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Predictive factors of pathological lateral pelvic lymph node metastasis in patients without clinical lateral pelvic lymph node metastasis (clinical stage II/III): The analysis of data from the clinical trial (JCOG0212)

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ABSTRACT

Background: Mesorectal excision (ME) is the standard surgical procedure for lower rectal cancer. However, in Japan, total or tumor-specific ME with lateral pelvic lymph node dissection (LLND) is the standard surgical procedure for patients with clinical stages II or III lower rectal cancer, because lateral pelvic lymph node metastasis occasionally occurs in these patients. The aim of study was to elucidate the predictive factors of pathological lateral pelvic lymph node metastasis in patients without clinical lateral pelvic lymph node metastasis.

Methods: Data form the clinical trial (JCOG0212) was analyzed. The JCOG0212 was a randomized controlled trial to confirm the non-inferiority of mesorectal excision alone to mesorectal excision with lateral lymph node dissection for clinical stage II/III patients who don't have clinical lateral pelvic lymph node metastasis in terms of relapse free survival. This study was conducted at a multitude of institution33 major hospitals in Japan. Among the 351 patients who underwent lateral lymph node dissection in the JCOG0212 study, 328 patients were included in this study. Associations between pathological lateral pelvic lymph node metastasis and preoperative and postoperative factors were investigated. The preoperative factors were age, sex, clinical stage, tumor location, distance from anal verge, tumor size, and short-axis diameter of lateral pelvic lymph node on computed tomography and the postoperative factors were pathological T, pathological N, and histological grade.

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Results: Among the 328 patients, 24 (7.3%) had pathological lateral pelvic lymph node metastasis. In multivariable analysis of the preoperative factors, patient age ($p = 0.067$), tumor location ($p = 0.025$), and short-axis diameter of lateral pelvic lymph node ($p = 0.002$) were significantly associated with pathological lateral pelvic lymph node metastasis.
Conclusions: Patient age, tumor location, and short-axis diameter of lateral pelvic lymph node were predictive factors of pathological lateral pelvic lymph node metastasis.

Introduction

Mesorectal excision (ME) is the standard surgical procedure for lower rectal cancer [1]. However, in Japan, total or tumor-specific ME with lateral pelvic lymph node dissection (LLND) is the standard surgical procedure for patients with clinical stages II or III lower rectal cancer, because lateral pelvic lymph node metastasis occasionally occurs in these patients [2]. Therefore, we conducted a randomized controlled trial (JCOG0212, UMIN-CTR, number C000000034) to confirm the non-inferiority of ME alone in terms of relapse free survival and the trial concluded that the non-inferiority of ME alone to ME with LLND could not be confirmed in the intent-to-treat analysis.[3 4]

Generally, enlargement of lateral pelvic lymph nodes can be detected by computerized tomography (CT) or magnetic resonance imaging (MRI) and can help predict whether or not metastasis has occurred. A boundary value, which can help to assess how pronounced lateral pelvic lymph metastasis is, has been examined in retrospective studies [5–13]. However, the factors have not been investigated in prospective studies.

Therefore, we investigated the predictive factors of pathological lateral pelvic lymph node metastasis in patients without clinical lateral pelvic lymph node metastasis using the data from JCOG0212 study [3].

Materials and methods

Inclusion criteria of the JCOG0212 study have been reported previously [3,4]. Eligibility criteria included histologically proven rectal cancer at clinical stage II or III; main lesion located in the rectum, with the lower margin below the peritoneal reflection; no lateral pelvic lymph node enlargement (i.e., lymph nodes with a short-axis diameter of <10 mm on CT or MRI); Eastern Cooperative Oncology Group performance status 0 (fully active) or 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature); and age 20–75 years.

A total of 701 patients were randomized to the ME with LLND group ($n = 351$) or the ME alone group ($n = 350$). The patients in the ME alone group were excluded in this study, because pathological lateral pelvic lymph node metastasis was not examined and 23 patients in the ME with LLND group were excluded (20 were excluded because data of short-axis diameter of lateral pelvic lymph node were missing and 3 were excluded because data of distance from anal verge were missing). Finally, 328 patients in the ME with LLND group were included in this study (Fig. 1).

