Role of Lateral Pelvic Lymphadenectomy in Rectal Cancer: A Meta-Analysis

SHERIF A. ALMAGHRABY, M.D.; IBRAHIM M. ABDEL-MAKSOUD, M.D. and MOHAMED G.M.G. ALNOMANY, M.Sc.

The Department of General Surgery, Faculty of Medicine, Ain Shams University

Abstract

Background: The role of lateral pelvic lymph node dissection (LPLD) in the treatment of rectal cancer is still controversial. This study examines the outcomes and possible benefits of adding LPLD to the gold standard surgery for rectal cancer: Total mesorectal excision (TME).

Aim of Study: Compare the outcomes of adding LPLD to TME vs TME alone for management of rectal cancer in terms of recurrence, survival, and complications.

Patients and Methods: A systematic review and metaanalysis comparing outcomes of TME + LPLD versus TME alone in over 6000 patients. Studied outcomes are recurrence, survival, and complications.

Results: 18 studies were included comparing outcomes in 2762 patients treated by TME+LPLD versus 3371 patients treated by TME alone for low rectal cancer. Outcomes compared are overall survival (OR: 1.02), 5-year overall survival (OR: 1.01), disease free survival (OR: 1.07), 5-year disease free survival (OR: 1.07), local recurrence (OR: 1.01), distant recurrence (OR: 0.96), total recurrence (OR: 0.97), postoperative complications (OR: 1.59), urinary dysfunction (OR: 6.66), sexual dysfunction (OR: 9.67), and operative time (mean difference: 116.02).

Conclusion: Adding LPLD to TME for rectal cancer treatment is associated with higher rates of complications and longer operative time, with no added value regarding recurrence or survival when compared with TME alone as a treatment modality.

Key Words: Lateral pelvic lymph node dissection – Rectal cancer – Total mesorectal excision.

Introduction

RECTAL cancer, which accounts for 35-40% of all colorectal cancers, [1] is among the most prevalent tumors in developed countries and ranks third in terms of incidence. It is the second leading cause of neoplastic death. The 5-year survival rates range from 50-60%, depending on the stage of the disease. However, the best treatment for locally advanced rectal cancer is not entirely clear. The surgical treatment of rectal cancer has presented significant challenges, with a high incidence of local recurrence reported until the introduction of total mesorectal excision (TME) by Heald et al., [2]. This concept has had a significant impact and reduced the rates of local recurrence after curative resection of rectal cancer.

In addition to TME, neoadjuvant therapy in the form of radiotherapy, chemotherapy, or a combination of both has been introduced as a significant breakthrough in management of rectal cancer. This therapy serves to reduce the tumor burden in advance of curative surgery and address the extramesorectal lateral pelvic lymph nodes (LPLN) [3,4]. The role of LPLN dissection (LPLD) remains a controversial aspect regarding the treatment of locally advanced rectal cancer [5].

While guidelines followed in the West have recommended the liberal use of neoadjuvant therapy rather than LPLD for locally advanced rectal carcinoma, the Japanese guidelines have routinely employed LPLD with or without neoadjuvant treatment. This difference in management policy is attributed to different perspectives as the guidelines in the West consider lateral lymph node metastasis to be a systemic disease, while the Japanese guidelines define it as a local disease [6]. LPLN metastasis is present in 16% to 23% of patients with lower rectal cancer as per the Japanese guideline for surgical treatment of colorectal cancer [7].

In the past, surgeons in Japan routinely employed prophylactic LPLD in the management of locally advanced rectal cancer. However, due to the increasing use of preoperative chemoradiotherapy, selective LPLD is now more frequently per-

Correspondence to: Dr. Mohamed G.M.G. Alnomany, <u>E-Mail. Dr.md.gooda@gmail.com</u>

formed. The indications for prophylactic LPLD for negative nodes differ from therapeutic dissection for positive nodes, and the value of combining LPLD with neoadjuvant therapy remains unresolved [8]. LPLD is not without an increase in morbidity, with longer operation time, more blood loss, and a higher incidence of urinary and male sexual dysfunction reported [9,10].

To assess the current literature for the outcome of LPLD with TME in the treatment of locally advanced rectal cancer, this systematic review and meta-analysis aimed to focus on the incidence of local and distant recurrence, complications, and overall and disease-free survival after resection compared to treatment by TME alone.

Material and Methods

This study was conducted in compliance with the screening guidelines from the preferred reporting items for systematic reviews and meta-analyses checklist (PRISMA) [11], done over the period from April 2021 till April 2023.

A systematic search of the literature was carried out on several bibliographic databases including PubMed, MEDLINE, Ovid, Embase, Cochrane library, ClinicalTrials.gov and World Health Organization International Clinical Trials Registry for all studies from 2000 through 2020 using the following keywords: "lateral pelvic lymph nodes rectal cancer," "lateral pelvic lymph node dissection rectal cancer," "lateral lymph node dissection rectal cancer," "lateral pelvic lymph node," "lateral lymph node dissection," "LPLN dissection," "rectal malignancy," "locally advanced," "outcome," "morbidity," "lateral pelvic lymph node dissection," "obturator lymphadenectomy," "iliac lymphadenectomy," "total mesorectal excision," and "rectal cancer".

