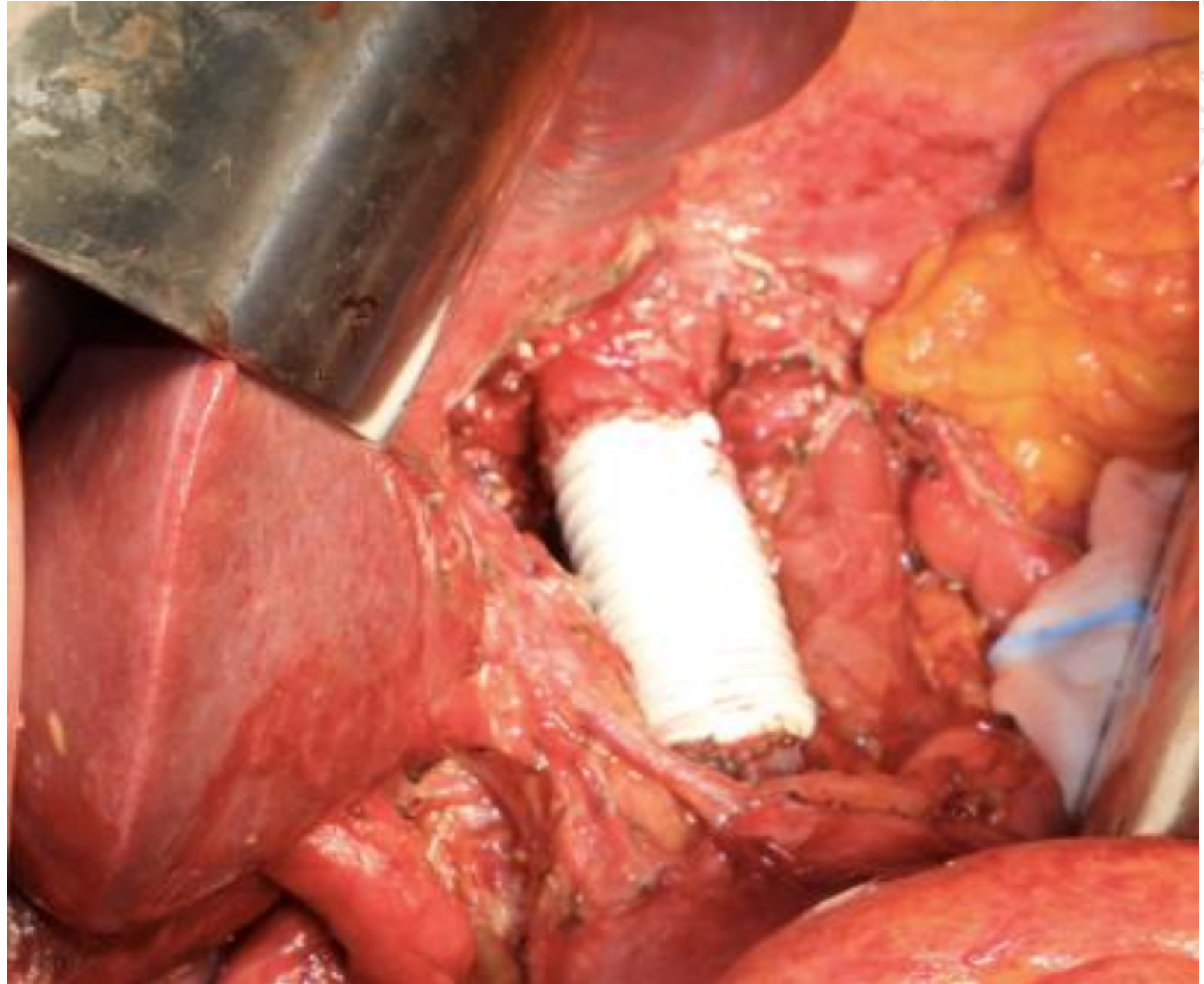


- Single
- Single with Satellites
- Multifocal



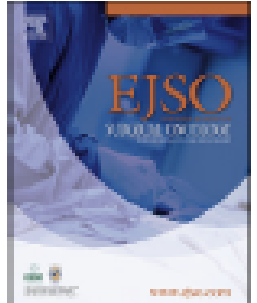


# ICC - Vascular resection to obtain R0 resection

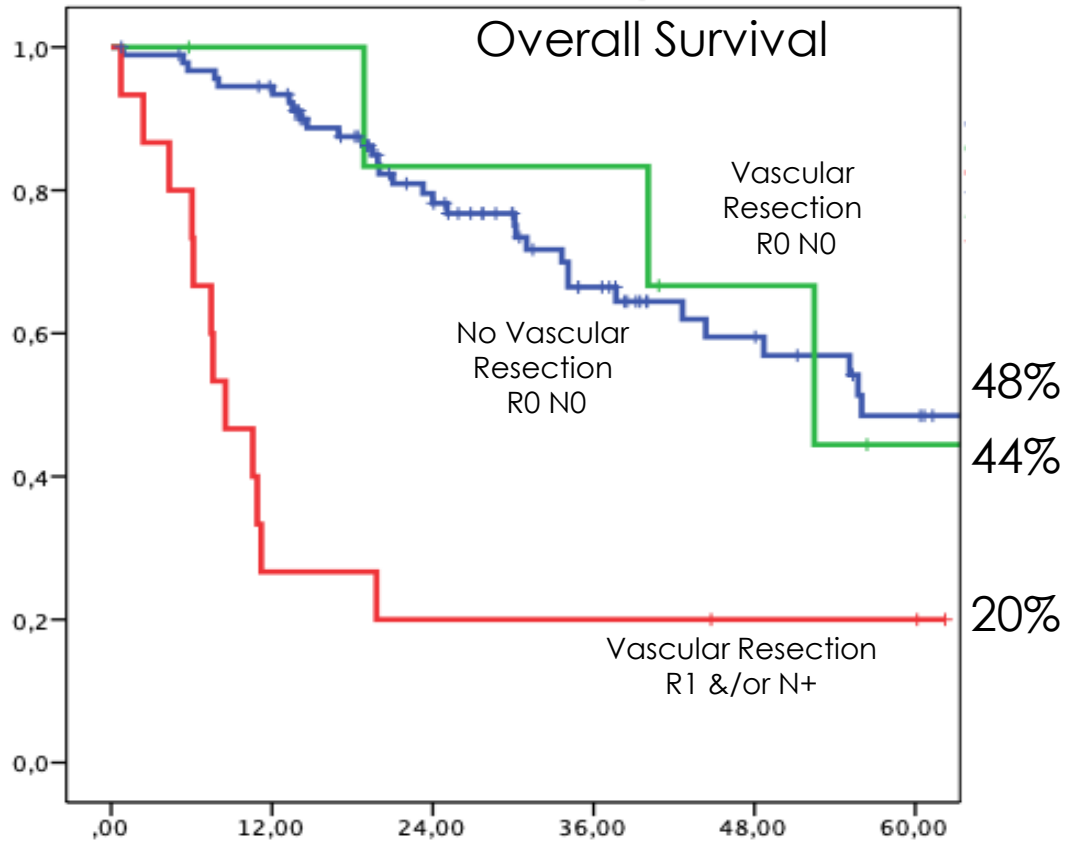


# Outcomes of vascular resection associated with curative intent hepatectomy for intrahepatic cholangiocarcinoma

Simone Conci <sup>a,\*</sup>, Luca Viganò <sup>b</sup>, Giorgio Ercolani <sup>c</sup>, Esteban Gonzalez <sup>e</sup>,  
 Andrea Ruzzenente <sup>a</sup>, Giulia Isa <sup>a</sup>, Claudia Salaris <sup>a,e</sup>, Andrea Fontana <sup>b</sup>, Fabio Bagante <sup>a</sup>,  
 Corrado Pedrazzani <sup>a</sup>, Tommaso Campagnaro <sup>a</sup>, Calogero Iacono <sup>a</sup>,  
 Eduardo De Santibanes <sup>d</sup>, Daniele Antonio Pinna <sup>c</sup>, Guido Torzilli <sup>b,2</sup>, Alfredo Guglielmi <sup>a,2</sup>



2020



} p = NS

**Best Survivors**  
**Vascular Resection R0 N0**

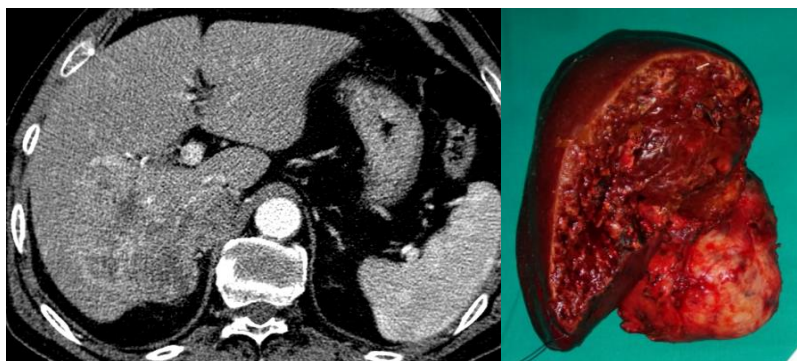


