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ORIGINAL SCIENTIFIC REPORT

Impact of Lateral Pelvic Lymph Node Dissection on the Survival of Patients with T3 and T4 Low Rectal Cancer

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Abstract

Background The aim of this study was to clarify the survival benefit of lateral pelvic lymph node dissection (LPLND) for patients with pathological T3 and T4 (pT3/T4) low rectal cancer.

Methods We evaluated the impact of LPLND on survival for pT3/T4 low rectal cancer patients. The primary endpoint of the study was overall survival (OS). The large-scale database of the Japanese Society for Cancer of the Colon and Rectum registration system was accessed and the data were analyzed using a propensity score matching method based on the likelihood of receiving LPLND. Using seven covariates, the propensity scores were calculated with multivariate logistic regression. A total of 499 propensity score-matched pairs of patients were selected from the entire cohort of 1,840 patients who had received curative resection for pT3/T4 low rectal cancer between 1995 and 2004.

Results In the matched cohort, the 5-year OS of the patients who had and had not undergone LPLND were 68.9 and 62.0 %, respectively ($p = 0.013$; hazard ratio [HR], 0.755; 95 % confidence interval [CI], 0.604–0.944). The 5-year OS of the patients with node-negative disease who had and had not received LPLND differed statistically significantly (5-year OS were 82.1 and 71.4 %, respectively. $p = 0.006$; HR, 0.579; 95 % CI 0.389–0.862). However, those with node-positive disease did not differ significantly (5-year OS were 55.5 and 53.8 %, respectively. $p = 0.415$; HR 0.893; 95 % CI 0.681–1.172).

Conclusions The impact of LPLND on OS for patients with node-negative pT3/T4 low rectal cancer was suggested in this retrospective cohort study. To determine true benefits and harms of LPLND, further prospective studies may be warranted.

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Introduction

Lymph node (LN) metastasis is one of the most robust prognostic factors in colorectal cancer (CRC) [1–3]. There are two lymphatic pathways involved in low rectal cancer, namely superior and lateral drainage along the superior rectal artery to the inferior mesenteric artery, and the middle rectal artery to the internal iliac artery, respectively [4, 5]. Regarding the superior pathway, total mesorectal excision (TME) has contributed to an improvement in the oncological outcomes of rectal cancer, in terms of local control of the disease and long-term survival [6–10]. However, the effectiveness of surgical eradication of metastasis in the lateral pathway remains controversial.

In 1942, Grinnell et al. demonstrated that the main pathway in the lower rectum involves upward spread along the superior hemorrhoidal vessels, and lateral spread along the middle hemorrhoidal vessels to the internal iliac vessels, which function as a sub-pathway when the upward pathway has been blocked by extensive nodal metastases [5]. However, lateral pelvic lymph node (LPLN) metastasis has been reported to occur at a rate of 8.8–24 % in low rectal cancer [11–16], and those without upward spread in the mesorectum are not uncommon [17, 18]. In the past, some expert surgeons in Western countries have challenged the use of extended LN dissection, including lateral nodal spread, for the purpose of improving local control of this disease [19, 20]. In the West, however, this surgical approach is not widely disseminated partly because of a paucity of evidence regarding the survival benefits, a high operative morbidity rate, and sexual and urinary dysfunction. In contrast, Japanese surgeons have reported some benefits on oncological outcomes by such an extended procedure [12, 21–23]. Consequently, TME with LPLND has been regarded as a standard surgical procedure for a treatment of low rectal cancer in Japan [24]. The present study was conducted to clarify the degree of survival advantage associated with treatment involving LPLND in patients with surgically curable T3/T4 low rectal cancer using a Japanese large-scale multi-institutional database.

Patients and methods

Patients

The Japanese Society for Cancer of the Colon and Rectum (JSCCR) has a hospital-based registration system that originated in 1980. The member hospitals of the JSCCR voluntarily register clinical and pathological information regarding patients with CRC. The database currently contains detailed clinical and pathological information on over 170,000 CRC patients treated between 1974 and 2005 in accordance with Japanese classification for CRC [24]. However, the database does not contain information on operation-related data (such as operative time, amount of blood loss, duration of hospital stay, and so forth), operative morbidity, and functional results of surgery. As for an adjuvant chemotherapy, this database did not record the type of regimen, dose, or duration of administration. Furthermore, information of accurate site and timing of disease recurrences were insufficient to compute disease-free survival.

