Surgery 165 (2019) 586–592

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Effect of lateral lymph node dissection for mid and low rectal cancer: An ad-hoc analysis of the ACTS-RC (JFMC35-C1) randomized clinical trial

Eiji Oki, MD, PhD, FACS[a,*], Mototsugu Shimokawa, PhD[b], Koji Ando, MD, PhD[a], Akihiko Murata, MD, PhD[c], Takao Takahashi, MD, PhD[d], Kiyoshi Maeda, MD, PhD[e], Tetsuya Kusumoto, MD, PhD, FACS[f], Yoshinori Munemoto, MD, PhD[g], Ryota Nakanishi, MD, PhD[a], Yuichiro Nakashima, MD, PhD[a], Hiroshi Saeki, MD, PhD, FACS[a], Yoshihiko Maehara, MD, PhD, FACS[a]

[a] Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[b] Clinical Research Institute, Cancer Biostatistics Laboratory, National Kyushu Cancer Center, Fukuoka, Japan
[c] Department of Gastroenterological Surgery, Hirosaki University Graduate School of Medicine, Aomori, Japan
[d] Department of Surgical Oncology, Gifu University Graduate School of Medicine, Gifu, Japan
[e] Department of Surgical Oncology, Osaka City University Graduate School of Medicine, Osaka, Japan
[f] Department of Surgery, Gastrointestinal Center, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan
[g] Department of Surgery, Fukui-ken Saiseikai Hospital, Fukui, Japan

ARTICLE INFO

Article history:
Accepted 28 August 2018
Available online 9 October 2018

ABSTRACT

Background: Lateral lymph node dissection has been 1 of the standard treatments for mid and ow rectal cancer in Japan. The aim of this ad-hoc analysis was to evaluate the impact of lateral lymph node dissection on outcomes in the randomized clinical trial, referred to as the Adjuvant Chemotherapy for Stage II/III Rectal Cancer trial.

Methods: The Adjuvant Chemotherapy for Stage II/III Rectal Cancer trial was a randomized, phase III trial of adjuvant chemotherapy of 2 different oral fluoropyrimidines; 445 patients with lower rectal cancer were studied in this ad-hoc analysis out of 959 patients in total, 215 of whom underwent lateral lymph node dissection and 230 did not.

Results: There were no significant differences in background characteristics of the patients in the group, except for in age and number of dissected lymph nodes, between the lateral lymph node dissection and without lateral lymph node dissection groups. The age of the younger patients was often used to select candidates for lateral lymph node dissection (lateral lymph node dissection versus non–lateral lymph node dissection; 63.5 ± 8.9 vs 60.7 ± 9.4 [$P = .0017$]). Lateral lymph node dissection had no impact on relapse-free survival (hazard ratio = 0.941, 95% confidence interval: 0.696–1.271) or overall survival (hazard ratio = 0.858, 95% confidence interval: 0.601–1.224) in all patients with mid and low rectal cancer. In subset analysis, lateral lymph node dissection improved relapse-free survival in female patients and in patients with stage B/C or N3/4 disease. For cumulative recurrence across all patients, the proportion of patients with distant recurrence was slightly greater in the lateral lymph node dissection group but there was no difference in local recurrence.

Conclusion: This exploratory analysis did not show that lateral lymph node dissection improves relapse-free survival and overall survival in patients with mid and low rectal cancer. Lateral lymph node dissection may, however, have a prognostic impact on patients with highly invasive rectal cancer.

Introduction

Colorectal cancer is 1 of the most prevalent cancers worldwide, and rectal cancer accounts for 40% of all colorectal cancers.[1] Western countries have taken various approaches to its treatment, which includes conducting clinical studies of neoadjuvant

* Corresponding author: Kyushu University, Department of Surgery and Science, Graduate School of Medical Sciences 3-1-1, Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.
E-mail address: okieiji@surg2.med.kyushu-u.ac.jp (E. Oki).

https://doi.org/10.1016/j.surg.2018.08.027
0039-6060/

chemotherapy without radiotherapy and following the "watch and wait" philosophy[2]; however, the standard treatment for rectal cancer is total mesorectal excision (TME) after preoperative radiation (or chemoradiation) therapy.[3,4] Nevertheless, lateral pelvic lymph node metastases occur in 10%–25% of patients with rectal cancer, and they are associated with a greater incidence of local recurrence and decreased survival rates. Therefore, in Japan, a D3 dissection with preservation of the autonomic nerves, a technique in which the lateral pelvic lymph nodes are dissected while preserving the autonomic nerves of the pelvis, is a standard treatment option for mid and low rectal cancer[5,6]; this operative approach is thought to decrease the recurrence rate. Lateral lymph node dissection (LLND) is not performed routinely in Western countries because of the high morbidity associated with the operation and the uncertain oncologic benefit. Thus, there is a lack of international consensus on the appropriate management of lateral nodal disease.

