Management of Lateral Lymph Node Metastasis in Rectal Cancer

by

Associate Professor Hidde Maarten Kroon, MD, PhD

Discipline of Surgery
Adelaide Medical School
Faculty of Health and Medical Sciences
The University of Adelaide

Thesis submitted February 2022 to the University of Adelaide for the degree of Master of Philosophy (M.Phil)

Supervisors

Dr. Michelle L. Thomas, MBBS, PhD, FRACS (Principal Supervisor)
Associate Professor Tarik Sammour, MBChB, PhD, FRACS

To Noah and Hannah

Table of Contents

Publications included in this Thesis

Kroon HM, Malakorn S, Dudi-Venkata NN, Bedrikovetski S, Liu J, Kenyon-Smith T, Bednarski BK, Ogura A, Van de Velde CJH, Rutten HJT, Beets GL, Thomas ML, Kusters M, Chang GJ, Sammour T. Local recurrences in Western low rectal cancer patients treated with or without lateral lymph node dissection after neoadjuvant (chemo)radiotherapy: An international multi-centre comparative study. Eur J Surg Oncol 2021;47:2441-9. doi: 10.1016/j.ejso.2021.06.004.

Kroon HM, Kusters M, Chang GJ, Sammour T. Reply to: Lateral lymph node dissection in low rectal cancers: Call for standardized reporting of results to unify the global practice. Eur J Surg Oncol 2021;47:2477-8. doi: 10.1016/j.ejso.2021.06.030.

Kroon HM, Hoogervorst L, Hanna-Rivero N, Traeger L, Dudi-Venkata NN, Bedrikovetski S, Kusters M, Thomas ML, Sammour T. Systematic review on long-term oncological outcomes of lateral lymph node dissection for metastatic nodes after neoadjuvant chemoradiotherapy in rectal cancer. Submitted.

Kroon HM, Dudi-Venkata NN, Bedrikovetski S, Liu J, Haanappel H, Ogura A, Van de Velde CJH, Rutten HJT, Beets GL, Thomas ML, Kusters M, Sammour T. Malignant features in pre-treatment metastatic lateral lymph nodes in locally advanced low rectal cancer predict distant metastases. Ann Surg Oncol 2022;29:1194-1203. doi: 10.1245/s10434-021-10762-z.

Kroon HM, Kusters M, Sammour T. ASO author reflection: Lateral pelvic lymph nodes in rectal cancer: Not all are created equal. Ann Surg Oncol 2022;29:1204-5. doi: 10.1245/s10434-021-10815-3.

Thesis abstract

Introduction: Pre-treatment abnormal lateral lymph nodes (LLNs) are present in approximately 20% of patients with locally advanced rectal cancer. Western treatment of LLNs consists of neoadjuvant (chemo)radiotherapy (nCRT) followed by total mesorectal excision (TME), meaning these nodes are not removed surgically. There is, however, potential benefit in performing an additional lateral lymph node dissection (LLND) as enlarged LLNs have been shown to be predictive for local recurrence. Furthermore, the impact on oncological outcomes when enlarged LLNs harbour malignant features is currently unknown. Therefore, the aims of this thesis were to investigate if patients benefit from an additional LLND after nCRT and to determine oncological outcomes when malignant features are present in enlarged LLNs.

Methods: A multi-centre cohort study was conducted at six tertiary referral centres in the US, the Netherlands and Australia. All patients had locally advanced rectal cancer with enlarged LLNs with a short-axis of ≥5mm. Malignant features were defined as nodes with internal heterogeneity and/or border irregularity. Firstly, patients who underwent nCRT followed by TME (LLND-) were compared to those who underwent a LLND in addition to nCRT and TME (LLND+). Next, a systematic review and meta-analysis was performed on studies comparing LLND- versus LLND+. Finally, patients with and without malignant features were compared. Outcomes of interest were local recurrence-free survival (LRFS), distant metastatic-free survival (DMFS), disease-free survival (DFS), and overall survival (OS).

Results: LLND+ patients (n=44) were younger with higher ASA-classifications and ypN-stages compared to LLND- patients (n=115). LLND+ patients had larger median LLNs short-axes and received more adjuvant chemotherapy (100 vs. 30%; $p<0.0001$). Between groups,

LRFS was 97% for LLND+ versus 89% for LLND- (p=0.13). DFS (p=0.94) and OS (p=0.42) were similar. LLND was an independent significant factor for local recurrences (p=0.01) in the multi-variate analysis. Sub-analysis of patients who underwent long-course nCRT and had adjuvant chemotherapy (LLND- n=30, LLND+ n=44) demonstrated a higher LRFS for LLND+ patients (97% versus 84% for LLND-; p=0.04). DFS (p=0.10) and OS (p=0.11) were similar between groups.

Seven studies were included in the systematic review. Five-year LRFS after LLND+ was improved (range 85-95%) compared to LLND- (43-89%; statistically significant in three studies). DFS was increased after LLND+ (range 61-74%) compared to LLND- (54-79%; significant in three studies). No study reported five-year overall survival benefit after LLND+ (range 72-80%; 69-91% for LLND-).

In the analysis of malignant features, median LLNs short-axis was 7mm (range 5-28) for the complete cohort, of whom 60 patients (52%) had malignant features. LLNs with malignant features showed no difference in LRFS (p=0.20) but had worse DMFS (p=0.004) and OS (p=0.006) compared to those without malignant features. Cox regression analysis confirmed malignant features as an independent factor for DMFS.

Conclusions: This thesis suggests that a LLND in addition to nCRT in locally advanced rectal cancer improves LRFS and DFS, and that malignant features present in enlarged LLNs are predictive for a worse DMFS. More high-quality studies are required to further explore the value of LLND and the role of malignant features in LLNs.

Statement of Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I acknowledge that the copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Hidde Maarten Kroon

February 2022

Abbreviations

95%CI: 95% confidence interval

χ^2: Chi squared (Chi 2) test

%: percentage

AJCC: American Joint Committee on Cancer

APR: Abdomino-perineal resection

ASA: American Society of Anesthesiologists classification

AUS: Australia

BMI: Body mass index

cm: centimetres

CRM: Circumferential resection margin

cCRM: Clinical/pre-treatment circumferential resection margin

CRT: chemoradiotherapy

nCRT: Neoadjuvant chemoradiotherapy

CT: Computer Tomography

DFS: Disease-free survival

DMFS: Distant metastatic-free survival

FOLFOX: folinic acid, fluorouracil and oxaliplatin

HR: Hazard ratio

IV: intravenous

LAR: Low anterior resection

LLNs: Lateral lymph nodes

LLND: lateral lymph node dissection

LLND+: LLNs patients who underwent a LLND

LLND-: LLNs patients who did not undergo a LLND

LLR: Lateral local recurrence

LLRR: lateral local recurrence rate

LLRFS: Lateral local recurrence-free survival

LN: Lymph nodes

LR: Local recurrence

LRR: local recurrence rate

LRFS: Local recurrence-free survival

LOS: Length of stay

MDACC: MD Anderson Cancer Center

MeSH: Medical Subject Heading

MRI: Magnetic Resonance imaging

NL: The Netherlands

NCI-AvL: Netherlands Cancer institute – Antoni van Leeuwenhoek

OS: overall survival

RAH: Royal Adelaide Hospital

RT: Radiotherapy

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

TNM-stage: Tumour, nodal and distant metastasis stage

cTNM-stage: Clinical tumour, nodal and distant metastasis stage

cT-stage: Clinical tumour stage

cN-stage: Clinical nodal stage

ypTNM-stage: Post-neoadjuvant pathological tumour, nodal and distant metastasis stage

ypT: Post-neoadjuvant pathological tumor stage

ypN: Post-neoadjuvant pathological nodal stage

TME: Total mesorectal excision

US: The United States of America

vs: versus

Index of Figures

Index of Tables

General introduction

The incidence of colorectal cancer in Australia is 15,540 patients per year, with over 5,000 patients dying from this disease annually.[1] In approximately a third of patients with colorectal cancer, the tumour is located in the rectum. Of these, 20-25% suffer from locally advanced rectal cancer (American Joint Committee on Cancer [AJCC] Stage III disease) with disease progression to the loco-regional lymph nodes, either to the nodes directly surrounding the rectum in the mesorectum, or farther from the rectum to the so-called lateral lymph nodes (LLNs) in the pelvic side-wall in one of the following drainage basins: obturator, internal iliac, external iliac and/or common iliac basin.[2-6] (Figure I.1)

Pre-treatment, LLNs are considered metastatic when they are enlarged, commonly ≥5mm in short-axis diameter, although size criteria have been debated, with or without one of the following malignant features: border irregularity or internal heterogeneity.[4-6] (Figure I.2)

Figure I.1a: Lymphatic drainage of the rectum and lateral pelvic lymph nodes. (adopted from: Otero de Pablos, et al.)[5]

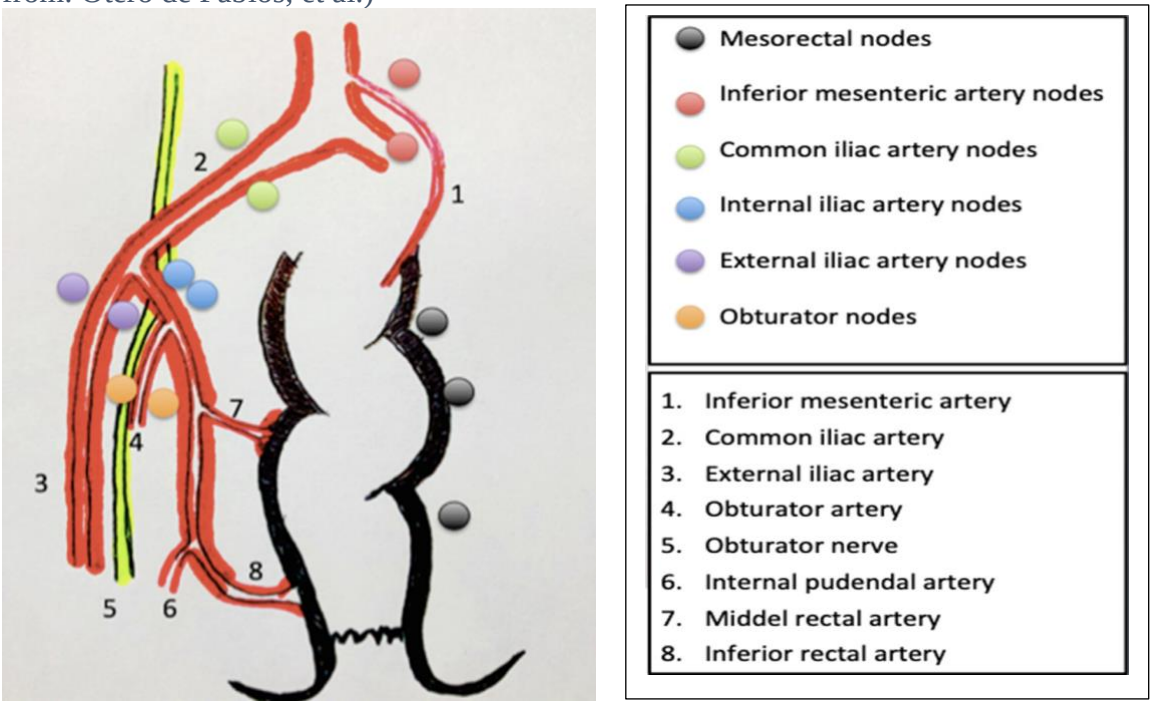


Figure I.1b: External iliac basin (red), obturator basin (green) and internal iliac basin (blue) on MRI. (adopted from: Ogura, et al.)[6]

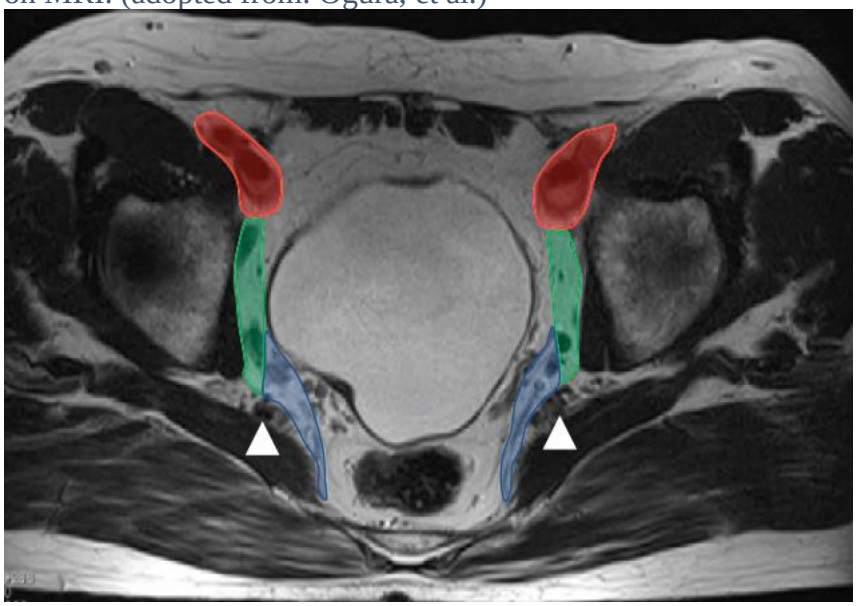
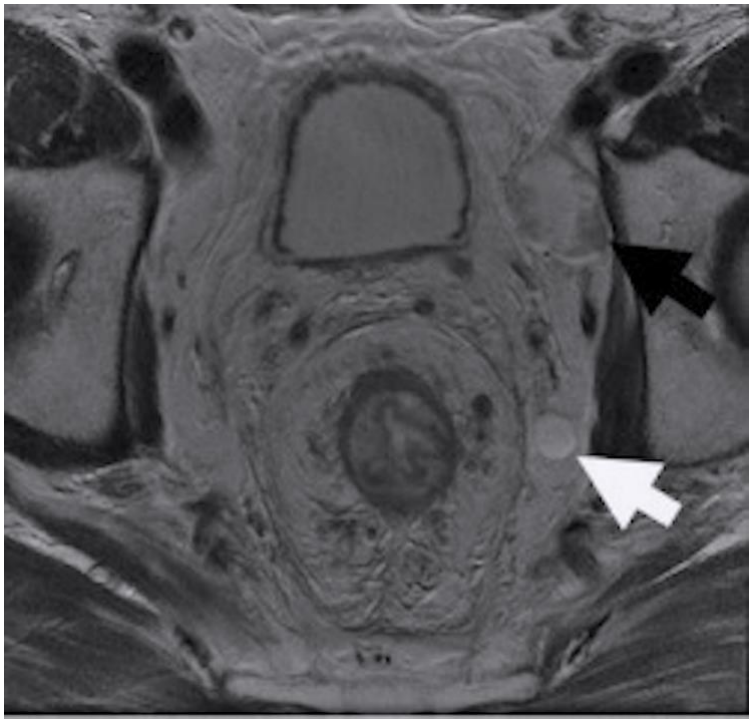


Figure I.2: Pre-treatment pelvic MRI of patient with locally advanced rectal cancer with enlarged lateral lymph nodes with (black arrow) and without (white arrow) malignant features.



There is some divergence in cancer treatment paradigms between Eastern and Western centres in this area. In the West, standard treatment of patients with rectal cancer and disease progression to the mesorectal lymph nodes consists of neoadjuvant chemoradiotherapy

(nCRT) followed by total mesorectal excision (TME) surgery, during which the rectum with the tumour and the surrounding lymph nodes in the mesorectum are removed.[7] Contrary to involved mesorectal lymph nodes, pre-treatment enlarged LLNs are normally not removed surgically. In these patients, it is assumed LLNs are neutralised by nCRT, however, it is unclear if this treatment is indeed sufficient.[8-9] In comparison to patients with metastatic mesorectal lymph nodes only, patients with LLNs have an increased risk of developing local recurrences (LR), which can severely impact quality of life due to symptoms such as pain and limb swelling, and can reduce overall survival (OS).[4,10-12]

In contrast, for AJCC Stage III rectal cancer patients with pre-treatment enlarged LLNs, the treatment strategy in the East (mainly South Korea and Japan) has evolved differently, consisting of TME, often without nCRT, but with a lateral lymph node dissection (LLND).[3] Interestingly, comparisons of the Western (nCRT) and the Eastern (LLND) treatments for pre-treatment enlarged LLNs have shown similar LR and OS rates, despite the differences in approach.[4,9,13]

In recent years, an increasing number of studies suggest beneficial long-term oncological outcomes when a LLND during TME is performed in addition to nCRT in patients with pre-treatment enlarged LLNs.[14-16] Therefore, combining both treatment modalities may improve oncological outcomes. However, since these studies have mostly been conducted in the East without a comparative group, it remains unclear whether an additional LLND after nCRT leads to improved LR rates and OS in Western patients.

This thesis comprises three chapters investigating the metastatic potential and long-term oncological outcomes of pre-treatment abnormal LLNs and evaluates the results of an addition LLND following nCRT.

Chapter 1 is the first comparative study describing long-term oncological outcomes of Western patients with rectal cancer, all treated with nCRT and undergoing either a LLND

during TME (LLND+ group) or TME only (LLND- group). An international multi-centre collaborative was formed between six international tertiary referral centres from the Netherlands (NL: Antoni van Leeuwenhoek-Netherlands Cancer Institute in Amsterdam, Catharina Hospital in Eindhoven and Leiden University Medical Center in Leiden), Australia (AUS: Royal Adelaide Hospital and St. Andrew's hospital both in Adelaide) and the United States (US: MD Anderson Cancer Center in Houston (MDACC), Texas). From these centres, data were compiled and analysed. Results show that a LLND in addition to nCRT may improve loco-regional control in Western patients with rectal cancer and pre-treatment enlarged LLNs, with significantly lower LR rates (LRR) in the LLND+ group in the multivariate analysis as well as in the univariate analysis of the subgroup of patients who all had adjuvant chemotherapy.

Chapter 2 brings together the work from chapter 1 with the current literature, which developed during the course of the thesis, in a systematic review and meta-analysis. This study includes seven studies that reported long-term oncological outcomes of rectal cancer patients with pre-treatment enlarged LLNs undergoing a LLND at the time of TME in addition to nCRT (LLND+ group) versus patients who underwent nCRT and TME only (LLND- group). The results of this systematic review show lower LR rates for the LLND+ group but no difference in disease-free survival and OS between both groups.

Chapter 3 aims to further refine which patient may benefit most from a LLND. Previous studies have suggested that enlarged LLNs are predictive of LR after standard Western treatment, consisting of nCRT followed by TME, which was confirmed in Chapter 1 and 2.[4,12,17,18] but not much is known of the impact when malignant features are also present. Therefore, this chapter compares long-term oncological outcomes of patients from the above-mentioned centres, with pre-treatment enlarged LLNs and malignant features to those without malignant features, who were all treated according to the Western standard of nCRT followed

by TME, without a LLND. The results confirm that pre-treatment enlarged LLNs are predictive of LR in the univariate and multivariate analyses. In addition, the presence of malignant features are predictive for a worse distant metastatic-free survival, suggesting an increased metastatic potential of these nodes.

Considering the results described in the chapters of this thesis, an argument could be made to perform an additional LLND during TME after nCRT in rectal cancer patient with pre-treatment abnormal LLNs, with size and morphology influencing decision making.

References

1. Australian Government, Cancer Australia [Internet]. Canberra, ACT, Australia; 2021 [updated 2021 August 26; cited 2021 September 24th]. Available from: www.canceraustralia.gov.au/cancer-types/bowel-cancer/statistics
2. Amin MB, Edge S, Greene F, Byrd DR, et al. AJCC cancer staging manual. 8th ed. New York, NY, USA: Springer, 2017:252-54.
3. Hashiguchi Y, Muro K, Saito Y, et al. Japanese society for cancer of the colon and rectum. Japanese society for cancer of the colon and rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol 2020;25:1-42.
4. Kusters M, Uehara K, Velde CJHV, Moriya Y. Is there any reason to still consider lateral lymph node dissection in rectal cancer? Rationale and technique. Clin Colon Rectal Surg 2017;30:346-56.
5. Otero de Pablos J, Mayol J. Controversies in the management of lateral pelvic lymph nodes in patients with advanced rectal cancer: East or West? Front Surg 2020;6:79.
6. Ogura A, Konishi T, Beets GL, et al. Lateral nodal features on restaging magnetic resonance imaging associated with lateral local recurrence in low rectal cancer after neoadjuvant chemoradiotherapy or radiotherapy. JAMA Surg 2019;154:e192172.
7. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114-23.
8. 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;60:577-85.
9. Williamson JS, Quyn AJ, Sagar PM. Rectal cancer lateral pelvic sidewall lymph nodes: a review of controversies and management. Br J Surg 2020;107:1562-9.
10. 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;21:189-96.
11. Ishihara S, Kawai K, Tanaka T, et al. Oncological outcomes of lateral pelvic lymph node metastasis in rectal cancer treated with preoperative chemoradiotherapy. Dis Colon Rectum 2017;60:469-76.
12. Haanappel A, Kroon HM, Schaap DP, et al. Lateral lymph node metastases in locally advanced low rectal cancers may not be treated effectively with neoadjuvant chemoradiotherapy only. Front Oncol 2019;9:1355.
13. Kusters M, Beets GL, van de Velde CJ, Beets-Tan RG, Marijnen CA, Rutten HJ, et al. A comparison between the treatment of low rectal cancer in Japan and the Netherlands, focusing on the patterns of local recurrence. Ann Surg 2009;249:229-35.
14. Ogura A, Konishi T, Cunningham C, et al. Neoadjuvant (chemo)radiotherapy with total mesorectal excision only is not sufficient to prevent lateral local recurrence in enlarged nodes: Results of the multicenter lateral node study of patients with low cT3/4 rectal cancer. J Clin Oncol 2019;37:33-43.
15. Kim MJ, Chang GJ, Lim HK, et al. Oncological impact of lateral lymph node dissection after preoperative chemoradiotherapy in patients with rectal cancer. Ann Surg Oncol 2020;27:3525–33.
16. Jones HG, Radwan RW, Sams E, et al. Incidence and treatment of positive pelvic sidewall lymph nodes in patients with rectal cancer. Colorectal Dis 2020;22:1560-7.
17. Malakorn S, Yang Y, Bednarski BK, et al. Who should get lateral pelvic lymph node dissection after neoadjuvant chemoradiation? Dis Colon Rectum 2019;62:1158-66.

18. Atef Y, Koedam TW, van Oostendorp SE, Bonjer HJ, Wijsmuller AR, Tuynman JB. Lateral pelvic lymph node metastases in rectal cancer: A systematic review. World J Surg 2019;43:3198-206.

