Journal of Gastrointestinal Surgery (2019) 23:1454–1460
https://doi.org/10.1007/s11605-019-04224-x

2018 SSAT PLENARY PRESENTATION

Oncological Outcomes of Patients with Locally Advanced Rectal Cancer and Lateral Pelvic Lymph Node Involvement

Ipek Sapci[1] · Conor P. Delaney[1] · David Liska[1] · Sudha Amarnath[2] · Matthew F. Kalady[1] · Scott R. Steele[1] · Emre Gorgun[1]

Received: 14 June 2018 / Accepted: 29 March 2019 / Published online: 22 April 2019

Abstract

Introduction The optimal management of patients with radiologically positive lateral pelvic lymph nodes in locally advanced rectal cancer remains unclear. We compared local recurrence rates and oncological outcomes of patients with locally advanced cancer with and without lateral pelvic lymph nodes.

Methods Patients who underwent curative surgery for stage III rectal adenocarcinoma between 2009 and 2014 and had a preoperative MRI at our institution as well as preoperative neoadjuvant treatment were included. Patients with positive lateral pelvic lymph nodes (iliac or obturator nodes) on preoperative MRI (LPND +) were compared to patients with no lateral pelvic nodal disease (LPND −). Data were collected from a prospectively maintained institutional database. Differences between the groups were compared in univariate analysis. Log-rank test was used to evaluate overall and disease-free survival between the groups.

Results A total of 125 patients met inclusion criteria with a mean age of 56.3 ± 12.2 and 75% were male. Median follow-up was 44 months (IQR 32, 106). Positive LPND was present on preoperative MRI in 43/125 (34.4%) patients who were in the LPND (+) group. Seventeen out of 43 patients had a post-neoadjuvant treatment MRI and 15 patients had a decrease in size of nodes or disappearance of LPND. On univariate analysis, LPND (+) and LPND (−) groups were comparable. Local recurrence rates were higher in the LPND (+) group, although this was not statistically significant (16.3% vs. 6%, $p = 0.06$). Overall and disease-free survival rates were comparable between the LPND (+) and LPND (−) groups ($p = 0.97$, $p = 0.51$).

Conclusions Management of patients with advanced rectal cancer and radiologically positive lateral pelvic lymph nodes is challenging due to high local recurrence rates. Further studies are needed to develop care pathways for the optimal treatment processes.

Keywords Locally advanced rectal cancer · Lateral pelvic lymph node · Lymph node dissection · Chemoradiation

Introduction

Rectal cancer treatment was revolutionized by adopting total mesorectal excision (TME) as the standard of care, which involves the removal of the mesorectal lymph nodes.[1] This approach, combined with neoadjuvant chemoradiation therapy, reduced local recurrence rates and resulted in better overall survival.[2] Nonetheless, this approach did not achieve recurrence-free survival in all patients.[2,3]

Lateral pelvic lymph nodes located around the iliac and obturator vessels are thought to be a major cause of local recurrence in patients with rectal cancer, and can be found in up to 23% of patients with locally advanced rectal cancer.[4,5] Lateral lymph node metastases have also been identified as a risk factor for locoregional recurrence in rectal cancer treated with preoperative neoadjuvant chemoradiation.[4,6]

Management of lateral lymph nodes in rectal cancer remains debatable and historically, the development of the management is likewise different between Eastern countries like Japan and the West.[3] In the West, management of these patients is mainly based on neoadjuvant therapy followed by

Presented as a Plenary Presentation at Digestive Disease Week, June 2–5, 2018, Washington D.C.

✉ Emre Gorgun
gorgune@ccf.org

[1] Department of Colorectal Surgery, Digestive Disease and Surgery Institute, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, USA

[2] Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, USA

total mesorectal excision, and lateral pelvic lymph node dissection has not been accepted as a standard of care. Mainly, this is due to the technical challenge and the association with sexual and urinary dysfunction.[7] There are also no clear benefits shown in decreasing recurrence rates or increasing survival in the earlier studies with the addition of routine lateral lymph node dissection.[8,9]

On the other hand, in Eastern surgical practice, nerve-preserving lateral node dissection is more widely adopted.[10] Reports from the East are mostly from Japan and they state that pelvic lymph node dissection results in favorable outcomes and, therefore, is more commonly performed.[3,7]

Routine application of lateral pelvic lymph node dissection remains controversial, and currently, there is no consensus regarding the management of lateral pelvic nodal disease in rectal cancer patients.[4] Studies from North America describing the management of lateral lymph nodes are scarce.[3,8] Therefore, the aim of our study was to report long-term oncological outcomes in patients with rectal cancer who had suspicious lateral pelvic nodal disease on preoperative imaging and to compare local recurrence rates between patients with and without lateral pelvic lymph node involvement in locally advanced rectal cancer. Our hypothesis was that patients who had locally advanced rectal cancer with lateral pelvic lymph node involvement would have higher local recurrence rates compared to those without lateral pelvic lymph node involvement.

