XIXth Post Graduate Course
Primary Liver Tumors

Primary cancer in healthy liver
Size, number and location: where is the limit for surgical resection?

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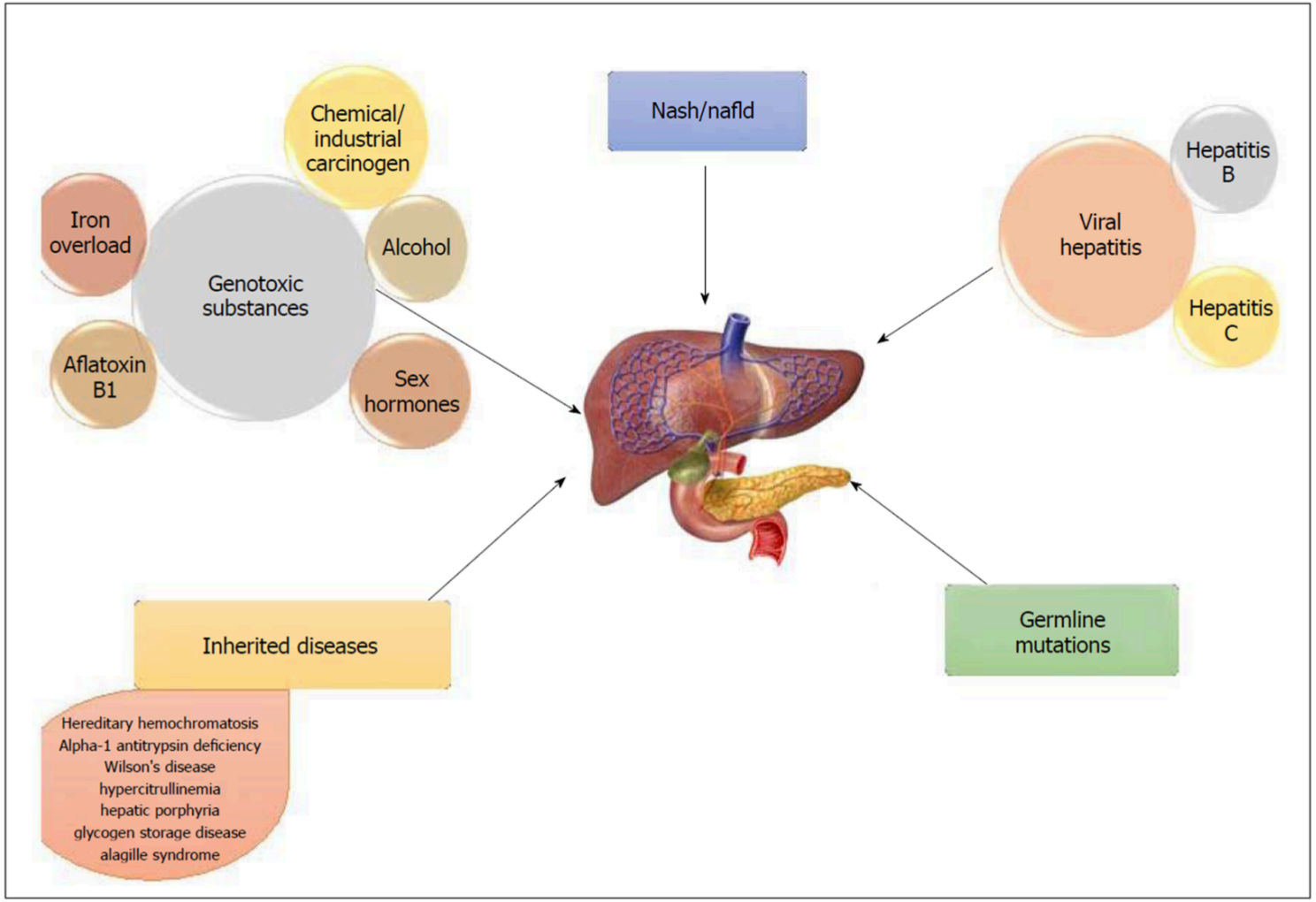
Lamot Congress Center
Mechelen

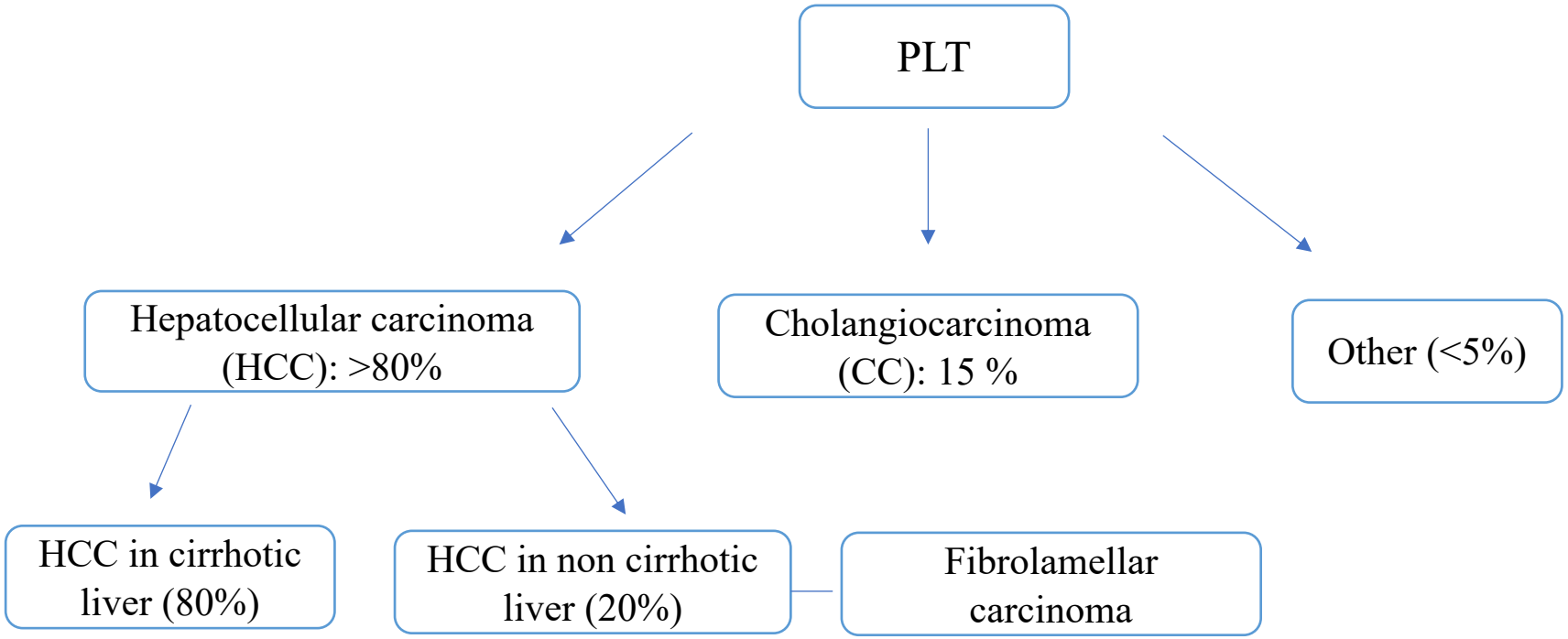
Non cirrhotic liver ≠ healthy liver



PLC can develop directly from inflammation without cirrhosis

Primary Liver Tumour (PLT)