Chapter 1

Local recurrences in Western low rectal cancer patients treated with or without lateral lymph node dissection after neoadjuvant (chemo)radiotherapy: An international multi-centre comparative study.

Hidde M. Kroon[1,2], Songphol Malakorn[3], Nagendra N. Dudi-Venkata[1,2], Sergei Bedrikovetski[1,2], Jianliang Liu[1], Tim Kenyon-Smith[1], Brian K. Bednarski[3], Atsushi Ogura[4,5], Cornelis J.H. van de Velde[4], Harm J.T. Rutten[6,7], Geerard L. Beets[8], Michelle L. Thomas[1], Miranda Kusters[9], George J. Chang[3], Tarik Sammour[1,2].

[1] Colorectal Unit, Department of Surgery, Royal Adelaide Hospital, Adelaide, South Australia, Australia
[2] Faculty of Health and Medical Science, Adelaide Medical School, University of Adelaide, Adelaide, South Australia, Australia
[3] Department of Surgical Oncology, Division of Surgery, MD Anderson Cancer Center, Houston, Texas, USA
[4] Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands
[5] Department of Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan
[6] Department of Surgery, Catharina Hospital, Eindhoven, the Netherlands
[7] GROW, School of Oncology and Developmental Biology, University of Maastricht, Maastricht, the Netherlands
[8] Department of Surgery, the Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, the Netherlands
[9] Department of Surgery, Amsterdam University Medical Centers, location VUmc, Amsterdam, the Netherlands

Eur J Surg Oncol 2021;47:2441-9. doi: 10.1016/j.ejso.2021.06.004.

Statement of Authorship

Title of Paper	Local recurrences in Western low rectal cancer patients treated with or without lateral lymph node dissection after neoadjuvant (chemo)radiotherapy: An international multi-centre comparative study.
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Kroon HM, Malakorn S, Dudi-Venkata NN, Bedrikovetski S, Liu J, Kenyon-Smith T, Bednarski BK, Ogura A, Van de Velde CJH, Rutten HJT, Beets GL, Thomas ML, Kusters M, Chang GJ, Sammour T. Local recurrences in Western low rectal cancer patients treated with or without lateral lymph node dissection after neoadjuvant (chemo)radiotherapy: An international multi-centre comparative study. Eur J Surg Oncol 2021;47:2441-9. doi: 10.1016/j.ejso.2021.06.004.

Principal Author

Name of Principal Author (Candidate)	Hidde M. Kroon		
Contribution to the Paper	Conception and design of the project Acquiring research data Analysis and interpretation of research data Drafting the article Critically revising of article		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	13/09/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Songphol Malakorn		
Contribution to the Paper	Acquiring research data Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Nagendra N. Dudi-Venkata		
Contribution to the Paper	Conception and design of the project Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Sergei Bedrikovetski		
Contribution to the Paper	Conception and design of the project Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Jianliang Liu		
Contribution to the Paper	Acquiring research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Tim Kenyon-Smith		
Contribution to the Paper	Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Brian K. Bednarski		
Contribution to the Paper	Conception and design of the project Acquiring research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Atsushi Ogura		
Contribution to the Paper	Conception and design of the project Acquiring research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Cornelis J.H. van de Velde		
Contribution to the Paper	Conception and design of the project Acquiring research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Harm J.T. Rutten		
Contribution to the Paper	Conception and design of the project Acquiring research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Geerard L. Beets		
Contribution to the Paper	Conception and design of the project Acquiring research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Michelle L. Thomas		
Contribution to the Paper	Conception and design of the project Acquiring research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Miranda Kusters		
Contribution to the Paper	Conception and design of the project Acquiring research data Interpretation of research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	George J. Chang		
Contribution to the Paper	Conception and design of the project Acquiring research data Interpretation of research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Tarik Sammour		
Contribution to the Paper	Conception and design of the project Acquiring research data Interpretation of research data Critically revising of article		
Signature		Date	13/09/2021

Abstract

Introduction: In the West, low rectal cancer patients with abnormal lateral lymph nodes (LLNs) are commonly treated with neoadjuvant (chemo)radiotherapy (nCRT) followed by total mesorectal excision (TME). Additionally, some perform a lateral lymph node dissection (LLND). To date, no comparative data (nCRT vs. nCRT+LLND) are available in Western patients.

Methods: An international multi-centre cohort study was conducted at six centres from the Netherlands, US and Australia. Patients with low rectal cancers from the Netherlands and Australia with abnormal LLNs (≥5mm short-axis in the obturator, internal iliac, external iliac and/or common iliac basin) who underwent nCRT and TME (LLND- group) were compared to similarly staged patients from the US who underwent a LLND in addition to nCRT and TME (LLND+ group).

Results: LLND+ patients (n=44) were younger with higher ASA-classifications and ypN-stages compared to LLND- patients (n=115). LLND+ patients had larger median LLNs short-axes and received more adjuvant chemotherapy (100 vs. 30%; p<0.0001). Between groups, the local recurrence rate (LRR) was 3% for LLND+ vs. 11% for LLND- (p=0.13). Disease-free survival (DFS, p=0.94) and overall survival (OS, p=0.42) were similar. On multivariable analysis, LLND was an independent significant factor for local recurrences (p=0.01). Sub-analysis of patients who underwent long-course nCRT and had adjuvant chemotherapy (LLND- n=30, LLND+ n=44) demonstrated a lower LRR for LLND+ patients (3% vs. 16% for LLND-; p=0.04). DFS (p=0.10) and OS (p=0.11) were similar between groups.

Conclusion: A LLND in addition to nCRT may improve loco-regional control in Western patients with low rectal cancer and abnormal LLNs. Larger studies in Western patients are required to evaluate its contribution.

Introduction

Pre-treatment abnormal lateral lymph nodes (LLNs; ≥5mm short-axis in the obturator, internal iliac, external iliac and/or common iliac basin) are present in 16-23% of patients with a primary locally advanced low rectal cancer.[1] These LLNs are associated with increased risk of developing local recurrences (LR).[2] In most Western centres, standard treatment for patients with LLNs is similar to the treatment of those without LLNs and consists of neoadjuvant (chemo)radiotherapy (nCRT), mostly with extended beam radiotherapy to include the LLNs basins, followed by total mesorectal excision (TME).[3-5] This means that, in the West, abnormal LLNs are normally not resected but are assumed to be sterilized by nCRT. It is, however, unclear how effective this Western treatment approach in neutralizing LLNs.[6-9]

In contrast, for similarly staged patients, the treatment strategy in the East (mainly Japan) has evolved in a different direction, consisting of TME, often without nCRT, but with a lateral lymph nodal dissection (LLND).[1,10] Recent data from primarily Eastern centres and two Western centres performing LLNDs have suggested oncological benefit in terms of lower local recurrence rates (LRR), when, after nCRT, a LLND is carried out at the time of TME compared to nCRT and TME alone.[11] This is likely due to residual disease in the LLNs after nCRT.[8,9] For this reason, some centres in the West now treat patients with low rectal cancer and LLNs with nCRT and LLND.[12,13]

To date, however, no studies exist in Western LLNs patients comparing those undergoing a TME with LLND to TME only after nCRT. It remains therefore unclear whether a LLND after nCRT leads to lower LRR in this population. In order to investigate its value, we conducted an international multi-centre study including Western patients only with locally advanced low rectal cancers and LLNs who underwent nCRT followed by a LLND at the

time of TME, or TME only, with the hypothesis that an additional LLND results in a lower LRR.

Methods

The 'Strengthening the Reporting of Observational Studies in Epidemiology' guideline was used for this paper.[14]

A retrospective comparative cohort study was conducted at six international tertiary referral centres from the Netherlands (NL: Antoni van Leeuwenhoek-Netherlands Cancer Institute in Amsterdam, Catharina Hospital in Eindhoven and Leiden University Medical Center in Leiden), Australia (AUS: Royal Adelaide Hospital and St. Andrew's hospital both in Adelaide) and the MD Anderson Cancer Center in Houston (MDACC), Texas, USA. Patients from MDACC underwent nCRT and a LLND with TME and were compared to NL/AUS patients who were treated with nCRT and TME only (without LLND). The study was approved by the human research ethics committee at each site.

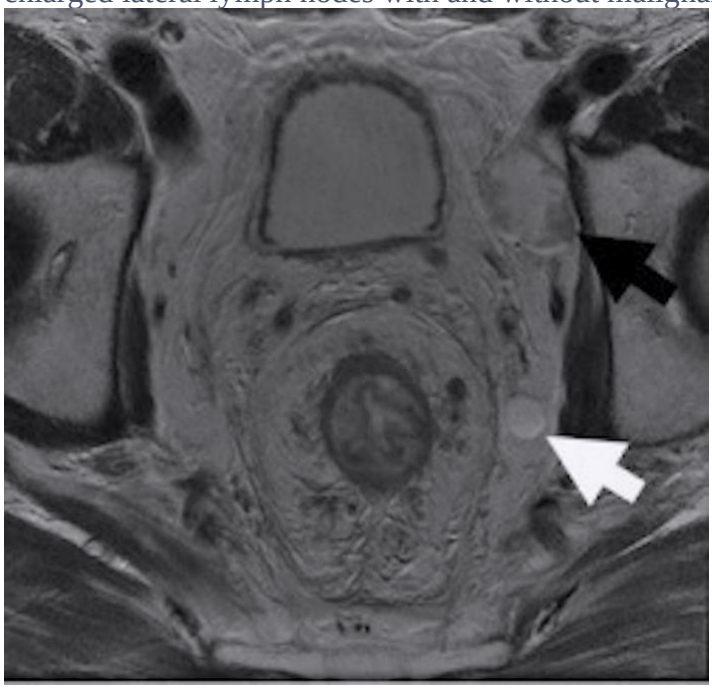
For the current study, patient inclusion criteria from the Lateral Node Study Consortium were adopted.[11] Included were consecutive patients from each centre, ≥18 years with a primary locally advanced rectal cancer ≤8 cm of the anal verge with abnormal pre-treatment lateral lymph nodes on staging MRI, without distant metastases, who were treated with curative intent between January 2009 and December 2016, with a minimum of three-year follow-up.[1,11] LLNs were considered abnormal in case of a short-axis of ≥5 mm in the following anatomical locations: the obturator, internal iliac, external iliac and/or common iliac basins.[1,15-17] The MRI's were re-reviewed and reported by dedicated radiologists. All patients underwent neoadjuvant therapy which consisted of either short-course radiotherapy (5x5 Gray) or long-course chemoradiotherapy (45-50.4 Gray in 28 fractions over 5.5 weeks) with one of the following concomitant chemotherapy regimens: FOLFOX (folinic acid, fluorouracil and oxaliplatin), capecitabine, or 5-fluorouracil. In all participating centres, radiotherapy routinely a boost and fields were extended to include LLNs basins. Restaging

after nCRT was not performed routinely at all participating sites. A TME with curative intent was carried out 6-8 weeks after completion of nCRT. Additionally, MDACC patients underwent an indicated LLND at the time of TME to remove the pre-treatment abnormal LLN basins according to a previously described technique.[3,6,18] None of the AUS/NL patients underwent a LLND. All operations were performed by two to five senior attending surgeons per centre at least three years before data analysis. Following surgery, routine oncological follow-up took place. LR was defined as tumour regrowth in the pelvis at the site of the anastomosis, the previously resected mesorectal tissues, or in one or more of the LLNs basins. Lateral local recurrence (LLR) was defined as tumour regrowth in one or more of the LLNs basins. Distant metastases were defined as tumour growth in inguinal and/or para-aortic lymph nodes, peritoneum and/or in distant organs. Excluded were patients with a high rectal cancer (>8cm), those with distant metastatic disease beyond the LLNs at the time of diagnosis, patients with LR after previous rectal resections, patients who did not receive nCRT, and patients who did not undergo TME.

Preoperative data collected included age, sex, body mass index (BMI), ASA-classification, cTNM-stage, height of tumour from the anal verge on MRI, clinical circumferential resection margin (cCRM), side of LLNs, short-axis and malignant features (defined as nodes with internal heterogeneity and/or border irregularity; Figure 1.1) of LLNs and type of neoadjuvant therapy. Peri-operative data included: type of resection, operation time, side and sites of LLNs resected (MDACC only), Clavien-Dindo complication grade[19], Length of hospital stay (LOS), ypTNM-stage, resection margins, lymphovascular invasion, number of lymph nodes resected, and adjuvant chemotherapy. Primary outcomes were LLR and LR. Secondary outcomes were: postoperative complications, 30-day mortality, distant metastatic-free survival (DMFS), disease-free survival (DFS) and overall survival (OS). Time to LLR and LR, and DMFS, DFS and OS were all calculated from time of surgery until occurrence of

event. Data were collected at the six participating hospitals using departmental prospective colorectal databases, and electronic and paper medical records.

Figure 1.1: Pre-treatment pelvic MRI of a patient with locally advanced rectal cancer with enlarged lateral lymph nodes with and without malignant features.



De-identified data of all participating centres were collected, forming a new database which was collectively analysed. Patients were divided into two groups: LLND+ group (MDACC data) and LLND- group (NL/AUS data). Two analyses were performed: one including the complete cohort and one including only those patients receiving adjuvant chemotherapy. Continuous variables are shown as medians with range and categorical variables are presented as absolute numbers with percentages. Differences in characteristics between groups were evaluated with the Mann Whitney U-test for continuous variables, and the Chi-square or the Fisher's exact test (in tables indicated with *) for categorical variables.[20] Lateral local recurrence rate (LLRR), LRR, DMFS, DFS, and OS were estimated using the Kaplan-Meier method, with the Mantel-Haenszel tests from the day of surgery.[21] For LLRFS, an event was defined as tumour recurrence in one or more of the LLNs basins. For LRFS, this

was defined as tumour recurrence in the pelvis at the site of the anastomosis, the previously resected mesorectal tissues, or in one or more of the LLNs basins. For DMFS, an event was defined as distant tumour recurrence in liver, lung, peritoneum, or any other distant organ site. For DFS, this was defined as lateral and local tumour recurrence, and distant metastases. For OS, an event was defined as death from all causes. Multivariable survival analysis was performed using the Cox proportional hazard model with stepwise backward method. A p-value of ≤ 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 25.0 (IBM Corp, Armonk, NY, USA) and GraphPad Prism version 8.0.2 (GraphPad Software Inc., San Diego, CA, USA).

Results

Complete cohort

In total, 159 rectal cancer patients with pre-treatment abnormal LLNs met the inclusion criteria; 44 of whom in the LLND+ group and 115 in the LLND- group.

LLND+ patients were significantly younger (median 56 vs. 64 years; p=0.0009), included more female patients (52 vs. 25%; p=0.002) and had higher ASA-classifications (p<0.0001; Table 1.1). The tumour was located more proximally in the LLND+ patients (median 5.0 vs. 3.3cm from the anal verge; p=0.016) with significantly fewer having cT4 disease (20 vs. 36%; p=0.023) but more with advanced mesenteric nodal stages (cN1/2 in 95 vs. 83%; p=0.032). The LLNs in LLND+ patients had a larger median short-axis diameter (11.0 vs. 7.0mm; p<0.0001), but showed fewer malignant features on MRI compared to LLND- patients (29 vs. 52%; p=0.012). Furthermore, LLND+ patients had more LLNs located in multiple nodal basins (34 vs. 7%; p<0.0001). All LLND+ patients received long-course nCRT, whereas 17% of the LLND- patients received a short-course regimen (p=0.001).

Table 1.1: Baseline patient and tumour characteristics of complete cohort of low rectal cancer patients with pre-treatment abnormal lateral lymph nodes either undergoing neoadjuvant (chemo)radiotherapy followed by lateral lymph node dissection at the time of total mesenteric excision (TME), or had neoadjuvant (chemo)radiotherapy and TME only.

	Abnormal LLNs not resected (n=115)	**Abnormal LLNs resected** (n=44)	**P-value**
Age in years, median (range)	64 (26 - 85)	56 (20 - 82)	**0.0009**
Sex (%) Male Female	 86 (75) 29 (25)	 21 (48) 23 (52)	**0.002**
BMI, median (range)	26.6 (16.9 - 46.2)	26.7 (17.2 - 48.5)	0.36
ASA-classification (%) 1	 9 (16)	 1 (2)	**<0.0001**

2 3 4	32 (58) 14 (26) 0 (0)[1]	5 (11) 38 (87) 0 (0)	
cT-stage (on MRI) (%) cT1 cT2 cT3 cT4	 0 (0) 1 (1) 72 (63) 42 (36)	 0 (0) 3 (7) 32 (73) 9 (20)	**0.023**
cN-stage mesenteric (on MRI) (%) cN0 cN1 cN2	 19 (17) 38 (33) 58 (50)	 2 (5) 23 (52) 19 (43)	**0.032**
Height of tumour in cm, median (range)	3.3 (0.0 - 9.5)	5.0 (0.0 - 10.0)	**0.016**
cCRM-involvement (on MRI) (%)* Yes No	 48 (42) 67 (58)	 17 (39) 27 (61)	0.86
Side of LLNs (%) Left Right Both	 49 (43) 59 (51) 7 (6)	 15 (34) 17 (39) 12 (27)	**0.001**
Site of LLNs (%) External iliac Internal iliac Obturator Common iliac	 9 (8) 34 (29) 73 (61) 3 (2)[3]	 1 (2) 35 (60) 16 (28) 6 (10)[2]	**<0.0001**
Short-axis LLNs in mm, median (range)	7.0 (5 - 28)	11.0 (5 - 70)	**<0.0001**
Malignant features LLNs (%)* Yes No	 61 (52) 54 (48)	 13 (29) 31 (71)	**0.012**
Malignant features LLNs (%) No Heterogeneity Irregular border Both	 54 (47) 24 (21) 11 (9) 26 (23)	 31 (71) 7 (16) 5 (11) 1 (2)	**0.009**

Neoadjuvant therapy (%)*			
Short-course RT	20 (17)	0 (0)	**0.001**
Long-course CRT	95 (83)	44 (100)	

LLNs: lateral lymph nodes, BMI: body mass index, ASA: American Society of Anaesthesiologists, cT-stage: clinical tumour stage, MRI: magnetic resonance imaging, cN-stage: clinical nodal stage, cCRM: clinical circumferential resection margin, RT: radiotherapy, CRT: chemoradiotherapy, [1] 60 patients missing, [2] 58 sites involved, [3] 119 sites involved. *Fisher's exact test.

There was an equal distribution in the procedure type between groups (Table 1.2). The surgery was performed more often by an open approach (77 vs. 46%; p=0.0005) and took longer in LLND+ patients (median 436 vs. 255 minutes; p<0.0001) but they had a shorter median hospital stay (8 vs. 11 days; p=0.0004). On pathological analysis, LLND+ patients had more advanced nodal (ypN)-stage (ypN I/II in 61 vs. 37%; p=0.018). In the LLND+ group, the median number of LLNs removed was 3, with a median of 0.5 being tumour positive upon histopathology. In 22 (50%) of the LLND+ patients, metastases were found in the LLNs upon histopathology. Two out of the eight patients (25%) with LLNs with a short-axis of 5-6mm had metastatic nodes upon histopathology. Adjuvant chemotherapy was administered to significantly more LLND+ patients (100 vs. 30%; p<0.0001).

Table 1.2: Peri-operative characteristics and postoperative histopathology of complete cohort of low rectal cancer patients with pre-treatment abnormal lateral lymph nodes either undergoing neoadjuvant (chemo)radiotherapy followed by lateral lymph node dissection at the time of total mesenteric excision (TME), or had neoadjuvant (chemo)radiotherapy and TME only.

	Abnormal LLNs not resected (n=115)	**Abnormal LLNs resected** (n=44)	**P-value**
Type of resection (%)			
LAR	53 (46)	19 (43)	0.30
APR	62 (54)	22 (50)	
Exenteration	0 (0)	3 (7)	
Approach (%)*			
Open	48 (46)	34 (77)	**0.0005**

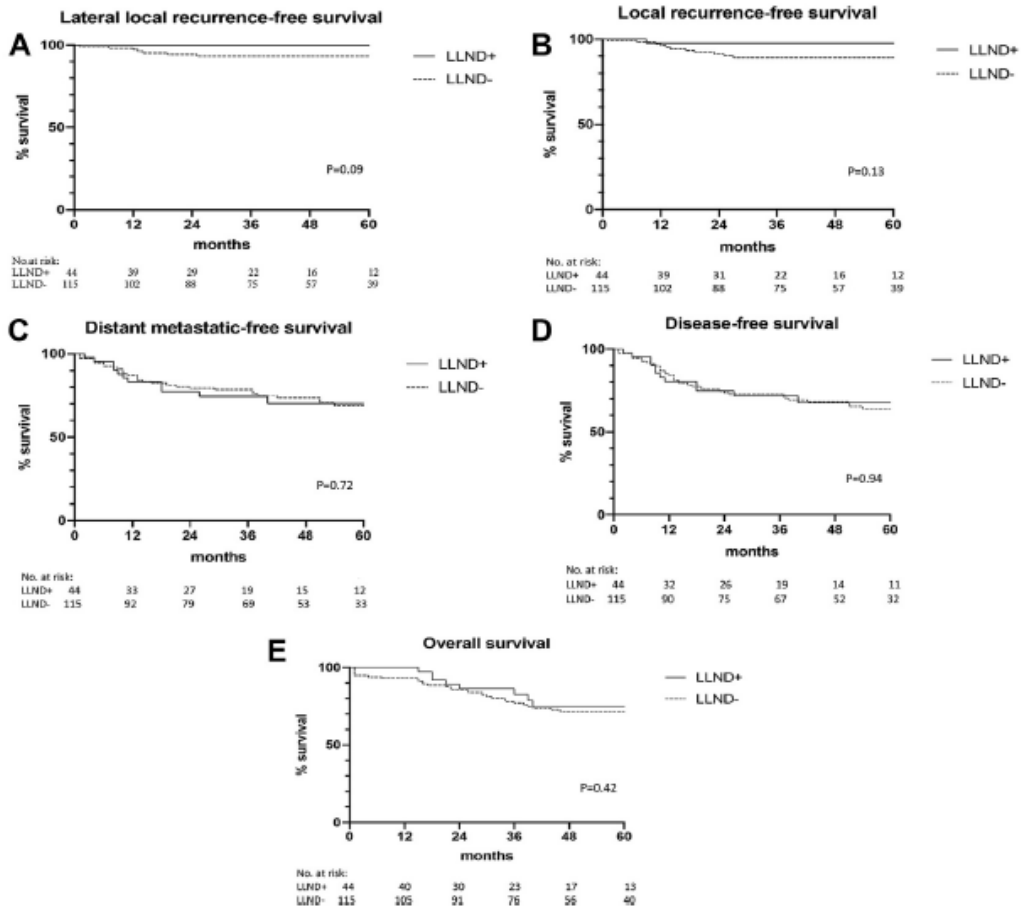
Minimally invasive	56 (54)[1]	10 (23)	
Operation time in minutes, median (range)	255 (78 - 675)[2]	436 (176 - 898)[3]	**<0.0001**
Side of LLNs resected (%) Left Right Both	N/A	15 (34) 17 (39) 12 (27)	N/A
Clavien-Dindo grade (%)[19] 0 1 2 3 4 5	 19 (41) 0 (0) 21 (45) 3 (6) 3 (6) 1 (2)[4]	 20 (46) 1 (2) 13 (30) 9 (20) 1 (2) 0 (0)	0.64
Length of hospital stay in days, median (range)	11 (4 - 62)[2]	8 (2 - 58)	**0.0004**
ypT-stage (%) ypT0 ypT1 ypT2 ypT3 ypT4	 12 (11) 6 (5) 30 (26) 54 (47) 13 (11)	 4 (9) 4 (9) 9 (20) 21 (48) 6 (14)	0.85
ypN-stage (%) ypN0 ypN1 ypN2	 72 (63) 29 (25) 14 (12)	 17 (39) 16 (36) 11 (25)	**0.018**
Resection margins (%) R0 R1 R2	 103 (89) 11 (10) 1 (1)	 39 (89) 5 (11) 0 (0)	0.78
Lympho-vascular invasion (%)* Yes No	 23 (22) 83 (78)[5]	 13 (30) 31 (70)	0.30

Total number of mesorectal LN harvested, median (range)	16 (5 - 46)	22.5 (6 - 60)	**0.004**
Total number of LLNs harvested, median (range)	N/A	3 (0 - 15)	N/A
Tumour positive mesorectal lymph nodes, median (range)	0 (0 - 14)	0 (0 - 13)	0.15
Tumour positive LLNs, median (range)	N/A	0.5 (0 - 3)	N/A
Adjuvant chemotherapy (%)*			
No	80 (70)	0 (0)	**<0.0001***
Yes	35 (30)	44 (100)	

LLNs: lateral lymph nodes, LAR: low anterior resection, APR: abdomino-perineal resection, ypT-stage: post-neoadjuvant pathological tumour stage, ypN-stage: post-neoadjuvant nodal stage, LN: lymph nodes, N/A: not-applicable, [1] 11 patients missing, [2] 60 patients missing [3]10 patients missing, , [4] 68 patients missing, [5] 9 patients missing. *Fisher's exact test.