Methods

Patients who underwent curative resections for clinical stage III rectal adenocarcinoma between 2009 and 2014 were identified from a prospectively maintained Institutional Review Board approved database in a tertiary medical center in the USA. Additional chart reviews were conducted as needed by the primary author. Patients who did not have a preoperative magnetic resonance imaging (MRI) of the pelvis at our institution and patients who underwent surgery for recurrent rectal cancer were excluded. Pretreatment and post-treatment MRI reports were identified and reviewed in detail by specialized radiologists. Lateral pelvic nodes were documented separately and suspicious lymph nodes based on size/morphology on the pretreatment MRI were documented in the lateral pelvic nodal disease (+) group. Lymph node sites were the internal iliac, external iliac, and obturator compartment. All lymph nodes determined to be radiologically positive were larger than 5 mm and had morphological features such as heterogeneity or border irregularity. Patients who met these criteria were grouped as positive lateral pelvic nodal disease [LPND (+)], and patients without pelvic nodal disease were grouped as negative lateral pelvic nodal disease [LPND (−)]. Patients with perirectal nodal disease confined in the mesorectum were not included in the LPND (+) group.

Preoperative radiation therapy was generally given in a total dose of 50–50.4 Gy in 1.8–2 Gy per fraction with concurrent chemotherapy. Pelvic target volumes included primary tumor and mesorectum, presacral, internal iliac, or external iliac lymph nodes. Radiation therapy dose adjustments were made according to the patient characteristics and invasion of the tumor. Concurrent chemotherapy was radiosensitizing infusional fluorouracil (5-FU) 225 mg/m^2 over 24 h 7 days/week or capecitabine 825 mg/m^2 per oral, two times a day, 5 days/week.

Patient demographics included age, gender, body mass index, American Society of Anesthesiologists score, and clinical staging based on TNM classification. Pathological variables included pathological staging based on TNM classification and margins. Overall survival, local recurrence rates, and local recurrence–free survival were also analyzed for both groups.

Statistical Analysis

A univariate analysis was conducted to evaluate the association of patient characteristics with suspicious lateral lymph nodes [LPND (+) group], comparing it with [LPND (−) group]. Data are reported as mean ± standard deviation, median [25th percentile, 75th percentile], or frequency (column %). Pearson's chi-square test or Fisher's exact test was used for categorical variables, and ANOVA or the Kruskal-Wallis test was used for continuous variables. p values < 0.05 are considered statistically significant.

Kaplan-Meier curves for overall survival were plotted for the LPND (+) and LPND (-) groups, and a corresponding log-rank test was used to compare them. Disease-free survival, local recurrence, and distal recurrence were also analyzed in this manner.

Multivariable cox-proportional hazard (Cox-PH) models were fit for comparisons with significant log-rank tests. Radial margin and TME completeness were included as covariates. In cases where scarcity of events limited the number of covariates that could be included, the one with the lower p value was chosen. The corresponding direct-adjusted survivor function was plotted for each model. All analyses were conducted using SAS (version 9.4; Cary, NC).

Results

During the study period, 822 patients underwent treatment for rectal cancer of all stages, of which 226 were stage III. A total of 125 patients met inclusion criteria, who underwent curative intent surgery for rectal adenocarcinoma, had preoperative neoadjuvant chemotherapy and had pretreatment institutional MRIs with a median follow-up of 44 months (IQR 32, 106).

Of these, 43 were in the LPND (+) and 82 in the LPND (−) group. Among 43 patients in the LPND (+) group, 17 had both pretreatment and post-treatment MRIs (Fig. 1). Fifteen of them showed response of the radiologically positive lymph node in the post-treatment MRI. In 2 patients, post-treatment MRI showed no response of the detected nodes and only these patients underwent lateral pelvic lymph node dissection. Postoperative pathology showed no metastasis in these nodes. Mean involved pelvic lymph node size was 9.9 mm (SD 3.9, range 5–18 mm). Thirty-seven of the 43 lymph nodes were found in the iliac compartment and 6 in the obturator compartment.

