Supplementary Materials

Impact of Total Neoadjuvant Therapy vs Standard Chemoradiotherapy in Locally Advanced Rectal Cancer: A Systematic Review and Meta-Analysis of Randomized Trials

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Text S1. Search Strategy.

#1 rectal cancer [Mesh]
#2 rectal cancer [All fields]
#3 rectal neoplasm [All fields]
#4 #1OR #2 OR #3
#5 chemoradiotherapy [Mesh]
#6 chemoradiotherapy [All fields]
#7 chemoradiation [All fields]
#8 radiotherapy [Mesh]
#9 radiotherapy [All fields]
#10 neoadjuvant therapy [Mesh]
#11 neoadjuvant treatment [All fields]
#12 induction therapy [All fields]
#13 total neoadjuvant [All fields]
#14 chemotherapy [Mesh]
#15 chemotherapy [All fields]
#16 neoadjuvant chemotherapy [All fields]
#17 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18 randomized controlled trial [Mesh]
#19 randomized [All fields]
#20 controlled [All fields]
#21 #18 OR #19 OR #20
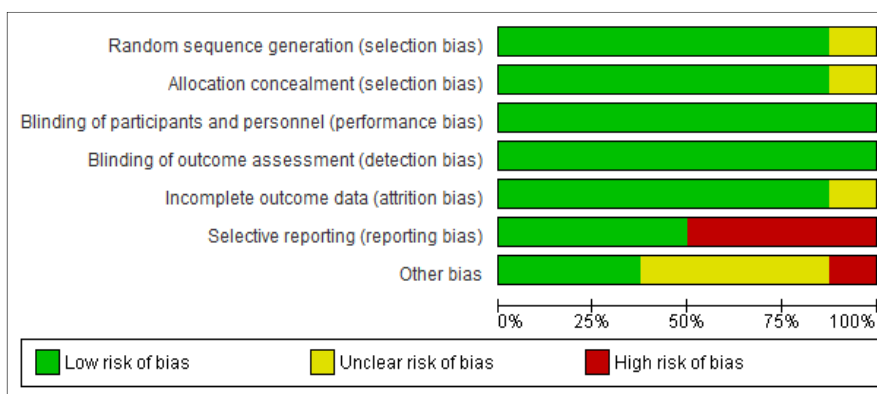#22 #4 AND #17
#23 #22 AND #21

Figure S1. Risk of bias summary of included trials organized by domain.

