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Positive Lateral Pelvic Lymph Nodes in Low Rectal Cancer: should we change our practice now?

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Abstract

Background: The role of lateral lymph node dissection (LLND) in the treatment of patients with low rectal cancer with enlarged lateral lymph nodes (LLN+) is under investigation. Enthusiasm for LLND stems from a perceived reduction in local recurrence (LR). We aimed to compare the local recurrence rate for LLN+ patients with LLN- patients, treated with neoadjuvant chemoradiotherapy (nCRT) and surgery, in a hospital that does not perform LLND.

Methods: A retrospective study of all patients with clinical stage 3 low rectal cancer who completed nCRT and surgery between 2008 and 2017 at Western Health was performed. Outcomes for LLN+ patients were compared with LLN- patients. The primary outcome was LR. Secondary outcomes included distant metastases, disease-free survival (DFS) and overall survival (OS).

Results: There were 110 patients treated for stage 3 low rectal cancer over 10 years. There was no significant difference in the LR rate, with one LR from 28 LLN+ patients and one LR from 82 LLN- patients (4% vs 1.2%, p=0.44). There were no significant differences in median DFS (41 vs 52 months, p=0.19) or mean OS (62 vs 60 months, p=0.80). Of all patients studied, 21% developed distant metastases.

Conclusion: LR after nCRT and surgery in patients with stage 3 rectal cancer is rare, irrespective of lateral pelvic node status. These data, along with the uncertain benefit and known risks of LLND, supports the continued use of standard therapy in these patients. Strategies to address distant failure in these patients should be explored.

Key Words: Rectal cancer, lateral lymph nodes, Lateral lymph node dissection, Neoadjuvant chemoradiotherapy, local recurrence

Introduction

Marked differences exist in the management of rectal cancer patients with enlarged lateral pelvic lymph nodes (LLN+) between Eastern and Western countries. In Japan, the addition of lateral lymph node dissection (LLND) to total mesorectal excision (TME) in the treatment of rectal cancer below the peritoneal reflection is routine[1]. In Australia, the standard of care is neoadjuvant chemotherapy (nCRT) followed by TME alone, with consideration of adjuvant chemotherapy informed by pathology[2]. In Japan, the addition of lateral lymph node dissection (LLND) to total mesorectal excision (TME) in the treatment of rectal cancer below the peritoneal reflection is routine[1]. In Australia, the standard of care is neoadjuvant chemotherapy (nCRT) followed by TME alone, with consideration of adjuvant chemotherapy informed by pathology[2]. Whilst the benefits of LLND in the absence of nCRT have been demonstrated, the utility in patients undergoing nCRT is uncertain[3-6].

A recent edition of the ANZ Journal of Surgery provided an editorial, perspective and an updated review on the latest evidence for LLND and proposed a treatment algorithm that recommended LLND in select patients whilst awaiting future trials[4, 7-9]. Two recent systematic reviews sought to determine the role of LLND in patients undergoing nCRT but drew different conclusions[10, 11]. Recent guidelines published by the American Society of Colon and Rectal Surgeons recommended LLND in the setting of LLN+ based on a local recurrence (LR) risk of up to 19.5% after nCRT and TME[12, 13]. This has led some within Australia to advocate for the adoption of LLND for selected patients[3-5, 14, 15].

Barriers to the adoption of selective LLND in Australia are numerous, beginning with the lack of funding for repeat MRI staging. Additionally, LLND is a radical non-standardised procedure that requires significant upskilling, additional operating time and is associated with increased surgical morbidity even in experienced hands[7, 8 16, 17]. Adopting this approach may place undue pressure on current health care resources. Furthermore, other treatment paradigms such as total neoadjuvant therapy (TNT) and 'watch and wait' are emerging. It is difficult to have patients enrolled in multiple studies. Given that recommendations for LLND are currently based on international local recurrence rates, there is an imperative to first establish the local experience in order to justify the additional risks and resources of LLND against the uncertain benefit.

