

Systematic review and pooled analysis – Locoregional treatment for iCC

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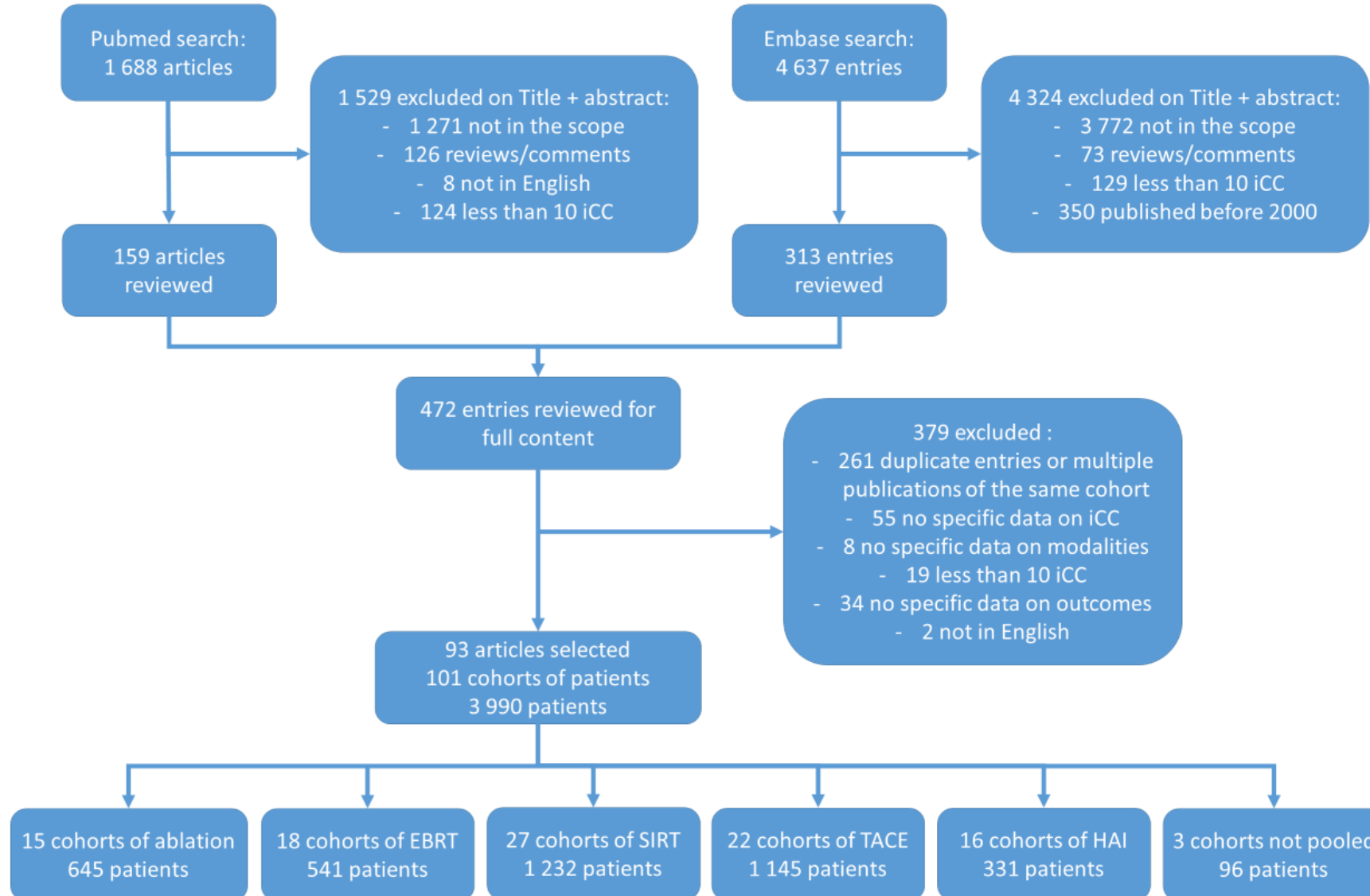


Background:

- ▶ Intra-hepatic cholangiocarcinoma may present as an unresectable liver-only disease
- ▶ Different locoregional treatments have been applied for these patients, however the value has not been clearly defined
- ▶ We thus performed a systematic review looking for studies published in Pubmed and EMBASE, focusing on the following treatments:
 - ▶ Ablation
 - ▶ External beam radiotherapy
 - ▶ Intra-arterial therapies, including TransArterial ChemoEmbolsation (TACE), radioembolisation (SIRT) and Hepatic Arterial Infusion (HAI)