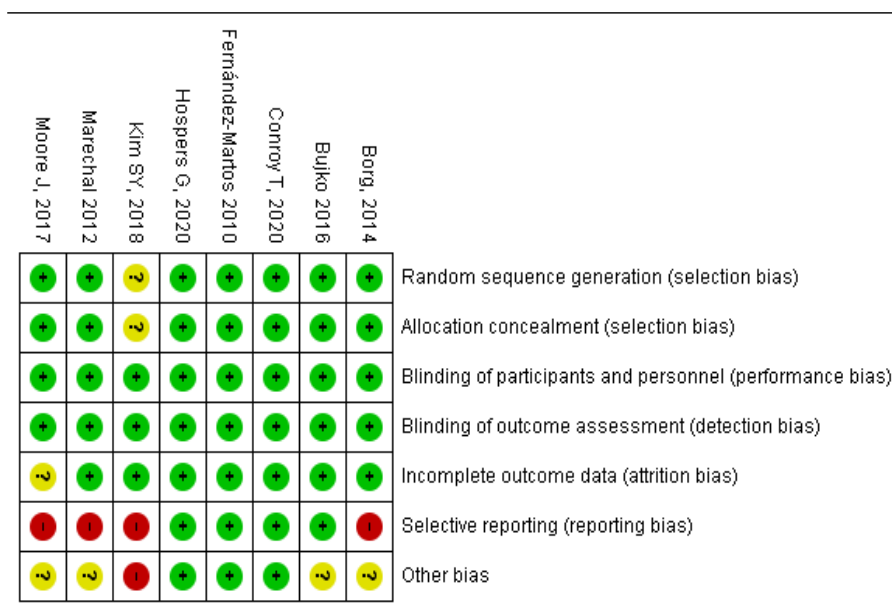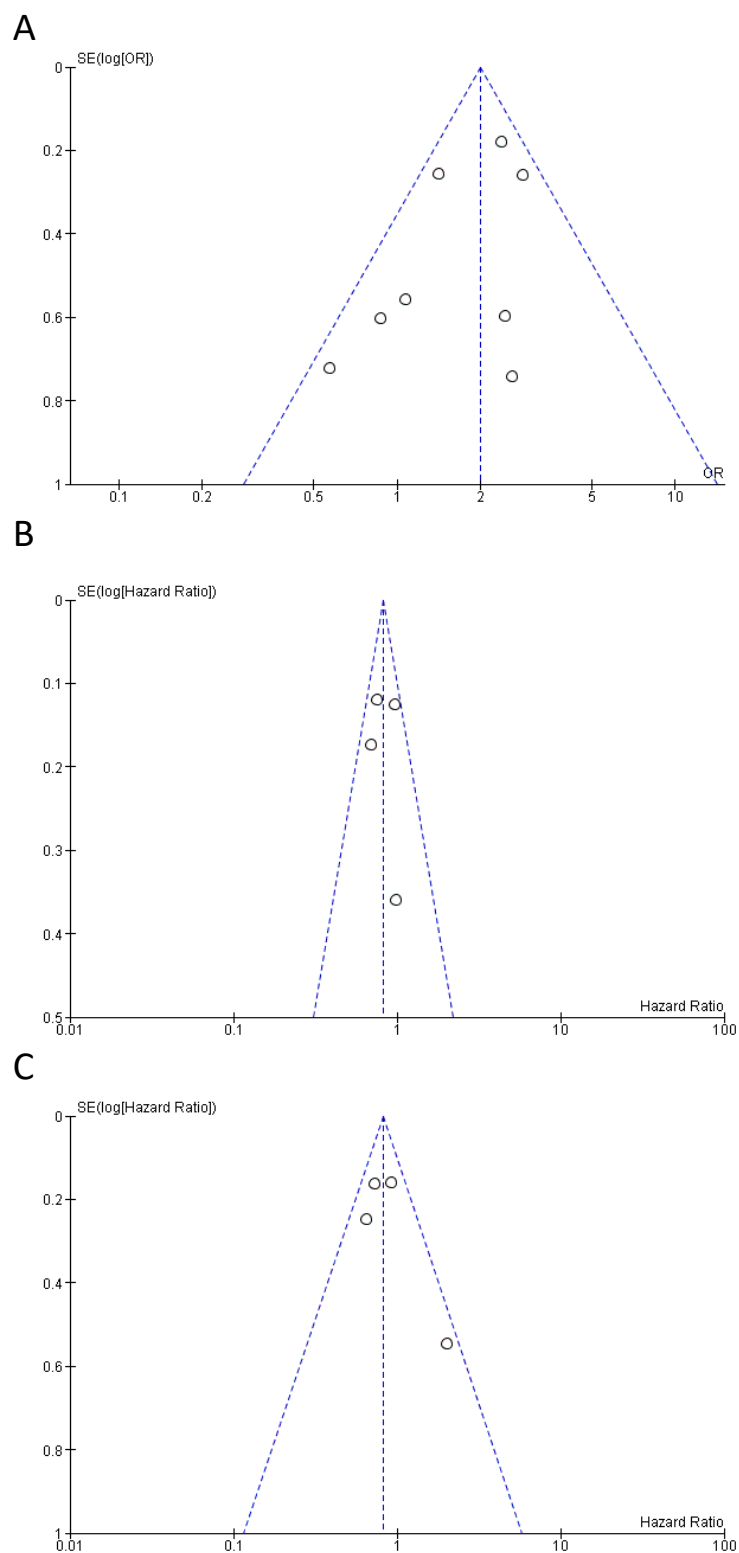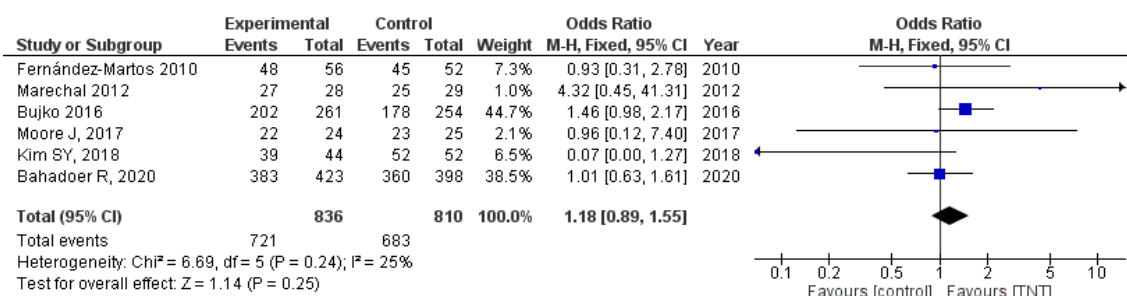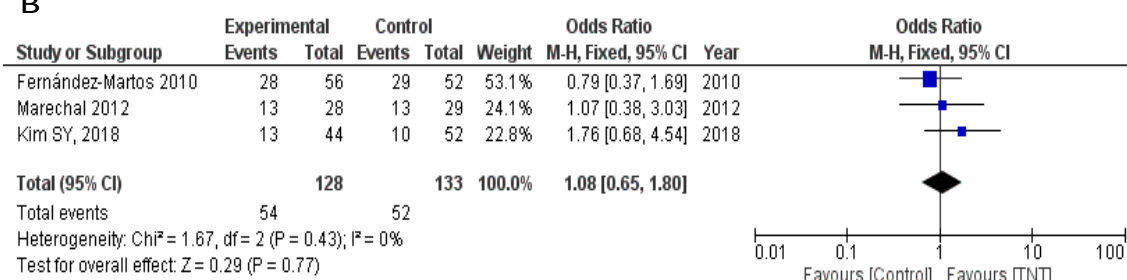**Figure S2.** Risk of bias summary of included trials organized by study.