# Resection of adjacent organs

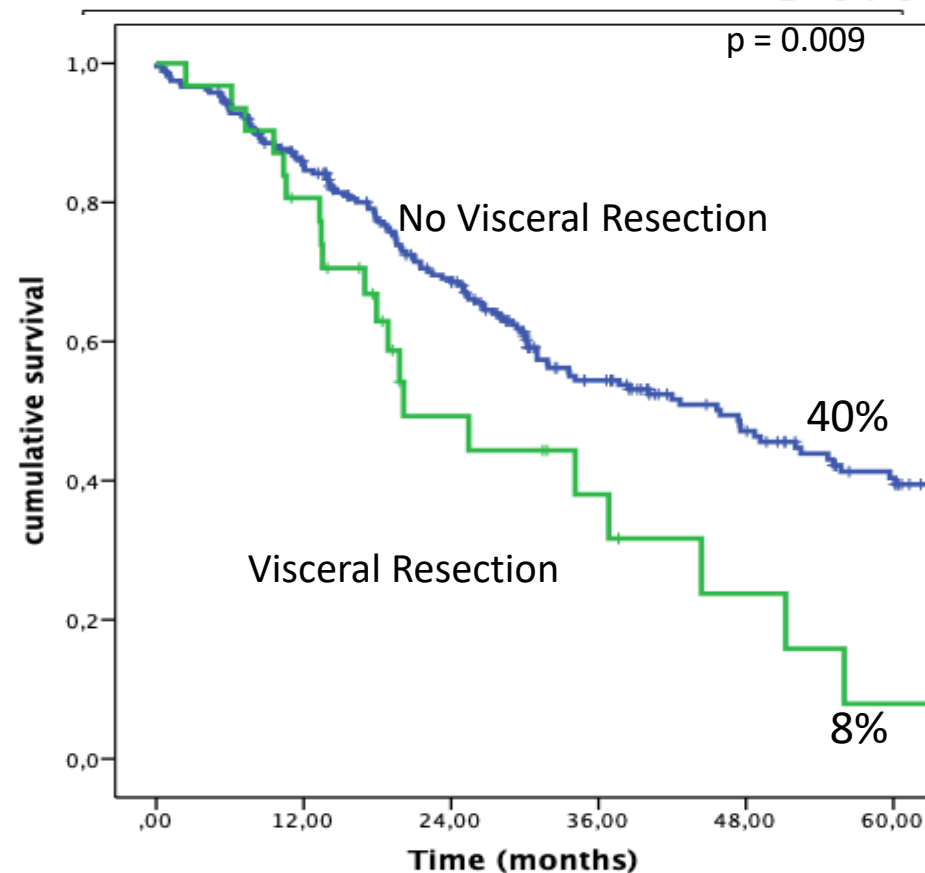
270 patients resected for ICC

University of Verona – Guglielmi; Humanitas University – Rozzano – Torzilli  
University of Bologna – Pinna; Hospital Italiano de Buenos Aires – De Santibanes


Visceral Resection	11,5% (n 31)
Diaphragm	1.9% (n 5)
Hepatic Hilum	7% (n 19)
Adrenal Gland	0.7% (n 2)
Colon	0.7% (n 2)
Peritoneum-Omentum	1.1% (n 3)



Overall Survival



# Role of Lymph Node Dissection in Small ( $\leq 3$ cm) Intrahepatic Cholangiocarcinoma

Andrea Ruzzenente<sup>1</sup>  • Simone Conci<sup>1</sup> • Luca Viganò<sup>2</sup> • Giorgio Ercolani<sup>2</sup> •  
 Serena Manfreda<sup>1</sup> • Fabio Bagante<sup>1</sup> • Andrea Ciangherotti<sup>1</sup> • Corrado Pedrazzani<sup>2</sup> •  
 Antonio D. Pinna<sup>1</sup> • Calogero Iacono<sup>1</sup> • Guido Torzilli<sup>3</sup> • Alfredo Guglielmi<sup>1</sup>

