

## Meta-Analysis of Lateral Lymph Node Dissection for Mid Lower Rectal Cancer: Is It Needed?

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### Keywords:

Lateral lymph node dissection; Lateral pelvic lymph node dissection; Total mesorectal excision; Rectal cancer

### Abbreviation:

LLND: Lateral Lymph Node Dissection; PR: Abdominoperineal Resection; ISR: Intersphincteric Resection; LAR: Lower Anterior Resection; LLNM: Lateral Lymph Node Metastasis; TME: Total Mesorectal Excision

### 1. Abstract

**1.1. Background:** Presence of lateral lymph node metastasis in rectal cancer was originally reported in the 1950s. Lateral lymph node metastasis occurs in 15 to 20% of patients with locally advanced low rectal cancer which escalates likelihood of local recurrence and reduced survival following neoadjuvant chemoradiotherapy (nCRT) and Total Mesorectal Excision (TME).

**1.2. Aim:** Our objective was to analyze the significance of lateral lymph node dissection for patients with mid lower rectal cancer.

**1.3. Method:** Cochrane, EMBASE, PubMed, Google Scholar, and Medline databases were searched for original studies, and relevant literature published between the years 1992 and 2020 concerning Lateral lymph node dissection for patients with mid lower rectal cancer were selected. A total of 27 studies were included. The preoperative, postoperative outcomes and complications were assessed. Meta-analyses were performed using Rev-Man 5.3.

**1.4. Result:** 27 studies were included in the analyses. Compared with the LLND No, the LLND Yes had longer operative time (WMD=86.26, 95% CI [79.59,92.93], p<0.00001), increase blood loss (WMD=148.21, 95% CI [122.29, 174.13], p=0.006), and five-year disease-free survival was favoring LLND No (OR= 1.58, 95% CI [1.12, 2.22], p=0.009). The LLND Yes resulted in a high risk of

urinary dysfunction (OR= 0.16, 95% CI [0.04, 0.28], p=0.008 and there was a high risk of sexual dysfunction with LLND Yes group (OR= 2.42, 95% CI [1.55, 3.78], p=0.0009). No other significant differences were observed.

**1.5. Conclusion:** We discovered that lateral lymph node dissection is not necessary because it did not favor the patients. It leads to longer operation time, increase blood loss and also increase morbidity rate, high risk of urinary and sexual dysfunction. Nevertheless, as there are limitations of this meta-analysis, decisions should be observed with some skepticism.

### 2. Introduction

Colorectal Cancer (CRC) is one of the most common cancers diagnosed and is a chief cause of cancer death worldwide [1]. In recent years, its overall occurrence rate displays a slow but stable increase in China [2]. In spite of the extraordinary accomplishments in the treatment of CRC, argument still stands concerning the management of Lateral Pelvic Lymph Node (LPLN) in patients with locally advanced lower rectal cancer (LALRC). Presence of lateral pelvic lymph node metastasis in rectal cancer was initially stated in the 1950s [3]. The management of lateral pelvic lymph nodes (LPLNs) in patients with low rectal cancer varies significantly amid Western countries and Japan. In Western countries,

preoperative chemoradiotherapy with Total Mesorectal Excision (TME) is the typical management for low rectal cancer. Lateral Pelvic Lymph Node Dissection (LPLD) is not often executed in Western countries, since LPLN metastasis is habitually measured to be a systemic disease, and because LPLD constantly leads to urinary and sexual dysfunction [4-6]. Meanwhile, in Japan, the occurrence of LPLN metastasis from low rectal cancer is stated to be about 15 %, and TME with LPLD has been the standard technique for patients with low rectal cancer [7-9]. It was reported that LPLD can recover the 5-year survival rate of patients with T3–T4 low rectal cancer by 8 % and can decrease the local recurrence rate by half [9]. The sign for LPLD in Japan is “T3 or T4 rectal cancer that spreads beneath the peritoneal reflection” according to the Japanese guidelines (Japan Society for Cancer of the Colon and Rectum Guidelines 2010 for the Treatment of Colorectal Cancer). As mentioned above, there has been an excessive argument on the effectiveness of LLND for locally advanced low rectal cancer amid Western countries and Japan.

This study aims to update and confirm the necessity of lateral lymph node dissection and reiterate its safety and feasibility.

### 3. Materials and Method

#### 3.1. Search Strategy

Studies published in English between the years of 1992 to 2020, were searched in the databases of Cochrane, EMBASE, PubMed, Google Scholar, and Medline using the main search terms lateral lymph node dissection, lateral pelvic lymph node dissection, total mesorectal excision, rectal cancer. The search strategy differed per database by their different requirements. Additionally, relevant studies in the references of related articles were also screened (Fig 3).