Title screening was done, and all relevant abstracts, studies, and citations were reviewed.

Inclusion criteria:

All human studies (whether cohort or randomized controlled trials) that reported the comparative outcome between TME with LPLD for advanced rectal cancer versus TME.

Primary outcomes:

- 1-Local recurrence.
- 2- Overall survival.
- 3- Disease free survival.

Secondary outcomes:

- 1-Distant recurrence.
- 2- Postoperative complications.
- 3- Operative time.
- 4- Sexual and urinary dysfunction.

TME is the only intervention searched for, whether done laparoscopically/laparoscopicassisted, or by open anterior resection / abdominoperineal resection.

Exclusion criteria:

- 1- Intervention not TME.
- 2- Did not clearly demonstrate LPLD outcome.
- 3- Editorials /reviews/meta-analyses.
- 4- Published before 2000.
- 5- Unclear research methodology.
- 6- Non-rectal cancer pathology.
- 7- Not written in English.
- 8- Insufficient relevant data (ex: articles without full-text availability).
- 9- Animal studies.

Meta-analysis outcomes:

The primary outcomes used to compare the two intervention modalities is local recurrence, overall survival, disease-free survival.

Secondary outcomes include distant recurrence, post-operative complications, time of operation, urinary function disorder, and sexual function disorder.

Study selection and data extraction:

The previously mentioned search strategy was implemented according to the pre-defined criteria mentioned above, and literature was reviewed after screening titles and abstracts of relevant articles.

Studies meeting the pre-defined eligibility criteria were first identified, then full texts of these studies were acquired. Data extraction was conducted using the following parameters:

- 1- Study title and reference data (first author name, journal name, publication year, country).
- 2- Study population characteristics (total patient number, number per each intervention modality, age, and gender).
- 3- Study design type, Follow-up period.
- 4- Disease characteristics (tumor stage, tumor distance from anal verge).
- 5- Treatment details (neo-adjuvant chemoradiotherapy use, adjuvant chemotherapy use).

- 6- Operative time and post-operative complications including male sexual dysfunction (erectile dysfunction/premature ejaculation), urinary dysfunction (retention, incontinence, infections, dysuria), and anastomotic leakage.
- 7- Oncological outcomes (local recurrence, distant recurrence, overall survival, disease free survival).

Data extraction and study selection were done independently by two separate literature reviewers in separate databases. A third author reviewed the databases to limit selection bias. A discussion between all authors was conducted to reach a consensus and clear disparities. Duplicate studies were deleted. No automation tools were used in data collection.

Quality assessment:

The RoB2 tool (Revised Cochrane risk-of-bias tool for randomized trials) was utilized to evaluate the methodological quality of RCTs in terms of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias to calculate the total risk of bias [12].

The ROBINS-I tool (Risk of Bias in Nonrandomized Studies - of Interventions) was utilized to evaluate the methodological quality of nonrandomized comparative studies in terms of bias due to confounding, intervention classification, unavailable data, deviations from intended interventions, incomplete outcome data, participant selection, result selection, and outcome measurement [13].

Risk of bias assessment was done independently by two separate literature reviewers. A discussion between all authors was conducted to reach a consensus and clear disparities. No automation tools were used.

Statistical analysis:

The RevMan software (Version 5.3; Copenhagen, Denmark) software was used for statistical analysis. We used forest plots to present the metaanalysis results.

Binary outcome data were reported as odd ratios (OR) and 95% confidence interval (95% CI) were estimated using the Mantel-Haenszel method and used for dichotomous variables (overall survival at maximum follow-up; 5-year overall survival; disease-free survival at maximum follow-up; 5-year disease-free survival; local recurrence; distant

recurrence; total recurrence; postoperative complications; urinary dysfunction; sexual dysfunction; operative time.) If OR was smaller than 1, this favored the LPLD group.

Outcome measures (mean + standard deviation and median + interquartile range) were recorded.

The heterogeneity was quantified and reported as I² using Cochran Q test (X²). We interpreted I² as low heterogeneity if <50%, 50%-75% = moderate heterogeneity, >75% = high heterogeneity. If no significant statistical heterogeneity was present, a fixed-effect model was used to pool data; whereas in the case of significant (p<0.05) statistical heterogeneity, the random-effect model was used.

Results

This review included 18 studies [14-31] published between 2001 and 2017.

Initial screening using the previously mentioned search strategy identified 2067 studies. Further screening excluded 124 duplicates followed by 1884 studies not meeting inclusion criteria. The filtered 59 studies were sought for retrieval, of which 4 were non retrievable. The remaining 55 studies were further reviewed, and 37 studies were further excluded considering the predefined exclusion criteria.

The remaining 18 studies were then included in this review (Fig. 1). These included 16 observational studies 15-30 and 2 randomized controlled studies [14,31] studying 6,133 patients with low rectal cancer.

