Where Does IO Stand in the NCCN Guidelines: Intrahepatic Cholangiocarcinoma

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Disclosures

- Research Support: Sirtex, Guerbet
- Speaker: Cook Medical
- Consulting: BD/Bard, Astra-Zeneca

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Intrahepatic Cholangiocarcinoma

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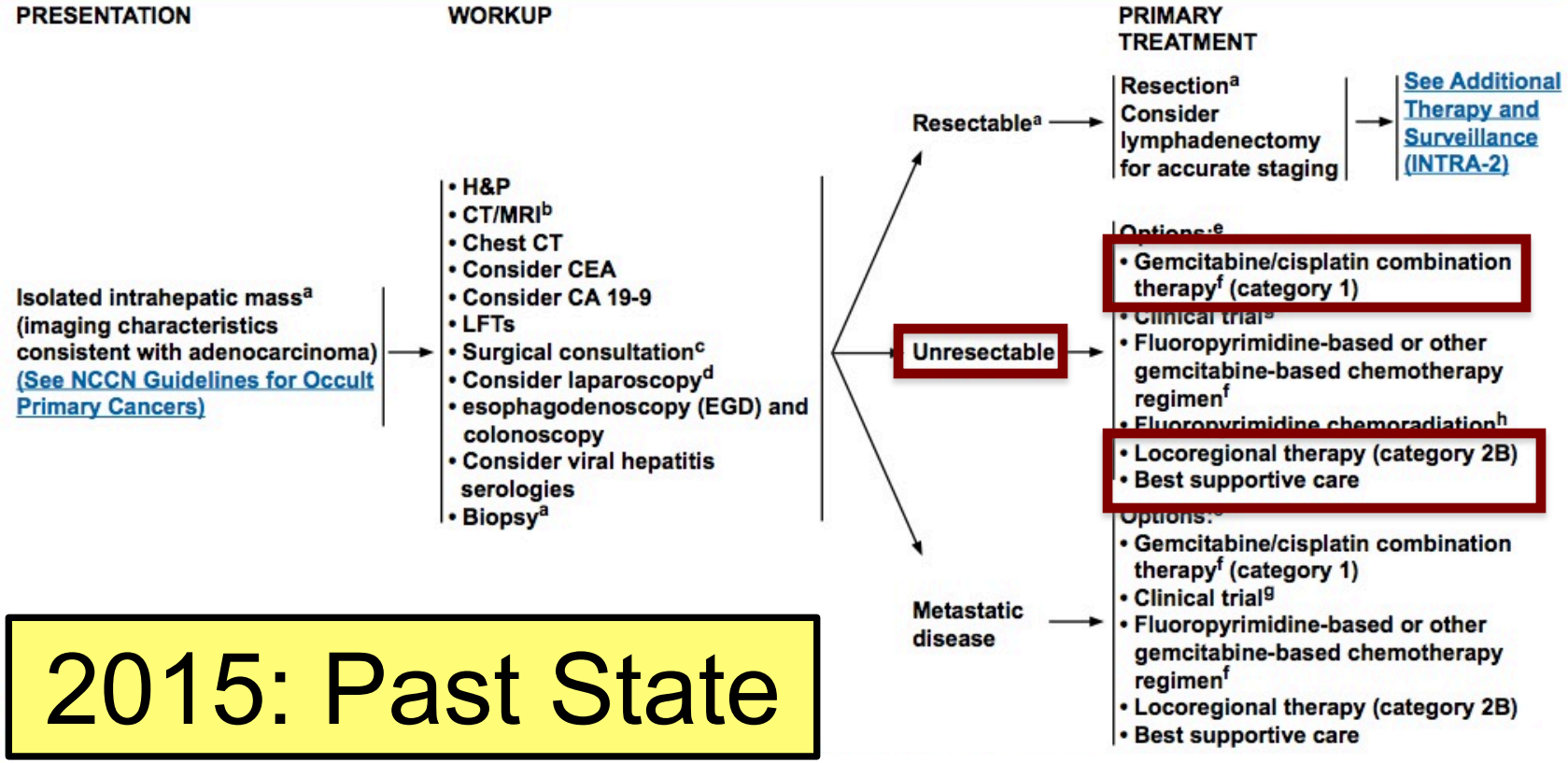

2015: Past State

2020-2021

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National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2020
Biliary Tract Cancers: Intrahepatic Cholangiocarcinoma