#### 3.2. Data Extraction

Data extraction was performed by using a special designed data extraction sheets. After we collected 27 full papers; Author name, year, nationality, study design, type of surgery and number of patients (Table 1). One large randomized control trial from JCOG gave its results, publish in three papers. These papers were including in the meta-analysis due to different outcomes they recorded that is (Fujita S et al 2012 [10]; postoperative time, blood loss, anastomotic leakage, bowel obstruction and wound infection, Fujita s et al 2017 [11]; local recurrence and five-year disease free-survival and Masaki ito et al2018 [12]; urinary dysfunction). The main research results of this meta-analysis were operation time, blood loss, anastomotic leakage, hospital stay, Urinary dysfunction, Sexual dysfunction, wound infection, bowel obstruction, five-year disease free survival, serum CEA level and wound infection were all considered. LLND YES denote patients that underwent lateral lymph node dissection and LLND NO is patients without lymph node dissection.

#### Inclusion criteria

- Only full original published paper in English.
- Comparative studies included.
- TME, APR, ISR, LAR Hartman’s procedure etc. done with or without Lateral lymph node dissection was included
- If the same research team participated in multiple studies, only the study with the most comprehensive data was included.

#### Exclusion criteria

- Case reports, conference abstracts and papers without full-text articles were excluded from the review.
- Studies that explored colorectal cancer instead of rectal cancer were actively excluded as well.
- Animal studies or lab studies

### 3.3. Statistical Analysis

Statistical analysis was performed using the Review Manager (RevMan) software, version 5.3 offered by the Cochrane collaboration. Continuous variables were pooled using the Mean Difference (MD) with a 95% confidence interval (95% CI), and dichotomous variables were pooled using the Odds Ratio (OR) with a 95% CI. Random effect and fixed effect models were computed under statistical methods of Mantel-Haenszel (for OR or RR). Studies that reported only the median, range, and size of the trial, the 137 means and standard deviations were calculated according to Hozo et al [13]. Heterogeneity among studies was assessed using the inconsistency statistic (I). If I was < 50%, the eligible studies were considered to be homogenous; hence, the fixed effect model was used. In contrast, if I was > 50%, the pooled results were said to be significant, heterogeneous, and the random effect model was used instead. We interpreted I<sup>2</sup> as 0% to 50% means low heterogeneity, 50% to 75% means moderate heterogeneity, 75% to 100% means high heterogeneity. For outcomes reported at least 10 studies, we aimed to generate funnel plots and planned to examine the possibility of publication bias by assessing the symmetry of the funnel plots.

### 4. Results

900 studies were identified by the search strategy previously described. 555 after duplicates removed. Then 555 studies underwent vigorous screening process. After we came out with 67 studies after reading the full article. After reading the full article, 27 studies were considered for the meta-analysis base on the inclusion and exclusion criteria (Fig. 3). Studies were made up of 24 retrospective cohorts, 1 prospective studies and 2 randomized control trial studies. LLND yes represent patient with dissected lymph node and LLND No represented patients without lymph node dissection. The studies were from UK, USA, Japan, Turkey and Korea. In total, there were 8175 patients; LLND Yes (n=3999) and LLND No (n=4176) (Table 1).