LPLD+TME was performed in 2,762 patients; whereas TME only was performed in 3,371 patients.

Characteristics of the 18 included studies are demonstrated in Tables (1,2).

Comparative outcomes:

These results are summarized in Table (3) and demonstrated as forest plots (Figs. 2-12).

Primary outcomes:

Overall survival:

Overall survival was analyzed in 4,124 patients from 9 different studies [14,15,16,18,19,21,26,27,31]. The result was similar between TME alone vs TME + LPLD (OR: 1.02, 95% CI 0.83=1.25, p=.86).

Heterogeneity between studies was judged to be low ($I^2=22\%$, p=.24).



Fig. (1): Prisma flowchart.

5-year overall survival:

5-year Overall Survival was analyzed in 3,671 patients from 6 different studies [14,15,18,21,26,31]. The result was similar between TME alone vs TME + LPLD (OR: 1.01, 95% CI 0.78=1.30, p=.94). Heterogeneity between studies was judged to bemoderate ($I^2=50\%$, p=.07).

Disease free survival:

Disease Free Survival at maximum follow-up was analyzed in 2,286 patients from 9 different studies [14,16,17,19,21,28-31]. The result was similar between TME alone vs TME + LPLD (OR: 1.07, 95% CI 0.88=1.31, p=.50). Heterogeneity between studies was judged to be low (I²=0%, p=.50).

5-year disease -free survival:

5-year disease-free survival was analyzed in 1,890 patients from 7 different studies [14,17,21, 28,29,30,31]. The result was similar between TME alone vs TME + LPLD (OR: 1.07, 95% CI 0.86= 1.32, p=.54). Heterogeneity between studies was judged to be low (I²=0%, p=.60).

Local recurrence:

Local recurrence analyzed in 3,990 patients from 13 different studies [14,16,17,18,21,22,23,26-31]. The result was similar between TME alone vs TME + LPLD (OR: 1.01, 95% CI 0.72=1.42, p=.97) Heterogeneity between studies was judged to be low ($I^2=34\%$, p=.11).

Secondary outcomes:

Distant recurrence:

Distant recurrence was analyzed in 1,078 patients from 6 different studies [21,26,27,29,30,31]. The result was similar between TME alone vs TME + LPLD (OR: 0.96, 95% CI 0.62=1.46, p=.84). Heterogeneity between studies was judged to be low (I²=18%, p=.30).

Total recurrence:

Total recurrence was analyzed in 1,118 patients from 6 different studies [21,26-31]. The result was similar between TME alone vs TME + LPLD (OR: 0.97, 95% CI 0.72=1.29, p=.82). Heterogeneity between studies was judged to be low ($I^2=0\%$, p=.50).

Postoperative complications:

Postoperative complications was analyzed in 873 patients from 6 different studies [16,17,19,27, 29,31]. The result was a higher risk of postoperative complications in TME + LPLD compared to TME alone (OR: 1.59, 95% CI 1.14=2.24, p=.007). Heterogeneity between studies was judged to be low (I^2 =0%, p=.99).

Urinary dysfunction:

Urinary dysfunction was analyzed in 478 patients from 5 different studies [19,25,27,28,31]. The result was a higher risk of urinary dysfunction in TME + LPLD compared to TME alone (OR: 6.66, 95% CI 3.31,13.39, p<.00001). Heterogeneity between studies was judged to be low (I²=23%, p=.26).

Sexual dysfunction:

Sexual dysfunction was analyzed in 144 patients from 3 different studies [19,25,31]. The result was

a higher risk of sexual dysfunction in TME + LPLD compared to TME alone (OR: 9.67, 95% CI 2.38=39.26, p=.002). Heterogeneity between studies was judged to be moderate (I²=51%, p=.13).

Operative time:

Operative time was analyzed in 958 patients from 5 different studies [16,26,28,29,31]. The result was longer operative time in TME + LPLD compared to TME alone (mean difference: 11 6.02, 95% CI 89.20=142.83, p<.00001). Heterogeneity between studies was judged to be moderate (I²=68%, p=.01).

Quality assessment:

The outcome of quality assessment of RCTs using the RoB2 tool [12] is presented in Fig. (13).

The outcome of quality assessment of nonrandomized comparative studies using the ROB-INS-I tool [13] is presented in Fig. (14).

