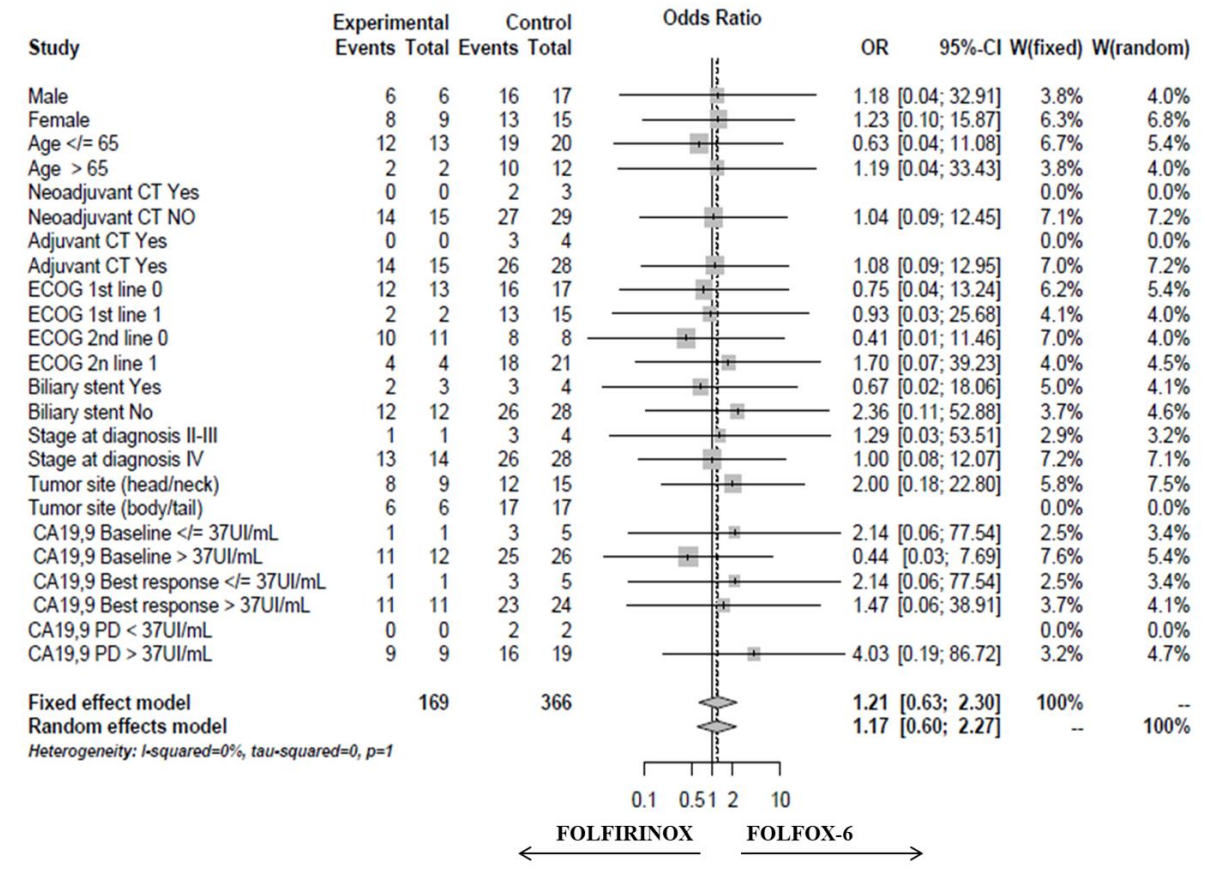
Supplementary Table 1. First line treatments for patients included in the final analysis.

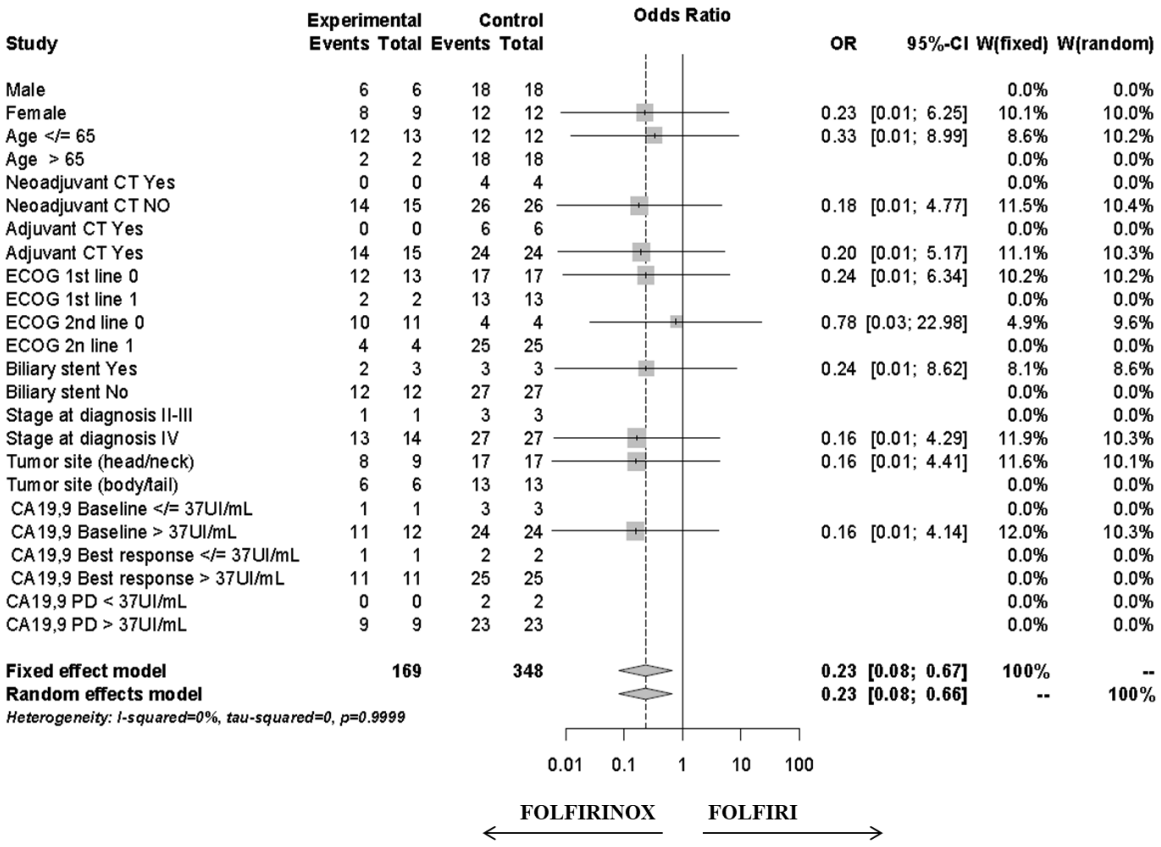
First line chemotherapy	FOLFIRINOX n. patients (%)	FOLFOX n. patients (%)	FOLFIRI n. patients (%)
Gemcitabine	0	0	0
Gemcitabine + Nab-paclitaxel	15 (100%)	31 (97%)	30 (100%)
Gemcitabine + Capecitabine	0	1 (3%)	0
Gemcitabine + Oxaliplatin	0	0	0