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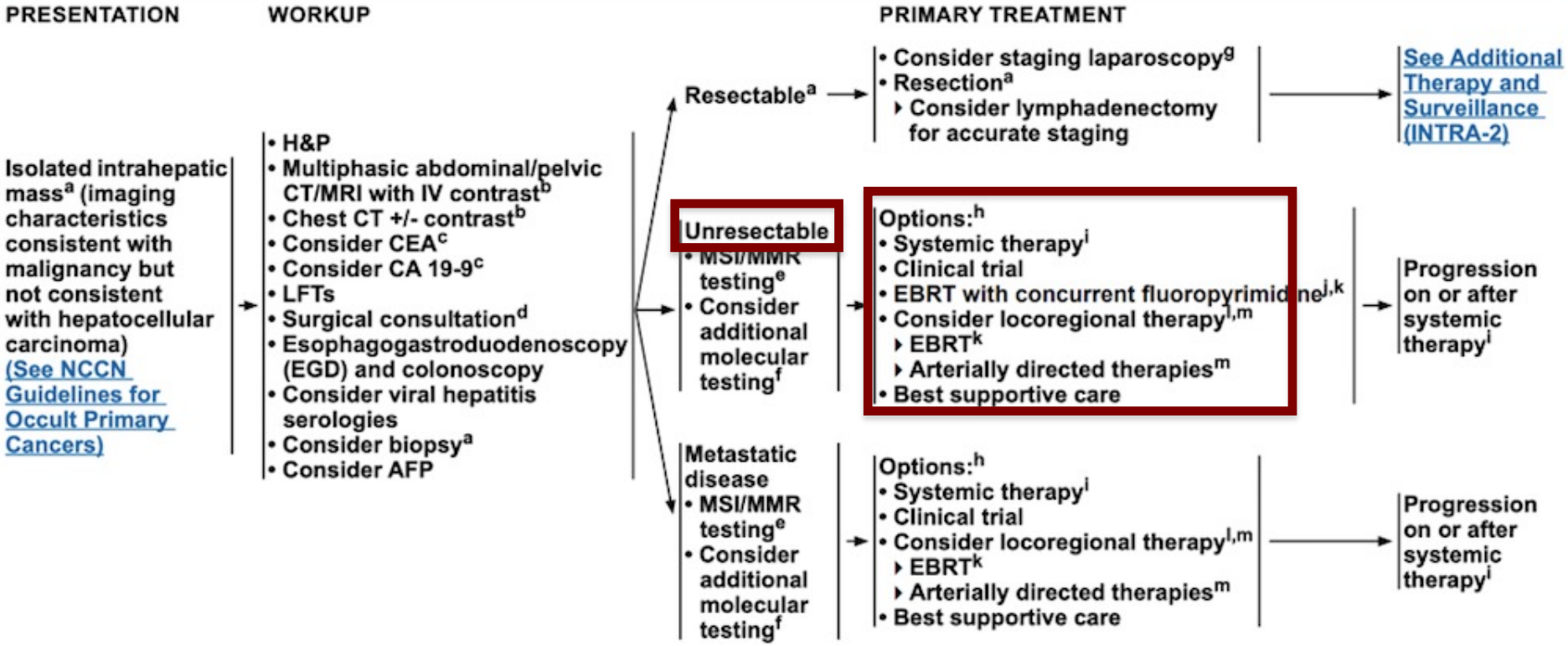

Resectable Disease

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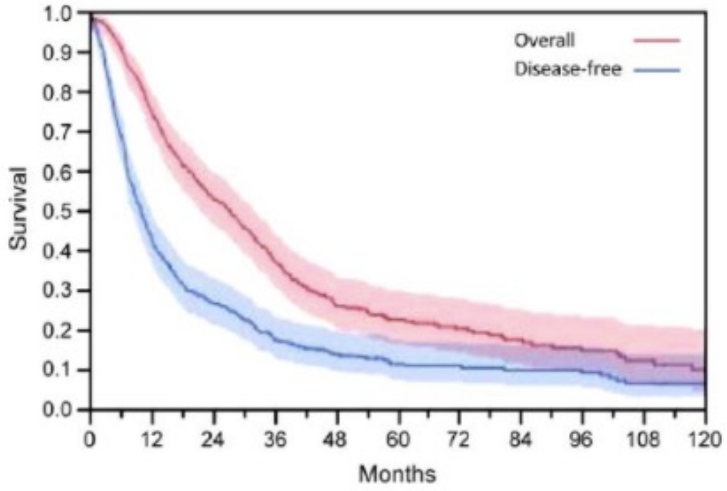
Can Hepatic Resection Provide a Long-Term Cure for Patients With Intrahepatic Cholangiocarcinoma?

TABLE 3. Multivariate Cure Model in Relation to Clinical and Tumor Features

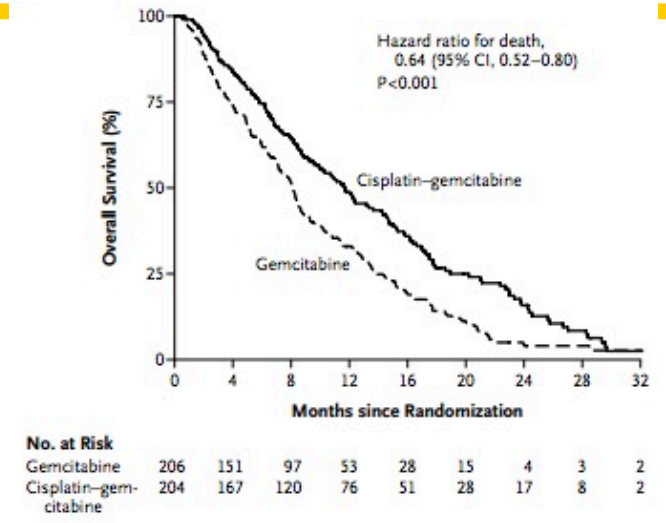
Variable	Coefficient (95% CI)	*P*
Constant	−1.057 (−1.574 to −0.541)	<.001
Positive resection margin	−0.292 (−1.104 to 0.521)	.482
Size >5 cm	− 0.763 (−1.305 to −0.220)	.006
Multifocal	−0.883 (−1.536 to −0.231)	.008
Poor tumor grade	−0.691 (−1.361 to −0.021)	.043
Bilobar	−0.029 (−0.650 to 0.591)	.926
Lymph node metastasis	−1.136 (−2.023 to −0.248)	.012
Major vascular invasion	−0.337 (−1.402 to 0.728)	.535
Minor vascular invasion	−1.333 (−2.097 to −0.568)	.001
Invasion of adjacent organs	−0.718 (−1.830 to 0.393)	.205
Periductal invasion	−1.352 (−2.406 to −0.297)	.012