Selection of articles



► From 6 325 entries, 93 articles covering 101 cohorts selected

► Largest systematic review to date



Description of studies: limited quality

	All studies (n=93)	Ablation (n=14)	EBRT (n=17)	SIRT (n=25)	TACE (n=20)	HAI (n=14)
Prospective trial	16 (17%)	0 (0%)	3 (18%)	2 (8%)	3 (15%)	7 (50%)
Prospective cohort	8 (9%)	2 (14%)	1 (6%)	3 (12%)	2 (10%)	0 (0%)
Retrospective study	69 (74%)	12 (86%)	13 (77%)	20 (80%)	15 (75%)	7 (50%)
Multicenter	23 (25%)	1 (7%)	4 (24%)	6 (24%)	9 (45%)	3 (21%)
No or inadequate control group	86 (93%)	12 (86%)	15 (88%)	25 (100%)	18 (90%)	13 (93%)
Adequate not randomized	6 (7%)	2 (14%)	2 (12%)	0 (0%)	1 (5%)	1 (7%)
Randomized	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)
Clearly Defined Incl/Excl	55 (59%)	10 (71%)	9 (53%)	12 (48%)	12 (60%)	10 (71%)
Clear definition of outcomes	59 (63%)	11 (79%)	12 (71%)	12 (48%)	14 (70%)	8 (57%)
Only abstract available	18 (19%)	1 (7%)	1 (6%)	9 (36%)	5 (25%)	2 (14%)
Risk of bias Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Risk of bias Intermediate	14 (15%)	0 (0%)	3 (18%)	2 (8%)	3 (15%)	5 (36%)
Risk of bias High	79 (85%)	14 (100%)	14 (82%)	23 (92%)	17 (85%)	9 (64%)



Description of cohorts: heterogeneous population

for all variables, values then ; number of cohorts with data	All cohorts (n=101 cohorts, 3990 patients)	Ablation (n=15 cohorts, 645 patients)	EBRT (n=18 cohorts, 541 patients)	SIRT (n=27 cohorts, 1232 patients)	TACE (n=22 cohorts, 1145 patients)	HAI (n=16 cohorts, 331 patients)
N patients per cohort, median (range)	25 (10-183) ; 101	27 (10-107) ; 15	25 (10-79) ; 18	29 (16-125) ; 27	35 (11-183) ; 22	14 (10-78) ; 16
N lesions, median (range)	33 (10-171) ; 13	35 (10-171) ; 12	NA ; 0	NA ; 1	NA ; 0	NA ; 0
Age, mean (range of means of studies)	64 (51-78) ; 69	61 (51-73) ; 13	66 (56-76) ; 12	64 (55-76) ; 17	62 (59-75) ; 13	62 (57-78) ; 13
Gender, male	1791/3270 (54.8%) ; 74	400/625 (64.0%) ; 14	209/396 (52.8%) ; 12	478/966 (49.4%) ; 21	502/918 (54.7%) ; 15	128/269 (47.6%) ; 12
ECOG PS0	614/1251 (49.1%) ; 29	NA ; 0	125/284 (44.0%) ; 8	340/665 (51.1%) ; 12	112/241 (46.5%) ; 5	37/61 (60.7%) ; 4
Underlying cirrhosis	308/1306 (23.6%) ; 23	140/449 (31.1%) ; 9	14/94 (14.9%) ; 2	82/486 (16.9%) ; 8	71/261 (27.2%) ; 3	NA ; 0
Previous chemo	734/1671 (43.9%) ; 44	0/56 (0%) ; 1	131/247 (53.0%) ; 6	469/782 (60.0%) ; 18	91/371 (24.5%) ; 9	43/180 (23.9%) ; 10
Previous surgery	738/2008 (36.8%) ; 43	280/547 (51.2%) ; 10	12/190 (6.3%) ; 5	166/726 (22.9%) ; 16	261/486 (53.7%) ; 8	19/59 (32.2%) ; 4
Previous locoregional treatment	137/1001 (13.6%) ; 25	56/133 (42.1%) ; 2	12/118 (10.2%) ; 4	30/425 (7.1%) ; 10	22/233 (9.4%) ; 6	4/57 (7.0%) ; 3
Previous biliary drainage	50/413 (12.1%) ; 9	NA ; 0	21/157 (13.4%) ; 3	20/196 (10.2%) ; 4	NA ; 0	NA ; 0