Supplementary Figure 1. Forest plot of the Treatment effect on PFS in Subgroup analysis. **(a)** Forest plot of the Treatment effect on PFS between FOLFIRINOX and FOLFOX-6. **(b)** Forest plot of the Treatment effect on PFS between FOLFIRINOX and FOLFIRI. **(c)** Forest plot of the Treatment effect on PFS between FOLFOX-6 and FOLFIRI.

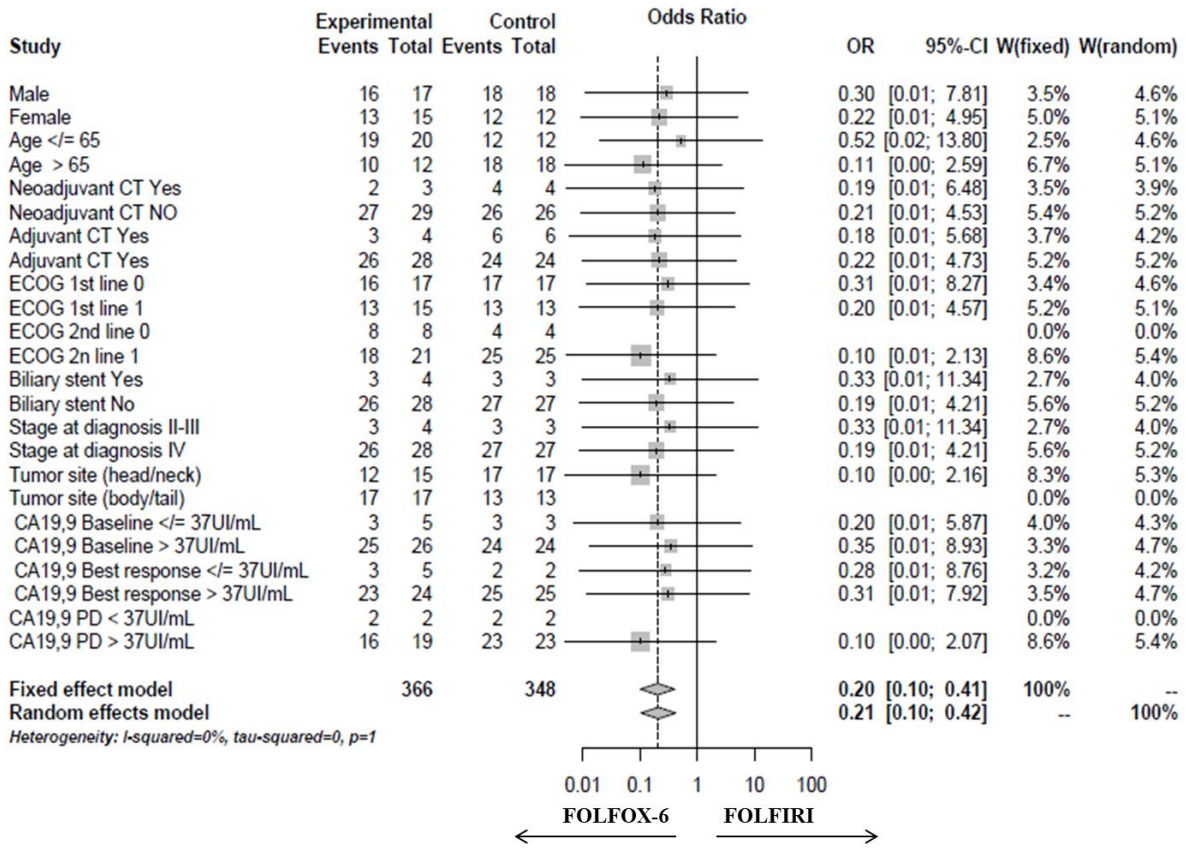
a



b

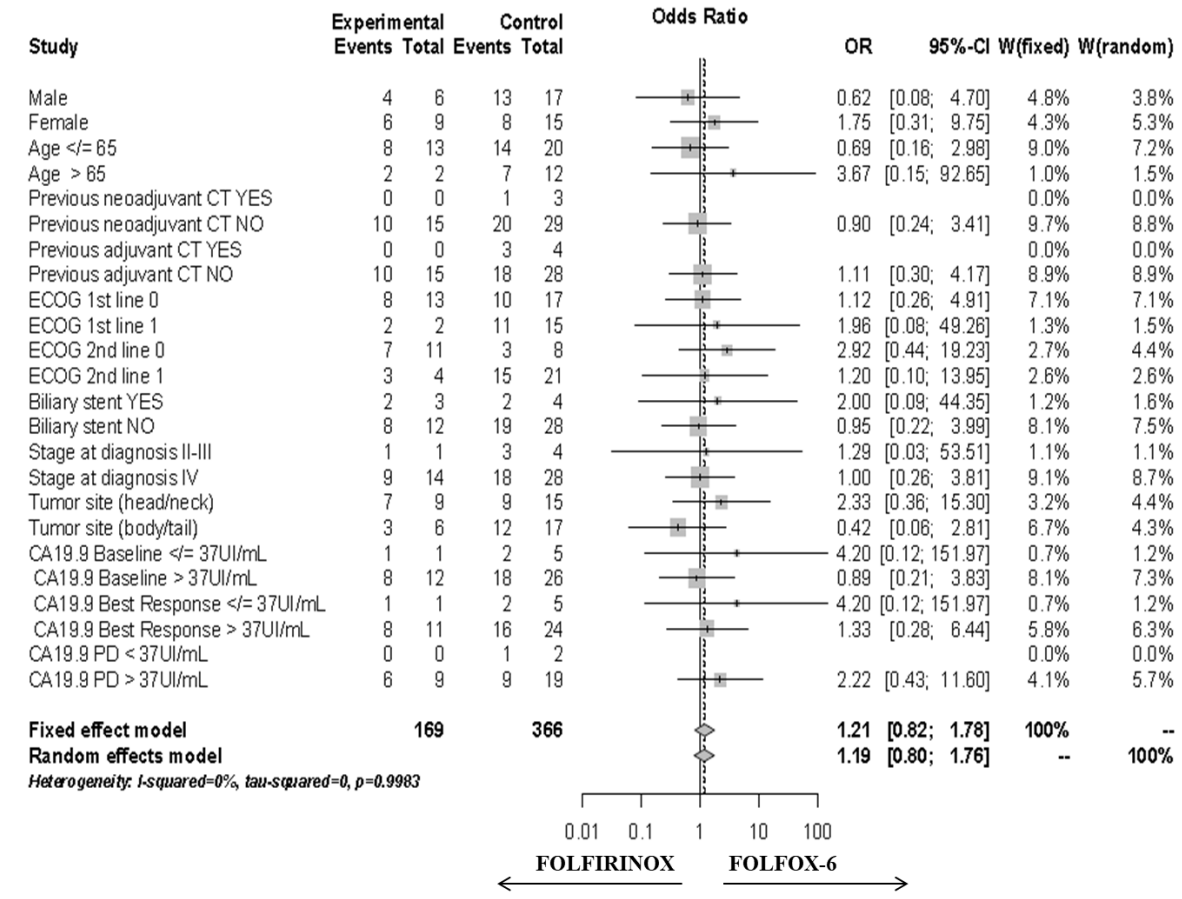

Odds Ratio
Study
Experimental Events Total
Control Events Total
OR 95%-CI W(fixed) W(random)
Male 6 6 18 18 0.0% 0.0%
Female 8 9 12 12 0.23 [0.01; 6.25] 10.1% 10.0%
Age </= 65 12 13 12 12 0.33 [0.01; 8.99] 8.6% 10.2%
Age > 65 2 2 18 18 0.0% 0.0%
Neoadjuvant CT Yes 0 0 4 4 0.0% 0.0%
Neoadjuvant CT NO 14 15 26 26 0.18 [0.01; 4.77] 11.5% 10.4%
Adjuvant CT Yes 0 0 6 6 0.0% 0.0%
Adjuvant CT Yes 14 15 24 24 0.20 [0.01; 5.17] 11.1% 10.3%
ECOG 1st line 0 12 13 17 17 0.24 [0.01; 6.34] 10.2% 10.2%