To show the benefit of local control with LLND, many retrospective studies have examined the impact of LLND on the prognosis of mid and low rectal cancer.[7–9] A meta-analysis undertaken to assess the value of LLND in the operative management of rectal cancer showed that LLND did not confer a significant overall cancer-specific advantage, and seemed to be associated with increased urinary and sexual dysfunction.[10] Recently, however, a Japanese phase III study confirmed the noninferiority of TME alone compared with TME with LLND in terms of efficacy, but importantly, there was no statistically significant difference between the 2 techniques.[6] Therefore, LLND is still a standard option for lower rectal cancer in Japan.

The aim of this ad-hoc analysis was to evaluate the impact of LLND on outcomes in the Adjuvant Chemotherapy for Stage II/III Rectal Cancer (ACTS-RC) randomized clinical trial, which evaluated the superiority of S-1 to UFT (tegafur/uracil) in the adjuvant setting for stage II/III rectal cancer.[11] This trial was conducted in Japan and performance of an LLND was not mandatory. As a result, half of the patients with mid and low rectal cancer underwent LLND. Therefore, we evaluated the survival of these patients prospectively. This is the only study to investigate the clinical benefit of LLND prospectively, although it is important to realize that the patients were not randomized.

Methods

Patients

The inclusion criteria of ACTS-RC were histologically proven stage II or stage III rectal cancer (pathologicaT3–4N0 or any TN1–2) [TNM Classification, UICC 6th Edition, 2002]), a (systematic) D2 or D3 lymph node dissection, curatively resected, age 20–80 years, no previous chemotherapy or radiation therapy, ability to take oral drugs, and adequate organ function. A total of 959 patients were enrolled and randomized into S-1 or UFT arm at 222 sites from April 2006 to March 2009; 480 patients in the UFT arm and 479 patients in the S-1 arm were included in the primary endpoint analysis. A total of 445 patients with mid and low rectal cancer (which called Rb cancer in Japan) (stage I/II/IIIA/IIIB/IIIC: 1/130/10/59/165/80) from the 959 patients with rectal cancer in the ACTS-RC trial were analyzed in this ad-hoc analysis; 215 underwent LLND and 230 did not. UFT and S-1 therapy was prescribed for 110 and 105 patients with LLND, and for 111 and 119 patients without LLND, respectively (Fig 1). In upper rectal cancer, only 48 of the 500 patients (9.6%) were subjected to LLND; thus, patients with upper rectal cancer were excluded from this analysis. Many institutions selected the treatment plan for LLND according to the Japanese Society for Cancer of the Colon and Rectum guidelines.[12] In the guidelines, LLND is indicated when the distal border of the tumor is located distal to the peritoneal reflection and the tumor has invaded beyond the muscularis propria. In some institutions, additional requirements were applied, such as suspected lymph node metastasis in preoperative evaluation. Because the indications for LLND were decided by the preoperative diagnosis, many cases without LLND were included in this clinical trial. Therefore, no specific institutions omitted LLND, and there were few variations among institutions.

Procedures

Originally, patients were enrolled within 42 days after operation and started study treatment within 7 days after enrollment. UFT was administered orally at 1 of 2 dosages according to body surface area ([BSA] (500 mg/day for BSA <1.25 m^2; 600 mg/day for BSA ≥ 1.25 m^2). S-1 was administered orally at dosages according to the BSA (80 mg/day for BSA <1.25 m^2; 100 mg/day for BSA 1.25–1.50 m^2; 120 mg/day for BSA ≥ 1.50 m^2). The dose was decreased when the criteria for dose reduction were met. Recurrence was assessed using imaging by computed tomography, colonoscopy, and tumor markers. These assessments were performed every 4 months during the first 2 years after operation and once every 6 months from the third year onward. The median follow-up time of this trial was 5 years. There were only 38 cases (8.5%) censored for unknown reasons among 445 mid and low rectal cancer cases. Therefore, at least 91.5% cases were investigated continuously with computed tomography over 5 years.

