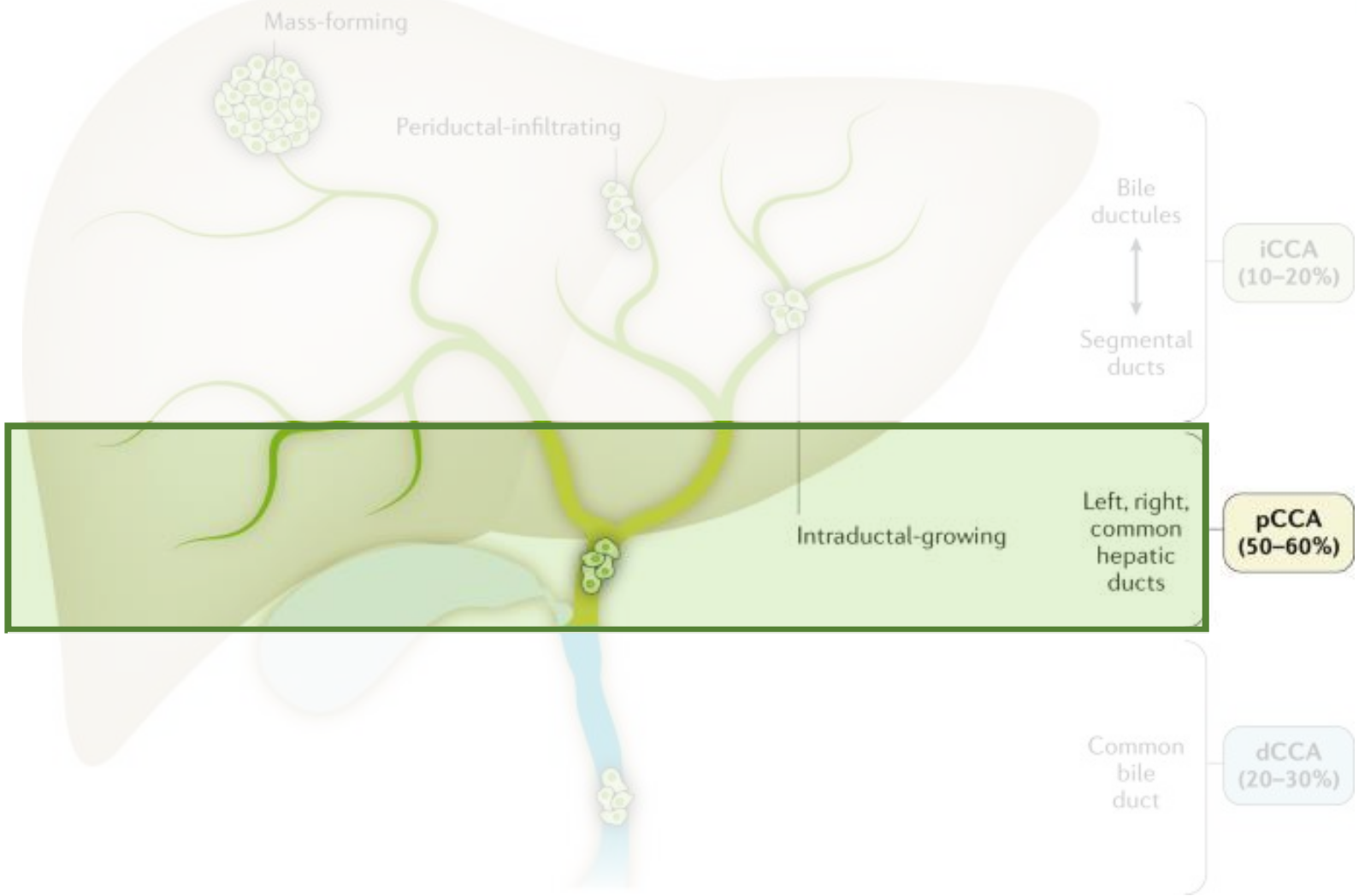
Trapianto di Fegato per Colangiocarcinoma
LIRICA & LITALHICA

Prof. Enrico GRINGERI, MD, PhD

Chirurgia Generale 2
Chirurgia Epato-bilio-pancreatica e Trapianti di Fegato
Azienda Università Padova
(Direttore: Prof. Umberto CILLO)

LIVER TRANSPLANTATION FOR pCCA
WHAT'S NEW?



LIVER TRANSPLANTATION FOR pCCA

The Mayo Clinic Protocol

MAYO CLINIC

Mayo clinic protocol

External beam radiation therapy (45 Gy in 30 fractions, 1.5 Gy twice daily) and continuous infusion 5-FU – administered over 3 weeks

↓

Brachytherapy (20 Gy at 1 cm in approximately 20–25 hours) – administered 2 weeks following completion of external beam radiation therapy

↓

Capecitabine – administered until the time of transplantation, held during perioperative period for staging

↓

Abdominal exploration for staging – as time nears for deceased donor transplantation or day prior to living donor transplantation

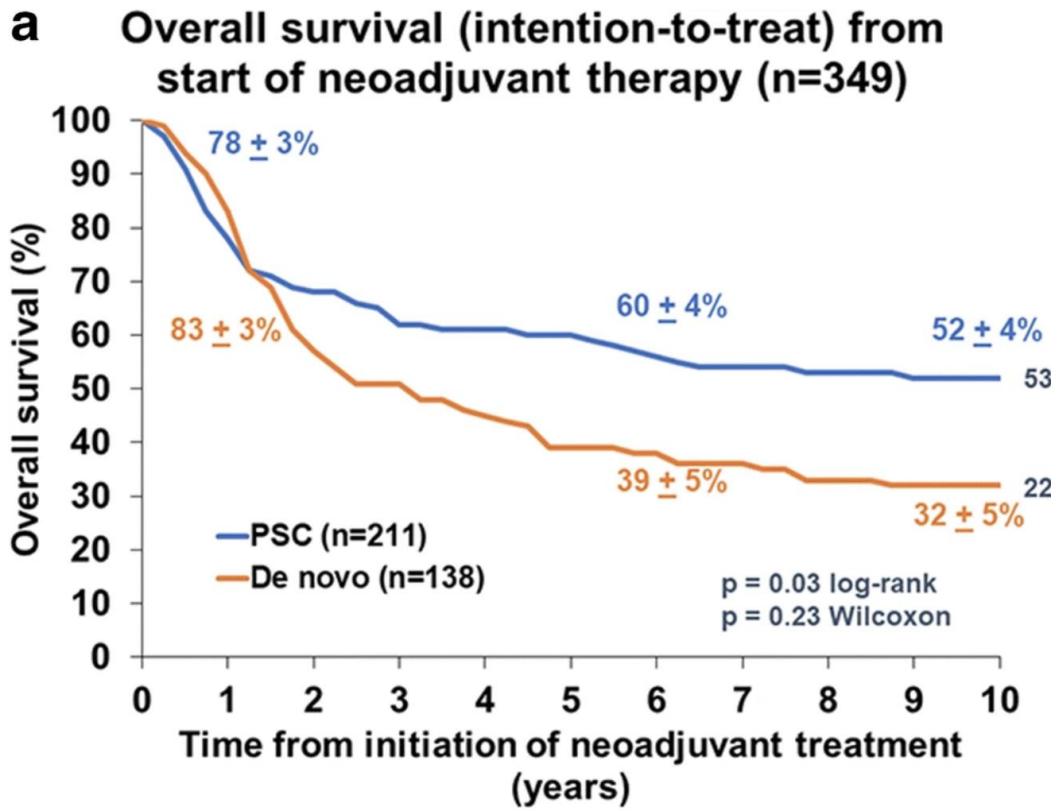
↓

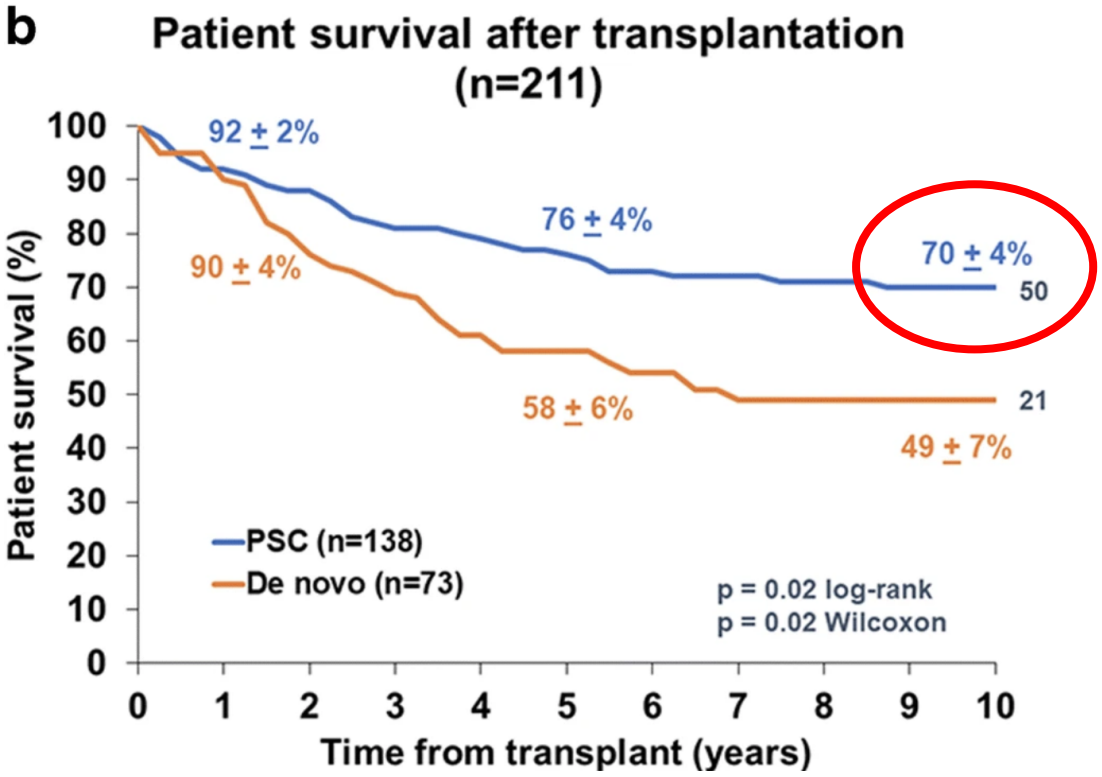
Liver transplantation

Rosen CB et al, *Transpl Int 23 (2010) 692–697*

LIVER TRANSPLANTATION FOR pCCA

The Mayo Clinic experience (1993-2018)





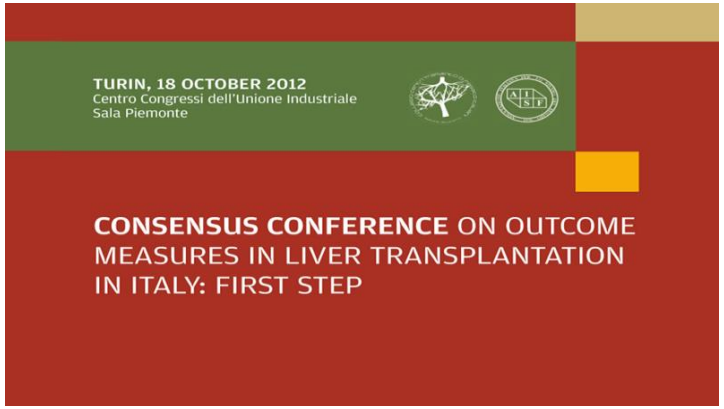
Tan EK et al, *J Gastrointest Surg 2020*

LIVER TRANSPLANTATION FOR pCCA

Table 2. Agreed priority stratafor MELD exceptions and correspondingorgan-sharing areas.

Priority and Sharing	LT Indication
P1 (Macro-area sharing after serving those with MELD>30)*	Rendu-Osler-Weber Hepatoblastoma (young adult) Hemangioma (if Kasabach Merritt syndrome) Acute late ReLT FAP (if domino)
P2 (Sharing at regional level)	Hepato-pulmonary syndrome PPH Refractory hydrothorax Chronic late ReLT Hepato-renal syndrome (if not automatically equated to MELD) Previous severe infections
P3(Sharing at regional level)	Refractory ascites FAP Wilson's (with compensated cirrhosis and initial neurological symptoms) NET metastases Hemangioendotheliomas
P4(Sharing at regional level)	PSC or PBC with intractable pruritus Polycystic disease Complicated adenoma Hemangiomas
P Multidisciplinary (Center-based)	Hepatic encephalopathy Fibrolamellar HCC Liver adenomatosis (not complicated) Hilarcholangiocarcinoma CRC metastases

Cillo U et al, Am J Transpl; 2015



2.5 In selected cases (note 1) and in association with precise neo-adjuvant radio/chemotherapy protocols (note 2) 5-ys overall survival after LT is over 50% (68-75%) BII.

Based on these data, in selected cases and after radio/chemotherapy, H-CCA could be considered as an indication for LT. BII

To date I-CCA (mass forming) does not represent an indication to LT.

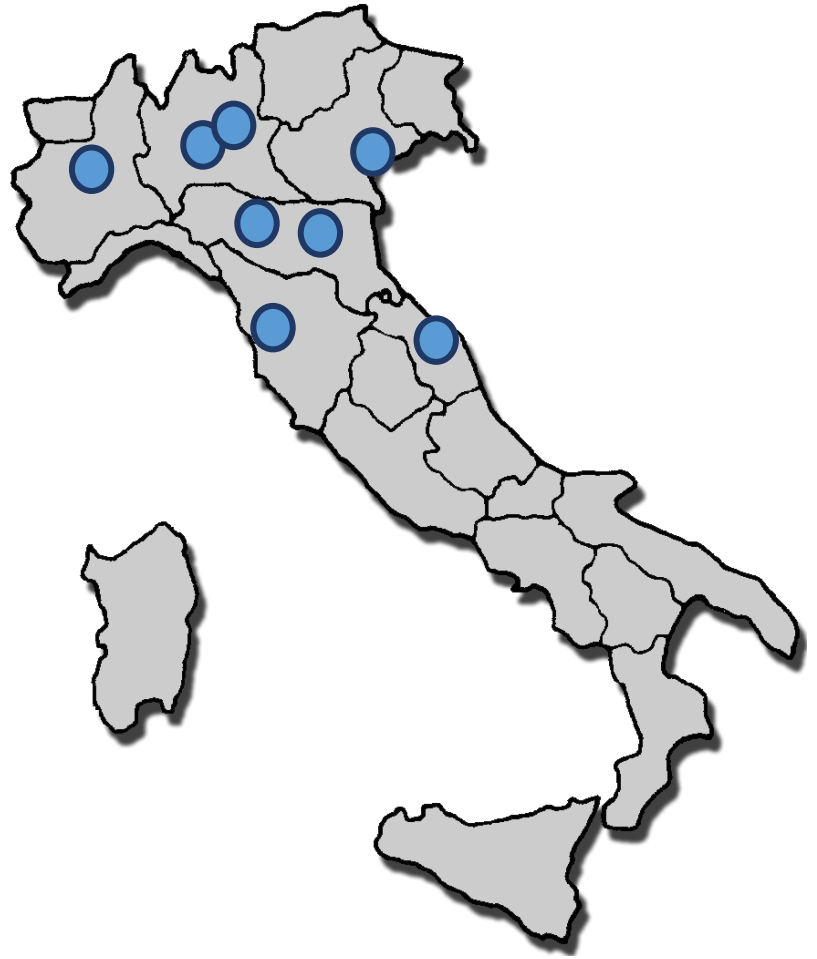
LIVER TRANSPLANTATION FOR pCCA

Italian experience

Liver transplantation for unresectable peri-hilar cholangiocarcinoma: an Italian survey

Gringeri E, Furlanetto A, Lanari J, Billato I, De Carlis L, Mazzaferro V, Romagnoli R, Cescon M, Vivarelli M, De Simone P, Rossi G, D'Amico FE, Gruttadauria S, Cardillo, M, Boggi U, Cillo U.

(Unpublished data)



Gringeri E et al, *Unpublished data*

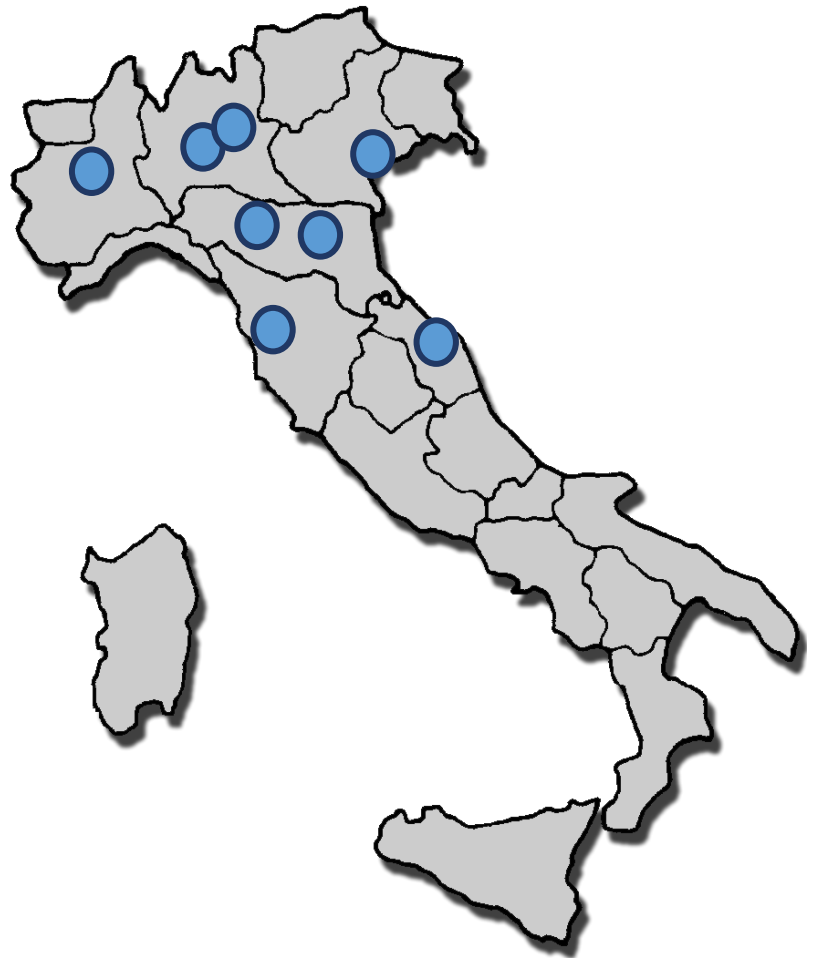
LIVER TRANSPLANTATION FOR pCCA

Italian experience

- Liver transplant centers involved: **22**
- Centers contacted by e-mail or phone: **22**
- Replies obtained and availability to collaborate: **22**
- Centers with no cases: **14**

Centers with at least one case: 8

Total cases in Italy: 53 (1986-2021)



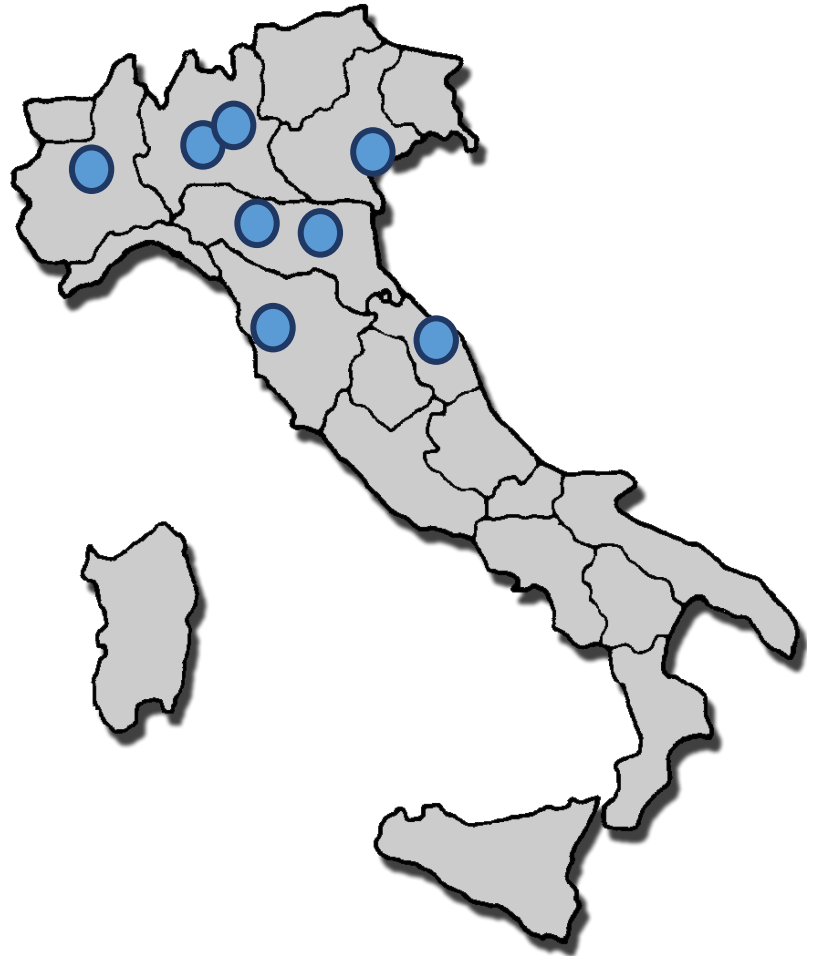
Gringeri E et al, *Unpublished data*

LIVER TRANSPLANTATION FOR pCCA

CENTRES	n° LT (53)	MAYO (25)	NOT MAYO (28)
ANCONA	2	1 / 2 (50%)	1 / 2 (50%)
BOLOGNA	12	7 / 12 (58%)	5 / 12 (42%)
MILANO NIGUARDA	10	0 / 10 (0%)	10 / 10 (100%)
MILANO TUMORI	8	8 / 8 (100%)	0 / 8 (0%)
MODENA	2	2 / 2 (100%)	0 / 2 (0%)
PADOVA	10	7 / 10 (70%)	3 / 10 (30%)
PISA	4	0 / 4 (0%)	4 / 4 (100%)
TORINO	5	0 / 5 (0%)	5 / 5 (100%)