- 6th most common malignant tumor and 3rd leading cause of cancer-related death worldwide



Calvet et al. J. of hepatology 1990
Gaddikeri et al. Am J Roentgenology 2014
Lee et al. Eur. J of radiology 2017

1. Non cirrhotic conventional HCC

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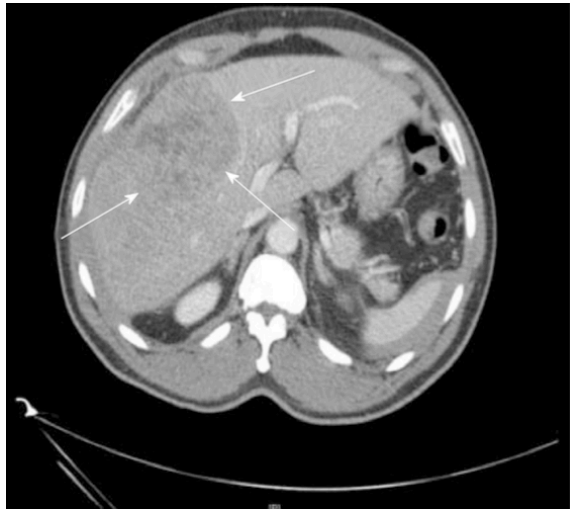
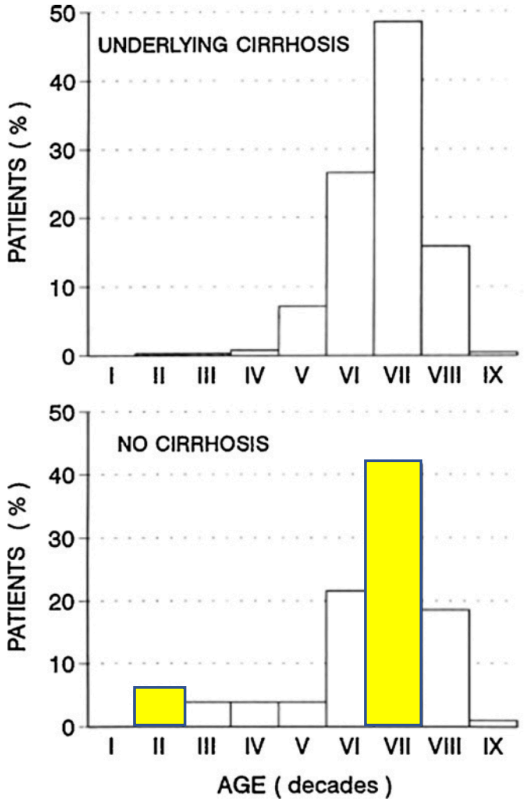


- 5.5 per 100000 in male and 2 per 100000 in female (USA)
- More frequent in developed countries
- Bimodal age distribution (2nd and 7th decade of life).
- Often detected at advanced stage
- Lack of significant data on HCC that arises in non-cirrhotic liver
- α-FP is normal in 60%
- Portal vein invasion +++



Trevisani et al. Digestive and liver disease 2010
Yan Liu et al. Med Sci Monit 2019

Treatment of choice = radical liver resection

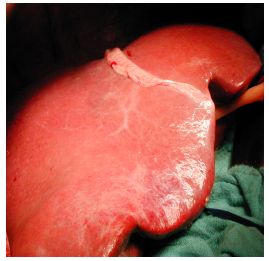
- Contraindication: extrahepatic spread of the disease or anatomical constraints related to the tumor.
- Majority of the patients requires a major hepatic resection
- Feasible due to the preserved liver function and low perioperative mortality compared to cirrhotic livers.

Trevisani et al. Digestive and liver disease 2010
Chiche et al. J.Visceral Surg. 2010
Yan Liu et al. Med Sci Monit 2019

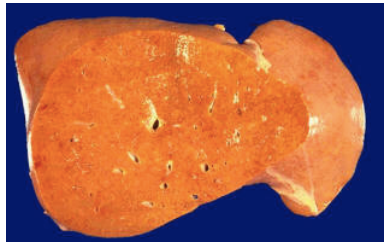
Treatment of choice = radical liver resection

Need for an accurate assessment of :

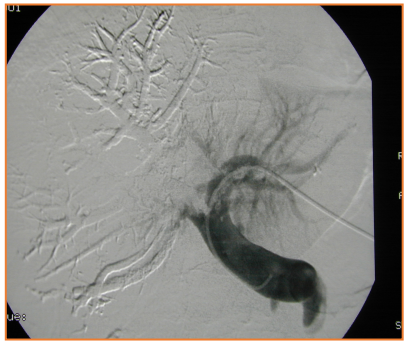
- The tumour characteristics (vascular relationship/ tumour thrombus in the PV, satellites nodules,…)
- Extra-hepatic extension
- The quality of the liver parenchyma and the volume of the future liver remnant
- *→Good quality CT scan of the chest and abdomen*



25-30 %



30 - 35 %



PVE

Trevisani et al. Digestive and liver disease 2010
Chiche et al. J.Visceral Surg. 2010
Yan Liu et al. Med Sci Monit 2019

Treatment of choice = radical liver resection

Surgical management recommandations :

- Predilection of HCC for endoportal spread→ anatomical resection
- 1 centimeter margin
- Additional lymphadectomy in young patients (FLC!)
- Recurrences must be aggressively treated (2nd R0 resection)

Boudjema et al. Monographie de l'AFC 2006
Chiche et al. J.Visceral Surg. 2010
Laurent et al. J am coll surg 2006

Prognostic factors of HCC in non-cirrhotic liver

Table 1 prognostic factors for hepatocellular cancer in non-cirrhotic liver.

1er author (references)	Number of patients	Dates of study	Overall 5 Year survival (%)	Factors of poor prognosis
Bege et al. [15]	116	1987–2005	40.0	R1 resection Vascular involvement HBV infection
Dupont-Bierre et al. [16]	84	1998–2003	44.4	Multiple tumors Gross vascular involvement
Lang et al. [17]	83	1998–2005	30.0	UICC stage Vascular involvement Tumor grade
Laurent et al. [18]	108	1987–2005	29.0	Blood transfusion Absence of capsule Satellite nodules Resection margin < 1cm
Capussotti et al. [19]	47	1985–2002	30.9	Size > 10 cm Satellite nodules

HBV: hepatitis B virus; UICC: Union Internationale Contre le Cancer

Chiche et al. J.Visceral Surg. 2010

- **R1 resection,**
- **tumor size, satellite nodules, vascular invasion and intraoperative transfusions**

Bege et al. J Gastrint surg 2007
Dupont-Bierre et al. J Am Coll Surg 2005
Lang et al. J Am Coll Surg 2007
Laurent et al. J Am Coll Surg 2005
Capussotti et al. Hepatogastroenterology 2006

https://doi.org/10.1016/j.hpb.2019.07.007 HPB

ORIGINAL ARTICLE

Development and validation of a risk score to predict the overall survival following surgical resection of hepatocellular carcinoma in non-cirrhotic liver

Bobby VM. Dasari[1], Sivesh K. Kamarajah[1], James Hodson[2], Timothy M. Pawlik[3], Jean-Nicholas Vauthey[4], Yuk T. Ma[5], Pankaj Punia[5], Chris Coldham[1], Manuel Abradelo[1], Keith J. Roberts[1], Ravi Marudanayagam[1], Robert P. Sutcliffe[1], Paolo Muiesan[1], Darius F. Mirza[1] & John Isaac[1]