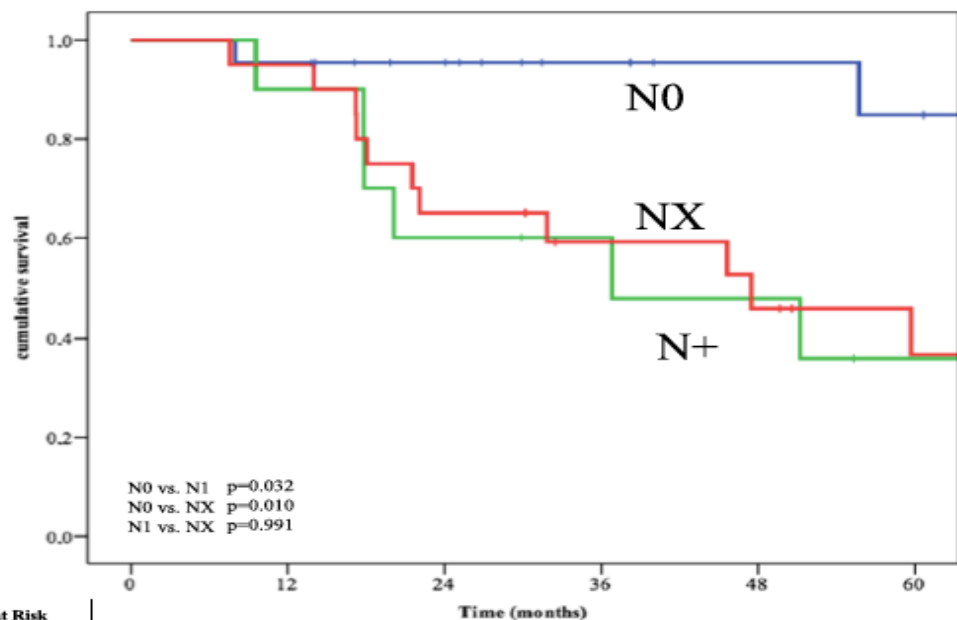
*J Gastrointest Surg* - 2019

194 resected ICC  $\rightarrow$  N positive 34%



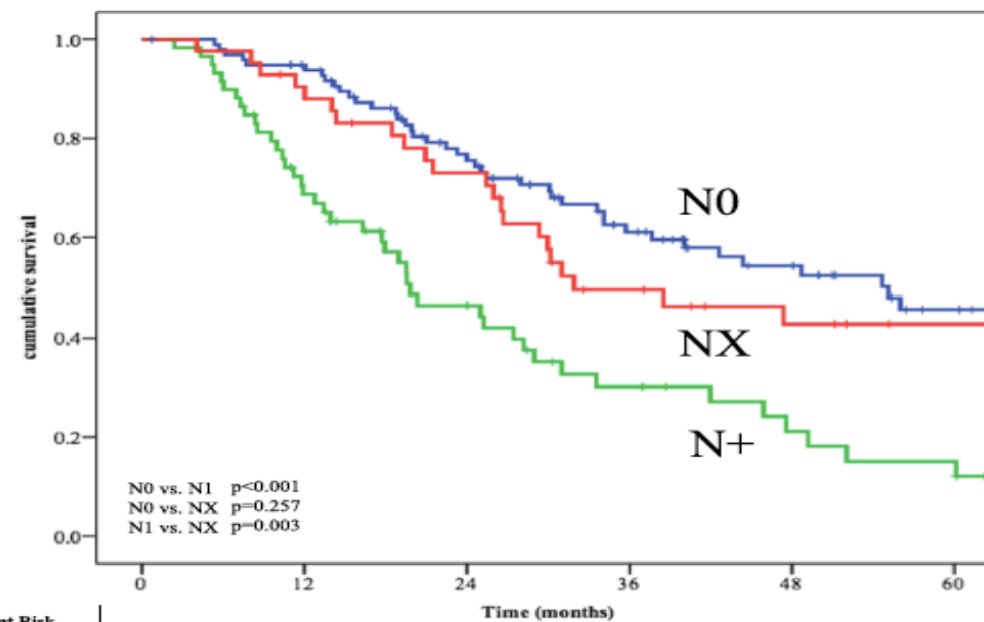
**b**

Small-ICC (< 3 cm)



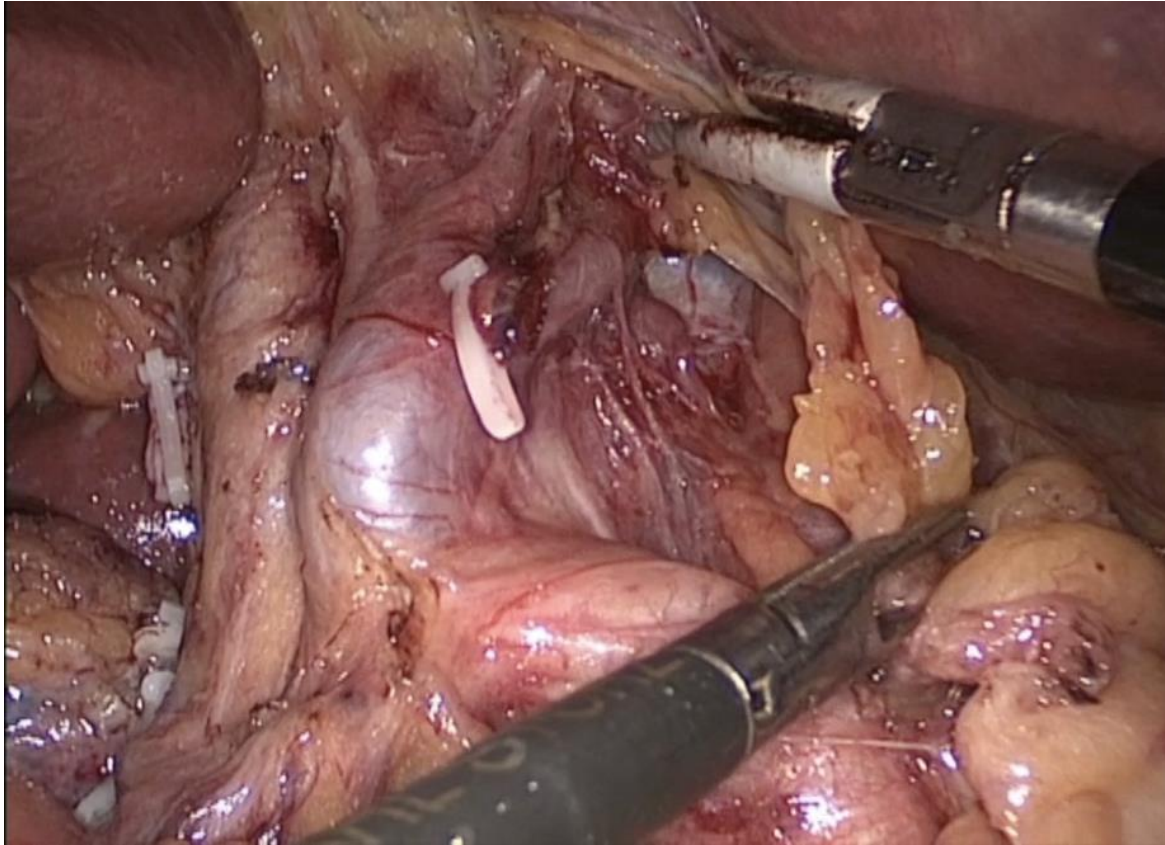
Patients at Risk	0	12	24	36	48	60
<b>N0</b>	22	21	17	12	9	8
<b>N+</b>	10	9	8	5	4	2
<b>No LND (NX)</b>	20	19	13	9	7	4