Western Health is a relatively high-volume centre for rectal cancer surgery. Over the past decade, the treatment of stage 3 rectal cancer has been consistent with current Australian guidelines[2]. MRI local staging is used, the cases discussed at a subspecialty multidisciplinary meeting with subspecialty staff, nCRT offered as a standard of care for stage 3 rectal cancer patients, and laparoscopic-assisted resection with open TME surgery is predominately performed. The primary aim of our study was to compare the LR rate for LLN+ patients with LLN- patients in stage 3 rectal cancer. We sought to determine if an unacceptably high rate of LR should lead to an immediate change in our practice with surgical upskilling for LLND.

Methods

A retrospective single-center study was performed at Western Health, Melbourne. The ACCORD is a prospectively maintained registry and was examined for all stage 3 patients with low rectal cancer between 1 January 2008 and 31 December 2017. These dates were chosen to allow at least 3 years of follow-up data. Ethics approval was provided by Western Health HREC (Project No: QA2020.27). Patient data including demographics, disease stage, neoadjuvant treatment, operative intervention, adjuvant treatment and outcomes were collected.

Inclusion criteria were patients 18 years or older who were treated with curative intent for a low rectal cancer, defined as within 8cm of the anal verge on MRI. All patients were AJCC stage 3 rectal cancers with abnormal mesorectal and/or extra-mesorectal lymph nodes on pre-treatment MRI. Patients who did not undergo or complete neoadjuvant therapy, had metastatic disease in distant organs or paraaortic lymph nodes or did not undergo TME were excluded.

Patients were divided into LLN+ and LLN- cohorts. LLN+ was defined as the presence of enlarged extra-mesorectal or lateral lymph nodes 7mm or greater in the short axis on pre-treatment MRI as defined by the Lateral Lymph Node Consortium[13, 18]. Over the study period, our centre did not routinely perform interval scans due to Medicare limitations, so post-adjuvant treatment measurements could not be used. All pre-treatment MRI images were re-reviewed by a specialist colorectal cancer radiologist with over 13 years of experience in pelvic MRI reporting prior to cohort allocation.

All patients were discussed at a multidisciplinary meeting and underwent long-course nCRT (50.4 Gray) applied over 28 fractions in combination with a fluoropyrimidine chemotherapy (infusional 5-fluorouracil or oral capecitabine). Following this, all patients underwent resection with TME surgery. Operations performed included abdominoperineal resection, anterior resection and Hartmann's procedure.

The primary endpoint was LR. This was diagnosed radiologically and defined as tumour regrowth at the anastomotic site, within the pelvis involving urological, gynecological organs or the sacrum, or in the lateral pelvic sidewall[19]. Secondary outcomes included distant metastases, disease-free survival (DFS) and overall survival (OS). DFS and OS were defined as the time from initial diagnosis until the date of recurrence or death due to any cause, respectively. Both were censored at the date of last review in the absence of an event. Follow-up time was calculated from the date of surgery. All latest surveillance scans were checked to ensure no recurrences were missed.

Statistical analyses were conducted using Stata/IC 16.0 software (StataCorp LLC, College Station, TX, United States, 2019). The p-values presented in the descriptive tables were derived from Pearson's chi-squared test. A p-value of <0.05 was regarded as significant. Kaplan-Meier plots were used to estimate survival for both DFS and OS. Univariate analyses included log-rank test of equality for categorical variables and univariate Cox regression for continuous variables. Cox regression assumptions were additionally assessed. Multivariable analysis was not performed due to the low event rate.

Results

From 2008 through 2017, 173 patients with stage 3 low rectal cancer underwent surgery with curative intent at Western Health. There were 21 patients excluded as they did not undergo or failed to complete nCRT. A further 42 patients were excluded due to the tumor height being over 8cm from the anal verge, after review by the specialist radiologist. The remaining 110 patients were included for final analysis (**Figure 1**). The median follow-up time for all patients was 59 months (IQR 39, 80).

Just over a quarter of the included patients were LLN+ (**Table 1**). There were no significant differences in baseline characteristics between LLN+ and LLN- patients. The mean age was 61 years. Approximately half of the cohort (56.4%) were under 65 years of age. The LLN+ group trended to have a higher proportion of younger patients, but this did not reach statistical significance (p = 0.079).