Outcomes and statistical analysis

For the ACTS-RC study, the primary endpoint was relapse-free survival (RFS) and the secondary endpoints were overall survival (OS) and adverse events. OS was defined as the duration of time from the date of operation until death from any cause. Stratified log-rank tests with all stratification factors except for institution were used to assess superiority in terms of RFS in all enrolled patients (2-sided tests with a significance level of 5%). Patient background characteristics were summarized using descriptive statistics or contingency tables and compared using Student's *t*-test or Fisher's exact test. The RFS and OS curves were estimated using the Kaplan-Meier method, and differences in survival were compared using the log-lank test. Hazard ratios (HRs) were estimated using Cox regression models. To estimate the cumulative recurrences by each location (local/distant), respective recurrences were considered as events; recurrences other than these and deaths were censored at the time of their occurrence. These were reported as cumulative recurrences using the reverse Kaplan–Meier method. Distant recurrences were defined as hematogenous recurrences and lymphatic recurrences. *P* values correspond to 2-sided tests, and those $<.05$ were considered statistically significant. The calculations of statistical power of this ad-hoc analysis were not carried before treatment because this ad-hoc analysis was not preplanned.

Continous data are presented as means $\pm$ standard deviation. Data were analyzed using SAS 9.4 (SAS Institute, Cary, NC). This ACTS-RC trial is registered with UMIN-CTR (http://www.umin.ac.jp/ctr/[C000000385]).

Results

There were no significant differences in patient background characteristics, except for age and number of resected lymph nodes between the LLND and without-LLND groups (Table 1). Younger patients were often selected for LLND. The average age of the without-LLND group was 63.5 $\pm$ 8.9 years, whereas the average age with LLND group was 60.7 $\pm$ 9.4 years ($P = .0017$). The number of examined lymph nodes was 27.9 $\pm$ 7.9 in the LLND group and 14.7$\pm$ 9.23 in the without-LLND group. T stage and N stage

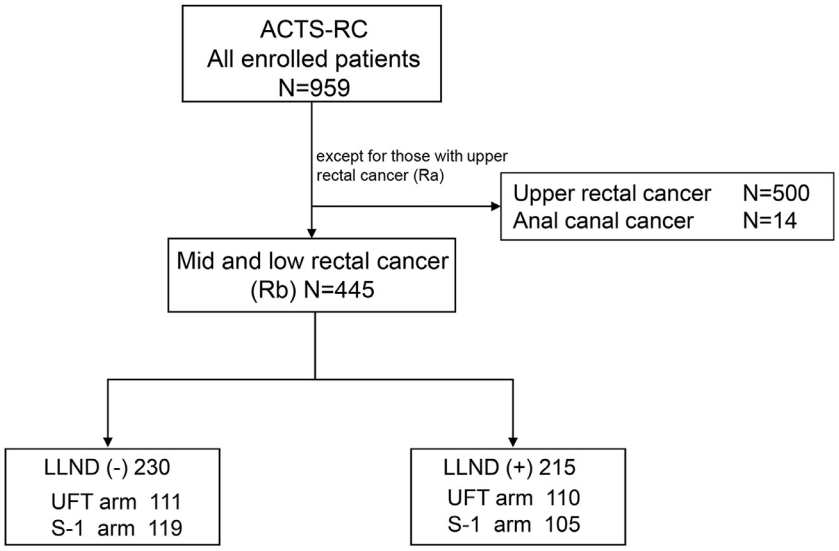


Fig. 1. CONSORT diagram.