ECOG 1st line 1 2 2 13 13 0.0% 0.0%
ECOG 2nd line 0 10 11 4 4 0.78 [0.03; 22.98] 4.9% 9.6%
ECOG 2n line 1 4 4 25 25 0.0% 0.0%
Biliary stent Yes 2 3 3 3 0.24 [0.01; 8.62] 8.1% 8.6%
Biliary stent No 12 12 27 27 0.0% 0.0%
Stage at diagnosis II-III 1 1 3 3 0.0% 0.0%
Stage at diagnosis IV 13 14 27 27 0.16 [0.01; 4.29] 11.9% 10.3%
Tumor site (head/neck) 8 9 17 17 0.16 [0.01; 4.41] 11.6% 10.1%
Tumor site (body/tail) 6 6 13 13 0.0% 0.0%
CA19,9 Baseline </= 37UI/mL 1 1 3 3 0.0% 0.0%
CA19,9 Baseline > 37UI/mL 11 12 24 24 0.16 [0.01; 4.14] 12.0% 10.3%
CA19,9 Best response </= 37UI/mL 1 1 2 2 0.0% 0.0%
CA19,9 Best response > 37UI/mL 11 11 25 25 0.0% 0.0%
CA19,9 PD < 37UI/mL 0 0 2 2 0.0% 0.0%
CA19,9 PD > 37UI/mL 9 9 23 23 0.0% 0.0%
Fixed effect model 169 348 0.23 [0.08; 0.67] 100% --
Random effects model 0.23 [0.08; 0.66] -- 100%
Heterogeneity: I-squared=0%, tau-squared=0, p=0.9999
0.01 0.1 1 10 100
FOLFIRINOX
FOLFIRI