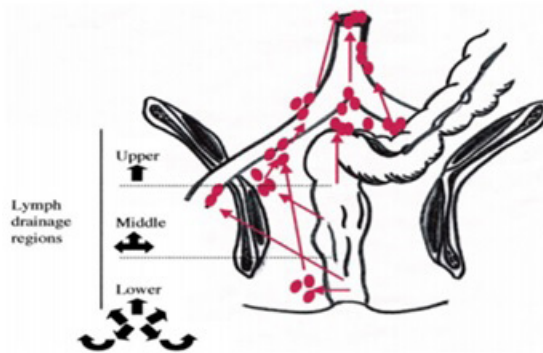


Figure 1: Lymphatic drainage of the rectum

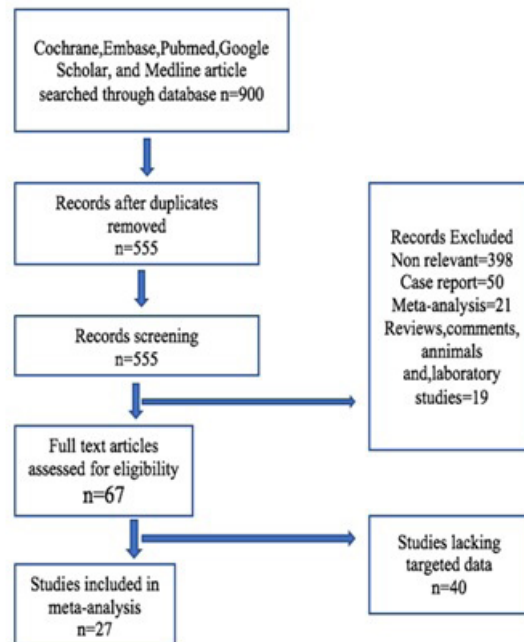


Figure 2: Prisma flow diagram of included studies

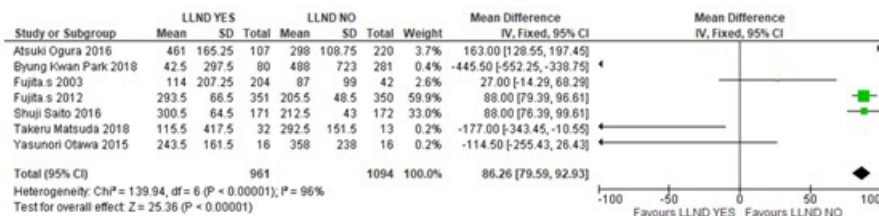


Figure 3: Forest plot of Operative time

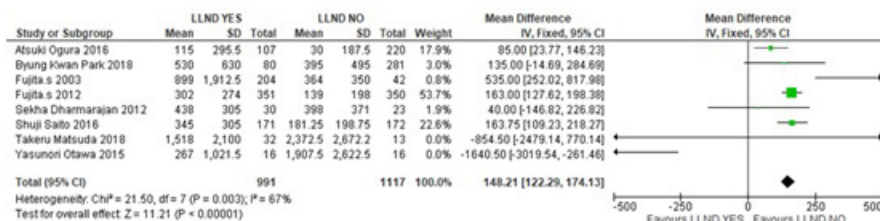


Figure 4: Forest plot of Blood loss

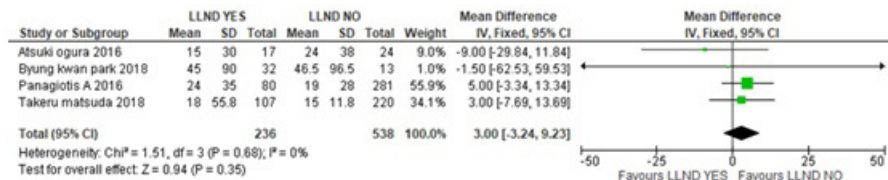


Figure 5: Forest plot of Hospital stay

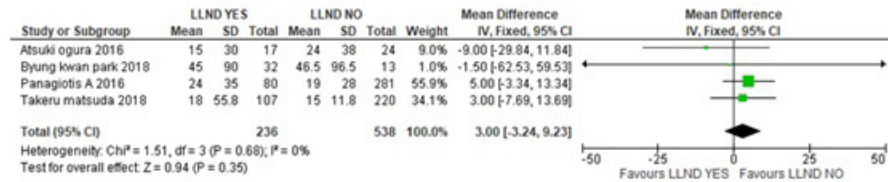