Demographics and clinical characteristics are shown in Table 1 and groups were comparable in univariate analysis. Univariate analysis for pathological outcomes is shown in Table 2.

Median follow-up after surgery was 44 months (CI 40–50, IQR 26–55). Distant recurrences were seen in 25 patients [8 in LPND (+) group, 17 in LPND (−) group, $p = 0.78$]. Local recurrences were seen in a total of 12 patients (7 patients in LPND (+) group and 5 patients in LPND (−) group). Local recurrences occurred in the lateral pelvic side wall ($n = 3$) and in the pelvis ($n = 4$) in the LPND (+) group. Local recurrence rates were higher in the LPND (+) group, although this was not statistically significant (16.3% vs. 6%, $p = 0.06$).

The 4-year overall survival and disease-free survival rates were comparable between the groups [(81.6% vs. 82.5%, $p = 0.97$), (81.6% vs. 77.8%, $p = 0.51$)]. Local recurrence–free survival was also not different between the groups ($p = 0.089$) (Fig. 2). Local recurrence–free survival was compared between the LPND (−) group and patients who had response of the lymph nodes in the post-treatment MRI. This showed significantly better local recurrence–free survival for the LPND (−) group (92.3% vs. 73.1%, $p = 0.004$) (Fig. 3).

Multivariate analysis was conducted for factors affecting the local recurrence rates between the groups and results are shown in Table 3. Radiological lateral pelvic node positivity, mesorectal grade, circumferential resection margin, and type of procedure did not independently affect local recurrence.

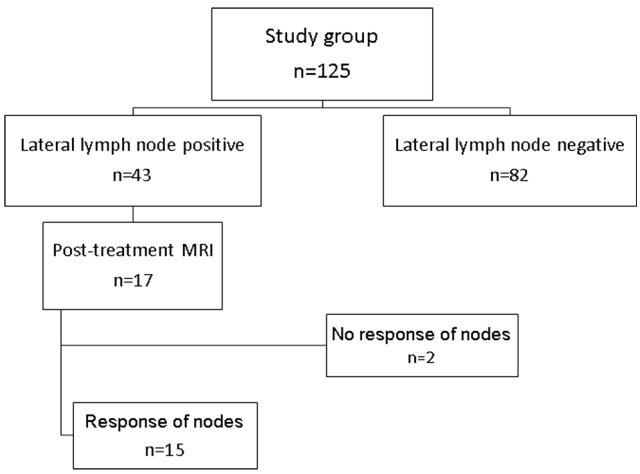

Fig. 1 Organization chart showing subgroups based on MRI

Table 1 Univariate analysis results of comparison between two groups in terms of demographics and clinical staging

	LPND (−) ($N = 82$)	LPND (+) ($N = 43$)	p value
Age	56.1 ± 12.4	56.6 ± 12.1	0.83[a]
Gender (male)	60 (73.2)	34 (79.1)	0.47[c]
General BMI	28.9 [24.1, 31]	27.1 [24.3, 31]	0.42[b]
Distance from AV	5 [0, 7]	5 [2, 7]	0.65[b]
ASA			0.31[d]
1	1 (0.8)	0 (0.0)	
2	23 (28)	18 (41.9)	
3	56 (68.3)	25 (58.1)	
4	2 (2.4)	0 (0.0)	
Clinical stage T			0.17[c]
T1	1 (1.2)	0 (0)	
T2	13 (15.9)	4 (9.3)	
T3	60 (73.1)	29 (67.5)	
T4	8 (9.8)	10 (23.2)	
Clinical stage N			0.33[c]
N1	61 (74.4)	27 (62.8)	
N2	21 (25.6)	16 (37.2)	
Procedure			0.71[d]
APR	25 (30.5)	14 (32.6)	
LAR	57 (69.5)	29 (67.4)	

LPND lateral pelvic nodal disease based on radiological evidence, *BMI* body mass index, *AV* anal verge, *ASA* American Society of Anesthesiologists score

[a] ANOVA

[b] Kruskal-Wallis test

[c] Pearson's chi-square test

[d] Fisher's Exact test

Discussion

Our study shows that the presence of lateral pelvic lymph nodes in preoperative MRI affects local recurrence–free outcomes in patients with locally advanced rectal cancer even if there is clinical or pathological evidence of response following neoadjuvant chemotherapy and/or surgery. Patients with radiologically positive lymph nodes can have high rates of local recurrence even after treatment.

