

## RESEARCH COMMUNICATION

# Lateral Lymph Node Dissection with Radical Surgery versus Single Radical Surgery for Rectal Cancer: a Meta-analysis

Huan Cheng, Zhonglei Deng, Zeng-jun Wang, Wei Zhang, Jian-tang Su\*

### Abstract

**Objectives:** To assess the value of lateral lymph node dissection (LLND) in the radical surgery of rectal cancer. **Methods:** The published Chinese and English literature was retrieved. A total of 15 papers fitted the selection criteria, including 4,858 patients. Among them 2,401 were in the LLND group and 2,457 in the non-LLND (NLLND) group. Evaluation parameters included 5-year survival rate recurrence rate, peri-operative outcomes, postoperative urinary and sexual functions. **Results:** The operating time was significantly shorter in the NLLND group than that in the LLND group (weighted mean difference (WMD)=109 min, 95 confidence interval(CI):90-129,  $P < 0.001$ ). Intra-operative blood loss was greater in the LLND group, but the difference was not significant (WMD=429 mL, 95 CI:325-854,  $P = 0.05$ ). The frequency of peri-operative morbidity (OR, 1.57 95 CI:1.06-2.33,  $P = 0.02$ ) was also significantly higher in the LLND group. There were no significant differences in 5-year survival rate and recurrence rate between the two groups. Data from individual studies (three) showed that the frequency of male urinary dysfunction (OR=5.12, 95 CI 2.15-12.19,  $P=0.0002$ ) and sexual dysfunction ( $P < 0.05$ ) were greatly lower in the NLLND group. **Conclusion:** Meta analysis showed that LLND did not have specific advantage in decreasing postoperative recurrence and prolonging survival time. Furthermore it was associated with prolonged operation time, increased blood loss and elevated incidence of peri-operative complications and urinary and sexual dysfunction.

**Keywords:** Rectal neoplasm - surgery - lateral lymph node excision - complications - survival analysis - meta-analysis

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### Introduction

Colorectal cancer remains the second commonest cause of cancer death in North America and Western Europe (Poston, 2004), worstly, lateral lymph node metastasis was observed in 10%~25% of patients with rectal cancer, the recurrence rate of patients with metastasis to the lateral lymph nodes was comparatively higher and the survival rate was shorter (Sugihara et al., 1996; Hida et al., 1997), surgery remains the mainstay of treatment. until now, the rectal extended radical resection with the lateral lymph node dissection (LLND) as the main technique on patients with metastasis to the lateral lymph nodes was first implemented in Japan around the 1970s and was gradually accepted. However, there was controversy that whether LLND could reduce the recurrence after radical resection of rectal carcinoma and prolong survival. Our study firstly objectively evaluates the value of LLND in radical resection of rectal carcinoma, which provides reference for clinical decision making.

### Materials and Methods

#### Objects of study

We selected published prospective randomized

studies or well-designed non-randomized controlled experiments about the comparison between rectal radical resection with LLND (LLND group) and rectal simple resection (NLLND group) in the recent seventeen years, furthermore, these studies included complete and accurate follow-up data.

#### Data source

We electronically searched EMBASE, PubMed, Ovid, Cochrane Library, China Biomedical Document Database (CBM) and Foreign Biomedical Literature Database by using the terms including lateral lymph node dissection, total mesorectal excision, radical resection, rectal cancer, comparative study, randomized study and treatment outcome according to Cochrane Handbook (Version 4.2.2). English language restriction was applied.

#### Inclusion criteria

- (1) Source materials were published literatures.
- (2) Original documents included the comparison between rectal radical resection with LLND (LLND group) and rectal simple resection (NLLND group).
- (3) The type of original documents was prospective randomized studies or well-designed non-randomized controlled experiments.
- (4) The objects, design and statistics methods of these

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documents were similar. (5) Original documents had unambiguous enumeration data when the follow-up was truncated, or could get relevant data by calculation. (6) Summarized results could be showed by relevant statistical criteria e.g. odds ratio (OR), weighted mean difference (WMD) and relative risk (RR). (7) The follow-up rate was over 90 %.