Figure S3. Funnel plots analysis of publication bias for (**A**) pathological complete response; (**B**) 3-year disease free survival; (**C**) 3-year overall survival.

A

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Fernández-Martos 2010	48	56	45	52	7.3%	0.93 [0.31, 2.78]	2010
Marechal 2012	27	28	25	29	1.0%	4.32 [0.45, 41.31]	2012
Bujko 2016	202	261	178	254	44.7%	1.46 [0.98, 2.17]	2016
Moore J, 2017	22	24	23	25	2.1%	0.96 [0.12, 7.40]	2017
Kim SY, 2018	39	44	52	52	6.5%	0.07 [0.00, 1.27]	2018
Bahadoer R, 2020	383	423	360	398	38.5%	1.01 [0.63, 1.61]	2020
Total (95% CI)		836		810	100.0%	1.18 [0.89, 1.55]	
Total events	721		683				

Heterogeneity: Chi² = 6.69, df = 5 (P = 0.24); I² = 25%
Test for overall effect: Z = 1.14 (P = 0.25)

B

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Fernández-Martos 2010	28	56	29	52	53.1%	0.79 [0.37, 1.69]	2010
Marechal 2012	13	28	13	29	24.1%	1.07 [0.38, 3.03]	2012
Kim SY, 2018	13	44	10	52	22.8%	1.76 [0.68, 4.54]	2018
Total (95% CI)		128		133	100.0%	1.08 [0.65, 1.80]	
Total events	54		52				

Heterogeneity: Chi² = 1.67, df = 2 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.29 (P = 0.77)

Figure S4. (**A**) Forest plot for R0 resection rate of TNT vs. standard neoadjuvant CRT. (**B**) Forest plot for tumor regression grade 3-4 rate of TNT vs. standard neoadjuvant CRT.