Median follow-up for LLND+ patients was 47 months (range 1-141), and 59 months (range 1-106) for LLND- patients. No patients were lost to follow-up. There were no significant differences between groups in three-year LLRR (0% for LLND+ vs. 7% for LLND-; p=0.09), LRR (3% for LLND+ vs. 11% for LLND-; p=0.13), DMFS (p=0.72), DFS (p=0.94) and OS (p=0.42). (Figure 1.2)

Figure 1.2: Kaplan-Meier survival curves of complete cohort showing lateral local recurrence-free survival (2a; p=0.09), local recurrence-free survival (2b; p=0.13), distant metastatic-free survival (2c; p=0.72), disease-free survival (2d; p=0.94) and overall survival (2e; p=0.42) for LLND+ vs. LLND- patients.



Cox multivariable analysis showed that LLND was an independent significant factor for LRs (p=0.01). (Table 1.3)

Table 1.3: Complete cohort - Cox regression analysis summary.

Endpoint - Variable	p-value	HR	95%CI
Lateral local recurrence			
ypN-stage	0.04	4.26	1.28 – 14.74
Local recurrence			
Age	0.02	0.91	0.84 – 0.99
Short axis	0.02	1.33	1.06 – 1.68
ypN-stage	0.04	9.89	1.06 – 22.75
LLND	0.01	8.34	3.07 – 32.94
Distant metastasis			
cCRM involved	0.04	2.37	1.04 – 5.40
Malignant features	0.03	0.35	0.14 – 0.91
Resection margin	0.01	4.20	1.39 – 12.76
Adjuvant chemotherapy	0.04	4.63	1.64 – 13.04
Overall survival			
Age	0.05	1.03	1.01 – 1.06
Resection margin	0.04	4.89	1.68 – 14.27

HR: hazard ratio, 95%CI: 95% confidence interval, ypN-stage: post-neoadjuvant pathological nodal stage, LLND: lateral lymph node dissection, cCRM: clinical circumferential resection margin.

Adjuvant chemotherapy cohort

Table 1.4 shows the analysis of the baseline patient and tumour characteristics of patients who all underwent long-course nCRT and had adjuvant chemotherapy (n=44 for the LLND+ group; n=30 for the LLND- group). The LLND+ group consisted of more female patients (52 vs. 30%; p=0.09) and consisted of more patients with ASA grade 3 (87 vs. 29%; p<0.0001). Patient groups had similar ages, BMI, cT- and mesenteric cN-stages, height of tumour from the anal verge and cCRM involvement. The LLND+ group had larger median short-axis diameter of the LLNs (11.5 vs. 7.5mm; p=0.05) but a lower percentage of LLNs with malignant features (29 vs. 60%; p=0.02).

Table 1.4: Baseline patient and tumour characteristics of low rectal cancer patients with pre-treatment abnormal lateral lymph nodes who had adjuvant chemotherapy after either undergoing long-course neoadjuvant chemoradiotherapy followed by lateral lymph node dissection at the time of total mesenteric excision (TME), or had long-course neoadjuvant chemoradiotherapy and TME only.

	Abnormal LLNs not resected (n=30)	**Abnormal LLNs resected** (n=44)	**P-value**
Age in years, median (range)	58 (26 - 80)	56 (20 - 82)	0.78
Sex (%)* Male Female	 21 (70) 9 (30)	 21 (48) 23 (52)	0.09
BMI, median (range)	27.2 (20.8 - 40.1)	26.7 (17.2 - 48.5)	0.90
ASA-classification (%) 1 2 3 4	 2 (8) 15 (63) 7 (29) 0 (0)[1]	 1 (2) 5 (11) 38 (87) 0 (0)	**<0.0001**
cT-stage (on MRI) (%) cT1 cT2 cT3 cT4	 0 (0) 1 (3) 21 (70) 8 (27)	 0 (0) 3 (7) 32 (73) 9 (20)	0.58

cN-stage mesenteric (on MRI) (%) cN0 cN1 cN2	 1 (3) 13 (43) 16 (53)	 2 (5) 23 (52) 19 (43)	 0.69
Height of tumour in cm, median (range)	3.4 (0.0 - 9.5)	5.0 (0.0 - 10.0)[2]	0.29
cCRM-involvement (on MRI) (%)* Yes No	 14 (47) 16 (53)	 17 (39) 27 (61)	 0.63
Side of LLNs (%) Left Right Both	 14 (47) 10 (33) 6 (20)	 15 (34) 17 (39) 12 (27)	 0.54
Site of LLNs (%) External iliac Internal iliac Obturator Common iliac	 2 (6) 13 (39) 16 (49) 2 (6)[4]	 1 (2) 35 (60) 16 (28) 6 (10)[3]	 0.12
Short-axis LLNs in mm, median (range)	7.5 (5 - 26)	11.5 (5 - 70)	**0.05**
Malignant features LLNs (%)* Yes No	 18 (60) 12 (40)	 13 (29) 31 (71)	 **0.02**
Malignant features LLNs (%) No Heterogeneity Irregular border Both	 12 (40) 9 (30) 5 (17) 4 (13)	 31 (71) 7 (16) 5 (11) 1 (2)	 **0.04**

LLNs: lateral lymph nodes, BMI: body mass index, ASA: American Society of Anaesthesiologists, cT-stage: clinical tumour stage, MRI: magnetic resonance imaging, cN-stage: clinical nodal stage, cCRM: clinical circumferential resection margin, RT: radiotherapy, CRT: chemoradiotherapy, [1] 6 patients missing, [2] 1 patient missing; [3] 58 sites involved, [4] 33 sites involved. *Fisher's exact test.

The surgery was performed more often by an open approach (77 vs. 40%; p=0.004) and median operation time was longer in LLND+ patients (436 vs. 255 minutes; p<0.0001) but they had a shorter hospital stay (8 vs. 13 days; p=0.004). All other peri-operative and histopathology results were similar between both groups (Table 1.5).

Table 1.5: Peri-operative characteristics and postoperative histopathology of low rectal cancer patients with pre-treatment abnormal lateral lymph nodes who had adjuvant chemotherapy after either undergoing long-course neoadjuvant chemoradiotherapy followed by lateral lymph node dissection at the time of total mesenteric excision (TME), or had long-course neoadjuvant chemoradiotherapy and TME only.

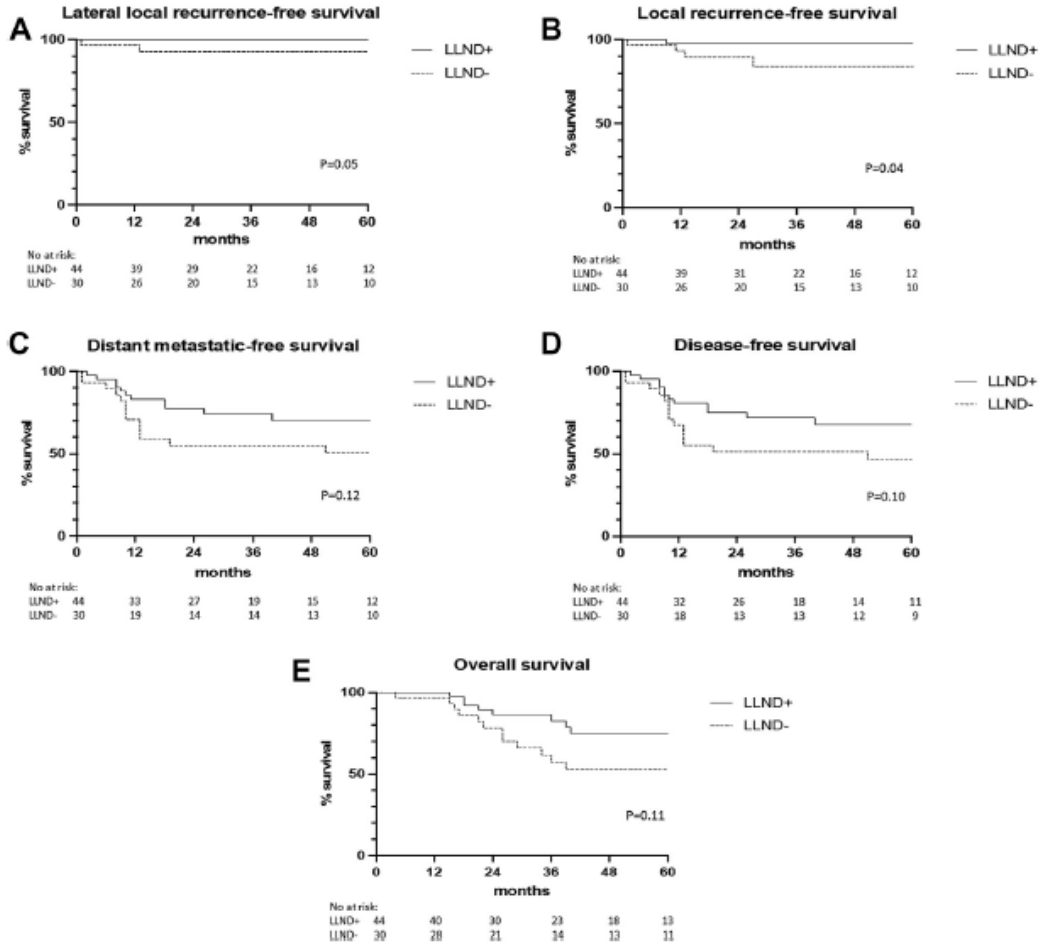
	Abnormal LLNs not resected (n=30)	**Abnormal LLNs resected** (n=44)	**P-value**
Type of resection (%) LAR APR Exenteration	 13 (43) 17 (57) 0 (0)	 19 (43) 22 (50) 3 (7)	 0.33
Approach (%)* Open Minimally invasive	 10 (40) 15 (60)[1]	 34 (77) 10 (23)	 **0.004**
Operation time in minutes, median (range)	255 (78 - 675)[2]	436 (176 - 898)[3]	**<0.0001**
Side of LLNs resected (%) Left Right Both	 N/A	 15 (34) 17 (39) 12 (27)	 N/A
Clavien-Dindo grade (%)[19] 0 1 2 3 4 5	 5 (23) 0 (0) 14 (64) 2 (9) 1 (4) 0 (0)[4]	 20 (46) 1 (2) 13 (30) 9 (20) 1 (2) 0 (0)	 0.38
Length of hospital stay in days, median (range)	13 (6 - 35)[2]	8 (2 - 58)	**0.004**

ypT-stage (%) ypT0 ypT1 ypT2 ypT3 ypT4	 2 (6) 1 (3) 8 (27) 14 (47) 5 (17)	 4 (9) 4 (9) 9 (20) 21 (48) 6 (14)	 0.84
ypN-stage (%) ypN0 ypN1 ypN2	 14 (47) 12 (40) 4 (13)	 17 (39) 16 (36) 11 (25)	 0.47
Resection margins (%) R0 R1 R2	 24 (80) 5 (17) 1 (3)	 39 (89) 5 (11) 0 (0)	 0.36
Lympho-vascular invasion (%)* Yes No	 10 (30) 20 (70)	 13 (30) 31 (70)	 0.80
Total number of mesorectal LN harvested, median (range)	20 (6 - 46)	22.5 (6 - 60)	0.18
Total number of LLNs harvested, median (range)	N/A	3 (0 - 15)	N/A
Tumour positive mesorectal lymph nodes, median (range)	0.5 (0 - 13)	0 (0 - 13)	0.84
Tumour positive LLN, median (range)	N/A	0.5 (0 - 3)	N/A

LLNs: lateral lymph nodes, LAR: low anterior resection, APR: abdomino-perineal resection, ypT-stage: post-neoadjuvant pathological tumour stage, ypN-stage: post-neoadjuvant pathological nodal stage, LN: lymph nodes, N/A: not applicable, [1] 5 patients missing, [2] 7 patients missing, [3] 10 patients missing; [4] 8 patients missing. *Fisher's exact test.

Median follow-up for LLND+ patients was 47 months (range 1-141), and 64 months (range 1-98) for LLND- patients. Three-year LLRR was 0% for LLND+ vs. 8% for LLND- patients (p=0.05), and LRR was 3% for LLND+ vs. 16% for LLND- (p=0.04). DMFS was 74% for LLND+ vs. 55% for LLND- (p=0.12), DFS was 72% for LLND+ vs. 51% for LLND- (p=0.10), and OS was 86% vs. 62%, respectively (p=0.11). (Figure 1.3)

Figure 1.3: Kaplan-Meier survival curves of long-course nCRT and adjuvant chemotherapy cohort showing lateral local recurrence-free survival (3a; p=0.05), local recurrence-free survival (3b; p=0.04), distant metastatic-free survival (3c; p=0.12), disease-free survival (3d; p=0.10) and overall survival (3e; p=0.11) for LLND+ vs. LLND- patients.



Discussion

The current study suggests beneficial oncological outcomes when a LLND is performed in addition to TME surgery after nCRT in Western patients with pre-treatment abnormal LLNs in terms of lower LLRR and LRR.

A recent international multi-centre study in 223 patients comparing those with mesorectal nodes only to those with LLNs showed a lower LRR and a longer DFS in patients with mesorectal nodes only.[2] Another study showed that four years after treatment, 33% of LLNs patients developed a LR when treated with nCRT only.[22] These studies show that pre-treatment abnormal LLNs are more advanced disease than metastatic mesorectal lymph nodes and that they may have been undertreated with nCRT alone.

In the East, mainly Japan, treatment differs from the West, as most patients with LLNs undergo a LLND at the time of TME, however, often without nCRT.[10] Despite these differences in treatment between the East and the West, comparable LRRs have been reported.[23] Interestingly, it has been shown that if LLNs harbour tumour upon pathology, a LLND alone, without nCRT, may not be adequate treatment to prevent LRs.[24]

Multiple centres, again mainly from the East, have published their experience combining both treatment strategies, performing a LLND after nCRT. Similarly to the current study, in these series, metastatic disease was found upon histopathology in 22-66% of the resected LLNs, demonstrating that LLNs are not eradicated completely by nCRT only.[6-8,17] Furthermore, Ishihara et al. reported that a LLND after nCRT resulted in a 0% LRR and improved OS.[7] Similar results have been presented by a large multi- centre LLNs analysis, showing a reduction of the 5-year LRR from 19.5% for those treated with nCRT only, to 5.7% after an additional LLND.[11] These studies, however, included almost exclusively Eastern patients in the dissected group, which may represent significant bias. Since it is not clear whether the

biological behaviour of rectal cancer is different in Eastern patients, or whether there are other geographical confounders impacting outcomes, the current study contributes as the first to directly compare outcomes in only Western patients with pre-treatment abnormal LLNs undergoing nCRT with or without a LLND. Interestingly, we found a reduction in the three-year LRR: from 14% to 3%, but this difference did not reach statistical significance in the adjuvant chemotherapy cohort, likely due to low patient numbers, but the 3% LRR in LLND+ patients is lower than would be expected and in the Cox multivariable analysis a LLND was a significant factor for less LRs.[11] This is an interesting finding, as LRs after rectal cancer are challenging to treat and associated with significant morbidity, and reduce quality of life and OS.[25]

In the complete cohort analysis, differences in baseline characteristics were found between both groups. These differences may have had an influence on the LRRs and other outcome measures. In particular, there was a higher rate of adjuvant chemotherapy use in the LLND+ group. It is unclear whether this was due to a higher rate of ypN+ disease or due to institutional differences in indications for adjuvant treatment. Anecdotally, particularly in the Netherlands, adjuvant chemotherapy is used sparingly and reserved for patients who are more likely to develop recurrences. To overcome the difference in adjuvant chemotherapy between groups, the analysis only including patients who underwent adjuvant chemotherapy was performed. In this subset analysis, most of the previously significant baseline characteristics, such as the cTNM-stage, were now more similar between both cohorts.

A LLND is a complex procedure with associated risks of intra- and postoperative complications.[26-28] Although the operating time was longer in the LLND group, complications were similar to patients who underwent TME only, and LOS was shorter. While LOS may have been influenced by the hospital's local protocols, the current results suggest that a LLND is not associated with significant short-term adverse events.

Some limitations of the current study have to be mentioned. Firstly, due to the retrospective nature of the study, exact details of radiotherapy could not be retrieved. However, all participating centres include LLNs during radiotherapy. Interpretation of the results is also limited by the retrospective nature of the study, heterogeneity between centres and of the patient populations, (neoadjuvant) treatment strategies and surgical technique. We did not capture functional outcomes and therefore cannot report on long-term morbidity such as sexual and urinary dysfunction. The results of the JCOG0212 trial suggested similar morbidity and functional outcomes after LLND.[29] Furthermore, there was variability in the median length of follow-up, however, as a minimum 3-year follow-up was mandated for inclusion in the study, most recurrences are likely to have been captured.[30] The sites of the involved LLNs basins were different between LLND+ and LLND- cohorts, which may have been the results of a difference in definition between the participating centres.[11] Interestingly, a recent multi-centre cohort study showed a difference in LRR between internal iliac and obturator LLNs, indicating the need for uniform definition.[9] Similar to the definition of the anatomical location of the LLNs, a cut-off short-axis size of ≥5mm for LLNs was chosen based on previous publications and threshold of surgical management, yet, in literature the definition of LLNs varies between a short-axis of 5-10mm, making comparisons challenging.[9,11,15-17] Lastly, despite including patients treated at tertiary referral centres, the number of patients meeting the inclusion criteria was relatively low. This could indicate that patients with low rectal cancer and abnormal LLNs are missed at diagnosis as the incidence of abnormal LLNs is estimated to be 16-23%.[1]

In future studies it would be beneficial if more Western centres could participate, especially those centres performing LLNDs, although this may be difficult considering the number of Western centres who have experience performing the procedure. For this reason, it is unlikely that a randomised trial in Western patients will be conducted in the foreseeable future.

Therefore, the results of the soon to open Lateral Nodal Recurrence in Rectal Cancer (LaNoReC) study and the currently recruiting trial by Wei et al., randomising Chinese LLNs patients after nCRT for a LLND at the time of TME to TME only, are eagerly awaited.[31,32]

In conclusion: A lateral lymph node dissection at the time of total mesorectal excision in addition to neoadjuvant (chemo)radiotherapy may improve loco-regional control in Western patients with low rectal cancer and abnormal lateral lymph nodes. Larger studies in Western patients are required to evaluate its contribution.

Acknowledgement

This project was undertaken whilst holding a Royal Adelaide Hospital Florey Fellowship by Hidde M. Kroon.