Overall, 2 patients (1.8%) experienced LR. One patient from the LLN+ group (4%) suffered recurrence at the common and internal iliac chain after 13 months. This patient had small pulmonary nodules detected 3 months post operatively that were deemed to be metastatic after approximately 18-24 months on serial imaging. One patient from the LLN- cohort (1%) suffered recurrence at the rectal stump after 53 months and was also found to have metastatic hepatic and peritoneal disease.

Out of 110 patients, a total of 24 experienced local and/or distant recurrence (21.8%) (**Table 2**). Twenty-two patients (20%) developed distant metastatic disease only. In the LLN+ group, 8 patients (29%) developed metastatic disease, compared with 15 (18%) in the LLN- group; hazard ratio 3.57 (95% CI, 1.84, 6.94). The overall median DFS was 52 months (IQR 29,71). The LLN+ group had a median DFS of 41 months (18,68), compared with 52 months (32,72) for the LLN- group (p = 0.19). Mean OS for the entire cohort was 61 months (SD, 25.5).

Kaplan-Meier plots for DFS and OS were used to graphically assess the differences in survival between LLN+ and LLN- groups (**Figure 2**). Log-rank test values for DFS and OS were 0.0954 and 0.439, respectively.

Discussion

In this single centre retrospective study, 110 patients with stage 3 low rectal cancer were treated consistently over a 10-year period with nCRT and TME surgery. We found a local recurrence rate of 1.8% overall. The local recurrence rate for LLN+ patients was 4% versus 1% for LLN- patients with no significant difference.

The local recurrence rate for patients in our study was low compared with international rates, irrespective of LLN status. The quoted local recurrence rates on which LLND algorithms have been proposed range from 6 to 25%[13, 18]. These may be outdated rates, as the more widespread use of nCRT has seen local recurrence rates fall[20]. In our study, although there appeared to be a trend toward shorter DFS in LLN+ patients compared with LLN- patients, this did not reach statistical significance. Likewise, OS was not significantly different and this is consistent with the multinational Mercury Study and other single-centre experiences[21-23].

A more recent multinational study in a Western population found that the addition of LLND to TME surgery after nCRT was associated with a local recurrence rate of 3% compared with 7% in those without LLND[24]. The difference was not statistically significant, nor were there any significant differences between groups with respect to DFS or OS. One of the largest multinational studies from the Netherlands and Australia analysed 223 patients (125 LLN+) and found a LR rate of 11% in LLN+ patients compared with 2% in LLN- patients. This difference was not statistically significant. Again, there was no significant difference in DFS or OS between the groups[19].

A possible explanation for our low LR rate and key strength of our study is that we are a high-volume centre with a consistent approach in the multidisciplinary management of low rectal cancer. This includes surgical technique, systemic treatment regimens and radiological reporting. Larger studies in Western and European cohorts[19, 21-23] are multicentric in order to mitigate low event rates. However, the compromise is variation in diagnostics, classifications and treatments according to local practices.

Another major difficulty in studies seeking to define differences in outcomes between LLN+ and LLN- patients is that the true pathological status of the LLN remains unknown. Further complicating this point is that what constitutes a "clinically positive" LLN remains controversial. Malakorn et al found that in patients undergoing nCRT and TME, a LLN size cut-off of ≥5mm on interval scans was 100% sensitive for predicting pathological LLN status[14]. However, if this criterion was used for selective LLND, then almost one-third of patients would undergo LLND for pathologically negative LLN.

A significant finding in our study was the burden of distant metastasis that eventuated in 21% of the patients overall. Although there was no statistical difference in the rate of distant metastasis between LLN+ and LLN- patients, 27% of LLN+ patients in our study suffered distant disease. This impacted on their DFS, which suggests LLN+ is a risk factor for systemic failure. For the single LLN+ patient in our study that suffered a local recurrence, it is difficult to see how addition of LLND would have altered their overall prognosis given the development of distant disease. The significance of metastatic disease in patients with stage 3 rectal cancer was also a major finding from a recent study from regional Australia on patients with stage 1 to 3 rectal cancer[25]. In the cohort of clinical stage 3 patients, strategies to reduce the development of distant metastasis may have greater benefit.