Description of cohorts: heterogeneous tumors

for all variables, values then ; number of cohorts with data	All cohorts (n=101 cohorts, 3990 patients)	Ablation (n=15 cohorts, 645 patients)	EBRT (n=18 cohorts, 541 patients)	SIRT (n=27 cohorts, 1232 patients)	TACE (n=22 cohorts, 1145 patients)	HAI (n=16 cohorts, 331 patients)
Largest tumor size in mm, mean (range)	60 (15-115) ; 38	27 (15-44) ; 11	58 (43-79) ; 8	68 (60-77) ; 5	81 (54-115) ; 9	94 (83-114) ; 4
Bilobar disease	712/1186 (60.0%) ; 25	NA ; 0	NA ; 0	416/769 (54.1%) ; 16	197/285 (69.1%) ; 6	99/132 (75.0%) ; 3
Multifocal disease	1103/2206 (50%) ; 44	163/483 (33.7%) ; 9	78/270 (28.9%) ; 8	435/696 (62.5%) ; 11	278/514 (54.1%) ; 7	137/208 (65.9%) ; 9
> 50% liver involvement	84/610 (13.8%) ; 15	0/205 (0%) ; 3	NA ; 0	28/260 (10.8%) ; 8	56/145 (38.6%) ; 4	NA ; 0
MacroVascular Invasion	268/1491 (18.0%) ; 26	4/448 (0.9%) ; 8	27/103 (26.2%) ; 2	129/454 (28.4%) ; 7	83/421 (19.7%) ; 5	20/50 (40.0%) ; 4
ExtraHepatic Spread	510/2210 (23.1%) ; 48	10/491 (2.0%) ; 10	60/188 (31.9%) ; 5	260/847 (30.7%) ; 18	142/569 (25.0%) ; 9	38/115 (33.0%) ; 6
Visceral metastasis	153/1608 (9.5%) ; 39	2/474 (0.4%) ; 9	41/279 (14.7%) ; 8	66/400 (16.5%) ; 10	21/328 (6.4%) ; 5	23/127 (18.1%) ; 7
Lymph nodes involvement	409/1871 (21.9%) ; 41	19/489 (3.9%) ; 9	120/252 (47.6%) ; 7	117/400 (29.3%) ; 10	73/552 (13.2%) ; 7	49/143 (34.3%) ; 8



Description of treatments

▶ Ablation:

- ▶ RFA in 7/15 cohorts, MWA in 4, mixed in 4
- ▶ No concomitant chemotherapy

▶ EBRT:

- ▶ SBRT in 8/17 cohorts, conformational in 3, Proton in 4, carbon-ion in 1 and mixed in 1
- ▶ Median dose 50Gy (range: 30-72) in 5 to 15 fractions
- ▶ Concomitant chemotherapy in 158/217 (72.8%) ; data from 6 studies



Description of treatments

▶ SIRT:

- ▶ Glass in 7/24 cohorts, resin in 12, mixed in 5 ;
- ▶ Mean of 1.3 sessions (data from 12 cohorts) ; Activity provided in 12 cohorts, tumor dose in 4
- ▶ Concomitant systemic chemo in 63/221 patients (29.9%), data from 4 cohorts)

▶ TACE:

- ▶ Lipiodol in 7/19; DEB in 6; other or mixed in 6
- ▶ TAE in 2/22 cohorts; Anthracycline in 3; platinum in 2; multidrug in 6; mixed or other in 9
- ▶ Mean of 3.0 sessions
- ▶ Concomitant systemic chemo in 29/39 patients (74.4%), but data only from 2 cohorts

▶ HAI:

- ▶ FUDR in 2/13 cohorts, Gem-based in 3, Platinum-based in 4, mixed in 4
- ▶ Mean of 9.3 cycles (data from 10 cohorts)
- ▶ Concomitant chemotherapy in 193/201 (96.0%) ; data from 8 cohorts