References

1. Hashiguchi Y, Muro K, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol 2020;25:1-42.
2. 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;60:577–85.
3. Kusters M, Uehara K, Velde CJH, Moriya Y. Is there any reason to still consider lateral lymph node dissection in rectal cancer? Rationale and technique. Clin Colon Rectal Surg 2017;30:346-56.
4. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114-23.
5. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-40.
6. 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;21:189-96.
7. Ishihara S, Kawai K, Tanaka T, et al. Oncological outcomes of lateral pelvic lymph node metastasis in rectal cancer treated with preoperative chemoradiotherapy. Dis Colon Rectum 2017;60:469-76.
8. Atef Y, Koedam TW, van Oostendorp SE, Bonjer HJ, Wijsmuller AR, Tuynman JB. Lateral pelvic lymph node metastases in rectal cancer: A systematic review. World J Surg 2019;43:3198-206.
9. Ogura A, Konishi T, Beets GL, et al. Lateral nodal features on restaging magnetic resonance imaging associated with lateral local recurrence in low rectal cancer after neoadjuvant chemoradiotherapy or radiotherapy JAMA Surg 2019;154:e192172.
10. Watanabe T, Muro K, Ajioka 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.
11. Ogura A, Konishi T, Cunningham C, et al. Neoadjuvant (chemo)radiotherapy with total mesorectal excision only is not sufficient to prevent lateral local recurrence in enlarged nodes: Results of the multicenter lateral node study of patients with low cT3/4 rectal cancer. J Clin Oncol 2019;37:33-43.
12. Shin US, You YN, Nguyen AT, et al. Oncologic outcomes of extended robotic resection for rectal cancer. Ann Surg Oncol 2016;23:2249-57.
13. Malakorn S, Yang Y, Bednarski BK, et al. Who should get lateral pelvic lymph node dissection after neoadjuvant chemoradiation? Dis Colon Rectum 2019;62:1158-66.
14. Von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453-57.
15. Kim MJ, Kim TH, Kim DY, et al. Can chemoradiation allow for omission of lateral pelvic node dissection for locally advanced rectal cancer? J Surg Oncol 2015;111:459-64.
16. Lim SB, Yu CS, Kim CW, et al. Clinical implication of additional selective lateral lymph node excision in patients with locally advanced rectal cancer who underwent preoperative chemoradiotherapy. Int J Colorectal Dis 2013;28:1667-74.
17. Oh HK, Kang SB, Lee SM, et al. Neoadjuvant chemoradiotherapy affects the indications for lateral pelvic node dissection in mid/low rectal cancer with clinically

suspected lateral node involvement: a multicenter retrospective cohort study. Ann Surg Oncol 2014;21:2280-7.
18. Malakorn S, Ouchi A, Sammour T, Bednarski BK, Chang GJ. Robotic lateral pelvic lymph node dissection after neoadjuvant chemoradiation: View from the West. Dis Colon Rectum 2018;61:1119-20.
19. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187-96.
20. Mann HB, Whitney, D. R. On a test of whether one of two random variables is stochastically larger than the other. Ann Math Statist 1947;18:50-60.
21. Kaplan EL, Meier, P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
22. Haanappel A, Kroon HM, Schaap DP, et al. Lateral lymph node metastases in locally advanced low rectal cancers may not be treated effectively with neoadjuvant chemoradiotherapy only. Front Oncol 2019;9:1355.
23. Kusters M, Beets GL, van de Velde CJ, et al. A comparison between the treatment of low rectal cancer in Japan and the Netherlands, focusing on the patterns of local recurrence. Ann Surg 2009;249:229-35.
24. Kanemitsu Y, Komori K, Shida D, 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;162:303-14.
25. Yun JA, Huh JW, Kim HC, et al. Local recurrence after curative resection for rectal carcinoma: The role of surgical resection. Medicine (Baltimore) 2016;95:e3942.
26. Nakamura T, Watanabe M. Lateral lymph node dissection for lower rectal cancer. World J Surg 2013;37:1808-13.
27. Georgiou P, Tan E, Gouvas N, et al. Extended lymphadenectomy versus conventional surgery for rectal cancer: a meta-analysis. Lancet Oncol 2009;10:1053-62.
28. Nagawa H, Muto T, Sunouchi K, et al. Randomized, controlled trial of lateral node dissection vs. nerve-preserving resection in patients with rectal cancer after preoperative radiotherapy. Dis Colon Rectum 2001;44:1274-80.
29. Fujita S, Mizusawa J, Kanemitsu Y, et al. Colorectal Cancer Study Group of Japan Clinical Oncology Group. Mesorectal excision with or without lateral lymph node dissection for clinical stage II/III lower rectal cancer (JCOG0212): A multicenter, randomized controlled, noninferiority trial. Ann Surg 2017;266:201-7.
30. Cunningham D, Atkin W, Lenz HJ, et al. Colorectal cancer. Lancet 2010;375:1030-47.
31. Kusters M; VU University Medical Center. Lateral Nodal Recurrence in Rectal Cancer (LaNoReC) [Internet]. Amsterdam, the Netherlands: Clinicaltrials.gov; 2020 July 24 [updated 2021 April 1; cited 2021 April 27]. Available from: https://clinicaltrials.gov/ct2/show/NCT04486131.
32. Wei M, Wu Q, Fan C, et al. Lateral pelvic lymph node dissection after neoadjuvant chemo-radiation for preoperative enlarged lateral nodes in advanced low rectal cancer: study protocol for a randomized controlled trial. Trials 2016;17:561.

Chapter 1, Appendix 1

European Journal of Surgical Oncology 47 (2021) 2475–2476

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Lateral lymph node dissection in low rectal cancers: Call for standardized reporting of results to unify the global practice

Keywords:
Lateral lymph node dissection
Chemoradiation
Rectal cancer

Retrospective review by Kroon et al. attempts to establish the role of lateral lymph node dissection (LLND) in improving outcomes in low rectal cancers in the western hemisphere [1] This approach of LLND in carefully selected patients post neoadjuvant chemoradiation (nCRT) is already well established in the East. While we agree with the concept, the study appears weak and deserves consideration of the following aspects.

The groups compared in the study, Total Mesorectal Excision (TME) only versus TME with LLND, are heterogenous. The TME only group had more T4 tumors with higher frequency of N2 nodal disease and tumors closer to anal verge. All these factors suggest a higher likelihood of lateral nodes in this group. More number of patients here were operated after short course radiation therapy without any mention of consolidation chemotherapy. No exenteration procedures were performed in this group with only 30% patients receiving adjuvant chemotherapy. This group had a locoregional recurrence rate (LRR) of 11% at 3 years with lateral nodal recurrence in 7%. In comparison, the TME and LLND group had higher number of patients undergoing exenteration which almost always ensures removal of inferior vesical group of nodes, an important site of lateral recurrence. All patients in this group received long course nCRT with higher possibility of boost radiation therapy and a larger proportion received adjuvant chemotherapy. This group had LRR of 3% with no lateral recurrences. Baseline heterogeneity between the two groups makes the comparison ineffective.

The low number of procedures (LLND = 44), included in this study along with variation in practices with respect to administration of radiotherapy (external beam radiation therapy with or without boost), consolidation chemotherapy (if any) and adjuvant chemotherapy, across the participating centers decreases the applicability of the results.

Statistically speaking, there are too few events (lateral recurrences) in the LLND group for the multi-variate analyses to implicate a practical significance. A propensity matched analyses in a cohort with overcoming the baseline differences would add more meaning to the results.

44 LLND procedures performed over a period of 6 years with a node positivity rate of 50% and no lateral recurrences, especially in a population with relatively higher body mass index indicates overcoming the longer learning curve which is often associated with the procedure. Such positive results have only been shown by Akiyoshi et al., who reported lateral nodal recurrence rate of 0% with LLND albeit with lower numbers (n = 38) [2] Kim et al. have reported lateral recurrence rates as high as 20% after standardized LLND, with recurrence rates often correlating with the size of lateral nodes [3] These overwhelming positive results from MD Anderson Cancer Centre demand validation in a larger cohort with standardized practices.

The template of lymph node dissection in rectal cancer differs from other pelvic malignancies as it extends beyond and below the obturator fossa, with inferior vesical group of nodes forming an important site of recurrence. The extent and template of LLND needs consideration when interpreting results. The radiological characterization of lateral nodes has been established by Ogura et al. and should be preferably adopted when reporting results [4] The current study has included only the baseline MRI information without any mention of the restaging MRI. Performing LLND on the basis of index MRI scan can lead to overtreatment in some patients. Residual suspicious nodes on the response assessment MRI directing the necessity of LLND promotes a more selective approach and should form the basis of practice as suggested by Ogura et al. In addition, more suspicious looking but smaller nodes in the TME only group could be the reason for higher lateral recurrences.

Histology, presence of mucin and presence of extra mural venous invasion (EMVI) needs description when interpreting survival for rectal cancers, in light of the recent evidence towards the same.

While we believe that LLND decreases lateral recurrences, it needs a global standardization with respect to conduct and reporting on similar lines as that of development of TME which significantly changed the outlook of survival in rectal cancers. We await the LaNoReC study with global participation for generating evidence in the western population where the quality of radiology, practice of radiation therapy (without extra boost) and surgical quality would be controlled prospectively.

Sources of funding

None.

DOI of original article: https://doi.org/10.1016/j.ejso.2021.06.004.

https://doi.org/10.1016/j.ejso.2021.06.029

Disclosures

None.

Declaration of competing interest

None.

References

[1] Kroon HM, Malakorn S, Dudi-Venkata NN, Bedrikovetski S, Liu J, Kenyon-Smith T, et al. Local recurrences in western low rectal cancer patients treated with or without lateral lymph node dissection after neoadjuvant (chemo)radiotherapy: an international multi-centre comparative study. Eur J Surg Oncol 2021 Jun 6. https://doi.org/10.1016/j.ejso.2021.06.004. S0748798321005667.

[2] 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. Ann Surg Oncol 2014;21(1):189–96. Jan.

[3] Kim TH, Jeong S-Y, Choi DH, Kim DY, Jung KH, Moon SH, 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. Mar.

[4] Ogura A, Konishi T, Beets GL, Cunningham C, Garcia-Aguilar J, Iversen H, et al. Lateral nodal features on restaging magnetic resonance imaging associated with lateral local recurrence in low rectal cancer after neoadjuvant chemoradiotherapy or radiotherapy. JAMA Surg 2019;154(9):e192172. Sep. 18.

Swapnil Patel[a], Mufaddal Kazi[b], Avanish Saklani[b,*]

[a] *Department of Surgical Oncology, Homi Bhabha Cancer Hospital, Varanasi, India*

[b] *Colorectal Division, Department of Surgical Oncology, Tata Memorial Hospital, Mumbai, India*

[*] Corresponding author. Colorectal Division, Department of GI & HPB Surgery, Tata Memorial Centre, Mumbai, 400012 , India.
E-mail address: asaklani@hotmail.com (A. Saklani).

13 June 2021
Available online 29 June 2021

Chapter 1, Appendix 2

Reply to: Lateral lymph node dissection in low rectal cancers: Call for standardized reporting of results to unify the global practice

Hidde M. Kroon[1,2], Miranda Kusters[3], George J. Chang[4], Tarik Sammour[1,2].

[1] Colorectal Unit, Department of Surgery, Royal Adelaide Hospital, Adelaide, South Australia, Australia

[2] Adelaide Medical School, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, South Australia, Australia

[3] Department of Surgery, Amsterdam University Medical Centers, location VUmc, Amsterdam, the Netherlands

[4] Department of Surgical Oncology, Division of Surgery, MD Anderson Cancer Center, Houston, Texas, USA

Eur J Surg Oncol 2021;47:2477-8. doi: 10.1016/j.ejso.2021.06.030.

Statement of Authorship

Title of Paper	Reply to: Lateral lymph node dissection in low rectal cancers: Call for standardized reporting of results to unify the global practice.
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Kroon HM, Kusters M, Chang GJ, Sammour T. Reply to: Lateral lymph node dissection in low rectal cancers: Call for standardized reporting of results to unify the global practice. Eur J Surg Oncol 2021;47:2477-8. doi: 10.1016/j.ejso.2021.06.030.

Principal Author

Name of Principal Author (Candidate)	Hidde M. Kroon		
Contribution to the Paper	Conception and design of the project Drafting the article Critically revising of article		
Overall percentage (%)	90%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	13/09/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Miranda Kusters		
Contribution to the Paper	Conception and design of the project Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	George J. Chang		
Contribution to the Paper	Conception and design of the project Drafting significant parts of the article Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Tarik Sammour		
Contribution to the Paper	Conception and design of the project Critically revising of article		
Signature		Date	13/09/2021

Dear editor,

We would like to thank Patel, et al.[1] for their interest in our work on the benefit of lateral lymph node dissection (LLND) following neoadjuvant (chemo)radiotherapy (nCRT) in Western patients with low rectal cancers and pre-treatment abnormal lateral lymph nodes (LLN).[2] We appreciate the opportunity to reply.

Patel et al. state that the groups compared, those undergoing an additional LLND during total mesorectal excision (TME) following nCRT vs. patients who underwent TME after nCRT only, are heterogeneous at baseline, making comparison ineffective as the TME only group had more T4 tumours, more N2 disease and tumours closer to anal verge, all factors with a higher likelihood of abnormal lateral lymph nodes. However, both cohorts in our study were already diagnosed with abnormal LLN, making this argument less valid. Furthermore, because of these differences in baseline characteristics and use of (neo)adjuvant therapy, we performed a second analysis in a subset of patients who all underwent long-course nCRT as well as adjuvant chemotherapy. In this subset, the baseline characteristics mentioned above were no longer different between groups. Interestingly, the local recurrence rates were now significantly different in favour of the TME and LLND group.

As the authors of the letter correctly noticed, consolidation therapy was not part of our study, because during the study period (2009-2016), consolidation chemotherapy and total neoadjuvant therapy regimes were not yet implemented at the centres participating in this study. Also, radiotherapy boosts that were administered were not given to the LLN.

Our study did have limitations. Restaging, for instance, was not performed at all centres, which could have led to overtreatment of some patients, and due to the retrospective nature of the study, diagnosis of mucinous tumours and extra mural venous invasion (EMVI) could not be retrieved. Also, despite including tertiary referral centres, the number of patients meeting

the inclusion criteria was relatively low, with a low number of events for lateral local recurrence, potentially reducing its statistical power. Performing a propensity matched analysis as suggested, however, would not overcome this problem in a small cohort, as an insufficient number of patients would remain in each group after matching. The Cox regression analysis, on the other hand, did identify LLND as an independent significant factor for reduced local recurrences, despite the low number of patients.

The TME and LLND group included exenterations (n=3; 7%). Due to the extended resection, these patients likely had a further reduced risk of local recurrences compared to LLND alone. In the Cox regression analysis, however, the type of resection was not a significant factor for any of the oncological outcomes. Lastly, we agree that the outcomes of the LLND performed by the MD Anderson Cancer Centre require validation in a larger cohort.

Despite these limitations, our study is the first describing the potential benefit in terms of loco-regional control of a LLND in addition to nCRT in Western patients with rectal cancer with pre-treatment abnormal LLN.

In future studies, it would be beneficial if more Western centres participate, performing LLND and reporting in a standardized fashion. We are therefore looking forward to the future results of the Lateral Nodal Recurrence in Rectal Cancer (LaNoReC) study, in which a standardised LLND and radiological characterization for reporting of LLN as established by Ogura et al. will be included.[3,4]

References

1. Patel S, Kazi M, Saklani A. Lateral lymph node dissection in low rectal cancers: Call for standardized reporting of results to unify the global practice. Eur J Surg Oncol 2021;47:2475-6.
2. Kroon HM, Malakorn S, Dudi-Venkata NN, Bedrikovetski S, Liu J, Kenyon-Smith T, et al. Local recurrences in Western low rectal cancer patients treated with or without lateral lymph node dissection after neoadjuvant (chemo)radiotherapy: An international multi-centre comparative study. Eur J Surg Oncol 2021;47:2441-9.
3. Ogura A, Konishi T, Beets GL, Cunningham C, Garcia-Aguilar J, Iversen H, et al. Lateral nodal features on restaging magnetic resonance imaging associated with lateral local recurrence in low rectal cancer after neoadjuvant chemoradiotherapy or radiotherapy. JAMA Surg 2019;154:e192172.
4. Kusters M; VU University Medical Center. Lateral Nodal Recurrence in Rectal Cancer (LaNoReC) [Internet]. Amsterdam, the Netherlands: Clinicaltrials.gov; 2020 July 24 [updated 2021 April 1; cited 2021 June 22]. Available from: https://clinicaltrials.gov/ct2/show/NCT04486131.

Chapter 2

Systematic review and meta-analysis of long-term oncological outcomes of lateral lymph node dissection for metastatic nodes after neoadjuvant chemoradiotherapy in rectal cancer.

Hidde M. Kroon[1,2], Lotje A. Hoogervorst[1], Nicole Hanna-Rivero[1], Luke Traeger[1,2], Nagendra N. Dudi-Venkata[1,2], Sergei Bedrikovetski[1,2], Miranda Kusters[3], George J. Chang[4], Michelle L. Thomas[1,2], Tarik Sammour[1,2].

[1] Colorectal Unit, Department of Surgery, Royal Adelaide Hospital, Adelaide, South Australia, Australia

[2] Adelaide Medical School, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, South Australia, Australia

[3] Department of Surgery, Amsterdam University Medical Centers, location VUmc, Amsterdam, the Netherlands

[4] Department of Surgical Oncology, Division of Surgery, MD Anderson Cancer Center, Houston, Texas, USA

Submitted

Statement of Authorship

Title of Paper	Systematic review and meta-analysis of long-term oncological outcomes of lateral lymph node dissection for metastatic nodes after neoadjuvant chemoradiotherapy in rectal cancer.
Publication Status	☐ Published ☐ ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Kroon HM, Hoogervorst L, Hanna-Rivero N, Traeger L, Dudi-Venkata NN, Bedrikovetski S, Kusters M, Chang GJ, Thomas ML, Sammour T. Systematic review and meta-analysis of long-term oncological outcomes of lateral lymph node dissection for metastatic nodes after neoadjuvant chemoradiotherapy in rectal cancer. Submitted for publication

Principal Author

Name of Principal Author (Candidate)	Hidde M. Kroon		
Contribution to the Paper	Conception and design of the project Acquiring research data Analysis and interpretation of research data Drafting the article Critically revising of article		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	13/11/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Lotje A. Hoogervorst		
Contribution to the Paper	Acquiring research data Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/11/2021

Name of Co-Author	Nicole Hanna-Rivero		
Contribution to the Paper	Acquiring research data Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/11/2021

Name of Co-Author	Luke Traeger		
Contribution to the Paper	Acquiring research data Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/11/2021

Name of Co-Author	Nagendra N. Dudi-Venkata		
Contribution to the Paper	Acquiring research data Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/11/2021

Name of Co-Author	Sergei Bedrikovetski		
Contribution to the Paper	Acquiring research data Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/11/2021

Name of Co-Author	Miranda Kusters		
Contribution to the Paper	Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/11/2021

Name of Co-Author	George J. Chang		
Contribution to the Paper	Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/11/2021

Name of Co-Author	Michelle L. Thomas		
Contribution to the Paper	Conception and design of the project Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/11/2021

Name of Co-Author	Tarik Sammour		
Contribution to the Paper	Conception and design of the project Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/11/2021

Abstract

Background: Standard Western management of rectal cancers with pre-treatment metastatic lateral lymph nodes (LLNs) is neoadjuvant (chemo)radiotherapy (nCRT) followed by total mesorectal excision (TME). In recent years, there is growing interest in performing an additional lateral lymph node dissection (LLND). The aim of this systematic review and meta-analysis was to investigate long-term oncological outcomes of nCRT followed by TME with or without LLND in patients with pre-treatment metastatic LLNs.

Methods: PubMed, Ovid MEDLINE, Embase, Cochrane Library and Clinicaltrials.gov were searched to identify comparative studies reporting long-term oncological outcomes in pre-treatment metastatic LLNs of nCRT followed by TME and LLND (LLND+) vs. nCRT followed by TME only (LLND-). Newcastle-Ottawa risk-of-bias scale was used. Outcomes of interest included local recurrence (LR), disease-free survival (DFS), and overall survival (OS). Summary meta-analysis of aggregate outcomes was performed.

Results: Seven studies, including 946 patients, were analysed. One (1/7) study was of good-quality after risk-of-bias analysis. Five-year LR rates after LLND+ were reduced (range 3-15%) compared to LLND- (11-27%; RR=0.40, 95%CI[0.25-0.62], p<0.001). Five-year DFS was not significantly different after LLND+ (range 61-78% vs. 46-79% for LLND-; RR=0.72, 95%CI[0.51-1.02], p=0.143), and neither was five-year OS (range 69-91% vs. 72-80%; RR=0.72, 95%CI[0.45-1.14], p=0.163).

Conclusion: In rectal cancers with pre-treatment metastatic LLNs, nCRT followed by an additional LLND during TME reduces local recurrence risk, but does not impact disease-free or overall survival. Due to the low quality of current data, large prospective studies will be required to further determine the value of LLND.

Introduction

Between 15-20% of patients with locally advanced rectal cancer have metastases to the lateral lymph nodes (LLNs) in the pelvic side-wall at diagnosis at diagnosis.[1] Historically, treatment paradigms for these pre-treatment metastatic LLNs differs between the East and the West.[2,3] Standard treatment in the East does not include neoadjuvant (chemo)radiotherapy (nCRT), but consists of upfront rectal resection adhering to total mesorectal excision (TME) principles and a lateral lymph node dissection (LLND) to remove the tumour and the metastatic LLNs.[1,4] In contrast, standard treatment in the West consists of nCRT followed by only TME, without a LLND.[5,6]

This difference in approach to similar disease finds its origin in the definition of LLNs. In the East, LLNs are considered regional, surgically treatable disease, while historically the West has defined LLNs as distant metastatic disease, with the assumption that outcomes are not altered by a LLND.[7-9] However, there is growing debate as to whether TME and nCRT adequately treats LLNs given studies have shown that nCRT sterilises metastatic LLNs in less than 50% of patients, and therefore, whether a LLND should be performed in addition for optimal long-term oncological outcomes and local control.[2,6,10-12]

On the other hand, a LLND is associated with increased operation time, blood loss, and potential postoperative morbidity such as urinary, sexual, and lower limb movement dysfunction.[13-15] Furthermore, the incidence of these complications is potentially higher in the West than that reported in the East, as LLND is technically more complex in patients with a higher BMI and after pelvic radiotherapy.[2] As a result, there has been reluctance to perform a LLND in the West when metastatic LLNs are present.

Recently, however, some Western centres have reported favorable outcomes of LLND after nCRT in patients with pre-treatment metastatic LLNs.[10,12,16] Likewise, a number of Eastern

centres are now administering nCRT before TME and LLND to patients these patients.[3,17] Therefore, the aim of this systematic review and meta-analysis was to investigate long-term oncological outcomes in patients with rectal cancer and pre-treatment metastatic LLNs, treated with nCRT followed by TME with or without an additional LLND.

Methods

A comprehensive systematic review of the literature was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Supplementary Tables 2.1 and 2.2).[18,19] The study protocol was registered prospectively at the PROSPERO database of systematic reviews (CRD42021275927).

Search strategy

Searches to identify relevant publications were performed independently by two reviewers (HK and LH) on PubMed, Ovid MEDLINE, Embase, Cochrane Library and Clinicaltrials.gov. Searches were conducted from 1st January 1985 (since the first publications on neoadjuvant therapy for rectal cancer) to 30th September 2021.[20,21] Medical Subject Headings (MeSH) terms and key words that were used included:'rectal neoplasm', 'pelvic neoplasm', 'rectal cancer', 'lymphatic metastasis', 'lateral lymph node', 'lateral pelvic lymph node', 'pelvic side wall node', 'neoadjuvant therapy', 'chemoradiotherapy', 'proctectomy', 'rectal resection', 'total mesorectal excision', 'lymph node dissection', 'extended lymphadenectomy', 'lateral lymph node dissection', 'lateral pelvic lymph node dissection', 'pelvic side wall dissection', 'comparative study'.