C

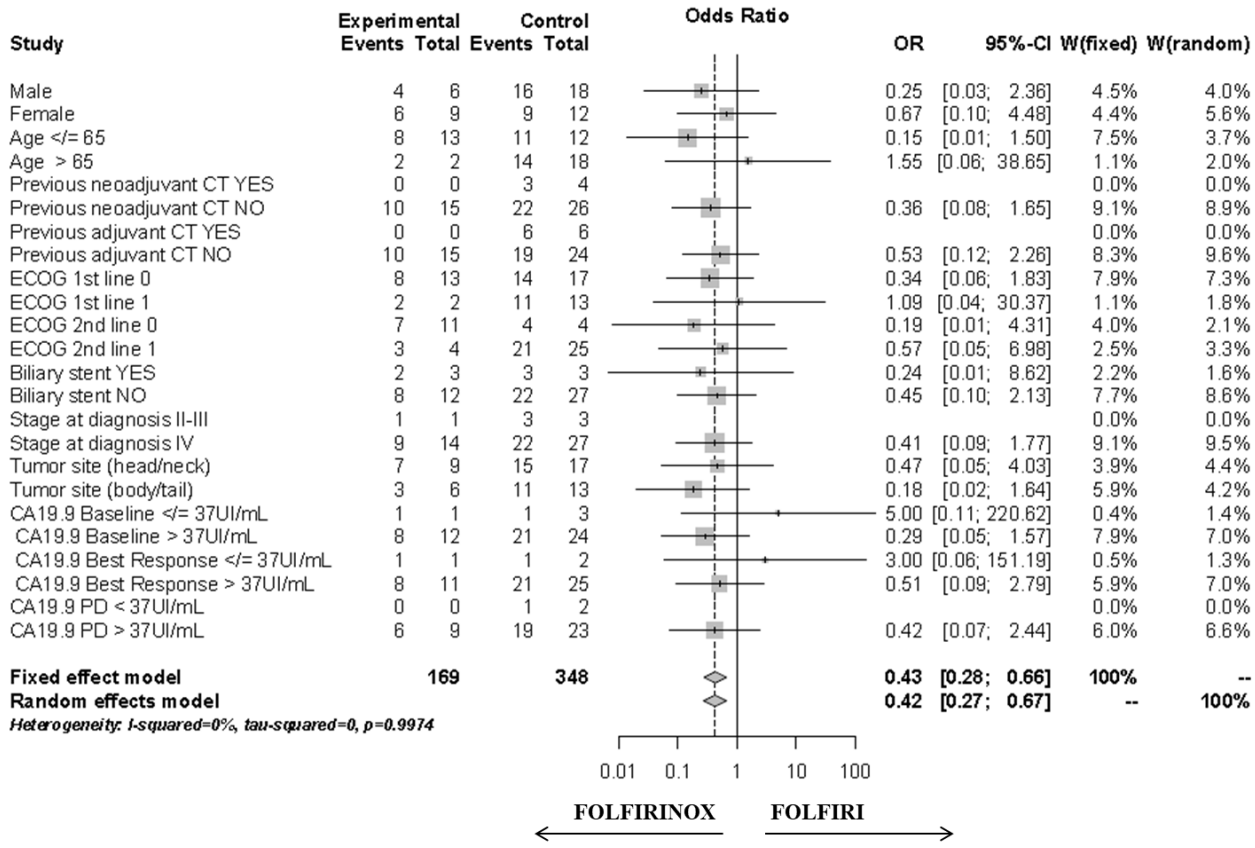

Study
Experimental Events Total
Control Events Total
Odds Ratio
OR 95%-CI W(fixed) W(random)
Male 16 17 18 18 0.30 [0.01; 7.81] 3.5% 4.6%
Female 13 15 12 12 0.22 [0.01; 4.95] 5.0% 5.1%
Age </= 65 19 20 12 12 0.52 [0.02; 13.80] 2.5% 4.6%
Age > 65 10 12 18 18 0.11 [0.00; 2.59] 6.7% 5.1%
Neoadjuvant CT Yes 2 3 4 4 0.19 [0.01; 6.48] 3.5% 3.9%
Neoadjuvant CT NO 27 29 26 26 0.21 [0.01; 4.53] 5.4% 5.2%
Adjuvant CT Yes 3 4 6 6 0.18 [0.01; 5.68] 3.7% 4.2%
Adjuvant CT Yes 26 28 24 24 0.22 [0.01; 4.73] 5.2% 5.2%
ECOG 1st line 0 16 17 17 17 0.31 [0.01; 8.27] 3.4% 4.6%
ECOG 1st line 1 13 15 13 13 0.20 [0.01; 4.57] 5.2% 5.1%
ECOG 2nd line 0 8 8 4 4 0.0% 0.0%
ECOG 2n line 1 18 21 25 25 0.10 [0.01; 2.13] 8.6% 5.4%
Biliary stent Yes 3 4 3 3 0.33 [0.01; 11.34] 2.7% 4.0%
Biliary stent No 26 28 27 27 0.19 [0.01; 4.21] 5.6% 5.2%
Stage at diagnosis II-III 3 4 3 3 0.33 [0.01; 11.34] 2.7% 4.0%
Stage at diagnosis IV 26 28 27 27 0.19 [0.01; 4.21] 5.6% 5.2%
Tumor site (head/neck) 12 15 17 17 0.10 [0.00; 2.16] 8.3% 5.3%
Tumor site (body/tail) 17 17 13 13 0.0% 0.0%
CA19,9 Baseline </= 37UI/mL 3 5 3 3 0.20 [0.01; 5.87] 4.0% 4.3%
CA19,9 Baseline > 37UI/mL 25 26 24 24 0.35 [0.01; 8.93] 3.3% 4.7%
CA19,9 Best response </= 37UI/mL 3 5 2 2 0.28 [0.01; 8.76] 3.2% 4.2%
CA19,9 Best response > 37UI/mL 23 24 25 25 0.31 [0.01; 7.92] 3.5% 4.7%
CA19,9 PD < 37UI/mL 2 2 2 2 0.0% 0.0%
CA19,9 PD > 37UI/mL 16 19 23 23 0.10 [0.00; 2.07] 8.6% 5.4%
Fixed effect model 366 348 0.20 [0.10; 0.41] 100% --
Random effects model 0.21 [0.10; 0.42] -- 100%
Heterogeneity: I-squared=0%, tau-squared=0, p=1
0.01 0.1 1 10 100
FOLFOX-6
FOLFIRI

Supplementary Figure 2. Forest plot of the Treatment effect on OS1 in Subgroup analysis. **(a)** Forest plot of the Treatment effect on OS1 between FOLFIRINOX and FOLFOX-6. **(b)** Forest plot of the Treatment effect on OS1 between FOLFIRINOX and FOLFIRI.