In this study, information on 1840 patients with pT3/4 lower rectal cancer was extracted from a total of 52,126 patients with CRC who had undergone surgery for CRC between 1995 and 2004, and was used for the analysis. Patients with the following characteristics were excluded from the analysis: multiple primary cancer ($n = 259$), multiple colorectal cancers ($n = 134$), remote metastasis ($n = 375$), histology other than adenocarcinoma ($n = 3$), no major rectal surgery ($n = 58$), unknown age ($n = 7$), unknown pathological LN status ($n = 125$), unknown follow-up information ($n = 64$), unknown LPLND status ($n = 151$), and ones who had preoperative adjuvant chemotherapy or radiotherapy ($n = 233$) (Fig. 1).

In this study, LPLNs were defined as LNs located along the internal iliac vessels, common iliac vessels, and obturator nerve according to the Japanese classification of CRC [24], and LPLN metastases were classified into Stage III [24]. Otherwise, clinical and pathological staging were classified according to the 7th TNM classification of UICC/AJCC [25]. Generally, LPLND has been performed following TME procedure in patients with cT3/4 lower rectal cancer in Japan. The indication to perform LPLND was decided by each institution's own judgment [24].

Statistical analysis

The significance of treatment with LPLND on overall survival (OS) was explored using the propensity score matching method to adjust for potential bias. We calculated propensity scores using multivariate logistic regression. Sex, age at surgery, cT-stage, cN-stage, preoperative serum carcinoembryonic antigen (CEA) level, adjuvant chemotherapy, and surgical methods were used as covariates. Using the propensity score with 1:1 nearest neighbor matching using a caliper of 0.01, a total of 998 patients were selected as the propensity score-matched cohort. We performed propensity-adjusted Cox regression analyses to determine the effect of LPLND on OS.

The statistical analysis was performed using SPSS Statistics version 22 (IBM Corporation, Somers, New York, USA), the SPSS plug-in PSMATCHING.3, and R version 2.15.0 (R Foundation for Statistical Computing; http://www.r-project.org). Continuous variables are

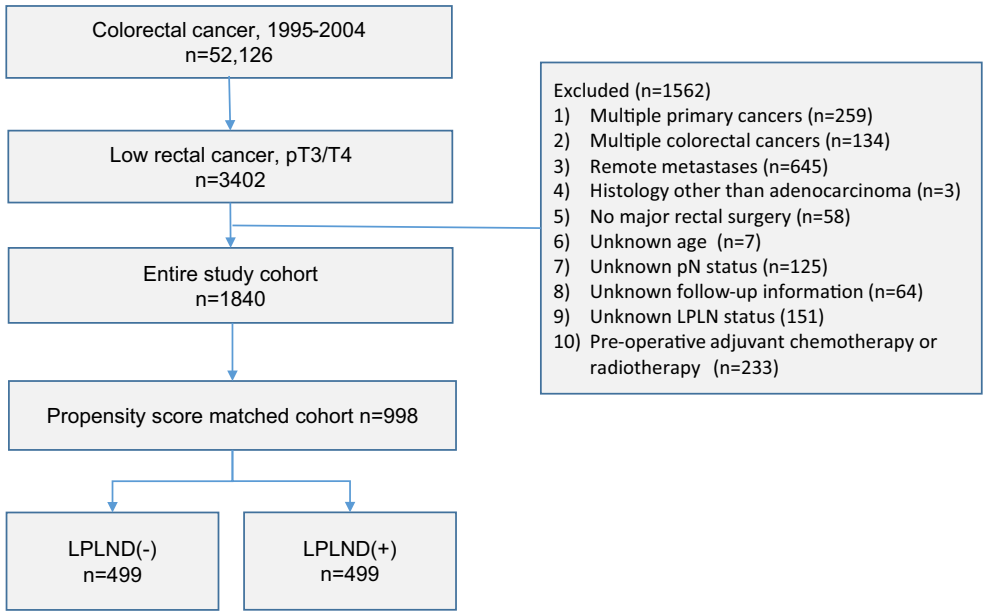

Fig. 1 Flow diagram of the entire study cohort and the propensity score-matched cohort

presented as median values. The Chi-square test was used to determine significant differences in the categorical variables between two groups. The Kaplan–Meier method was used to calculate the actual survival rate, and log-rank tests were performed to examine the associations between the survival time and the clinical variable. Variables found to be significant in univariate testing were subjected to Cox regression modeling to determine factors affecting OS. Statistical significance was established at $p < 0.05$ for all results.