Table 1
Characteristics of patients with mid and low rectal cancer

Factor		LLND (−)$n=230$ n (%)	LLND (+) $n=215$ n (%)	Total $n=445$ n (%)	P value
Age	Mean ± SD	63.5 ± 8.9	60.7 ± 9.4	62.1 ± 9.3	$P=.0017$
Sex	Male	151(65.7)	159(74.0)	310(69.7)	$P=.0635$
	Female	79(34.3)	56(26.0)	135(30.3)	
Pathology	Well	74(32.2)	60(27.9)	134(30.1)	$P=.1943$
	Mod	146(63.5)	135(62.8)	281(63.1)	
	Poor	5(2.2)	11(5.1)	16(3.6)	
	Mu	5(2.2)	9(4.2)	14(3.1)	
T	T1	14(6.1)	5(2.3)	19(4.3)	$P=.0849$
	T2	27(11.7)	23(10.7)	50(11.2)	
	T3	179(77.8)	169(78.6)	348(78.2)	
	T4	10(4.3)	18(8.4)	28(6.3)	
No. of lymph nodes examined	<12	99(43.0)	26(12.1)	125(28.1)	$P<.0001$
	≥12	131(57.0)	189(87.9)	320(71.9)	
N	N0	79(34.3)	62(28.8)	141(31.7)	$P=.1460$
	N1	117(50.9)	107(49.8)	224(50.3)	
	N2	34(14.8)	46(21.4)	80(18.0)	
Stage	I	1(0.4)	0(0.0)	1(0.2)	$P=.1293$
	IIA	74(32.2)	56(26.0)	130(29.2)	
	IIB	4(1.7)	6(2.8)	10(2.2)	
	IIIA	36(15.7)	23(10.7)	59(13.3)	
	IIIB	81(35.2)	84(39.1)	165(37.1)	
	IIIC	34(14.8)	46(21.4)	80(18.0)	
Operation	LAR	118(51.3)	93(43.3)	211(47.4)	$P=.3323$
	Hartmann	1(0.4)	1(0.5)	2(0.4)	
	APR	104(45.2)	112(52.1)	216(48.5)	
	Others	7(3.0)	9(4.2)	16(3.6)	
Extent of lymph node dissection	D1	3(1.3)	2(0.9)	5(1.1)	$P<.0001$
	D2	161(70.0)	33(15.3)	194(43.6)	
	D3	66(28.7)	180(83.7)	246(55.3)	
Treatment group	UFT	111(48.3)	110(51.2)	221(49.7)	$P=.5698$
	S-1	119(51.7)	105(48.8)	224(50.3)	

Well, well differentiated adenocarcinoma; Mod, moderately differentiated adenocarcinoma; Poor, poorly differentiated adenocarcinoma; Muc, mucinous adenocarcinoma.

were slightly higher in the LLND group but were not significant. In the Supplemental Table, the patient background characteristics of the full cohort are shown.

Patients with LLND showed better survival; however, this was not significant in terms of RFS in the group with mid to low rectal cancer (HR = 0.941, 95% CI: 0.696–1.271; Fig 2, *A*) and OS (HR = 0.858, 95% CI: 0.601–1.224; Fig 2, *B*). In Supplemental Fig 1, *A* and *B*, the RFS and OS of the full cohort, including also the upper rectal cancers, are shown. In the subgroup analysis of RFS (Fig 3), a small interaction was observed between allocated tumor invasiveness and lymph node metastasis. The HR of T3–4 patients was 0.911 (95% CI: 0.653–1.271), and that of N1–2 patients was 0.838 (95% CI: 0.603–1.165). In patients with stage IIIB/C disease, LLND improved RFS (HR = 0.762, 95% CI: 0.533–1.091; Fig 4). This trend was the same in both the S-1 (HR = 0.766, 95% CI: 0.449–1.306) and UFT arms (HR = 0.790, 95% CI: 0.487–1.283; log-rank $P=.0268$), despite the better RFS in the S-1 arm than in the UFT arm (Supplemental Fig 2). This finding means that the power and efficacy of adjuvant chemotherapy were different from that of LLND. LLND did not show a major impact on OS in patients