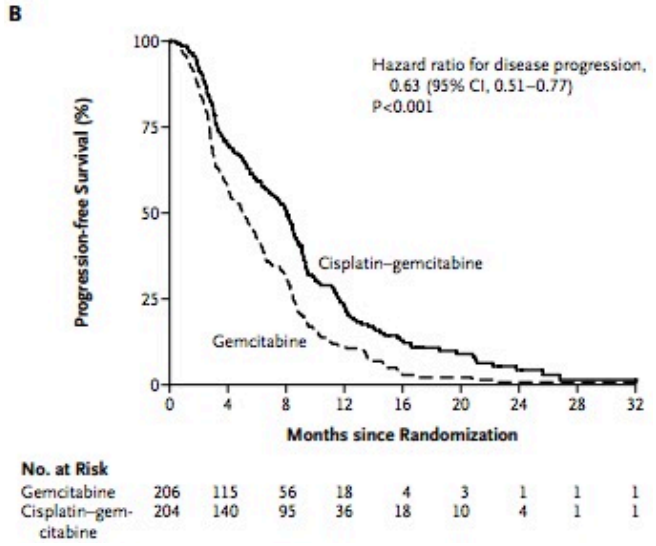


~10% survival dependent on numerous variables

Spolverato G, et al Cancer 2015;121:3998

Unresectable Disease





Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

Juan Valle, M.D., Harpreet Wasan, M.D., Daniel H. Palmer, M.D., Ph.D., David Cunningham, M.D., Alan Anthoney, M.D., Anthony Maraveyas, M.D., Ph.D., Srinivasan Madhusudan, M.D., Ph.D., Tim Iveson, M.D., Sharon Hughes, B.Sc., Stephen P. Pereira, M.D., Ph.D., Michael Roughton, M.Sc., and John Bridgewater, M.D., Ph.D., for the ABC-02 Trial Investigators*

OS 11.7 months combination vs. 8.1 (p<0.001)

Disease control better in combination group 81.4% vs 71.8%, p=0.049

68-71% Grade 3+ toxicities/arm

N Engl J Med 2010;362:1273-1281

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Intrahepatic Cholangiocarcinoma Treated with Transarterial Yttrium-90 Glass Microsphere Radioembolization: Results of a Single Institution Retrospective Study

Table 1. Demographic Characteristics of Patients

	n	%
Age (years)		
<70	35	41.2
≥70	50	58.8
Sex		
Men	41	48.2
Women	44	51.8
ECOG score		
0	35	41.2
1	22	25.9
2	28	32.9
Tumor grade		
Well differentiated	8	9.4
Moderately differentiated	30	35.3
Poorly differentiated	34	40.0
Not reported	13	15.3
Distribution		
Unilobar	54	63.5
Bilobar	31	36.5
Number of tumors		
Solitary	52	61.2
Multiple	33	38.8
Tumor morphology		
Mass-forming	32	37.6
Infiltrative	53	62.4
Tumor enhancement		
Nonenhancing	33	38.8
Enhancing	49	57.7
Contrast study not available	3	3.5
Extrahepatic metastasis		
No	49	57.6
Yes	36	42.4
Previous chemotherapy		
None	24	28.2
Yes	61	71.8
Previous liver-directed therapy		
None	67	78.8
Resection	14	16.5
Radiation	4	4.7

85-Patient Single-Arm Retrospective
Median OS from Treatment 12 Months (95% CI: 8-15.2)

High Rate:

- **ECOG 2**
- **Poorly Differentiated Tumor**
- **Extrahepatic Disease**

Gangi A, et al. JVIR 2018;29:1101-1108

ECOG 0-1 vs 2
18.5 vs 5.5 months, p=0.0012

Well vs. Poorly Differentiated
18.6 vs 9.7 months, p=0.012

Solitary vs Multiple Tumors
25 vs 6.1 months, p=0.006
Univariate only

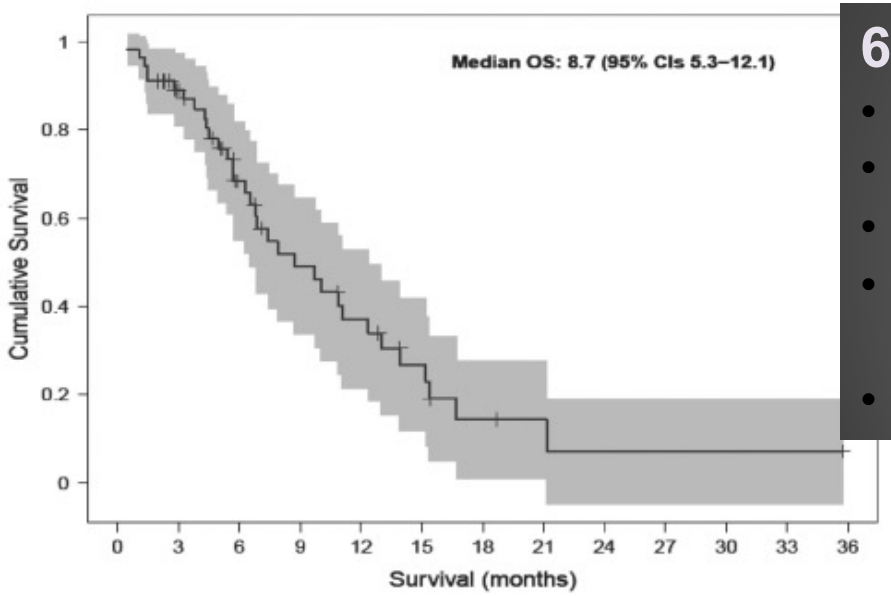
Table 2. Effects of Categorical Variables on Survival after Radioembolization Treatment