Supplementary Tables 2.3 and 2.4 provide the search strategies. Boolean AND/OR operators were used to combine MeSH terms and keywords. The related-articles function was used to broaden the searches.

Eligibility criteria for including studies

Included studies were those describing outcomes of patients with rectal cancer with pre-treatment metastatic LLNs, without distant metastatic disease, who underwent a LLND during TME surgery after nCRT compared to patients who underwent nCRT and TME only: nCRT+TME+LLND (LLND+ group) vs. nCRT+TME (LLND- group). Randomised controlled trials (RCTs) as well as prospective and retrospective cohort studies were considered for inclusion.

Excluded were non-English studies, letters, short communications, reviews, commentaries, and case reports. Also excluded were studies describing treatment of malignancies other than rectal cancer, single-arm non-comparative studies (e.g. nCRT+TME or nCRT+TME+LLND only), studies in which no nCRT was used, studies including rectal cancer patients without metastatic LLNs, those including patients with distant metastases, recurrent rectal cancer and multivisceral resection studies, and those describing other surgical procedures (e.g. LLN sampling or pelvic exenterations).

Study Selection

Following the searches, all identified titles and abstracts were reviewed independently by two reviewers (HK and LH), followed by full-text review of potentially eligible studies. Reference lists of full-text articles were manually searched to identify additional eligible studies. Any differences in study selection were resolved by consensus and, if needed, discussed with a third reviewer (NHR) to reach agreement.

Risk of bias assessment

The methodological quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS) independently by two reviewers (HK and NHR), examining three factors:

method of patient selection, comparability of the study groups, and number of outcomes reported.[22] A rating of 0–9 was allocated to each study based on these parameters. Publications with a score of *≥7 were considered good-quality studies.

Data extraction

A predefined spreadsheet (Supplementary Table 2.5) was used to extract data from the included studies independently by two reviewers (HK and LH). Any discrepancies were discussed and resolved by a third author (NHR). The data extracted from each article included first author, country, publication year, study design, single or multi-centre, number of patients in each arm, population characteristics, tumour characteristics, surgical procedures, postoperative pathology, adjuvant therapy, follow-up times, and survival analyses.

Outcomes of interest and statistical analysis

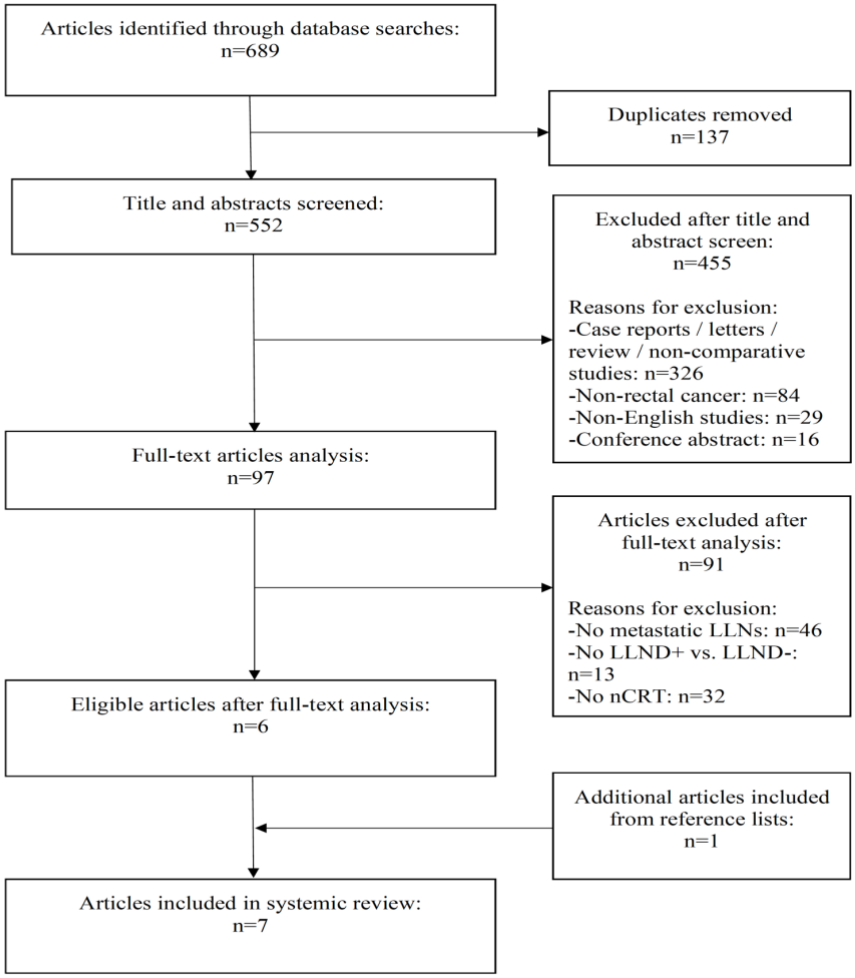
The primary outcomes of interest were local recurrence, disease-free survival, and overall survival. Secondary outcomes included lateral local recurrences and distant metastases in LLND+ vs. LLND- groups. Descriptive statistics were used for individual patient data analysis. No assumptions for missing data were made. Summary meta-analysis of aggregate data, using relative risk (RR), was performed on the outcomes of interest using StatsDirect software Version 3 (StatsDirect Ltd, Birkenhead, Wirral, United Kingdom) as only summary statistics were provided or able to be extracted from the included studies.[23] Survival data extracted from Kaplan-Meier curves and hazard ratios (HR) were used for the corresponding quantitative analysis using the method of inverse of the invariance (fixed effect model) in absence of sensitive heterogeneity. Results are presented as RR with 95% confidence intervals (95%CI) and in forest plots. For overall effect $p<0.05$ was considered statistically

significant. Cochran's Q test and I^2 results were used to estimate heterogeneity. Heterogeneity was considered statistically significant when $p<0.05$ for the Cochran's Q test and $I^2>50\%$. Risk of bias was analysed using the Eggar method, in which $p<0.05$ indicated significant bias.[24]

Results

The search identified 689 studies. After removing duplicate entries (n=137), 552 article titles and abstract were screened. Ninety-seven articles were selected for full-text analysis, after which seven were eligible for this systematic review, with one additional article included from the reference list (Figure 2.1).[2,10,16,25-28]

Figure 2.1: PRISMA chart outlining the selection of included articles.



LLNs, lateral lymph nodes; LLND, lateral lymph node dissection; nCRT, neoadjuvant (chemo)radiotherapy.

Table 2.1 demonstrates the patient characteristics and preoperative management of the included studies. All studies were retrospective observational in design. Four were multi-centre studies,[2,10,16,27] and three single-centre.[25,26,28] The seven studies included a total of 946 patients who all underwent neoadjuvant therapy: 266 underwent a LLND during TME (LLND+ group), and 640 underwent TME only (LLND- group) One study did not report size of the groups.[27]

Tumour height was reported with a range of 3.3-5.2cm from the anal verge in three studies reporting median distance[10,26,27] and four studies reported the majority of tumours were located in the lower rectum (range 53-81%).[2,16,25,28] Three studies used short-axis of ≥5mm as LLNs size selection criteria for suspicion of metastases,[10,25,28] Ogura et al. used short-axis cut-off of ≥7mm, and Shiratori used LLNs long-axis cut-off of ≥6mm.[2,26] Five studies described the anatomical location of metastatic LLNs as enlarged nodes in the internal iliac, external iliac and obturator basins. Three studies included the common iliac basin also and one study included enlarged LLNs at the aortic bifurcation.[10,25,26] In five studies all patients underwent nCRT, and in two studies a small percentage underwent radiotherapy only: 11% of patients in the study by Ogura et al. and 17% of the LLND- group in the study by Kroon et al.[2,10,16,25-28]

Table 2.1: Patient characteristics and preoperative management included studies.

Author, country, year	**Study design**	**Single/ multi centre**	**No. of patients**		**Male/ female** (%)		**Age**(median)		**Tumour height** (median / %)		**cT-stage** (%)		**LLNs size criteria** (mm)	**Site of LLNs**	**Neoadjuvant CRT/RT** (%)	
LLND + or -			+	-	+	-	+	-	+	-	+	-			+	-
Kim HJ, Korea, 2017[25]	Retrospective observational	Single	53	31	58/42	81/19	13% ≥70 yr	15% ≥70 yr	81% <5cm	65% <5cm	T2: 7 T3: 76 T4: 17	T2: 12 T3: 76 T4: 12	≥5 SA	Internal iliac External iliac Obturator Common iliac Aortic bifurcation	100/0	100/0
Shiratori, Japan, 2018[26]	Retrospective observational	Single	34	206	65/35 [a]	-	63 yr[1]	-	4.4 cm[a]	-	T2: 1 T3: 92 T4: 7[a]	-	≥6 LA	Internal iliac External iliac Obturator Common iliac	100/0[a]	-
Ogura, international collaborative, 2018[2]	Retrospective observational	Multi	53	118	58/42 [b]	-	45% ≥62 yr[2]	-	68% low[b,c]	-	T3: 59 T4: 41[b]	-	≥7 SA	Internal iliac External iliac Obturator	89/11[a]	-
Nishizaki, Japan, 2019[27]	Retrospective observational	Multi	40[d]	-	-	-	-	-	5.2 cm[a]	-	-	-	≥5	-	100/0	100/0
Jones, UK, 2020[16]	Retrospective observational	Multi	13	68	54/46	76/24 [e]	57 yr	64 yr[5]	54% ≤5cm	53% ≤5cm [e]	Mean cT: 3.25	Mean cT: 3.3	-	Internal iliac External iliac Obturator	100/0	100/0
Kim MJ, Korea, 2020[28]	Retrospective observational	Single	69	102	-	-	58 yr	55 yr	60% ≤5cm	60% ≤5cm	-	-	≥5 SA	-	100/0	100/0
Kroon, US/AUS/NL, 2021[10]	Retrospective observational	Multi	44	115	48/52	75/25	56 yr	64 yr	5.0 cm	3.3 cm	T2: 7 T3: 73 T4: 20	T2: 1 T3: 63 T4: 36	≥5 SA	Internal iliac External iliac Obturator Common iliac	100/0	83/17

LLND, lateral lymph node dissection; LLNs, lateral lymph nodes; CRT, chemoradiotherapy; RT, radiotherapy; SA, short-axis; LA, long-axis - not reported; [a] reported for complete cohort; [b] reported for complete cohort with LLNs ≥7mm; [c] according to LOREC criteria[29]; [d] number of patients per group not reported; [e] reported for standard TME cohort (no CRT n=24, CRT n=68).

Five studies reported details of the operative management (Table 2.2).[2,10,16,25,28] A low anterior resection was performed in the majority of patients in the two Korean studies,[25,28] while in the two studies including Western patients an abdominoperineal resection was performed more often.[2,10] Single side LLND was performed mostly in two studies,[10,16] and in one study a bilateral LLND was performed in 75% of the patients.[25] Operating time was reported in one study, which was longer in the LLND+ group (436 vs. 255 minutes for LLND- group) with higher postoperative complication rates (Clavien-Dindo grade ≥3: 22% vs. 14%), but with shorter hospital stay (8 vs. 11 days).[10] There was a wide range in the use of adjuvant chemotherapy in both groups: LLND+ range 43-100%, LLND- range 30-98%.[2,10,25,28] No study reported long-term morbidity.

Range of pathological (yp)T3/4 stage for the LLND+ group was 50-70% and 52-58% in the LLND- group.[2,10,25,26,28] Pathological (yp)N+ was present in 23-81% of the LLND+ group, and in 23-43% of the LLND- group.[2,10,25,26,28] Resection margins were positive in 8-23% of the LLND+ group, and 9-12% of the LLND- group.[2,10,16,25,28] Of the LLNs resected, 8-56% were tumour positive.[16,25,26,28]

Table 2.2: Operative, postoperative and pathological outcomes of included studies.

Author, country, year	**Operation performed:** LAR/APR, (%)		**LLND:** single/bilateral (%)		**Adjuvant therapy** (%)		**ypT-stage** (%)		**ypN+** (%)		**Positive resection margins** (%)		**Tumour positive LLNs** (%)	
LLND + or -	+	-	+	-	+	-	+	-	+	-	+	-	+	-
Kim HJ, Korea, 2017[25]	85/15	90/10	25/75	N/A	95[a]	-	T0-2: 34 T3-4: 66	T0-2: 48 T3-4: 52	45	23	8[a]	-	38	N/A
Shiratori, Japan, 2018[26]	-	-	-	N/A	-	-	T0-2: 50 T3-4: 50[a]	-	23[a,b]	-	-	-	56	N/A
Ogura, international collaborative, 2018[2]	47/53[a]	-	-	N/A	43[c]	-	T0-2: 45 T3-4: 55[a]	-	81[d]	-	9[d]	-	-	N/A
Nishizaki, Japan, 2019[27]	-	-	-	N/A	-	-	-	-	-	-	-	-	-	N/A
Jones, UK, 2020[16]	-	-	100/0	N/A	-	-	Mean: 2.55	Mean: 2.45	Mean: 0.62	Mean: 0.66	23	9	8	N/A
Kim MJ, Korea, 2020[28]	97/3	79/21	-	N/A	84	98	T0-2: 30 T3-4: 70	T0-2: 42 T3-4: 58	52	37	22	12	35	N/A
Kroon, US/AUS/NL, 2021[10]	43/50	46/54	73/27	N/A	100	30	T0-2: 38 T3-4: 62	T2-3: 42 T3-4: 58	61	43	11	11	0.5[e]	N/A

LLND, lateral lymph node dissection; LLNs, lateral lymph nodes; N/A, not applicable; LAR, low anterior resection; APR, abdominoperineal resection; - not reported; [a] reported for complete cohort; [b] reported as mesenteric ypN; [c] reported for complete cohort with LLNs ≥7mm; [d] reported for complete cohort with LLNs ≥7mm; [e] median number of positive LLNs resected per patient.

Table 2.3 lists survival outcomes. Follow-up ranged between 34-59 months. Two studies reported five-year lateral local recurrence rates with ranges of 0-6% for LLND+ and 7-20% for LLND-.[2,10] Local recurrence rates were reported in five studies and ranged from 3-15% for LLND+ and 11-27% for LLND-.[2,10,16,25,28] Five-year distant metastatic rate was reported in three studies with a range of 14-41% for LLND+ and 26-31% for LLND-.[2,10,25] Five-year disease-free survival was reported in five studies with a range of 61-78% for LLND+ and 46-79% for LLND-.[10,16,25,27,28] Ogura et al. reported five-year cancer-specific survival rates of 94% and 79% for LLND+ and LLND-, respectively.[2] Range of five-year overall survival was 69-91% for LLND+ and 72-80% for LLND-.[10,16,25,28]

Table 2.3: Postoperative survival outcomes of included studies.

Author, country, year	**Follow-up** in months (median)		**5-year lateral local recurrence rate** (%)		**5-year local recurrence rate** (%)		**5-year distant metastatic rate** (%)		**5-year disease-free survival** (%)		**5-year cancer-specific survival** (%)		**5-year overall survival** (%)	
LLND + or -	+	-	+	-	+	-	+	-	+	-	+	-	+	-
Kim HJ, Korea, 2017[25]	34[a]	-	-	-	8[b,c]	23[*,c]	41[b,c]	26[c]	61[b,c]	54[*,c]	-	-	84[b,c]	80[c]
Shiratori, Japan, 2018[26 d]	47[a]	-	-	-	-	-	-	-	-	-	-	-	-	-
Ogura, international collaborative, 2018[2]	57[a]	-	6	20[*]	6	26[*]	14	31[*]	-	-	94	79[*]	-	-
Nishizaki, Japan, 2019[27]	-	-	-	-	-	-	-	-	78	46[*]	-	-	-	-
Jones, UK, 2020[16]	-	-	-	-	15	12	-	-	69	79	-	-	69	80
Kim MJ, Korea, 2020[28]	37	54	-	-	5	27[*]	-	-	74	61[*]	-	-	91	77
Kroon, US/AUS/NL, 2021[10]	47	59	0	7	3	11	29	30	68	64	-	-	74	72

- not reported; *significant difference between rates was reported; [a] reported for complete cohort; [b] combined for reported groups (LLND+ after response to nCRT) and (LLND+ with no response to nCRT); [c] 3-year rates; [d] Shiratori did not report survival analysis for LLND+ vs. LLND-.

Risk of bias assessment of the included studies using the NOS is listed in Table 2.4. One article qualified as a good-quality study (*≥7). Most studies were retrospective comparative series, and no RCTs were available. Selection bias was present in three studies.[2,10,26] Issues pertaining to follow-up (e.g. no follow-up, short follow-up, or high number of patients lost to follow-up) were a common recurrent theme in the studies.[2,10,16,25-28]

Table 2.4: Newcastle Ottawa quality assessment for included studies.

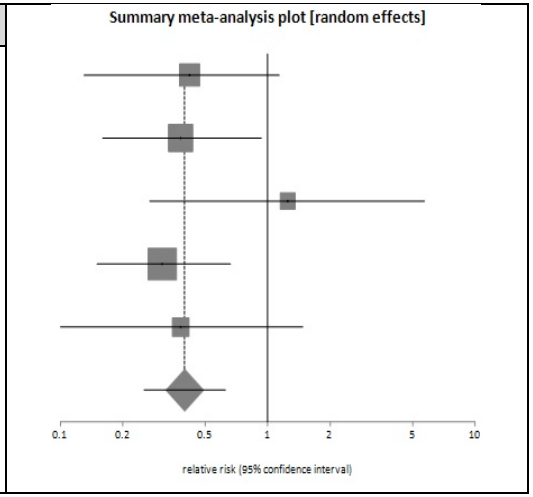
Author, country, year	**Selection** (0-4)	**Comparability** (0-2)	**Outcome** (0-3)	**Total** (0-9)
Kim HJ, Korea, 2017[25]	****	*	*	6
Shiratori, Japan, 2018[26]	***	-	**	5
Ogura, international collaborative, 2018[2]	**	*	**	5
Nishizaki, Japan, 2019[27]	***	*	-	4
Jones, UK, 2020[16]	****	*	*	6
Kim MJ, Korea, 2020[28]	****	*	**	7
Kroon, US/AUS/NL, 2021[10]	**	*	***	6

Meta-analysis could be performed for local recurrence, disease-free survival, and overall survival with respectively five, four and four studies reporting on these outcomes (Table 2.5). This showed that local recurrence was significantly lower in the LLND+ group (RR=0.40, 95%CI[0.25-0.62], p<0.0001) compared to the LLND- group.[2,10,16,25,28] Disease-free survival (RR=0.72, 95%CI[0.51-1.02], p=1.43) and overall survival (RR=0.72, 95%CI[0.45-1.14], p=0.163) were not significantly different between both groups.[10,16,25,28] Meta-analysis on lateral local recurrences and distant metastases could not be performed due to lack of studies reporting these outcomes (two and three, respective).

Table 2.5: Meta-analysis of (A) local recurrences, (B) disease-free survival and (C) overall survival of included studies.

A. Summary meta-analysis for local recurrence.

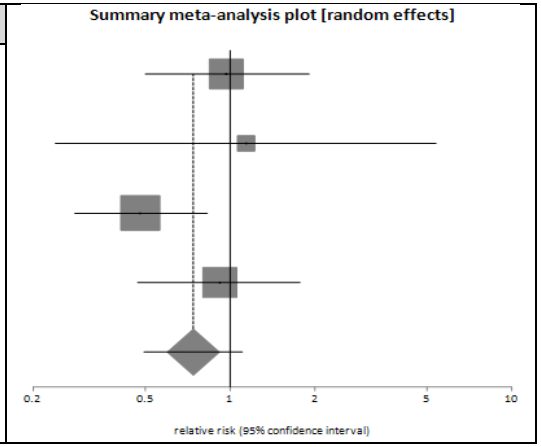
Study	Log (HR)	SE	Weight (%)	RR (fixed 95%CI)
Kim HJ[25]	-0.86	0.62	17.1	0.42 (0.13-1.14)
Ogura[2]	-0.96	0.49	26.2	0.38 (0.16-0.93)
Jones[16]	0.22	0.78	8.7	1.25 (0.27-5.71)
Kim MJ[28]	-1.16	0.37	36.9	0.31 (0.15-0.66)
Kroon[10]	-0.96	0.69	11.1	0.38 (0.10-1.48)
Total			**100**	**0.40 (0.25-0.62)**



Heterogeneity: Cochran Q=2.62 (df=4), p=0.622, I^2=0%
Test for overall effect: Z=4.02 (p<0.0001)
Egger: bias=2.26 (95%CI=-0.86 to 5.38), p=0.104

B. Summary meta-analysis for disease-free survival.

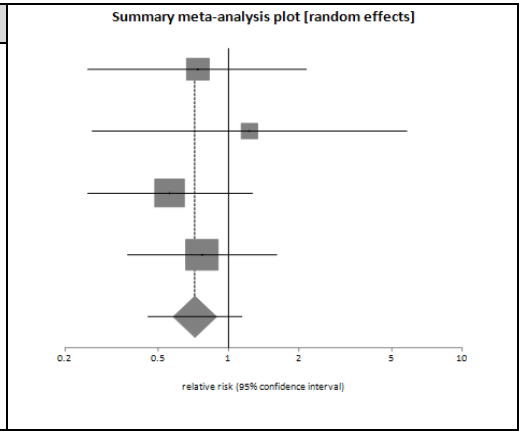
Study	Log (HR)	SE	Weight (%)	RR (fixed 95%CI)
Kim HJ[25]	-0.03	0.34	26.8	0.97 (0.50-1.91)
Jones[16]	0.13	0.79	5.0	1.14 (0.24-5.38)
Kim MJ[28]	-0.73	0.28	40.8	0.48 (0.28-0.83)
Kroon[10]	-0.09	0.34	27.4	0.92 (0.47-1.77)
Total			**100**	**0.72 (0.51-1.02)**



Heterogeneity: Cochran Q=3.76 (df=3), p=0.289, I^2=20.2%
Test for overall effect: Z=1.47 (p=0.143)
Egger: bias=1.75 (95%CI=-6.21 to 9.72), p=0.442

C. Summary meta-analysis for overall survival.

Study	Log (HR)	SE	Weight (%)	RR (fixed 95%CI)
Kim HJ[25]	-0.30	0.55	18.6	0.74 (0.25-2.16)
Jones[16]	0.21	0.79	8.9	1.23 (0.26-5.8)
Kim MJ[28]	-0.57	0.41	32.6	0.56 (0.25-1.27)
Kroon[10]	-0.26	0.37	39.9	0.77 (0.37-1.61)
Total			**100**	**0.72 (0.45-1.14)**



Heterogeneity: Cochran Q=0.86 (df=3), p=0.835, I^2=0%
Test for overall effect: Z=1.40 (p=0.163)
Egger: bias=1.19 (95%CI=-2.89 to 5.28), p=0.34

Discussion

To our knowledge, this is the first systematic review and meta-analysis of current literature specifically looking at the role of adding a LLND at the time of TME in patients with pre-treatment metastatic LLNs who all had nCRT. The results show that local recurrence rates are significantly reduced when a LLND is performed, but no difference in disease-free survival or overall survival was observed.