Table S1. Surgical Outcomes.

Study	n	Arm	None n (%)	Anterior Resection n (%)	APR n (%)	Missing	Post-Operative Mortality n (%)	p
Fernandez-Martos C (GCR-3)	108	Std: 52 Exp:56	6 (11) 2 (4)	29 (56) 27 (48)	17 (33) 23 (40)	0 (0) 2 (4)	3 (7) 0 (0)	ns
Marechal R	57	Std: 29 Exp:28	1 (3) 1 (4)	23 (79) 5 (17)	24 (86) 3 (11)	-	NR	
Borg C (INOVA)	91	Std: 45 Exp:46		NR			0(0) 0(0)	ns
Bujko K	515	Std: 254 Exp:261	49 41	100 (49) 110 (50)	83 82	-	4 (2) 0 (0)	ns
Moore J (WAIT)	49	Std: 24 Exp: 25	0 (0) 0 (0)	12(50) 18 (72)	12 (50) 7 (28)	-	0(0) 0(0)	ns
Kim SY	108	Std:55 Exp:53	-	46 (88.5) 34 (77.3)	0 (0.0) 3 (6.8)	-	0(0) 0(0)	ns
Conroy T (PRODIGE23)	461	Std:230 Exp:231		NR		-	6(2.8) 0(0)	0.03
Badahoer R (RAPIDO)	912	Std:450 Exp:462	2 (0.5) 3 (0.7)	33 (8.3) 40 (9.4)	157 (39.3) 147 (34.5)	-	NR	

APR: abdominoperineal resection; Exp: experimental arm; n: number of patients; NR: not reported; ns: not significant; std: standard arm.

Table S2. Sensitivity analysis for pathological complete response.

Study Excluded	Fixed Effect		I^2 (%)	I^2- p Value
	OR	95% CI		
Fernandez-Martos C	2.04	1.62–2.57	38	0.14
Marechal	2.05	1.63–2.58	34	0.17
Borg	1.97	1.57–2.48	45	0.09
Bujko	2.17	1.68–2.79	31	0.19
Moore	2.06	1.64–2.59	24	0.24
Kim SY	1.98	1.57–2.48	45	0.09
Conroy T	1.82	1.41–2.34	30	0.20
Bahadoer R	1.75	1.30–2.35	35	0.16

CI: confidence interval; I^2: ; OR: Odds Ratio.

Table S3. Sensitivity analysis for pathological complete response in trials using induction chemotherapy.

Study Excluded	Fixed Effect		I^2 (%)	I^2- p Value
	OR	95% CI		
Fernández-Martos C	2.37	1.54–3.63	38	0.20
Marechal M	2.39	1.57–3.66	20	0.29
Borg C	2.10	1.38–3.20	59	0.09
Conroy T	1.32	0.69–2.53	0	0.44

CI: confidence interval; I^2: ; OR: Odds Ratio.

Table S4. Sensitivity analysis for pathological complete response in trials using consolidation chemotherapy.

Study Excluded	Fixed Effect		I² (%)	I²- *p* Value
	OR	95% CI		
Bujko K	2.19	1.58–3.05	46	0.16
Moore J	2.02	1.53–2.68	32	0.23
Kim SY	1.90	1.44–2.51	65	0.06
Bahadoer R	1.36	0.87–2.12	9	0.33

CI: confidence interval; I²: ; OR: Odds Ratio.

Table S5. Sensitivity analysis for pathological complete response in trials using long-course chemoradiotherapy.

Study Excluded	Fixed Effect		I² (%)	I²- *p* Value
	OR	95% CI		
Fernández-Martos C	2.12	1.44–3.14	41	0.15
Marechal R	2.15	1.46–3.16	35	0.19
Borg C	1.92	1.31–2.82	50	0.09
Moore J	2.16	1.48–3.17	20	0.29
Kim SY	1.93	1.32–2.82	50	0.09
Conroy T	1.28	0.75–2.20	0	0.43

CI: confidence interval; I²; OR: Odds Ratio.