Total Neoadjuvant Therapy (TNT) is an emerging systemic treatment regimen that incorporates combination chemotherapy into the neoadjuvant therapy[26-28]. It aims to improve rates of pathological complete response and reduce the risk of distant failure, which is the ultimate determinant of OS[28, 29]. A recent meta-analysis found TNT was associated with improved OS compared with historical series using standard nCRT[26]. These studies were performed in patients at high risk of LR, including some patients with enlarged lateral nodes. Recently, several reports of randomised studies have been presented in abstract form. The PRODIGE 23 and the RAPIDO studies both compared TNT with standard neoadjuvant treatments[30, 31]. Preliminary data report improvements in pathological complete response as well as DFS.

Our study had several limitations. Although our centre can be considered to be relatively high-volume for rectal cancer patients, the study may be underpowered to show a statistically significant difference. This is the result of the low incidence of locally advanced low rectal cancer and by the low rates of LLN+ and LR. A study powered to show a difference in LR between 2.5 and 5%, would require an estimated sample size of 2552 patients. This demonstrates the considerable difficulties and time required for studies to show a benefit with LLND. Secondly, in the absence of post-treatment MRI scans, we were unable to determine how many of our 28 LLN+ patients responded to nCRT. Interestingly, as most studies compare outcomes between cohorts based on whether or not they have undergone LLND, there is less research pertaining to outcomes in patients with LLN+ who respond well to nCRT[3]. Thirdly, it is possible that some LLN+ patients with normal mesorectal nodes were incorrectly staged in the early part of the study period, and therefore excluded from analysis. We believe this possible cohort of patients is negligible and unlikely to influence our conclusion, as the simultaneous presence of histologically abnormal LLN with normal mesorectal lymph nodes is small[32-34]. Furthermore, we have had consistent specialist radiologists reporting and reviewing the MRI scans at regular multidisciplinary meetings throughout the study period.

A fourth major limitation of our study was that we excluded all patients who failed to complete nCRT. Our aim was to determine the outcomes for patients having standard neoadjuvant treatment. It is possible that for the patients who could not tolerate nCRT, LLND could decrease their risk of local recurrence, however their overall prognosis would remain unchanged[19, 24]. Finally, the ACCORD database is prospectively maintained and provides reliable longitudinal data, but a small proportion of patients were lost to follow-up.

Given the low rates of LR for patients with stage 3 low rectal cancer treated with nCRT and TME surgery, there is insufficient evidence to adopt LLND for LLN+ patients in our institution. We would advocate for rectal cancer centres to know their current LR rates to inform local practices.

Conclusion

The local recurrence rate for patients with stage 3 low rectal cancer treated with nCRT and TME surgery is low. There were no significant differences in local recurrence or overall survival outcomes in patients with or without enlarged LLN. Whilst we await the results of future trials, we believe that nCRT and TME surgery for LLN+ low rectal cancer is appropriate. Strategies to address distant failure in these patients should continue to be explored.

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Disclosure statement

There are no conflicts of interest to disclose.