Lymphatic spread of rectal cancer occurs in two directions: medially along the inferior mesenteric artery and laterally along the internal iliac artery into the lateral nodal basins. In lateral spread, the Mercury study has shown that patients with metastatic LLNs on pre-treatment MRI, have lower five-year disease-free survival rates than patients without metastatic LLNs on MRIs.[30] Therefore, to reduce the chance of recurrences, metastatic LLNs should pro-actively be treated.[31] In most Western centers, nCRT is considered adequate treatment to sterilise LLNs after which TME is performed to remove the tumour, while in the East, LLND is performed during TME, however, often without nCRT.[7,8,31,32] Because of this difference in management of rectal cancer with pre-treatment metastatic LLNs between the East and West, it is difficult to compare both treatment approaches.

In recent years, emerging evidence has shown that local recurrences are a significant clinical issue in patients with pre-treatment metastatic LLNs, due to the risk of failure of nCRT followed by TME only.[2,11,33] Also, surgeons from Japan are re-evaluating the role of nCRT, as this may reduce the need for prophylactic LLNDs, reserving the procedure for patients with metastatic LLNs.[14,32] Therefore, the treatment philosophies of the East and West are moving closing together, highlighting the concept that LLND after nCRT in locally advanced rectal cancer can be complementary in the management of metastatic LLNs.[2,34]

A number of systematic reviews on the benefits of LLND in rectal cancer have been published over the past years. However, none have addressed the clinically relevant question of the benefit of the addition of LLND in patients with pre-treatment metastatic LLNs after nCRT. Three reviews, for instance, examined recurrence and survival outcomes, but also included studies that did not use nCRT and studies in which a prophylactic LLND was performed in patients without metastatic LLNs.[35-37] It was therefore not surprising that, similarly to the early landmark systematic review on this topic by Georgiu et al., none of these studies found local recurrence or survival benefits of LLND.[38] Overall, the null findings of these previous reviews can be explained by the broad selection of studies reporting on rectal cancers with heterogeneous stages, overshadowing the group of patients in whom a LLND after nCRT could be of added value; those with pre-treatment metastatic LLNs. Including patients without metastatic LLNs is likely to have diluted the findings of these reviews as it has previously been shown that these patients do not have local recurrence or survival benefit from a LLND after nCRT.[39-41] The current systematic review and meta-analysis is the first to report local recurrence benefit of LLND after nCRT in patients with pre-treatment metastatic LLNs, and thus the first to answer this clinical dilemma.

Some limitations of the current study have to be addressed. Firstly, the number of studies in current literature that report on long-term oncological outcomes of LLND during TME after nCRT vs. TME only after nCRT is low. Furthermore, all included studies are retrospective series, with a high risk of bias, mainly in patient selection. There are currently no prospective or RCTs available. Thirdly, the studies included relatively low patient numbers and limited follow-up for the survival analyses. Fourthly, details on operative management, especially the technical aspect of how a LLND was performed, in-hospital recovery, and long-term morbidity were not reported in the majority of studies. Finally, for the study by Nishizaki et al. only an abstract was available with to date no full article published, and Shiratori et al.

reported the combined survival outcomes for the complete cohort without reporting long-term oncological outcomes for LLND+ vs. LLND- separately.[26,27]

Considering the outcomes of this systematic review and meta-analysis, an argument could be made to perform a LLND following nCRT in rectal cancers with metastatic LLNs to reduce local recurrence rates. However, because data is limited, more robust prospective results are eagerly awaited. In view of this, it is unfortunate the RCT by Wei et al. (NCT02614157) has been recently terminated, leaving the multi-center Lateral Nodal Recurrence in Rectal Cancer (LaNoReC) study as the only currently recruiting prospective study to in the future provide more evidence on the value of an additional LLND after nCRT in rectal cancers with metastatic LLNs.[42,43]

In conclusion, this systematic review and meta-analysis suggests that in rectal cancer patients with pre-treatment metastatic LLNs, nCRT followed by an additional LLND during TME results in a lower local recurrence rate. Due to the low quality of current literature, future higher quality studies will determine the true value of a LLND in this setting.

Acknowledgement

This project was undertaken whilst holding a Royal Adelaide Hospital Florey Fellowship by Hidde M. Kroon.

References

1. Hashiguchi Y, Muro K, Saito Y, et al. Japanese society for cancer of the colon and rectum. Japanese society for cancer of the colon and rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol 2020;25:1-42.
2. Ogura A, Konishi T, Cunningham C, et al. Neoadjuvant (chemo)radiotherapy with total mesorectal excision only is not sufficient to prevent lateral local recurrence in enlarged nodes: results of the multicenter lateral node study of patients with low cT3/4 rectal cancer. J Clin Oncol 2019;37:33–43.
3. Ishihara S, Kawai K, Tanaka T, et al. Oncological outcomes of lateral pelvic lymph node metastasis in rectal cancer treated with preoperative chemoradiotherapy. Dis Colon Rectum 2017;60:469–76.
4. Watanabe T, Muro K, Ajioka 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.
5. 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;60:577-85.
6. Atef Y, Koedam TW, Van Oostendorp SE, Bonjer HJ, Wijsmuller AR, Tuynman JB. Lateral pelvic lymph node metastases in rectal cancer: a systematic review. World J Surg 2019;43:3198-206.
7. De Pablos JO, Mayol J. Controversies in the management of lateral pelvic lymph nodes in patients with advanced rectal cancer: East or West? Front Surg 2020;6:79.
8. Kusters M, Uehara K, Velde CJ, Moriya Y. Is there any reason to still consider lateral lymph node dissection in rectal cancer? Rationale and technique. Clin Colon Rectal Surg 2017;30:346-56.
9. Akiyoshi T, Watanabe T, Miyata S, Kotake K, Muto T, Sugihara K, Japanese Society for Cancer of the Colon and Rectum. 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;255:1129-34.
10. Kroon HM, Malakorn S, Dudi-Venkata NN, et al. Local recurrences in Western low rectal cancer patients treated with or without lateral lymph node dissection after neoadjuvant (chemo)radiotherapy: An international multi-centre comparative study. Eur J Surg Oncol 2021;47:2441-9.
11. Haanappel A, Kroon HM, Schaap DP, et al. Lateral lymph node metastases in locally advanced low rectal cancers may not be treated effectively with neoadjuvant chemoradiotherapy only. Front Oncol 2019;9:1355.
12. Malakorn S, Yang Y, Bednarski BK, et al. Who should get lateral pelvic lymph node dissection after neoadjuvant chemoradiation? Dis Colon Rectum 2019;62:1158-66.
13. Otowa Y, Yamashita K, Kanemitsu K, et al. Treating patients with advanced rectal cancer and lateral pelvic lymph nodes with preoperative chemoradiotherapy based on pretreatment imaging. Onco Targets Ther 2015;8:3169–73.
14. Matsuda T, Sumi Y, Yamashita K, et al. Outcomes and prognostic factors of selective lateral pelvic lymph node dissection with preoperative chemoradiotherapy for locally advanced rectal cancer. Int J Colorectal Dis 2018;33:367–74.
15. Hajibandeh S, Hajibandeh S, Matthews J, Palmer L, Maw A. Meta-analysis of survival and functional outcomes after total mesorectal excision with or without lateral pelvic lymph node dissection in rectal cancer surgery. Surgery 2020;168:486-96.

16. Jones HG, Radwan RW, Sams E, et al. Incidence and treatment of positive pelvic sidewall lymph nodes in patients with rectal cancer. Colorectal Dis 2020;22:1560-7.
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;246:754–62.
18. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–12.
19. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. J Clin Epidemiol 2021;134:178-89.
20. Gerard A, Buyse M, Nordlinger B, et al. Preoperative radiotherapy as adjuvant treatment in rectal cancer. Final results of randomized study (EORTC). Ann Surg 1988;208:606-14.
21. Mendenhall WM, Millon RR, Bland KI, Pfaff V, Copeland EM. Preoperative radiation therapy for clinically resectable adenocarcinoma of the rectum. Ann Surg 1985;202:215-22.
22. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. Ottawa, Canada: The Ottawa Hospital Research Institute; 2021. [Cited 15 September 2021]. Available from: www.ohri.ca/programs/clinical_epidemiology/oxford.asp
23. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;7:8:16.
24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
25. Kim HJ, Choi GS, Park JS, et al. Optimal treatment strategies for clinically suspicious lateral pelvic node metastasis in rectal cancer. Oncotarget 2017;8:100724-33.
26. Shiratori H, Kawai K, Hata K, et al. Correlations between the recurrence patterns and sizes of lateral pelvic lymph nodes before and after chemoradiotherapy in patients with lower rectal cancer. Oncology 2019;96:33-43.
27. Nishizaki D, Hida1 K, Sumii A, et al. Neoadjuvant chemoradiotherapy with/without lateral lymph node dissection for low rectal cancer: Which patients can benefit? Ann Oncol 2019;30(S5):V205.
28. Kim MJ, Chang GJ, Lim HK, et al. Oncological impact of lateral lymph node dissection after preoperative chemoradiotherapy in patients with rectal cancer. Ann Surg Oncol 2020;27:3525–33.
29. Kusters M, Slater A, Betts M, et al. The treatment of all MRI-defined low rectal cancers in a single expert centre over a 5-year period: is there room for improvement? Colorectal Dis 2016;18:O397-O404.
30. MERCURY Study Group. Relevance of magnetic resonance imaging-detected pelvic sidewall lymph node involvement in rectal cancer. Br J Surg 2011;98:1798–1804.
31. Nakamura T, Watanabe M. Lateral lymph node dissection for lower rectal cancer. World J Surg 2013;37:1808-13.
32. Akiyoshi T, Matsueda K, Konishi T, 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;21:189-96.
33. Kim TH, Jeong SY, 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;15:729-37.

34. Sammour T, Chang GJ. Lateral pelvic lymph node dissection and radiation treatment for rectal cancer: Mutually exclusive or mutually beneficial? Ann Gastroenterol Surg 2018;2:348-50.
35. Longchamp G, Meyer J, Christou N, et al. Total mesorectal excision with and without lateral lymph node dissection: a systematic review of the literature. Int J Colorectal Dis 2020;35:1183–92.
36. Wang X, Qiu A, Liu X, Shi Y. Total mesorectal excision plus lateral lymph node dissection vs TME on rectal cancer patients: a meta-analysis. Int J Colorecal Dis 2020;35:997–1006.
37. Liu Y, Shang L, Zhou C, Fang Z, Du F, Wu H, Li L. Prognostic value of lateral pelvic lymph node dissection for rectal cancer: A meta-analysis. J Surg Res 2021;267:414-23.
38. Georgiou P, Tan E, Gouvas N, Antoniou A, Brown G, Nicholls RJ, Tekkis P. Extended lymphadenectomy versus conventional surgery for rectal cancer: a meta-analysis. Lancet Oncol 2009;10:1053–62.
39. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al., on behalf of the Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638-46.
40. Kusters M, Beets GL, Van De Velde CJH, et al. A comparison between the treatment of low rectal cancer in Japan and the Netherlands, focusing on the patterns of local recurrence. Ann Surg 2009;249:229–35.
41. Ogawa S, Itabashi M, Hirosawa T, Hashimoto T, Bamba Y, Kameoka S. Lateral pelvic lymph node dissection can be omitted in lower rectal cancer in which the longest lateral pelvic and perirectal lymph node is less than 5 mm on MRI. J Surg Oncol 2014;109:227-33.
42. Wei M, Wu Q, Fan C, et al. Lateral pelvic lymph node dissection after neoadjuvant chemo-radiation for preoperative enlarged lateral nodes in advanced low rectal cancer: study protocol for a randomized controlled trial. Trials 2016;17:561.
43. Kusters M. VU University Medical Center. Lateral nodal recurrence in rectal cancer (LaNoReC) [Internet]. Amsterdam, the Netherlands: Clinicaltrials.gov; 24 July 2020 [updated 1 April 2021; cited 15 September 2021]. Available from: https://clinicaltrials.gov/ct2/show/NCT04486131.

PRISMA 2020 Checklist

Supplementary Table 2.1: Prisma 2020 Checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p. 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p. 2 Supplement 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p. 3,4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p. 3,4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p. 5,6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p. 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	p. 5 Supplement 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p. 5,6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p. 7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p. 7 Supplement 4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p. 7 Supplement 4

Section and Topic	Item #	Checklist item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p. 6,7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	p. 7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	p. 6,7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p. 7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p. 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	p. 7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	p. 7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	p. 7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	p. 6,7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	p. 7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p. 8 Fig. 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Fig. 1
Study characteristics	17	Cite each included study and present its characteristics.	p. 8,9 Table 1,2,3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p. 9,10 Table 4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	p. 9,10 Table 5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	p. 9,10 Table 4,5
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	p. 10 Table 5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	p. 10

Section and Topic	Item #	Checklist item	Location where item is reported
			Table 5
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	p. 10 Table 5
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	p. 10 Table 5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	p. 10 Table 5
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	11,12,13
	23b	Discuss any limitations of the evidence included in the review.	12,13
	23c	Discuss any limitations of the review processes used.	12,13
	23d	Discuss implications of the results for practice, policy, and future research.	11,12,13
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	1
Competing interests	26	Declare any competing interests of review authors.	1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	5,6,7

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71 For more information, visit: http://www.prisma-statement.org/

PRISMA 2020 for Abstracts Checklist

Supplementary Table 2.2: Prisma 2020 for Abstracts Checklist.

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Supplementary Table 2.3: Search terms and strategies.

Databases	Search strategies
PubMed	((((((((((((((((((rectal neoplasm) OR (pelvic neoplasm)) OR (rectal cancer)) AND (lymphatic metastasis)) OR (lateral lymph node)) OR (lateral pelvic lymph node)) OR (pelvic side wall node)) AND (neoadjuvant therapy)) OR (chemoradiotherapy)) AND (proctectomy)) OR (rectal resection)) OR (total mesorectal excision)) AND (lymph node dissection)) OR (extended lymphadenectomy)) OR (lateral lymph node dissection)) OR (lateral pelvic lymph node dissection)) OR (pelvic side wall dissection)) AND (comparative study)
Ovid Medline	(Rectal cancer and neoadjuvant and lateral lymph node dissection | Total mesorectal excision and neoadjuvant and lateral lymph node)
EMBASE	(rectum cancer and lateral lymph node metastasis | lateral lymph node metastasis and neoadjuvant therapy)
Cochrane Library	((rectal cancer or rectal neoplasm) and lateral lymph nodes and (neoadjuvant or chemoradiotherapy))
Clinicaltrials.gov	(rectal cancer or rectal neoplasm | lateral lymph nodes or pelvic side wall node)

Supplementary Table 2.4: Search terms and strategies.

Databases searched: PubMed, Ovid MEDLINE, EMBASE, Cochrane Library, Clinicaltrials.gov Between: 1st January 1985 and 30th September 2021	
	Search Terms
Rectal cancer	1. Rectal neoplasm 2. Pelvic neoplasm 3. Rectal cancer 4. OR 1-3
Lateral lymph node	5. Lymphatic metastasis 6. Lateral lymph node 7. Lateral pelvic lymph node 8. LPLN 9. Pelvic side wall node 10. OR 5-9
Neoadjuvant chemoradiotherapy	11. Neoadjuvant therapy 12. Chemoradiotherapy 13. OR 12-13
Total mesorectal excision	14. Proctectomy 15. Rectal resection 16. Total mesorectal excision 17. Mesorectal excision 18. OR 14-17
Lateral lymph node dissection	19. Lymph node dissection 20. Extended resection 21. Extended lymphadenectomy 22. Lateral lymph node dissection 23. LLND 24. Lateral pelvic lymph node dissection 25. Pelvic side wall dissection 26. OR 19-25
Comparative study	27. Comparative study 28. Randomized-controlled trial 29. OR 27-28
	30. AND 4, 10, 13, 18, 26, 29

Supplementary Table 2.5: Data extraction sheet.

Name of Study		
First author		
Country		
Publication year		
Study design		
Single/multi center		
	LLND+	**LLND-**
No. of patients in each arm		
Gender M/F (%)		
Age in years (median)		
Tumour height from anal verge in cm (median / %)		
cT stage (%)		
Size criteria used for metastatic lateral lymph nodes (mm)		
Site of metastatic lateral lymph nodes		
Type of neoadjuvant therapy (%)		
type of operation performed LAR/APR (%)		
Operation time (mins)		
LLND performed single/bilateral (%)		
Postoperative complications Clavien-Dindo (%)		
Hospital stay (days)		
Adjuvant therapy (%)		
Long-term morbidity (%)		
ypT-stage (%)		
ypN-stage (%)		
Resection margins (%)		
Tumour positive LLNs (%)		
Follow up (months)		
5-year lateral local recurrence rate (%)		
5-year local recurrence rate (%)		
5-year distant metastatic rate (%)		
5-year disease-free survival rate (%)		
5-year cancer-specific survival (%)		
5-year overall survival rate (%)		

Chapter 3

Malignant features in pre-treatment metastatic lateral lymph nodes in locally advanced low rectal cancer predict distant metastases.

Hidde M. Kroon[1,2], Nagendra N. Dudi-Venkata[1,2], Sergei Bedrikovetski[1,2], Jianliang Liu[1], Anouck Haanappel[1], Atsushi Ogura[3,4], Cornelis J.H. van de Velde[3], Harm J.T. Rutten[5,6], Geerard L. Beets[7], Michelle L. Thomas[1], Miranda Kusters[8], Tarik Sammour[1,2].

[1] Colorectal Unit, Department of Surgery, Royal Adelaide Hospital, Adelaide, South Australia, Australia
[2] Adelaide Medical School, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, South Australia, Australia
[3] Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands
[4] Department of Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan
[5] Department of Surgery, Catharina Hospital, Eindhoven, the Netherlands
[6] GROW, School of Oncology and Developmental Biology, University of Maastricht, Maastricht, the Netherlands
[7] Department of Surgery, the Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, the Netherlands
[8] Department of Surgery, Amsterdam University Medical Centers, location VUmc, Amsterdam, the Netherlands

Ann Surg Oncol 2022;29:1194-1203. doi: 10.1245/s10434-021-10762-z.

Statement of Authorship

Title of Paper	Malignant features in pre-treatment metastatic lateral lymph nodes in locally advanced low rectal cancer predict distant metastases.
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Kroon HM, Dudi-Venkata NN, Bedrikovetski S, Liu J, Haanappel H, Ogura A, Van de Velde CJH, Rutten HJT, Beets GL, Thomas ML, Kusters M, Sammour T. Malignant features in pre-treatment metastatic lateral lymph nodes in locally advanced low rectal cancer predict distant metastases. Ann Surg Oncol 2022;29:1194-1203. doi: 10.1245/s10434-021-10762-z.

Principal Author

Name of Principal Author (Candidate)	Hidde M. Kroon		
Contribution to the Paper	Conception and design of the project Acquiring research data Analysis and interpretation of research data Drafting the article Critically revising of article		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	13/09/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Nagendra N. Dudi-Venkata		
Contribution to the Paper	Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Sergei Bedrikovetski		
Contribution to the Paper	Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Jianliang Liu		
Contribution to the Paper	Acquiring research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Anouck Haanappel		
Contribution to the Paper	Acquiring research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Atsushi Ogura		
Contribution to the Paper	Acquiring research data Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Cornelis J.H. van de Velde		
Contribution to the Paper	Acquiring research data Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Harm J.T. Rutten		
Contribution to the Paper	Acquiring research data Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Geerard L. Beets		
Contribution to the Paper	Acquiring research data Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Michelle L. Thomas		
Contribution to the Paper	Acquiring research data Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Miranda Kusters		
Contribution to the Paper	Acquiring research data Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/09/2021

Name of Co-Author	Tarik Sammour		
Contribution to the Paper	Conception and design of the project Acquiring research data Analysis and interpretation of research data Critically revising of article		
Signature		Date	13/09/2021

Abstract

Introduction: Pre-treatment enlarged lateral lymph nodes (LLNs) in patients with locally advanced low rectal cancer are predictive for local recurrences after neoadjuvant (chemo)radiotherapy (nCRT) followed by total mesorectal excision (TME). Not much is known of the impact on oncological outcomes when in addition malignant features are present in enlarged LLNs.

Methods: A multi-centre retrospective cohort study was conducted at five tertiary referral centres in the Netherlands and Australia. All patients were diagnosed with locally advanced low rectal cancer with LLNs on pre-treatment MRI and underwent nCRT followed by TME. LLNs were considered enlarged with a short-axis of ≥5mm. Malignant features were defined as nodes with internal heterogeneity and/or border irregularity. Outcomes of interest were local recurrence-free survival (LRFS), distant metastatic-free survival (DMFS), and overall survival (OS).

Results: Out of 115 patients, the majority was male (75%) and the median age was 64 years (range 26-85). Median pre-treatment LLNs short-axis was 7mm (range 5-28) and 60 patients (52%) had malignant features. After a median follow-up of 47 months, patients with larger LLNs (7+mm) had a worse LRFS (p=0.01), but no difference in DMFS (p=0.37) and OS (p=0.54) compared to patients with smaller LLNs (5-6mm). LLNs patients with malignant features had no difference in LRFS (p=0.20), but worse DMFS (p=0.004) and OS (p=0.006) compared to patients without malignant features in the LLNs. Cox regression analysis identified LLNs short-axis as an independent factor for local recurrences. Malignant features in LLNs was an independent factor for DMFS.

Conclusion: The current study suggests that pre-treatment enlarged LLNs that also harbor malignant features are predictive of a worse DMFS. More studies will be required to further explore the role of malignant features in LLNs.