	TME + L	PLD	TME			Odds Ratio			Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year		M-H, Rand	om, 95% CI	
Nagawa 2001 [30]	17	23	16	22	2.2%	1.06 [0.28, 3.98]	2001			_	
Matsuoka 2005 [26]	13	15	37	42	1.3%	0.88 [0.15, 5.09]	2005				
Hasdemir 2005 [25]	13	24	86	146	4.9%	0.82 [0.35, 1.96]	2005			-	
Kim 2007 [20]	130	176	242	309	15.6%	0.78 [0.51, 1.20]	2007		-		
Kobayashi 2009 [17]	594	784	388	488	27.3%	0.81 [0.61, 1.06]	2009		-		
Akasu 2009 [18]	41	42	27	27	0.4%	0.50 [0.02, 12.80]	2009				
Ozawa 2016 [14]	344	499	309	499	28.6%	1.36 [1.05, 1.77]	2016		2 A 4	•	
Ogura 2016 [15]	102	107	208	220	3.3%	1.18 [0.40, 3.43]	2016				
Fujita 2017 [13]	304	351	294	350	16.3%	1.23 [0.81, 1.87]	2017		12	-	
Total (95% CI)		2021		2103	100.0%	1.02 [0.83, 1.25]					
Total events	1558		1607								
Heterogeneity: Tau ² =	0.02; Chi2	= 10.31	df = 8 (F	= 0.24); l ² = 22%				-	+	
Test for overall effect:	Z = 0.18 (F	9 = 0.86)					0.001	0.1 Favours [TME]	10 Favours [TM	E + LPLD]

Fig. (2): Forest plot of comparison outcome of overall survival.

	TME + L	TME + LPLD		TME		Odds Ratio			Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year		M-H, Rand	om, 95% Cl	
Nagawa 2001 [30]	17	23	16	22	3.3%	1.06 [0.28, 3.98]	2001			-	
Hasdemir 2005 [25]	13	24	86	146	6.9%	0.82 [0.35, 1.96]	2005			-	
Kim 2007 [20]	130	176	242	309	18.0%	0.78 [0.51, 1.20]	2007			1	
Kobayashi 2009 [17]	594	784	388	488	26.2%	0.81 [0.61, 1.06]	2009				
Ozawa 2016 [14]	344	499	309	499	26.9%	1.36 [1.05, 1.77]	2016			•	
Fujita 2017 [13]	304	351	294	350	18.5%	1.23 [0.81, 1.87]	2017		-	-	
Total (95% CI)		1857		1814	100.0%	1.01 [0.78, 1.30]					
Total events	1402		1335								
Heterogeneity: Tau ² =	0.04; Chi ²	= 10.03,	df = 5 (P	= 0.07); * = 50%			-	1	1	1000
Test for overall effect:	Z = 0.08 (F	0 = 0.94))					0.001	0.1 Favours [TME]	Favours [TME	1000 E + LPLD]

Fig. (3): Forest plot of comparison outcome of 5-year overall survival.

	TME + LPLD TME		Odds Ratio			Odds Ratio						
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year		M-H, Rand	om, 95% CI	_	_
Nagawa 2001 [30]	14	23	16	22	2.6%	0.58 [0.17, 2.05]	2001					
Watanabe 2002 [29]	48	76	25	40	6.5%	1.03 [0.47, 2.27]	2002					
Fujita 2003 [28]	124	204	20	42	9.1%	1.71 [0.87, 3.32]	2003		-	-		
Col 2005 [27]	13	24	86	146	5.4%	0.82 [0.35, 1.96]	2005					
Kim 2007 [20]	121	176	208	309	25.8%	1.07 [0.72, 1.59]	2007		-	-		
Akasu 2009 [18]	35	42	26	27	0.9%	0.19 [0.02, 1.66]	2009			-		
Akiyoshi 2014 [16]	32	38	66	89	4.1%	1.86 [0.69, 5.02]	2014		_	-		
Ogura 2016 [15]	91	107	180	220	10.2%	1.26 [0.67, 2.38]	2016			•		
Fujita 2017 [13]	260	351	261	350	35.4%	0.97 [0.69, 1.37]	2017		-	F		
Total (95% CI)		1041		1245	100.0%	1.07 [0.88, 1.31]				•		
Total events	738		888									
Heterogeneity: Tau ² =	0.00; Chi ²	= 7.31,	df = 8 (P	= 0.50)	; 2 = 0%				t.		+	100
Test for overall effect:	Z = 0.67 (F	P = 0.50)					0.01 F	avours [TME]	Favours [TI	ME + LP	LD]

Fig. (4): Forest plot of comparison outcome of disease-free survival.



Fig. (5): Forest plot of comparison outcome of 5-year disease-free survival.

	TME + L	PLD	TME			Odds Ratio		Odds Rat	lo
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random,	95% CI
Nagawa 2001 [30]	3	23	0	22	1.2%	7.68 [0.37, 157.91]	2001		
Watanabe 2002 [29]	9	75	3	40	5.1%	1.68 [0.43, 6.60]	2002		-
Fujita 2003 [28]	26	204	8	42	9.7%	0.62 [0.26, 1.49]	2003		
Matsuoka 2005 [26]	1	15	1	42	1.4%	2.93 [0.17, 50.00]	2005		
Col 2005 [27]	3	24	22	146	5.5%	0.81 [0.22, 2.93]	2005		·
Hasdemir 2005 [25]	3	24	22	146	5.5%	0.81 [0.22, 2.93]	2005		·
Kim 2007 [20]	18	176	19	309	13.1%	1.74 [0.89, 3.41]	2007		•
Shiozawa 2007 [21]	25	146	6	26	8.0%	0.69 [0.25, 1.89]	2007	-+-	
Yano 2007 [22]	5	35	5	68	5.4%	2.10 [0.56, 7.81]	2007	+-	
Kobayashi 2009 [17]	82	784	36	488	19.3%	1.47 [0.97, 2.21]	2009	-	
Akiyoshi 2014 [16]	1	38	7	89	2.3%	0.32 [0.04, 2.67]	2014		
Ogura 2016 [15]	4	107	11	220	6.5%	0.74 [0.23, 2.37]	2016		
Fujita 2017 [13]	26	351	44	350	16.8%	0.56 [0.33, 0.93]	2017	-	
Total (95% CI)		2002		1988	100.0%	1.01 [0.72, 1.42]		•	
Total events	206		184						
Heterogeneity: Tau ² =	0.11: Chi2	= 18.32.	df = 12 (P = 0.1	1); 2 = 349	%		-too	1 1
Test for overall effect:	Z = 0.04 (F	= 0.97)					0.002 0.1 1	10 500