Preoperative factors including age (<60 vs. ≥60 years, since the median was 60 years), sex (male vs. female), clinical stage (II vs. III), tumor location (Ra: tumor center located above peritoneal reflection vs. Rb: tumor center located below peritoneal reflection), distance form anal verge (<5 cm vs. ≥5 cm, since the median was 5 cm), tumor size (<5 cm vs. ≥5 cm, since the median was 5 cm), and size of lateral pelvic lymph nodes on preoperative CT with 5 mm or less thick sections (<5 mm vs. ≥5 mm) were investigated. The size of lateral pelvic lymph nodes was the largest short-axis diameter of lateral pelvic lymph nodes. In many retrospective studies, a short-axis cutoff of 5 mm was used for lateral pelvic lymph node diagnosis. Therefore, a short-axis cutoff of 5 mm was used in this study [5,6,14]. Postoperative factors including pathological T (pT1–2 vs. pT3–4), pathological N (pN0–1 vs. pN2), and histological grade (G1 vs. G2 vs. G3-4) were investigated.

Statistical analysis

Statistical analysis was performed using Fisher's exact test for categorical variables as an univariable analysis. Multivariable logistic regression analysis with a stepwise selection method with an alpha value of 0.1 was subsequently performed to identify factors considered to have an influence on lymph node metastasis. Statistical significance was set at two-sided $p < 0.05$.

Results

Of the 328 patients, 24 (7.3%) had pathological lateral pelvic lymph node metastasis. In univariable analysis of preoperative factors, age ($p = 0.055$), tumor location ($p = 0.007$), and short-axis diameter of lateral pelvic lymph node on CT ($p = 0.001$) were significantly associated with pathological lateral pelvic lymph node metastasis (Table 1). In multivariable analysis of the preoperative factors, tumor location Rb ($p = 0.034$, odds ratio: 8.95), and size of lateral pelvic lymph node > 5 mm ($p = 0.003$, odds ratio: 4.06) were significantly associated with pathological lateral pelvic lymph node metastasis.

In univariable analysis of postoperative factors, pT($p = 0.001$), pathological N2 ($p < 0.001$), and histological grade ($p = 0.031$) were significantly associated with pathological lateral pelvic lymph node metastasis. In multivariable analysis of the pre and postoperative factors, tumor location Rb ($p = 0.025$, odds ratio: 10.84), size of lateral pelvic lymph node > 5 mm ($p = 0.002$, odds ratio: 5.07), pathological N2 ($p < 0.001$, odds ratio: 5.10) and histological grade 3–4 ($p = 0.011$, odds ratio: 11.52) were significantly associated with pathological lateral pelvic lymph node metastasis. pT could not be evaluated owing to the lack of pathological lateral pelvic lymph node metastasis in pT1–2 cases.

Discussion

Several previously reported papers which included the patients who had clinical lateral pelvic lymph node metastasis. demonstrated the predictive factors of lateral pelvic lymph node metastasis in rectal cancer patients [5–14].However, these studies were based on retrospectively collected data and this study is the first study of the risk factors of lateral pelvic lymph node metastasis using prospectively collected data in a clinical trial. The findings of the previous reports and present study of the predictive factors of

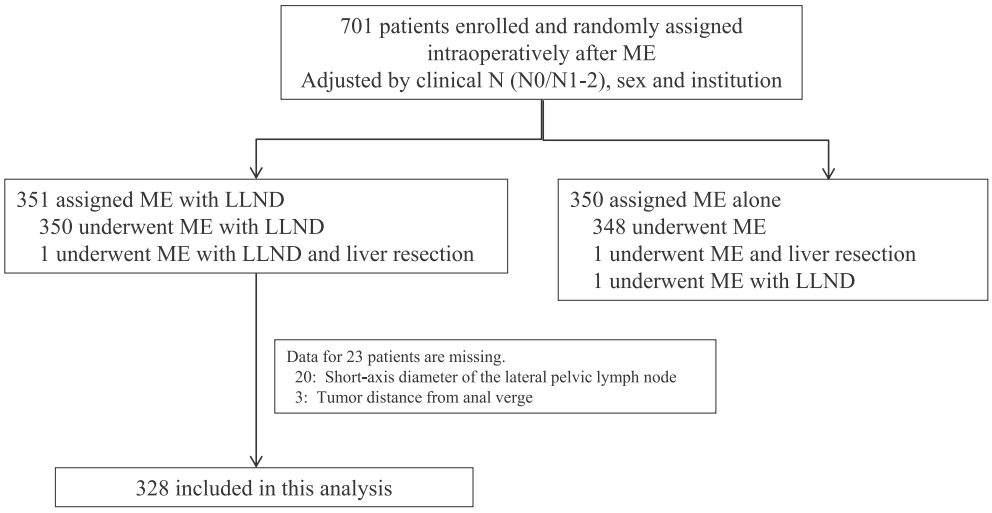

Fig. 1. Patients flow diagram for this study.