Results

In a total of 1,840 eligible patients who underwent curative resection for pT3/T4 low rectal cancer, 1,264 (68.7 %) had undergone LPLND. Table 1 details the selected variables of the entire cohort and the propensity score-matched cohort. The entire cohort included 1,264 patients who had received LPLND and 576 patients (LPLND (+) group) who had not (LPLND (−) group). Both groups were evenly matched in terms of sex and preoperative serum CEA level; however, LPLND was more likely to have been performed in younger patients (<65 years; 60.3 vs. 44.3 %; $p < 0.01$). LPLND (+) group was significantly more likely to have experienced deeper tumor invasion > cT4 ($p < 0.001$), positive LNs ($p < 0.007$), administration of adjuvant chemotherapy ($p < 0.001$), and abdominoperineal resection (APR) ($p < 0.001$). In the propensity score-matched cohort, no significant differences in the baseline characteristics of the patients were observed between the two groups.

In the matched cohort, the 5-year OS of the LPLND (+) group was significantly higher than that of LPLND (−) group (5-year OS, 68.9 vs. 62.0 %; $p = 0.013$; HR 0.755; 95 % confidence interval, 0.604–0.944) (Fig. 2) as well as those in the entire cohort (data not shown). Subset analysis revealed that the benefit of LPLND (+) group on OS was observed in essentially all of the subgroups that were stratified by investigated variables with a few exceptions: female, less than 65 years, low level of preoperative serum CEA, adjuvant chemotherapy, cT4, positive regional LNs, positive LPLNs, and APR (Fig. 3). Although OS was significantly higher in LPLND (+) group with both cN0 and cN+, LPLND did not significantly increase OS of patients with pN + (or pStage III). Furthermore, it did not significantly increase the OS of patients with positive LPLN metastasis. The 5-year OS for 57 patients with positive LPLN and 442 patients with negative LPLN was 45.1 % (±7.1 %) and 71.9 (±2.3 %), respectively.

In pStage II patients, there was a significant difference in 5-year OS between LPLND (+) group and LPLND (−) group (5-year OS, 82.1 vs. 71.4 %; $p = 0.006$; HR 0.579; 95 % confidence interval, 0.389–0.862) (Fig. 4). In contrast, in pStage III population, 5-year OS did not differ whether they had received LPLND or not (5-year OS, 55.5 vs. 53.8 %; $p = 0.415$; HR 0.893; 95 % confidence interval, 0.681–1.172) (Fig. 5).

Table 1 Characteristics of patients who underwent curative surgery for pT3 or pT4 low rectal cancer

	Entire cohort ($n = 1840$)					Matched cohort ($n = 998$)				
	LPLND (−)		LPLND (+)		p value	LPLND (−)		LPLND (+)		p value
	$n = 576$		$n = 1264$			$n = 499$		$n = 499$		
Sex										
Male	368	63.9 %	859	68.0 %	0.086	334	66.9 %	356	71.3 %	0.132
Female	208	36.1 %	405	32.0 %		165	33.1 %	143	28.7 %	
Age at surgery										
<65	255	44.3 %	762	60.3 %	<0.001	240	48.1 %	235	47.1 %	0.751
≥65	321	55.7 %	502	39.7 %	<0.001	259	51.9 %	264	52.9 %	
cT										
≤cT2	64	11.1 %	51	4.0 %	<0.001	36	7.2 %	27	5.4 %	0.140
cT3	222	38.5 %	429	33.9 %		199	39.9 %	176	35.3 %	
cT4	275	47.7 %	761	60.2 %		254	50.9 %	289	57.9 %	
cTX	15	2.6 %	23	1.8 %		10	2.0 %	7	1.4 %	
cN										
cN0	227	39.4 %	410	32.4 %	0.007	194	38.9 %	200	40.1 %	0.826
cN+	334	58.0 %	829	65.6 %		295	59.1 %	287	57.5 %	
cNX	15	2.6 %	25	2.0 %		10	2.0 %	12	2.4 %	
Preoperative serum CEA level										
≤cut-off	261	45.3 %	568	44.9 %	0.122	227	45.5 %	239	47.9 %	0.635
>cut-off	235	40.8 %	559	44.2 %		211	42.3 %	207	41.5 %	
No examination	80	13.9 %	137	10.8 %		61	12.2 %	53	10.6 %	
Adjuvant chemotherapy										
No	353	61.3 %	647	51.2 %	<.001	292	58.5 %	306	61.3 %	0.366
Yes	223	38.7 %	617	48.8 %		207	41.5 %	193	38.7 %	
Operative methods										
LAR	274	47.6 %	473	37.4 %	<.001	230	46.1 %	235	47.1 %	0.556
APR	289	50.2 %	750	59.3 %		261	52.3 %	252	50.5 %	
Others	8	1.4 %	34	2.7 %		5	1.0 %	10	2.0 %	
Missing	5	0.9 %	7	0.6 %		3	0.6 %	2	0.4 %	