Fig. (6): Forest plot of comparison outcome of local recurrence.

	TME + L	PLD	TME			Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
Nagawa 2001 [30]	5	23	5	22	8.4%	0.94 [0.23, 3.85]	2001	
Watanabe 2002 [29]	16	75	0	0		Not estimable	2002	
Fujita 2003 [28]	66	204	11	42	24.7%	1.35 [0.64, 2.85]	2003	
Matsuoka 2005 [26]	4	15	6	42	8.1%	2.18 [0.52, 9.15]	2005	
Hasdemir 2005 [25]	4	24	20	146	11.7%	1.26 [0.39, 4.07]	2005	
Kim 2007 [20]	32	176	79	309	47.0%	0.65 [0.41, 1.03]	2007	
Total (95% CI)		517		561	100.0%	0.96 [0.62, 1.46]		+
Total events	127		121					
Heterogeneity: Tau ² =	0.05; Chi ²	= 4.87,	df = 4 (P :	= 0.30)	; 2 = 18%			
Test for overall effect:	Z = 0.21 (F	> = 0.84)					Favours [TME + LPLD] Favours [TME]

Fig. (7): Forest plot of comparison outcome of distant recurrence.

	TME + L	PLD	TME			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Ye	ar M-H, Random, 95% Cl
Nagawa 2001 [30]	8	23	5	22	4.9%	1.81 [0.49, 6.76] 20	01
Watanabe 2002 [29]	25	75	11	40	12.0%	1.32 [0.57, 3.07] 20	
Fujita 2003 [28]	77	204	19	42	19.0%	0.73 [0.38, 1.43] 20	03
Hasdemir 2005 [25]	7	24	42	146	9.4%	1.02 [0.39, 2.64] 20	D5 —
Matsuoka 2005 [26]	5	15	7	42	4.7%	2.50 [0.65, 9.60] 20	05
Kim 2007 [20]	47	176	93	309	50.0%	0.85 [0.56, 1.28] 20	7 -
Total (95% CI)		517		601	100.0%	0.97 [0.72, 1.29]	+
Total events	169		177				
Heterogeneity: Tau ² = 1	0.00; Chi2	= 4.37,	df = 5 (P	= 0.50)	; l² = 0%		
Test for overall effect:	Z = 0.23 (F	9 = 0.82)				Favours [TME + LPLD] Favours [TME]

Fig. (8): Forest plot of comparison outcome of total recurrence.

	TME + L	PLD	TME			Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl	
Nagawa 2001 [30]	13	23	11	22	8.3%	1.30 [0.40, 4.21]	2001		
Fujita 2003 [28]	66	204	9	42	18.1%	1.75 [0.79, 3.88]	2003	+	
Matsuoka 2005 [26]	4	15	6	42	5.5%	2.18 [0.52, 9.15]	2005		
Akasu 2009 [18]	8	42	3	29	5.6%	2.04 [0.49, 8.45]	2009		
Akiyoshi 2014 [16]	14	38	26	89	17.7%	1.41 [0.63, 3.15]	2014		
Ogura 2016 [15]	36	107	54	220	44.7%	1.56 [0.94, 2.58]	2016		
Total (95% CI)		429		444	100.0%	1.59 [1.14, 2.24]		•	
Total events	141		109						
Heterogeneity: Tau ² =	0.00; Chi ²	= 0.56,	df = 5 (P :	= 0.99)	; 2 = 0%		1.1	0.001 01 1 10 1	000
Test for overall effect:	Z = 2.71 (F	P = 0.00	7)					Favours [TME + LPLD] Favours [TME]	1000

Fig. (9): Forest plot of comparison outcome of postoperative complications.