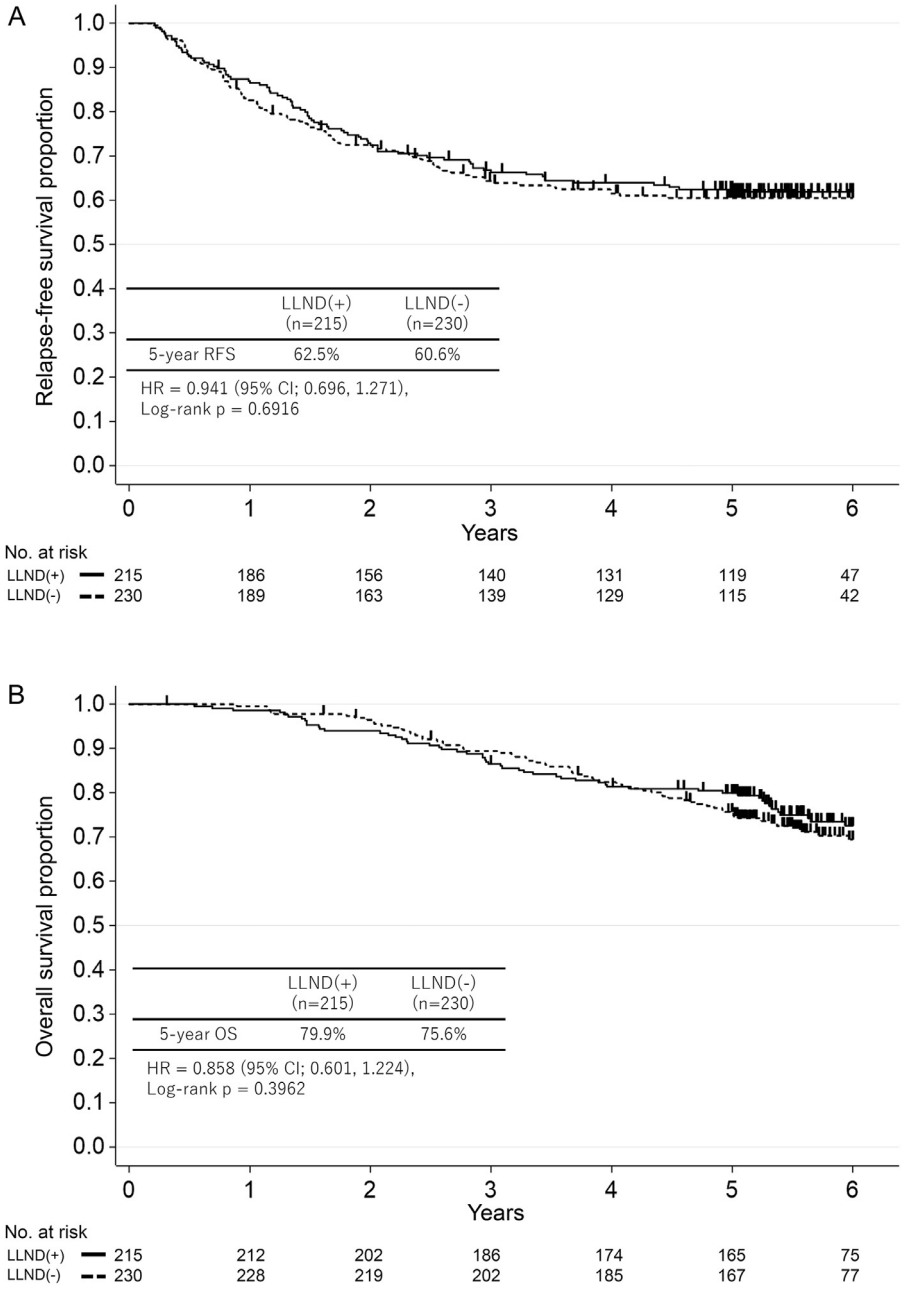


Fig. 2. (*A*) RFS (*solid line*: patient with LLND; *dotted line*: patient without LLND); (*B*) OS (*solid line*: patient with LLND; *dotted line*: patient without LLND).

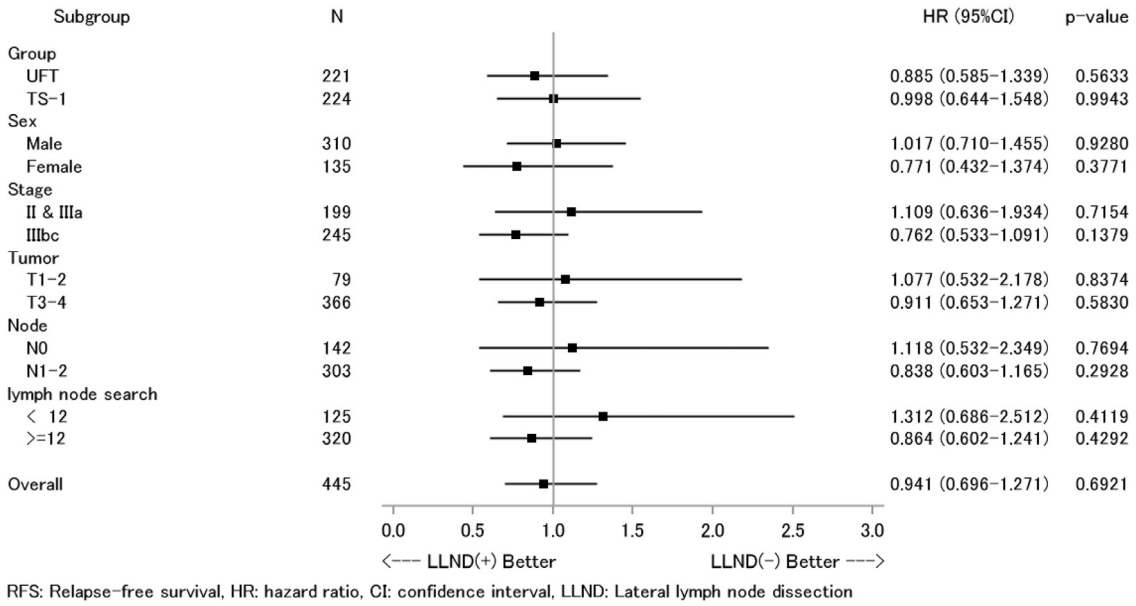
with stage IIIB/C disease (HR = 0.763, 95% CI; 0.503–1.157; log-rank $P = .2011$), which is similar to adjuvant chemotherapy[11] (Supplemental Fig 3).