[1]Department of Hepatobiliary and Pancreatic Surgery, Queen Elizabeth Hospital, Birmingham, B15 2WB, [2]Institute of Translational Medicine, Queen Elizabeth Hospital, [3]Wexner Medical Centre, The Ohio State University, [4]Department of Surgical Oncology, M.D. Anderson Medical Centre, and [5]Department of Oncology, Queen Elizabeth Hospital, Birmingham, B15 2TH, United Kingdom

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Table 1 Patient demographics of the SEER cohort

	Available N	Statistic
Age at Diagnosis (Years)	3897	64 (55–72)
Sex (% Male)	3897	2770 (71.1%)
Ethnicity (% White)	3889	2263 (58.2%)
Year of Diagnosis	3897	
2004–2007		1384 (35.5%)
2008–2010		1240 (31.8%)
2011–2013		1273 (32.7%)
Radiotherapy	3895	104 (2.7%)
Type of Surgery	3688	
Minor		2011 (54.5%)
Major Hepatectomy		1361 (36.9%)
Extended Hepatectomy		316 (8.6%)
Tumour Grade	3334	
Good		736 (22.1%)
Moderate		1746 (52.4%)
Poor/Anaplastic		852 (25.6%)
Tumour Size (mm)	3746	55 (35–91)
T–Stage	3760	
T1a		216 (5.7%)
T1b		1767 (47.0%)
T2		940 (25.0%)
T3		451 (12.0%)
T4		386 (10.3%)
Multiple Tumours	3380	788 (23.3%)
Bilobar Tumours	3844	1562 (40.6%)
Local Invasion	3819	217 (5.7%)
Vascular Invasion	3393	
No		2400 (70.7%)
Microscopic		779 (23.0%)
Macroscopic		214 (6.3%)
N–Stage	3897	
Nx		3335 (85.6%)
N0		507 (13.0%)
N1		55 (1.4%)

Table 3 Multivariable analysis of survival in the SEER derivation set

	Coefficient	HR (95% CI)	p-Value
Sex			**0.003**
Female	–	–	–
Male	0.24	1.28 (1.09–1.50)	**0.003**
Tumour Size			**<0.001**
<35 mm	–	–	-
35–54 mm	0.25	1.28 (1.04–1.59)	**0.022**
55–94 mm	0.21	1.24 (1.00–1.53)	**0.046**
95 + mm	0.45	1.57 (1.27–1.95)	**<0.001**
Number of Tumours			**0.019**
Solitary	–	–	–
Multiple	0.26	1.30 (1.04–1.61)	**0.019**
Tumour Lobes			**0.014**
Unilobar	–	–	–
Bilobar	0.23	1.26 (1.05–1.52)	**0.014**
Major Vascular Invasion			**<0.001**
No	–	–	–
Yes	1.07	2.93 (2.28–3.76)	**<0.001**

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X4

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No	–	–	–
Yes	1.07	2.93 (2.28–3.76)	**<0.001**

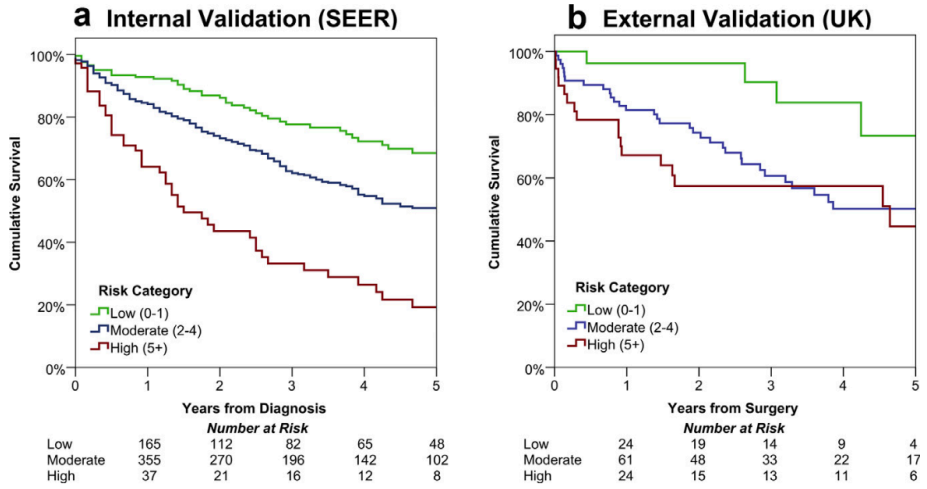
Table 4 Risk score

	Points
Sex	
Female	0
Male	1
Tumour Size	
<35 mm	0
35–94 mm	1
95 + mm	2
Number of Tumours	
Solitary	0
Multiple	1
Tumour Lobes	
Unilobar	0
Bilobar	1
Major Vascular Invasion	
No	0
Yes	4

The score is based on the multivariable model in Table 3. The number of points associated with each factor was calculated by multiplying the coefficient by four, and rounding to the nearest integer. The score can be calculated for an individual by looking up the points value of each factor, and adding together the resulting four numbers to give a score in the range 0–9.

Table 7 Risk score validation

Score	Risk Category	*N*	5 Year Survival	HR (95% CI)
SEER Derivation Set				
0–1	Low	621	68.0%	–
2–4	Moderate	1462	52.2%	1.72 (1.43–2.08)
5+	High	200	24.5%	4.16 (3.26–5.30)
SEER Internal Validation Set				
0–1	Low	204	68.5%	–
2–4	Moderate	487	51.0%	1.86 (1.33–2.60)
5+	High	70	19.2%	4.56 (2.99–6.95)
UK External Validation Set				
0–1	Low	27	73.4%	–
2–4	Moderate	76	50.2%	3.71 (1.32–10.4)
5+	High	37	44.6%	4.22 (1.42–12.5)



2. Fibrolamellar carcinoma (FLC)

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Prognosis of Fibrolamellar Carcinoma Compared to Non-cirrhotic Conventional Hepatocellular Carcinoma

Suguru Yamashita[1] · Jean-Nicolas Vauthey[1] · Ahmed O. Kaseb[2] · Thomas A. Aloia[1] · Claudius Conrad[1] · Manal M. Hassan[2] · Guillaume Passot[1] · Kanwal P. Raghav[2] · Mohamed A. Shama[3] · Yun Shin Chun[1]

Factor	Fibrolamellar carcinoma, $n = 65$	Conventional HCC, $n = 158$	p
Male gender	31 (48)	96 (61)	0.073
Age, years, median (range)	25 (14–67)	64 (12–86)	<0.001
Caucasian race	56 (86)	106 (67)	0.004
Hepatitis B or C	0	40 (25)	<0.001
Preoperative treatment	14 (22)	41 (26)	0.49
Largest tumor diameter, cm, median (range)	10.5 (3.5–21.0)	6.6 (0.4–29.0)	<0.001
Multiple tumors	13 (20)	35 (22)	0.72
Major hepatectomy	48 (74)	93 (59)	0.016
R1 margin	11 (17)	14 (9)	0.062
Vascular invasion	38 (58)	78 (49)	0.22
Lymph node metastases	28 (43)	2 (1)	<0.001
AJCC stage			
I	15 (23)	67 (42)	<0.001
II	10 (15)	51 (32)	
III	10 (15)	31 (20)	
IV	30 (46)	9 (6)	
Median follow-up, months (range)	48 (2–254)	52 (1–292)	0.69

Normal α-FP!