Variables	Univariate Analysis			Multivariate Analysis	
	Median survival (months)	Hazard Ratio (95% CI)	*P* value	Hazard Ratio (95% CI)	*P* value
Age (years)					
< 70	11.97	1.00	.21	1.00	.74
≥ 70	11.71	0.73 (0.45, 1.19)		1.12 (0.58, 2.17)	
Sex					
Women	12.57	1.00	.54	NA	NA
Men	10.76	1.16 (0.72, 1.86)			
ECOG score					
0–1	18.49	1.00	.0001	1.00	.0012
2	5.46	4.28 (2.52, 7.26)		3.40 (1.62, 7.13)	
Extrahepatic metastasis					
No	15.2	1.00	.003	1.00	.26
Yes	6.84	2.05 (1.26, 3.32)		1.47 (0.76, 2.86)	
Prior chemotherapy					
No	5.69	1.00	.61	NA	NA
Yes	12.14	1.16 (0.66, 2.01)			
Tumor distribution					
Solitary	25.0	1.00	.006	1.00	.41
Multiple	6.06	1.94 (1.19, 3.14)		1.32 (0.69, 2.52)	
Tumor Grade					
Well diff.	18.62	1.00	.28	1.00	.0119
Moderately diff.	13.45	1.96 (0.76, 5.07)		2.62 (.86, 7.96)	
Poorly diff.	9.74	2.14 (0.81, 5.67)		5.73 (1.73, 19.01)	

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; NA = not applicable.

Yttrium-90 Transarterial Radioembolization for Chemotherapy-Refractory Intrahepatic Cholangiocarcinoma: A Prospective, Observational Study

White J, et al
JVIR 2019;30:1185-1192



- 61 patients from prospective registry
- 38% extrahepatic disease
- 92% previous chemotherapy
- 64% bilobar disease
- 41% > 5 tumors

- Median OS: 8.7 months (95% CI: 5-12)

Toxicities

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Adverse event category	Number of adverse events	Number of grade ≥3 adverse events
Fatigue	16	2
Abdominal pain	11	0
Nausea	2	0
Vomiting	0	0
Fever	2	1
Gastritis	0	0
Gastrointestinal ulcer	0	0
REILD	1	0
Radiation pneumonitis	0	0
Radiation cholecystitis	1	0
Radiation pancreatitis	0	0
Other	16	1
Total adverse events	49	4

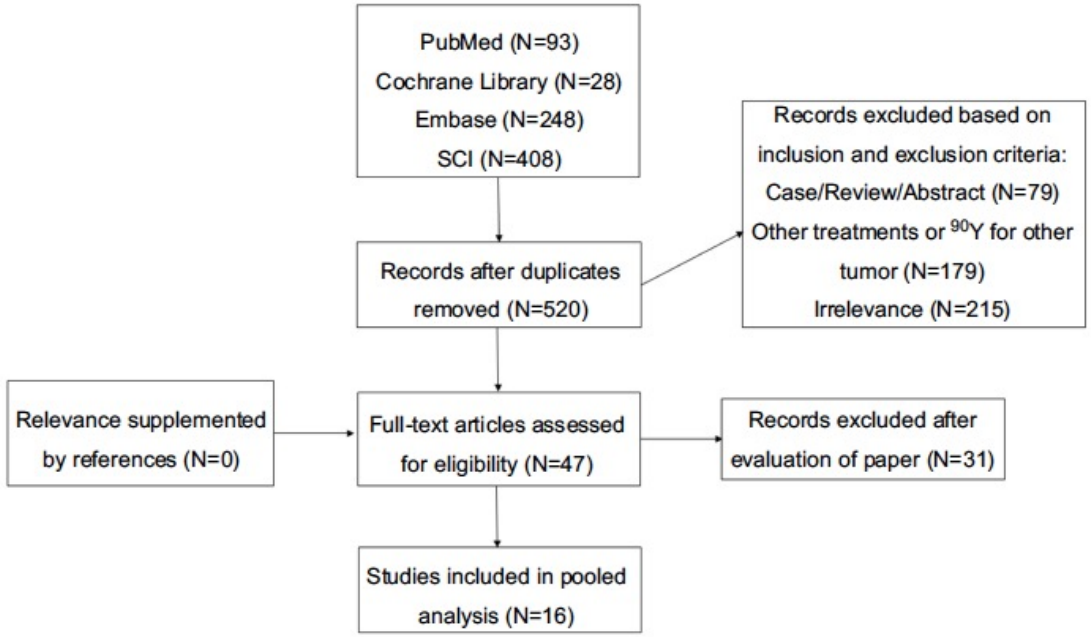
Abnormal laboratory result event category	Number of events	Number of grade ≥3 events
AST increased	17	1
ALT increased	14	0
Hypoalbuminemia	12	0
Hyperbilirubinemia	10	2
INR increased	0	0
Neutrophil count decreased	1	0
Platelet count decreased	12	0
Other	11	0
Total abnormal laboratory result events	77	3

7 TOTAL Grade 3+ events
11.4% of patients

A pooled analysis of transarterial radioembolization with yttrium-90 microspheres for the treatment of unresectable intrahepatic cholangiocarcinoma

T UNIVERSITY CAL CENTER

OncoTargets and Therapy 2019;12:4489-4498



- 472 patients
- ECOG
- Extrahepatic Disease?
- Chemotherapy?
- Type of Y90
- Dosimetry
- OS
- 1-year survival
- Tumor Response
- Toxicity