a



b

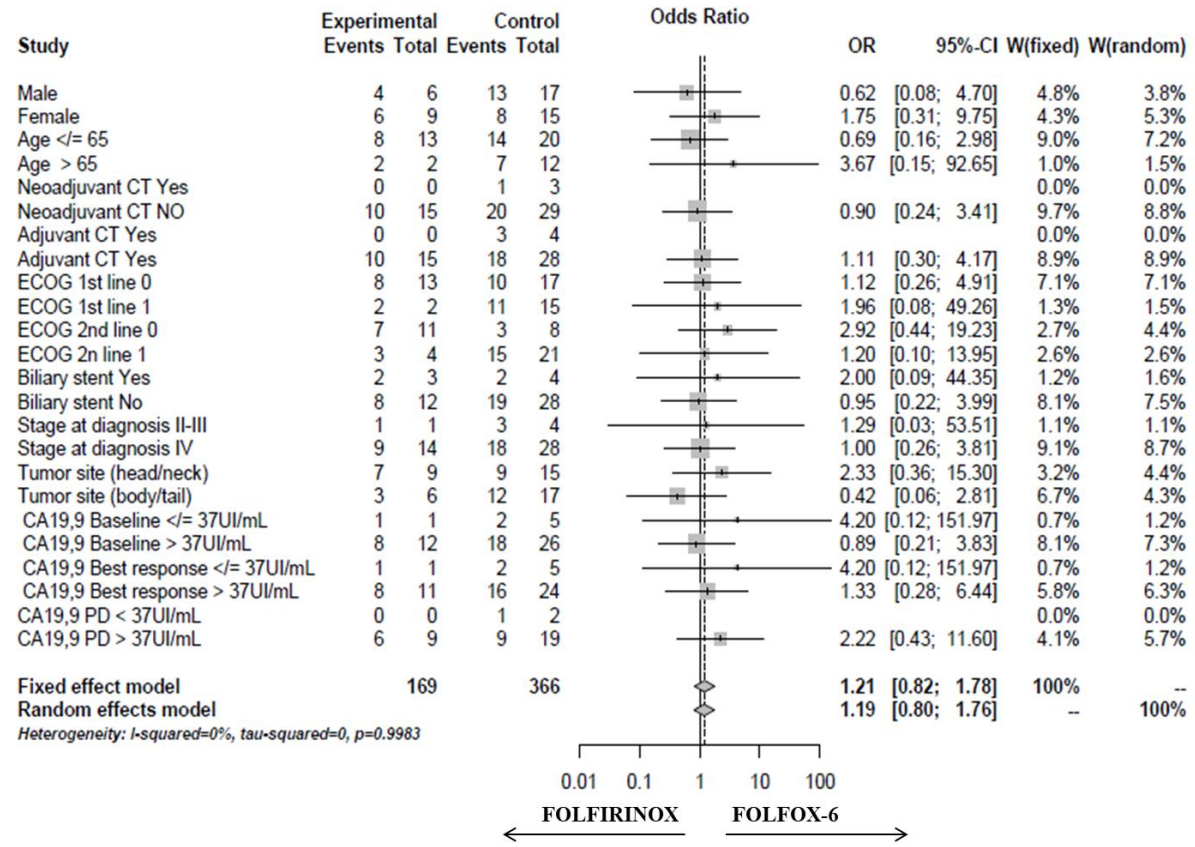


Study	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%-CI	W(fixed)	W(random)
Male	4	6	16	18	0.25	[0.03; 2.36]	4.5%	4.0%
Female	6	9	9	12	0.67	[0.10; 4.48]	4.4%	5.6%
Age </= 65	8	13	11	12	0.15	[0.01; 1.50]	7.5%	3.7%
Age > 65	2	2	14	18	1.55	[0.06; 38.65]	1.1%	2.0%
Previous neoadjuvant CT YES	0	0	3	4			0.0%	0.0%
Previous neoadjuvant CT NO	10	15	22	26	0.36	[0.08; 1.65]	9.1%	8.9%
Previous adjuvant CT YES	0	0	6	6			0.0%	0.0%
Previous adjuvant CT NO	10	15	19	24	0.53	[0.12; 2.26]	8.3%	9.6%
ECOG 1st line 0	8	13	14	17	0.34	[0.06; 1.83]	7.9%	7.3%
ECOG 1st line 1	2	2	11	13	1.09	[0.04; 30.37]	1.1%	1.8%
ECOG 2nd line 0	7	11	4	4	0.19	[0.01; 4.31]	4.0%	2.1%
ECOG 2nd line 1	3	4	21	25	0.57	[0.05; 6.98]	2.5%	3.3%
Biliary stent YES	2	3	3	3	0.24	[0.01; 8.62]	2.2%	1.6%
Biliary stent NO	8	12	22	27	0.45	[0.10; 2.13]	7.7%	8.6%