Pooled outcomes: survival

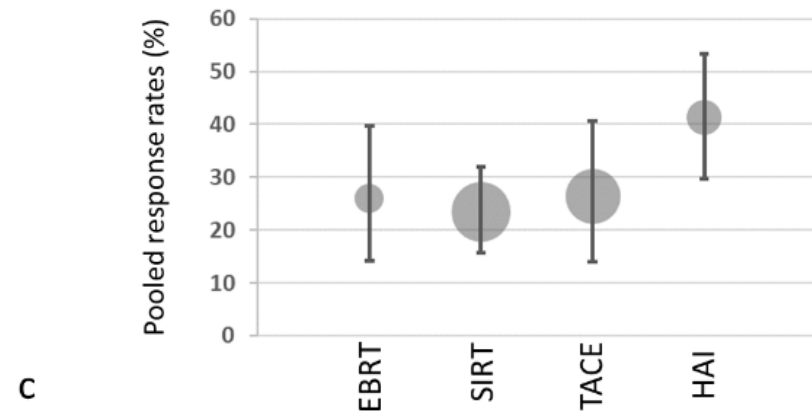
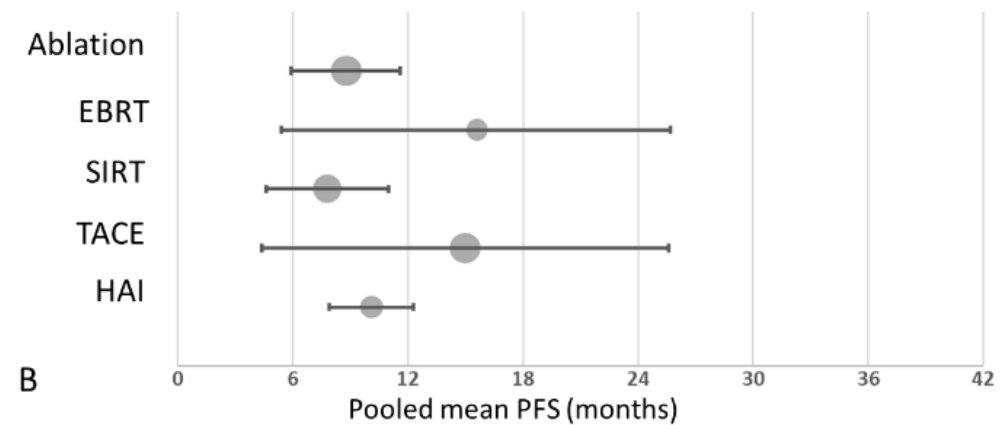
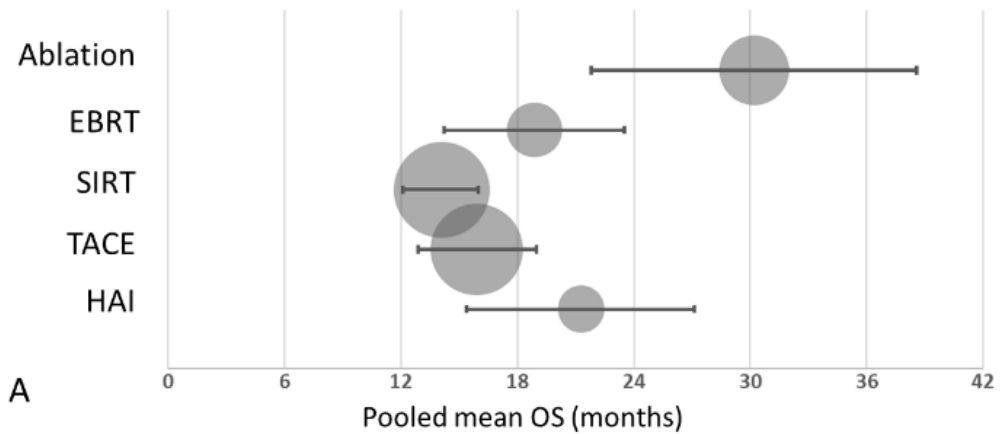
	Ablation	EBRT	SIRT	TACE	HAI
Pooled mean weighted OS months (95% CI); number of studies with data available	30.2 (21.8-38.6) ; 14	18.9 (14.2-23.5) ; 15	14.1 (12.1-16.0) ; 26	15.9 (12.9-19.0) ; 20	21.3 (15.4-27.1) ; 13
Pooled mean weighted PFS months (95% CI) ; number of studies with data available	8.8 (5.9-11.6) ; 9	15.6 (5.4-25.7) ; 5	7.8 (4.6-11.0) ; 8	15.0 (4.4-25.6) ; 7	10.1 (7.9-12.3) ; 9
Pooled mean weighted liver PFS months (95% CI) ; number of studies with data available	15.6 (0-140.5) ; 2	4.1 (n/a) ; 1	4.9 (0.8-9.2) ; 3	4.9 (0-43.0) ; 2	8.8 (0-64.0) ; 2