Left column: Entire cohort, Right column: propensity score-matched cohort

LAR low anterior resection; *APR* abdominoperineal resection

Discussion

Historically, LPLN metastasis has been regarded as a systemic disease in Western countries, because the prognosis has been reported to be extremely poor [26]. Furthermore, recent two meta-analyses by Georgiou et al. and Chen et al. that evaluated the benefits and adverse effects of LPLND have shown that LPLND did not increase OS nor decrease recurrence rates. Moreover, sexual and urinary dysfunction were significantly worse in patients who had undergone LPLND than those who had not (Table 2) [27, 28]. However, a major limitation of these meta-analyses was that almost all studies included were small-scale single-institution retrospective studies, and even prospective randomized controlled study evaluated a small number of patients.

The strength of the present study was the ability to access a large-scale multi-institutional database and to adjust confounders using propensity score-matched analysis; this is generally recognized as representing a quasi-randomized controlled trial. The study showed that the survival rate of the patients who had received LPLND for pT3/T4 low rectal cancer was superior to that of patients who had not received LPLND in the entire cohort. Our study also found that, in the propensity score-matched cohort, the OS of pT3/T4 low rectal cancer patients who had received LPLND was significantly longer than that for patients who had not received LPLND, with a relative

reduction in the risk of death of 6.9 % (Fig. 2). In the subset analysis, the HR for patients who had undergone LPLND among those male, aged ≥65 years, with a higher preoperative serum CEA level, no adjuvant chemotherapy, cT3, clinical any N-stage, pT3/T4, pN0, LPLN negative, and low anterior resection, was significantly lower than that for patients who had not undergone LPLND (Fig. 3). Although these results warrant further investigation, it is noteworthy that the HR of patients with pStage II who had received LPLND was significantly lower than that of patients who had not received LPLND (82.1 vs. 71.4 %; HR 0.579; 95 % confidence interval, 0.389–0.862; $p = 0.006$) (Fig. 4). A possible explanation for this finding may partly involve the result of stage migration, as well as resection of micrometastasis in the LPLNs. Coy et al. reported that 3/15 (20 %) patients with hematoxylin–eosin (HE) staining negative for LPLNs had occult metastases that were detected using immunohistochemical analysis with pancytokeratins [29]. Shimoyama also reported that among 57 patients with negative LPLNs after HE staining, cytokeratin staining-positive metastasis was detected in 19 (2.7 %) LNs from 11 (19.3 %) patients; these 11 patients with micrometastasis in the LPLNs exhibited a significantly high recurrence rate and a lower survival rate than micrometastasis-negative patients [30]. In this context, our results suggest that clinically latent LPLN micrometastasis in patients with T3/T4 low rectal cancer may benefit from prophylactic LPLND. Recently, Fujita et al. have reported the short-term outcome of a Japanese nationwide multicenter randomized controlled trial (JCOG0212 study), which evaluated the benefits and adverse effects of prophylactic LPLND for clinically negative LPLN low rectal cancer; the TME plus LPLND arm was compared with the TME-alone arm [31]. In this study, the incidence of grade 3 or 4 morbidities and urinary and sexual dysfunction were almost identical in both arms, although patients in the TME plus LPLND arm required a significantly longer operative time; this resulted in significantly greater blood loss than was experienced by the patients in the TME-alone arm. In