Survival

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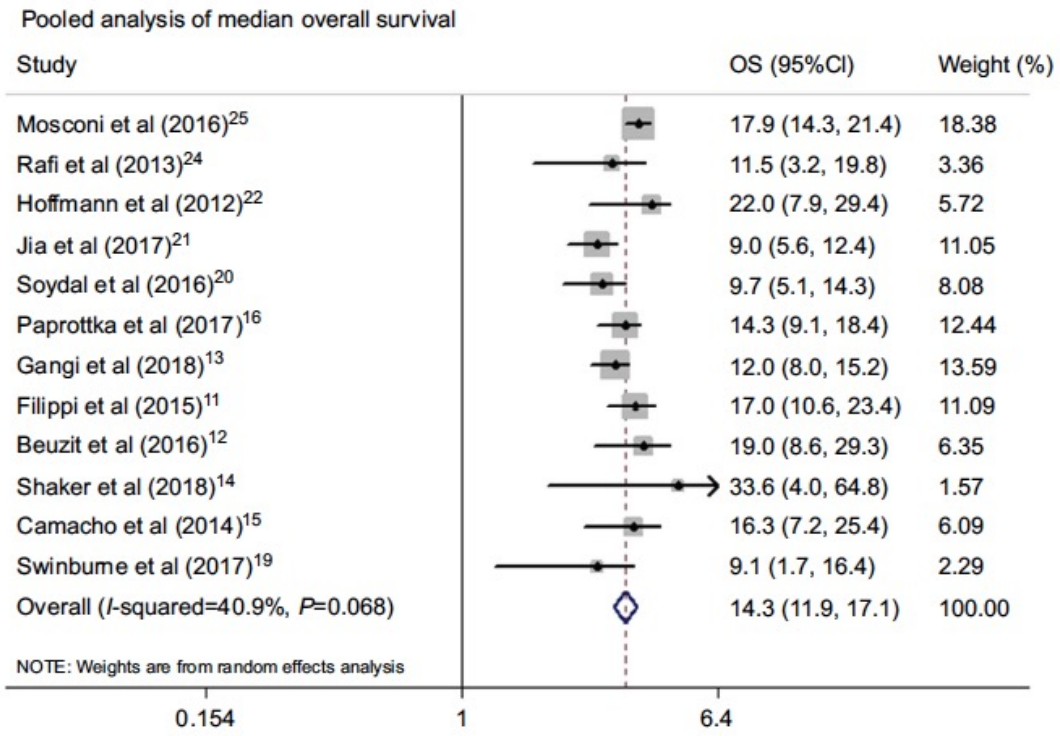
Median OS: 14.3 months (95% 11.9-17.1)
DCR: 77.2% (95% CI 70.2-84.2%)



Glass OS: 14 months (9.1-21.4)
Resin OS: 14.3 months (11.5-17.8)

Glass DCR: 77.3% (63.5-91.1%)
Resin DCR: 77.4% (66.8-87.9%)

Toxicity

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Grade 3+: 7.8% (0-25%)

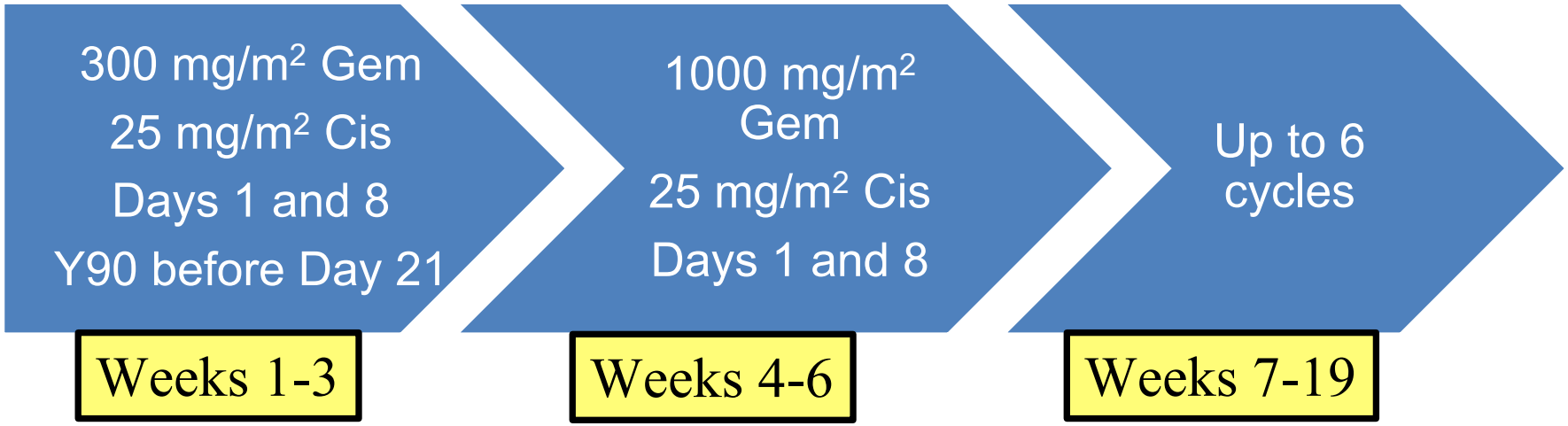
Most Common Constitutional:
Fatigue: 31.7% (0-87.5%)
Anorexia: 10% (0-79.2%)
Abd Pain: 30% (0-85%)

Most Common Lab:
Albumin: 2% (0-9%)
Bilirubin: 5.7% (0-70%)

Ulcer: 4% (0-5%)