Yamashita et al. J gastrointest.Surg.2016

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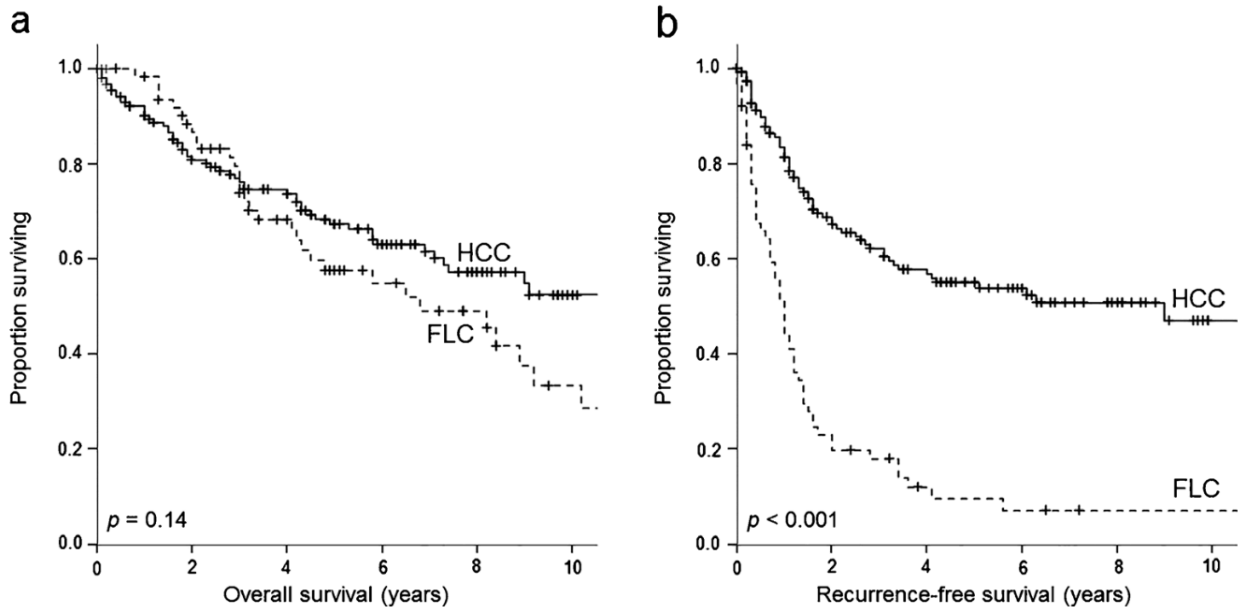
J gastrointest.Surg.2016

Fig. 1 Overall and recurrence-free survival after resection of non-cirrhotic conventional hepatocellular carcinoma (HCC) and fibrolamellar carcinoma (FLC)



5-Y OS: 67% (conv HCC) vs 58%(FLC)

5-Y RFS: 55% (conv HCC) vs 10 %(FLC)

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J gastrointest.Surg.2016

Table 2 Univariate analysis of overall (OS) and recurrence-free survival (RFS) after resection of fibrolamellar carcinoma ($n = 65$)

Factor	*n*	Median OS (months)	*p*	Median RFS (months)	*p*
Gender					
Male	31	57	0.32	9	0.17
Female	34	100		13	
Age, years					
≤25	35	52	0.069	11	0.006
>25	30	107		17	
Preoperative treatment					
Yes	14	36	0.057	12	0.46
No	51	100		11	
Hepatectomy					
Major	48	69	0.31	11	0.53
Minor	17	111		14	
Lymph node dissection or sampling					
Yes	34	54	0.09	11	0.56
No	31	107		12	
Lymph node metastases					
Yes	28	52	0.15	6	0.10
No	37	100		12	
Vascular invasion					
Yes	38	50	0.040	8	0.034
No	27	100		17	
Number of tumors					
Solitary	52	107	0.001	12	0.10
Multiple	13	40		4	
Size of tumors, cm[a]					
≤10.5	30	78	0.93	14	0.15
>10.5	27	57		9	
Extranodal metastases					
Yes	6	111	0.88	13	0.83
No	59	81		11	
Surgical margin					
R0	54	78	0.95	12	0.91
R1	11	81		5	
Postoperative chemotherapy					
Yes	20	81	0.98	12	0.46
No	45	78		11	

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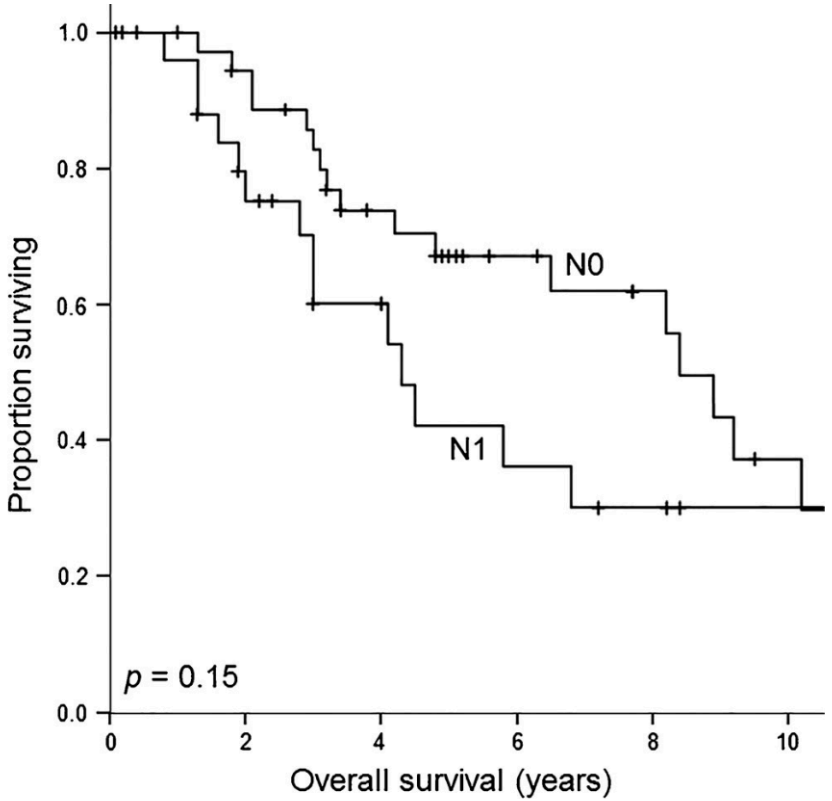

Fig. 3 Overall survival was not significantly different between FLC patients presenting with (N1) and without (N0) lymph node metastases