The 5-year cumulative rate of local recurrence was 18.5% in patients with LLND and 19.2% in the non-LLND group (HR = 1.028, 95% CI: 0.632–1.672), whereas the 5-year cumulative rate of distant recurrence was 30.7% in the LLND group and 27.4% in the non-LLND group (HR = 1.114, 95% CI: 0.771–1.608; Fig 5).

Discussion

Although lateral lymphatic flow from the rectum has been identified, controversy remains concerning the appropriate treatment of metastatic lateral pelvic lymph nodes (LPLN) in locally advanced rectal cancer. In Japan, prophylactic or therapeutic LLND is recommended routinely for advanced mid and low rectal cancer because a considerable number of patients develop LPLN recurrence.[8,12–14] Surgeons in many or most Western countries prefer preoperative chemoradiotherapy (CRT) to manage metastatic LPLN because the rate of LPLN metastasis is relatively low; CRT is believed to be as effective as LPLN and avoids the complications of LLND, the most common of which is urinary dysfunction.[10,15] Recently, a Japanese group reported the results of the Japanese Clinical Oncology Group (JCOG) 0212, a randomized trial of TME with or without LLND for clinical stage II/III lower rectal cancer with clinically negative lateral nodes.[6] The results did not show non-inferiority in terms of OS with TME without LLND compared to TME with LLND. Also, this study did not show a survival advantage of LLND.

We examined the prognostic benefit of LLND for rectal cancer, comparing patients treated with and without LLND in the ACTS-RC phase III trial. In Japan, LLND was usually indicated for Rb (rectum below the peitoneal reflection) rectal cancer



RFS: Relapse–free survival, HR: hazard ratio, CI: confidence interval, LLND: Lateral lymph node dissection

Fig. 3. Subset analysis of RFS: HR, CI.

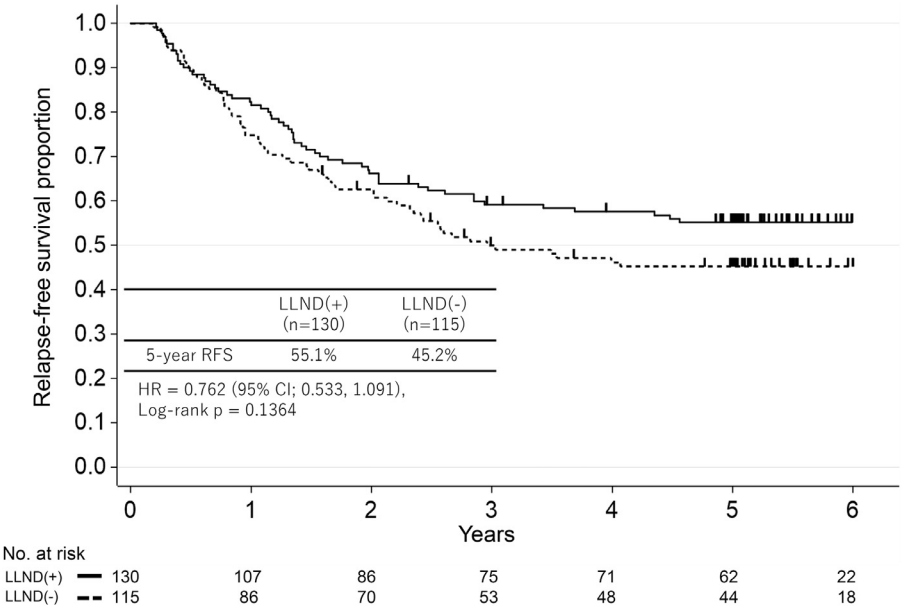


Fig. 4. RFS of patients with stage BC disease (*solid line*: patients with LLND; *dotted line*: patients without LLND).

that invaded the muscle of the rectal wall. Rb rectal cancer is defined as tumors with a lower margin below the peritoneal reflection. In this analysis, an Ra (rectum above the peritoneal reflection) tumor was defined as a tumor mainly located above the peritoneal reflection, and an Rb tumor was defined as a tumor mainly located below the peritoneal reflection. Therefore, in our study, we analyzed the role of LLND in only the Rb tumors, which involved the mid to low rectum, for this ad-hoc analysis. Though the procedure with and without LLND was not preplanned, the patients' backgrounds in the 2 groups (with LLND and without LLND) were balanced, and the survival of the patients was investigated prospectively as a clinical trial. As a result, RFS and OS did not improve in patients with LLND in this ad-hoc analysis.