Pooled outcomes: Response

	Ablation	EBRT	SIRT	TACE	HAI
Pooled response rate % (95% CI); heterogeneity I ² -p value; number of studies with data available	n/a; n/a; 1	26.0 (14.2-39.7); 68.3%-0.004; 7	23.4 (15.7-31.9); 85.0%-0.000; 18	26.3 (14.0-40.6); 92.8%-0.000; 15	41.3 (29.7-53.3); 70.3%-0.000; 13
Pooled complete response rate % (95% CI); heterogeneity I ² -p value; number of studies with data available	93.9 (90.9-96.5); 0.0%-0.742; 8	5.2 (0-17.7); 70.9%- 0.008; 5	0.2 (0.0-1.4); 22.1%-0.233; 11	0.1 (0-0.1); 32.9%- 0.105; 15	0.4 (0-3.4); 0.0%- 0.925; 8
Pooled disease control rate % (95% CI); heterogeneity I ² -p value; number of studies with data available	97.4 (90.4-100); n/a; 2	75.5 (53.8-92.4); 79.9%-0.001; 5	76.7 (66.3-85.8); 87.2%-0.000; 13	82.7 (73.9-90.1); 84.4%-0.000; 15	76.8 (68.4-84.4); 27.0%-0.187; 11
Pooled secondary resection rate % (95% CI); heterogeneity I ² -p value; number of studies with data available	n/a; n/a; 1	n/a; n/a; 1	7.6 (3.7-12.5); 68.4%-0.002; 8	12.7 (6.4-20.3); 3.5%-0.375; 4	8.3 (3.2-14.9); 23.0%-0.261; 6
Pooled mean weighted 2-year local control rate % (95% CI); number of studies with data available	79.3 (0-100); 2	69.1 (48.1-90.2); 6	n/a	n/a	n/a

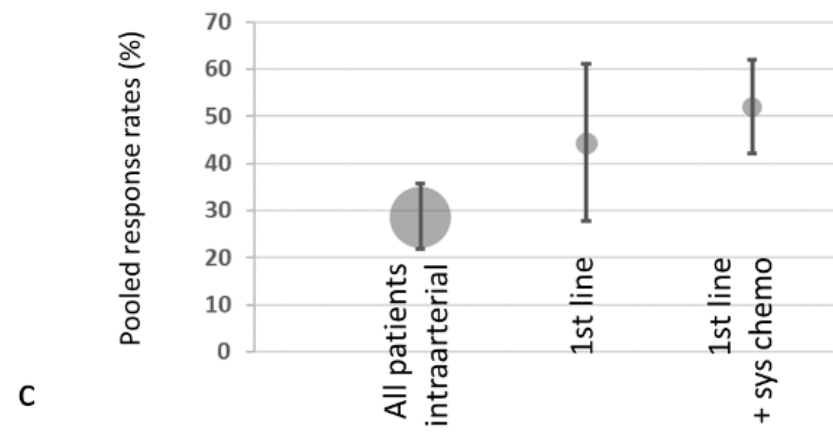
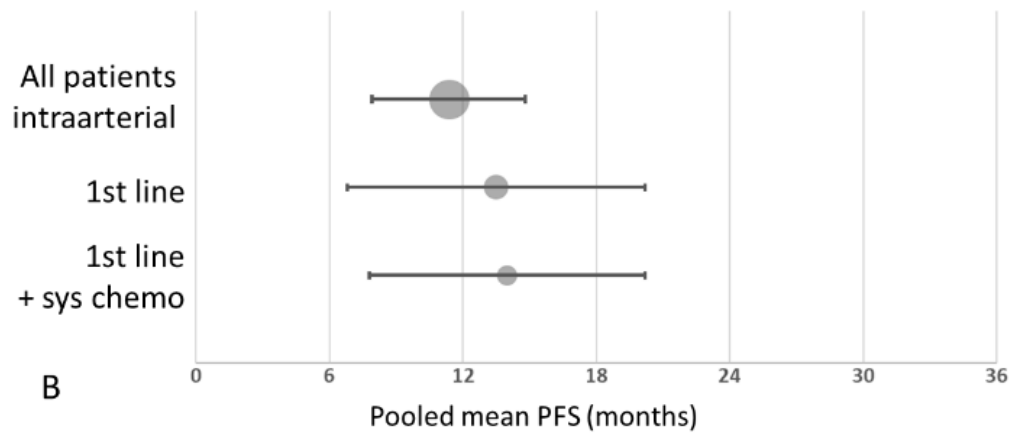
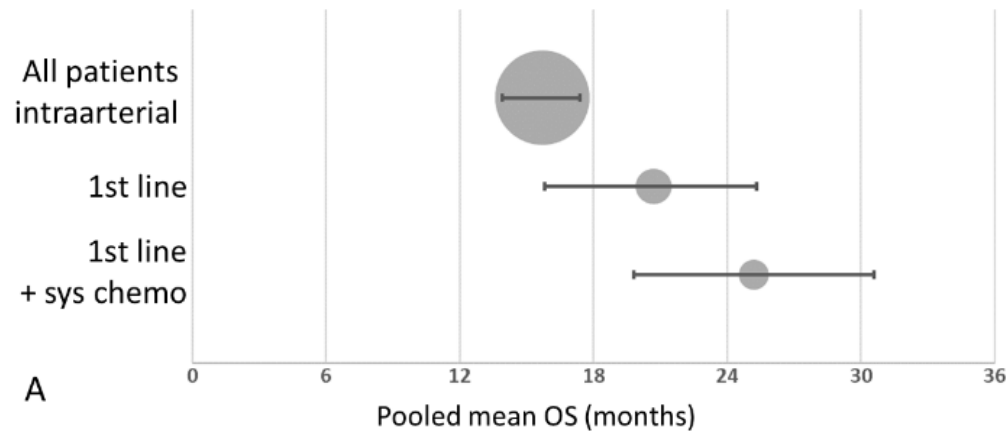