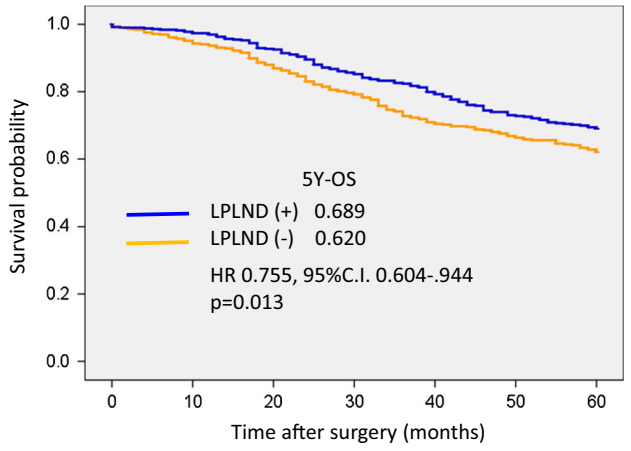

Fig. 2 Overall survival for patients with pT3/T4 low rectal cancer according to rectal surgery with and without LPLND in the propensity score-matched cohort

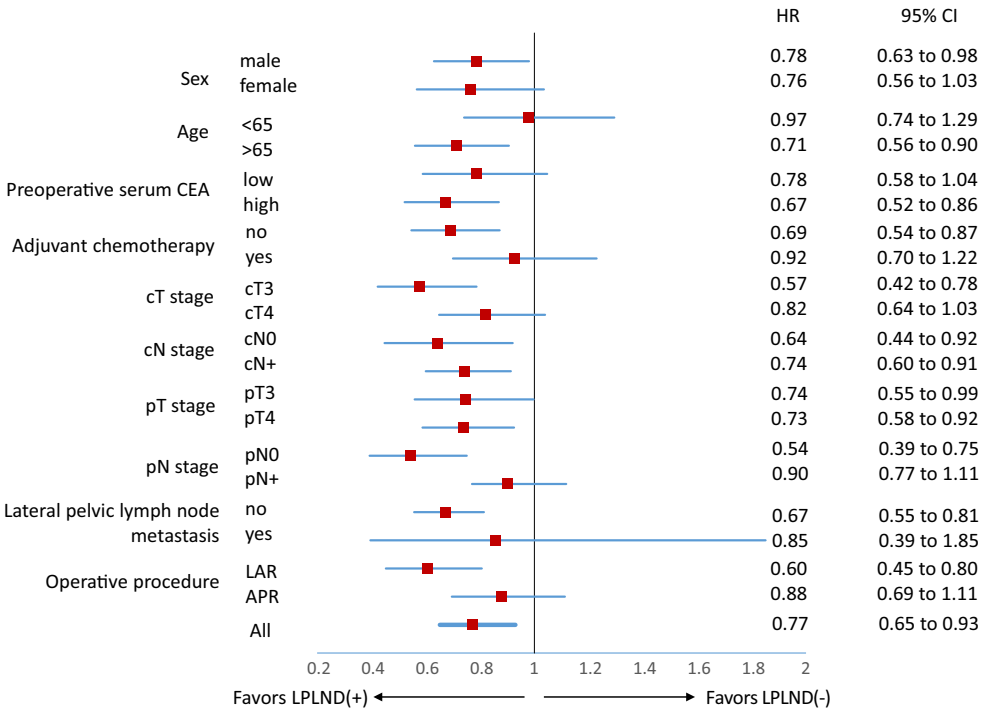

Fig. 3 Forrest plot showing adjusted hazard ratios (*squares*) and 95 % CI (*horizontal bars*) for overall survival rate in 998 low rectal cancer patients undergoing potentially curative resection surgery, according to rectal surgery with LPLND and without LPLND. *CEA* carcinoembryonic antigen; *LAR* low anterior resection; *APR* abdominoperineal resection. *First tier* indicates rectal surgery with LPLND; *second tier* indicates rectal surgery without LPLND

particular, LPLN metastasis was found in 26/351 (7 %) patients in the TME plus LPLND arm; the 5-year OS rate of patients with positive LPLNs who had received LPLND was 45.1 % [31]. This high OS rate was consistent with previous studies carried out by Japanese surgeons where the OS ranged from 24.1 to 43 % [32–36]. These findings are comparable with those from patients who had undergone R0 resection for liver and/or lung metastasis, suggesting that there are some patients with LPLN metastasis who can benefit from LPLND.