The subgroup analysis of RFS, however, did show some interesting findings. There were some interactions in stage IIIBC and female patients. Tumor invasiveness and lymph node metastasis also had weak interactions. The JCOG0212 randomized trial also showed a small interaction of LLND with stage III, lymph node metastasis and female patients in the subset analysis.[6] The subset analysis of our study and JCOG0212 have very similar findings. Another Japanese study has showed the advantage of LLND for T3/4 disease.[16] We are unable to provide a reasonable explanation for the interaction between female sex and LLND, but the incidence of lateral lymph node metastasis has been reported to be more frequent in women than men in a large-scale cohort study[17]; thus, it is possible that lateral lymph node metastasis is more frequent in women. To prove the importance of LLND, a prospective study of only female patients with lymph node metastasis and T3/4 in preoperative diagnosis is needed.

The proportion of patients experiencing cumulative distant recurrence was slightly greater in the LLND group even though the local recurrence rate was not different. In the JCOG0212 random-

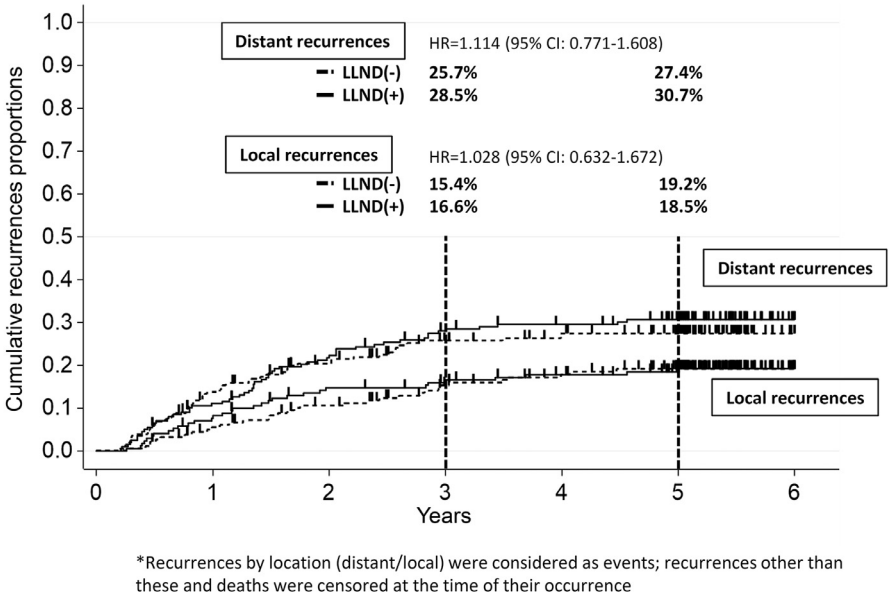


Fig. 5. Cumulative recurrences by location (*solid line*: patients with LLND; *dotted line*: patients without LLND).

ized study, Fujita et al reported that only local RFS improved significantly, and the RFS and OS of all patients were not different between the LLND and non-LLND groups.[6,18] Therefore, poor control of distant metastasis in LLND is one of the reasons for the lack of improvement of OS and RFS in LLND.

The limitations of this study are as follows. These analyses were performed in the ACTS-RC trial, in which patients only received fluoropyrimidine as adjuvant chemotherapy; therefore, caution should be taken when interpreting these results for use in clinical practice. Patients with and without LLND were not randomized, and we have no information on preoperative patient characteristics. Our analyses used pathologic characteristics for the subgroup analysis because clinical diagnoses were not collected in the case report form of the ACTS-RC study. It may be easier to diagnose more advanced stage cancer in the LLND group with a greater number of dissected lymph nodes.

Conclusion

We believe our study is the only ad-hoc analysis to investigate the advantage of LLND in patients included in a randomized phase III trial comparing adjuvant chemotherapy regimens without preoperative CRT. Although the oncologic effect of LLND was not elucidated clearly in all patients with mid and low rectal cancer, subset analysis suggested that specific cases, such as those in female patients and highly invasive tumors, were potential candidates for LLND.

Acknowledgments

We thank all the patients, their families, the investigators, and the medical staff.