JAMA Oncology | Original Investigation

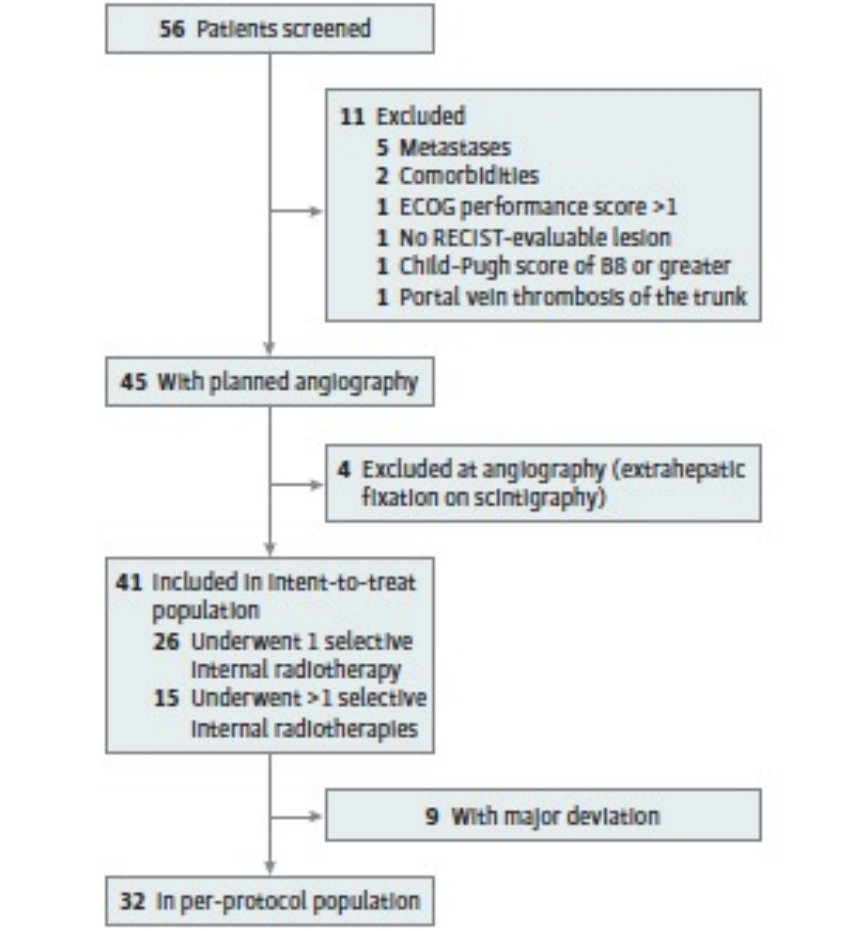
Radioembolization Plus Chemotherapy for First-line Treatment of Locally Advanced Intrahepatic Cholangiocarcinoma
A Phase 2 Clinical Trial



Lower dose gemcitabine w/ Y90
2nd Y90 treatment for bilobar disease allowed in 2nd cycle of therapy
JAMA Oncol 2020;6:51-59

Dosimetry:
MIRD (120 Gy)
Treatment Personalization
(>205 Gy to tumor) allowed

Major Deviation (9/41):
Went to surgery



ECOG indicates Easter Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors.

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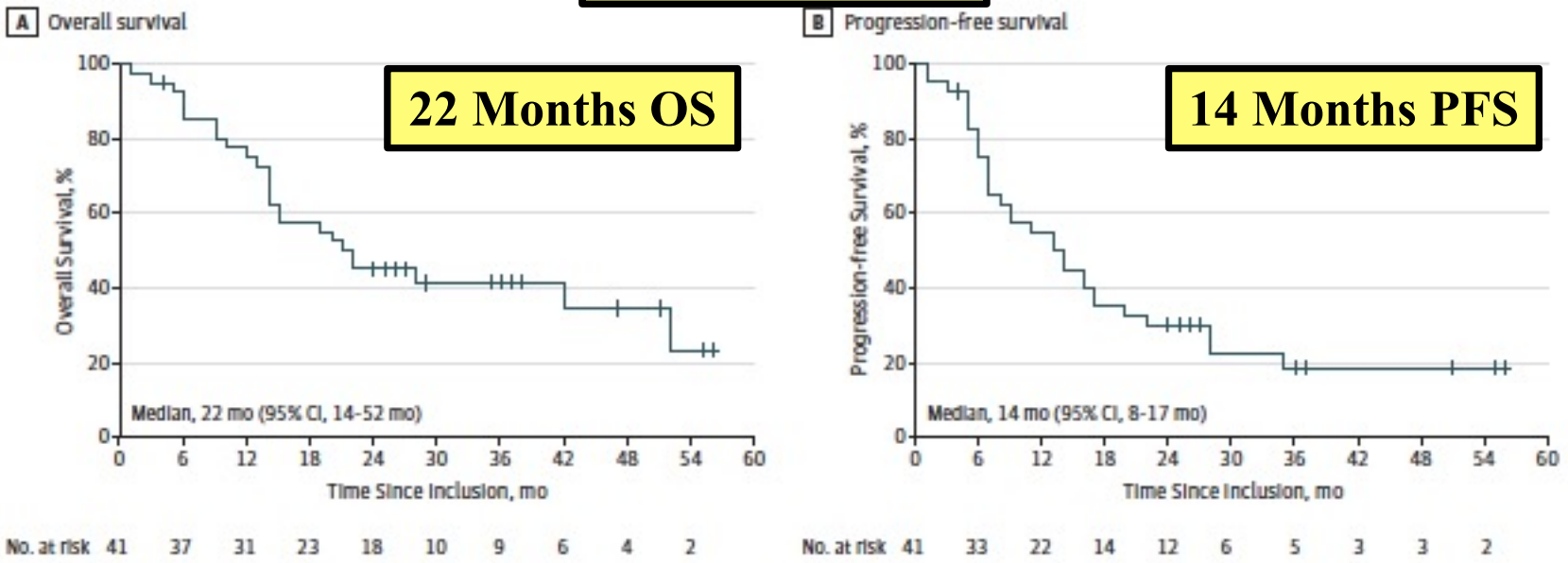
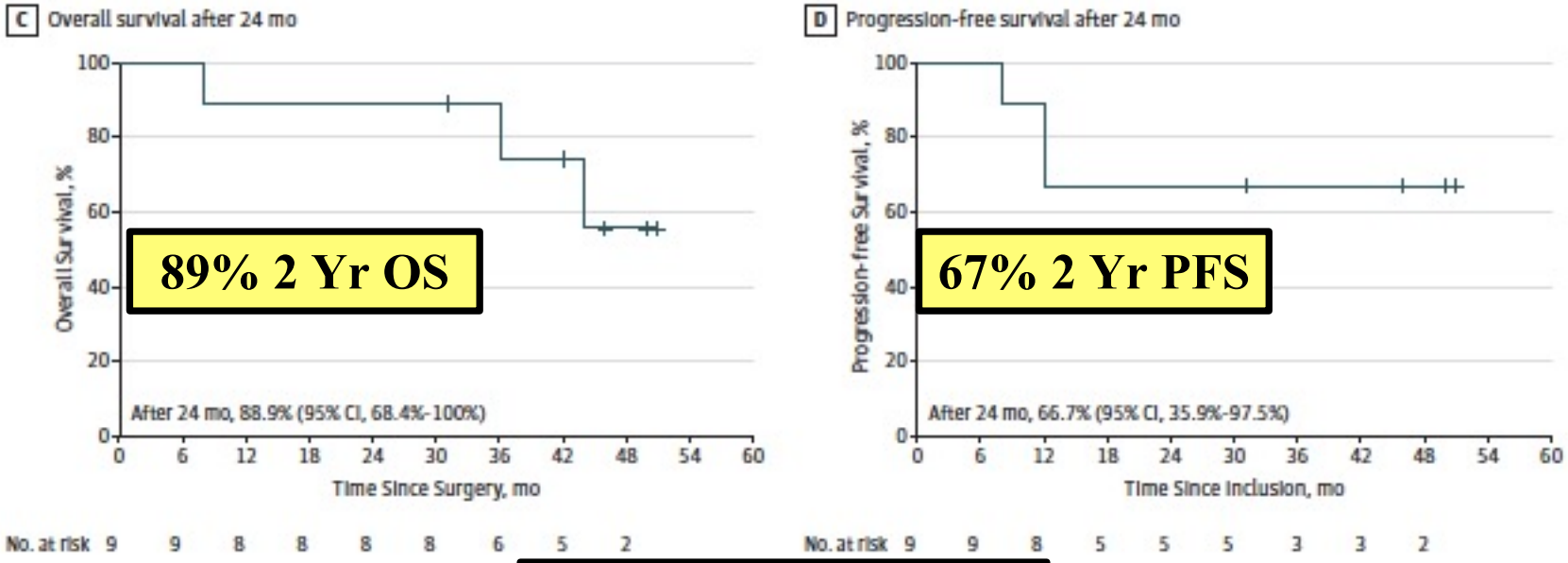
Entire Cohort