**Exclusion criteria**

(1) The research samples were too small and the cases were less than 20 cases. (2) There was no initial data or cannot search original literatures. (3) The patients accepted other treatments before and after surgery and these treatments could lead to distinct prognosis. (4) Original documents had ambiguous enumeration data when the follow-up was truncated, or could not get these data by calculation.

**Data extraction**

Two reviewers searched and selected literatures independently ,then extracted relevant data according to a data extraction table ,these extracted data included mainly the first author, the date of publish , the standard for selected patients, the randomized protocol, the cases of LLND group and NLLND group, the operative plan, the operative implementation status, the endpoints, the withdrawal cases, statistical methods ,the five-year survival rate (SR), the recurrence or distant metastasis status and the complications.

**Statistical analysis**

Meta-analysis proceeded by adopting RevMan4.2 software. Heterogeneity among included studies was tested by using  $\chi^2$  test ( $\alpha = 0.05$ ). The data that existed in no heterogeneity was treated by fixed effect model. If heterogeneity existed, the data was treated by random effects model. We adopted  $I^2$  to carry on quantitative analysis of heterogeneity,  $I^2 > 75\%$  represented high heterogeneity. The total effective rate was represented by odds ratio (OR) and weighted mean difference (WMD),and the effect size was represented by 95% reliable interval (CI).we performed a quantitative appraisal for publication bias by adopting funnel plot.

**Results**

**Overview of included studies**

Totally, fifteen studies involved one prospective randomized study and fourteen well-designed non-randomized controlled experiments were included , and these studies involved 4858 cases (2402 cases in LLND group and 2457 cases in NLLND group). (Table 1)

**Comparison of perioperative outcomes**

Three studies evaluate the duration of operation (Nagawa H et al., 2001; Fujita S et al., 2003; Hasdemir O et al., 2005), results of the pooled analysis showed that the operation time of NLLND group was significantly shorter than that in LLND group ( WMD =109 min,95 % CI:90-129 P < 0.001). The results of homogeneity test showed that  $\chi^2=4.19,df=2, P=0.12, I^2=52.3\%$ . Three

**Table 1. Characteristics of Included Studies of Rectal Carcinoma**

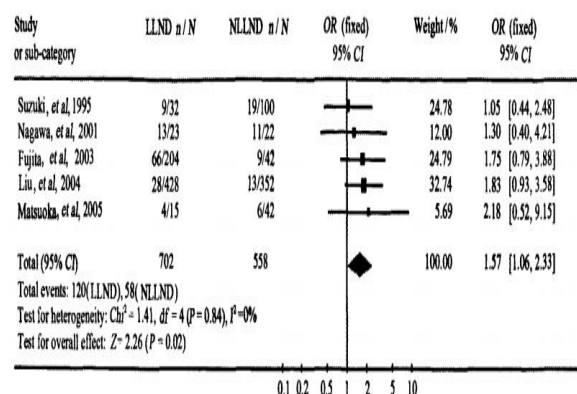
Study	Year	Total	Group	
			LLND	NLLND
Nagawa et al	2001	45	23	22
Fujita et al	2003	246	204	42
Hasdemir et al	2005	184	24	106
Liu et al	2004	780	428	352
Suzuki et al	1995	132	32	100
Matsuoka et al	2005	57	15	42
Moreira et al	1994	178	95	83
Shiozawa et al	2007	169	143	26
Kobayashi et al	2009	1072	784	288
Kim et al	2007	485	176	309
Watanabe et al	2002	115	75	40
Yano et al	2007	109	39	70
Kusters et al	2009	1079	324	755
Kyo et al	2006	37	15	22
Col et al	2005	170	24	146