Large-ICC (> 3 cm)



Patients at Risk	0	12	24	36	48	60
<b>N0</b>	98	89	63	42	29	18
<b>N+</b>	59	38	21	12	7	5
<b>No LND (NX)</b>	42	37	29	17	12	9

# MINIMAL ACCESS APPROACH FOR CHOLANGIOCARCINOMA



**RESPECT OF ONCOLOGICAL PRINCIPLES  
OF R0 RESECTIONS:**

- **Negative Margins**
- **Lymph-nodes dissection**

# MILS vs OPEN: Results

Multi-institutional study  
1084 patients

PSM

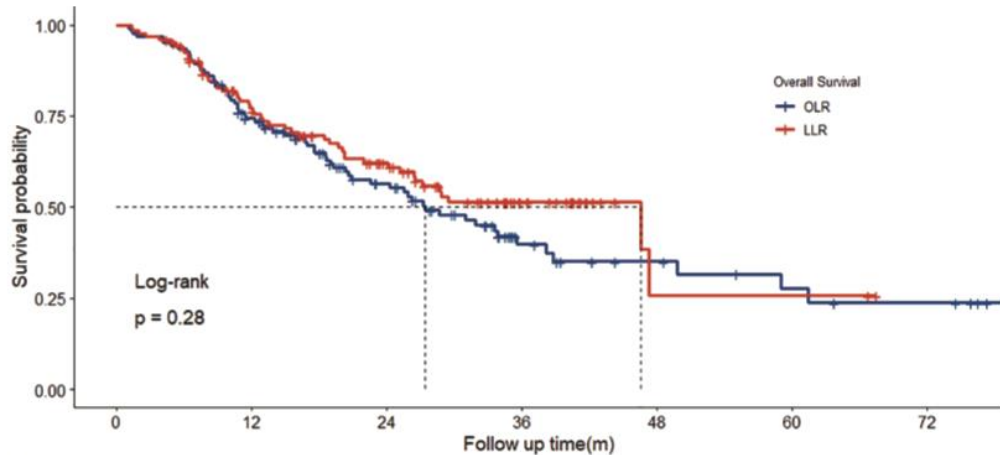
122 Open  
122 MILS

Better short term  
outcomes

Similar long term  
outcomes

A1

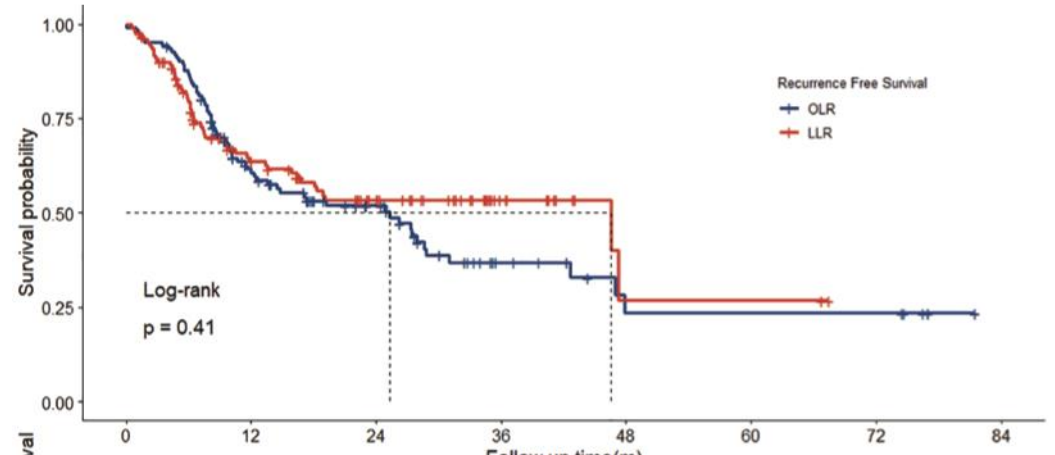
OS



		Number at risk: n (%)						
Overall Survival		0	12	24	36	48	60	72
	OLR	122 (100)	85 (70)	49 (40)	18 (15)	11 (9)	7 (6)	5 (4)
LLR	122 (100)	83 (68)	52 (43)	20 (16)	2 (2)	2 (2)	0 (0)	