22 Months OS

14 Months PFS



89% 2 Yr OS

67% 2 Yr PFS

Surgical Subgroup

Downstaging with Radioembolization or Chemotherapy for Initially Unresectable Intrahepatic Cholangiocarcinoma

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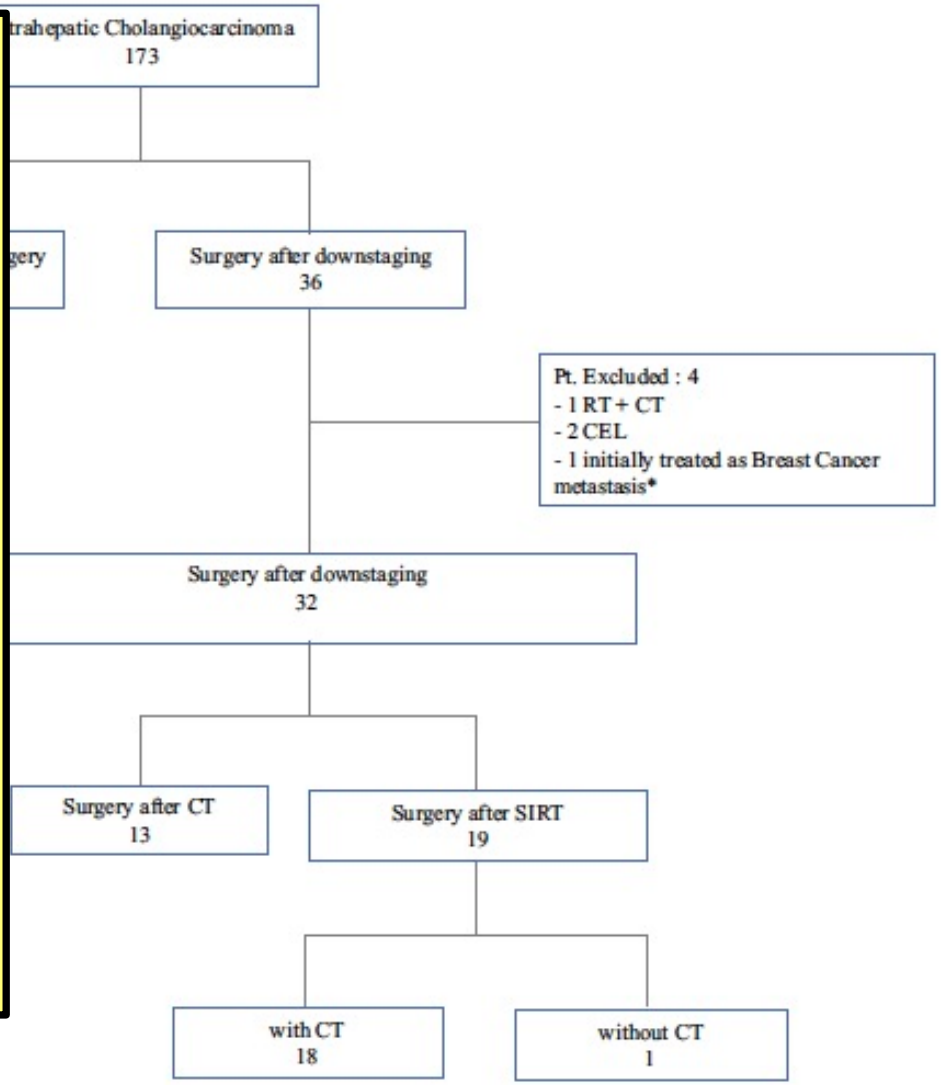
Does downstaging lead to outcomes similar to patients with initially resectable disease?