Figure 6: Forest plot of serum CEA level

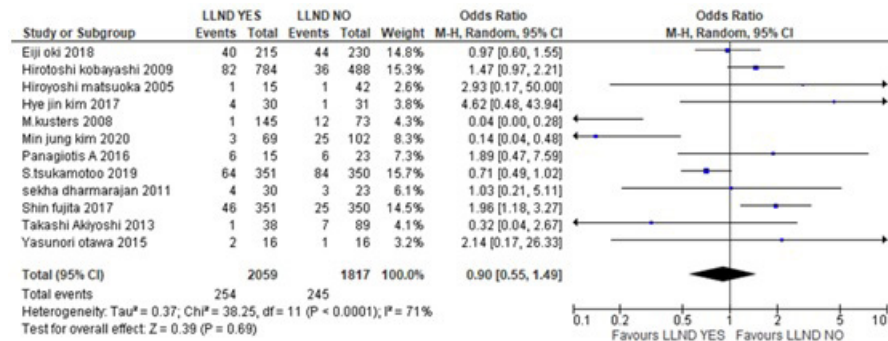


Figure 7: Forest plot of local recurrence

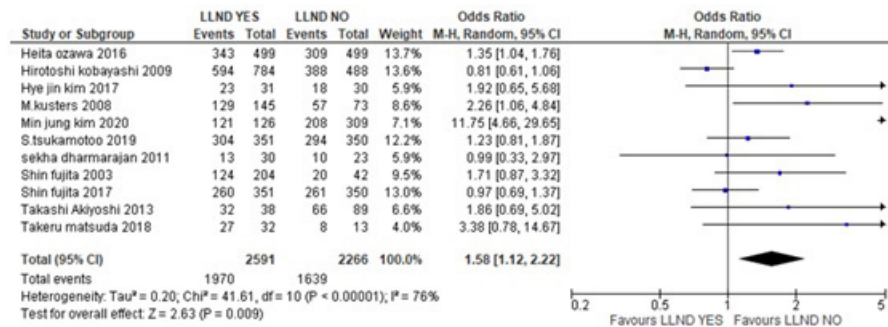


Figure 8: Forest plot of Five-year disease-free survival

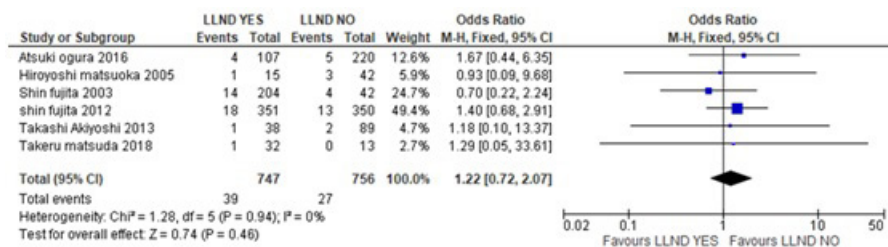


Figure 9: Forest plot of Anastomotic leakage

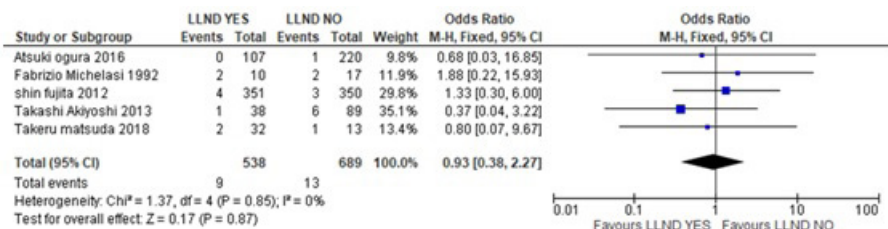
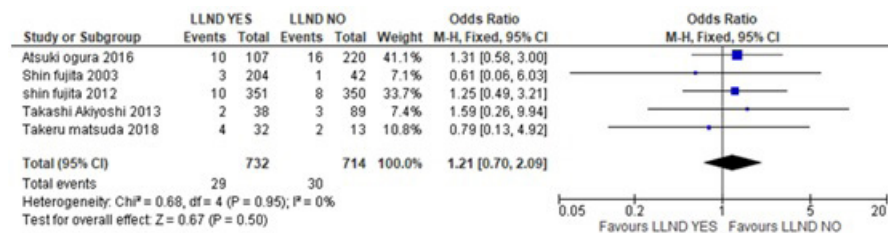


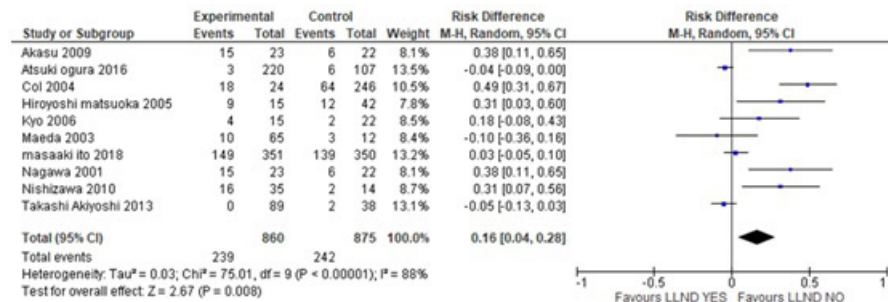
Figure 10: Forest plot of Bowel obstruction