53 OLTx for pCCA (1986 – 2021)

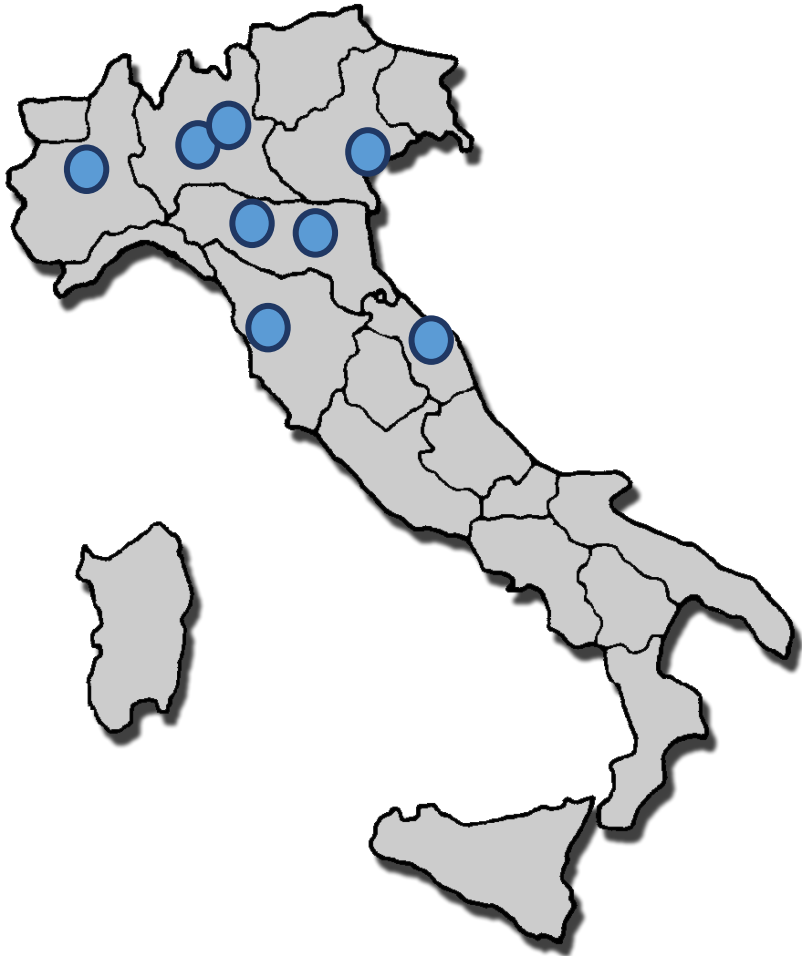
- 25 MAYO
- 28 NOT Mayo



Gringeri E et al, *Unpublished data*

LIVER TRANSPLANTATION FOR pCCA

		BEFORE 2015 (25 – 47.2%)		AFTER 2015 (28 – 52.8%)	
CENTRES	**n° LT (M - NM)**	**MAYO (8 - 32%)**	**NOT MAYO (17 – 68%)**	**MAYO (17 – 60.7%)**	**NOT MAYO (11 – 39.3%)**
ANCONA	2 (1-1)	0	0	1	1
BOLOGNA	12 (7-5)	2	0	5	5
MILANO NIGUARDA	10 (0-10)	0	8	0	2
MILANO - TUMORI	8 (8-0)	5	0	3	0
MODENA	2 (2-0)	0	0	2	0
PADOVA	10 (7-3)	1	3	6	0
PISA	4 (0-4)	0	1	0	3
TORINO	5 (0-5)	0	5	0	0



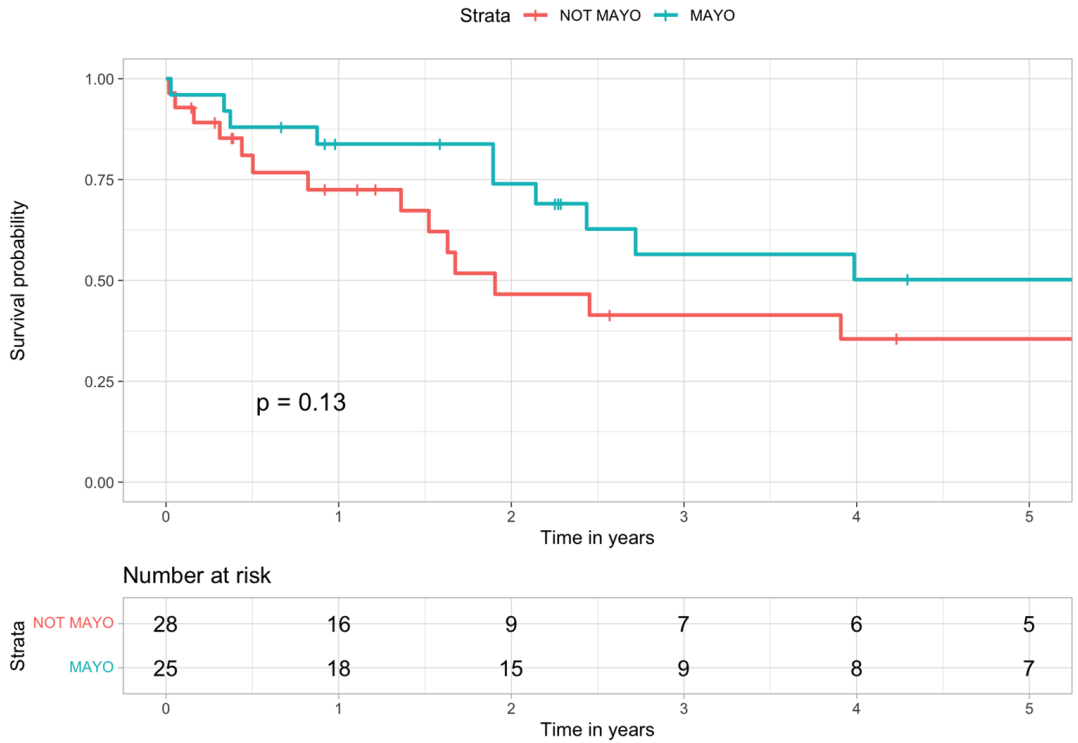
53 OLTx for pCCA

AFTER 2015 11 (39.3%) NOT MAYO

Gringeri E et al, *Unpublished data*

LIVER TRANSPLANTATION FOR pCCA

Overall Survival (OS)



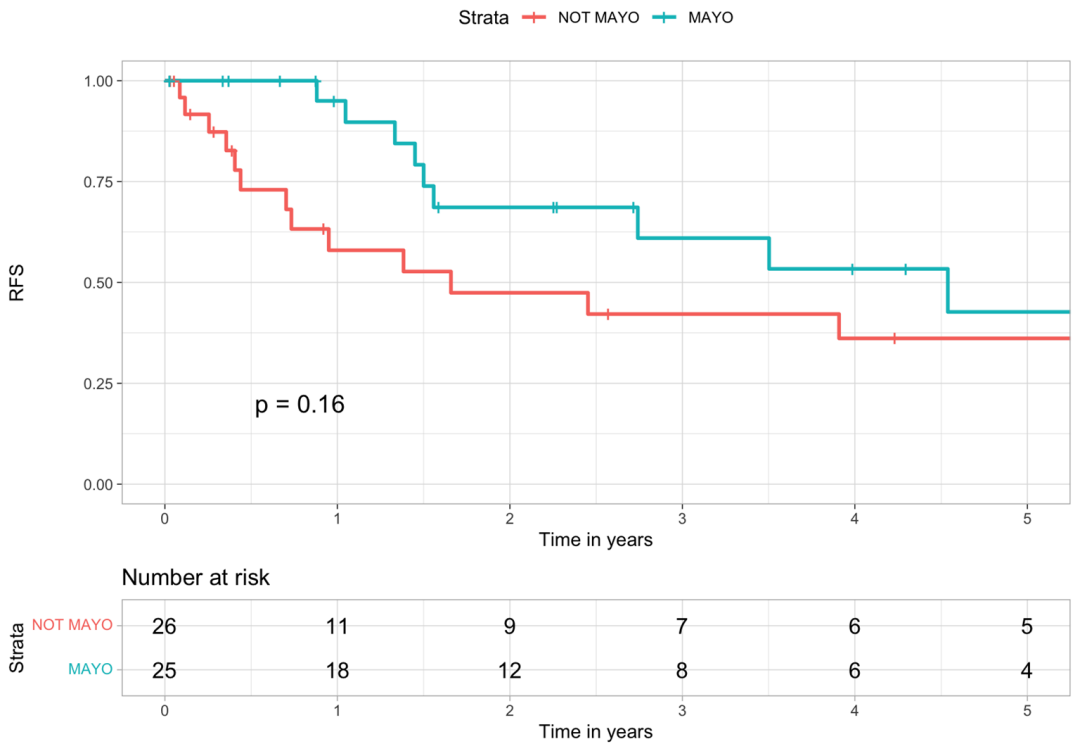
Overall survival and recurrence-free survival were compared using the Kaplan-Meier method; log-rank test significance levels were sets at P<0.05; all tests were two sided.

	LT cases (53)	Not Mayo Protocol (28)	Mayo Protocol (25)
1 yr OS (%)	78.2	72.4	83.8
3 yr OS (%)	49.3	41.4	56.6
5 yr OS (%)	43.1	35.5	50.6
Median OS (mo)	57	41	54
P-value		0.13	

Gringeri E et al, *Unpublished data*

LIVER TRANSPLANTATION FOR pCCA

Recurrence-free survival (RFS)



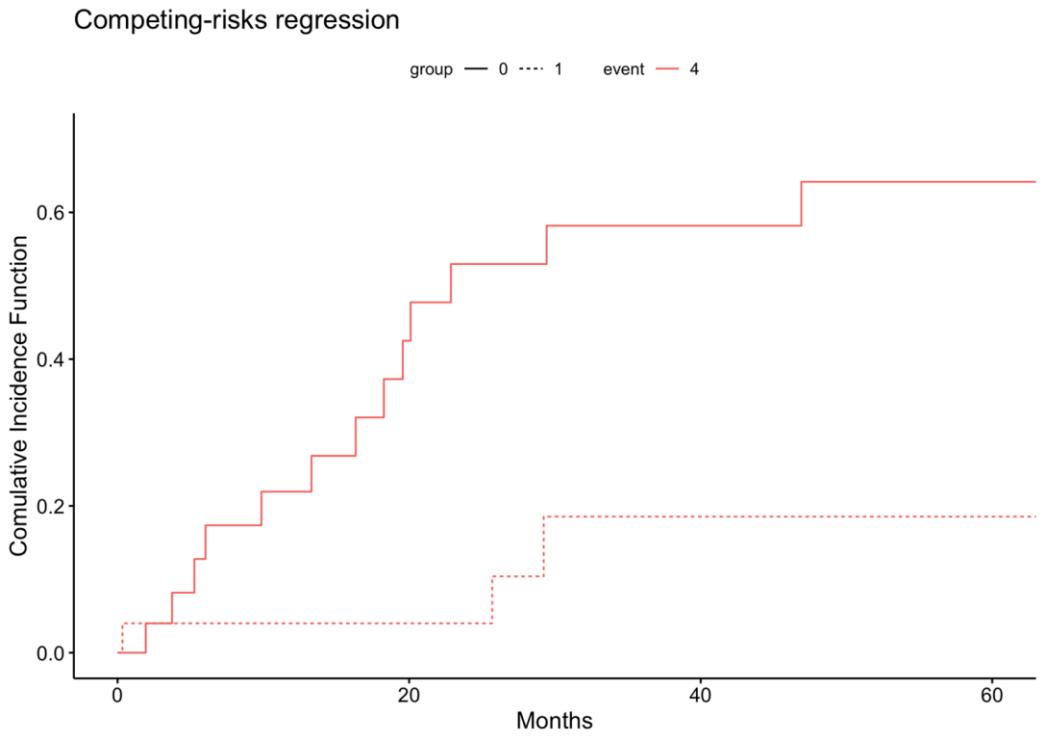
Overall survival and recurrence-free survival were compared using the Kaplan-Meier method; log-rank test significance levels were sets at P<0.05; all tests were two sided.

	LT cases (53)	Not Mayo Protocol (28)	Mayo Protocol (25)
1 yr RFS (%)	76.9	58.2	91.2
3 yr RFS (%)	51.7	42.2	61.1
5 yr RFS (%)	40.3	36.1	47.2
P-value		0.16	

Gringeri E et al, *Unpublished data*

LIVER TRANSPLANTATION FOR pCCA

Cancer-related death



Competing risk regression analysis was performed considering cancer-related-death and other-causes-of death as competing events.

Risk of Cancer Related Death		
	Not Mayo Protocol	Mayo Protocol
5 yr	62.3 %	19%
Hazard Ratio 0.31 (95% CI 0.10-0.98, p=0.047)		

Gringeri E et al, *Unpublished data*

LIVER TRANSPLANTATION FOR pCCA

The Mayo Clinic Protocol

MAYO CLINIC

pCCA: NEW PROTOCOL FOR LIVER TRANSPLANTATION

LIver TrAnspLantation for non-resectable peri-HIlar cholangioCArcinoma (LITALHICA)

The study would investigate if LT provides better outcomes in patients with unresectable pCCA, compared to a similar population undergoing chemotherapy (standard of care) in the same time period. No randomization.

Participants will receive downstaging therapies prior to transplantation. ***Follow-up = 5 years*** *from the time of LT.*

Main outcome measures: OS, DFS, Survival from recurrence, QoL, drop-out %…

Same Inclusion and Exclusion Criteria

Table 1. Criteria for neoadjuvant therapy and liver transplantation.

Diagnosis of cholangiocarcinoma
Transcatheter biopsy or brush cytology
CA-19.9 > 100 mg/ml and/or a mass on cross-sectional imaging with a malignant appearing stricture on cholangiography
Biliary ploidy by FISH with a malignant appearing stricture on cholangiography
Unresectable tumor above cystic duct
Pancreatoduodenectomy for microscopic involvement of CBD
Resectable CCA arising in PSC
Radial tumor diameter ≤3 cm
Absence of intra- and extrahepatic metastases
Candidate for liver transplantation

CBD, common bile duct; CCA, cholangiocarcinoma; PSC, primary sclerosing cholangitis.

Table 2. Exclusion criteria.

Intrahepatic cholangiocarcinoma
Uncontrolled infection
Prior radiation or chemotherapy
Prior biliary resection or attempted resection
Intrahepatic metastases
Evidence of extrahepatic disease
History of other malignancy within 5 years
Transperitoneal biopsy (including percutaneous and EUS guided FNA)

EUS, endoscopic ultrasound; FNA, fine needle aspiration.

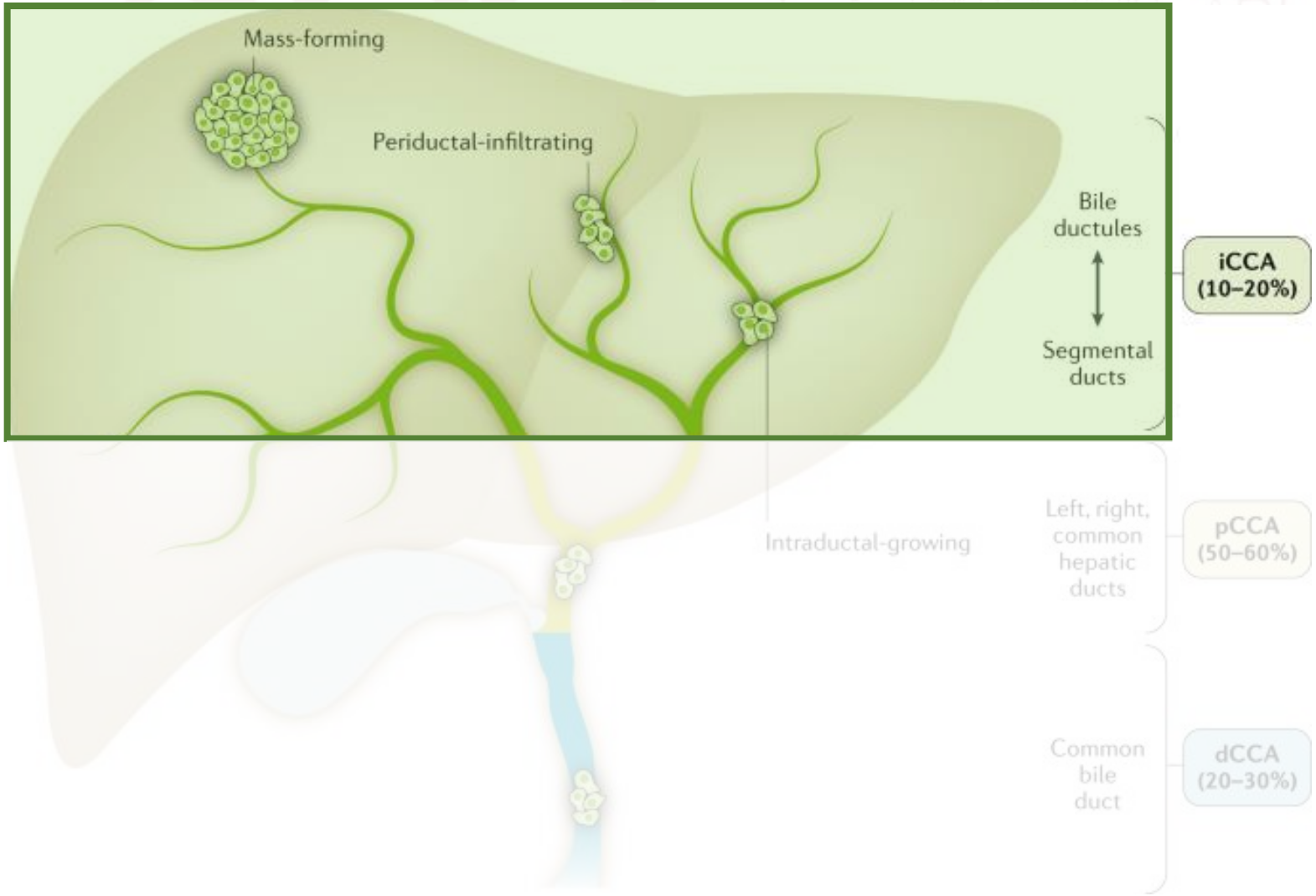
PI Enrico Gringeri – enrico.gringeri@unipd.it

pCCA: NEW PROTOCOL FOR LIVER TRANSPLANTATION

LIver TrAnspLantation for non-resectable peri-HIlar cholangioCArcinoma (LITALHICA)

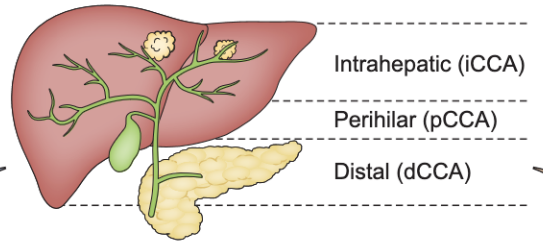
PI Enrico Gringeri – enrico.gringeri@unipd.it

LIVER TRANSPLANTATION FOR iCCA



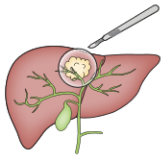
Intrahepatic cholangiocarcinoma: Surgical management

Intrahepatic cholangiocarcinoma (iCCA) is a predominantly mass-forming and lymphophilic malignancy of the intrahepatic bile ducts. It is the second most common primary liver cancer after HCC. While relatively rare, the incidence of iCCA is increasing.

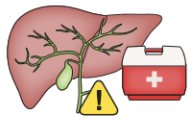


iCCA
- is increasing in incidence
- is usually diagnosed at a late stage
- has poor prognosis

Liver resection (LR)



LR is the only available curative treatment for iCCA, though only 12-40% of patients referred are resectable. Overall survival at 5-years is 25-40%, and 50-70% face tumor recurrence.



Currently not a standard therapy!

Liver transplant (LT)

Retrospective studies are now being conducted with more stringent selection criteria. One major study found a 5-year overall survival of 65% after transplantation for single tumors ≤2 cm.