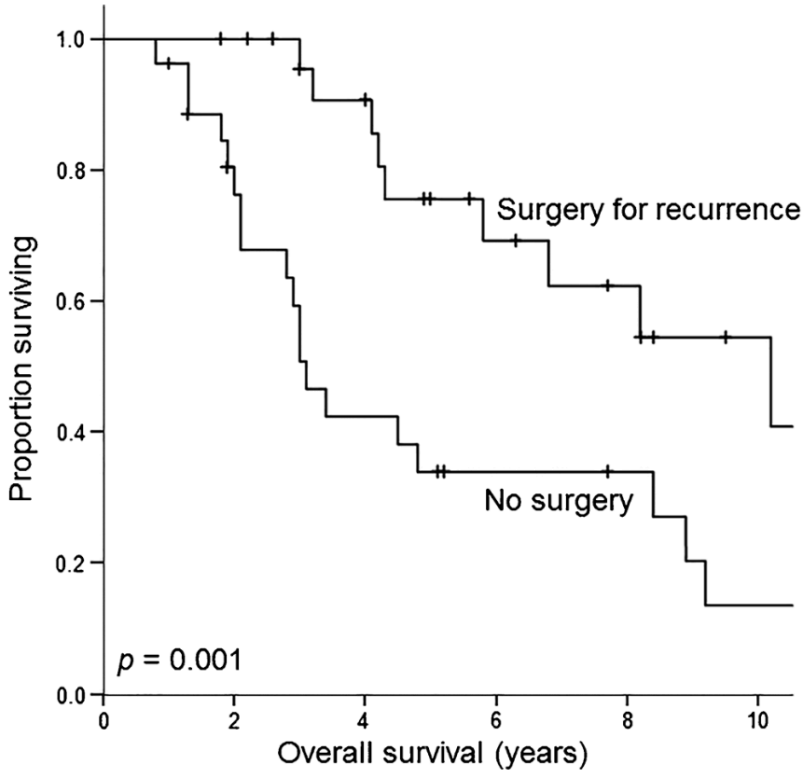

Fig. 4 Overall survival among patients with fibrolamellar carcinoma undergoing surgical resection vs. no surgery for recurrent disease

3. Intrahepatic cholangiocarcinoma (ICC)

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- Rare (0.85 per 100 000 population in 2000 in USA)
- The only potentially curative treatment option for patients who have resectable disease is surgery.
- But …with a 5-year survival rate of only 20% to 35% (tumor recurrence).
- Lack of reports on the characteristics of patients with ICC as well as predictors of recurrence and survival

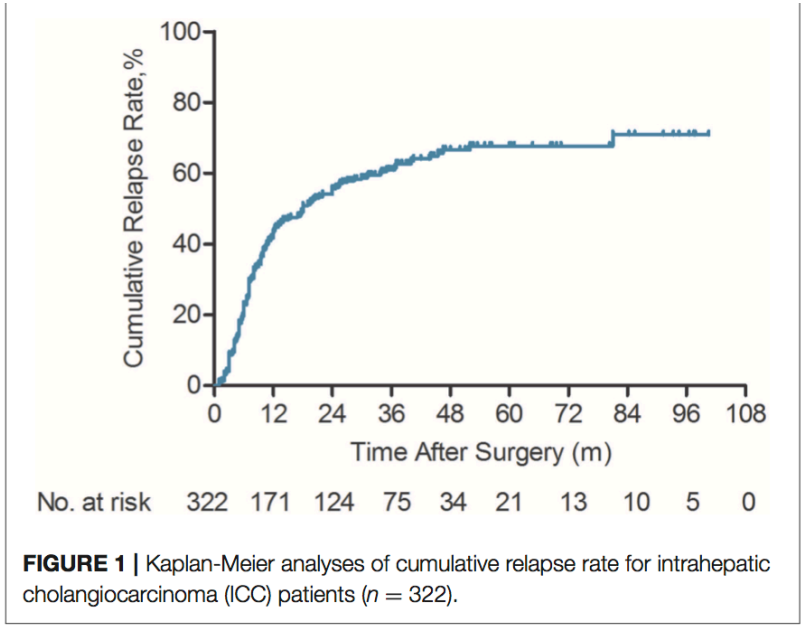


FIGURE 1 | Kaplan-Meier analyses of cumulative relapse rate for intrahepatic cholangiocarcinoma (ICC) patients ($n = 322$).

Mavros et al. JAMA Surgery 2014
Yang et al. frontiers in oncology 2019

Risk Factors and Outcomes of Early Relapse After Curative Resection of Intrahepatic Cholangiocarcinoma

Hua Yang[1†], Jie Wang[2†], Zehuan Li[3†], Yi Yang[4†], Liuxiao Yang[4†], Yong Zhang[1], Yinghong Shi[4], Ya Cao[5], Jian Zhou[4,6,7], Zheng Wang[4] and Qing Chen[1*]*

Yang et al. frontiers in oncology 2019

TABLE 2 | Univariate and multivariate cox regression analyses of time to early relapse in patients who were relapse at 2 years after resection with curative intent for intrahepatic cholangiocarcinoma ($n = 168$).

Variable	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, year (≤50 vs. >50)	1.299 (0.913–1.849)	0.147	NA	NA
Sex (female vs. male)	0.884 (0.647–1.208)	0.440	NA	NA
HBsAg (negative vs. positive)	0.805 (0.592–1.096)	0.168	NA	NA
HCV (negative vs. positive)	0.305 (0.074–1.248)	0.098	NA	NA
AFP, ng/ml (≤20 vs. >20)	1.490 (0.910–2.439)	0.113	NA	NA
Child-Pugh (A vs. B or C)	1.030 (0.381–2.785)	0.953	NA	NA
Liver cirrhosis (no vs. yes)	1.108 (0.794–1.547)	0.545	NA	NA
Tumor size, cm (≤5 vs. >5)	1.167 (0.856–1.591)	0.329	NA	NA
Tumor number (single vs. multiple)	1.986 (1.409–2.799)	**0.000**	1.951(1.382–2.755)	**0.000**
Lymphonodus node metastasis (no vs. yes)	1.558 (1.093–2.219)	**0.014**	1.517(1.061–2.168)	**0.022**
Microvascular invasion (no vs. yes)	1.593 (0.960–2.643)	0.072	NA	NA
Tumor differentiation[a] (P vs. M,W)	1.107 (0.815–1.502)	0.516	NA	NA
TNM stage[b] (I+II vs. III+IVA)	1.336 (0.962–1.856)	0.084	NA	NA
NLR (low vs. high)	1.318 (0.968–1.795)	0.080	NA	NA
PLR (low vs. high)	1.259 (0.927–1.710)	0.140	NA	NA
LMR (low vs. high)	0.812 (0.584–1.128)	0.214	NA	NA
CA19-9, U/ml (≤89 vs. >89)	1.478 (1.084–2.016)	**0.013**	1.495 (1.095–2.039)	**0.011**