A2

RFS

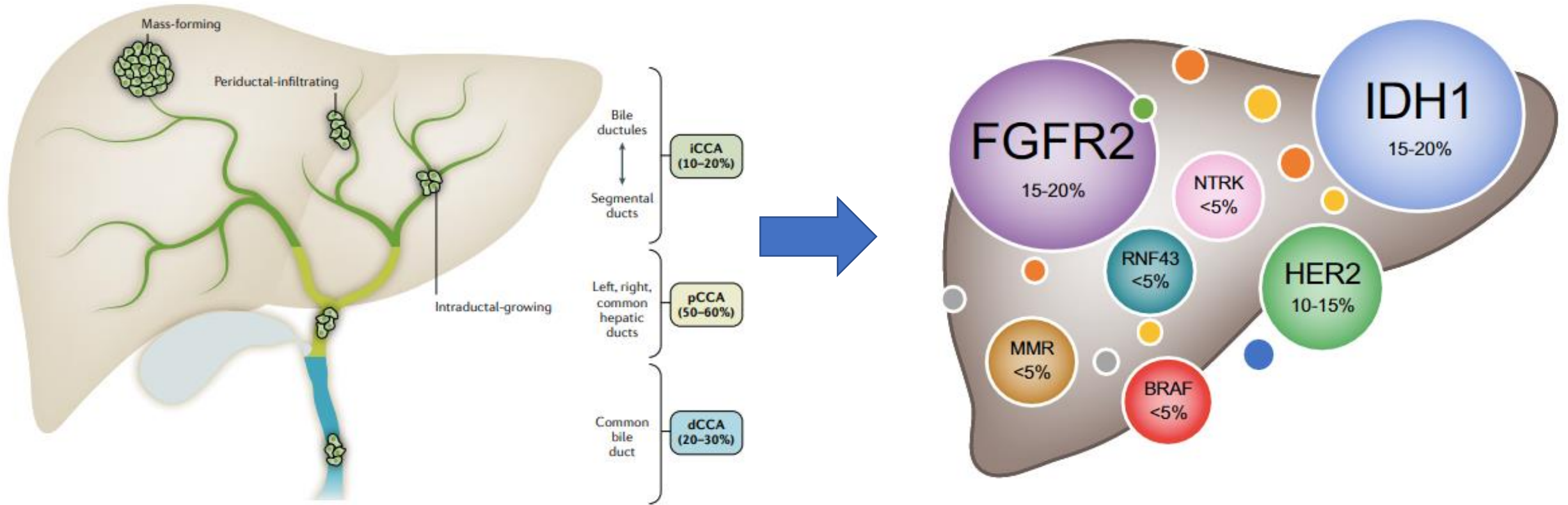


		Number at risk: n (%)							
Recurrence Free Survival		0	12	24	36	48	60	72	84
	OLR	122 (100)	61 (50)	36 (30)	12 (10)	5 (4)	5 (4)	5 (4)	0 (0)
LLR	122 (100)	61 (50)	38 (31)	13 (11)	2 (2)	2 (2)	0 (0)	0 (0)	



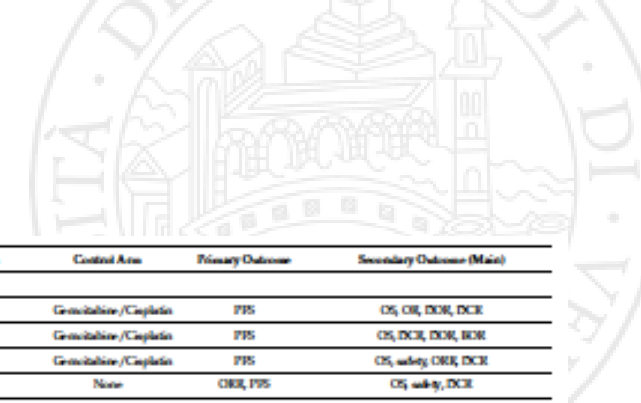
# From Anatomical to Molecular Classification...

Is it Time to Overcome the Anatomical Classification ?



Up to **45%** of CCA have Potentially Targettable Mutations

# Evolution of the Targeted Therapy Landscape for Cholangiocarcinoma: Is Cholangiocarcinoma the 'NSCLC' of GI Oncology?



Amol Gupta <sup>1</sup>, Razelle Kurzrock <sup>2,3,4</sup> and Jacob J. Adashek <sup>5,\*</sup>

32 ongoing trials

Target	Phase	Clinical Trial Identifier	Treated Cancer Group	Experimental Arm	Control Arm	Primary Outcome	Secondary Outcome (Main)
FGFR2 fusion/rearrangement	III	NCT04562336	CCA	Fevipretinib	Gemcitabine/Caplatin	FFS	OS, OR, DOR, DCR
	III	NCT04773302	CCA	Idagliticarb	Gemcitabine/Caplatin	FFS	OS, DCR, DOR, BOR
	III	NCT04600362	CCA	Futibaterib	Gemcitabine/Caplatin	FFS	OS, safety, ORR, DCR
	II	NCT04230319	CCA	Demucicarb	None	ORR, FFS	OS, safety, DCR
HER2 mutations	I/II	NCT04526336	CCA and other advanced tumors	HS-4009	None	ORR, MTD, safety	DCR, DCR, pharmacokinetics
	II	NCT04333336	BTCA	Trastuzumab plus gemcitabine/caplatin	None	BOR, safety	FFS, OS
NTRK gene fusion	I/II	NCT04692336	BTCA	Vanfaterib plus gemcitabine/caplatin	None	MTD, safety, FFS, ORR	OS, DOR, DCR, PK
	II	NCT04692336	Advanced solid tumors	Lansectinib	None	ORR	FFS, OS, safety, DOR, GM, CBR
Non-V600E BRAF mutations	I	NCT04692336	Advanced solid tumors	Lansectinib	None	ORR	FFS, safety, PK, changes in tumor genomics
	I	NCT04692336	Advanced solid tumors	Enzastatib + Tricostatin	None	ORR	FFS, safety, DCR
KRAS G12C mutations	I	NCT04692336	Advanced solid tumors	Adagrasib	None	Safety, MTD	FFS, OS, PK, ORR, DCR, DOR
	I	NCT04692336	Advanced solid tumors	DS-1167 monotherapy or in combination with dabrafenib	None	Safety	FFS, OS, ORR, DCR, time to response, DCR, PK
KRAS G12C mutations	II	NCT04692336	CCA	Davlatinib	None	ORR	FFS, OS, safety
	II	NCT04692336	CCA	Claparit	None	ORR	FFS, OS, safety
	II	NCT04692336	CCA	Combavertib + Claparit	None	ORR	FFS, OS, safety, DCR
	I/II	NCT04692336	Advanced solid tumors	Trametinib	None	DLT, EDCG	Plasma concentration metrics
JAK2/MSH1	I	NCT04692336	CCA	LY4040398 LY4040398 + Gemcitabine/Caplatin	None	MTD	ORR, safety and tolerability, efficacy, PK
	I/II	NCT04692336	Advanced solid tumors	Ibravostat in combination with Tricostatin	None	Recommended phase 2 dose, ORR	FFS, OS, safety, changes in protein modifying
HER2 mutations	II/III	NCT04692336	BTCA	Vanfaterib with Capecitabine	Capecitabine	ORR, FFS	OS, safety, DCR, DCR, tumor size, EDCG
	II	NCT04692336	Metastatic carcinoma of digestive system including BTCA	Trastuzumab plus 5-FU or BB or Capecitabine	None	RR	OS, FFS, DCR, DOR, time of response, EDCG
	II	J0C72031100536	Advanced solid tumors	Trastuzumab and Pertuzumab	None	ORR	FFS, OS, safety, DOR
	II	NCT04692336	CCA	Trastuzumab entansine	None	BOR	FFS, OS, safety, PK
	II	NCT04692336	Advanced solid tumors	Ado-Trastuzumab entansine	None	ORR	None
	II	NCT04692336	Advanced solid tumors	Trastuzumab Derivatase	None	ORR	OS, FFS, safety, DOR, DCR, PK, immunogenicity
	I/II	NCT04692336	Advanced solid tumors	DS-5026	None	Safety, ORR	OS, DOR, PK, DCR
	I	NCT04692336	CCA	Ninaparib + Alectinib	None	DLT, MTD	FFS, ORR
	I	NCT04692336	Advanced solid tumors	Zaricostatib plus abiraterone	None	MTD, Safety	FFS, ORR, PK, anticlog antibodies
	I	NCT04692336	Non-brain/non-gastro solid tumors	Trastuzumab Derivatase	None	ORR	DCR, BOR, DCR, FFS, OS, pharmacokinetics, safety
BAP1 and other DDR genes	II	NCT04692336	CCA	Ninaparib	None	ORR	FFS, OS, safety
DNA repair gene mutation	II	NCT04692336	CCA	Ninaparib	None	ORR	FFS, OS, safety
Matched molecular therapy							
Matched molecular therapy	N/A	NCT04692336	Rare tumors	FoundationOne CDx and FoundationOne Liquid CDx	None	See to receive a molecularly targeted matched, FFS	Tumor molecular profiles correlation to treatment outcome.