First treatment option

Solitary iCCA

Hepatectomy plus lymphadenectomy

Selection

Selection of candidates for liver resection is based on oncological-, patient-, and liver-related factors

Indications
- FLR >25% in normal liver
- FLR >40% in chronic liver disease
- High quality FLR
- Solitary iCCA
- Peripheral/accessible location (Low morbidity/mortality)

Contraindications
- FLR <25% in normal liver
- FLR <40% in chronic liver disease
- Low quality FLR (Steatosis, atrophy, cirrhosis, fibrosis) (relative)
- Peritoneal/distant metastasis
- Distant lymph node involvement
- Central location (relative) (High morbidity/mortality)
- Portal hypertension (relative)

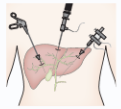
Surgery

Operative technique is a focus for research to improve outcomes and increase resectability

Ideal…

Anatomic resection

Laparoscopic resection



Lymphadenectomy (≥6 nodes for staging)

Consider…

Vascular resection
- For infiltrative iCCA
- Comparable outcomes

Repeat resection
- For recurrent iCCA
- Acceptable morbidity/ mortality

Cirrhosis < 2 cm

Experimental for larger and multifocal

Clinical trials

Selection

Use of LT in iCCA and selection criteria for these patients is under active study. LT is considered for patients that are unresectable due to location, liver dysfunction, or bilobar disease

Indications
- Unresectable (ex. cirrhotic FLR)
- Early stage iCCA (Single tumor ≤2 cm)
- Locally advanced iCCA
  - Response to neoadjuvant
  - Favorable tumor biology

Contraindications
- Vascular invasion
- Extrahepatic disease
- Lymph node spread
- Locally advanced iCCA
  - No response to neoadjuvant
  - Unfavorable tumor biology

Surgery

Consider the source of a donor liver and pre-transplant lymph node procurement

Living donor liver transplant *vs.* Deceased donor liver transplant

Portal lymphadenectomy

Staging and prognosis

EASL-ILCA Guidelines – Journal of Hepathology 2023

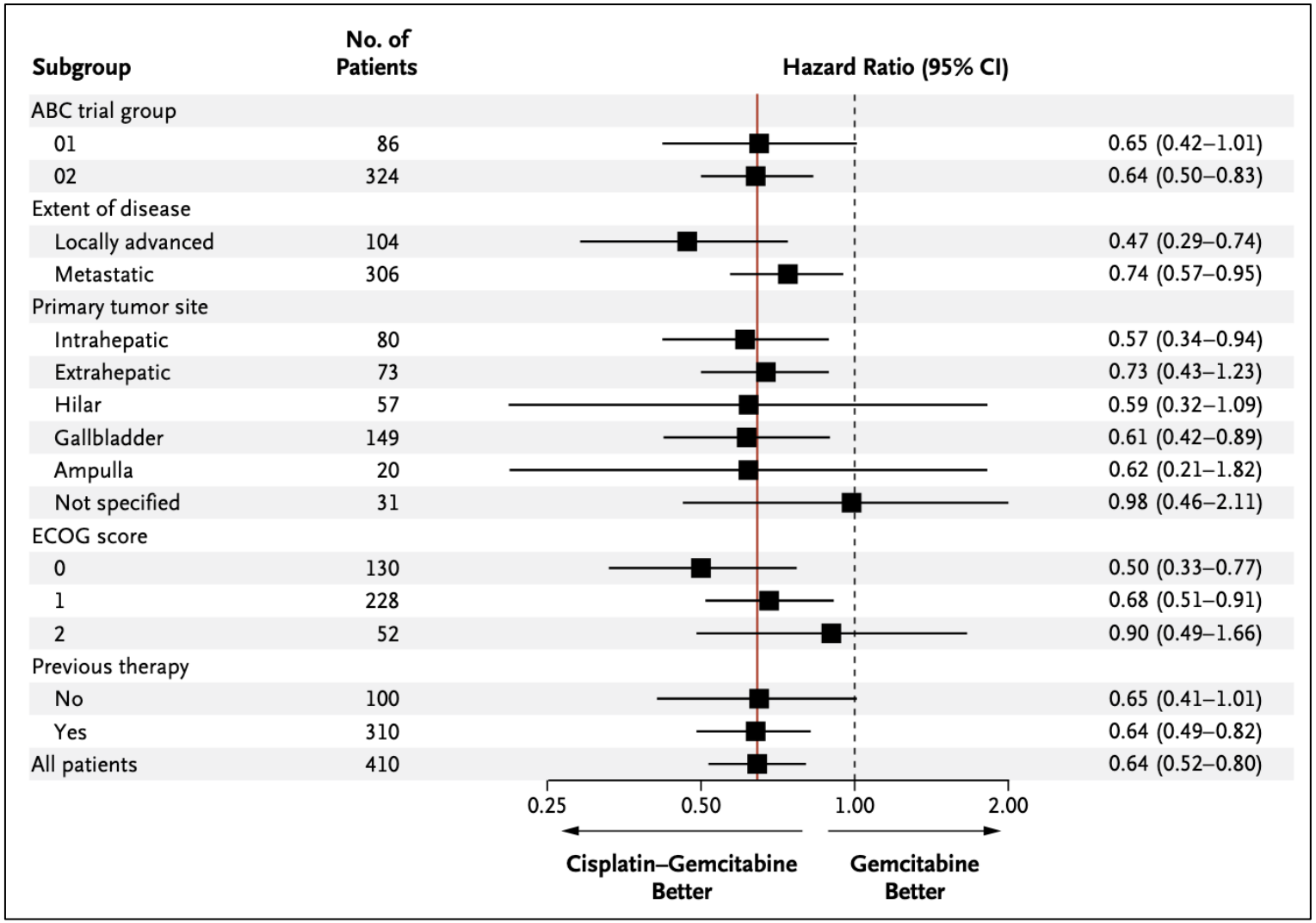
Time to reconsider liver transplantation for intrahepatic cholangiocarcinoma?

- ✓ Hepatectomy is the only curative treatment, (R0, N0, M0, no vascular invasion) -> median OS 51 mo
- ✓ Only 25% cadidate for surgery
- ✓ Non-resectable patients have a median OS 11.7 mo after GEM-CIS
- ✓ encouraging results of LT for pCCA after neoadjuvant therapy

THE EMERGING CONCEPT OF TRANSPLANT ONCOLOGY

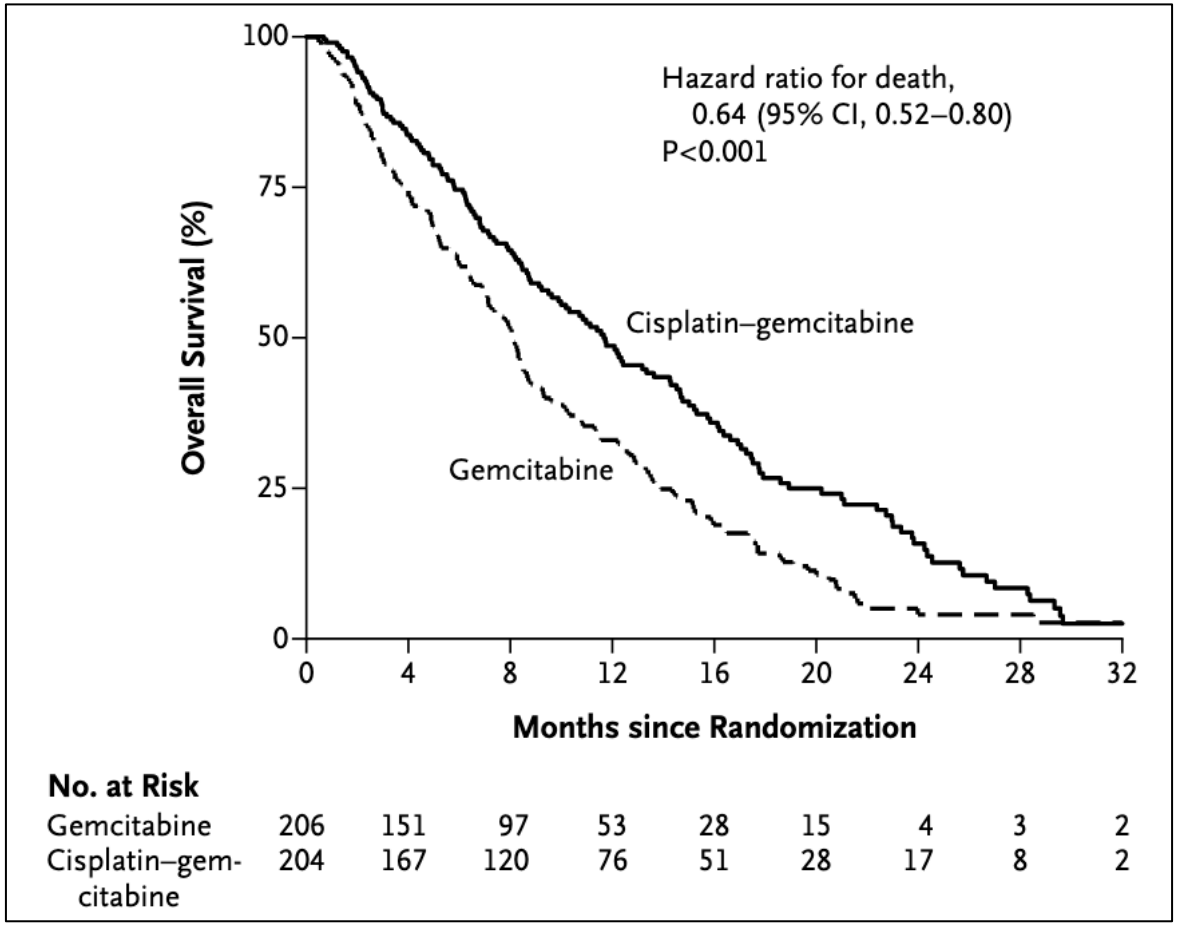
G. Sapisochin – Lancet Gastrenterology & Hepatology, 2018

Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer



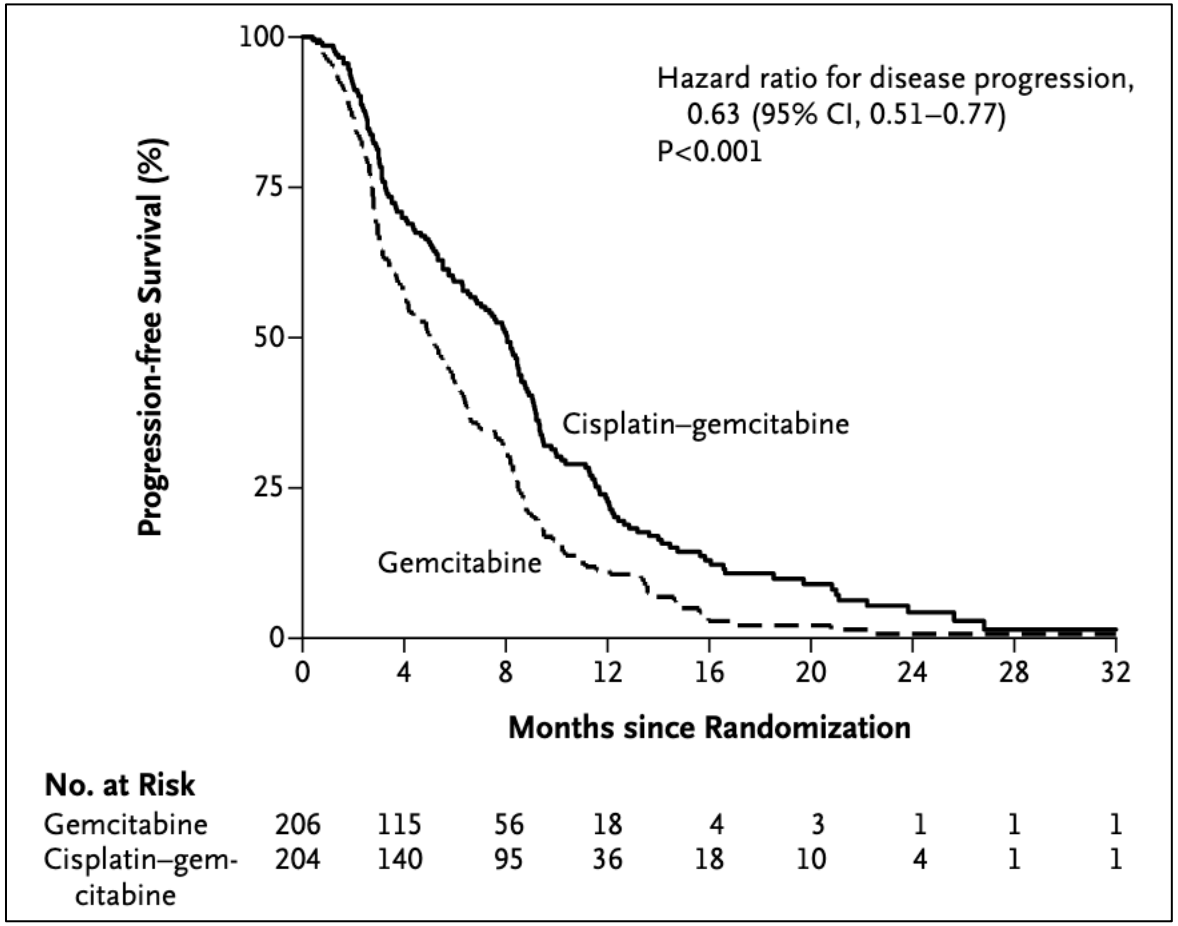
Valle JW et al – New Engl J Med, 2010

Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer



No. at Risk

Gemcitabine	206	151	97	53	28	15	4	3	2
Cisplatin–gemcitabine	204	167	120	76	51	28	17	8	2

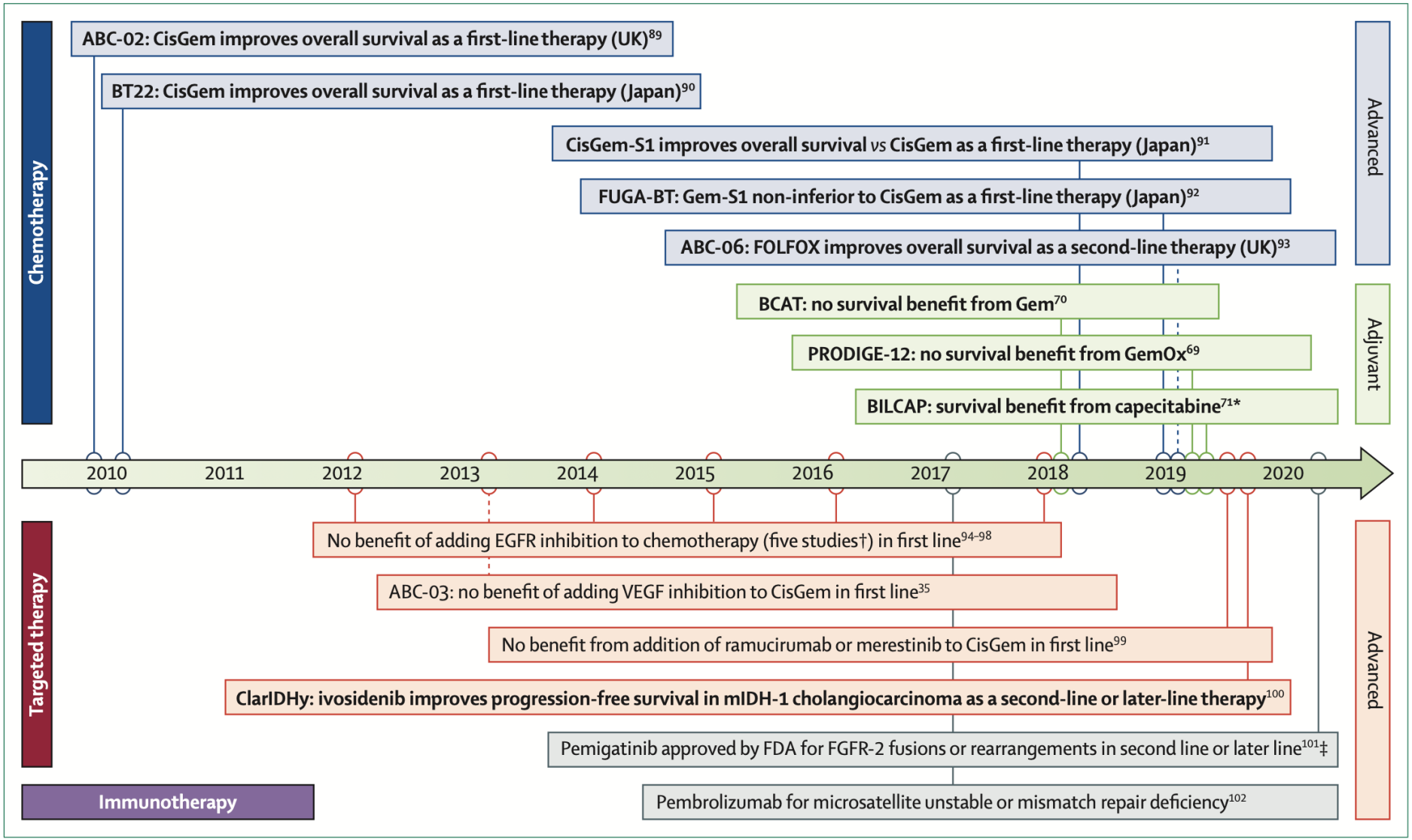


No. at Risk

Gemcitabine	206	115	56	18	4	3	1	1	1
Cisplatin–gemcitabine	204	140	95	36	18	10	4	1	1

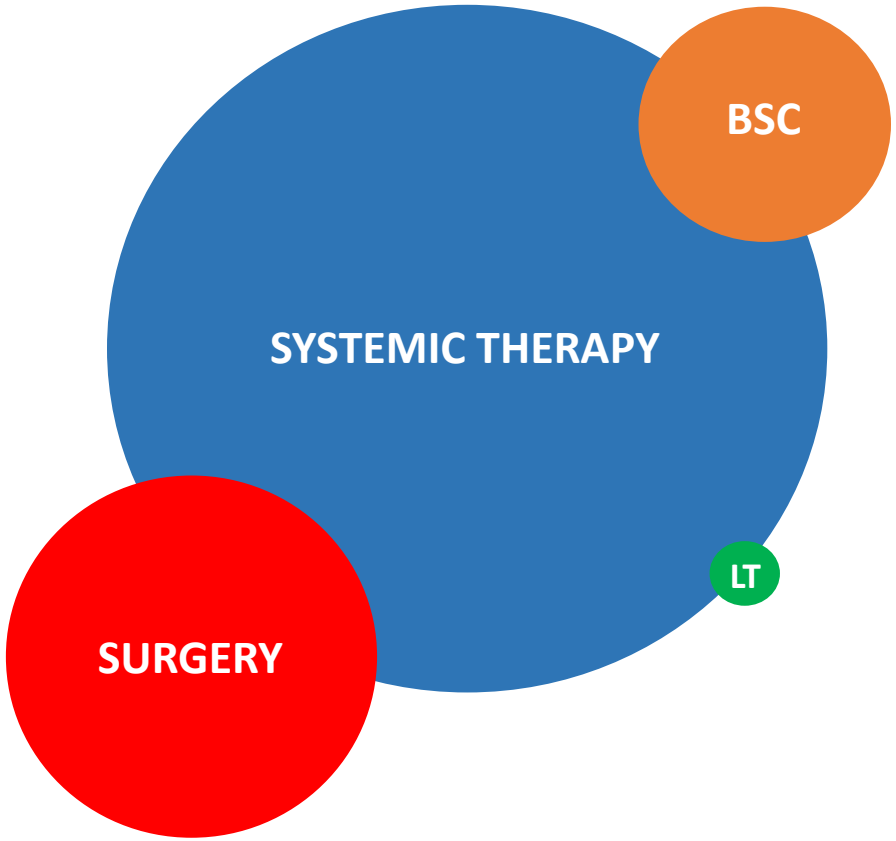
Valle JW et al – New Engl J Med, 2010

iCCA: SYSTEMIC THERAPY

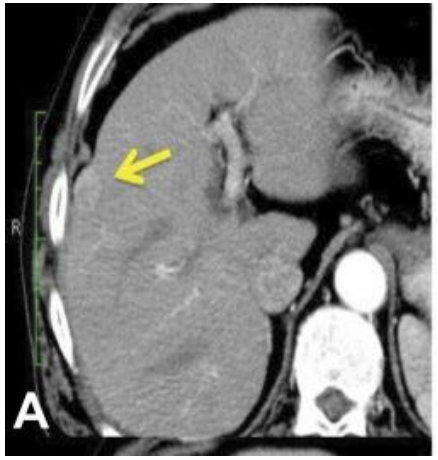


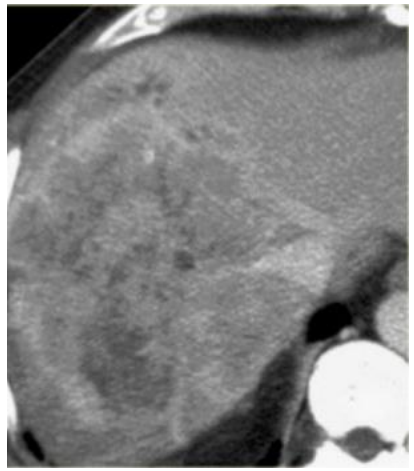
Valle JW et al – Lancet, 2021

LIVER TRANSPLANTATION FOR iCCA



LT FOR iCCA: DIFFERENT SCENARIOS





SCENARIO 1

patients with very early disease (single tumor, ≤2 cm) with cirrhosis and are not candidates for liver resection

LIVER TRANSPLANTATION?

SCENARIO 2

patients with locally advanced iCCA, but where the extent of LR would be too extensive to be feasible.

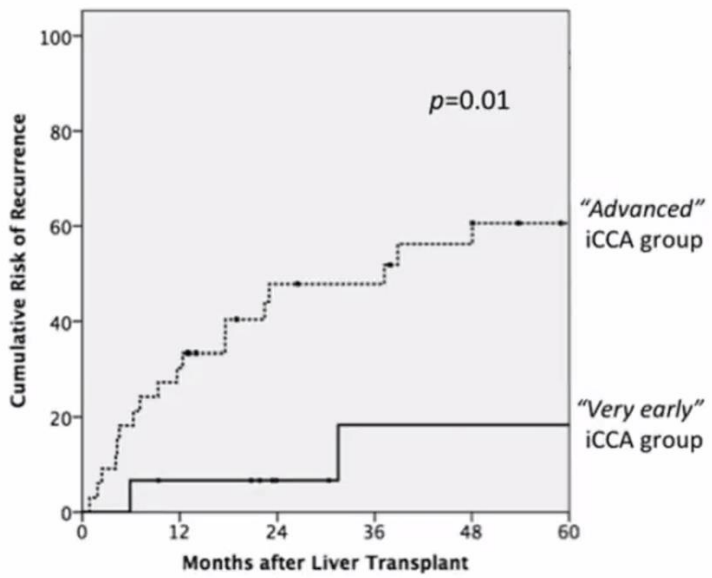
LIVER TRANSPLANTATION?