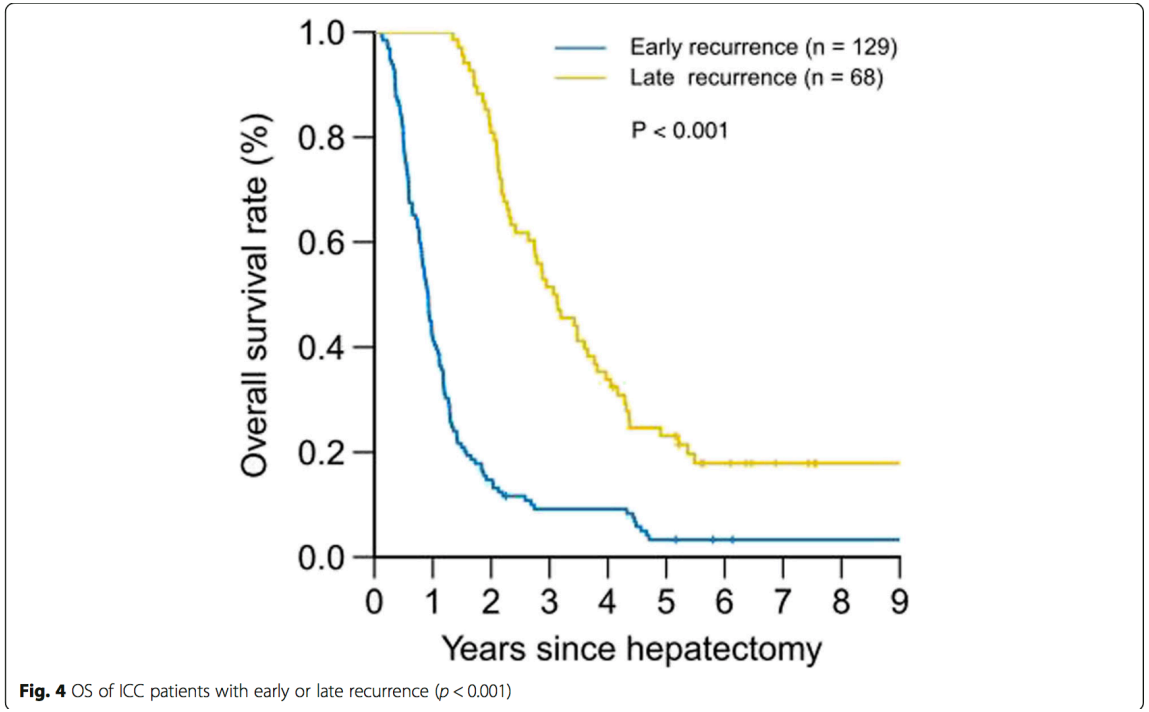


Fig. 4 OS of ICC patients with early or late recurrence ($p < 0.001$)

The overall survival of the early relapse group was lower than that of the late relapse group ($P < 0.0001$)

Treatment and Prognosis for Patients With Intrahepatic Cholangiocarcinoma
Systematic Review and Meta-analysis

Michael N. Mavros, MD; Konstantinos P. Economopoulos, MD;
Vangelis G. Alexiou, MD, PhD; Timothy M. Pawlik, MD, MPH, PhD

57 Studies included; 4756 patients

Patients characteristics:

- Median age range from 47to 69
- 57% of male patients
- Tumor median size: 4,5 -8 cm
- LN M+: 34%
- Major LR: 82%
- Lymphadenectomy: 67%

Survival:

- Median OS=28 months (9-53)
- 5 years OS=30% (5%-56%)

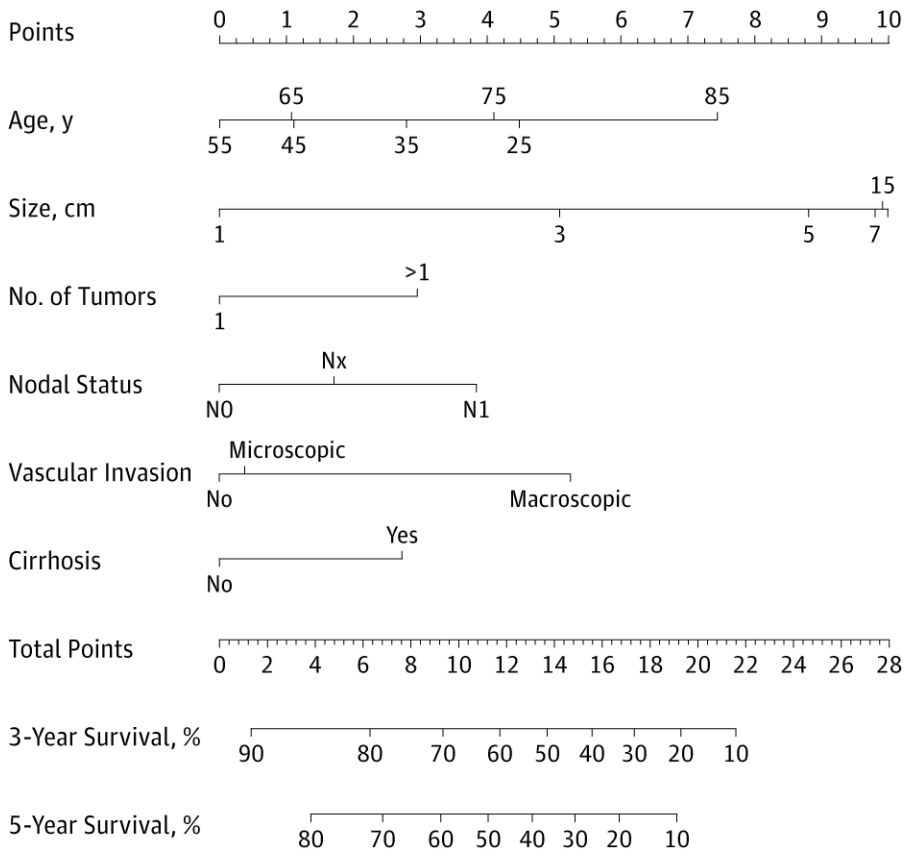
Prognostic factors of shorter OS (multivariate analysis):

- Age
- Tumor size
- Multiple tumors
- Lymphnodes metastases
- Vascular invasion

***Mavros et al. JAMA Surgery** 2014*

From: **A Nomogram to Predict Long-term Survival After Resection for Intrahepatic Cholangiocarcinoma: An Eastern and Western Experience**

JAMA Surg. 2014;149(5):432-438. doi:10.1001/jamasurg.2013.5168



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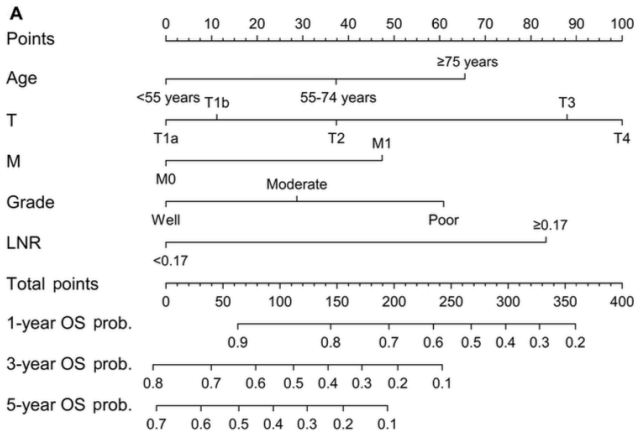
ORIGINAL RESEARCH

Nomograms for predicting overall survival and cancer-specific survival in patients with surgically resected intrahepatic cholangiocarcinoma



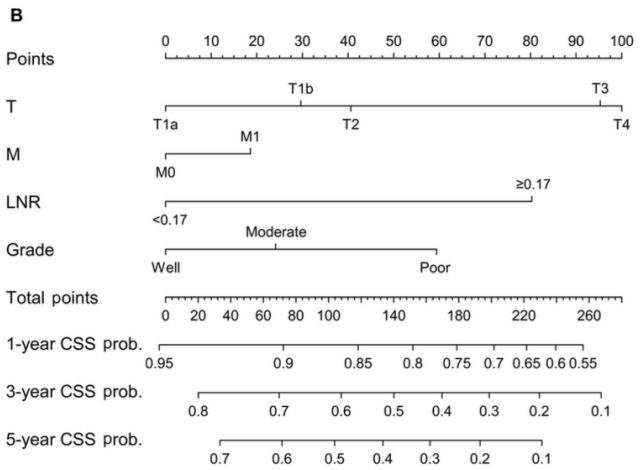


Figure 2 Nomograms predicting 1-, 3- and 5-year OS (**A**) and CSS (**B**) in patients with ICC after surgery. Each subtype within these variables was assigned a score on the point scale. By summing up the total score and locating it on the total point scale, we could draw a vertical line down to get the nomogram-predicted probability at each time point.
Abbreviations: CSS, cancer-specific survival; ICC, intrahepatic cholangiocarcinoma; LNR, lymph node ratio; OS, overall survival.