# Current Role and Future Perspectives of Immunotherapy and Circulating Factors in Treatment of Biliary Tract Cancers

Int J med Sci - 2023

Simone Conci, MD, PhD<sup>1</sup>✉; Giovanni Catalano, MD<sup>1</sup>; Diletta Roman, MD<sup>1</sup>; Camilla Zecchetto, MD<sup>2</sup>; Eleonora Lucin, MD<sup>2</sup>; Mario De Bellis, MD<sup>1</sup>; Marzia Tripepi, MD<sup>1</sup>; Alfredo Guglielmi, MD<sup>1</sup>; Michele Milella, MD<sup>2</sup>; Andrea Ruzzenente, MD, PhD<sup>1</sup>

**Table 2.** Published results of main clinical trials for immunotherapy in BTC.

Study name	Phase	Drug/Target	Setting	Outcomes
KEYNOTE-028 <sup>33</sup>	1b	Pembrolizumab / PD-1	Histologically confirmed advanced BTC, with disease progression after $\geq 1$ prior standard therapy.	ORR 13% PFS 1.8 months OS 5.7 months
KEYNOTE-158 <sup>33</sup>	2	Pembrolizumab / PD-1	Previously resected unresectable or metastatic MSI-H/dMMR non-colorectal cancer, including advanced BTC.	ORR 5.8% PFS 2 months OS 7.4 months
NCT02829918 <sup>37</sup>	2	Nivolumab / PD-1	Histologically confirmed advanced refractory BTC undergoing treatment with 1-3 lines of systemic therapy.	ORR 22% PFS 3.68 months
CA209-538 <sup>40</sup>	2	Nivolumab / PD-1 Ipilimumab / CTLA4	Unresectable or metastatic rare cancers, including advanced BTC.	ORR 23% PFS 2.9 months OS 5.7 months
TOPAZ-1 (NCT03875235) <sup>44</sup>	3	GEMCIS + durvalumab / PD-L1	Chemotherapy-naïve patients with advanced BTC.	ORR 26.7%
INTR@PID BTC <sup>47</sup> (NCT03833661) <sup>48</sup>		Bintrafusp-alfa / PD-L1:TGF- $\beta$	Second-line treatment in patients with advanced or metastatic BTC who have failed or are intolerant to first-line platinum-based chemotherapy.	ORR 10.1% PFS 1.8 months OS 7.6 months
NCT01938611 <sup>49</sup>	1	Durvalumab / PD-L1 Tremelimumab / CTLA4	Second line treatment for advanced or metastatic solid tumors.	ORR 10.8% OS 10.1 months
JapicCTI-153098 <sup>119</sup>	1	GEMCIS + Nivolumab / PD-1	First line treatment of unresectable BTC.	ORR 37% PFS 4.2 months
NCT03311789 <sup>120</sup>	2	GEMCIS + Nivolumab / PD-1	First line treatment of unresectable BTC.	ORR 55.6% PFS 6.1 months
NCT01869166 <sup>54</sup>	1	CART / EGFR		
NCT01935843 <sup>55</sup>	1	CART / HER2		

**Table 3.** Main ongoing trials for immunotherapy in BTCs.

Study name	Phase	Drug/Target	Setting
Keynote - 158 (NCT02628067) <sup>33</sup>	2	Pembrolizumab / PD-1	Histologically confirmed unresectable advanced BTC, disease progression after $\geq 1$ prior standard therapy, ECOG-PS 0-1, no prior exposure to ICIs.
CA 209-538 (NCT02923934) <sup>40</sup>	2	Ipilimumab / CTLA4 + Nivolumab / PD-1	First or second line therapy in neuroendocrine tumors, rare gynaecological tumors and advanced upper GI tumors, including BTC.
Keynote-966 (NCT04003636) <sup>117</sup>	3	GEMCIS + Pembrolizumab / PD-1	First line therapy for advanced or unresectable BTC.
NCT03797326 <sup>121</sup>	2	Lenvatinib / VEGFR + Pembrolizumab / PD-1	Second line therapy in selected solid tumors, including BTC.
NCT04720131 <sup>122</sup>	2	Capecitabine + Camrelizumab / PD-1 + Apatinib / VEGFR2	First or second line treatment for advanced BTC.
NCT02628067 <sup>123</sup>	1	RT + Bintrafusp-alfa/PD-L1:TGF- $\beta$	Second line treatment for advanced or metastatic iCCC.