SCENARIO 1

LIVER TRANSPLANTATION FOR iCCA

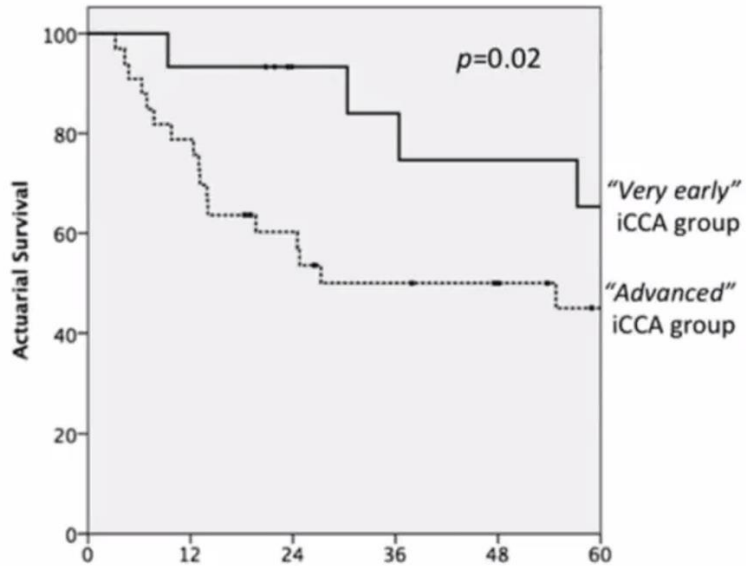
UNIVERSITÀ DEGLI STUDI DI PADOVA

Liver Transplantation for "Very Early" Intrahepatic Cholangiocarcinoma: International Retrospective Study Supporting a Prospective Assessment



Patients at risk

"Very Early"	15	13	9	7	7	7
"Advanced"	33	23	14	13	10	6



Patients at risk

"Very Early"	15	14	10	9	8	7
"Advanced"	33	26	18	14	12	8

5-year recurrence 18%. 5-year survival 65%

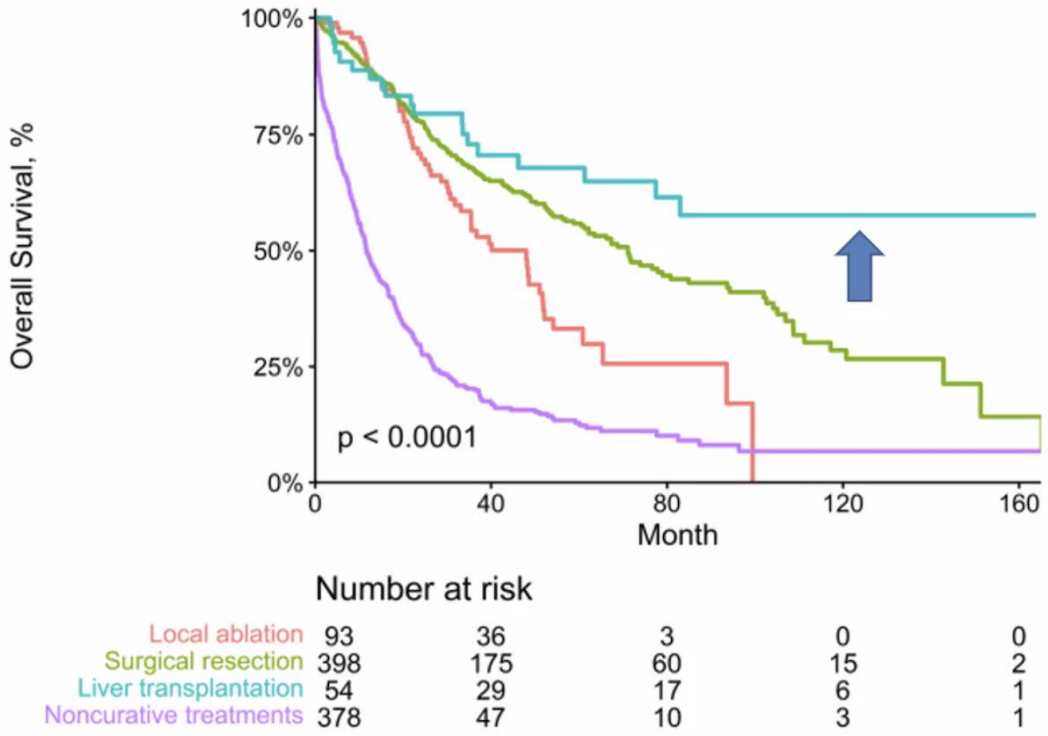
Sapisochin G et al. Hepatology 2016

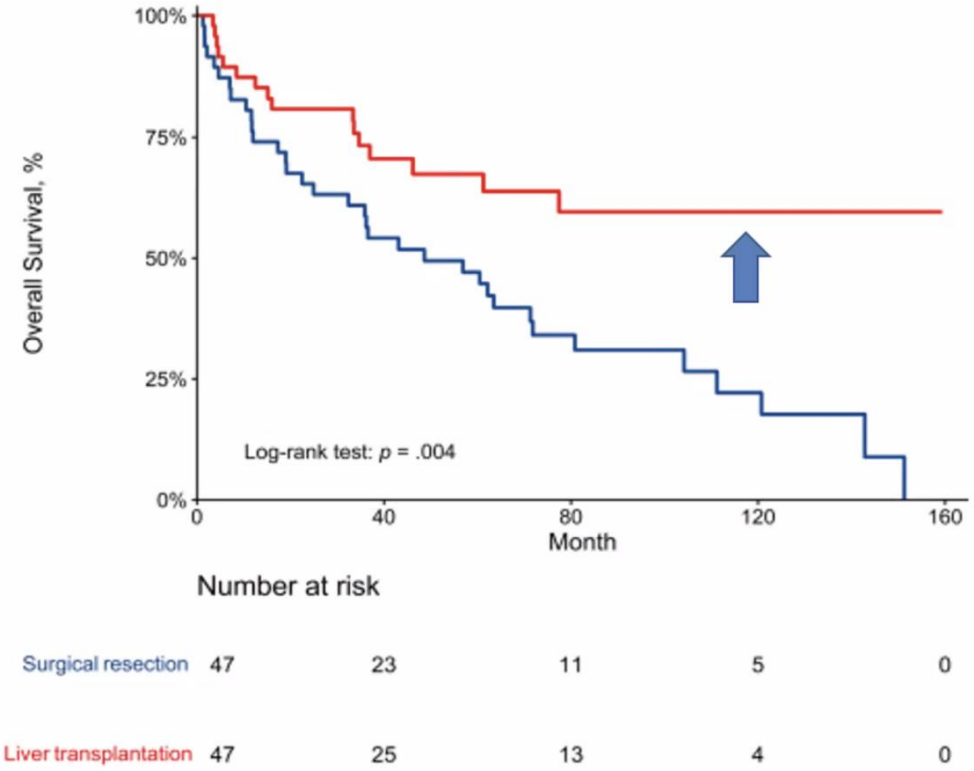
SCENARIO 1

LIVER TRANSPLANTATION FOR iCCA

Università degli Studi di Padova

US National Cancer Database
Treatments for early stage iCCA (single tumor < 3cm)





UHN Ajmera Transplant Centre

Lee Yi-Te, et al. Cancers 2022

SCENARIO 1

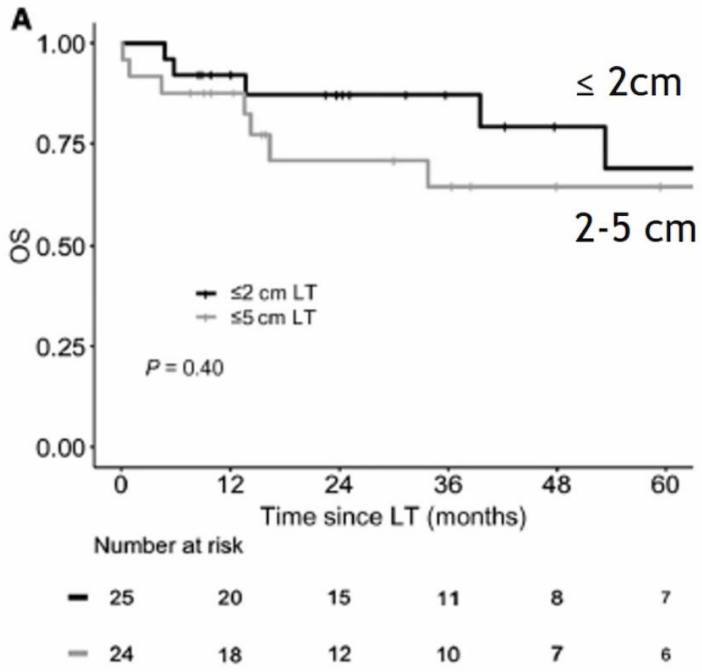
LIVER TRANSPLANTATION FOR iCCA

UNIVERSITÀ DEGLI STUDI DI PADOVA

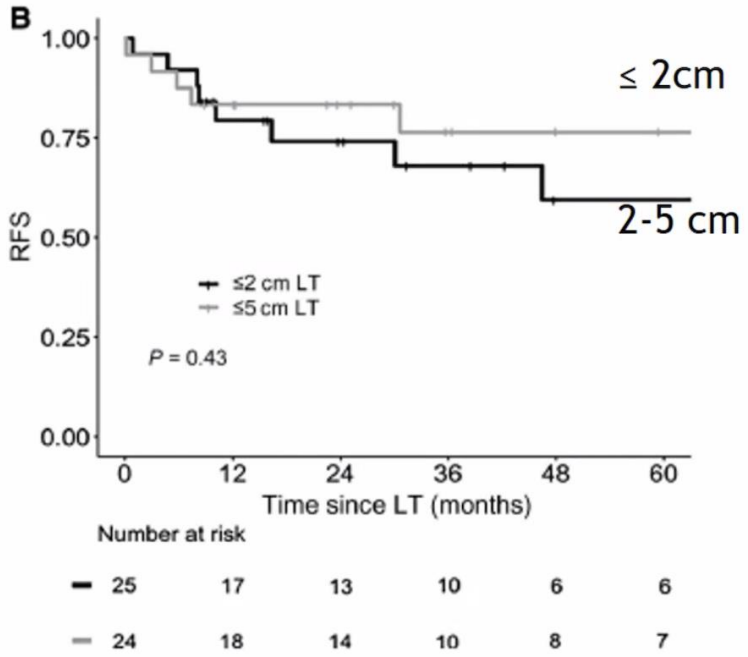
Liver Transplantation ≤2 cm vs. 2-5 cm

Conversazione in corso: Gonzalo...

Overall Survival



Disease-Free Survival



UHN Ajmera Transplant Centre

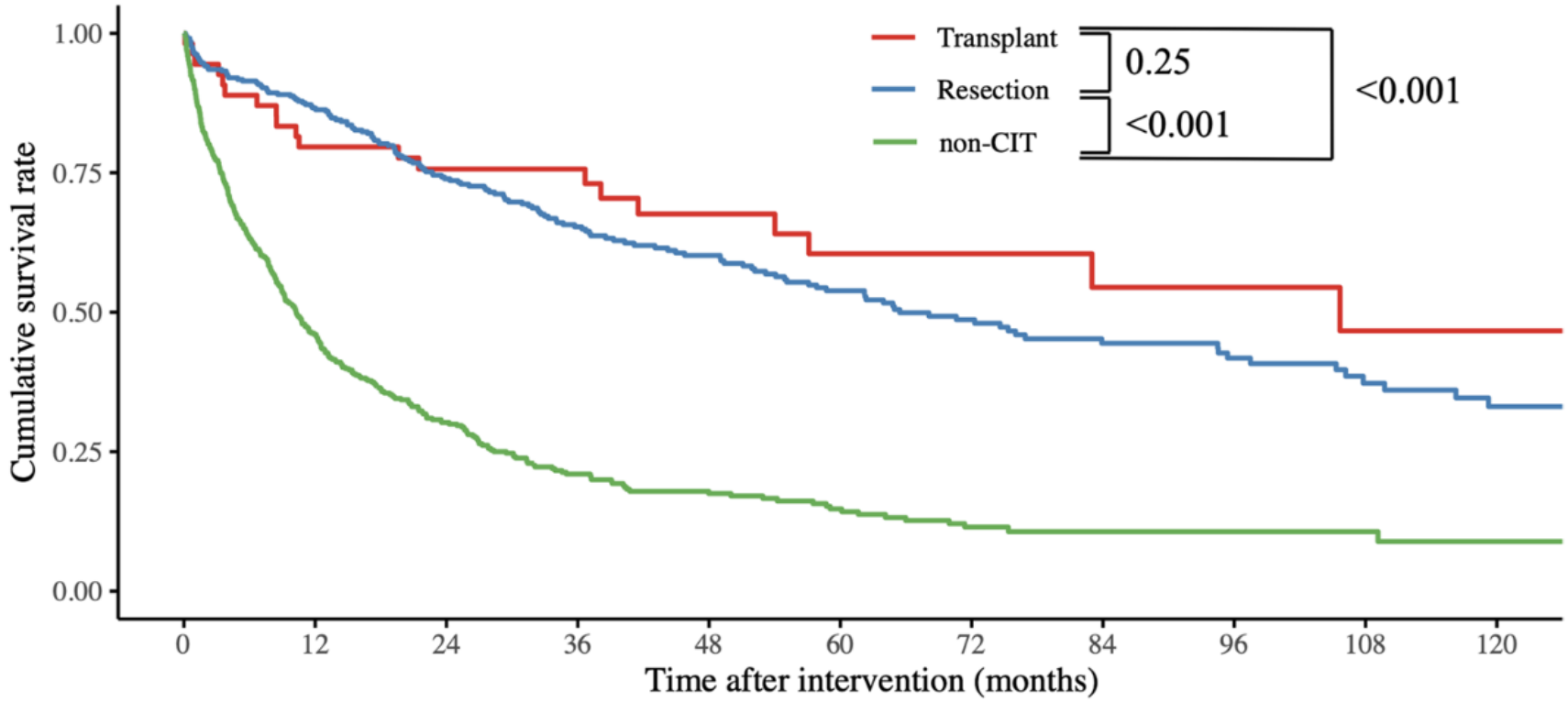
De Martin E, et al. Liver Transpl. 2020

SCENARIO 1

ORIGINAL ARTICLE

Survival Benefit Relative to Treatment Modalities Among Patients with Very Early Intrahepatic Cholangiocarcinoma: an Analysis of the National Cancer Database

Fig. 2 Kaplan-Meier curves relative to treatment modalities for very early intrahepatic cholangiocarcinoma. Non-CIT, non-curative intent treatment



Endo Y, Pawlik TM – J Gatrointest Surg, 2023

SCENARIO 1

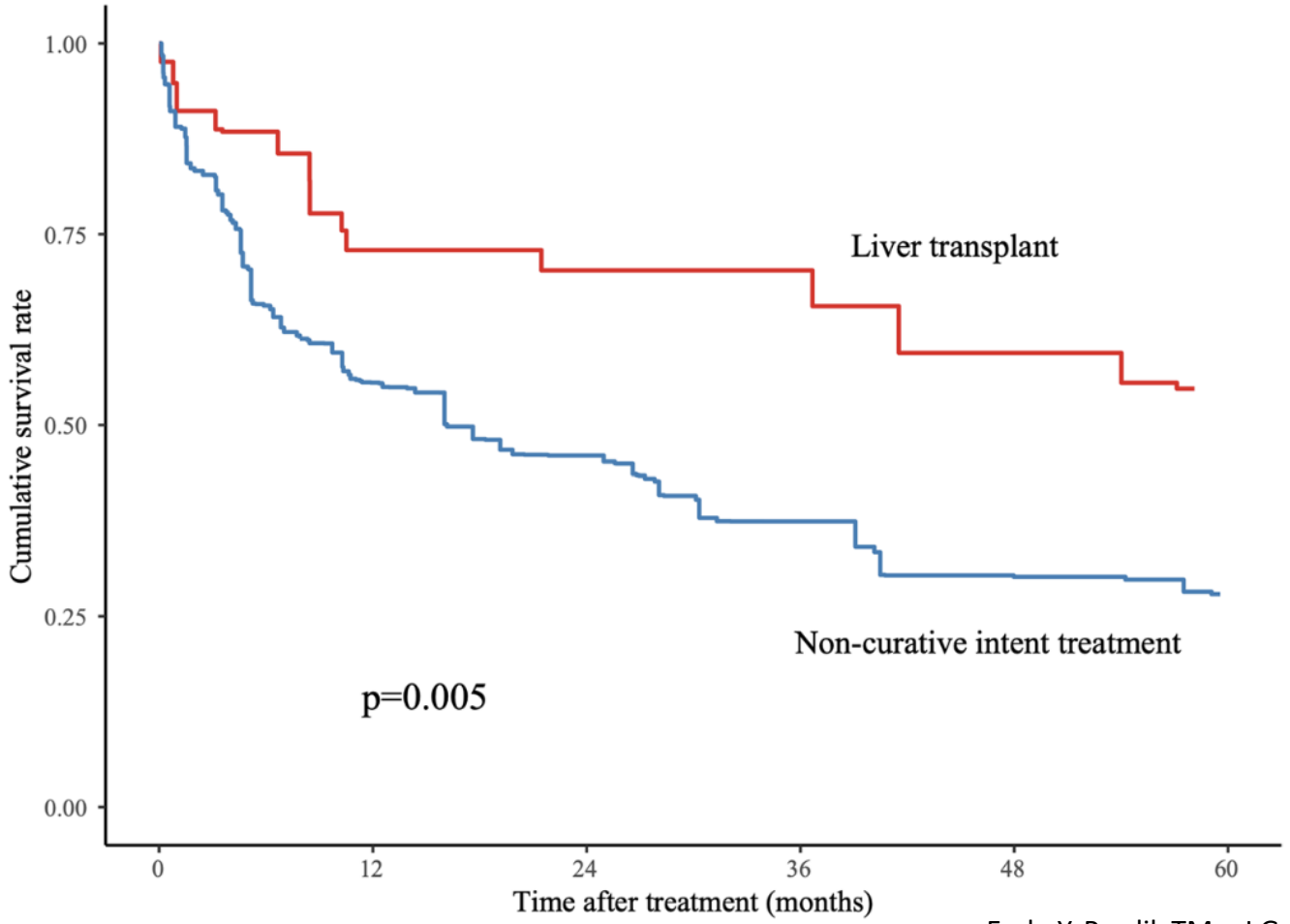
ORIGINAL ARTICLE

Check for updates

UNIVERSITÀ DEGLI STUDI DI PADOVA

Survival Benefit Relative to Treatment Modalities Among Patients with Very Early Intrahepatic Cholangiocarcinoma: an Analysis of the National Cancer Database

Fig. 4 Kaplan-Meier curve for liver transplantation and non-curative intent treatment groups after propensity score over-lapped weighting adjustment



Endo Y, Pawlik TM – J Gatrointest Surg, 2023

SCENARIO 1

ORIGINAL ARTICLE

Check for updates

UNIVERSITÀ DEGLI STUDI DI PADOVA

Survival Benefit Relative to Treatment Modalities Among Patients with Very Early Intrahepatic Cholangiocarcinoma: an Analysis of the National Cancer Database

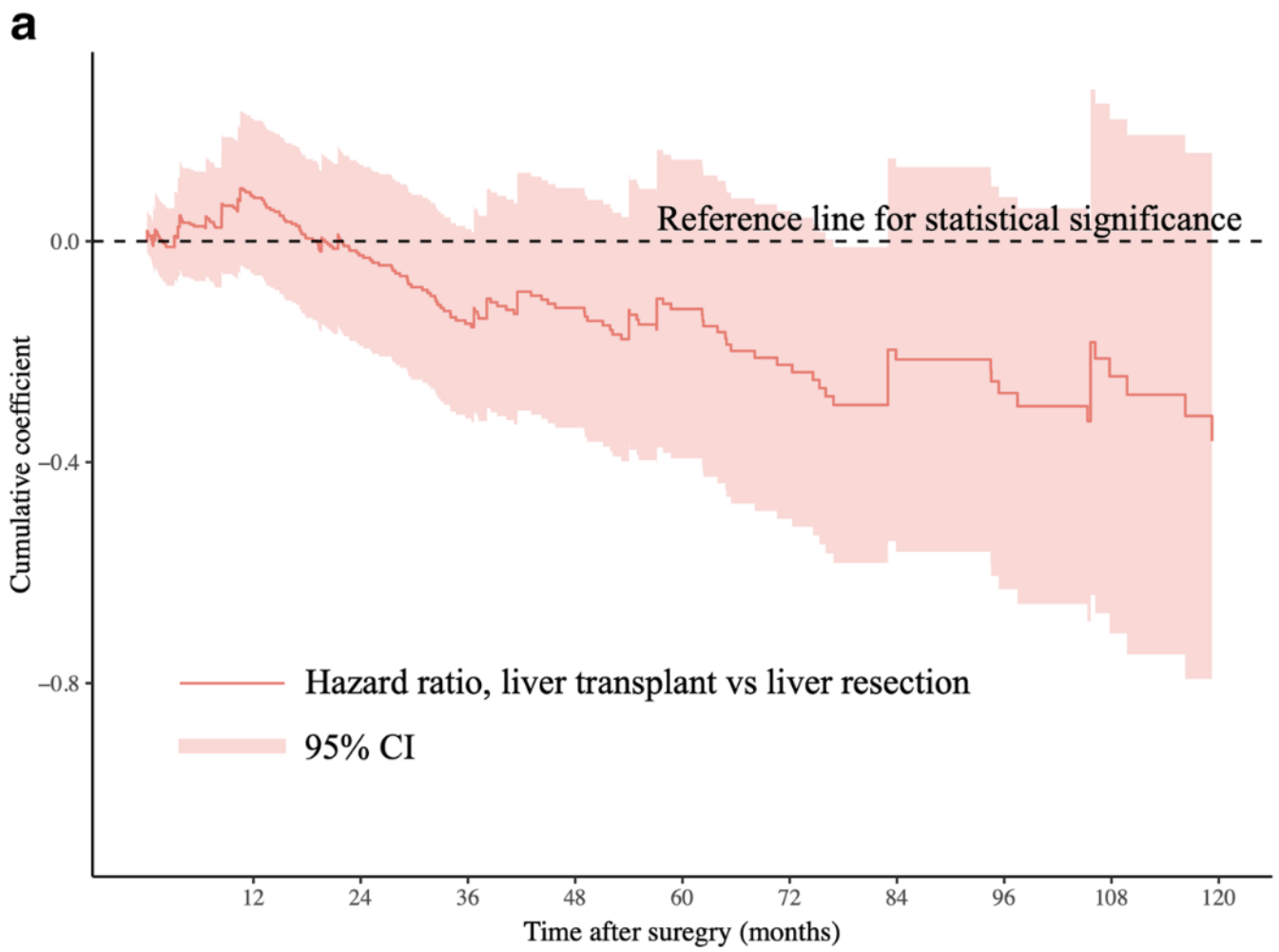
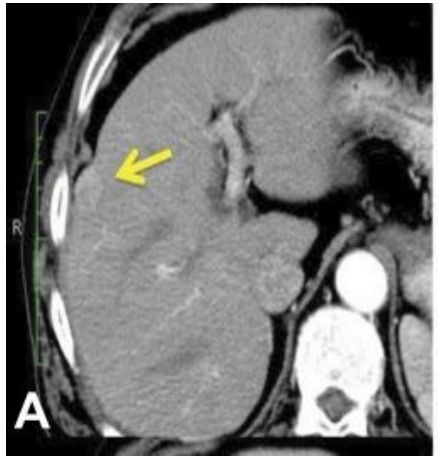


Fig. 3 **a** Aalen's linear hazards plot comparing the overall survival of patients treated with liver transplantation and those undergoing surgical resection of very early intrahepatic cholangiocarcinoma. **b** Conditional survival relative to treatment options and age. LT, liver transplant; LR, liver resection

LT FOR iCCA: DIFFERENT SCENARIOS



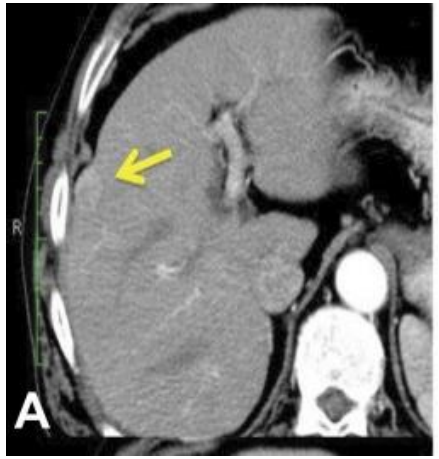
SCENARIO 1

patients with very early disease (single tumor, ≤2 cm) with cirrhosis and are not candidates for liver resection

LIVER TRANSPLANTATION?