Retro Review 1997-2017

137 Up-front surgery
13 Chemo Downstaging
19 Y90 Downstaging

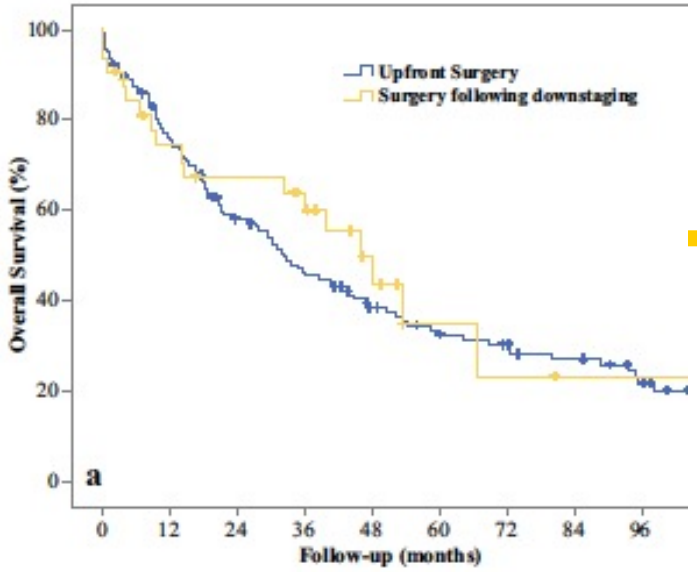
Riby D, et al. Ann Surg Oncol 2020; 27:3729-3737



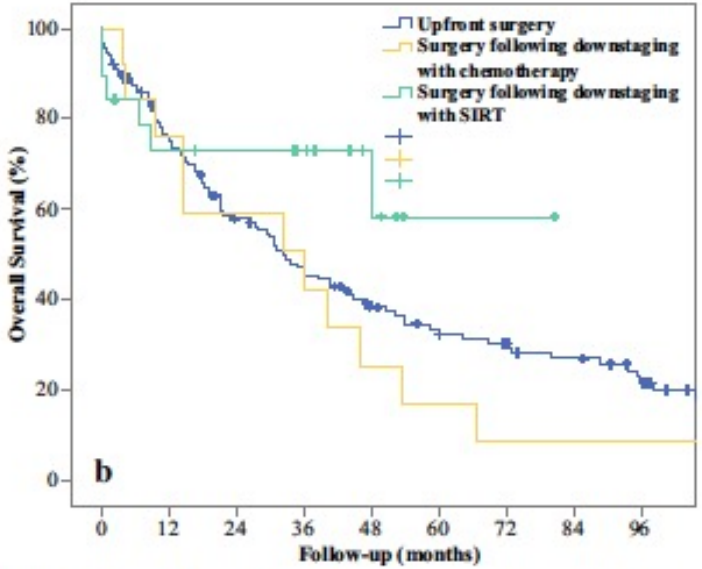
	Upfront surgery	Chemotherapy	Ytt-90	*p*-Value
Male	100 (73.0)	8 (61.5)	9 (47.4)	0.063
Median age, years (min–max)	67 [35–85]	60 [47–71]	66 [40–79]	0.034
Cirrhosis	33 (24.3)	2 (15.4)	0 (0)	0.052
Bilirubin, umol/L	11 [0–246]	12 [5–26]	9 [0–13]	0.187
Size, SD	6 [1–17]	7 (3–12)	7 [4–10]	0.272
Multifocal disease	29 (21.3)	5 (38.5)	6 (33.3)	0.236
Number of tumors	1 [1–10]	1 [1–10]	1 [1–10]	0.250
Major hepatectomy	104 (75.9)	12 (92.3)	19 (100)	0.025
Portal vein embolization	13 (9.5)	3 (23.1)	1 (5.3)	0.227
Number of segments resected	4 [1–7]	4 [2–7]	6 [4–6]	< 0.001
Macrovascular invasion	14 (10.2)	0 (0)	9 (50.0)	< 0.001
Perineural invasion	30 (22.4)	5 (38.5)	2 (11.8)	0.221
Margins, mm	4 [0–100]	3 [0 - 25]	1.5 [0–10]	0.115
Resection R1	26 (19.4)	5 (38.5)	2 (11.8)	0.174
Operative time, min	180 [0–840]	180 [80–180]	205 [140–360]	0.223

Data are expressed as median [range] or *n* (%) unless otherwise indicated

min minimum, *max* maximum, *SD* standard deviation



N at risk	0	12	24	36	48	60	72	84	96
UpSur	137	98	70	55	40	32	28	23	21
DowSur	32	22	19	16	8	3	2	1	1
Tot	169	120	89	71	48	35	30	24	17



N at risk	0	12	24	36	48	60	72	84	96
UpSur	137	98	70	55	41	32	28	23	16
CT	13	9	7	6	3	2	1	1	1
REL	19	13	12	10	5	1	1	-	-
Tot	169	120	89	71	49	35	30	24	17

Cohort OS: 35.8 months

Upfront Surg OS: 32.3 months
Downstaging OS: 45.9 months (p=0.54)

Median OS Chemo: 36 months
Median OS Y90: not reached

Use of Y90 associated with survival benefit
HR=0.34, p=0.019

Possible Future State?