**Table 1:** Basic characteristics of included studies

Authors	Year	Country	Study Design	LLND YES Patient	LLND NO Patient	Type of surgery
Fujita S et al [15]	2003	Japan	Retrospective	204	42	LAR,APR
Fujita S et al [10]	2012	Japan	Retrospective	351	350	ISR,LAR,APR,Hartmans proceure
Shin.F et al [11]	2017	Japan	RCT	351	350	-
Masaaki.I et al [12]	2018	Japan	RCT	351	350	ISR,LAR,APR,Hartmans proceure
Ogura,A et al [21]	2017	Japan	Retrospective	107	220	ISR,LAR,APR,Hartmans proceure
Park Byung kwan et al [19]	2018	Korea	Retrospective	80	281	ISR,LAR,APR,Hartmans proceure,combine resection,diverting ileostomy
Matsuda T et al [20]	2018	Japan	Retrospective	32	13	-
Kobayashi H et al [27]	2009	Japan	Retrospective	784	488	-
Akiyoshi T et al [31]	2013	Japan	Retrospective	38	89	ISR,LAR,APR,Hartmans proceure
kusters M et al [29]	2008	Netherland	Prospective	73	145	Sphincter-saving,Non- sphincter-saving
Georgiou, P.A et al [23]	2017	UK	Retrospective	17	24	APR,Pelvic exteneration,Flaps
Michelassi F et al [33]	1992	USA	Retrospective	10	17	LAR,APR,Proctocolectomy
Matsuoka H et al [28]	2005	Japan	Retrospective	15	42	TME
Kim H.J et al [24]	2017	Korea	Retrospective	31	30	LAR,APR
Tsukamotoo S et al [30]	2020	Japan	Retrospective	351	350	TME
Otawa Y et al [16]	2015	Japan		16	16	LAR,APR
Dharmarajan S et al [22]	2011	USA	Retrospective	30	23	Sphincter sacrificing (end stoma), Sphincter preserving, Lap assisted
Saito. S et al [18]	2016	Japan	Retrospective	171	172	LAR,APR
Oki E et al [32]	2019	Japan	Retrospective	215	230	-
Kim M.J et al [25]	2020	Korea	Retrospective	69	102	APR,Sphincter- preserving operation
Ozawa H et al[26]	2016	Japan	Retrospective	499	499	LAR,APR,Others
Nagawa et al[36]	2001	Japan	Retrospective	23	22	Autonomic nerve preservation
Col et al[35]	2004	Turkey	Retrospective	24	246	LAR,APR
Kyo et al[40]	2006	Japan	Retrospective	15	22	TME,Autonomic nerve preservation
Akasu et al[38]	2009	Japan	Retrospective	42	27	TME
Nishizawa et al[37]	2010	Japan	Retrospective	35	14	TME
Maeda et al[34]	2003	Japan	Retrospective	65	12	TME