YES

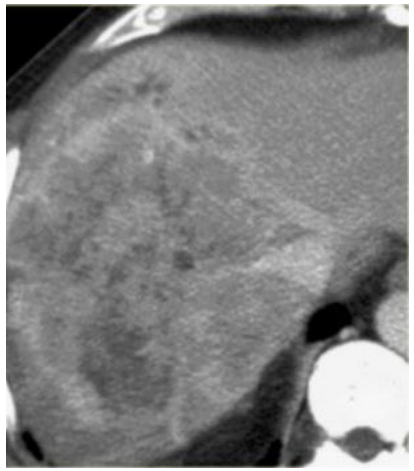
LT FOR iCCA: DIFFERENT SCENARIOS



SCENARIO 1

patients with very early disease (single tumor, ≤2 cm) with cirrhosis and are not candidates for liver resection

LIVER TRANSPLANTATION?



SCENARIO 2

patients with locally advanced iCCA, but where the extent of LR would be too extensive to be feasible.

SCENARIO 2

Original Research Article from the North Pacific Surgical Association

Neoadjuvant chemotherapy is associated with improved survival in patients undergoing hepatic resection for intrahepatic cholangiocarcinoma

Università degli Studi di Padova

Table 1
Clinicopathologic characteristics for n = 52 patients with resected ICC.

Characteristic	No Neoadjuvant (n = 42); N (%)	Neoadjuvant (n = 10); N (%)	*P*-value
Demographics			
Age at Resection (years); median [IQR]	65 [57–72]	58 [44–66]	0.02
Male Sex	23 (54.8)	3 (30)	0.16
Race			0.41
Asian	2 (4.8)	0 (0)	
Black/African American	1 (2.4)	0 (0)	
Nonhispanic Caucasian	38 (90.5)	10 (100)	
Pacific Islander	1 (2.4)	0 (0)	
BMI Categorization (kg/m^2)			0.27
Normal (18.5 -24.9)	9 (21.4)	0 (0)	
Overweight (25 to 29.9)	12 (28.6)	4 (40)	
Obese (30 or more)	21 (50)	6 (60)	
ASA Classification			0.41
1-2	13 (33.3)	2 (20)	
3-4	28 (66.7)	8 (80)	
ECOG Classification			0.80
0	35 (83.3)	8 (80)	
1-2	7 (16.7)	2 (20)	
Underlying Liver Disease			
Chronic Viral Hepatitis	4 (9.5)	0 (0)	0.31
Cirrhosis	3 (7.1)	0 (0)	0.38
Pre-operative Tumor Markers			
CA 19-9 (ng/mL); median [IQR]	10 [7.9–51]	62 [46–1445]	0.10
AFP (ng/mL); median [IQR]	2.7 [2–4.3]	3 [2.2–4.6]	0.80
CEA (ng/mL); median [IQR]	1.4 [0.9–1.8]	1.9 [1–3.3]	0.13
Neoadjuvant Chemotherapy			N/A
Gemcitabine/platinum	0 (0)	9 (90)	
FOLFOX	0 (0)	1 (10)	

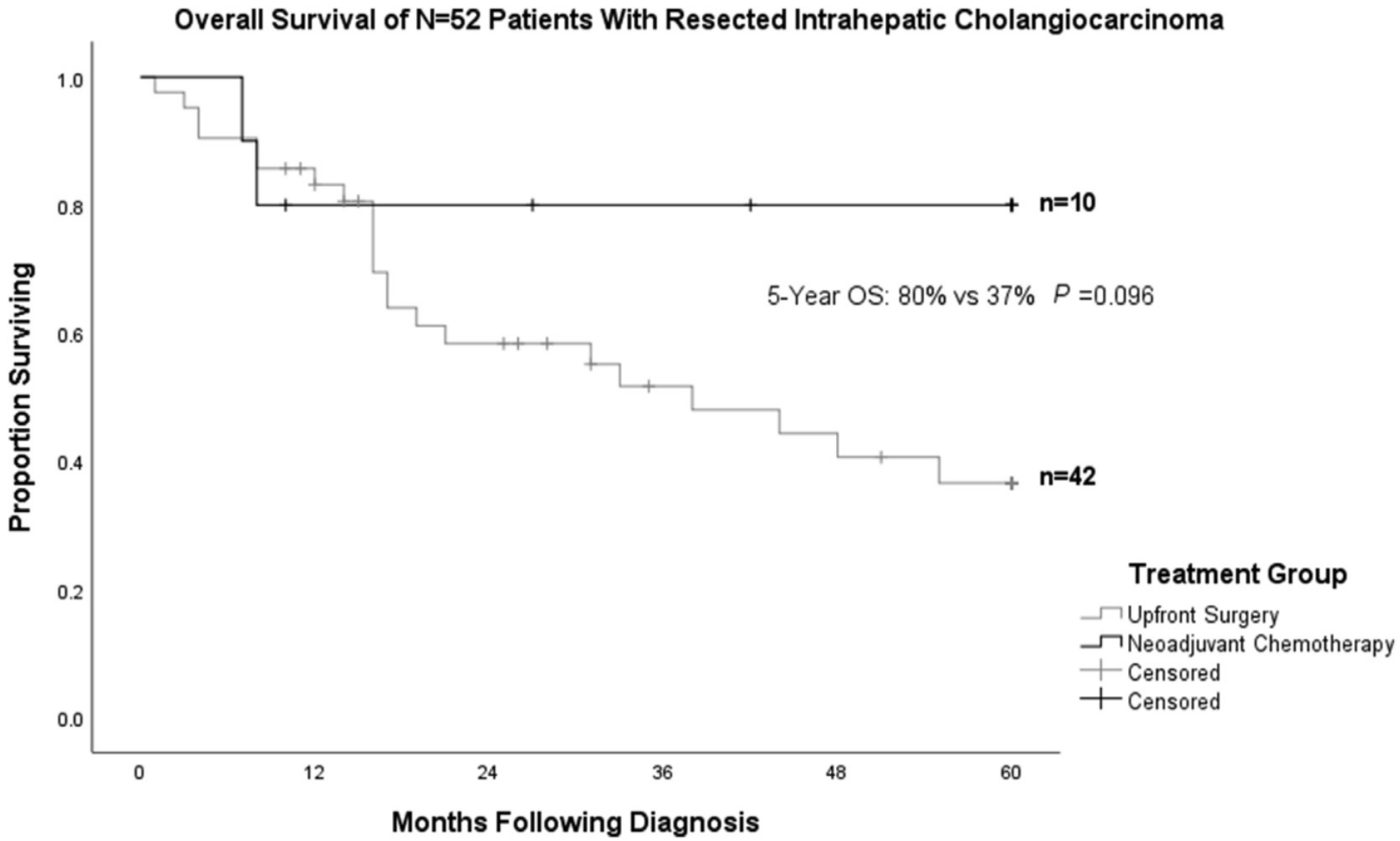
Abbreviations: ICC=Intrahepatic Cholangiocarcinoma; IQR=Interquartile Range; BMI=Body Mass Index; ASA = American Society of Anesthesiologists; CA=Cancer Antigen; AFP = Alpha-fetoprotein; CEA=Carcinoembryonic Antigen; FOLFOX = 5-Fluorouracil, Oxaliplatin, Folinic Acid.

Sutton TL – The America Journal of Surgery, 2021

SCENARIO 2

Original Research Article from the North Pacific Surgical Association

Neoadjuvant chemotherapy is associated with improved survival in patients undergoing hepatic resection for intrahepatic cholangiocarcinoma

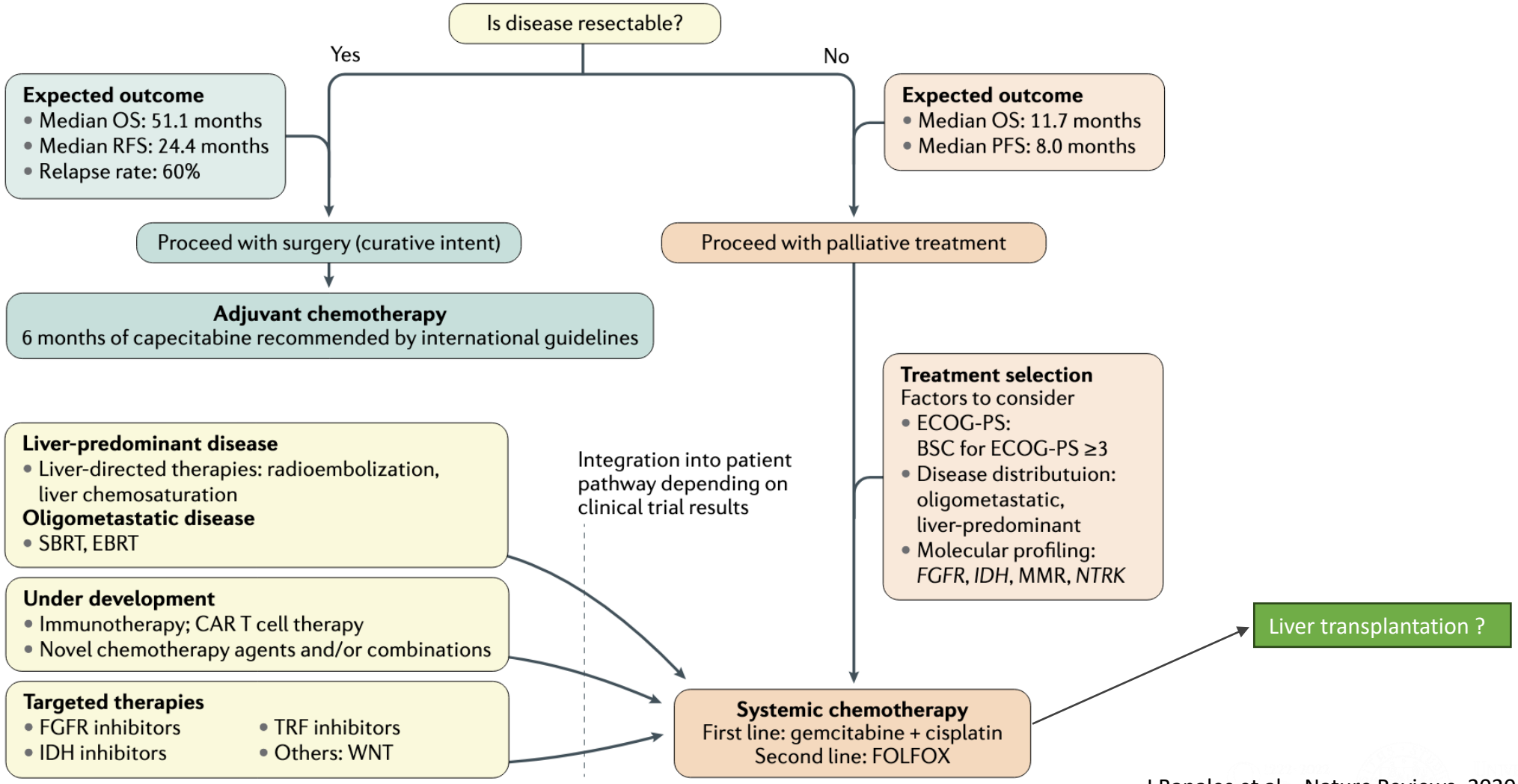


Sutton TL – The America Journal of Surgery, 2021

SCENARIO 2

Cholangiocarcinoma 2020: the next horizon in mechanisms and management

Università degli Studi di Padova



J Banales et al – Nature Reviews, 2020

SCENARIO 2

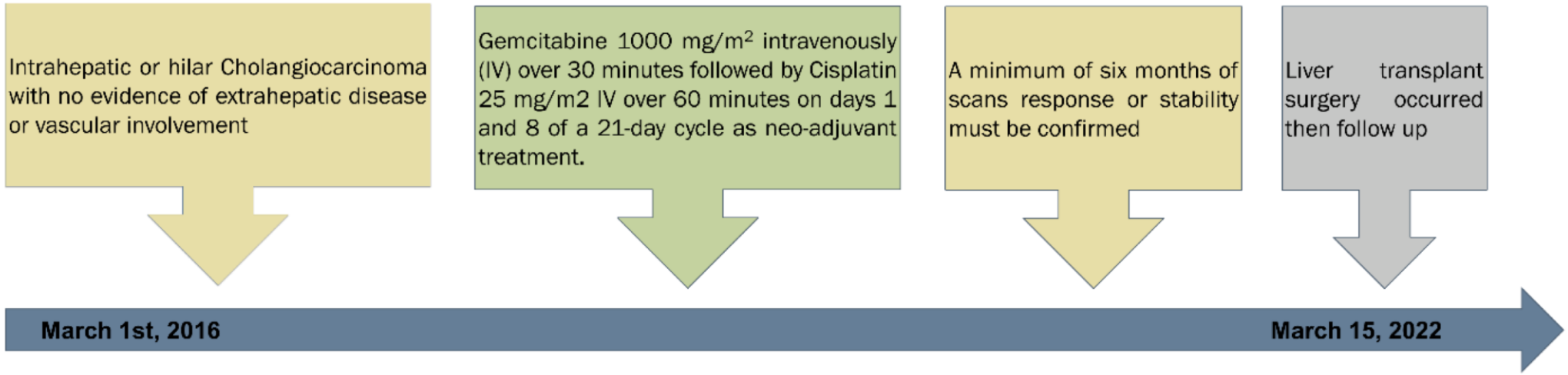
Current Oncology

MDPI

Università degli Studi di Padova

Case Report

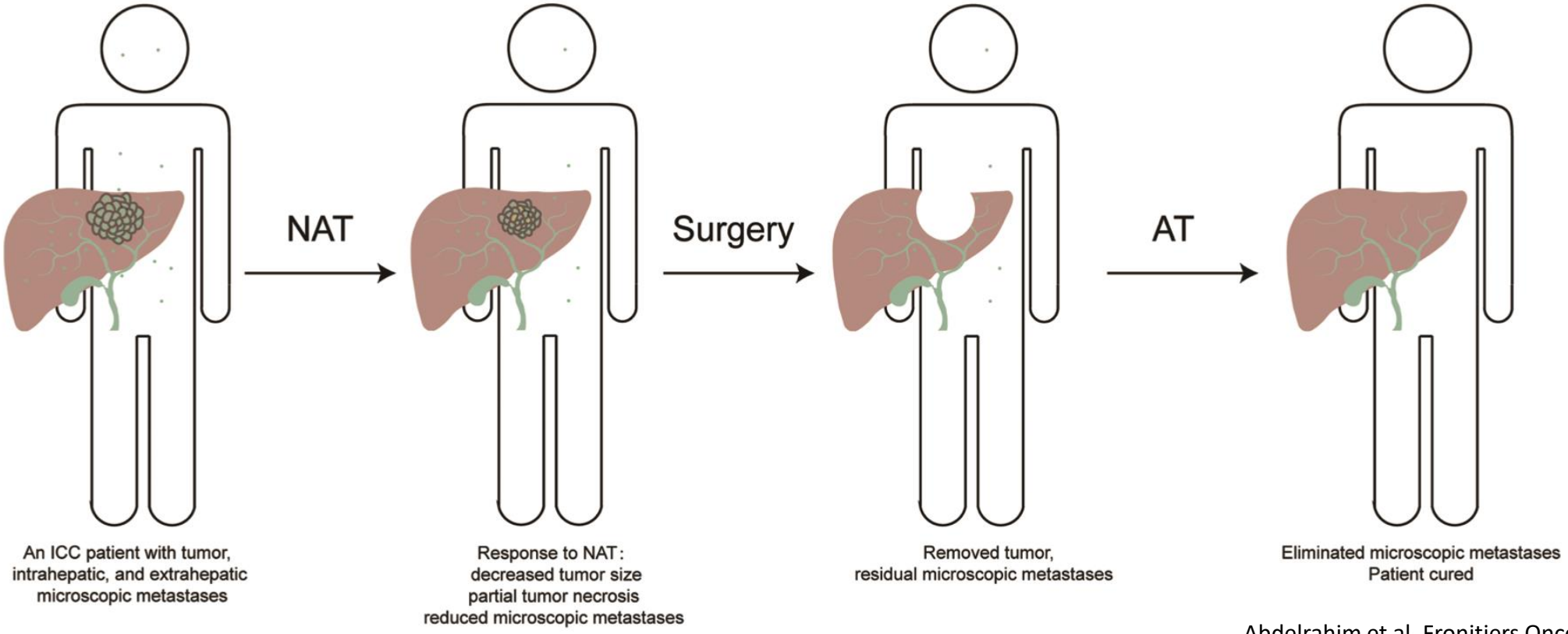
Gemcitabine and Cisplatin as Neo-Adjuvant for Cholangiocarcinoma Patients Prior to Liver Transplantation: Case-Series



Abdelrahim M et al – Current oncology, 2022

SCENARIO 2

Gemcitabine Plus Cisplatin Versus Non-Gemcitabine and Cisplatin Regimens as Neoadjuvant Treatment for Cholangiocarcinoma Patients Prior to Liver Transplantation: An Institution Experience



Abdelrahim et al, Fronitiers Oncology, 2022

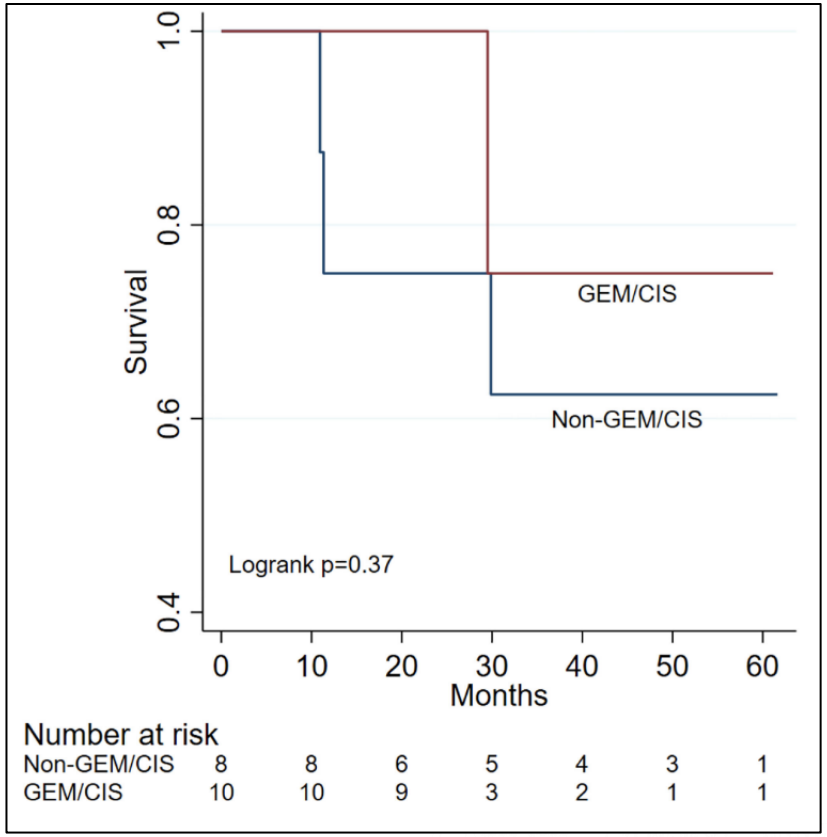
SCENARIO 2

Gemcitabine Plus Cisplatin Versus Non-Gemcitabine and Cisplatin Regimens as Neoadjuvant Treatment for Cholangiocarcinoma Patients Prior to Liver Transplantation: An Institution Experience

UNIVERSITÀ DEGLI STUDI DI PADOVA

TABLE 1 | Transplant related outcomes in patients who received Gemcitabine plus Cisplatin as neo-adjuvant treatment for cholangiocarcinoma prior to liver transplantation.