Conflicts of interest

The ACTS-RC trial was supported by JFMC with funding from Taiho Pharmaceutical Co. Ltd, Japan, under a research contract. Eiji Oki has received honoraria for lecturing from Taiho Pharmaceutical Co, Ltd, Yakult Honsha Co, Ltd, Merck Serono, Takeda Pharmaceutical Co, Ltd, and Chugai Pharmaceutical Co, Ltd. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.surg.2018.08.027.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136:E359–E386.
2. Dossa F, Chesney TR, Acuna SA, Baxter NN. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2017;2:501–513.
3. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *The Lancet Oncology*. 2011;12:575–582.
4. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery—the clue to pelvic recurrence? *The British Journal of Surgery*. 1982;69:613–616.
5. Kinugasa T, Akagi Y, Ochi T, Ishibashi Y, Tanaka N, Oka Y, et al. Lateral lymph-node dissection for rectal cancer: meta-analysis of all 944 cases undergoing surgery during 1975–2004. *Anticancer Research*. 2013;33:2921–2927.
6. Fujita S, Mizusawa J, Kanemitsu Y, Ito M, Kinugasa Y, Komori K, et al. Mesorectal excision with or without lateral lymph node dissection for clinical stage II/III lower rectal cancer (JCOG0212): a multicenter, randomized controlled, noninferiority trial. *Annals of Surgery*. 2017;266:201–207.
7. Yano H, Moran BJ, Watanabe T, Sugihara K. Lateral pelvic lymph-node dissection: still an option for cure. *The Lancet Oncology*. 2010;11:114.
8. Akiyoshi T, Watanabe T, Miyata S, Kotake K, Muto T, Sugihara K. Results of a Japanese nationwide multi-institutional study on lateral pelvic lymph node metastasis in low rectal cancer: is it regional or distant disease. *Annals of Surgery*. 2012;255:1129–1134.
9. Akiyoshi T, Ueno M, Matsueda K, Konishi T, Fujimoto Y, Nagayama S, et al. Selective lateral pelvic lymph node dissection in patients with advanced low rectal cancer treated with preoperative chemoradiotherapy based on pretreatment imaging. *Annals of surgical oncology*. 2014;21:189–196.
10. Georgiou P, Tan E, Gouvas N, Antoniou A, Brown G, Nicholls RJ, et al. Extended lymphadenectomy versus conventional surgery for rectal cancer: a meta-analysis. *Lancet Oncol*. 2009;10:1053–1062.
11. Oki E, Murata A, Yoshida K, Maeda K, Ikejiri K, Munemoto Y, et al. A randomized phase III trial comparing S-1 versus UFT as adjuvant chemotherapy for stage II/III rectal cancer (JFMC35-C1: ACTS-RC). *Ann Oncol*. 2016;27:1266–1272.
12. Watanabe T, Muro K, Ajioka Y, Hashiguchi Y, Ito Y, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. *Int J Clin Oncol*. 2018;23:1–34.
13. Kinugasa T, Akagi Y, Shirouzu K. Benefit of lateral lymph node dissection for rectal cancer: long-term analysis of 944 cases undergoing surgery at a single center (1975–2004). *Anticancer Research*. 2014;34:4633–4639.
14. Kanemitsu Y, Komori K, Shida D, Ochiai H, Tsukamoto S, Kinoshita T, et al. Potential impact of lateral lymph node dissection (LLND) for low rectal cancer on

prognoses and local control: a comparison of 2 high-volume centers in Japan that employ different policies concerning LLND. *Surgery*. 2017;162:303–314.
15. Min BS, Kim JS, Kim NK, Lim JS, Lee KY, Cho CH, et al. Extended lymph node dissection for rectal cancer with radiologically diagnosed extramesenteric lymph node metastasis. *Annals of Surgical Oncology*. 2009;16:3271–3278.
16. Ozawa H, Kotake K, Hosaka M, Hirata A, Sugihara K. Impact of lateral pelvic lymph node dissection on the survival of patients with T3 and T4 low rectal cancer. *World Journal of Surgery*. 2016;40:1492–1499.
17. Akiyoshi T, Watanabe T, Miyata S, Kotake K, Muto T, Sugihara K. Results of a Japanese nationwide multi-institutional study on lateral pelvic lymph node metastasis in low rectal cancer: is it regional or distant disease? *Ann Surg*. 2012;255:1129–1134.
18. Fujita S, Yamamoto S, Akasu T, Moriya Y. Prognostic factors of rectal cancer patients with lateral pelvic lymph node metastasis. *Hepato-gastroenterology*. 2012;59:2494–2497.