Kexin Ma et al. 2019

947 patients

In Cox regression multivariate analysis:

- Age, T stage, M stage, lymphnode ratio (LNR) level and tumor grade were independent prognostic predictors for OS in ICC patients.

- T stage, M stage, lymphnode ratio (LNR) level and tumor grade were independent prognostic predictors for DFS in ICC patients.

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AIM :to characterize the impact of ICC tumor burden on patient prognosis relative to other clinicopathological factors

In press

Statistics

The primary outcome for the survival analysis was **overall survival** (by Kaplan-Meier methodology)

Cox proportional hazards regression analysis was used to evaluate any **association among variables and survival outcomes.** Variables with a P value <0.1 on univariable analysis were included in the final multivariable model.

The **concordance index** (c-index) was used to assess the predictive abilities of different methods **to estimate tumor burden.** C-index is a statistic comparable to the AUC varying from 50% (no discrimination) to 100% (perfect discrimination).

The Classification and Regression Tree (**CART**) model, a machine-learning used **to identify groups of patients with a homogeneous risk of death and investigate the hierarchical association between variables and OS.**

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MF: mass forming
PI: periductal infiltrating

Table I
Baseline characteristics and 5-year OS of 1,116 patients undergoing liver resection for ICC

Variables	*N* = 1,116	5-Year OS	95% CI	*P* value
Sex				.33
Female	499 (44.7%)	43.7%	38.1–49.2	
Male	617 (55.3%)	38.0%	33.1–42.9	
Age (y)				.82
<65	698 (62.5%)	40.5%	35.9-45.0	
≥65	418 (37.5%)	40.4%	34.0-46.7	
ASA score				.012
1–2	626 (56.1%)	41.0%	35.9–46.1	
3–4	490 (43.9%)	39.4%	34.1–44.7	
Cirrhosis				.23
Yes	117 (12.1%)	38.9%	28.6–49.2	
No	852 (87.9%)	42.3%	37.7–46.9	
NA	147	—	—	
Tumor morphology type				<.001
MF	920 (86.9%)	42.6%	38.4–46.7	
PI/MF+PI	139 (13.1%)	26.1%	17.8–35.2	
NA	57	—	—	
Neoadjuvant chemotherapy				.92
No	823 (91.0%)	44.3%	39.7–48.7	
Yes	81 (9.0%)	46.3%	31.6–59.8	
NA	212	—	—	
Extent of resection				.008
Minor hepatectomy	399 (39.4%)	44.9%	38.4–51.2	
Major hepatectomy	388 (38.3%)	41.0%	35.0–46.9	
Extended hepatectomy	226 (22.3%)	35.0%	26.8–43.3	
NA	103	—	—	
Margins				<.001
Negative	968 (87.4%)	42.7%	38.5–46.4	
Positive	139 (12.6%)	26.5%	17.6–36.4	
NA	9	—	—	
Liver capsule involvement				.22
No	911 (81.6%)	40.9%	36.7–45.1	
Yes	205 (18.4%)	38.7%	30.9–46.4	
Invasion of adjacent organs				<.001
No	853 (93.5%)	43.7%	39.6–47.7	
Yes	66 (6.5%)	14.7%	6.4–26.5	
NA	197	—	—	
Tumor size (cm)				<.001
≤5	447 (40.1%)	51.7%	45.7–57.4	
>5	669 (59.9%)	32.6%	28.0–37.3	
Number of tumors				<.001
1	926 (82.9%)	44.6%	40.4–48.7	
2	110 (9.9%)	28.1%	17.6–39.6	
≥3	80 (7.2%)	14.2%	6.8–24.2	
Tumor grade				<.001
Well to moderately	862 (82.4%)	44.3%	39.9–48.5	
Poorly to undifferentiated	184 (17.6%)	23.4%	16.1–31.4	
NA	70	—	—	
Major vascular invasion				<.001
Not present	956 (86.4%)	42.9%	38.9–46.9	
Present	150 (13.6%)	24.6%	15.7–34.5	
NA	10	—	—	
Lymphovascular invasion				.007
Not present	755 (68.8%)	43.7%	39.3–48.1	
Present	342 (31.2%)	33.4%	26.5–40.4	
NA	19	—	—	
Perineural invasion				.001
Not present	789 (79.0%)	42.6%	38.3–46.8	
Present	210 (21.0%)	23.9%	15.6–33.3	
NA	117	—	—	
Lymph node status				<.001
Negative	307 (27.5%)	46.5%	39.1–53.7	
Positive	190 (17.0%)	16.7%	9.7–25.3	
Not assessed	619 (55.5%)	44.0%	39.1–48.8	
T stage (AJCC eighth edition)				<.001
T1a/T1b	511 (45.8%)	49.1%	43.5–54.5	
T2/T3/T4	605 (54.2%)	33.1%	28.4–37.9	

1116 patients

T+ size	% of patients
<5cm	40%
>5cm	60%
Number of T+	**% of patients**
1	83%
2	10%
3	7%

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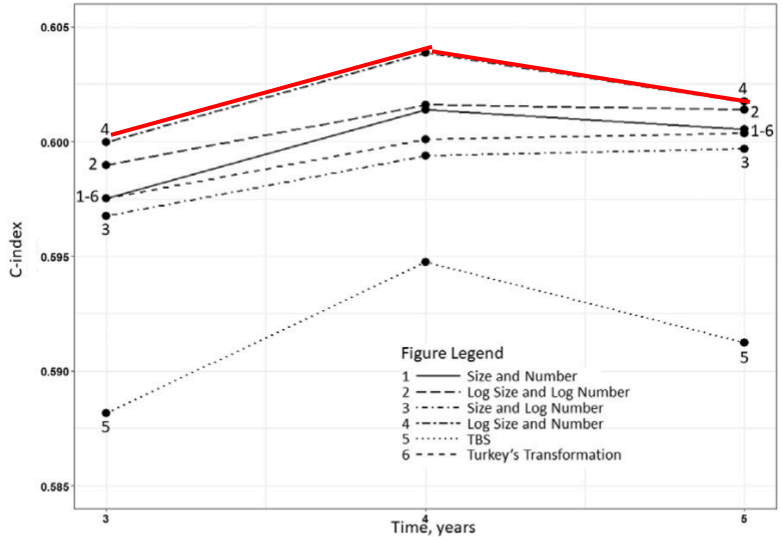

Fig 1. Trends of c-index values calculated for the different approaches to estimating ICC tumor burden.

Table III
Multivariable Cox proportional hazards regression analysis of risk factors associated with OS for patients undergoing liver resection for ICC

Variables	HR	95% CI	*P* Value
Tumor morphology type			
MF/IG	Reference	—	—
PI/MF+PI	1.41	1.09–1.83	.008
Margins			
Negative	Reference	—	—
Positive	1.43	1.10–1.87	.008
Tumor size (logistic transformation) (cm)	1.58	1.32–1.89	<.001
Number of tumors	1.19	1.12–1.27	<.001
Tumor grade			
Well to moderate	Reference	—	—
Poor to undifferentiated	1.49	1.19–1.88	<.001
Lymph node status			
Negative	Reference	—	—
Positive	2.45	1.89–3.23	<.001
Not assessed	1.56	1.24–1.97	<.001

In the multivariable Cox regression model, the risk of death increased by:
-58% for each increase in log tumor size (P < 0.001)
- 19% for each additional ICC lesion (P < 0.001).