Patients ID	Sex	Native Liver Diagnosis	Treatment	Treatment Duration- Days	Days to Transplant	Recurrence or Rejection	Days to The Date of Recurrence or Rejection	Days to The Last Follow up	Days to Death
1	Female	Hilar CCA	Gem/Cis	603	8	no		813	
2	Male	CCA	Gem/Cis	149	5	Yes	603	871	885
3	Male	CCA	Gem/Cis	250	20	no		824	
4	Male	CCA	Gem/Cis	120	369	no		967	
5	Male	CCA	Gem/Cis	83	472	no		1405	
6	Male	Hilar CCA	Gem/Cis	161	64	no		418	
7	Male	Hilar CCA	Gem/Cis	201	5	no		812	
8	Male	CCA	Gem/Cis	206	79	no		831	
9	Male	IHCCA	Gem/Cis	77	445	no		1834	
10	Female	IHCCA	Gem/Cis	200	113	no		870	



Abdelrahim et al, Fronitiers Oncology, 2022

REGIONE DEL VENETO
Azienda Ospedale Università Padova

pCCA *and* iCCA

SCENARIO 2

Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series

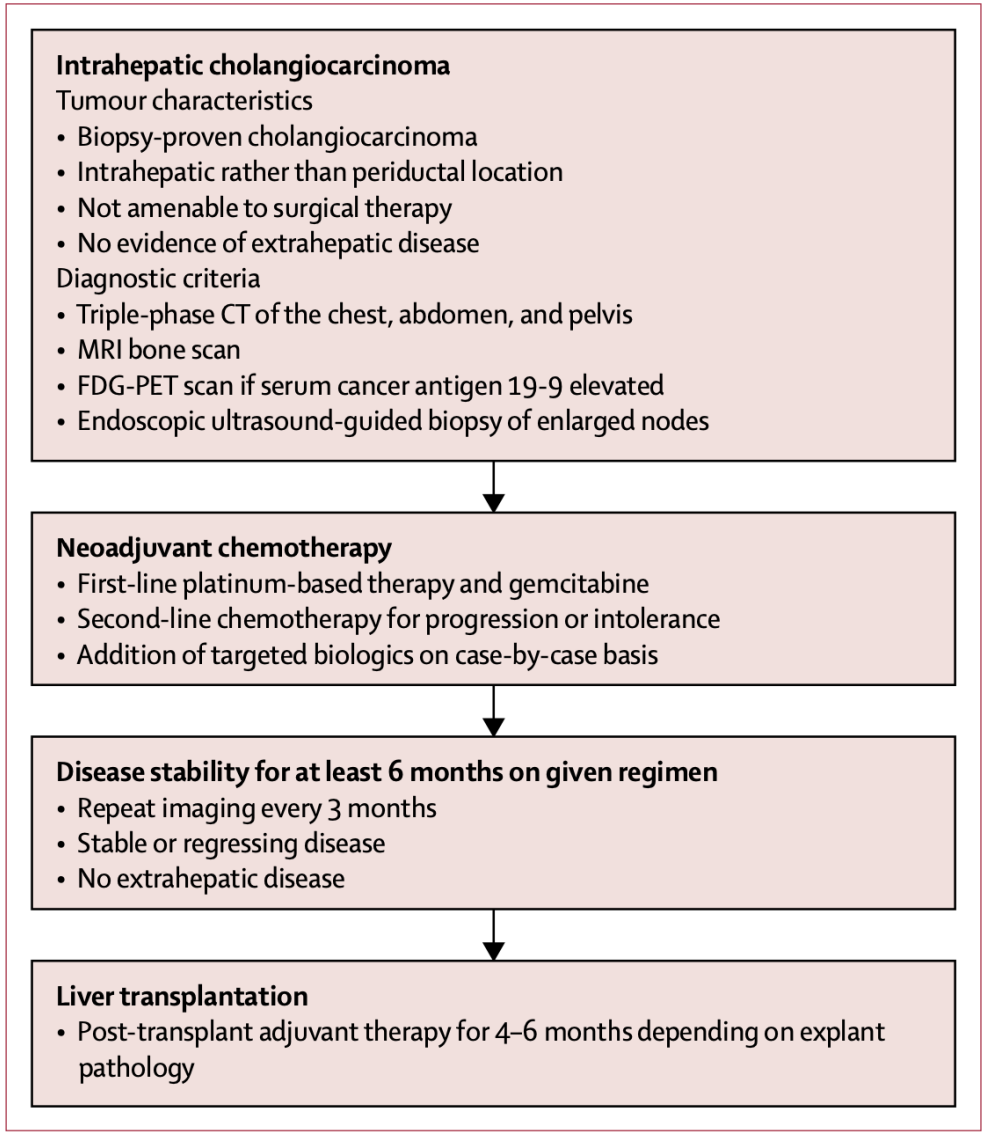


Figure 1: **Study flow diagram**
Methodist–MD Anderson selection criteria for liver transplantation are shown.

Lunsford KE et al – Lancet Gastroenterol Hepatol, 2018

SCENARIO 2

Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series

	Overall	Recipient 1	Recipient 2	Recipient 3	Recipient 4	Recipient 5	Recipient 6
Radiographic (pre-transplant)							
Stage	Stage II (T2bN0M0)	Stage II (T2bN0M0)	Stage II (T2aN0M0*)	Stage II (T2bN0M0*)	Stage IVB (T2bN1M0)	Stage I (T1N0M0)	Stage II (T2bN0M0)
Number of lesions	4·0 (3·0–5·8)†	3	5	>5	3	1	>5
Maximum size of largest lesion (cm)	7·0 (6·0–8·3)†	2·6	10·3	6·5	7·4	5·8	8·6
Cumulative diameter (cm)	10·5 (7·0–13·5)†	4·1	14·5	10·5	10·4	5·8	18·0
Explant							
Stage	Stage II (T2bN0M0)	Stage II (T2bN0M0)	Stage II (T2bN0M0*)	Stage II (T2bN0M0*)	Stage III (T3N0M0)	Stage I (T1N0M0)	Stage II (T2bN0M0)
Number of lesions	7 (2–10)†	8	6	10	1	1	10
Maximum size of largest lesion (cm)	5·9 (4·5–8·4)†	4·2	9·0	3·5	5·2	6·5	10·5
Cumulative diameter (cm)	14·2 (8·1–17·9)†	18·7	13·0	15·3	5·2	6·5	20
Location	NA	Bilobar	Bilobar	Bilobar	Left	Left	Bilobar
Differentiation	Moderate to poor	Poor	Well	Poor	Moderate	Moderate	Poor
Lymphovascular invasion	No	Yes	No	Yes	No	No	No
Perineural invasion	No	No	No	No	Yes	No	No
Microvascular invasion	No	Yes	No	Yes	No	No	No
Macrovascular invasion	No	No	No	No	No	No	No
Positive margins	No	No	No	No	Yes	No	No
Necrosis (%)	0%	0%	95%	0%	0%	0%	90%
Patient outcomes							
Post-transplant recurrence	NA	No	Yes	Yes	Yes	No	No
Post-transplant death	NA	No	No	Yes	No	No	No
Duration of follow-up (months)	36·3 (29·0–50·6)†	74·3	53·8	40·9	31·7	28·1	24·9

NA=not appropriate. *Retrospective radiographic analysis suggested that stable metastatic disease might have been present before liver transplantation. †Data are median (IQR).

Table 2: **Radiographic and explant tumour characteristics from liver transplant recipients with intrahepatic cholangiocarcinoma**

Lunsford KE et al
Lancet Gastroenterol Hepatol, 2018

SCENARIO 2

Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series

	Time from diagnosis to transplant (months)	Recipient outcomes	Neoadjuvant treatment therapies								Adjuvant therapy
			1	2	3	4	5	6	7	8	
1	34	Survived without recurrence	Anatomic liver resection	Capecitabine and stereotactic body radiotherapy	Gemcitabine, cisplatin, and erlotinib	Gemcitabine, cisplatin, and erlotinib	Gemcitabine	Erlotinib	Gemcitabine and capeciabine	Fluorouracil and gemcitabine	Gemcitabine
2	30	Survived with metastatic disease	Gemcitabine and cisplatin	Capecitabine and gemcitabine	Erlotinib	..	..	..	..	..	Gemcitabine and capecitabine
3	36	Death due to metastatic disease	Anatomic liver resection	Gemcitabine and cisplatin	Non-anatomic liver resection	Folinic acid, fluorouracil, and irinotecan	Gemcitabine, cisplatin, and erlotinib	Gemcitabine and erlotinib	Gemcitabine and cisplatin	..	Capecitabine
4	15	Survived with metastatic disease	Gemcitabine and cisplatin	Gemcitabine	Gemcitabine and cisplatin	..	..	..	..	..	Gemcitabine
5	10	Survived without recurrence	Gemcitabine and cisplatin	..	..	..	..	..	..	..	Gemcitabine
6	22	Survived without recurrence	Gemcitabine and cisplatin	Gemcitabine	..	..	..	..	..	..	Gemcitabine

Table 3: Details of neoadjuvant and adjuvant therapy in liver transplant recipients with intrahepatic cholangiocarcinoma

Lunsford KE et al – Lancet Gastroenterol Hepatol, 2018

LIVER TRANSPLANTATION for iCCA: ONGOING TRIALS

NIH National Library of Medicine
National Center for Biotechnology Information

PRS Login

ClinicalTrials.gov

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About This Site | Find Studies | Data About Studies | Study Basics | PRS Info | My Saved Studies (0)

ENROLLING BY INVITATION

NCT04195503

Liver Transplant for Stable, Advanced **Intrahepatic Cholangiocarcinoma**

Conditions

Cholangiocarcinoma, Intrahepatic

Locations

Toronto, Ontario, Canada

RECRUITING

NCT04556214

Liver Transplantation for Non-Resectable **Intrahepatic Cholangiocarcinoma**: a Prospective Exploratory Trial (TESLA Trial)

Conditions

Intrahepatic Cholangiocarcinoma

Locations

Oslo, Norway

RECRUITING

NCT02878473

Liver Transplantation for Early **Intrahepatic Cholangiocarcinoma**

Conditions

Intrahepatic Cholangiocarcinoma

Locations

Toronto, Ontario, Canada

RECRUITING

NCT04848805

Liver Transplantation in Patients With Incidental Hepatocellular-**cholangiocarcinoma** and **Intrahepatic Cholangiocarcinoma**: A Single-center Experience

Conditions

Adult Combined Hepatocellular-Cholangiocarcinoma

Locations

Istanbul, Turkey

iCCA: NEW PROTOCOL FOR LIVER TRANSPLANTATION

LIver transplantation for non-Resectable Intrahepatic cholangioCArcinoma (LIRICA)

The study would investigate if LT provides better outcomes in patients with unresectable iCCA, compared to a similar population undergoing chemotherapy (standard of care) in the same time period. No randomization.

Participants will receive *downstaging* therapies prior to transplantation. **Follow-up = 5 years** from the time of LT.

Main outcome measures: OS, DFS, Survival from recurrence, QoL, drop-out %…

PI Enrico Gringeri – enrico.gringeri@unipd.it

Inclusion Criteria:

- Eastern Cooperative Oncology Group (ECOG) 0 or 1
- Histologically verified diagnosis iCCA
- First time iCCA or liver only recurrence after previous liver resection **R0, N0, M0**
- Disease deemed not eligible for liver resection
- No vascular invasion, extrahepatic disease, or lymph node involvement detected on imaging (PET-CT scan, CT or MRI)
- Received at least 6 months of chemotherapy obtaining SD or PR (Recist 1.1) at listing
- Time span **≥ 6 months** from the diagnosis of iCCA and date of being listed for LT
- BMI ≥ 18 ed ≤ 30 kg/m^2
- Hb ≥ 9 g/dL, wbc ≥ 3,0 X 109/L, Neutrophil ≥ 1,5 X 109/L, platelet ≥ 100.000/mm3 (≥ 10 X 109/L), Bilirubin ≤ 3 mg/dL (≤ 51 umol/L), AST o ALT ≤ 5 upper normal value, Creatinin and Urea < 1,5 upper normal value

Exclusion Criteria:

- Major vascular or near extra-epatic tissue involvement (T4 AJCC 8°ed)
- Perforation of the visceral peritoneum (T3 AJCC 8°ed)
- Prior extrahepatic metastatic disease
- Other malignancies, except curatively treated more than 5 years ago without relapse
- Known history of human immunodeficiency virus (HIV) infection
- Prior history of solid organ or bone marrow transplantation
- Substance abuse, medical, psychological, or social conditions that may interfere with the patient's participation in the study or evaluations
- Surgical or medical contraindication to LT
- Women who are pregnant or breast feeding
- Any reason why, in the opinion of the investigator, the patient should not participate

The day of LT: exploratory laparotomy with clinical assessment and frozen section of the lymphnodes

iCCA: NEW PROTOCOL FOR LIVER TRANSPLANTATION

LIver transplantation for non-Resectable Intrahepatic cholangioCArcinoma (LIRICA)

National Library of Medicine
National Center for Biotechnology Information

PRS Login

ClinicalTrials.gov

Go to the classic website

About This Site | Find Studies | Data Ab | udy Basics | PRS Info | My Saved Studies (0)

NOT YET RECRUITING

NCT06098547 NEW

LIver **Transplantation** for Non-Resectable Intrahepatic CholAngiocarcinoma (**LIRICA**)

Conditions

Intrahepatic Cholangiocarcinoma

Locations

Padova, Italy

PI Enrico Gringeri – enrico.gringeri@unipd.it

LIRICA & LITALHICA APP

LIRICA & LITALHICA: WHERE WE ARE

Ott 2022
Riunione gruppo di lavoro CNT

Dic/Gen 2022
Definizione Oncologica E statistica

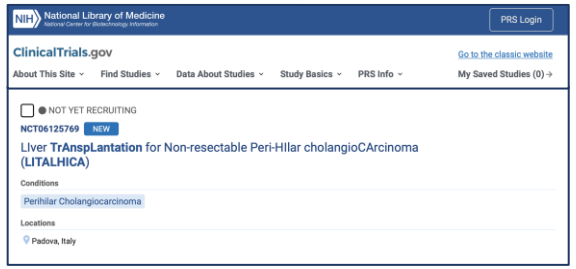
Mar 2023
Prima sottomissione CE

Mag 2023
Secondo CE

Set 2023
Terzo CE

Ott 2023
Approvazione CE*

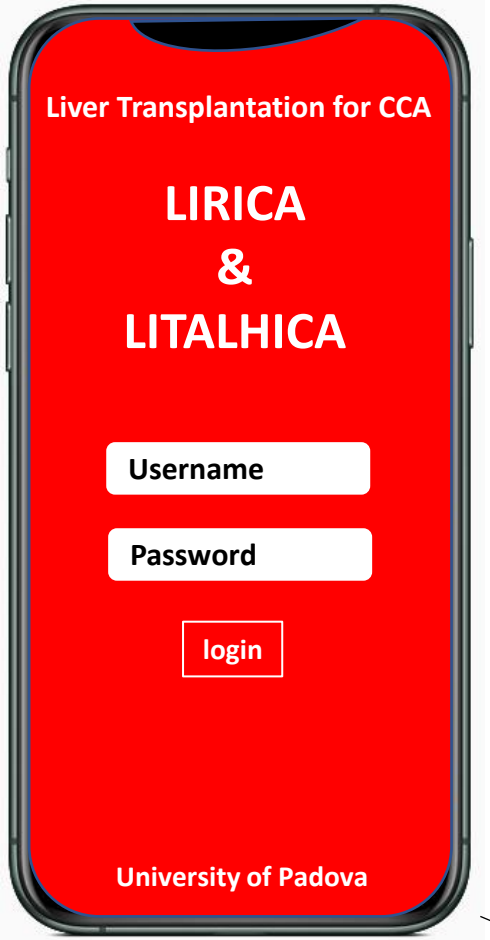
Nov 2023
polizza assicurativa (in attesa di appr. provveditorato)



enrico.gringeri@unipd.it

LIRICA & LITALHICA APP

LIRICA & LITALHICA: WHERE WE ARE



LITALHICA

Age	55
Diagnosis	pCCA
Unresectable?	Yes
Tumor diameter < 3 cm	Yes
Mets?	No
Prior CT or RT?	No
Prior biliary resection?	No
Extrahepatic disease?	No
Transperitoneal biopsy?	No

Consider Liver Transplantation

enrico.gringeri@unipd.it

Preliminary evaluation

PADOVA TB DISCUSSION

LIRICA & LITALHICA: PADOVA TUMOR BOARD DISCUSSION

LIRICA & LITALHICA
PADOVA TUMOR BOARD DISCUSSION

Tumor Board Date		Has Patient Been Previously Presented (If yes, provide date)	
Patient Gender		Patient Age	
Submitted by		Date of Diagnosis	
Institution and Location		Date of Submission	
Site of Primary Tumor			
Clinical information (including pertinent imaging findings, genetic testing results)			
Clinical Stage			
Surgery		Date(s)	
Radiotherapy		Date(s) and dosage	
Hormonal treatment		Date(s)	
TKIs		Date(s)	
Chemotherapy		Date(s) and # of cycles	
Other treatment		Date(s)	
Local Tumor Board Decision (If applicable, please briefly state outcome of local tumor board discussion)			
Outcome of Virtual Tumor Board Discussion and Recommendations			
Follow-up from Presented Case (Date and Outcome)			

enrico.gringeri@unipd.it

Preliminary evaluation | TB discussion

INFORMED CONSENT

LIRICA & LITALHICA: INFORMED CONSENT

Regione del Veneto
AZIENDA OSPEDALE – UNIVERSITA' PADOVA
Via Giustiniani, 1 – 35128 PADOVA – Tel.+ 39 049 8211111
Cod.Fisc./P.IVA 00349040287 – www.aopd.veneto.it – P.E.C.: protocollo.aopd@pecveneto.it

UNITÀ OPERATIVA COMPLESSA CHIRURGIA GENERALE 2
EPATO-BILIO-PANCREATICA E TRAPIANTI DI FEGATO
Direttore: Prof. Umberto Cillo

FOGLIO INFORMATIVO

LIver TrAnspLantation for non-resectable peri-HIlar cholangioCArcinoma

LITALHICA

Trapianto di fegato per colangiocarcinoma peri-ilare non resecabile

Gentile Signora / Gentile Signore,

Le proponiamo di partecipare a uno studio promosso dal Prof. Enrico Gringeri, professore associato presso il Dipartimento di Scienze Chirurgiche Oncologiche e Gastroenterologiche (DiSCOG) e dirigente medico della U.O.C. Chirurgia Generale 2 Epatobiliopancreatica e dei Trapianti di Fegato dell'Azienda Ospedale Università Padova, che si propone di studiare la sopravvivenza dei pazienti affetti da colangiocarcinoma intraepatico non operabile e sottoposti a trapianto di fegato.
Per svolgere questa ricerca, avremmo bisogno della Sua collaborazione.
Prima che Lei decida se partecipare, è importante che abbia tutte le informazioni sul perché questo studio viene fatto e che cosa Le viene chiesto. Può conservare questo foglio informativo e mostrarlo a persone di Sua fiducia (familiari, amici, il Suo medico di medicina generale) che possano aiutarLa a prendere una decisione. Nell'ultima pagina troverà anche i contatti di una persona che Lei può contattare per qualsiasi chiarimento o spiegazione Le dovesse servire.

Nel caso Lei acconsentisse a partecipare, Le verrà chiesto di firmare il Modulo per l'espressione del consenso informato alla partecipazione allo studio e il Modulo di consenso al trattamento dei dati personali.
Le ricordiamo che, anche se accetterà di partecipare, potrà comunque ritirare il Suo consenso in ogni momento, senza dover fornire alcuna motivazione e senza subire alcun tipo di penalizzazione.

1. Che cosa si propone questo studio?
Lo studio intende esplorare se il trapianto epatico in pazienti selezionati affetti da colangiocarcinoma peri-ilare non resecabile, può ottenere una lunga sopravvivenza globale e una buona qualità della vita. Si propone inoltre di esplorare se ci siano dei marcatori biologici e/o i fattori clinici pre-trapianto che possono definire un sottogruppo di pazienti con una sopravvivenza a 5 anni di almeno il 50%.

7° piano Policlinico
Segr. universitaria del Direttore Tel.+ 39 049 8211846 (09.00-12.00) email: alessandra.lenzo@unipd.it
Segr. assistenziale Tel.+ 39 049 8211896 (09.00-12.00) email: segreteria.chirepatobiliare@aopd.veneto.it

2° piano Policlinico
Segr. di Reparto Tel.+ 39 049 8212211 (09.00-12.00) email: chirurgiadelfegato@aopd.veneto.it

Regione del Veneto
AZIENDA OSPEDALE – UNIVERSITA' PADOVA
Via Giustiniani, 1 – 35128 PADOVA – Tel.+ 39 049 8211111
Cod.Fisc./P.IVA 00349040287 – www.aopd.veneto.it – P.E.C.: protocollo.aopd@pecveneto.it

MODULO PER L'ESPRESSIONE DEL CONSENSO INFORMATO

Io sottoscritto dichiaro di aver ricevuto spiegazioni esaurienti in merito alla richiesta di partecipazione allo studio *LIver TrAnspLantation for non-resectable peri-HIlar cholangioCArcinoma*, secondo quanto riportato nel foglio informativo qui allegato, copia del quale mi è stata consegnata in data _____.
Dichiaro di aver potuto discutere tali spiegazioni, di aver avuto modo di porre tutte le domande che ho ritenuto necessarie e di aver ricevuto in merito risposte soddisfacenti.
Accetto dunque liberamente di partecipare a questo studio, avendo compreso i rischi ed i benefici che esso implica.
Comprendo inoltre che riceverò una copia di questo documento, firmato e datato.