Recent publications on patients with radiologically positive lateral pelvic lymph nodes report higher rates of local recurrence in patients with radiologically positive lateral pelvic lymph nodes. Kusters et al. reported higher rates of local recurrence of 33% in patients with radiologically large (> 10 mm) malignant lateral pelvic lymph nodes.[10] Another study investigating local recurrence in patients with suspicious nodes reported rates as high as 35% in patients who only

Table 2 Results of univariate analysis of pathological outcomes

	LPND (−) ($N = 82$)	LPND (+) ($N = 43$)	p value
Differentiation			0.39
Moderately	52 (65)	29 (69)	
Poorly	10 (12.5)	2 (4.8)	
Well	18 (22.5)	11 (26.2)	
Pathology T stage			0.15
T0	4 (4.9)	2 (4.7)	
T1	6 (7.3)	2 (4.7)	
T2	2 8(34.1)	7 (16.3)	
T3	42 (51.2)	29 (67.4)	
T4	2 (2.4)	3 (7)	
Pathology N stage			0.93
N1	24 (29.3)	14 (32.6)	
N2	14 (17.1)	7 (16.3)	
No	44 (53.7)	22 (51.2)	
Angiolymphatic invasion	15 (18.3)	11 (25.6)	0.34
Distal margin involvement	0 (0)	1 (2.3)	0.34*
Circumferential margin involvement	5 (6.1)	3 (7)	0.85
Mesorectum quality			0.99*
Complete	67 (90.5)	35 (92.1)	
Near complete	3 (4.1)	1 (2.6)	
Incomplete	4 (5.4)	2 (5.3)	
Adjuvant chemotherapy	58 (71.6)	30 (69.8)	0.83

LPND lateral pelvic nodal disease, Pearson's chi-square test used

*Fisher's exact test

underwent TME. Kim et al. also identified the presence of lateral pelvic lymph nodes as a significant factor in predicting local recurrence.[4,11]

Standard management of locally advanced rectal cancer is neoadjuvant therapy followed by total mesorectal excision (TME) and lateral node dissection is not routine as part of a surgical practice in the West.[3] In our study, local recurrence–free survival was worse in the LPND (+) group; however, this was not statistically significant. We suspect this is potentially a result of low patient numbers and the sample size being underpowered to detect a statistically significant difference. The importance of MRI-detected lateral pelvic lymph nodes was assessed in the MERCURY study in 38 patients with suspicious lateral lymph node involvement. The authors found a significantly lower 5-year disease-free survival for patients who had suspicious nodes (42% vs. 70.7%), which improved with neoadjuvant therapy.[12]

Even though neoadjuvant chemoradiotherapy is imperative in managing these patients, lateral pelvic nodes may not be completely sterilized after treatment and curative resection.[10] Clinical response of the lateral nodes after neoadjuvant treatment was also previously studied. Akiyoshi et al. reported that disease-free survival was worse in patients who had lateral pelvic lymph node metastasis. In addition, they reported 20% (10 /49) of patients who had clinical response on post-neoadjuvant therapy imaging, but still had lateral pelvic lymph node metastases on final pathology, thus highlighting the potential difficulties with current imaging.[13] In our study, 15 patients who had response of positive nodes after neoadjuvant treatment on MRI had worse local recurrence–free survival when compared to patients in the LPND (−) group. We acknowledge that our sample size is small to draw definitive conclusions; however, the data suggest that response to chemoradiation may not sufficiently predict a relation to decreased local recurrence. Kim et al. advocates that lateral pelvic lymph node dissection may be needed even if post-treatment imaging shows good treatment response on imaging.[14]

The management of lateral pelvic lymph nodes is controversial and an evidence-based strategy has not been agreed upon between the East and the West. Literature from Japan suggests lateral pelvic lymph node dissection is more commonly performed in surgical practice and may improve oncological outcomes.[15] Sugihara et al. reported that lateral lymph node dissection for low rectal cancers is expected to decrease pelvic recurrence risk by 50%.[6] In a recent randomized controlled trial, it was found that TME combined with lateral lymph node dissection resulted in lower recurrence rates.[16] In our sample, only 2 patients underwent lateral pelvic lymph node dissection which makes it difficult for us to draw conclusions on the impact of resection based on this current data.