Stage at diagnosis II-III	1	1	3	3			0.0%	0.0%
Stage at diagnosis IV	9	14	22	27	0.41	[0.09; 1.77]	9.1%	9.5%
Tumor site (head/neck)	7	9	15	17	0.47	[0.05; 4.03]	3.9%	4.4%
Tumor site (body/tail)	3	6	11	13	0.18	[0.02; 1.64]	5.9%	4.2%
CA19.9 Baseline </= 37UI/mL	1	1	1	3	5.00	[0.11; 220.62]	0.4%	1.4%
CA19.9 Baseline > 37UI/mL	8	12	21	24	0.29	[0.05; 1.57]	7.9%	7.0%
CA19.9 Best Response </= 37UI/mL	1	1	1	2	3.00	[0.06; 151.19]	0.5%	1.3%
CA19.9 Best Response > 37UI/mL	8	11	21	25	0.51	[0.09; 2.79]	5.9%	7.0%
CA19.9 PD < 37UI/mL	0	0	1	2			0.0%	0.0%
CA19.9 PD > 37UI/mL	6	9	19	23	0.42	[0.07; 2.44]	6.0%	6.6%
Fixed effect model		**169**		**348**	**0.43**	**[0.28; 0.66]**	**100%**	**--**
Random effects model					**0.42**	**[0.27; 0.67]**	**--**	**100%**

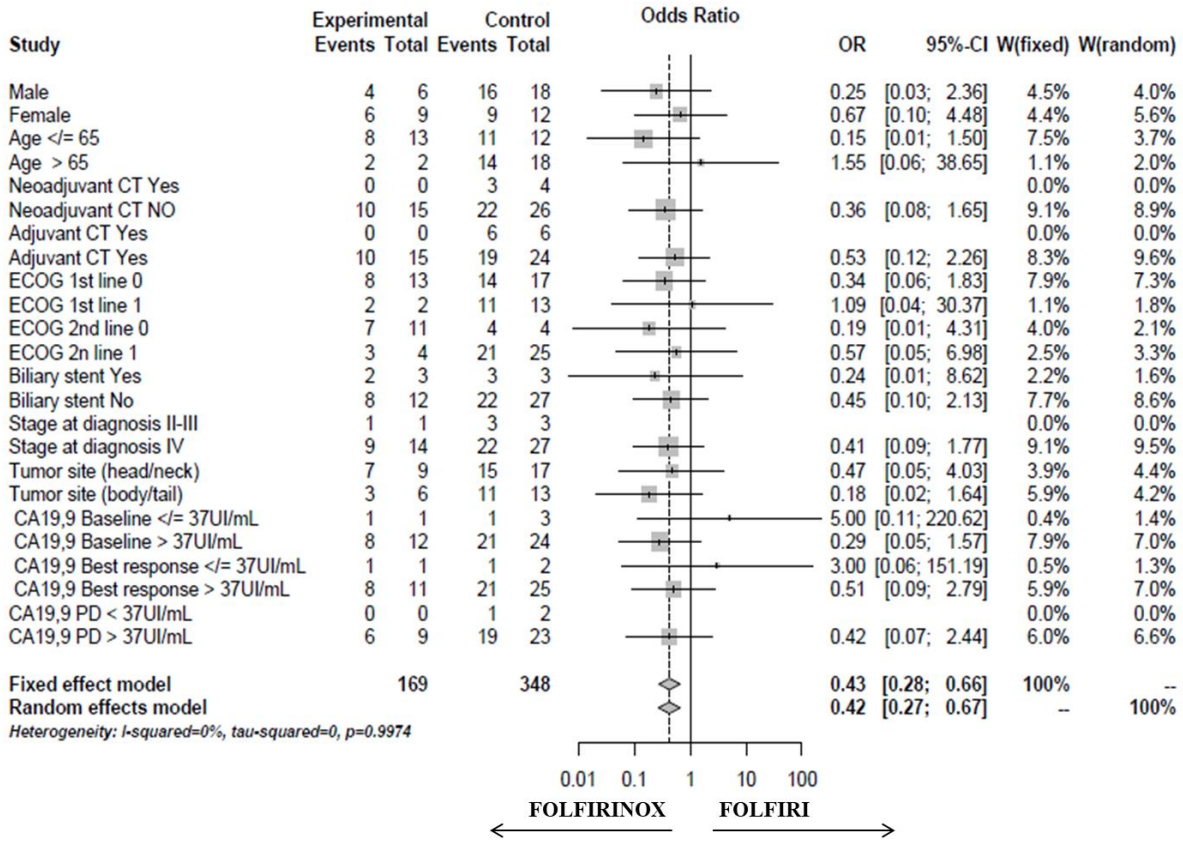
Heterogeneity: I-squared=0%, tau-squared=0, p=0.9974