Pooled outcomes: Intra-arterial therapies

	All combined	Subgroup First-line	Subgroup first-line + concomitant chemotherapy
Pooled mean weighted OS months (95% CI); number of studies with data available	15.7 (13.9-17.4) ; 59	20.7 (15.8-25.3) ; 14	25.2 (19.8-30.6) ; 8
Pooled mean weighted PFS months (95% CI) ; number of studies with data available	11.4 (7.9-14.8) ; 24	13.5 (6.8-20.2) ; 7	14.0 (7.8-20.2) ; 7
Pooled response rate % (95% CI); heterogeneity I ² -p value; number of studies with data available	28.6% (21.9-35.7) ; 88.9%-0.000 ; 46	44.2% (27.9-61.1) ; 33.7%-0.000 ; 7	52% (42.1-61.9) ; 5.8%-0.22 ; 5
Pooled disease control rate % (95% CI); heterogeneity I ² -p value; number of studies with data available	79.2% (73.7-84.3) ; 81.1%-0.000 ; 39	87.6% (72.0-97.9) ; 24.7%-0.000 ; 6	88.2% (72.9-98.3) ; 8.7%-0.034 ; 4
Pooled secondary resection rate % (95% CI); heterogeneity I ² -p value; number of studies with data available	8.6% (5.5-12.1) ; 52.8%-0.005 ; 18	12.8% (5.7 - 21.8) ; 18.3%-0.005 ; 7	14.0% (5.8% - 24.6%) ; 11.3%-0.024 ; 5





Messages

Quality of the evidence

- ▶ Patients population is there
- ▶ Poor quality of data
 - ▶ Design of the studies
 - ▶ Informations about the population
- ▶ Heterogeneity of the results
 - ▶ Different populations?
 - ▶ Difference in treatments?



Messages

Pooled results

- ▶ Ablation:
 - ▶ More studies, but reporting incomplete
 - ▶ 94% complete response... but lack of data on late control
 - ▶ mOS of 30 months suggestive of good control, similar as surgical series
- ▶ EBRT:
 - ▶ Few studies, but heterogenous...
 - ▶ Local control 70% at 2 years
- ▶ Intra-arterial treatments:
 - ▶ Response rates similar than 1st-line chemo
 - ▶ Trend for better results for HAI?
 - ▶ Better staging / laparo?
 - ▶ 1st-line Survival data suggesting higher OS and PFS than chemo



Recommendations