**Figure 11:** Forest plot of Wound Infection



**Figure 12:** Forest plot of Urinary dysfunction

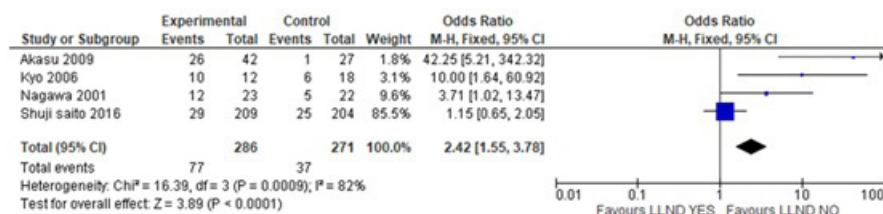


Figure 13: Forest plot of Sexual dysfunction

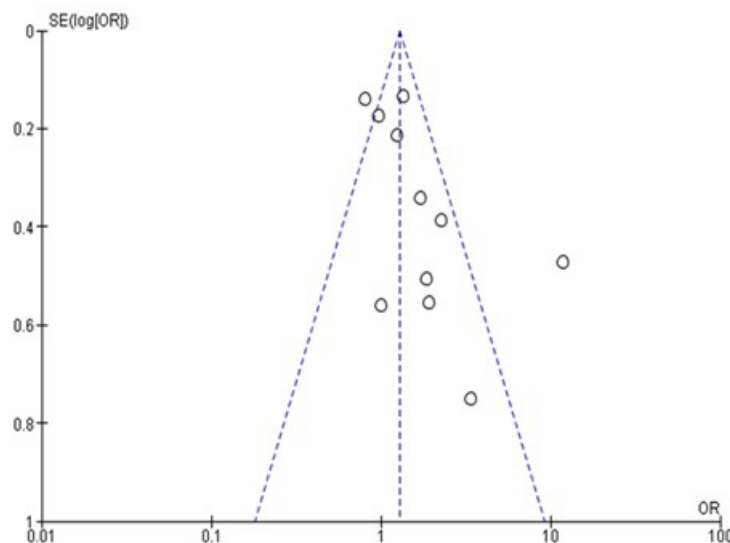


Figure 14: Publication Bias of five-year disease-free survival

**4.1. Anatomy of Lymphatic Drainage of the Colon and Rectum**

Comparable to venous drainage, lymphatic drainage of the colon and rectum mainly follows its arterial supply (Fig. 1). Thus, variations of the arterial supply have a significant influence on lymphatic drainage. Usually, three lymphatic drainage pathways can be distinguished: (I) lymphatic drainage of the right colon and proximal transverse colon following the arterial supply of the superior mesenteric artery and vein; (II) lymphatic drainage of the left colon and the upper two-thirds of the rectum along the inferior mesenteric artery and vein; and (III) lymphatic drainage from the lower two-thirds of the rectum occurs cephalad, along the superior rectal artery and the inferior mesenteric artery and, laterally, along the middle rectal vessels to the internal iliac lymph nodes. Studies using lymphoscintigraphy fail to exhibit communications amid inferior mesenteric and internal iliac lymphatics. In the anal canal, the dentate line signifies the essential landmark for two dissimilar systems of lymphatic drainage: above, to the inferior mesenteric nodes and, below, along the inferior rectal lymphatics to the superficial inguinal nodes, or less frequently, along the inferior rectal artery [14].

**5. Meta-Analysis Results**

**5.1. Operative Time**

Nine studies [10, 15-20] recorded a significant difference for operative time between LLND Yes compared to LLND No. Shorter

operative time was seen in the LLND No (WMD=86.26, 95% CI [79.59,92.93], p<0.00001). A fixed effect model was used due to significant heterogeneity (p<0.00001, I<sup>2</sup> = 96%) Heterogeneity: Chi<sup>2</sup> = 139.94, df = 6 (P < 0.00001); I<sup>2</sup> = 96%. Test for overall effect: Z = 25.36 (P < 0.00001) fig 3.

**5.2. Blood Loss**

The possibility of increase blood loss may occur in the LLND Yes due increase operative time, different operative technique complexity. Ten studies [10, 15, 16, 18-22] collected for blood loss observed a significant difference between LLND yes compared to LLND No. LLND No had a less blood loss (WMD=148.21, 95% CI [122.29, 174.13], p=0.006). A fixed effect model was used due to significant heterogeneity (p<0.00001, I<sup>2</sup> = 67%) Heterogeneity: Chi<sup>2</sup> = 21.50, df = 7 (P = 0.003); I<sup>2</sup> = 67%. Test for overall effect: Z = 11.21 (P < 0.00001) Fig 4.

**5.3. Hospital Stay**

Fours studies [19-21, 23] recorded hospital stay between the two groups. LLND Yes compared to LLND No showed no significant difference (WMD=3.00, 95% CI [-3.24, 9.23], p=0.35). Heterogeneity: Chi<sup>2</sup> = 1.51, df = 3 (P= 0.068); I<sup>2</sup> = 0%. Test for overall effect: Z =0.94 (P = 0.35). Fig 5.

**5.4. Serum CEA Level**

Grossly elevated CEA concentrations (>20 ng/mL) in patient with compatible symptoms are strongly suggestive of the cancer and

also suggestive metastasis. Four studies [19, 24-26] recorded serum CEA level between LLND Yes compared to LLND No. The analysis showed no significant difference (OR= 1.09, 95% CI [0.82, 1.35],  $p=0.39$ ). Heterogeneity:  $\text{Chi}^2 = 4.24$ ,  $\text{df} = 3$  ( $P = 0.24$ );  $I^2 = 29\%$ . Test for overall effect:  $Z = 0.85$  ( $P = 0.39$ ). Fig 6.

### 5.5. Local Recurrence

Twelve studies [11, 16, 22-25, 27-32] were recorded for local recurrence, but after the analysis there was no significant difference found between LLND Yes and LLND No (OR= 0.90, 95% CI [0.55, 1.49],  $p=0.69$ ). Heterogeneity:  $\text{Tau}^2=0.37$   $\text{Chi}^2 = 38.25$ ,  $\text{df} = 11$  ( $P < 0.0001$ );  $I^2 = 71\%$ . Test for overall effect:  $Z = 0.39$  ( $P = 0.68$ ). Fig 7.