Acconsento / Non acconsento che si comunichi al mio medico di medicina generale quanto a me spiegato sul significato della ricerca cui prenderò parte.

Sono stato inoltre informato del mio diritto ad avere libero accesso alla documentazione relativa alla sperimentazione e alla valutazione espressa dal Comitato Etico.

PARTECIPANTE

Nome e cognome: _____ Data: _____

Firma: _____

MEDICO (O RICERCATORE) CHE HA PRESENTATO LO STUDIO

Io sottoscritto dichiaro di aver spiegato lo studio in modo completo al partecipante e certifico che, al meglio delle mie conoscenze, egli/ella ha compreso la natura e le richieste correlate alla partecipazione a questo studio.
Dichiaro inoltre di aver consegnato al partecipante un originale del modulo di consenso informato, firmato e datato.

Nome e cognome: _____ Data: _____

Firma: _____

7° piano Policlinico
Segr. universitaria del Direttore Tel.+ 39 049 8211846 (09.00-12.00) email: alessandra.lenzo@unipd.it
Segr. assistenziale Tel.+ 39 049 8211896 (09.00-12.00) email: segreteria.chirepatobiliare@aopd.veneto.it

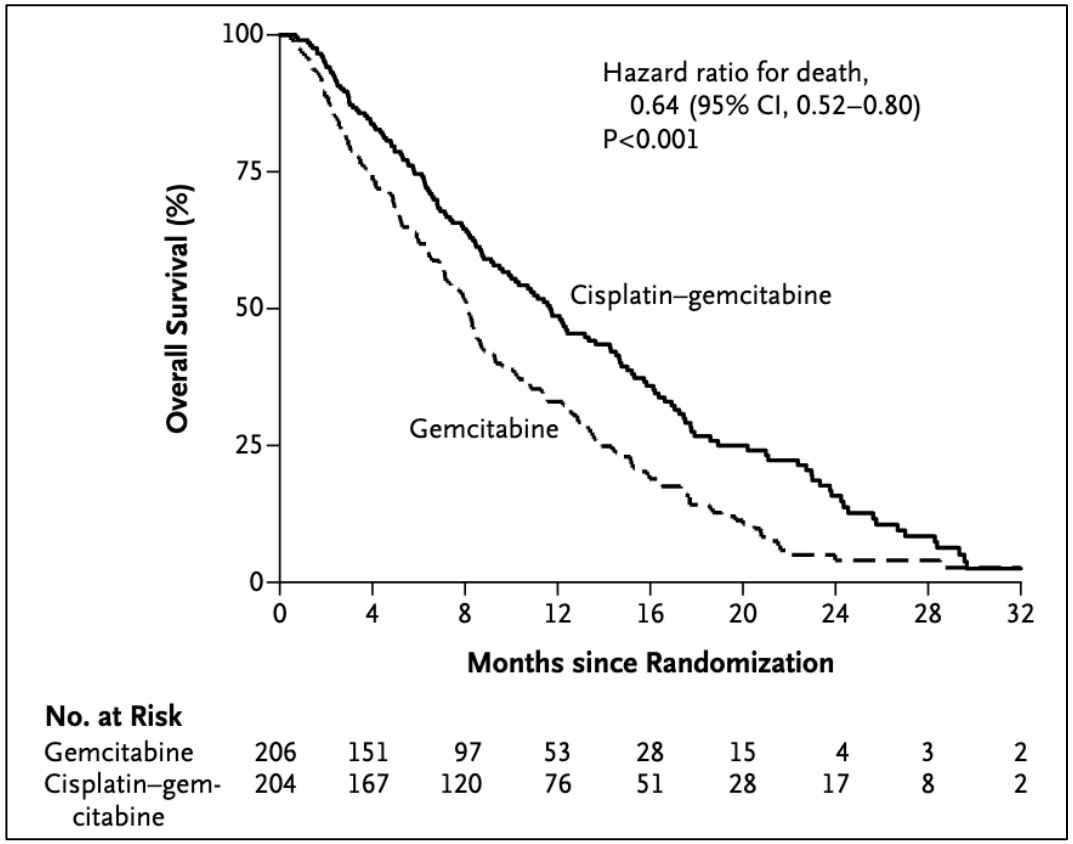
2° piano Policlinico
Segr. di Reparto Tel.+ 39 049 8212211 (09.00-12.00) email: chirurgiadelfegato@aopd.veneto.it

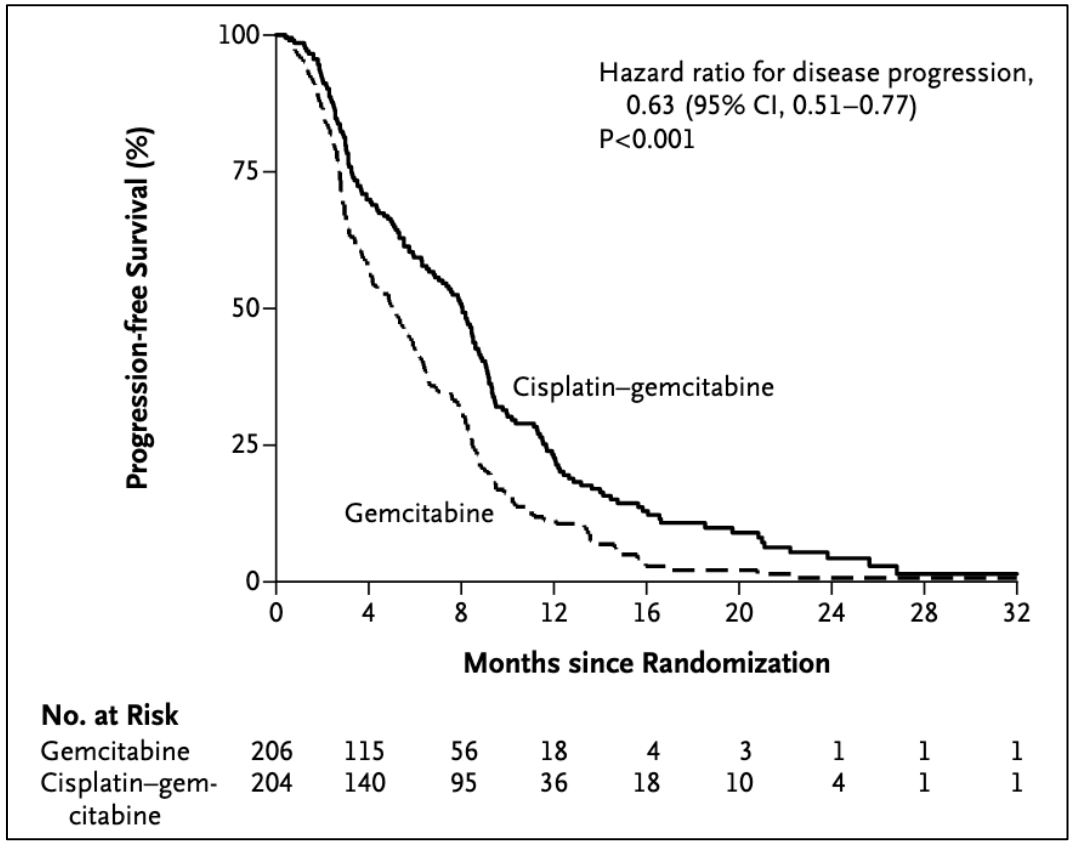
enrico.gringeri@unipd.it

NEOADJUVANT THERAPY

LIRICA & LITALHICA: NEOADJUVANT THERAPY

Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer





Valle JW et al – New Engl J Med, 2010

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NEOADJUVANT THERAPY

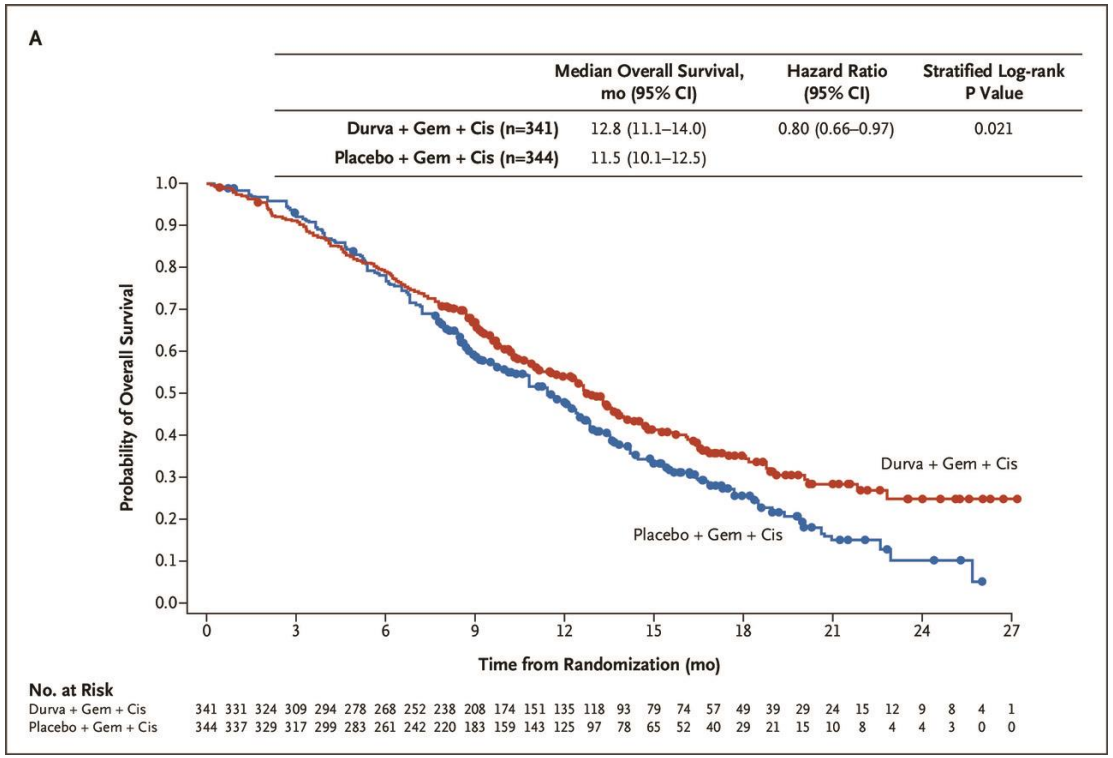
LIRICA & LITALHICA: NEOADJUVANT THERAPY

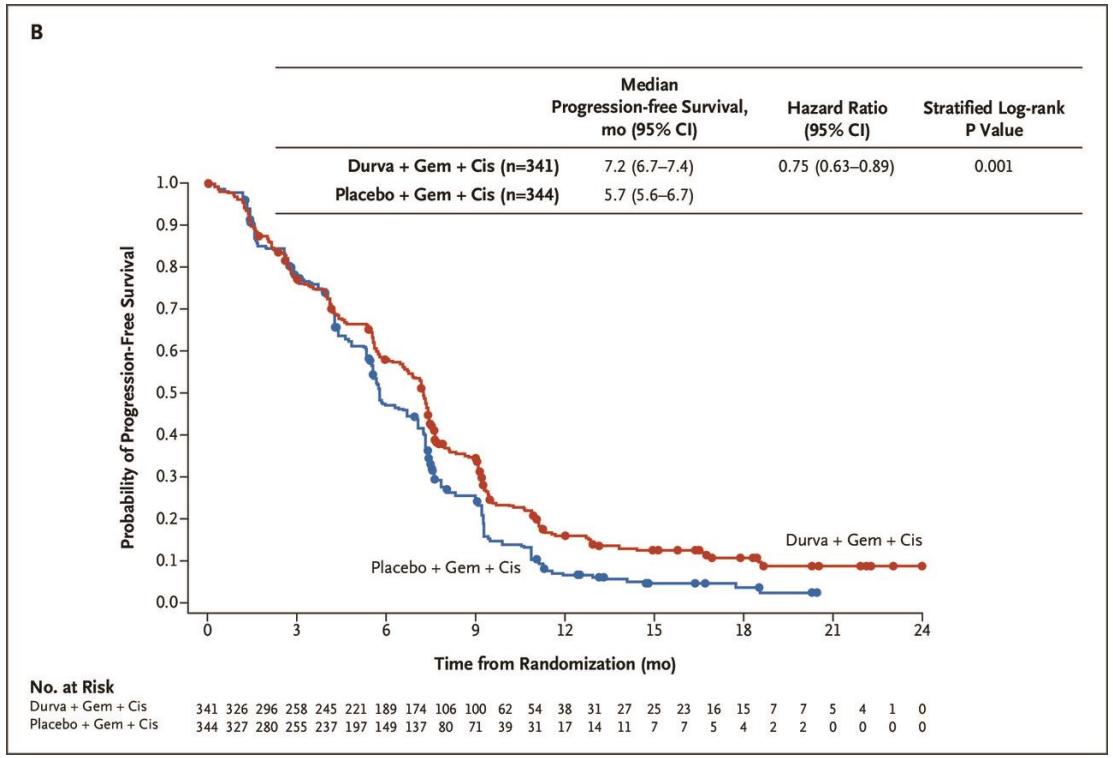
NEJM Evidence

Published June 1, 2022
NEJM Evid 2022; 1 (8)
DOI: 10.1056/EVIDoa2200015

ORIGINAL ARTICLE

Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer





Do-Youn Oh NEJM Evid, 2022

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NEOADJUVANT THERAPY

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NEJM Evidence

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ORIGINAL ARTICLE

Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer

Table 2. Tumor Response in the Full Analysis Set.*

Parameter	Durvalumab plus Gemcitabine and Cisplatin (n=341)	Placebo plus Gemcitabine and Cisplatin (n=343)
Objective response rate — no. (%)†	91 (26.7)	64 (18.7)
Complete response	7 (2.1)	2 (0.6)
Partial response	84 (24.6)	62 (18.1)
Disease control rate — no. (%)‡	291 (85.3)	284 (82.6)
Median duration of response (IQR) — mo§	6.4 (4.6–17.2)	6.2 (3.8–9.0)
Patients with continued response — %		
≥3 mo	88.9	89.0
≥6 mo	59.3	54.2
≥9 mo	32.6	25.3
≥12 mo	26.1	15.0
Median time to response (IQR) — mo¶	1.6 (1.3–3.0)	2.7 (1.4–4.1)

Do-Youn Oh NEJM Evid, 2022

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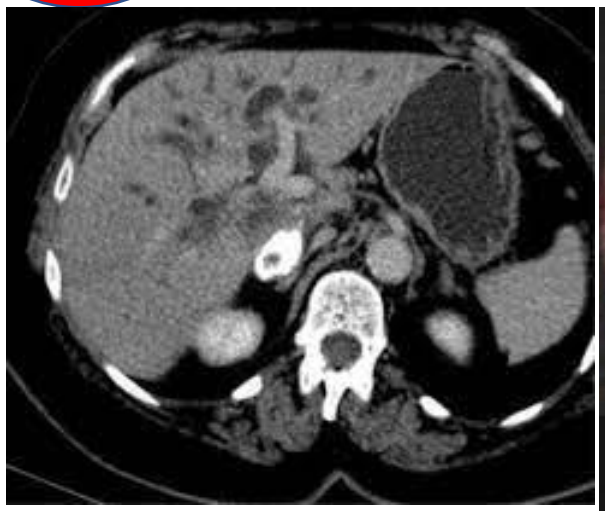
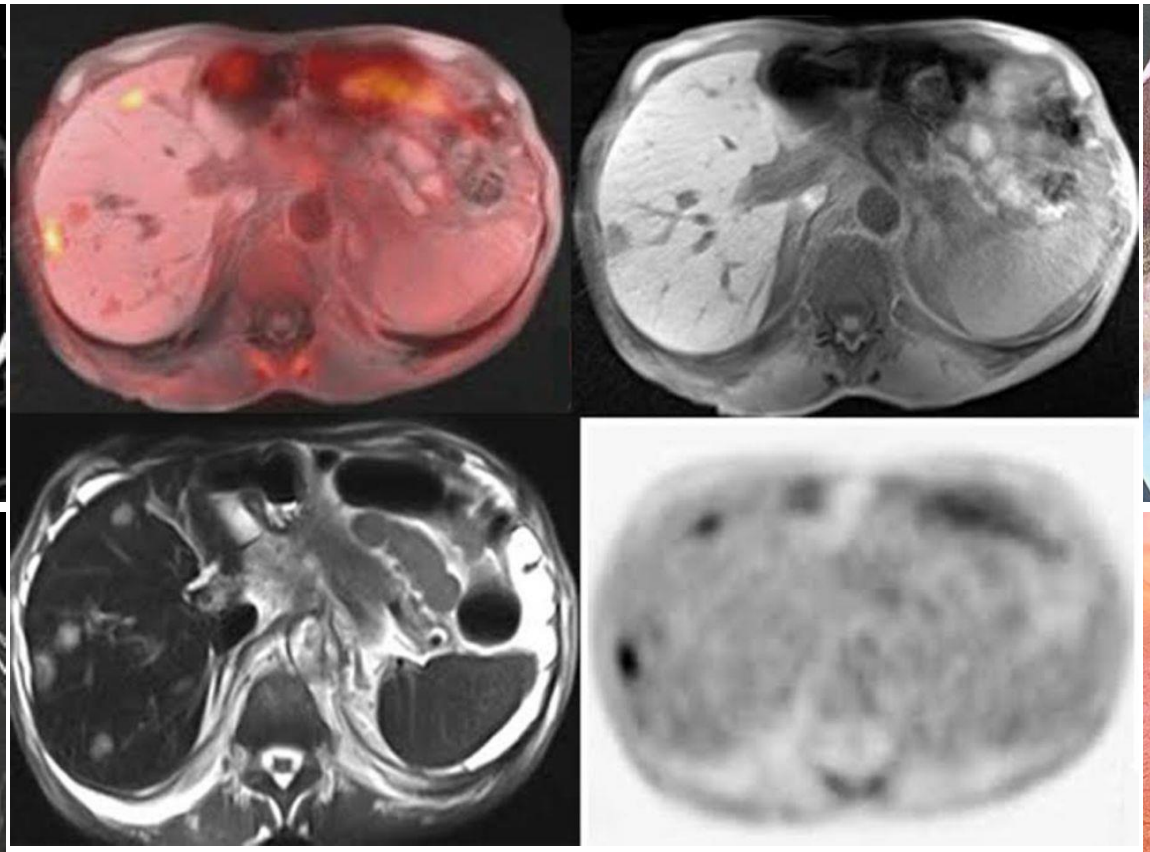
STADIATION

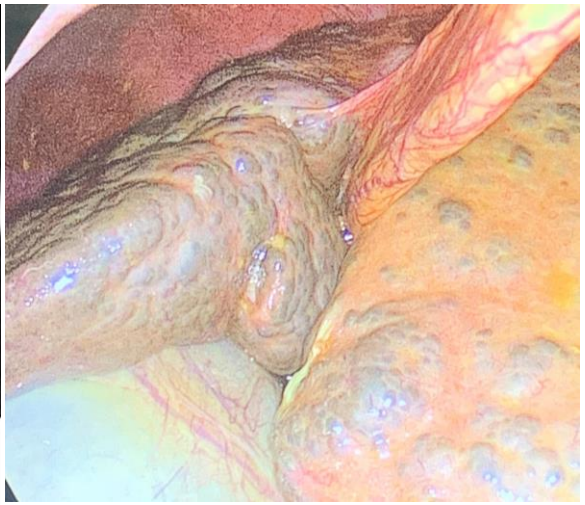
LIRICA & LITALHICA: STADIATION

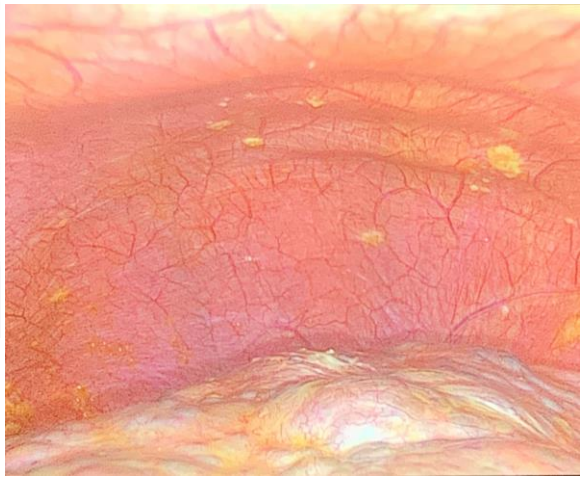


Thoraco-Abdominal CT scan



PET-MRI





VLS EXPLPORATION

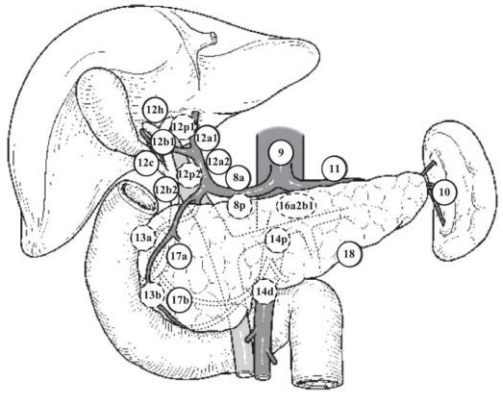
STADIATION

LIRICA & LITALHICA: STADIATION

DIPARTIMENTO ASSISTENZIALE INTEGRATO
SPERIMENTALE DI CHIRURGIA E TRAPIANTI D'ORGANO
U.O. DI CHIRURGIA EPATOBILIARE E CENTRO TRAPIANTI DI FEGATO
Direttore: Prof. Umberto Cillo

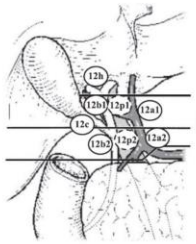
NUMERAZIONE DEI LINFONODI DELL'ILO EPATICO PER ANALISI ISTOLOGICA DEFINITIVA NEL COLANGIOCARCINOMA

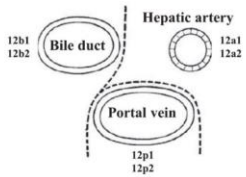
COGNOME..... **NOME**..... **NATO IL** .....
PET-RMN: □ non eseguita □ eseguita il.....
DIAGNOSI PREOPERATORIA: □ ISTOLOGICA □ RADIOLOGICA
SEDE DEL TUMORE:
□INTRAEPATICO □PERI-ILARE (Bismuth .....) □COLEDOCO DISTALE □INTRAPANCREATICO □PAPILLARE
INTERVENTO..... **DATA**.....