LLND group, Traditional radical resection + lateral lymph node dissection; NLLND group, Traditional radical resection

studies evaluate intra-operative blood loss of 1071 cases (Nagawa H et al., 2001; Fujita S et al., 2003; Liu BS et al., 2004), and results of the pooled analysis showed that intra-operative blood loss was greater in the LLND group than that in the NLLND group but the difference was not significant (WMD=429 mL, 95 CI 325-854, P =0.05),the results of homogeneity test showed that  $\chi^2=41.43,df=2, P=0.0001, I^2=95.2\%$ ,which suggested that existed heterogeneity and adopted random-effects model to analyze. Five studies evaluate the frequency of peri-operative morbidity of 1260 cases (Suzuki et al., 1995; Nagawa et al., 2001; Fujita et al., 2003; Liu et al., 2004; Matsuoka et al., 2005) and results of the pooled analysis showed that The frequency of peri-operative morbidity was significantly higher in the LLND groups compared with the NLLND group(OR=1.57, 95 CI 1.06-2.33, P = 0.02),the results of homogeneity test showed that  $\chi^2=1.41,df=4, P=0.84, I^2=0\%$ . (Figure 1).

**Comparison of 5-year survival rate outcomes**

Five studies evaluated 5-year survival rate after operation (Moreira et al., 1994; Liu et al., 2004; Hasdemir et al., 2005; Shiozawa et al., 2007; Kobayashi et al., 2009) (Figure 2), results of the pooled analysis showed that 5-year survival rate of LLND group was no significant



**Figure 1. Comparison of Perioperative Morbidity Between LLND and NLLND Groups**

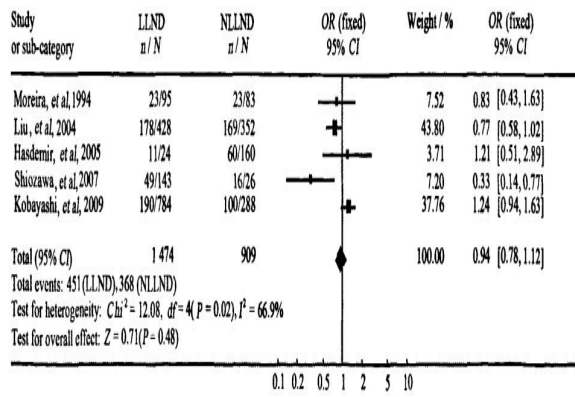


Figure 2. Comparison of Five-year Survival Between LLND and NLLND Groups

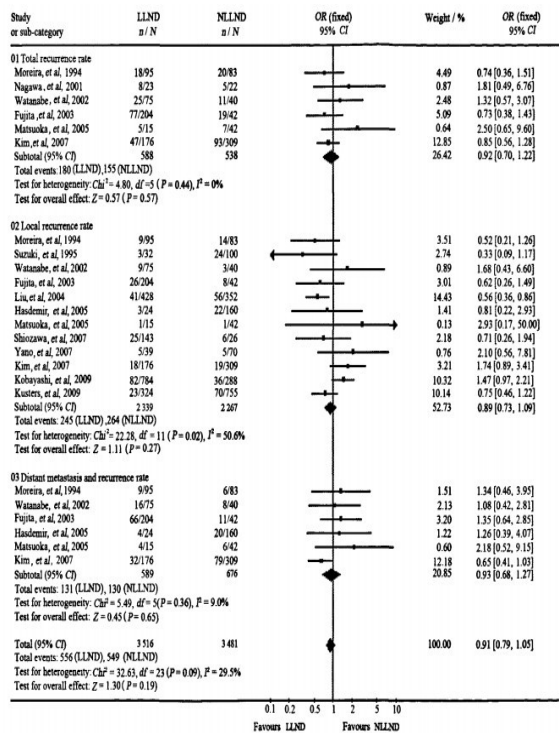


Figure 3. Comparison of Postoperative Recurrence Rates Between LLND and NLLND Groups

differences compared with the NLLND group (OR=0.94, 95 CI 0.78-1.12, P = 0.48 ).the results of homogeneity test showed that  $\chi^2=12.08,df=4, P=0.02, I^2=66.9\%$  ). The funnel plot test showed that individual points of the five studies were basically symmetrical and publication bias was little.