Introduction

Technical progress of magnetic resonance imaging (MRI) has greatly improved diagnostic and staging accuracy in patients with rectal cancer, allowing better identification of high-risk disease.[1,2] Specifically pre-treatment abnormal lateral lymph nodes (LLNs) can now more accurately be detected.[3] On staging MRI, LLNs are defined as enlarged nodes in one of the lateral nodal basins with or without malignant features, such as border irregularity or internal heterogeneity.[4,5] LLNs are present in approximately 20% of patients with locally advanced low rectal cancer (AJCC stage III), and are associated with worse oncological outcomes after treatment, which in the West normally consists of neoadjuvant (chemo)radiotherapy (nCRT) followed by total mesorectal excision (TME).[6-8]

Previous studies, mainly focused on size, have shown that larger pre-treatment LLNs are predictive for local recurrences.[5,9-11] Interestingly, not much is known about the impact on oncological outcomes when malignant features are present in LLNs.[4,7,8] Therefore, the aim of the current study was to investigate the effects on long-term oncological outcomes when malignant features are present in pre-treatment LLNs in patients with locally advanced low rectal cancer.

Methods

The 'Strengthening the Reporting of Observational Studies in Epidemiology' guideline was used for this paper.[12]

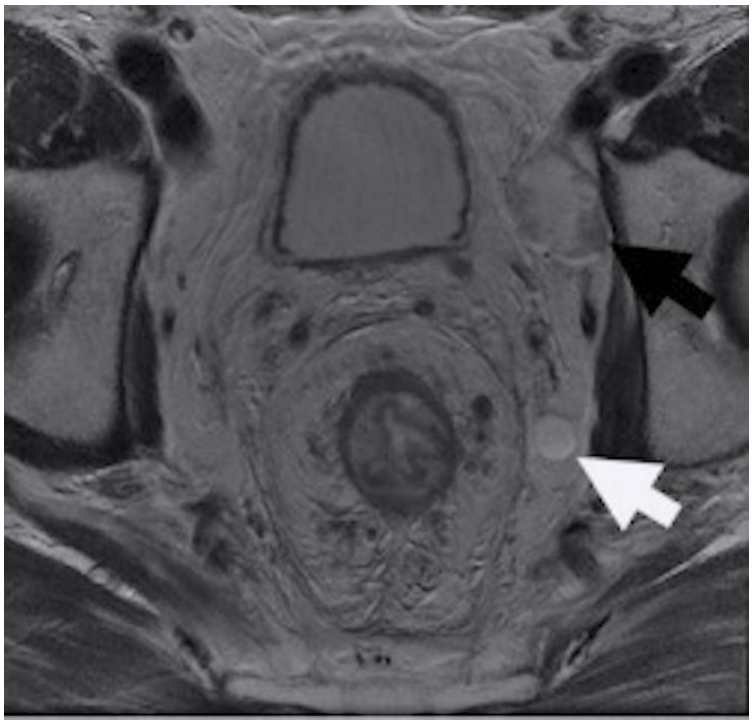
A retrospective cohort study was conducted at five tertiary referral centres in the Netherlands (NL: Antoni van Leeuwenhoek-Netherlands Cancer Institute in Amsterdam, Catharina Hospital in Eindhoven and Leiden University Medical Center in Leiden) and Australia (AUS: Royal Adelaide Hospital and St. Andrew's hospital both in Adelaide). The study was approved by the human research ethics committee at each site.

Included were patients ≥18 years with a primary locally advanced (AJCC stage III) rectal cancer, ≤9 cm of the anal verge with pre-treatment LLNs on MRI.[6] All patients were treated with curative intent, by nCRT followed by TME, between January 2009 and December 2016. Exclusion criteria were patients with a high rectal cancer (>9cm), those with distant metastatic disease at the time of diagnosis (AJCC stage IV), patients in whom lateral lymph nodes were resected during surgery, patients requiring pelvic exenteration surgery and other patients who did not undergo TME, patients who did not receive nCRT, and patients with locally recurrent disease after a previous rectal resection.

MRI assessment guidelines as published by the Lateral Node Study Consortium were followed.[8] In short, pre-treatment MRI's were reviewed by the same dedicated radiologist at each centre using a colour map atlas of the pelvis for re-evaluation of the LLNs status as described previously.[4] In addition to the AJCC TNM staging, circumferential resection margin, and tumour height, radiologists were asked to assess LLNs status, based on the node with the largest short-axis. LLNs were considered enlarged with a short-axis of ≥5 mm located in the following compartments: obturator, internal iliac, and external iliac basins.

Furthermore, the presence of malignant features in the LLNs, e.g., internal heterogeneity and/or border irregularity, was noted (Figure 3.1).

Figure 3.1: Pre-treatment pelvic MRI of patient with locally advanced rectal cancer with enlarged lateral lymph nodes with (black arrow) and without (white arrow) malignant features.



Neoadjuvant therapy consisted of either short-course radiotherapy (5x5 Gray) or long-course chemoradiotherapy (45-50.4 Gray in 28 fractions over six weeks with one of the following concomitant chemotherapy regimens: FOLFOX (folinic acid, fluorouracil and oxaliplatin), capecitabine, or 5-fluorouracil. Radiotherapy fields were routinely extended to include LLNs basins. TME with curative intent was carried out after nCRT. Following surgery, routine oncological follow-up was performed, with a minimum of three years for all patients. De-identified data were collected from the participating hospitals' departmental prospective databases, and electronic and paper medical records, forming a new database that was collectively analysed. Preoperative collected data included age, sex, body mass index (BMI), ASA-classification, cTNM-stage, height of tumour from the anal verge on MRI, clinical

circumferential resection margin (cCRM), side of LLNs, LLNs basin involved, short-axis and malignant features of LLNs, and type of neoadjuvant therapy. Peri-operative collected data included: type of resection and operative time, Clavien-Dindo complication grade, length of stay (LOS), ypTNM-stage, resection margins, lymphovascular invasion, number of mesorectal lymph nodes resected, and adjuvant chemotherapy.[13]

Lateral local recurrences (LLR) were defined as tumour regrowth in one of the LLNs basins. Local recurrences (LR) were defined as tumour regrowth in the pelvis at the site of the anastomosis, in the previously resected mesorectal tissues, or in one of the LLNs basins. Distant metastases were defined as tumour growth in the para-aortic lymph nodes and/or distant organs. For each patient, all events were recorded during follow-up. Outcomes of interest were: lateral local recurrence-free survival (LLRFS), local recurrence-free survival (LRFS), distant metastatic-free survival (DMFS) and overall survival (OS). For this analysis patients with malignant features in LLNs were compared to patients without malignant features. Two groups according to LLNs size were also created: 5-6mm and 7+mm.[4,8]

Continuous variables are shown as medians with range and categorical variables are presented as absolute numbers with percentages. Differences in characteristics between groups were evaluated with the Mann Whitney U-test for continuous variables, and the Chi-square or the Fisher's exact test (in tables indicated with *) for categorical variables.[14] Three-year oncological outcomes (lateral local recurrence, local recurrence, distant metastases and mortality rates) were evaluated with the Chi-square or the Fisher's exact test (indicated in the tables with *). LLRFS, LRFS, DMFS, and OS were estimated using the Kaplan-Meier method, with the Cochran-Mantel-Haenszel test from the day of surgery.[15] Multivariate survival analysis was performed using the Cox proportional hazard model with stepwise backward method. A p-value of ≤ 0.05 was considered statistically significant. Statistical

analyses were performed using SPSS version 25.0 (IBM Corp, Armonk, NY, USA) and GraphPad Prism version 8.0.2 (GraphPad Software Inc., San Diego, CA, USA).

Results

A total of 124 patients were identified. In 9 patients enlarged LLNs were removed during surgery, leaving 115 patients for inclusion in the study (Table 3.1). The median age of the complete cohort was 64 years (range 26-85 years) and the majority was male (75%). Most patients had a clinical tumour stage 3 (cT3; 63%) and clinical nodal stage 1 (cN1) and 2 (cN2) were equally distributed (50% each). Median short-axis of the LLNs was 7mm (range 5-28mm). Malignant features in the LLN were present in 60 patients (52%), and 55 patients had no malignant features (48%). Compared to patients without malignant features, patients with malignant features in the LLNs had higher rates of cT4a-stage disease (27% vs. 45%, respectively; not reaching significance: p=0.08) and cN-stage disease (40% vs. 60%, respectively; p=0.04). Median short-axis of LLNs in patients with malignant features was 8mm, and 6mm for patients without malignant features (p=0.01). Other baseline characteristics between groups were not significantly different. Most frequent malignant features present in LLNs were heterogeneity (38%) or both irregular borders and heterogeneity (43%).

Table 3.1: Baseline patient and tumour characteristics.

Variable	**Complete cohort** (n=115)	**Malignant features –** (n=55)	**Malignant features +** (n=60)	**P-value**
Age in years, median (range)	64 (26 - 85)	65 (30 - 82)	62 (26 - 85)	0.17
Sex (%) Male Female	 86 (75) 29 (25)	 43 (78) 12 (22)	 43 (72) 17 (28)	0.52*
BMI, median (range)	26.6 (16.9 - 46.2)[1]	26.8 (20.4 - 39.5)[1]	26.3 (16.9 - 46.2)[1]	0.60
ASA-classification (%)				

1 2 3 4	9 (16) 32 (58) 14 (26)[2] 0	5 (16) 18 (58) 8 (26)[2] 0	4 (17) 14 (58) 6 (25)[2] 0	0.94
cT-stage (%) cT2 cT3 cT4a	 1 (1) 72 (63) 42 (36)	 0 40 (73) 15 (27)	 1 (2) 32 (53) 27 (45)	0.08
cN-stage (%) cN1 cN2	 57 (50) 58 (50)	 33 (60) 22 (40)	 24 (40) 36 (60)	0.04
Height of tumour in cm, median (range)	3.2 (0.0 - 9.0)	3.6 (0.0 - 9.0)	2.8 (0.0 - 8.5)	0.11
cCRM-involvement (%) Yes No	 48 (42) 67 (58)	 20 (36) 35 (64)	 28 (47) 32 (53)	0.26
Side of LLNs (%) Left Right Both	 57 (50) 49 (42) 9 (8)	 28 (51) 24 (44) 3 (5)	 29 (48) 25 (42) 6 (10)	0.67
Involved LLNs basin (%) External iliac Obturator Internal iliac	 10 (14) 39 (55) 22 (31)[3]	 4 (12) 17 (52) 12 (36)[3]	 6 (16) 22 (58) 10 (26)[3]	0.65
Short-axis LLNs in mm, median (range)	7 (5 - 28)	6 (5 - 21)	8 (5 - 28)	0.01
Short-axis of LLNs by size group (%) 5-6mm 7mm+	 57 (50) 58 (50)	 38 (69) 17 (31)	 19 (32) 41 (68)	<0.0001*
Type of malignant features LLNs (%) Heterogeneity Irregular border Both	 -	 -	 23 (38) 11 (19) 26 (43)	 -
Neoadjuvant therapy (%) Short-course RT Long-course CRT	 20 (17) 95 (83)	 11 (20) 44 (80)	 9 (15) 51 (85)	0.62*

LLNs: lateral lymph nodes, BMI: body mass index, ASA: American Society of Anaesthesiologists, cT-stage: clinical tumour stage, cN-stage: clinical nodal stage, cCRM: clinical circumferential resection margin, RT: radiotherapy, CRT: chemoradiotherapy.
[1] 2 patients missing (1 malignant features -, 1 malignant features +), [2] 60 patients missing (24 malignant features -, 36 malignant features +), [3] 71 sites (33 malignant features -, 38 malignant features +), * Fisher's exact test.

None of the peri-operative and postoperative histopathology outcomes were significantly different between both groups (Table 3.2). Patients with malignant features underwent more frequently an abdomino-perineal resection (APR; 62% vs. 45% for patients without malignant features; not reaching significance: p=0.08) and had a wider range of tumour positive mesorectal nodes (0-14 nodes vs. 0-8 nodes for patients without malignant features; not reaching statistical significance p=0.09).

Table 3.2: Peri-operative characteristics and postoperative histopathology.

Variable	Complete cohort (n=115)	Malignant features – (n=55)	Malignant features + (n=60)	P-value
Type of resection (%) LAR APR	 53 (46) 62 (54)	 30 (55) 25 (45)	 23 (38) 37 (62)	0.08
Operation time in minutes, median (range)	255 (78 - 675)[1]	223 (117 - 675)[1]	262 (78 - 595)[1]	0.82
Clavien-Dindo grade (%)[13] 0/1 2 3 4 5	 19 (34) 23 (42) 8 (15) 4 (7) 1 (2)[1]	 11 (39) 11 (39) 3 (11) 2 (7) 1 (3)[1]	 8 (30) 12 (44) 5 (19) 2 (7) 0[1]	0.74
Length of hospital stay in days, median (range)	11 (4 - 62)[1]	11 (4 - 35)[1]	12 (6 - 62)[1]	0.63
ypT-stage (%) ypT0 ypT1 ypT2	 12 (11) 6 (5) 30 (26)	 8 (15) 3 (5) 14 (25)	 4 (7) 3 (5) 16 (26)	0.74

ypT3 ypT4a	54 (47) 13 (11)	24 (44) 6 (11)	30 (50) 7 (12)	
ypN-stage, mesorectal nodes only (%) ypN0 ypN1 ypN2	 72 (63) 29 (25) 14 (12)	 37 (67) 14 (26) 4 (7)	 35 (58) 15 (25) 10 (17)	 0.29
Lympho-vascular invasion (%) Yes No	 22 (22) 76 (78)[2]	 11 (22) 39 (78)[2]	 11 (23) 37 (77)[2]	 0.99*
Total number of mesorectal LN harvested, median (range) **Range** tumour positive mesorectal lymph nodes	13 (2 - 46) 0 - 14	16 (6 - 46) 0 - 8	16 (5 - 45) 0 - 14	0.24 0.09
Resection margins (%) R0 R1 R2	 103 (89) 11 (10) 1 (1)	 51 (93) 4 (7) 0	 52 (87) 7 (11) 1 (2)	 0.39
Adjuvant chemotherapy (%) No Yes	 80 (70) 35 (30)	 40 (73) 15 (27)	 40 (66) 20 (33)	 0.54*

LAR: low anterior resection, APR: abdomino-perineal resection, ypT-stage: post-neoadjuvant pathological tumour stage, ypN-stage: post-neoadjuvant pathological nodal stage, LN: lymph nodes, N/A: not-applicable.
[1] 60 patients missing (27 malignant features -, 33 malignant features +), [2] 17 patients missing (5 malignant features -, 12 malignant features +). * Fisher's exact test.

Type of neoadjuvant therapy and the rate of adjuvant chemotherapy administered were not significantly different between LLNs groups with or without malignant features (Table 3.1 and 3.2), or by LLNs size (Table 3.3).

Table 3.3: Administration of neoadjuvant and adjuvant therapies by lateral lymph node size.

Variable	Complete cohort (n=115)	LLN size 5-6 mm (n=57)	LLN size 7+ mm (n=58)	P-value
Neoadjuvant therapy (%)				
Short-course RT	20 (17)	10 (18)	10 (17)	0.99*
Long-course CRT	95 (83)	47 (82)	48 (83)	
Adjuvant chemotherapy (%)				
No	80 (70)	44 (77)	36 (62)	0.10*
Yes	35 (30)	13 (23)	22 (38)	

RT: radiotherapy, CRT: chemoradiotherapy. * Fisher's exact test.

Three years after surgery, LLR and LR rates were worse for patients with larger LLNs (7+mm; p=0.06 and p=0.03, respectively), while there was no significant difference in distant metastatic and mortality rates (p=0.67 and p=0.54, respectively; Table 3.4a).

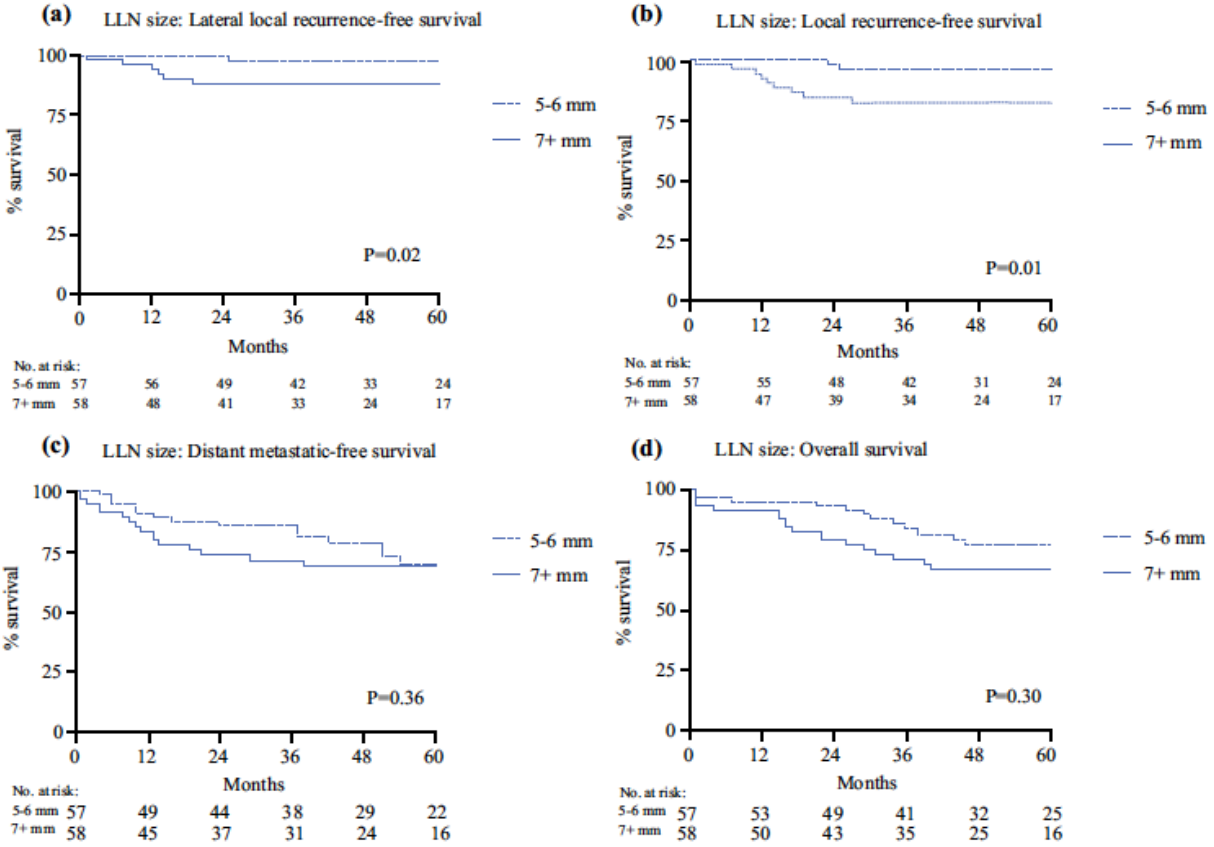
Table 3.4a: Three-year oncological outcomes for metastatic lateral lymph nodes according to short-axis size.

	5-6mm n=57	7+mm n=58	P-value
Lateral local recurrence (%)	1 (2)	7 (12)	0.06*
Local recurrence (%)	2 (4)	10 (17)	0.03*
Distant metastases (%)	14 (25)	17 (29)	0.67*
Mortality (%)	16 (28)	20 (34)	0.54*

* Fisher's exact test.

Similarly, after a median follow-up of 47 months, patients with larger LLNs (7+mm) had worse LLRFS (p=0.02) and LRFS (p=0.01), but no significant difference in DMFS (p=0.36) and OS (p=0.30; Figure 3.2).

Figure 3.2: Kaplan-Meier survival curves of lateral local recurrence-free survival (a; p=0.02), local recurrence-free survival (b; p=0.01), distant metastatic-free survival (c; p=0.36) and overall survival (d; p=0.30) by size of lateral lymph nodes.



In contrast, three years after surgery, LLR and LR rates were not different for LLNs patients with and patients without malignant features (p=0.28 and p=0.37, respectively; Table 3.4b), while distant metastatic and mortality rates were worse for LLNs patients with malignant features (p=0.02 and p=0.0003, respectively).

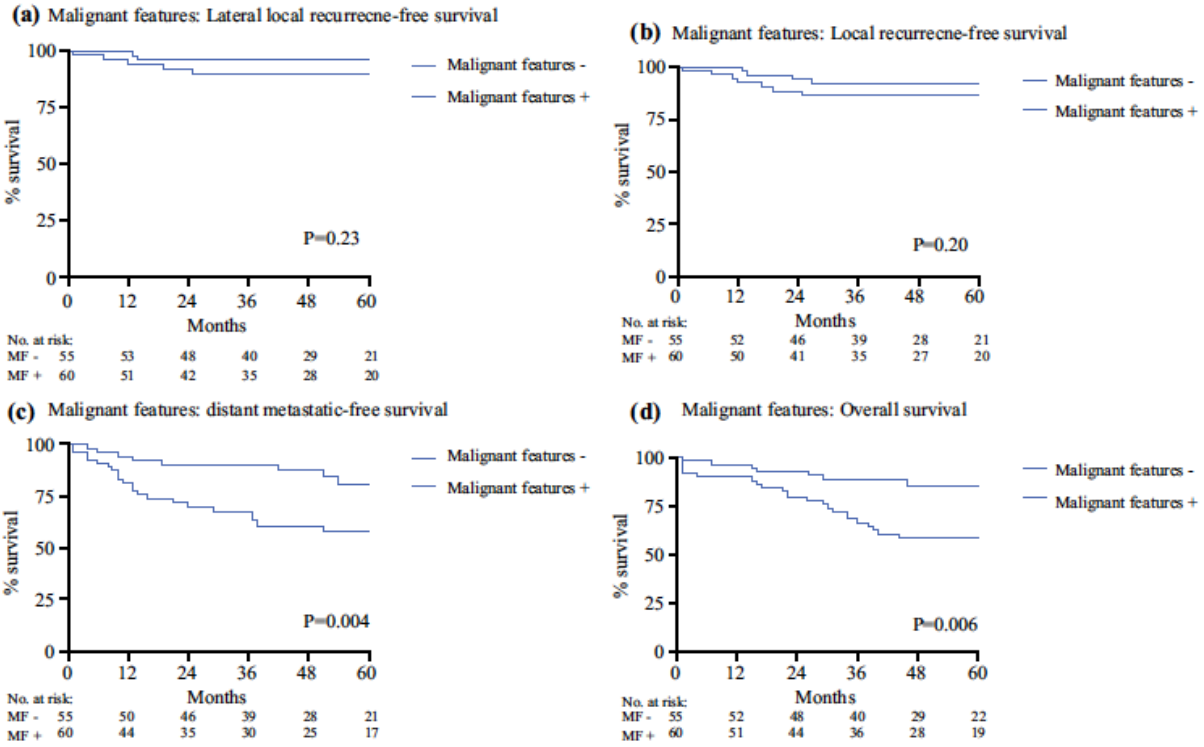
Table 3.4b: Three-year oncological outcomes for metastatic lateral lymph nodes with or without malignant features.