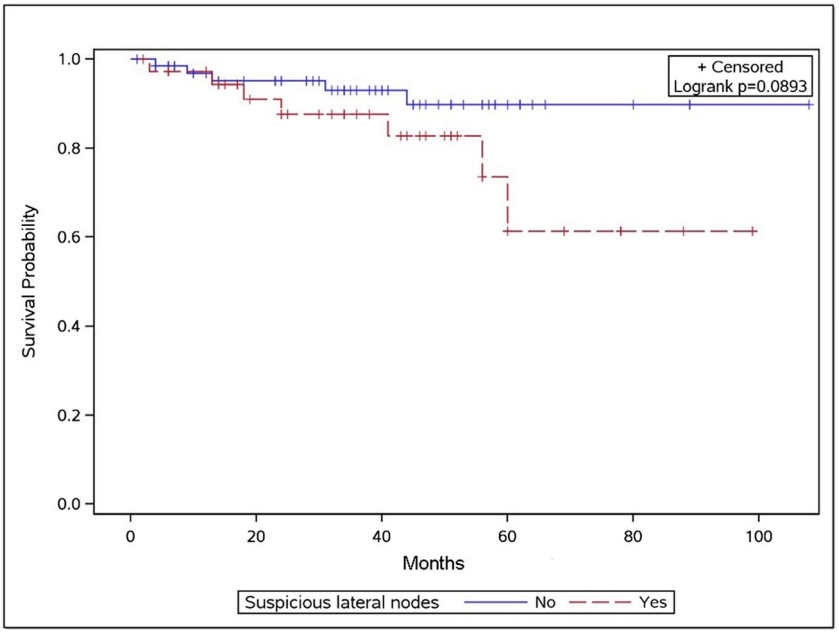

Fig. 2 Kaplan-Meier survival curves for local recurrence–free survival, LPND (+) vs. LPND (−)

Outcomes of the two different approaches to lateral lymph nodes have been investigated by comparing neoadjuvant therapy versus lateral node dissection by Kim et al.[17] The local recurrence rate was 16.7% in the lateral pelvic node dissection group,[17] who had a twofold increase in local recurrence when compared with the chemoradiotherapy only group. In another study, Watanabe et al. reported survival outcomes to be similar between patients who received radiotherapy and those who underwent extended lymphadenectomy.[18] Our small sample size for lateral node dissections precludes us to draw conclusions when comparing the two approaches.

Our findings support that neoadjuvant chemoradiotherapy is effective in managing patients with radiologically positive lateral pelvic lymph nodes; however, it is uncertain if this mode is sufficient to eradicate metastatic disease. Akiyoshi et al. showed that local recurrence rates after chemoradiation and TME with selective lateral pelvic lymph node dissection can be as low as zero.[15] They also showed that even patients without positive mesorectal nodes may have positive lateral pelvic nodes. This suggests that patients with positive lateral pelvic nodes may represent a new subgroup and due to this metastatic spread outside the TME plane, TME is obviously