Comparison of recurrence rate outcomes

Six studies evaluated total recurrence rate after operation (Moreira et al., 1994; Nagawa et al., 2001; Watanabe et al., 2002; Fujita et al., 2003; Matsuoka et al., 2005; Kim et al., 2007) results of the pooled analysis showed that total recurrence rate of LLND group was no significant differences compared with the NLLND group (OR=0.92, 95 CI 0.70-1.22, P = 0.57).the results of homogeneity test showed that  $\chi^2=4.80,df=5, P=0.44, I^2=0\%$  . Twelve studies compared local recurrence rate after operation between LLND group and NLLND group (Moreira et al., 1994; Suzuki et al., 1995; Watanabe et al., 2002; Fujita et al., 2003; Liu et al., 2004; Hasdemir et al., 2005; Matsuoka et al., 2005; Kim et al., 2007; Shiozawa et

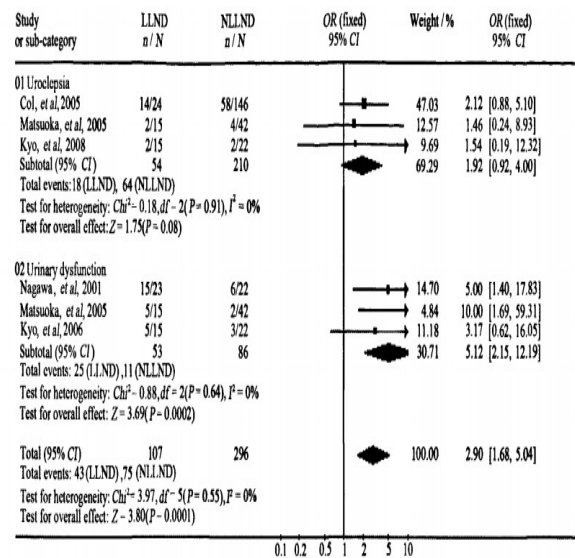


Figure 4. Comparison of Urinary and Sexual Dysfunction Between LLND and NLLND Groups

al., 2007; Yano et al., 2007; Kobayashi et al., 2009; Kusters et al., 2009) the results of homogeneity test showed that existed heterogeneity ( $\chi^2=22.28,df=11 P=0.02, I^2=50.6\%$ ) and adopted random-effects model to analyze. results of the pooled analysis showed that local recurrence rate of LLND group was no significant differences compared with the NLLND group (OR=0.89, 95 CI 0.73-1.09, P = 0.27). Six studies reported distant metastasis or recurrence rate after operation (Moreira et al., 1994; Watanabe et al., 2002; Fujita S et al., 2003; Hasdemir et al., 2005; Matsuoka et al., 2005; Kim et al., 2007 ), results of the pooled analysis showed that distant metastasis or recurrence rate of LLND group was no significant differences compared with the NLLND group (OR=0.93, 95 CI 0.68-1.27, P = 0.65).the results of homogeneity test showed that  $\chi^2=5.49,df=5, P=0.36, I^2=9.0\%$  (Figure 3). The funnel plot test showed that individual points of the five studies were basically symmetrical and publication bias was little.