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Figures

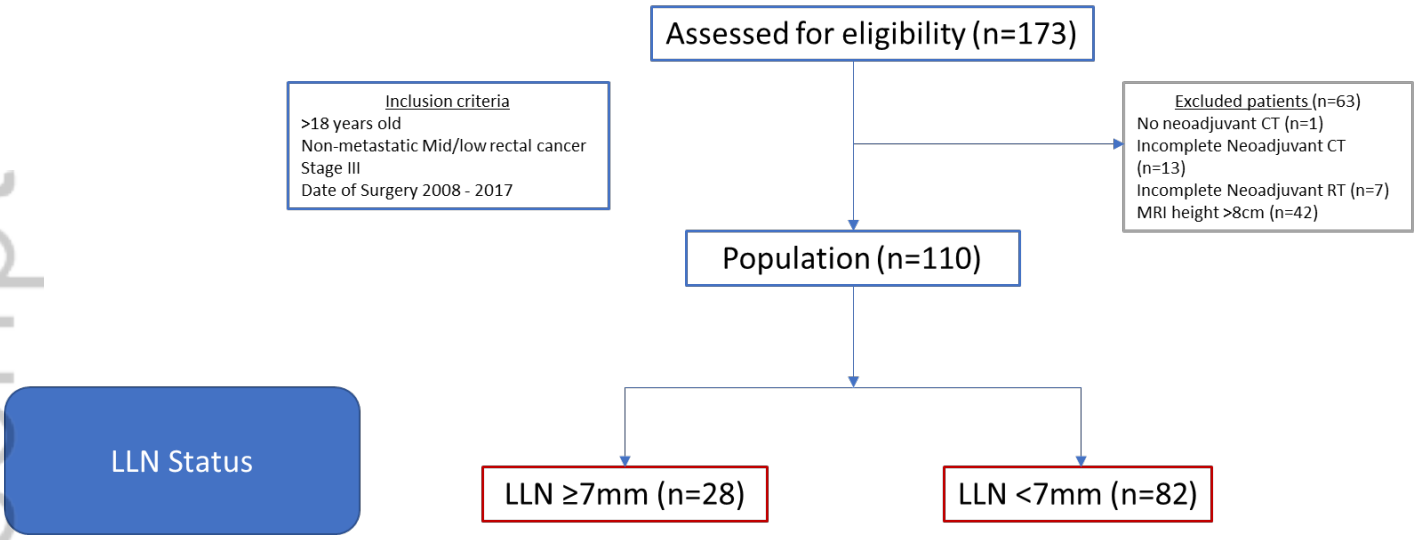
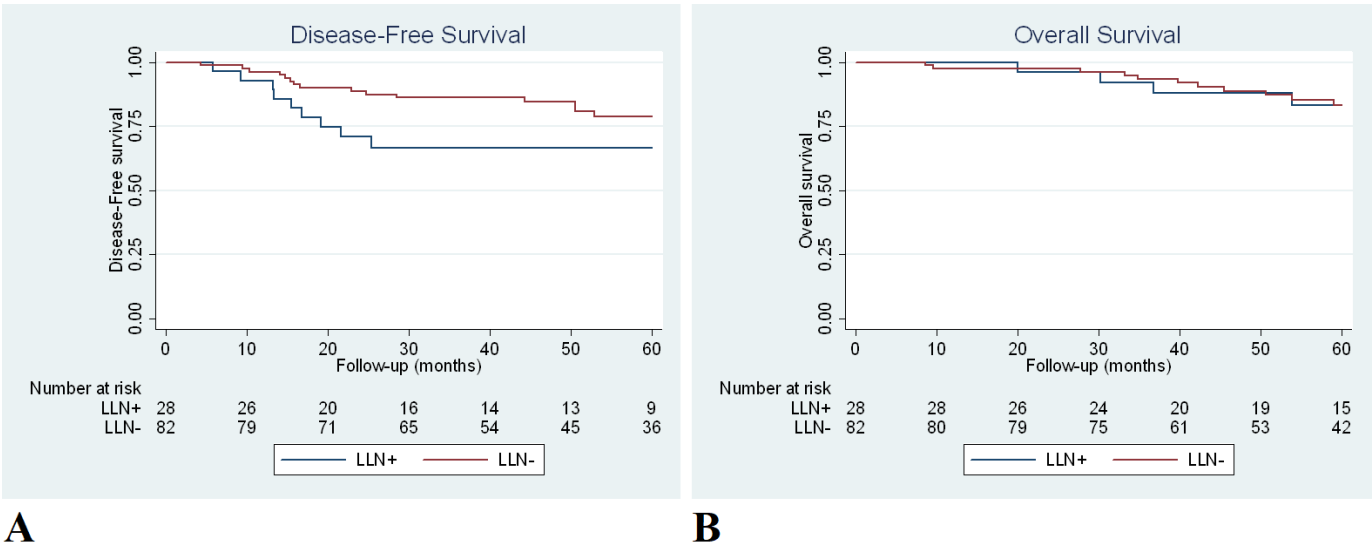


Figure 1. Patient population flow diagram



A **B**

Figure 2. A. Disease free survival (DFS) for enlarged lateral pelvic lymph nodes (LLN+) and non-enlarged lateral pelvic lymph nodes (LLN-) patients, and B. Overall survival (OS) for LLN+ and LLN- patients. Log-rank test values, $p = 0.0954$ for DFS, and $p = 0.439$ for OS.