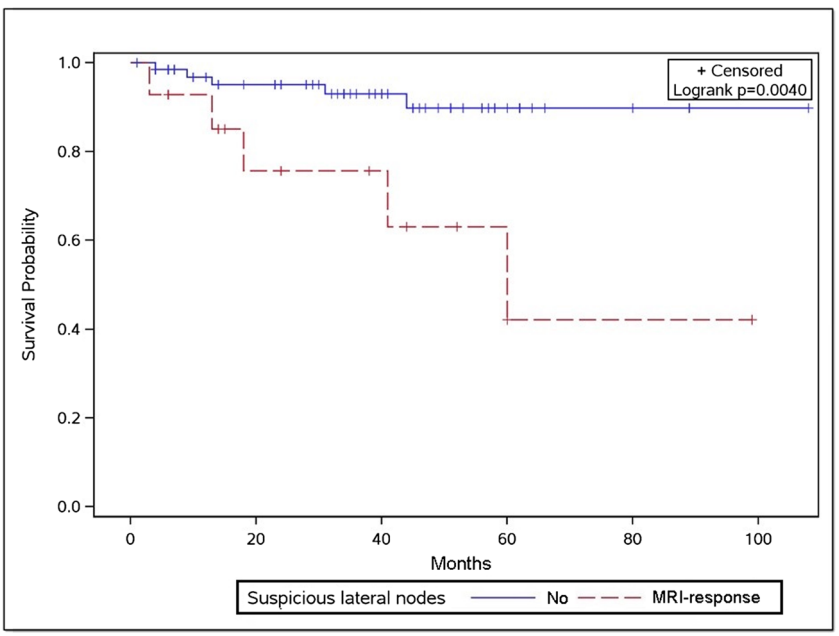

Fig. 3 Kaplan-Meier survival curves for local recurrence–free survival, LPND (−) vs. responsive LN in the post-treatment MRI

Table 3 Multivariable model for local recurrence

Factor	Level	HR (95% CI)	*p* value
Lateral lymph node positivity	Yes	2.1 (0.6, 7)	0.22
Mesorectal grade	Non-complete	2.8 (0.77, 10.1)	0.12
Circumferential resection margin	Involved	2.8 (0.48, 16.1)	0.25
Procedure type	APR	1.4 (0.44, 4.6)	0.56

HR hazard ratio, *CI* confidence interval

inadequate to eliminate the disease. For this particular group of patients, selective pelvic lymph node dissection may be beneficial. In the more recent years, our approach in patients with locally advanced rectal cancer and radiologically positive lateral LN is towards combining "selective lateral pelvic lymph node dissection" with chemoradiation followed by TME. Our selective approach consists of evaluating patients with post-treatment MRIs if they have positive nodes on the pretreatment MRI. Subsequently, patients without response to therapy are evaluated on the multidisciplinary meetings and decision for lateral lymph node dissection is made if no response of the LPLNs is observed.

We suspect that patients with evident lateral pelvic nodal disease on pretreatment imaging may represent a specific subgroup of patients with rectal cancer and further management with possible selective lateral lymphadenectomy combined with neoadjuvant treatment may possibly be administered to decrease local recurrence rates even if there is a treatment response evident in post-treatment MRI. It must be noted that most of the studies reporting the outcomes of lateral pelvic lymph node dissection are from the East and patient characteristics are different than the Western patient with a higher body mass index.[3] In order to draw accurate conclusions regarding this approach, further research from the West is needed to decide the applicability of lateral pelvic lymph node dissection in the Western patient population. Multi-institutional studies are required to validate the results from the East and elucidate the exact mechanism of lateral nodal disease and its effects on survival and recurrence.

Limitations

We recognize that our study has certain limitations. Our patient group does not represent all patients who had locally advanced rectal cancers during the time period as only those with institutional pretreatment MRIs were included in the study. Further limitations are our small sample size and differences in follow-up. Therefore, our sample size and compared subgroups are small in numbers. In our study, circumferential resection margin was not associated with local recurrence and this is thought to be due to our small sample size and small number of patients with positive margins. In addition, imaging after neoadjuvant treatment was not done for all patients. Another limitation of our study is that as chemoradiation followed by TME is the management strategy in our institution, we do not have pathological data to correlate the accuracy of MRI with the suspected lateral lymph nodes. Despite these limitations, we report one of the largest series from a tertiary referral center in the West that correlates imaging with oncological outcomes in patients with locally advanced rectal cancer and positive lateral pelvic lymph nodes.

Conclusion

The results of this study suggest that radiological lateral pelvic node positivity may lead to worse recurrence–free survival in patients with locally advanced rectal cancer and radiological treatment response. Current practice in the West is neoadjuvant chemoradiotherapy followed by TME in locally advanced rectal cancers with clinical lateral pelvic lymph node involvement. Our results suggest that management of these patients needs to be reevaluated.

Authors' Contributions Ipek Sapci: Design of the work; acquisition, analysis, and interpretation of data; drafting and revising the work; final approval of the version to be published.

Conor P. Delaney: Design of the work, analysis and interpretation of data, revising the work, final approval of the version to be published.

David Liska: Design of the work, interpretation of data, revising the work, final approval of the version to be published.

Sudha Amarnath: Design of the work, interpretation of data, revising the work, final approval of the version to be published.

Matthew F. Kalady: Design of the work, interpretation of data, revising the work, final approval of the version to be published.

Scott R. Steele: Design of the work, interpretation of data, final approval of the version to be published.