Table 1
Univariable and multivariable analysis of preoperative and postoperative factors.

	Lateral pelvic lymph node metastasis	Univariable	Multivariable with preoperative factors		Multivariable with pre and postoperative factors	
		p	*p*	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)
Age						
<60(n = 165)	17 (10.3%)	0.055	0.058	1		1
≥60(n = 163)	7 (4.3%)			0.40 (0.16–1.03)	0.067	0.39 (0.15–1.07)
Sex						
Male(n = 221)	18 (8.1%)	0.50				
Female(n = 107)	6 (5.6%)					
Clinical Stage						
II(n = 173)	10 (5.8%)	0.29				
III(n = 155)	14 (9.0%)					
Tumor location						
Ra(n = 89)	1 (1.1%)	0.007	0.034	1		1
Rb(n = 239)	23 (9.6%)			8.95 (1.18–68.04)	0.025	10.84 (1.35–86.80)
Distances from anal verge						
<5 cm(n = 138)	14 (10.1%)	0.13				
≥5 cm(n = 190)	10 (5.3%)					
Tumor size						
<5 cm(n = 168)	15 (8.9%)	0.29				
≥5 cm(n = 160)	9 (5.6%)					
Size of lateral pelvic lymph node						
<5 mm(n = 286)	15 (5.2%)	0.001	0.003	1		1
≥5 mm(n = 42)	9 (21.4%)			4.06 (1.59–10.34)	0.002	5.07 (1.81–14.25)
pT						
pT1-pT2(n = 86)	0	0.001				
pT3-pT4(n = 218)	24(9.9%)					
pN						
pN0-pN1(n = 252)	12(4.5%)	<0.001				1
pN2(n = 52)	12(18.8%)				<0.001	5.10 (1.98–13.14)
Histological grade						
G1(n = 99)	4(3.9%)	0.031				1
G2(n = 196)	17(8.0%)				0.11	2.75 (0.80–9.42)
G3-4(n = 9)	3(25.0%)				0.011	11.52 (1.73–76.45)

*Ra: Tumor center located above the peritoneal reflection, Rb: Tumor center located below the peritoneal reflection.

lateral pelvic lymph node metastasis are summarized in Table 2.

The predictive factors in the previous studies and this study were age, sex, tumor location, size of lateral pelvic lymph node, pT, pathological N2, and histological grade. It was easily suspected that the tumor location might be a predictive factor from the lymphatic channels in pelvic organ [15]. From previous reports, the post-operative pathological N2 and histological grade were reasonably given as the predictive factors. There is no obvious reason why the age was a predictive factor, but Ogawa et al. [14] dealt with the age as a predictive factor. Several studies have reported lateral pelvic lymph node cutoffs from 5 mm to 8 mm. Yano et al. [16] reported that 109 patients were preoperatively assessed with 5-mm-thick sections on CT examination, and high accuracy was obtained with regard to the concordance rates between the short-axis diameter of lateral pelvic lymph node and the histopathologic findings, with a sensitivity of 95% and specificity of 94%. The study by Fujita et al. [5] defined 5 mm as the cutoff. Akiyoshi et al. [6] defined 8 mm as the cutoff for the maximum short-axis diameter of the lateral pelvic

Table 2
Summary of the reported risk factors of pathological lateral pelvic lymph node metastasis.

Author	Years	Number of patients	Number of patients with pathological lateral pelvic lymph node	Preoperative factors				Postoperative factors		
				Age	Gender	Tumor location	Size of lateral pelvic lymph node(cutoff)	pT	pN	Histological grade
Ueno et al.	2005	237	41 (17.3%)			○	NA		○	○
Sugihara et al.	2006	930	129 (13.9%)		○(female)	○	NA		○	
Kobayashi et al.	2009	784	117 (14.9%)		○(female)		NA		○	○
Fujita et al.	2009	210	47 (22.4%)			○	○(5 mm)		○	○
Tan et al.	2010	1046	113 (10.8%)		○(female)		NA	○	○	○
Akiyoshi et al.	2012	5789	655 (11.3%)		○(female)		NA	○	○	○
Kinugasa et al.	2013	450	59 (13.1%)				NA		○	
Akiyoshi et al.	2015	279	77 (27.6%)		○(female)		○(8 mm)		○	
Nagayoshi et al.	2016	90	14 (15.6%)				NA		○	
Ogawa et al.	2016	230	39 (17.0%)	○(<64)			○(5 mm)		○	○
Present study (JCOG0212)		328	24 (7.3%)	○(<60)		○	○(5 mm)		○	○