Tables

Table 1. Baseline characteristics by LLN status

Factor		LLN+	LLN-	p-value
Patient characteristics				
N		28	82	
Age Group	**<65**	20 (71%)	42 (51%)	0.079
	65-74	7 (25%)	24 (29%)	
	≥75	1 (4%)	16 (20%)	
Sex	**M**	23 (82%)	58 (71%)	0.24
	F	5 (18%)	24 (29%)	
BMI, mean (SD)		26.9 (6.0)	27.1 (4.2)	0.82
Tumour characteristics				
Height cm, median (IQR)		4.8 (2.8, 6.5)	5.5 (4.0, 6.6)	0.23
cT Stage	**cT2**	4 (14%)	20 (24%)	0.14
	cT3	15 (54%)	49 (60%)	
	cT4	9 (32%)	13 (16%)	
cN Stage	**cN1**	13 (46%)	36 (44%)	0.82
	cN2	15 (54%)	46 (56%)	
CRM involvement	**No**	11 (39%)	45 (55%)	0.15
	Yes	17 (61%)	37 (45%)	
Adjuvant chemotherapy	**No**	8 (29%)	32 (39%)	0.32
	Yes	20 (71%)	50 (61%)	
Perioperative characteristics and histopathology				
Primary Procedure	**APR**	20 (72%)	39 (48%)	0.15
	Hartmann's	1 (4%)	2 (2%)	
	Low AR	0 (0%)	2 (2%)	
	Ultra-low anterior resection	6 (21%)	36 (44%)	
	Ultra-low Hartmann's	1 (4%)	3 (4%)	
ypT Stage	**ypT0**	8 (29%)	30 (37%)	0.33
	ypT1	1 (4%)	8 (10%)	
	ypT2	10 (36%)	18 (22%)	
	ypT3	8 (29%)	23 (28%)	
	ypT4	0 (0%)	1 (1%)	
	ypT4a	1 (4%)	0 (0%)	
	ypT4b	0 (0%)	2 (2%)	
ypN Stage	**ypN0**	20 (71%)	64 (78%)	0.18
	ypN1	5 (18%)	12 (15%)	
	ypN1a	0 (0%)	3 (4%)	
	ypN2	2 (7%)	1 (1%)	
	ypN2a	0 (0%)	2 (2%)	
	ypN2b	1 (4%)	0 (0%)	
Pathological Response	**Complete response**	8 (29%)	27 (33%)	0.16
Nodes Examined, median (IQR)		14 (11, 18)	12 (9, 16)	0.11

Table 2. Outcomes and follow up by LLN status. †Patient with both LR and Distant Metastasis. SD; standard deviation, IQR; interquartile range, CI; Confidence interval

Outcome	LLN+ (n=28)	LLN- (n=82)	All patients (n=110)	p-value
Local recurrence	1 (4%)	1† (1%)	2† (1.8%)	0.44
Distant Metastasis	8 (29%)	15† (18%)	23† (21%)	0.24
5-year Disease free survival (95% CI)	67% (44-82%)	79% (67-87%)	76% (66-83%)	0.10
5-year Overall survival	83% (61-93%)	83% (72-91%)	84% (74-90%)	0.44
Median Disease-free survival (months, IQR)	41 (18,68)	52 (33,72)	52 (29,71)	0.19
Mean OS (months, SD)	62 (28.0)	60 (24.8)	61 (25.5)	0.80
Median follow up (months, IQR)	62 (39, 80)	58 (39,80)	59 (39,80)	0.86