### 5.6. Five-Year Disease-Free Survival

A total of eleven studies [11, 15, 20, 22, 24-27, 29-31] were included in the meta-analysis for five-year disease-free survival. The analysis showed a significant difference found between LLND Yes and LLND No (OR= 1.58, 95% CI [1.12, 2.22],  $p=0.009$ ). The five-year disease free survival was favoring the LLND No. Heterogeneity:  $\text{Tau}^2=0.20$ ;  $\text{Chi}^2 = 41.61$ ,  $\text{df} = 10$  ( $P < 0.00001$ );  $I^2 = 76\%$ . Test for overall effect:  $Z = 2.63$  ( $P = 0.009$ ). Fig 8.

### 5.7. Anastomotic Leakage

When we compared LLND Yes and LLND No, the assembled data from 6 studies [10, 15, 20, 21, 28, 31] showed a significant difference (OR= 1.22, 95% CI [0.72, 2.07],  $p=0.46$ ). That is the LLND No observed less anastomotic leakage. Heterogeneity:  $\text{Chi}^2 = 1.28$ ,  $\text{df} = 5$  ( $P = 0.94$ );  $I^2 = 0\%$ . Test for overall effect:  $Z = 0.74$  ( $P = 0.46$ ). Fig 9.

### 5.8. Bowel Obstruction

A total of five studies [10, 20, 21, 31, 33] were collected for bowel obstruction for LLND Yes and LLND No. The result showed no significant difference (OR= 0.93, 95% CI [0.38, 2.27],  $p=0.87$ ). Heterogeneity:  $\text{Chi}^2 = 1.37$ ,  $\text{df} = 4$  ( $P = 0.85$ );  $I^2 = 0\%$ . Test for overall effect:  $Z = 0.17$  ( $P = 0.87$ ). Fig 10

### 5.9. Wound Infection

Five studies [10, 15, 20, 21, 31] were recorded for wound infection for the two groups. Both LLND Yes and LLND No did not observe any significant difference (OR= 1.21, 95% CI [0.70, 2.09],  $p=0.50$ ). Heterogeneity:  $\text{Chi}^2 = 0.68$ ,  $\text{df} = 4$  ( $P = 0.95$ );  $I^2 = 0\%$ . Test for overall effect:  $Z = 0.67$  ( $P = 0.50$ ). Fig 11

### 5.10. Urinary Dysfunction

Ten studies [12, 21, 28, 34-40] were collected for urinary dysfunction. The analysis showed a significance difference between the two groups. The patient with lateral lymph node dissection observed a higher risk as compared to those without lateral lymph node dissection (OR= 0.16, 95% CI [0.04, 0.28],  $p=0.008$ ). Heterogeneity:  $\text{Tau}^2 = 0.03$ ;  $\text{Chi}^2 = 75.01$ ,  $\text{df} = 9$  ( $P < 0.00001$ );  $I^2 = 88\%$ . Test for overall effect:  $Z = 2.67$  ( $P = 0.008$ ). Fig.12

### 5.11. Sexual Dysfunction

Four studies [18, 36, 38, 40] were recorded for sexual dysfunction. The patients with lateral lymph node dissection showed a high risk as compared to other group without lateral lymph node dissection. (OR= 2.42, 95%CI [1.55, 3.78],  $p=0.0009$ ). Heterogeneity:  $\text{Chi}^2 = 16.39$ ,  $\text{df} = 3$  ( $P = 0.0009$ );  $I^2 = 82\%$ . Test for overall effect:  $Z = 3.89$  ( $P < 0.0001$ ). Fig.13

### 5.12. Publication Bias

The funnel plot on the five-year disease-free survival is shown in figure 14. Because all studies laid inside the 95% CI limits, no evidence of publications bias was noted. Egger test was performed to provide statistical evidence regarding funnel plot symmetry. Result still did not reveal any evidence of publication bias in five-year disease-free survival Heterogeneity:  $\text{Tau}^2=0.20$ ;  $\text{Chi}^2 = 41.61$ ,  $\text{df} = 10$  ( $P < 0.00001$ );  $I^2 = 76\%$ . Test for overall effect:  $Z = 2.63$  ( $P = 0.009$ ).

