Neoadjuvant chemoradiotherapy with or without PD-1/PD-L1 inhibitors in locally advanced rectal cancer: a systematic review and meta-analysis

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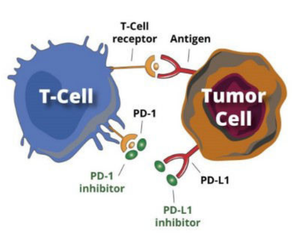
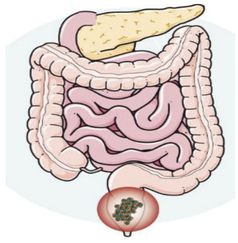
Introduction

Locally advanced rectal cancer (LARC) represents a pivotal stage of colorectal cancer where it is possible to completely cure the cancer before it's systematic spread, thus often requiring an aggressive multimodal therapy. Recent trials suggest that programmed death-1 (PD-1) inhibitors combined with neo-adjuvant chemo-radiotherapy (CRT) may improve treatment outcomes. This meta-analysis aimed to evaluate the efficacy and safety of PD-1 inhibitors when integrated into neoadjuvant CRT regimens for LARC patients.





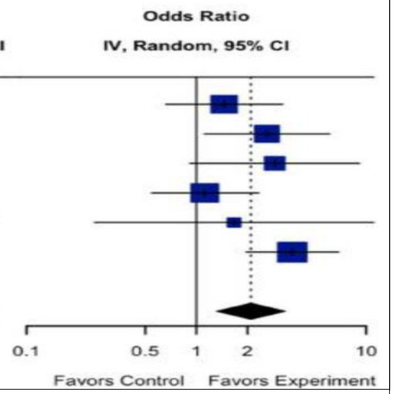
Methodology

A systematic search of PubMed, MEDLINE, Embase, and Cochrane CENTRAL was conducted up to 2024. Randomized controlled trials comparing neoadjuvant CRT with or without PD-1 inhibitors were included. Primary outcomes assessed were pathological complete response (pCR), clinical complete response (cCR), and serious adverse events (SAEs). Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using a random-effects model. Subgroup analyses were performed to explore variations in radiotherapy strategies and types of PD-1 inhibitors used.

a: Pathological Complete Response

Study	Experiment Events	Experiment Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI
Xiao 2024	21	57	16	56	19.3%	1.46 [0.66; 3.22]
Yang 2025	34	114	8	57	17.8%	2.60 [1.11; 6.08]
Li, H 2024	12	30	6	32	11.8%	2.89 [0.92; 9.12]
Rahma 2021	22	69	20	68	21.2%	1.12 [0.54; 2.32]
Li, W 2024	5	10	3	8	5.2%	1.67 [0.25; 11.07]
Lin 2024	45	113	18	118	24.6%	3.68 [1.96; 6.89]
Total (95% CI)		**393**		**339**	**100.0%**	**2.10 [1.32; 3.32]**

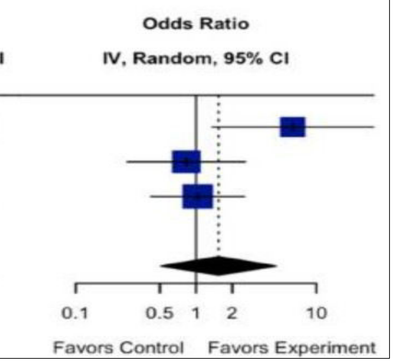
Heterogeneity: $Tau^2 = 0.1220$; $Chi^2 = 7.31$, df = 5 (P = 0.1984); $I^2 = 31.6\%$

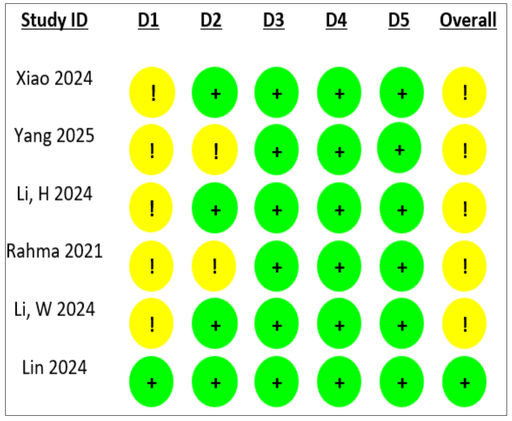


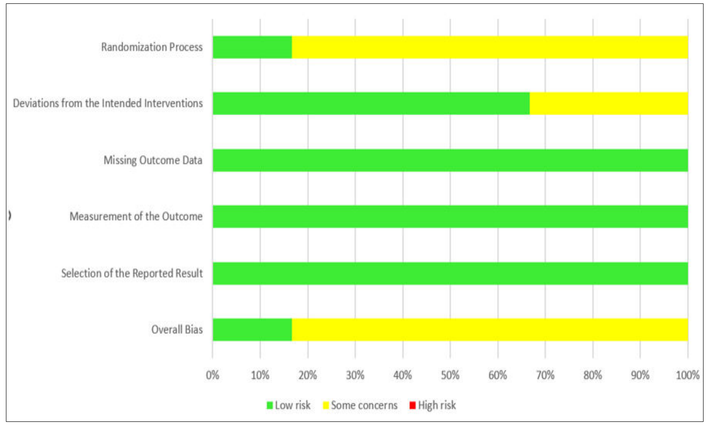
b: Clinical Complete Response

Study	Experiment Events	Experiment Total	Control Events	Control Total	Weight	Odds Ratio IV, Random, 95% CI
Xiao 2024	11	67	2	67	26.1%	6.38 [1.36; 30.03]
Li, H 2024	7	54	7	46	34.3%	0.83 [0.27; 2.57]
Rahma 2021	11	79	11	81	39.6%	1.03 [0.42; 2.53]
Total (95% CI)		**200**		**194**	**100.0%**	**1.54 [0.51; 4.63]**

Heterogeneity: $Tau^2 = 0.5890$; $Chi^2 = 4.92$, df = 2 (P = 0.0854); $I^2 = 59.4\%$







Results

Six RCTs with 876 patients met the inclusion criteria. PD-1 inhibitors significantly improved pCR rates (OR = 2.13, 95% CI: 1.34–3.38; p = 0.001), particularly with short-course radiotherapy (SCRT) and agents like camrelizumab and tislelizumab. The addition of PD-1 inhibitors did not significantly enhance cCR (OR = 1.54, 95% CI: 0.51–4.63; p = 0.44) and did not increase SAEs significantly (OR = 1.15, 95% CI: 0.77–1.73; p = 0.51). Moderate heterogeneity (I^2 = 34%) was noted for pCR, while other outcomes showed low heterogeneity.

Conclusion

Incorporating PD-1 inhibitors into neoadjuvant CRT regimens significantly enhances pCR rates in LARC without markedly increasing toxicity. These findings support their potential integration into standard treatment protocols, warranting further phase III trials to confirm long-term efficacy and safety.

References

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