Figures

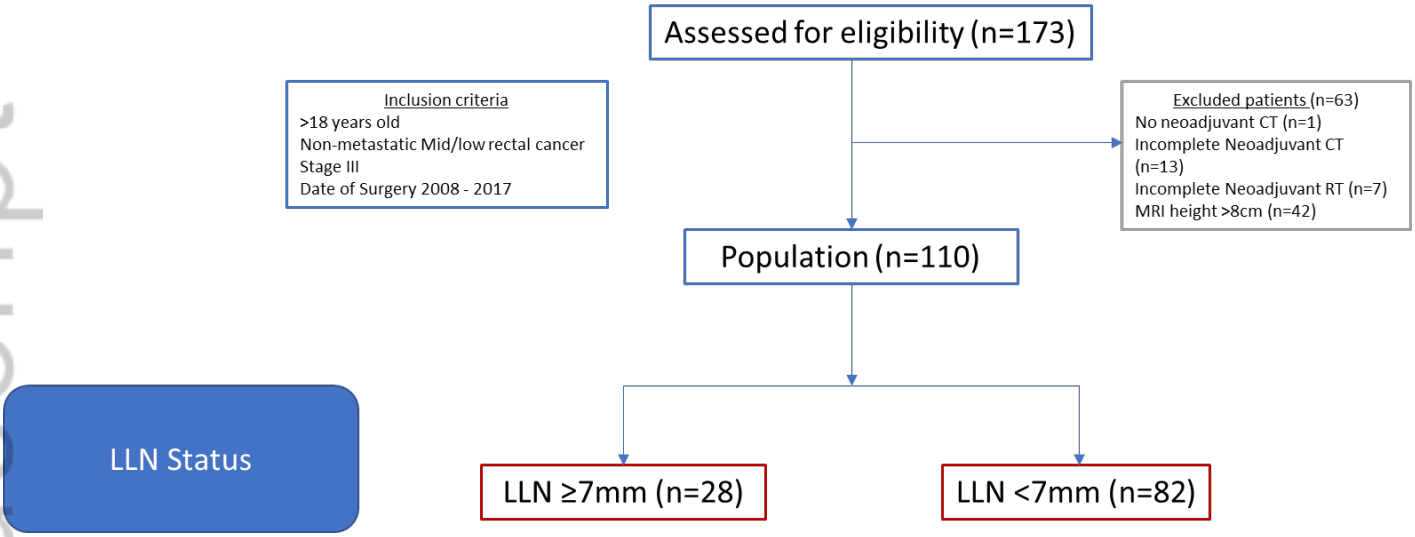


Figure 1. Patient population flow diagram

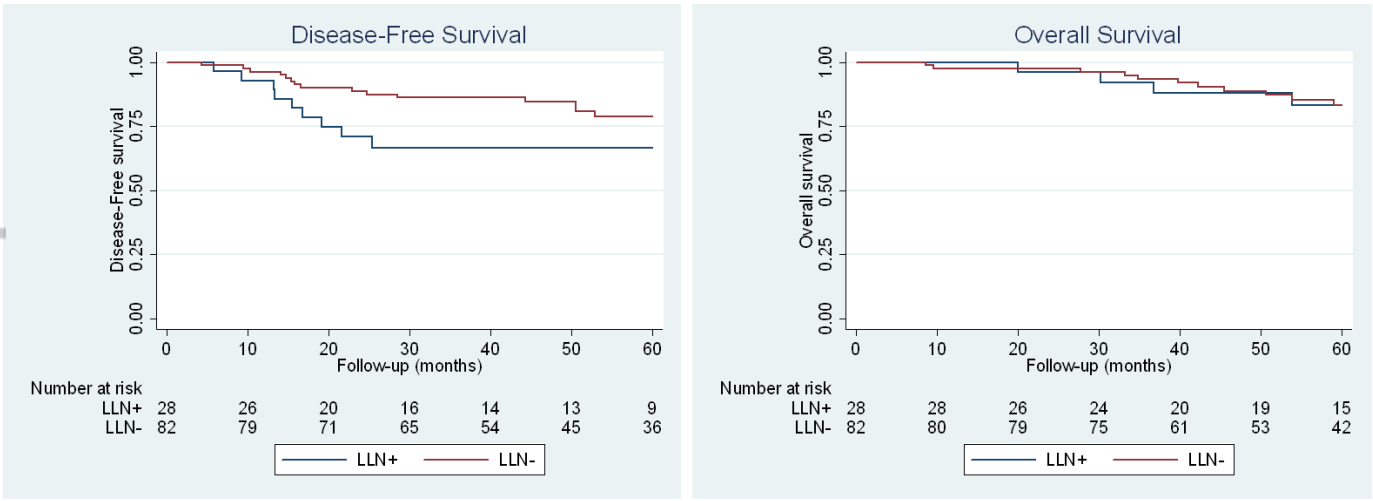


Figure 2. A. Disease free survival (DFS) for enlarged lateral pelvic lymph nodes (LLN+) and non-enlarged lateral pelvic lymph nodes (LLN-) patients, and B. Overall survival (OS) for LLN+ and LLN- patients. Log-rank test values, $p = 0.0954$ for DFS, and $p = 0.439$ for OS.

Table 1. Baseline characteristics by LLN status

Factor		LLN+	LLN-	p-value
Patient characteristics				
N		28	82	
Age Group	**<65**	20 (71%)	42 (51%)	0.079
	65-74	7 (25%)	24 (29%)	
	≥75	1 (4%)	16 (20%)	
Sex	**M**	23 (82%)	58 (71%)	0.24
	F	5 (18%)	24 (29%)	
BMI, mean (SD)		26.9 (6.0)	27.1 (4.2)	0.82
Tumour characteristics				
Height cm, median (IQR)		4.8 (2.8, 6.5)	5.5 (4.0, 6.6)	0.23
cT Stage	**cT2**	4 (14%)	20 (24%)	0.14
	cT3	15 (54%)	49 (60%)	
	cT4	9 (32%)	13 (16%)	
cN Stage	**cN1**	13 (46%)	36 (44%)	0.82
	cN2	15 (54%)	46 (56%)	
CRM involvement	**No**	11 (39%)	45 (55%)	0.15
	Yes	17 (61%)	37 (45%)	
Adjuvant chemotherapy	**No**	8 (29%)	32 (39%)	0.32
	Yes	20 (71%)	50 (61%)	
Perioperative characteristics and histopathology				
Primary Procedure	**APR**	20 (72%)	39 (48%)	0.15
	Hartmann's	1 (4%)	2 (2%)	
	Low AR	0 (0%)	2 (2%)	