	TME + L	PLD	TME			Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
Nagawa 2001 [30]	15	23	6	22	22.3%	5.00 [1.40, 17.83]	2001	
Col 2005 [27]	18	24	64	246	32.3%	8.53 [3.24, 22.43]	2005	
Matsuoka 2005 [26]	9	15	12	42	23.4%	3.75 [1.10, 12.84]	2005	
Kyo 2006 [24]	4	15	2	22	12.2%	3.64 [0.57, 23.13]	2006	
Akasu 2009 [18]	27	42	1	27	9.8%	46.80 [5.76, 380.14]	2009	
Total (95% CI)		119		359	100.0%	6.66 [3.31, 13.39]		+
Total events	73		85					I I I
Heterogeneity: Tau ² = Test for overall effect:	0.15; Chi ² Z = 5.32 (F	= 5.23,	df = 4 (P 001)	= 0.26)	; I² = 23%			0.001 0.1 1 10 100 Favours [TME + LPLD] Favours [TME]

Fig. (10): Forest plot of comparison outcome of urinary dysfunction.

Service and the	TME + LPLD TME			1.1.1.1.1	Odds Ratio		Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	Year		M-H, Rand	om, 95% Cl	
Nagawa 2001 [30]	12	23	5	22	42.1%	3.71 [1.02, 13.47]	2001				
Kyo 2006 [24]	10	12	6	18	31.3%	10.00 [1.64, 60.92]	2006				
Akasu 2009 [18]	26	42	1	27	26.6%	42.25 [5.21, 342.32]	2009				
Total (95% CI)		77		67	100.0%	9.67 [2.38, 39.26]				-	
Total events	48		12								
Heterogeneity: Tau ² =	0.78; Chi ²	= 4.07,	df = 2 (P	= 0.13)	; l ² = 51%			0.004		1	1000
Test for overall effect:	Z = 3.17 (F	P = 0.00	2)					Favours	[TME + LPLD]	Favours [TME]	1000





Fig. (12): Forest plot of comparison outcome of operative time.





				R	isk of bia	IS		
		D1	D2	D3	D4	D5	D6	D7
dy	Nagawa 2001	-	_		+	+	-	+
Stu	Fujita 2017	+	+		+	+	+	+

Judgement

+

High

Low

Unclear

D1: Random sequence generation.

D2: Allocation concealment.

D3: Blinding of participants and personnel.

D4: Blinding of outcome assessment.

D5: Incomplete outcome data.

D6: Selective reporting.

D7: Other sources of bias.

Fig. (13): Summary of bias assessment of rcts.

Study

					or orde			
	D1	D2	D3	D4	D5	D6	D7	D8
Watanabe 2002	-	+	+	+	+		+	+
Fujita 2003	-	+	+	+	+		+	+
Col 2005		+	+	+	+		+	+
Hasdemir 2005		+	+	+	+		+	+
Matsuoka 2005	-	+	+	+	+		+	+
Col 2006	-	+	+	+	+		+	+
Куо 2006		+	+	+	+		+	+
Ozawa 2016	I	+	+	+	+		+	+
Kim 2007	+	+	+	+	+		+	+
Shiozawa 2007	+	+	+	+	+		+	+
Yano 2007	-	+	+	+	+		+	+
Akasu 2009	-	+	+	+	+		+	+
Kobayashi 2009		+	+	+	+		+	+
Kusters 2009	-	+	+	+	+		+	+
Akiyoshi 2014		+	+	+	+		+	+
Ogura 2016	-	+	+	+	+		+	+

Risk of bias

D1: Confounding bias.

D2: Intervention classification bias.

D3: Unavailable data bias.

D4: Deviations from intended interventions bias.

D5: Incomplete outcome data bias.

D6: Participant selection bias.

D7: Result selection bias

D8: Oucome measurement bias.



Judgement

+

High

Low

Unclear



				F 11			<i>c i</i>	Sa	ample siz	e
First author	Country	Year	Study type	Follow-up period in years	Staging	Modality	modality	TME	TME+ LPLD	Total
Nagawa [85]	Japan	2001	RCT	5	II/III	TME+LPLD	TME	22	23	45
Watanabe [84]	Japan	2002	Retrospective	5	II/III	TME+LPLD	TME	40	75	115
Fujita [83]	Japan	2003	Retrospective	5	II/III	TME+LPLD	TME	42	204	246
Col [82]	Turkey	2005	Retrospective	5	I/II/III	TME+LPLD	TME	146	24	170
atsuoka [81]	Japan	2005	Retrospective	4	II/III	TME+LPLD	TME	42	15	57
Hasdemir [80]	Turkey	2005	Retrospective	5	I/II/III	TME+LPLD	TME	146	24	170
Kyo [79]	Japan	2006	Retrospective	1	II/III	TME+LPLD	TME	22	15	37
Col [78]	Turkey	2006	Retrospective	3	I/II/III	TME+LPLD	TME	78	13	91
Yano [77]	Japan	2007	Prospective cohort	5	I/II/III	TME+LPLD	TME	70	39	109
Shiozawa [76]	Japan	2007	Retrospective	5	II/III	TME+LPLD	TME	26	143	169
Kim [75]	Japan	2007	Retrospective	5	II/III	TME+LPLD	TME	309	176	485
Kusters [74]	Netherlands	2009	Retrospective	5	I/II/III	TME+LPLD	TME	755	190	945
Akasu [73]	Japan	2009	Retrospective	1	I/II/III	TME+LPLD	TME	27	42	69
Kobayashi [72]	Japan	2009	Retrospective	5	I/II/III	TME+LPLD	TME	488	784	1272
Akiyoshi [71]	Japan	2014	Retrospective	3	II/III	TME+LPLD	TME	89	38	127
Ogura [70]	Japan	2016	Retrospective	3	II/III	TME+LPLD	TME	220	107	327
Ozawa [69]	Japan	2016	Retrospective	5	II/III	TME+LPLD	TME	499	499	998
Fujita [68]	Japan	2017	RCT	5	II/III	TME+LPLD	TME	350	351	701

Table (1): Characteristics of the 18 included studies.