Log tumor size and ICC lesion numbers have been identified as the best estimators of tumor burden

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CART Algorythm

Lymph node status was the strongest predictor of survival in both the "classical" survival analysis and in the CART model

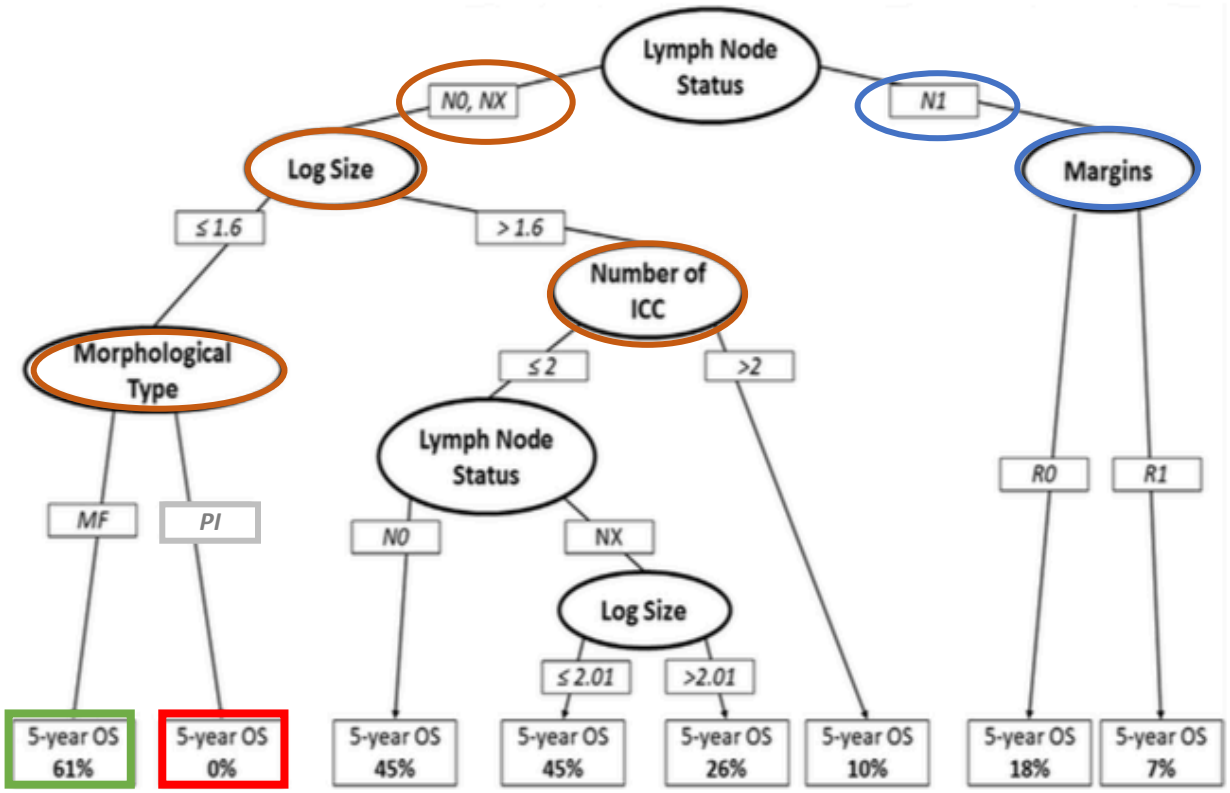

Fig 2. CART model representing the hierarchical association between tumor burden (log tumor size and number of tumors) and the other clinicopathological variables to predict patients' survival.

MF: mass forming
PI:Periductal infiltrating

Conclusions

Conventional HCC

- The tumour load in HCC is an important prognostic factor of OS.

  Tumor size, multiple tumors, bilobar tumors and vascular invasion are prognostic factors of bad survival

- However, these factors do not constitute a formal contra-indication for surgical resection that remains the best treatment option when R0 resection, leaving enough liver volume is possible in patients without extrahepatic disease.

- These prognostic factors have however to be considered when they are multiple in order:

- to make an appropriate selection of patients
- to make informed decisions about surgical resection versus other non-surgical options based on the expected OS in high risk patients.

The use of the risk score can help to better select the patients

Fibrolamellar Carcinoma

- More advanced stage (lymphnode metastases), which did not affect prognosis.
- Despite high recurrence rates, durable overall survival are achieved with surgical resection of recurrent disease

Conclusions

Intrahepatic cholangiocarcinoma (ICC)

- ✓ Prognostic factors of OS of ICC are

- lymphnode metastases
- tumor size
- number of tumors
- tumor type morphology
- vascular invasions
- age

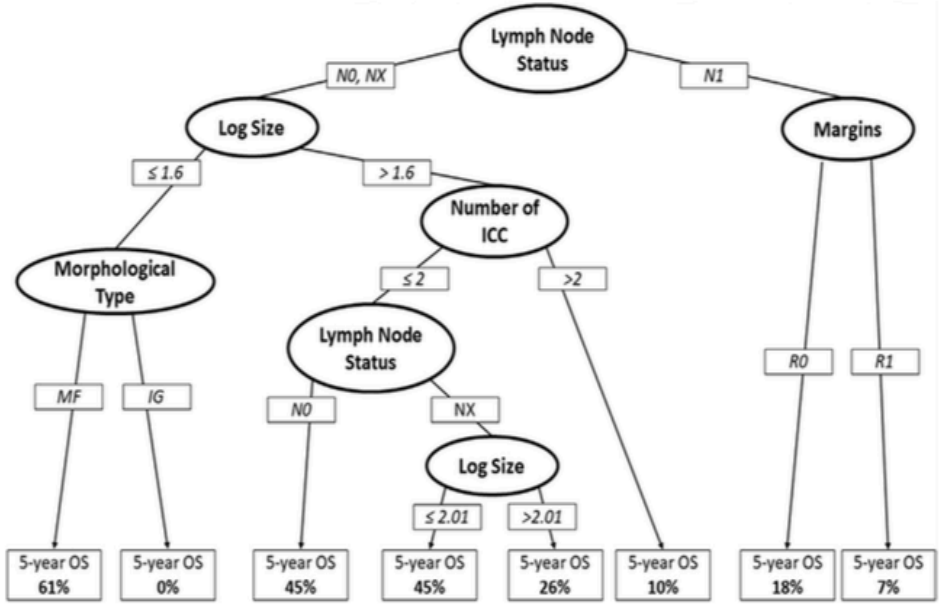

Fig 2. CART model representing the hierarchical association between tumor burden (log tumor size and number of tumors) and the other clinicopathological variables to predict patients' survival.

- ✓ Radical liver resection remains the best treatment (if no extrahepatic disease)
- ✓ A better selection of patients for surgery should be based by using the normogram or the CART model
- ✓ Patients who presents invaded lynphnodes and who are at high risk to have a R1 surgery have poor prognosis (7% 5-Years OS)
- ✓ Patient who have periductal infiltrating morphological type have the worst prognosis even if the tumor is small and if lymphnode status is N0

Thank you for your attention