	Ultra-low anterior resection	6 (21%)	36 (44%)	
	Ultra-low Hartmann's	1 (4%)	3 (4%)	
ypT Stage	**ypT0**	8 (29%)	30 (37%)	0.33
	ypT1	1 (4%)	8 (10%)	
	ypT2	10 (36%)	18 (22%)	
	ypT3	8 (29%)	23 (28%)	
	ypT4	0 (0%)	1 (1%)	
	ypT4a	1 (4%)	0 (0%)	
	ypT4b	0 (0%)	2 (2%)	
ypN Stage	**ypN0**	20 (71%)	64 (78%)	0.18
	ypN1	5 (18%)	12 (15%)	
	ypN1a	0 (0%)	3 (4%)	
	ypN2	2 (7%)	1 (1%)	
	ypN2a	0 (0%)	2 (2%)	
	ypN2b	1 (4%)	0 (0%)	
Pathological Response	**Complete response**	8 (29%)	27 (33%)	0.16
Nodes Examined, median (IQR)		14 (11, 18)	12 (9, 16)	0.11

Table 2. Outcomes and follow up by LLN status. [†]Patient with both LR and Distant Metastasis. SD; standard deviation, IQR; interquartile range, CI; Confidence interval

Outcome	LLN+ (n=28)	LLN- (n=82)	All patients (n=110)	p-value
Local recurrence	1 (4%)	1[†] (1%)	2[†] (1.8%)	0.44
Distant Metastasis	8 (29%)	15[†] (18%)	23[†] (21%)	0.24
5-year Disease free survival (95% CI)	67% (44-82%)	79% (67-87%)	76% (66-83%)	0.10
5-year Overall survival	83% (61-93%)	83% (72-91%)	84% (74-90%)	0.44
Median Disease-free survival (months, IQR)	41 (18,68)	52 (33,72)	52 (29,71)	0.19
Mean OS (months, SD)	62 (28.0)	60 (24.8)	61 (25.5)	0.80
Median follow up (months, IQR)	62 (39, 80)	58 (39,80)	59 (39,80)	0.86