Supplementary Figure 3. Forest plot of the Treatment effect on OS2 in Subgroup analysis. **(a)** Forest plot of the Treatment effect on OS2 between FOLFIRINOX and FOLFOX-6. **(b)** Forest plot of the Treatment effect on OS2 between FOLFIRINOX and FOLFIRI. **(c)** Forest plot of the Treatment effect on OS2 between FOLFOX-6 and FOLFIRI.

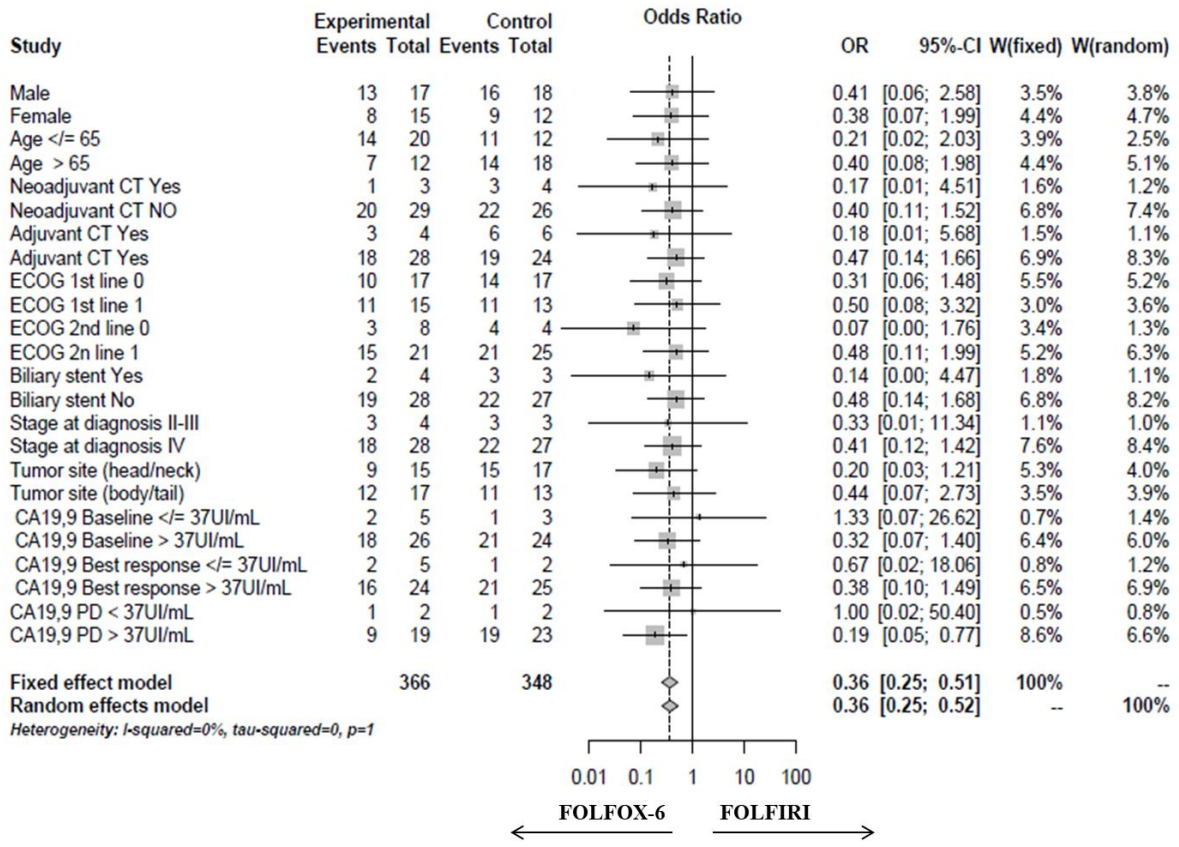
a



b


Study
Experimental Events Total
Control Events Total
Odds Ratio
OR 95%-CI W(fixed) W(random)
Male 4 6 16 18 0.25 [0.03; 2.36] 4.5% 4.0%
Female 6 9 9 12 0.67 [0.10; 4.48] 4.4% 5.6%
Age </= 65 8 13 11 12 0.15 [0.01; 1.50] 7.5% 3.7%
Age > 65 2 2 14 18 1.55 [0.06; 38.65] 1.1% 2.0%
Neoadjuvant CT Yes 0 0 3 4 0.0% 0.0%
Neoadjuvant CT NO 10 15 22 26 0.36 [0.08; 1.65] 9.1% 8.9%
Adjuvant CT Yes 0 0 6 6 0.0% 0.0%
Adjuvant CT Yes 10 15 19 24 0.53 [0.12; 2.26] 8.3% 9.6%
ECOG 1st line 0 8 13 14 17 0.34 [0.06; 1.83] 7.9% 7.3%
ECOG 1st line 1 2 2 11 13 1.09 [0.04; 30.37] 1.1% 1.8%
ECOG 2nd line 0 7 11 4 4 0.19 [0.01; 4.31] 4.0% 2.1%
ECOG 2n line 1 3 4 21 25 0.57 [0.05; 6.98] 2.5% 3.3%
Biliary stent Yes 2 3 3 3 0.24 [0.01; 8.62] 2.2% 1.6%
Biliary stent No 8 12 22 27 0.45 [0.10; 2.13] 7.7% 8.6%
Stage at diagnosis II-III 1 1 3 3 0.0% 0.0%
Stage at diagnosis IV 9 14 22 27 0.41 [0.09; 1.77] 9.1% 9.5%
Tumor site (head/neck) 7 9 15 17 0.47 [0.05; 4.03] 3.9% 4.4%
Tumor site (body/tail) 3 6 11 13 0.18 [0.02; 1.64] 5.9% 4.2%
CA19,9 Baseline </= 37UI/mL 1 1 1 3 5.00 [0.11; 220.62] 0.4% 1.4%
CA19,9 Baseline > 37UI/mL 8 12 21 24 0.29 [0.05; 1.57] 7.9% 7.0%
CA19,9 Best response </= 37UI/mL 1 1 1 2 3.00 [0.06; 151.19] 0.5% 1.3%
CA19,9 Best response > 37UI/mL 8 11 21 25 0.51 [0.09; 2.79] 5.9% 7.0%
CA19,9 PD < 37UI/mL 0 0 1 2 0.0% 0.0%
CA19,9 PD > 37UI/mL 6 9 19 23 0.42 [0.07; 2.44] 6.0% 6.6%
Fixed effect model 169 348 0.43 [0.28; 0.66] 100% --