Emre Gorgun: Conception and design of the work, analysis and interpretation of data, drafting and revising the work, final approval of the version to be published.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Disclaimer All authors agree to be accountable for all aspects of the work.

References

1. Heald RJ, Husband EM, Ryall RDH. The mesorectum in rectal cancer surgery–the clue to pelvic recurrence? Br J Surg. 1982;69(10):613–6.
2. Kodeda K, Johansson R, Zar N, et al. Time trends, improvements and national auditing of rectal cancer management over an 18-year period. Colorectal Dis. 2015; 17(9):O168–79.
3. Kusters M, Uehara K, Velde C, Moriya Y. Is There Any Reason to Still Consider Lateral Lymph Node Dissection in Rectal Cancer? Rationale and Technique. Clin Colon Rectal Surg. 2017 ;30(5): 346–56.
4. Kim TH, Jeong S-Y, Choi DH, et al. Lateral lymph node metastasis is a major cause of locoregional recurrence in rectal cancer treated with preoperative chemoradiotherapy and curative resection. Ann Surg Oncol. 2008;15(3):729–37.
5. Hojo K, Koyama Y, Moriya Y. Lymphatic spread and its prognostic value in patients with rectal cancer. Am J Surg. 1982;144(3):350–4.
6. Sugihara K, Kobayashi H, Kato T, et al. Indication and Benefit of Pelvic Sidewall Dissection for Rectal Cancer. Dis Colon Rectum. 2006;49(11):1663–72.
7. Yano H, Moran BJ. The incidence of lateral pelvic side-wall nodal involvement in low rectal cancer may be similar in Japan and the West. Br J Surg. 2007;95(1):33–49.
8. Michelassi F, Block GE. Morbidity and mortality of wide pelvic lymphadenectomy for rectal adenocarcinoma. Dis Colon Rectum. 1992;35(12):1143–7.
9. Akasu T, Sugihara K, Moriya Y. Male Urinary and Sexual Functions After Mesorectal Excision Alone or in Combination with Extended Lateral Pelvic Lymph Node Dissection for Rectal Cancer. Ann Surg Oncol. 2009;16(10):2779–86.
10. Kusters M, Slater A, Muirhead R, et al. What To Do With Lateral Nodal Disease in Low Locally Advanced Rectal Cancer? A Call for Further Reflection and Research. Dis Colon Rectum. 2017;60(6): 577–85.
11. Kim DJ, Chung J-J, Yu J-S, Cho ES, Kim JH. Evaluation of Lateral Pelvic Nodes in Patients With Advanced Rectal Cancer. Am J Roentgenol. 2014 J;202(6):1245–55.
12. MERCURY Study Group, Shihab OC, Taylor F, Bees N, et al. Relevance of magnetic resonance imaging-detected pelvic sidewall lymph node involvement in rectal cancer. Br J Surg. 2011;98(12): 1798–804.
13. Akiyoshi T, Matsueda K, Hiratsuka M, et al. Indications for Lateral Pelvic Lymph Node Dissection Based on Magnetic Resonance Imaging Before and After Preoperative Chemoradiotherapy in Patients with Advanced Low-Rectal Cancer. Ann Surg Oncol. 2015;22(S3):614–20.
14. Kim HJ, Choi G-S, Park JS, et al. Optimal treatment strategies for clinically suspicious lateral pelvic lymph node metastasis in rectal cancer. Oncotarget. 2017;8(59):100724–33.
15. Akiyoshi T, Ueno M, Matsueda K, et al. Selective lateral pelvic lymph node dissection in patients with advanced low rectal cancer treated with preoperative chemoradiotherapy based on pretreatment imaging. Ann Surg Oncol. 2014;21(1):189–96.
16. Fujita S, Mizusawa J, Kanemitsu Y, et al. Mesorectal Excision With or Without Lateral Lymph Node Dissection for Clinical Stage II/III Lower Rectal Cancer (JCOG0212). Ann Surg. 2017;266(2):201–7.
17. Kim JC, Takahashi K, Yu CS, et al. Comparative Outcome Between Chemoradiotherapy and Lateral Pelvic Lymph Node Dissection Following Total Mesorectal Excision in Rectal Cancer. Ann Surg. 2007;246(5):754–62.
18. Watanabe T, Tsurita G, Muto T, et al. Extended lymphadenectomy and preoperative radiotherapy for lower rectal cancers. Surgery. 2002;132(1):27–33.