○: Risk factor in each papers. NA: Data not available.

lymph nodes determined using MRI before and after CRT based on a receiver operating characteristics (ROC) curve analysis in order to predict lateral pelvic lymph node metastasis. The area under the ROC curve (AUC) was 0.86. The cutoff of 8 mm had a sensitivity of 68% and a specificity of 85%. Ogawa et al. [14] compared 5 mm and 10 mm according to the histological diagnosis, and the AUC value was significantly higher at a cutoff of 5 mm than at a cutoff of 10 mm; thus, a cutoff of 5 mm was adopted [13]. Kim et al. [17] reported the largest long-axis diameter, largest short-axis diameter, and long-to-short axis diameter ratio and concluded that it was better to select the largest short-axis diameter. According to these results, a cutoff value of 5 mm of the largest short-axis diameter of lateral pelvic lymph node was selected in this study.

The short-axis diameter of lateral pelvic lymph node was an important predictive factor of lateral pelvic lymph node metastasis, thus, accurate preoperative diagnosis of the diameter is essential. However, the accuracy of CT with 5 mm thick sections was not satisfactory because the accuracy was 87% (286/328). The accuracy of 87% was not enough to diagnose lateral pelvic lymph node metastasis. Therefore, the Japanese observational study to evaluate the accuracy of preoperative imaging diagnosis for lateral pelvic lymph node metastasis in rectal cancer is currently underway (JCOG1410A; JUPITER study, UMIN-CTR, number UMIN000016909). In the study, the short-axis diameter of lateral pelvic lymph node is being estimated using both CT with 1-mm-thick or 2.5-mm-thick in addition to 5-mm-thick sections and MRI with 3-mm-thick or 5-mm-thick. This study is expected to improve the diagnostic accuracy of lateral pelvic lymph node metastasis.

However, it was difficult to accurately detect metastatic lymph nodes in terms of the size of the lateral pelvic lymph nodes only. This, in turn, affected the accuracy of the preoperative diagnosis. Accordingly, the quantitative assessment, namely the lymph node size, was insufficient to determine whether or not metastasis occurred in lateral pelvic lymph nodes. The MERCURY Study Group [18] defined presence of mixed signal intensity or an irregular border of nodal capsule on MRI as lymph node metastasis including lateral pelvic lymph node metastasis. Matsuoka et al. [19] reported that an ovoid shape with a transverse axis diameter of 5 mm or higher on MRI was the optimal diagnostic criterion for lateral pelvic lymph node metastasis in patients with rectal carcinoma. Kim et al. [20] reported that morphologic criteria are helpful for nodal staging on high-resolution pelvic MRI by using diffusion weighted image and positron emission tomography (PET)/CT. Fusco et al. [21] advocated that in local staging, morphological MRI was superior to CT and PET/CT as it permitted a correct assessment of lymph node involvement with a high diagnostic accuracy. Liu et al. [22] established a predictive nomogram to improve the diagnostic accuracy of pre-therapeutic lymph node metastases in patients with rectal cancer by incorporating MRI imaging features. The best approach to diagnose lymph node is unknown because these study results were inconsistent. Therefore, improvements in approaches to qualitative assessment are needed.

Although the non-inferiority of ME alone to ME with LLND could not be confirmed in the intent-to-treat analysis of JCOG0212 study, patient selection for LLND is an important issue, given that LLND is associated with long operation time, large blood loss and somewhat frequent postoperative complication.3 This study demonstrated that age, tumor location and the short-axis diameter of lateral pelvic lymph node are preoperative predictive factors and these factors are important for patient selection. However, the result was not satisfactory, because of the low accuracy. Further study is required for patient selection for LLND.

This study has some limitations. First, the data from 23 patients could not be assessed. These patients represented 6.6% of the ME with LLND group. Second, the size of the pelvic lateral lymph node was estimated by using only CT and not MRI. Although the slice size of preoperative CT was defined as 5 mm or less, almost all the slice size was 5 mm. Therefore, the diagnosis of small lymph node was not accurate.

Conclusion

Patient age (<60 years), tumor location (Rb), and the short-axis diameter of lateral pelvic lymph node on CT (≥5 mm) were preoperative predictive factors, while pathological N and histological type were postoperative predictive factors of pathological lateral pelvic lymph node metastasis in patients without clinical lateral pelvic lymph node metastasis.

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