Comparison of postoperative urinary and sexual functions outcomes

Three studies reported urinary incontinence in 264 patients (Col et al., 2005; Matsuoka et al., 2005; Kyo et al., 2006), the results of homogeneity test showed that there was no significant heterogeneity ( $\chi^2=0.18,df=2, P=0.91, I^2=0\%$ ) and adopted fixed-effects model to analyze. results of the pooled analysis showed that the incidents of urinary incontinence of LLND group was no significant differences compared with the NLLND group (OR=1.92, 95 CI 0.92-4, P = 0.08). Three studies reported genitourinary dysfunction in 139 patients (Nagawa et al., 2001; Matsuoka et al., 2005; Kyo et al., 2006), results of the pooled analysis showed that the possibility of genitourinary dysfunction in NLLND group was lower than that in the LLND group (OR=5.12, 95 CI 2.15-12.19 P = 0.0002), the results of homogeneity test showed that there was no significant heterogeneity ( $\chi^2=0.88, df=2 P=2, I^2=0\%$ ) and adopted fixed-effects model to analyze (Figure 4).

Kyo et al found that the cases who suffered from dysuria, urinary tract infection and urinary catheterization



on request has no significant difference ( $P>0.05$ ) (Kyo K et al., 2006), but the frequency of micturition in LLND group was higher than that in NLLND group, furthermore, The cases with sexual dysfunction after operation were significantly higher in LLND group than those in NLLND group ( $P < 0.05$ ). Nagawa et al demonstrated that the frequency of sexual dysfunction in NLLND group (45.5 %, 5/11) was lower than that in LLND group (92.3 %, 12/13) ( $P= 0.012$ ) (Nagawa et al., 2001).

## Discussion

The results of metaanalysis indicated that LLND group could not increase 5-year survival rate and reduce recurrence compared with NLLND group. The results of sensitivity analysis were consistent, which suggested that reliability of these results was reasonable, the funnel plot test showed that individual points were basically symmetrical and publication bias was little. the results of homogeneity test showed that the survive rate and local recurrence existed heterogeneity, which probably correlated with sample size, the age of patients, tumor position, bilateral or unilateral lymphadenectomy, tumor stage and grade, and other correlative influencing factors. besides, the compared results of perioperative situation showed that operation time in LLND group was longer and incidence of peri-operative complications was higher compared with NLLND group ,there was statistical significance( $P<0.05$ ). Intra-operative blood loss in LLND group was obviously higher, but there was no significant difference ( $P=0.05$ ), which was caused by less included studies and small sample size. Furthermore, our studies found that the possibility of urinary dysfunction in NLLND group was lower than in the LLND group ( $P = 0.0002$ )

The argumentation intensity of our present study may be affected by the following factors: (1)the meta analysis was conditioned by the number of clinical trials and levels (Van Cutsem et al., 2009), while the present included studies involved only one prospective randomized study and the other fourteen studies were well-designed non-randomized controlled experiments, therefore methodological quality was inferior, lacked allocation concealment , the blind method was not adopted , follow up time was inconsistency, patients who are lost to follow-up were without reported and intent-to-treat (ITT) analysis was not carried out , Such limitations may lead to selection bias, implementation bias and measurement bias, thus the credibility of the results were affected.(2) selected standards of LLND in Japan were differ from that in Western Countries, they required that every patients with colorectal cancer undertook LLND and with or without preservation of nerve, while Western Countries rated preoperative radiochemotherapy more highly ,thereby ,these factors could influence the results.(3) these studies were completed in different clinical center, and the design of experiment ( DOE ), inclusion criteria, the levels of surgical dissection existed differences equally, these factors may affect the judgment of final results. (4) our present study included only Chinese and English literatures , therefore that may exist languages bias .(5)

the authors of original documents were often reluctant to offer inconclusive or negative results, moreover, partial documents could not be got original articles and were not included in this study, to a certain extent, existed publication bias. For reason given above, large-scale randomized controlled multi-center clinical trials are carried out for clearly defining the most effective Strategy for treating colorectal cancer by LLND.

As stated above, The results of our present meta analysis showed that LLND group did not have specific advantage in decreasing postoperative recurrence and prolonging survival time,. but LLND was associated with prolonged operation time, increased blood loss and elevated incidence of peri-operative complications and urinary and sexual dysfunction.

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