RCT = Randomized Controlled Study. TME = Total Mesorectal Excision. LPLD = Lateral Pelvic Lymph node dissection.

Tab	le (2):	Population	on characte	ristics of	the 18	included	studies.
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First outbor	Vaar	Tumor location	Adjuvant chemotherapy		Neoadjuvant chemotherapy		Median age		Male		Female	
	Tear		TME+ LPLD	TME	TME+ LPLD	TME	TME+ LPLD	TME	TME+ LPLD	TME	TME+ LPLD	TME
Nagawa [85]	2001	Low	23	22	23	23	59	60	17	16	6	6
Watanabe [84]	2002	Low	NA	NA	53	25	58	66	57	26	18	14
Fujita [83]	2003	Low	0	0	0	0	57	64	133	24	71	18
Col [82]	2005	Low	NA	NA	0	0	52	58	NA	NA	NA	NA
atsuoka [81]	2005	Low	6	8	0	0	63	63	12	26	2	15
Hasdemir [80]	2005	Low	NA	NA	0	0	52	58	NA	NA	NA	NA
Kyo [79]	2006	Low	NA	NA	0	0	61	61	15	22	0	0
Col [78]	2006	Low	13	78	0	0	51	57	13	78	0	0
Yano [77]	2007	Low	NA	NA	0	0	64	64	NA	NA	NA	NA
Shiozawa [76]	2007	Low	NA	NA	0	0	NA	NA	NA	NA	NA	NA
Kim [75]	2007	Low	0	309	0	0	59	55	120	191	56	118
Kusters [74]	2009	Low	28	84	0	379	58	64	125	478	65	277
Akasu [73]	2009	Low	NA	NA	0	0	54	57	42	27	0	0
Kobayashi [72]	2009	Low	NA	NA	0	0	NA	NA	507	296	277	192
Akiyoshi [71]	2014	Low	23	31	38	389	61	60	28	62	10	27
Ogura [70]	2016	Low	68	86	207	220	60	60	82	147	35	73
Ozawa [69]	2016	Low	193	207	0	0	NA	NA	356	334	143	165
Fujita [68]	2017	Low	163	153	0	0	61	62	236	236	115	114

NA = Non-Available data. TME = Total Mesorectal Excision. LPLD = Lateral Pelvic Lymphadenectomy.

Table (3): Meta-analysis results.

	Number of studies	Patients				n-	Heterogeneity				
Outcome		TME+ LPLD	TME	Total	OR/MD (95% CI)	value	Tau ²	Chi ²	df	I^2 %	<i>p</i> - value
Overall survival	9	2021	2103	4124	1.02 (0.83-1.25)	0.86	0.02	10.31	8	22	0.24
5-year overall survival	6	1857	1814	3671	1.01 (0.78-1.30)	0.94	0.04	10.03	5	50	0.07
Disease free survival	9	1041	1245	2286	1.07 (0.77-1.31)	0.50	0.00	7.31	8	0	0.50
5-year disease-free survival	7	892	998	1890	1.07 (0.86-1.32)	0.54	0.00	4.60	6	0	0.60
Local recurrence	13	2002	1988	3990	1.01 (0.72-1.42)	0.97	0.11	18.32	12	34	0.11
Distant recurrence	6	517	561	1078	0.96 (0.62-1.46)	0.84	0.05	4.87	4	18	0.30
Total recurreence	6	517	601	1118	0.97 (0.72-1.29)	0.82	0.00	4.37	5	0	0.50
Postoperative complications	6	429	444	873	1.59 (1.14-2.24)	0.007	0.00	0.56	5	0	0.99
Urinary dysfunction	5	119	359	478	6.66 (3.31-13.39)	< 0.00001	0.15	5.23	4	23	0.26
Sexual dysfunction	3	77	67	144	9.67 (2.38-39.26)	0.002	0.78	4.07	2	51	0.13
Operative time	5	382	576	958	116.02 (89.20-142.83)	< 0.00001	597.80	12.58	4	68	0.01

OR=Odds Ratio. MD=Mean Difference. CI=Confidence Interval. df=Degrees of freedom.