## 6. Discussion

Surgical methods in the management of rectal cancer have gone through a great modification over the previous times. Technical features have been considered and revised widely in an effort to lessen local recurrences and to decrease the occurrence of urinary and sexual morbidity, but the presence and composition of the Lateral Ligaments of the Rectum (LLR) are still the focus of anatomical misunderstanding and surgical misconception up to now [41, 42]. Though, this method was abandoned for lengthy period of time until late 1980s, perhaps due to procedural struggle, higher morbidity, and lack of oncological proof. In the Western countries, TME has now been commonly acknowledged as a gold standard to decrease local recurrence [43]. In the radical resection of rectal cancer, there has been much debate about whether or not to conventionally implement lateral lymph node dissection. But, there are growing evidences that LLND can help patients. According to Japanese reports, even though bilateral lymph node was defined negatively by Computed Tomography (CT) scanning or Magnetic Resonance Imaging (MRI) for the patients of low rectal cancer, 7.4% of patients in the LLND group were found to have LLNM [39], while the patients in whom TME+LLND was done had a local recurrence rate reduced by about 50% and the 5-year survival rate of patients with rectal cancer increased by 8-9% [10, 17, 39]. The current study was conducted to give an update on previous meta-analysis to launch high-level proof for whether lateral lymph node dissection is required or not. The present study verified that the LLND could not be confirmed to lessen operation time, and blood loss, local recurrence, urinary dysfunction, and sexual dysfunction and improve patient's survival etc. However, patient who did not undergo lateral lymph node dissection presented shorter operation time which leads to decrease blood loss making the lateral lymph node dissection not safe and feasible. In addition-high-

er heterogeneity of operative time ( $p < 0.00001$ ,  $I^2 = 99\%$ ), blood loss ( $p < 0.00001$ ,  $I^2 = 96\%$ ) and decrease disease free survival rate ( $P < 0.00001$ ;  $I^2 = 76\%$ ) were related to chemoradiotherapy. This was perhaps due because preoperative chemoradiotherapy reduced the tumor stage, at the same time affecting the blood supply and cell metabolism of local tissues, thereby causing inflammatory edema in local tissues and an increased operation time and blood loss [44]. The higher frequency of urinary dysfunction is an vital subject during follow up of patient after rectal surgery. Some studies recorded higher rates of urinary dysfunction such as 40%-45% in patients with lateral lymph node dissection [28, 33]. Our studies showed a higher incidence of urinary dysfunction ( $P < 0.00001$ );  $I^2 = 88\%$ ) and a higher incidence of sexual dysfunction ( $P = 0.0009$ );  $I^2 = 82\%$ ) with the lateral lymph node dissection. It was also essential to consider local recurrence, which was related to lateral lymph node contribution. Our studies showed no significant difference between those who had lateral lymph node dissection and those who did not ( $P < 0.0001$ );  $I^2 = 71\%$ . Although to prove whether LLND could profit patients with rectal cancer, the JCOG conducted a phase 3 clinical RCT to matched ME with and without LLND. Main endpoints, including 5-year recurrence-free survival, overall survival, and local-relapse-free survival showed a difference favoring the LLND group. The local recurrence rates were 7.4% and 12.6% in the ME with LLND and ME alone groups, respectively ( $P = 0.024$ ) [45-47]. The five-year disease free survival was in the favor of patient who did not have LLND ( $P < 0.00001$ );  $I^2 = 76\%$ ). Furthermore, recent two meta-analyses by Georgiou et al. [4] and Chen et al [48] that assessed the benefits and adverse effects of LLND have shown that LLND did not increase OS nor decrease recurrence rates. Our study also recorded no significant different for postoperative outcomes like anastomotic leakage, bowel obstruction and wound infection. These outcomes could have played a role in the length of hospital stay, even though this meta-analysis showed mild heterogeneity for hospital stay ( $P = 0.068$ );  $I^2 = 0\%$ ). Hiroyoshi matsuo et al [28] confirmed anastomotic leakage by recording 7% for both groups. Also S. Fujita et al [10] also recorded 1 % bowel obstruction for both groups confirming our meta-analysis results.

## 7. Limitations

It is recognized that numerous boundaries and limitations were met during this study. First, most studies were retrospective cohort, with few randomized control and prospective studies were accessible in this field, which may decrease each result's dependability. Second, the inadequate number of applicable studies may impact the statistical power. Third, the knowledge and expertise of each surgeon likely varied amid studies, which would produce certain bias. Lastly, some surgeries were LAR, ISR, APR, Hartman's procedure, laparoscopic or open which could also create an unavoidable bias.

## 8. Conclusion

In summary, our meta-analysis proposed that lateral lymph node dissection is not essential because it rather increases the length of operation, thereby increasing blood loss, higher incidence of urinary and sexual dysfunction and also the disease free survival rate did not show any favor for the lateral lymph node dissection. There was no significant difference for other postoperative complication between the two groups. Nevertheless, as there are limitations of this meta-analysis, decisions should be observed with some skepticism.

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