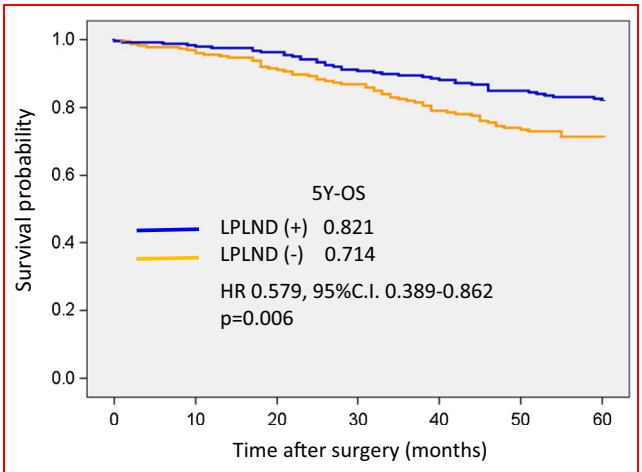

Fig. 4 Overall survival for patients with pT3/4 of pStage II low rectal cancer according to rectal surgery with and without LPLND in the propensity score-matched cohort

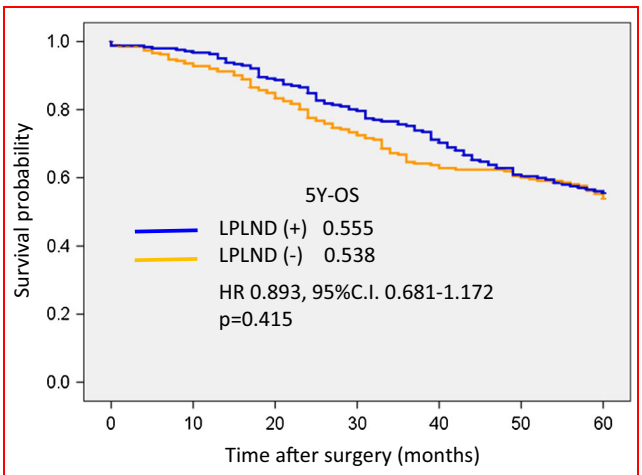

Fig. 5 Overall survival for patients with pT3/4 of pStage III low rectal cancer according to rectal surgery with and without LPLND in the propensity score-matched cohort

By contrast, LPLND did not significantly increase the OS of patients with LPLN metastasis in this study (Fig. 3). In general, the prognosis of patients who underwent LPLND is considered to be poorer than that of patients who did not. This may be the result of patient selection, in that LPLND is adopted for more advanced disease, especially for patients with clinically evident metastasis to the LPLNs, whose prognosis is almost equivalent to patients who receive R0 resection for stage IV disease [18]. This limited impact of LPLND on survival and patient selection could be the reason why LPLND did not significantly increase the OS in patients with positive LNs, even after adjusting for the available confounders using the propensity score-matched method. Although we should wait before reaching a definitive conclusion regarding LPLND for the treatment of clinically negative LPLN low rectal cancer until the long-term outcome of the JCOG0212 study is available, the present study offered some suggestive data regarding appropriate patient selection criteria for patients with both clinically negative and positive LPLNs, for whom LPLND may be beneficial.

Finally, several limitations of this study inherent to its retrospective nature and non-randomized design should be considered. These limitations include patient and treatment selection bias. The reasons patients were offered LPLND were not recorded in our database. Patients selected to undergo LPLND could have had more favorable clinical characteristics, including fewer comorbidities, better performance status, and a lower requirement for emergency surgery. Additionally, a non-randomized study may be confounded by other important contributing factors as a result of the lack of availability of sufficient information regarding variables, such as quality of surgery and pathological examination, which might have differed between each institute and individual surgeon. Furthermore, because patients who did not have follow-up information

Table 2 Recent reports of meta-analysis concerning compared to rectal surgery with and without LPLND

Author	Year	Number of patients		Number of studies			Improvement of OS	Urinary and sexual dysfunction
		LPLND (−)	LPLND (+)	RCT	Prospective	Retrospective		
Georgiou P	2009	2925	2577	1	3	16	Negative	Positive
Cheng H	2011	2457	2401	1	3	11	Negative	Positive

LPLND lateral pelvic lymph node dissection; *OS* overall survival; *RCT* randomized controlled trial

were excluded from the analyses, survival probabilities in the present study could have been over- or underestimated. In spite of these limitations, our findings were significant and warrant further investigations concerning both the benefits and adverse effects of this procedure.

Conclusion

In the current study, an improvement in the OS of node-negative pT3/T4 low rectal cancer patients after treatment with LPLND was suggested. To determine true benefits and harms of LPLND, further prospective studies may be warranted.

Compliance with Ethical standards

Conflict of interest The authors declare that they have no conflict of interest and grant support.

Ethics approval Ethics approval was obtained from the Tochigi Cancer Center's institutional review board, and for this type of study formal consent is not required.

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