Discussion

Despite the recent advances in surgery, the management of rectal cancer is still a challenge to even the most experienced surgeons. TME has become the gold standard approach in managing mid and low rectal cancers. However, the management approach varies greatly between the western and eastern surgical practice. While neoadjuvant therapy has proved effectiveness in improving management of locally advanced rectal cancers and has become common practice in western practice, LPLN metastasis remains an obstacle against achieving complete cure. On the other hand, LPLD is routine practice in eastern countries even though it is not commonly performed in the west.

Early on, Japanese surgeons added LPLD to conventional TME as a trial to obtain radical resection and improve surgical outcomes. However, this aggressive approach was reported to have a higher incidence of genitourinary dysfunction. Recent advances and development of autonomic nerve-sparing techniques may result in improved functional outcomes, although this needs more evidence from RCTs.

This study examined the outcomes and complications of LPLD when performed with TME. Most of the studies reviewed in this analysis were based in Japan. This is reasonable as the addition of LPLD was originally done in southeast Asian practice.

The primary outcomes of interest in this study are the measures to assess the surgical treatment success of rectal cancer and value of adding LPLD to the conventional TME alone approach. These outcomes included local recurrence, overall survival, and disease-free survival. Because the rationale of adding LPLD to TME is to improve these outcomes, we assessed them after TME alone and after TME + LPLD in an analysis of more than 6000 patients from 18 comparative studies done over the last two decades. This rationale was not confirmed as there were no notable differences found in terms of recurrence (local or distant) or survival (overall or disease-free) between the two groups.

Secondary functional outcomes of interest used in this study are measures to assess the safety profile of the surgical approach used. These included operative time and morbidity (postoperative complications, urinary and sexual dysfunction).

While survival and recurrence were comparable, secondary functional outcomes favored the TME

alone approach. The best available evidence shows that the addition of LPLD to TME resulted in a significantly longer operation time and morbidity when compared to the conventional TME alone.

We followed an objective approach in this study to find the best available evidence and to minimized selection bias among the reviewed studies. Nonetheless, we acknowledge that our review has some limitations. These limitations include the retrospective nature of most studies included. Of the 18 studies reviewed, 16 were nonrandomized observational studies while only 2 were RCTs, meaning a possible selection bias.

Another limitation is the moderate to high heterogeneity between studies. While Japanese centers have a much higher expertise performing LPLD, this is also a limitation as most of the reviewed studies were done in one country: Japan. There's also variations in patient selection between different institutions and patient populations were not meticulously matched between studies. The last limitation of concern is the variable LPLD technique.

Conclusion:

In conclusion, adding LPLD to TME for rectal cancer treatment is associated with higher rates of complications and longer operative time, with no added value regarding recurrence or survival when compared with TME alone as a treatment modality. Therefore, the routine use of LPLD should not be recommended for the treatment of rectal cancer.

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دور استئصال العقد اللمفية الحوضية الجانبية في علاج سرطان المستقيم تحليل تلوي

الخلفية والهدف : لا يزال دور استئصال الغدد الليمفاوية الحوضية الجانبية فى علاج سرطان المستقيم مثيراً للجدل. تبحث هذه الدراسة فى النتائج والفوائد المحتملة لإضافة استئصال الغدد الليمفاوية الحوضية الجانبية إلى الجراحة القياسية الذهبية لسرطان المستقيم : الاستئصال الكلى لمسراق المستقيم.

أساليب البحث : مراجعة منهجية تقارن نتائج الاستئصال الكلى لمسراق المستقيم + استئصال الغدد الليمفاوية الحوضية الجانبية مقابل الاستئصال الكلى لمسراق المستقيم وحده. النتائج التى تم دراستها هى رجوع الورم، والبقاء على قيد الحياة بدون أمراض، والبقاء على قيد الحياة بشكل عام، والمضاعفات.

النتائج : تم تضمين ١٨ دراسة لمقارنة النتائج فى ٢٧٦٢ مريضاً تم علاجهم بواسطة الاستئصال الكلى لمسراق المستقيم + استئصال الغدد الليمفاوية الحوضية الجانبية مقابل ٣٣٧١ مريضاً تم علاجهم بواسطة الاستئصال الكلى لمسراق المستقيم وحده لسرطان المستقيم المنخفض. النتائج التى تمت مقارنتها هى البقاء على قيد الحياة بشكل عام، البقاء على قيد الحياة لمدة ٥ سنوات ، بقاء خال من الأمراض، أو بقاء خال من الأمراض لمدة ٥ سنوات، رجوع محلى الورم، رجوع بعيد الورم بعيد، إجمالى رجوع الورم، مضاعفات ما بعد الجراحة، اختلال وظيفى في المسالك البولية، اختلال وظيفى جنسى، ووقت العملية الجراحية.

الخلاصة : ترتبط إضافة استئصال الغدد الليمفاوية الحوضية الجانبية إلى الاستئصال الكلى المسراق المستقيم لعلاج سرطان المستقيم بمعدلات أعلى من المضاعفات ووقت أطول للعملية، مع عدم وجود قيمة مضافة فيما يتعلق برجوع الورم أو البقاء على قيد الحياة عند مقارنتها مع الاستئصال الكلى لمسراق المستقيم وحدها كطريقة علاج.