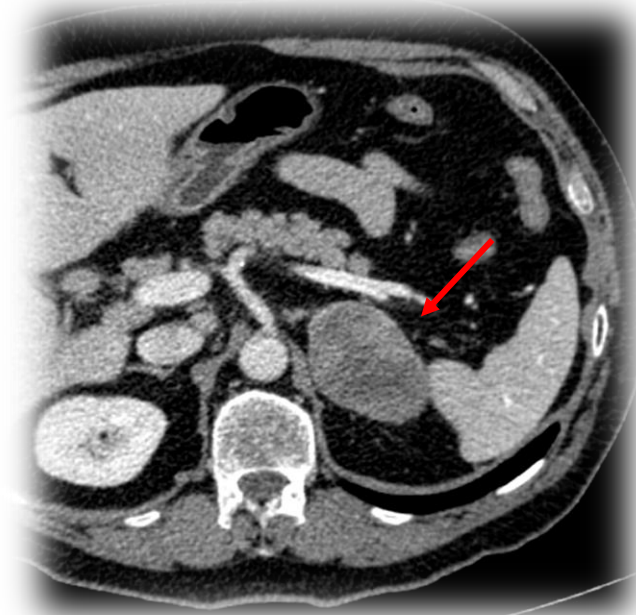
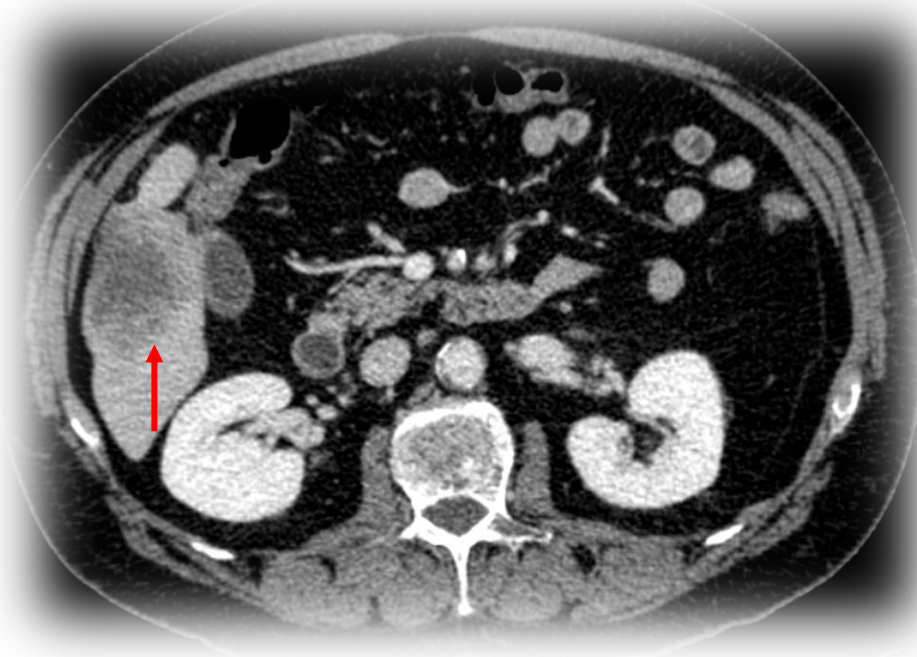
**Response Rate (CR, PR) 6-55%**  
**Median OS 6-10 months**