LINFONODI POSITIVI A PET-RMN

12H	
12a1	
12a2	
12p1	
12p2	
12b1	
12b2	
12C	
8 A	
8P	





DIPARTIMENTO ASSISTENZIALE INTEGRATO
SPERIMENTALE DI CHIRURGIA E TRAPIANTI D'ORGANO
U.O. DI CHIRURGIA EPATOBILIARE E CENTRO TRAPIANTI DI FEGATO
Direttore: Prof. Umberto Cillo

DEFINIZIONE ANATOMICA DELLE STAZIONI LINFONODALI

(1) LN paracardiali di destra

(2) LN paracardiali di sinistra

(3) LN della piccola curvatura dello stomaco

(4) LN della grande curvatura dello stomaco

(5) LN sovrapilorici

(6) LN infrapilorici

(7) LN arteria gastrica sinistra

(8) LN arteria epatica comune
- (8a) superficie antero-superiore
- (8p) superficie posteriore

(9) LN arteria celiaca (tratto comune del tripode)

(10) LN dell'ilo splenico

(11) LN dell'arteria splenica

(12) LN del legamento epato-duodenale
- **(12h)** LN alla confluenza dei dotti biliari di destra e di sinistra
- **(12a1)** LN arteria epatica propria, tratto craniale (verso il fegato)
- **(12a2)** LN arteria epatica propria, tratto caudale inclusi i LN dell'arteria epato-duodenale
- **(12p1)** LN superficie posteriore della vena porta, tratto craniale
- **(12p2)** LN superficie posteriore della vena porta, tratto caudale
- **(12b1)** LN superficie anteriore, posteriore e destra della via biliare, tratto craniale
- **(12b2)** LN superficie anteriore, posteriore e destra della via biliare, tratto caudale
- **(12c)** LN che circondano il dotto cistico

(13) LN della superficie posteriore della testa del pancreas
- **(13a)** LN craniali alla papilla duodenale
- **(13b)** LN caudali alla papilla duodenale

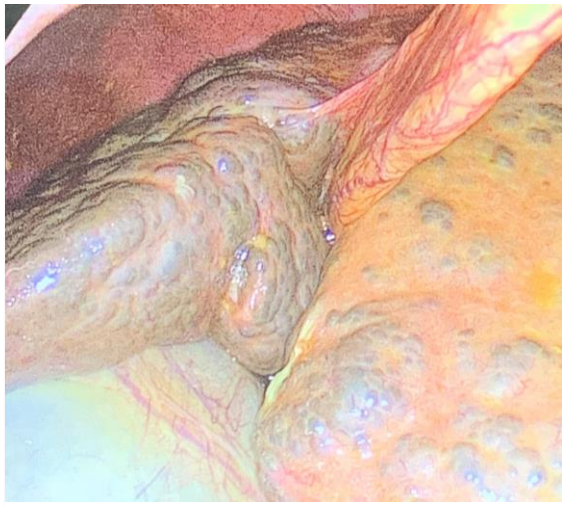
(14) LN della radice dell'arteria mesenterica superiore
- **(14p)** LN prossimali, fino a metà strada tra l'origine della mesenterica e l'origine della colica media
- **(14d)** LN distali, da metà all'origine della colica media

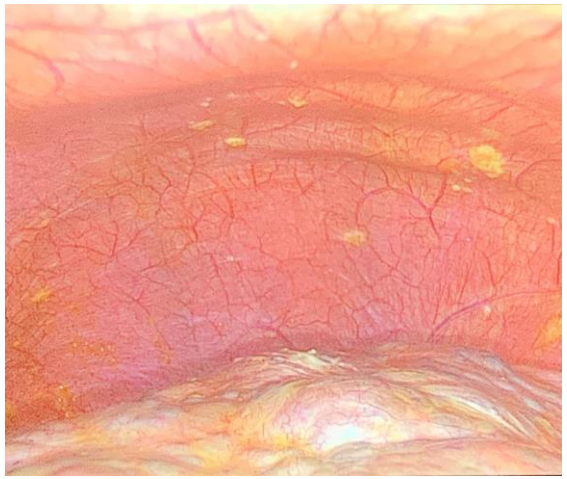
(15) LN dei vasi colici medi

(16) LN dell'aorta addominale
- **(16a1)** LN dello iato diaframmatico aortico
- **(16a2)** LN aortici dal trono celiaco fino all'altezza del margine inferiore della vena renale sinistra
- **(16b1)** LN dal margine inferiore della vena renale di sinistra e l'arteria mesenterica inferiore
- **(16b2)** LN dall'arteria mesenterica inferiore alla biforcazione aortica

(17) LN della superficie anteriore della testa del pancreas
- **(17a)** LN craniali alla papilla duodenale
- **(17b)** LN caudali alla papilla duodenale, compresi quelli della vena mesenterica superiore

(18) LN lungo il margine inferiore del corpo e della coda pancreatica





VLS EXPLPORATION

Preliminary evaluation | TB discussion | Informed consent | Neoadjuvant therapy | Stadiation

LIVER TRANSPLANT

LIRICA & LITALHICA: LIVER TRANSPLANTATION

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SCENARIO 2

iCCA: LIVER TRANSPLANTATION?

Future perspectives

- Expand the indication for oncologic patients?
- LT for resectable iCCA?
- Expand living donation program?
- Auxiliary liver transplantation?

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SCENARIO 2

iCCA: LIVER TRANSPLANTATION?

Liver Transplantation – 5y OS 65%

Transplant benefit

Liver resection (R0, N0, M0, no VI) – 5y OS 30-40%

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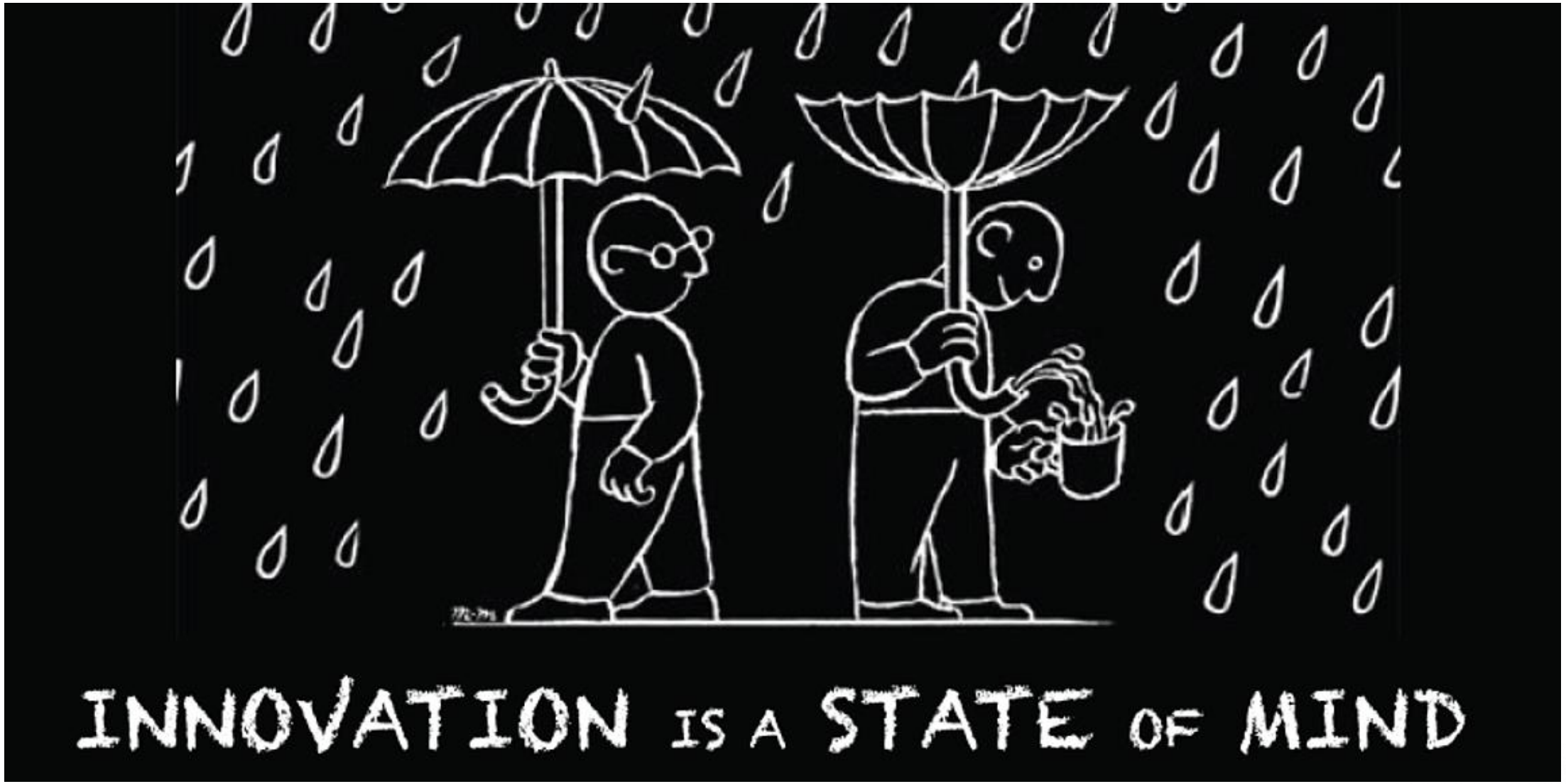
SPLIT LIVER TRANSPLANTATION
PUSH THE LIMIT



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SPLIT LIVER TRANSPLANTATION

In November 1997, the North Italy Transplant program (NITp) Working Group for Liver Transplantation decided to start an official Split-liver Program.

Transpl Int (2000) 13 [Suppl 1]: S144–S146

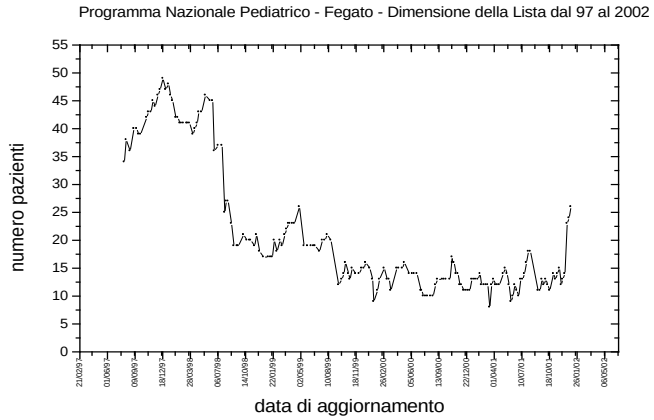
LIVER, INTESTINE

E. Porta
M. Cardillo
C. Pizzi
F. Poli
M. Scalamogna
G. Sirchia

Split liver is an effective tool to transplant paediatric patients

On 1st November 1997 pediatric mean waiting time was of **259 days** (range 1-919 days).

From 1st november 1997 to 31st may 1999 the mean waiting time became of 72 days (12-243 days)



Porta E, Transpl Int. 2000

SPLIT LIVER TRANSPLANTATION
PUSH THE LIMIT

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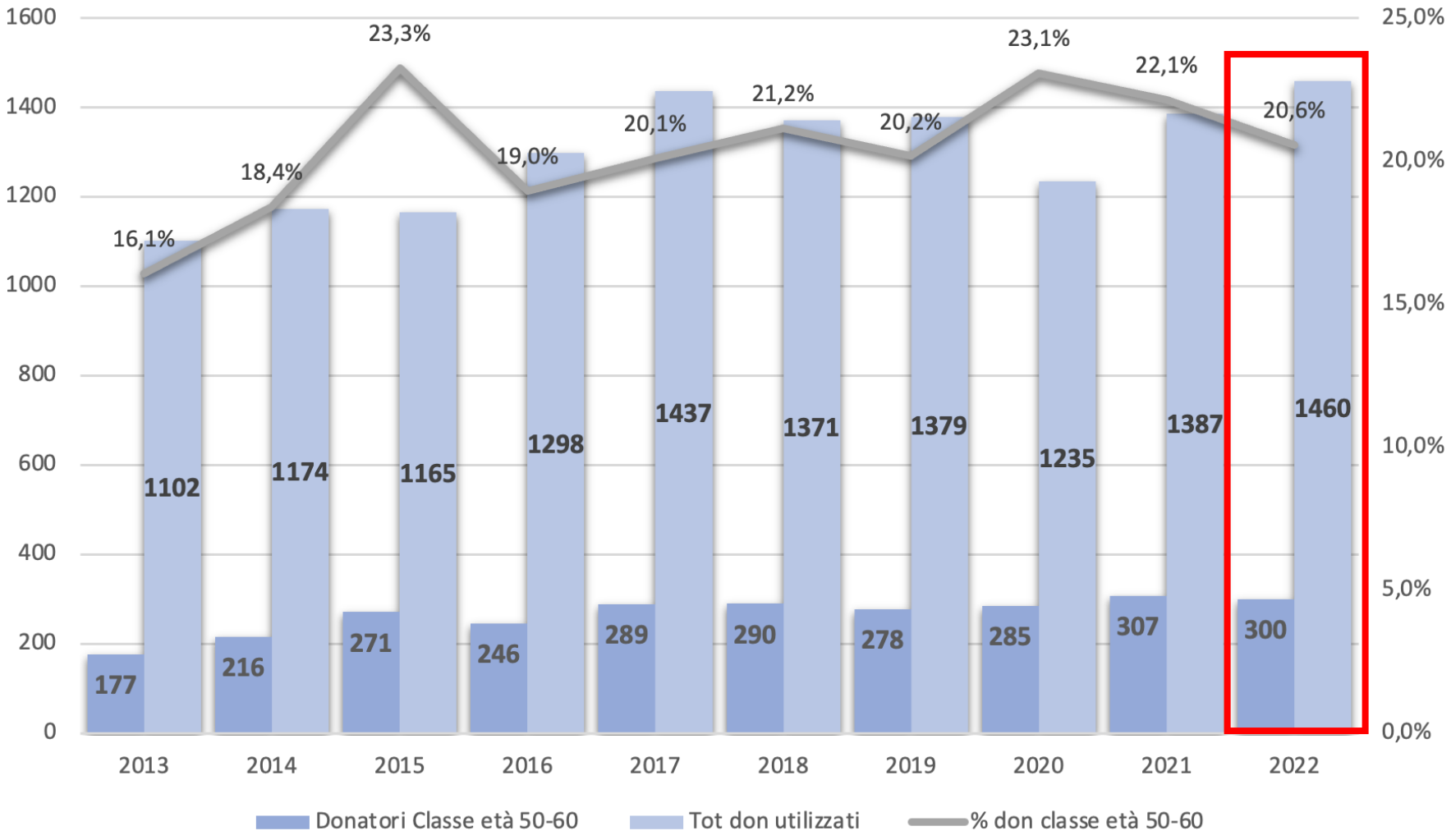
SPLIT LIVER TRANSPLANTATION
PUSH THE LIMIT



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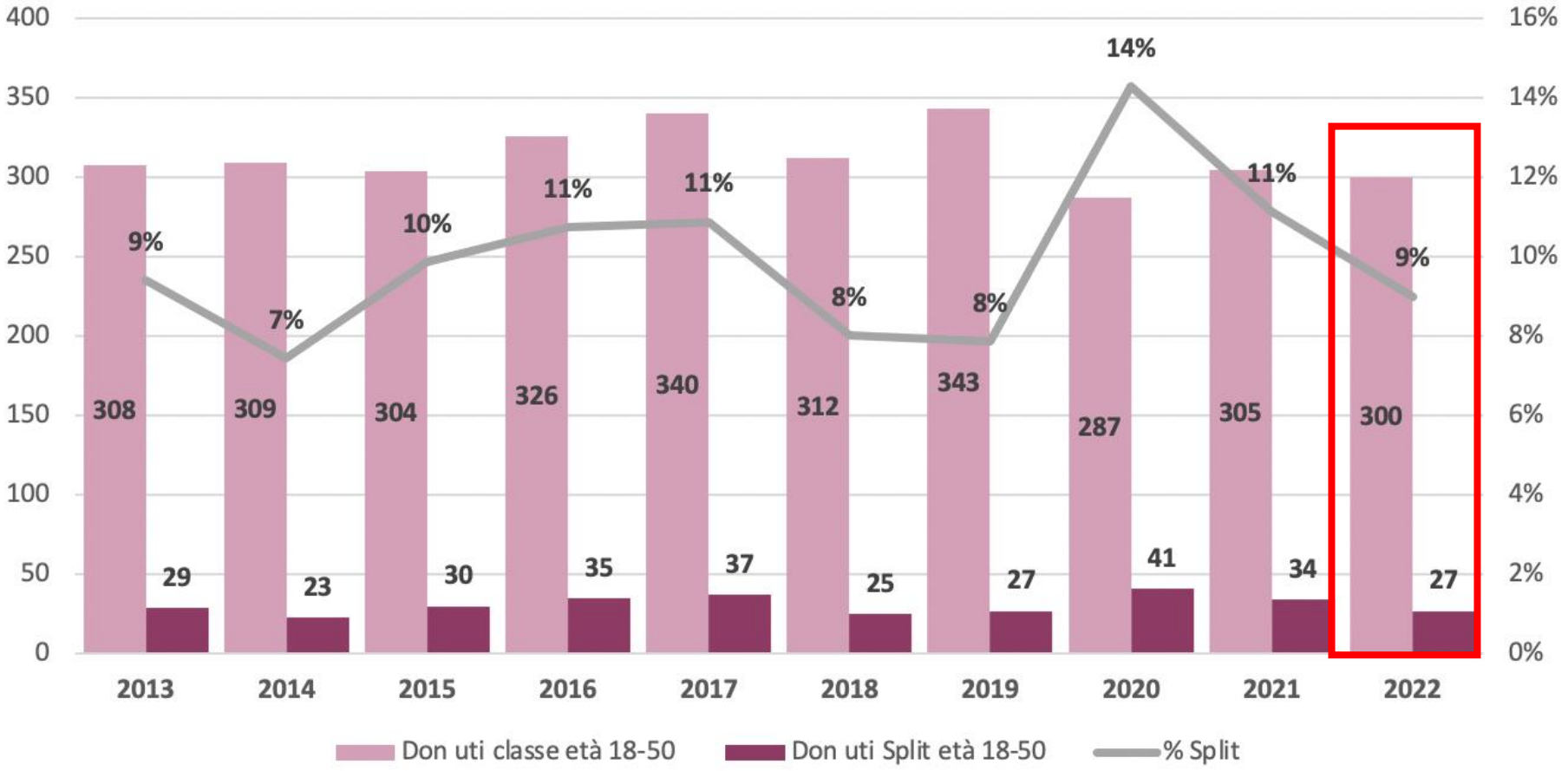
SPLIT LIVER TRANSPLANTATION
PUSH THE LIMIT



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SPLIT LIVER TRANSPLANTATION
PUSH THE LIMIT

Auxiliary Liver TRansplantation using OVEr 50-y old donors - ALTROVE

SEGNALAZIONE DONATORE 50-60 ANNI

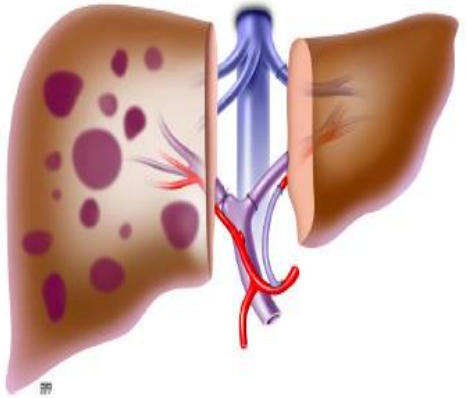
REVISIONE CENTRALIZZATA IMMAGINI

ALLOCAZIONE SPLIT SINISTRO (LISTA NAZIONALE PAZIENTE ONCOLOGICO - CRLM, pCCA, iCCA)

PRELIEVO GRAFT E SPLIT IN MACHINE PERFUSION

TRAPIANTO DI FEGATO AUSILIARIO (SPLIT SINISTRO)

TRAPIANTO DI FEGATO (SPLIT DESTRO)



Takamoto T - J Gastrointest Surg, 2022

Transpl Int (2000) 13 [Suppl 1]: S144–S146
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LIVER, INTESTINE

Split liver is an effective tool to transplant paediatric patients

E. Porta
M. Cardillo
C. Pizzi
F. Poli
M. Scalamogna
G. Sirchia

Liver Transplantation

OPEN

Ex Situ Dual Hypothermic Oxygenated Machine Perfusion for Human Split Liver Transplantation

Thorne AM - Liver Transplantation, 2021

enrico.gringeri@unipd.it

iCCA: EX SITU LIVER RESECTION PADOVA EXPERIENCE

➔ <u>Survival rate after propensity score match analysis:</u>

1-year OS 84.6% vs 46.7%;

3-year OS of 65.8% vs 4.4%;

5-year OS of 43.0% vs 0%;

➔ <u>Variables that impact on prognosis are:</u>

- Low PS;
- Ca 19-9 > 40 U/mL;
- Stage III-IV
- Type of treatment;

Enrico Gringeri – enrico.gringeri@unipd.it – Unpublished data

LIVER TRANSPLANT ONCOLOGY: BIOLOGY AND PATIENT SELECTION

Blake Cady, MD

"Biology is King; selection of cases is Queen, and the technical details of surgical procedures are princes and princesses of the realm who frequently try to overthrow the powerful forces of the King and Queen, usually to no long-term avail, although with some temporary apparent victories"