Random effects model 0.42 [0.27; 0.67] -- 100%
Heterogeneity: I-squared=0%, tau-squared=0, p=0.9974
0.01 0.1 1 10 100
FOLFIRINOX
FOLFIRI

C


Study
Experimental Events Total
Control Events Total
Odds Ratio
OR 95%-CI W(fixed) W(random)
Male 13 17 16 18 0.41 [0.06; 2.58] 3.5% 3.8%
Female 8 15 9 12 0.38 [0.07; 1.99] 4.4% 4.7%
Age </= 65 14 20 11 12 0.21 [0.02; 2.03] 3.9% 2.5%
Age > 65 7 12 14 18 0.40 [0.08; 1.98] 4.4% 5.1%
Neoadjuvant CT Yes 1 3 3 4 0.17 [0.01; 4.51] 1.6% 1.2%
Neoadjuvant CT NO 20 29 22 26 0.40 [0.11; 1.52] 6.8% 7.4%
Adjuvant CT Yes 3 4 6 6 0.18 [0.01; 5.68] 1.5% 1.1%
Adjuvant CT Yes 18 28 19 24 0.47 [0.14; 1.66] 6.9% 8.3%
ECOG 1st line 0 10 17 14 17 0.31 [0.06; 1.48] 5.5% 5.2%
ECOG 1st line 1 11 15 11 13 0.50 [0.08; 3.32] 3.0% 3.6%
ECOG 2nd line 0 3 8 4 4 0.07 [0.00; 1.76] 3.4% 1.3%
ECOG 2n line 1 15 21 21 25 0.48 [0.11; 1.99] 5.2% 6.3%
Biliary stent Yes 2 4 3 3 0.14 [0.00; 4.47] 1.8% 1.1%
Biliary stent No 19 28 22 27 0.48 [0.14; 1.68] 6.8% 8.2%
Stage at diagnosis II-III 3 4 3 3 0.33 [0.01; 11.34] 1.1% 1.0%
Stage at diagnosis IV 18 28 22 27 0.41 [0.12; 1.42] 7.6% 8.4%
Tumor site (head/neck) 9 15 15 17 0.20 [0.03; 1.21] 5.3% 4.0%
Tumor site (body/tail) 12 17 11 13 0.44 [0.07; 2.73] 3.5% 3.9%
CA19,9 Baseline </= 37UI/mL 2 5 1 3 1.33 [0.07; 26.62] 0.7% 1.4%
CA19,9 Baseline > 37UI/mL 18 26 21 24 0.32 [0.07; 1.40] 6.4% 6.0%
CA19,9 Best response </= 37UI/mL 2 5 1 2 0.67 [0.02; 18.06] 0.8% 1.2%
CA19,9 Best response > 37UI/mL 16 24 21 25 0.38 [0.10; 1.49] 6.5% 6.9%
CA19,9 PD < 37UI/mL 1 2 1 2 1.00 [0.02; 50.40] 0.5% 0.8%
CA19,9 PD > 37UI/mL 9 19 19 23 0.19 [0.05; 0.77] 8.6% 6.6%
Fixed effect model 366 348 0.36 [0.25; 0.51] 100% --
Random effects model 0.36 [0.25; 0.52] -- 100%
Heterogeneity: I-squared=0%, tau-squared=0, p=1
0.01 0.1 1 10 100
FOLFOX-6
FOLFIRI