# New systemic treatments

Male 63 years old

ICC right lobe + Adrenal gland metastases



**RCT - TOPAZ 1**

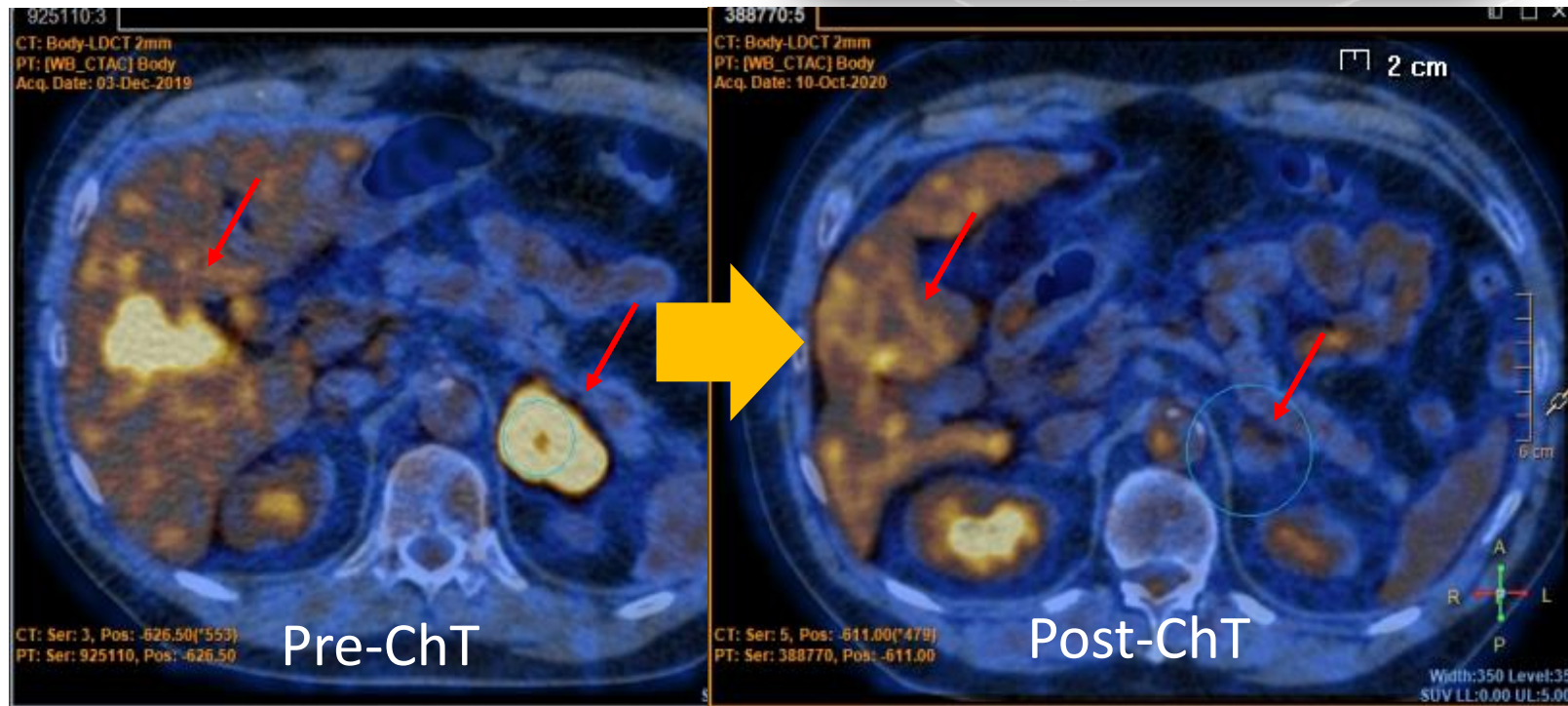
**Gemcitabine-Cisplatin**

**Durvalumab (Immunotherapy) vs Placebo**



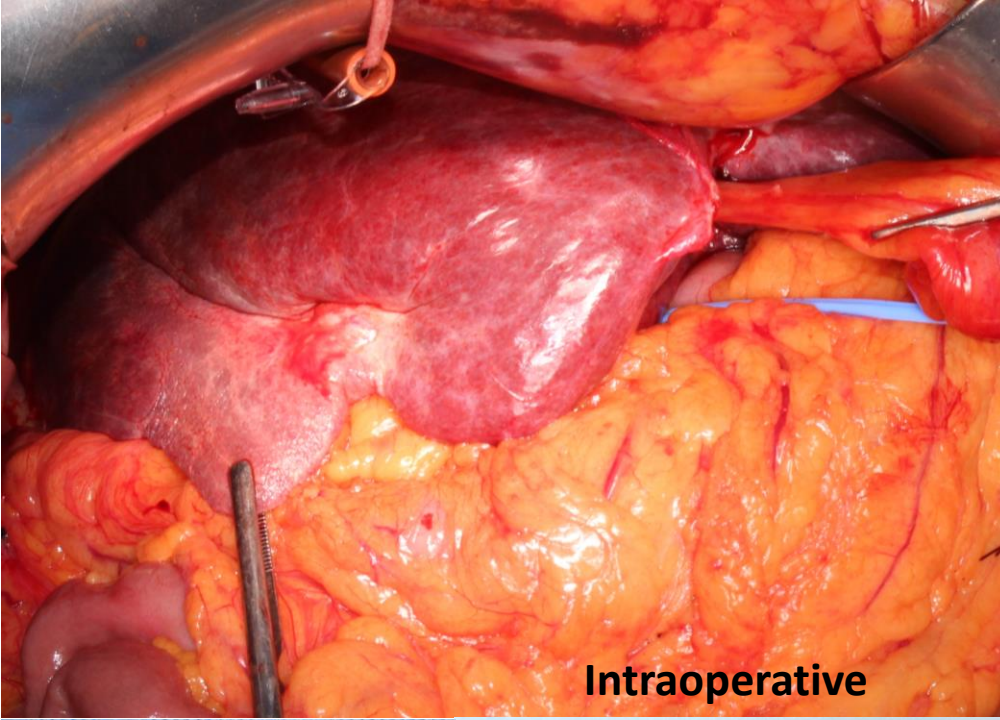
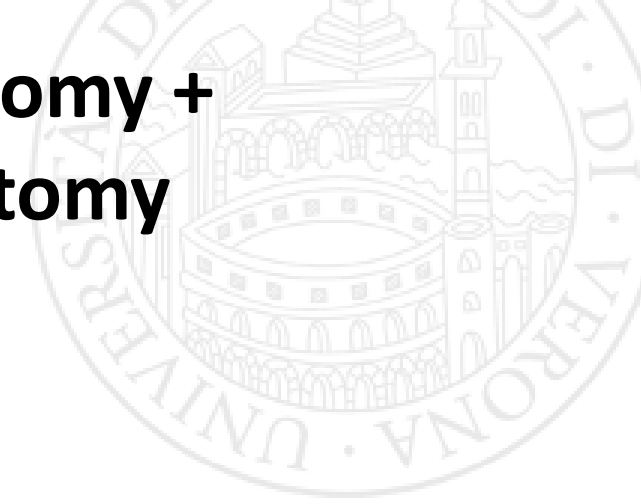
# New systemic treatments

7 Cycles  
Gem-Cis  
Durvalumab





# Right Hepatectomy + Left Adrenalectomy



Intraoperative

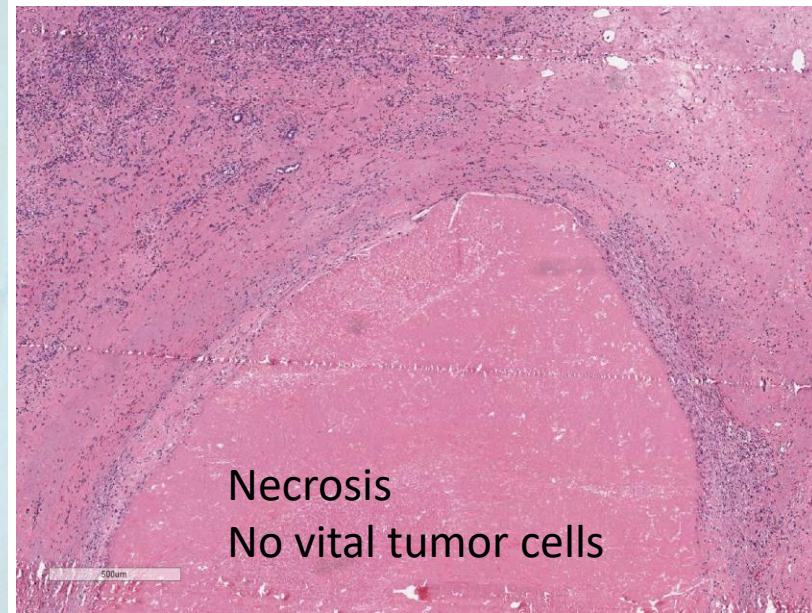


Left Adrenal Gland



Right hemiliver

## Pathology



Necrosis  
No vital tumor cells



# New systemic treatments

**TARGET THERAPY**

**IMMUNOTHERAPY**



**APPROVED FOR ADVANCED/METASTATIC  
(NOT SURGICAL PATIENTS)**

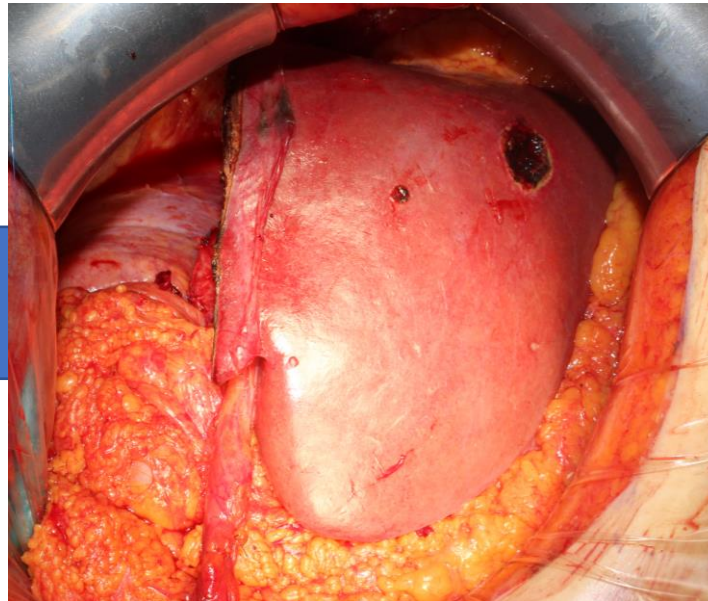


# New systemic treatments



Have we to change our  
surgical attitude ?

**NEOADJUVANT**  
(preop)



**ADJUVANT**  
(postop)



# Conclusion: Take home message

- Surgery offers the best chances of long term survival
- Resectability is very Low and Recurrence very High
- Main goal of surgery is R0 resection with low mortality and morbidity
- Multidisciplinary team dedicated is always required and recommended
- Integration with new systemic therapy (chemotherapy, target therapy, immunotherapy) are needed in the next future