	Malignant features - n=55	**Malignant features +** n=60	**P-value**
Lateral local recurrence (%)	2 (4)	6 (10)	0.28*
Local recurrence (%)	4 (7)	8 (13)	0.37*
Distant metastases (%)	9 (16)	22 (37)	0.02*
Mortality (%)	8 (15)	28 (47)	0.0003*

* Fisher's exact test.

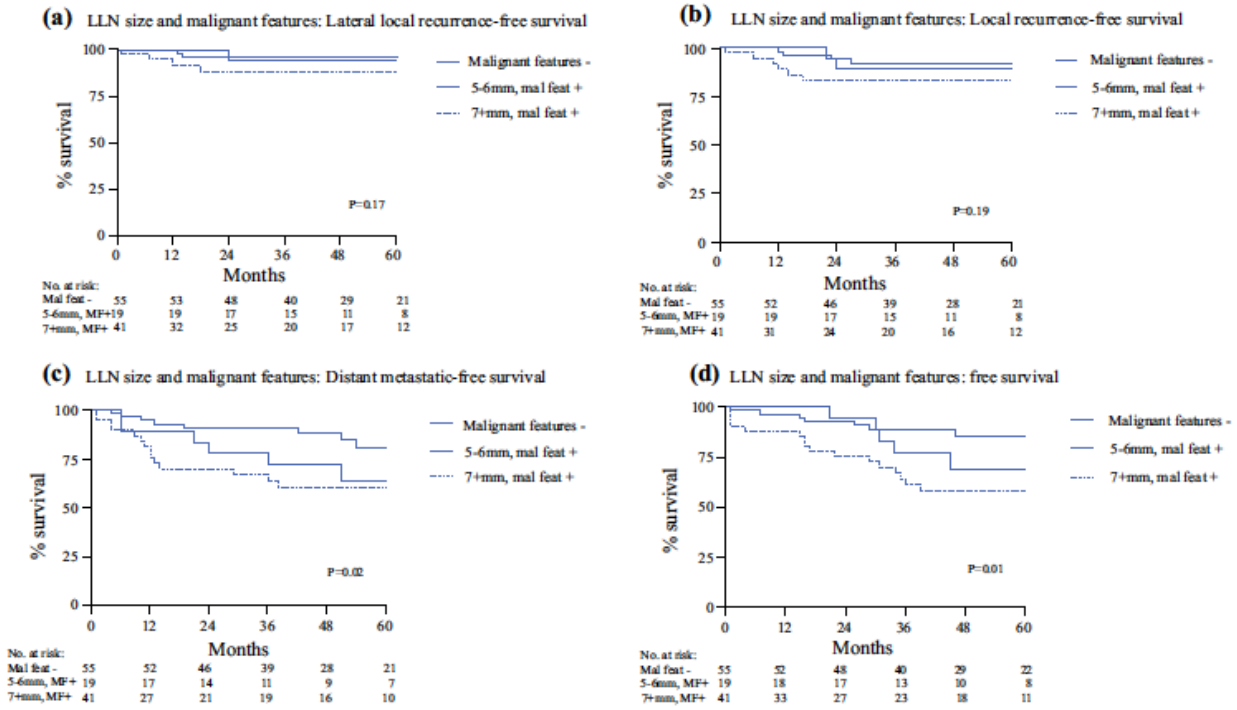
Also, LLRFS (p=0.23) and LRFS (p=0.20) were not significantly different for LLNs patients with or without malignant features, but DMFS (p=0.004) and OS (p=0.006) were worse for LLNs patients with malignant features (Figure 3.3).

Figure 3.3: Kaplan-Meier survival curves of lateral local recurrence-free survival (a; p=0.23), local recurrence-free survival (b; p=0.20), distant metastatic-free survival (c; p=0.004), and overall survival (d; p=0.006) of lateral lymph nodes with or without malignant features.



When analysing LLNs with malignant features by size, DMFS and OS were also worse for LLNs with 5-6mm short-axis compared to LLNs without malignant features (p=0.02 and p=0.01, respectively) (Figure 3.4).

Figure 3.4: Kaplan-Meier survival curves of lateral local recurrence-free survival (a; p=0.17), local recurrence-free survival (b; p=0.19), distant metastatic-free survival (c; p=0.02), and overall survival (d; p=0.01) of enlarged lateral lymph nodes without malignant features and by size groups with malignant features.



Cox regression analysis showed that short-axis size of the LLNs remained an independent significant factor for LR (p=0.02). Malignant features in LLNs remained an independent significant factor for DMFS (p=0.04) (Table 3.5).

Table 3.5: Summary of Cox regression analysis.

Endpoint - Variable	p-value	HR	95%CI
Lateral local recurrence			
ypN-stage	0.04	2.94	1.43 - 4.56
Local recurrence			
cT-stage	0.03	4.06	2.66 - 6.23
cN-stage	0.05	3.32	1.67 - 7.32
Short-axis size LLNs	0.02	1.31	1.21 - 2.12
Distant metastasis			
cN-stage	0.02	3.19	2.18 - 8.63
Malignant features LLNs	0.04	1.89	1.20 - 4.04
Overall survival			
Age	0.03	2.31	1.52 - 5.96
ypN-stage	0.05	2.14	1.35 - 4.90
Lymphovascular invasion	0.03	4.42	1.11 -10.53
Resection margins	0.02	3.54	2.15 - 10.91

HR: hazard ratio, 95%CI: 95% confidence interval.

Discussion

In rectal cancer, size criteria for LLNs are well established to predict loco-regional recurrences.[4,5,9-11] Using LLNs size criteria helps to identify patients who may benefit from local treatment.[8] The current study suggests that additional malignant features present in enlarged LLNs are predictive for worse DMFS. This could represent a poorer biology of the tumour and helps to select patients for systemic treatment.

Current knowledge about the clinical significance of enlarged LLNs also harbouring malignant features is limited. In a recent publication, the Lateral Node Study Consortium has been one of the few to investigate oncological outcomes of malignant features also.[4,7,8] In contrast to the current study, this consortium found that malignant features were associated with a worse LLR and LR, but not DMFS. In this study, a large number of patients from the East were included, 12% of whom underwent a lateral lymph node dissection (LLND) while 20% did not undergo any neoadjuvant treatment. In order to create a more homogeneous cohort, only Western patients were included in the current analysis, of whom all underwent neoadjuvant therapy, and none underwent a LLND, making the results more applicable to Western practices.

A study conducted in Oxford, suggested that LLNs with malignant features do not result in different LLR rates, DMFS or cancer specific survival.[7] However, this study only included 13 LLNs patients (10%) with malignant features, meaning that it likely underestimated the true impact of LLNs harbouring malignant features. Furthermore, 40 patients (31%) did not undergo any neoadjuvant therapy. Since increased LLNs size was significantly related to poorer cancer-specific survival and OS, it was concluded that LLNs size might is a better measure than assessment of malignant features. Additionally, Japanese surgeons mainly base their judgement of LLNs on size, and less on malignant features.[7]

Indeed, LLNs size is one of the most important prognostic factors for long-term oncological outcomes.[4,8] Additionally, the current study suggests that patients with enlarged LLNs harbouring malignant features have poorer DMFS compared to those without these features. This means that additionally to using LLNs short-axis size, taking malignant features into consideration, may result in improved diagnosis of smaller nodes.[16-20]

In the analysed cohort, patients with malignant features in enlarged LLNs had higher cN-stages and had larger LLNs compared to patients without malignant features. This could have impacted the distant metastatic rate, but in the Cox regression analysis, malignant features remained an independent factor for DMFS.

In the current cohort, no LLNDs were performed as the Western standard treatment of nCRT followed by TME, was followed. It is therefore unclear if enlarged LLNs, with or without malignant features, actually were metastatic or if they were inflammatory only, as no postoperative histopathology was available. Previous studies have shown that LLNs harboring metastases upon postoperative pathology are associated with decreased survival.[21,22,23] In light of this, another interpretation of the results of the current study could be that malignant features identified true metastatic LLNs more accurately, while those that were enlarged only could have been either inflammatory or metastatic, resulting in increased distant metastatic rates in LLNs with malignant features. For this reason, performing an additional LLND after nCRT in patients with enlarged LLNs could be of benefit, the more because some Western centres have recently reported reduced local recurrence rates after LLND, but evidence is limited.[8,9,24] In the future, more robust results from the currently recruiting multi-centre Lateral Nodal Recurrence in Rectal Cancer (LaNoReC) study are expected.[25]

Some limitations of the current study have to be addressed. Firstly, this is a retrospective cohort series conducted at multiple centres, resulting in unavailability of parameters, such as

extramural vascular invasion and number of LLNs, and in heterogeneity of patients and treatment modalities, such as nCRT and adjuvant chemotherapy regimens used. Particularly in the Netherlands, adjuvant chemotherapy is used sparingly in rectal cancer and reserved for patients who develop recurrences. However, all patients in the current study were treated according to the local protocol, independently of their LLNs status. Secondly, for each patient all events were recorded during follow-up to reflect the real-life setting of the study. This could have resulted in altered identification of a potential second recurrence due to adjuvant treatment that had been initiated following the first recurrence. Thirdly, due to differences in interpretation, radiologists at the participating institutions, although all with a special interest in rectal cancer imaging, may have interpreted the presence of malignant features variably, especially in smaller LLNs.[19,20] Also, we were not able to evaluate the LLNs response to nCRT as patients did not undergo a restaging MRI routinely. Lastly, despite including patients treated at five tertiary referral centres, the number of patients meeting the inclusion criteria was relatively low.

In conclusion: the current study suggests that pre-treatment enlarged LLNs that also harbor malignant features are predictive of a worse DMFS. More studies will be required to further explore the role of malignant features in LLNs.

Acknowledgement

This project was undertaken whilst holding a Royal Adelaide Hospital Florey Fellowship by Hidde M. Kroon.

References

1. Taylor FG, Quirke P, Heald RJ, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. J Clin Oncol 2014;32:34-43.
2. Beets-Tan RGH, Lambregts DMJ, Maas M, et al. Magnetic resonance imaging for clinical management of rectal cancer: Updated recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. Eur Radiol 2018;28:1465-75.
3. Ishibe A, Ota M, Watanabe J, et al. Prediction of lateral pelvic lymph-node metastasis in low rectal cancer by magnetic resonance imaging. World J Surg 2016;40:995-1001.
4. Ogura A, Konishi T, Beets GL, et al. Lateral nodal features on restaging magnetic resonance imaging associated with lateral local recurrence in low rectal cancer after neoadjuvant chemoradiotherapy or radiotherapy. JAMA Surg 2019;154:e192172.
5. Kusters M, Uehara K, Velde CJH, Moriya Y. Is there any reason to still consider lateral lymph node dissection in rectal cancer? Rationale and technique. Clin Colon Rectal Surg 2017;30:346-56.
6. Jessup JM, Goldberg RM, Asare EA, et al. Chapter 20: Colon and Rectum. In: Amin MB, Edge S, Greene F, et al., eds. AJCC cancer staging manual. 8th ed. New York, NY: Springer, 2017:251-74.
7. 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;60:577–85.
8. Ogura A, Konishi T, Cunningham C, et al. Neoadjuvant (chemo)radiotherapy with total mesorectal excision only is not sufficient to prevent lateral local recurrence in enlarged nodes: Results of the multicenter lateral node study of patients with low cT3/4 rectal cancer. J Clin Oncol 2019;37:33-43.
9. Malakorn S, Yang Y, Bednarski BK, et al. Who should get lateral pelvic lymph node dissection after neoadjuvant chemoradiation? Dis Colon Rectum 2019;62:1158-66.
10. Haanappel A, Kroon HM, Schaap DP, et al. Lateral lymph node metastases in locally advanced low rectal cancers may not be treated effectively with neoadjuvant chemoradiotherapy only. Front Oncol 2019;9:1355.
11. Atef Y, Koedam TW, van Oostendorp SE, Bonjer HJ, Wijsmuller AR, Tuynman JB. Lateral pelvic lymph node metastases in rectal cancer: A systematic review. World J Surg 2019;43:3198-206.
12. Von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453-57.
13. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187-96.
14. Mann HB, Whitney DR. On a test of whether one of two random variables is stochastically larger than the other. Ann Math Statist 1947;18:50-60.
15. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
16. Kim MJ, Kim TH, Kim DY, et al. Can chemoradiation allow for omission of lateral pelvic node dissection for locally advanced rectal cancer? J Surg Oncol 2015;111:459-64.

17. Lim SB, Yu CS, Kim CW, et al. Clinical implication of additional selective lateral lymph node excision in patients with locally advanced rectal cancer who underwent preoperative chemoradiotherapy. Int J Colorectal Dis 2013;28:1667-74.
18. Oh HK, Kang SB, Lee SM, et al. Neoadjuvant chemoradiotherapy affects the indications for lateral pelvic node dissection in mid/low rectal cancer with clinically suspected lateral node involvement: a multicenter retrospective cohort study. Ann Surg Oncol 2014;21:2280-7.
19. Matsuoka H, Nakamura A, Masaki T, et al. Optimal diagnostic criteria for lateral pelvic lymph node metastasis in rectal carcinoma. Anticancer Res 2007;27:3529–33.
20. Kim JH, Beets GL, Kim MJ, et al. High-resolution MR imaging for nodal staging in rectal cancer: are there any criteria in addition to the size? Eur J Radiol 2004;52:78–83.
21. Matsuda T, Sumi Y, Yamashita K, et al. Outcomes and prognostic factors of selective lateral pelvic lymph node dissection with preoperative chemoradiotherapy for locally advanced rectal cancer. Int J Colorectal Dis 2018;33:367-374.
22. Yang X, Gu C, Hu T, et al. Indications and oncological outcomes of selective dissection for clinically suspected lateral lymph node metastasis in patients with rectal cancer based on pretreatment imaging. Tech Coloproctol 2021;25:425-37.
23. Kim HJ, Choi GS, Park JS, et al. Optimal treatment strategies for clinically suspicious lateral pelvic lymph node metastasis in rectal cancer. Oncotarget 2017;8:100724-33.
24. Kroon HM, Malakorn S, Dudi-Venkata NN,et al. Lateral lymph node dissection after neoadjuvant (chemo)radiotherapy may improve oncological outcomes in Western patients with low rectal cancer. Eur J Surg Oncol 2021;47:2441-9.
25. Kusters M, Tuynman J. LaNoReC trial. Rectal Cancer Surgery. Available at: https://rectalcancersurgery.eu/lanorec-trial/. Published [2019]. Accessed [December 15, 2020].

Chapter 3, Appendix

ASO author reflection: Lateral pelvic lymph nodes in rectal cancer: Not All are created equal

Hidde M. Kroon[1,2], Miranda Kusters[3], Tarik Sammour[1,2].

[1] Colorectal Unit, Department of Surgery, Royal Adelaide Hospital, Adelaide, South Australia, Australia
[2] Adelaide Medical School, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, South Australia, Australia
[3] Department of Surgery, Amsterdam University Medical Centers, location VUmc, Amsterdam, the Netherlands

Ann Surg Oncol 2022:29;1204-5. doi: 10.1245/s10434-021-10815-3.

Statement of Authorship

Title of Paper	ASO Author Reflection: Lateral pelvic lymph nodes in rectal cancer: Not all are created equal.
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Kroon HM, Kusters M, Sammour T. ASO author reflection: Lateral pelvic lymph nodes in rectal cancer: Not all are created equal. Ann Surg Oncol 2022;29:1204-5. doi: 10.1245/s10434-021-10815-3.

Principal Author

Name of Principal Author (Candidate)	Hidde M. Kroon		
Contribution to the Paper	Conception and design of the project Drafting the article Critically revising of article		
Overall percentage (%)	90%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	20/09/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Miranda Kusters		
Contribution to the Paper	Conception and design of the project Critically revising of article		
Signature		Date	20/09/2021

Name of Co-Author	Tarik Sammour		
Contribution to the Paper	Conception and design of the project Critically revising of article		
Signature		Date	20/09/2021

Past

Pre-treatment metastatic lateral lymph nodes (LLNs) are present in approximately 20% of locally advanced low rectal cancers. LLNs are defined as enlarged nodes in one of the lateral nodal basins with or without malignant features, such as border irregularity or internal heterogeneity.[1] Previous research has shown that enlarged LLNs predict local recurrence after standard Western treatment, consisting of neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME).[2] Not much is known of the impact on oncological outcomes when additionally malignant features are present in LLNs.

Present

In the current international multi-centre study, it was confirmed that pre-treatment enlarged LLNs are predictive of local recurrence in univariate and multivariate analyses.[3] In addition, enlarged LLNs that also had malignant features on pre-treatment MRI were predictive of worse distant metastatic-free survival, suggesting increased metastatic potential. This can be interpreted as analogous to the behaviour of primary rectal cancers, with bulky locally advanced tumours representing a greater risk of local recurrence (so-called "ugly" tumours), and those with extra tumoral deposits representing a greater distant failure risk ("bad" tumours).

Future

In the current dataset, lateral lymph node dissection (LLND) was not performed after nCRT and TME.[3] Considering the outcomes of this paper, an argument could be made for performing LLND after nCRT in rectal cancers with abnormal LLNs, with potentially different roles depending on morphology (size, malignant features, or both). Some Western centres have recently reported reduced local recurrence rates after LLND, but evidence

remains limited and generally based on LLNs size rather than on morphology.[2,4] In the future, more robust results from the multi-centre Lateral Nodal Recurrence in Rectal Cancer (LaNoReC) study are expected, providing more evidence on the significance of size and morphology criteria of LLNs in rectal cancer.[5]

References

1. Ogura A, Konishi T, Beets GL, et al. Lateral nodal features on restaging magnetic resonance imaging associated with lateral local recurrence in low rectal cancer after neoadjuvant chemoradiotherapy or radiotherapy. JAMA Surg 2019;154:e192172.
2. Ogura A, Konishi T, Cunningham C, et al. Neoadjuvant (chemo)radiotherapy with total mesorectal excision only is not sufficient to prevent lateral local recurrence in enlarged nodes: Results of the multicenter lateral node study of patients with low cT3/4 rectal cancer. J Clin Oncol 2019;37:33-43.
3. Kroon HM, Dudi-Venkata NN, Bedrikovetski S, et al. Malignant features in pre-treatment metastatic lateral lymph nodes in locally advanced low rectal cancer predict distant metastases. Ann Surg Oncol 2022;29:1194-1203. doi: 10.1245/s10434-021-10762-z.
4. Kroon HM, Malakorn S, Dudi-Venkata NN,et al. Lateral lymph node dissection after neoadjuvant (chemo)radiotherapy may improve oncological outcomes in Western patients with low rectal cancer. Eur J Surg Oncol 2021;47:2441-9.
5. Kusters M, Tuynman J. LaNoReC trial. Dutch Colorectal Cancer Group; LaNoReC Trial. Available at: https://dccg.nl/trial/lanorec. Published [2019]. Accessed [August 19, 2021].

Thesis summary

Summary and Discussion

Pre-treatment enlarged lateral lymph nodes (LLNs) are present in approximately 20% of all patients with locally advanced rectal cancer. LLNs are defined as enlarged nodes in one of the lateral nodal basins with or without malignant features, such as border irregularity or internal heterogeneity.[1] In the West, standard treatment of LLNs consists of neoadjuvant (chemo)radiotherapy (nCRT) followed by total mesorectal excision (TME), meaning the LLNs are not resected surgically. Because of reports from the East, mainly Japan and South Korea, there is a recent growing interest in performing an additional lateral lymph node dissection (LLND) in these patients.[1-3]

For the studies included in this thesis, an international multi-centre database including patients with locally advanced rectal cancer and enlarged LLNs from six Western tertiary referral hospitals in the US, the Netherlands and Australia was constructed and analysed. All patients had locally advanced rectal cancer with enlarged LLNs, with a short-axis of ≥5mm, and underwent nCRT followed by TME. In addition, the patients from the US underwent a LLND.

Results showed that enlarged LLNs predict local recurrences after nCRT followed by TME, which is in accordance to previous literature,[4,5] and that enlarged LLNs with malignant features are predictive of worse distant metastatic-free survival, suggesting an increased metastatic potential.

Considering these outcomes, an argument could be made for performing a LLND after nCRT in rectal cancer patients with abnormal LLNs. Therefore, long-term oncological outcomes of the addition of a LLND after nCRT were studied compared to a group undergoing nCRT only, showing reduced local recurrences for patients who underwent an additional LLND.[6]

In a systematic review, including seven studies, the addition of a LLND after nCRT in patients with rectal cancer with LLNs was analysed compared to patients who were treated by nCRT only. This systematic review confirmed the results from the clinical study showing lower local recurrence rates, and in addition improved disease-free survival rates, both in favour of LLND.

Considering the results described in the chapters included in this thesis, an argument could be made to perform an additional LLND during TME after nCRT in rectal cancer patient with pre-treatment enlarged LLNs, with potentially different approaches depending on morphology (size, malignant features, or both).

Future

Due to the retrospective nature of the clinical studies included in this thesis and the low quality of the studies included in the review, high-quality studies are required to determine the value of LLND in this setting.

In future studies it would therefore be beneficial if more Western centres could participate, especially those centres performing LLNDs. However, for this to occur, increased experience with performing the LLND procedure in the West will be necessary. The results of the now open Lateral Nodal Recurrence in Rectal Cancer (LaNoReC) study are eagerly awaited.[7]

References

1. Ogura A, Konishi T, Cunningham C, et al. Neoadjuvant (chemo)radiotherapy with total mesorectal excision only is not sufficient to prevent lateral local recurrence in enlarged nodes: Results of the multicenter lateral node study of patients with low cT3/4 rectal cancer. J Clin Oncol 2019;37:33-43.
2. Malakorn S, Yang Y, Bednarski BK, et al. Who should get lateral pelvic lymph node dissection after neoadjuvant chemoradiation? Dis Colon Rectum 2019;62:1158-66.
3. Sammour T, Chang GJ. Lateral pelvic lymph node dissection and radiation treatment for rectal cancer: Mutually exclusive or mutually beneficial? Ann Gastroenterol Surg 2018;2:348-50.
4. Ogura A, Konishi T, Beets GL, et al. Lateral nodal features on restaging magnetic resonance imaging associated with lateral local recurrence in low rectal cancer after neoadjuvant chemoradiotherapy or radiotherapy. JAMA Surg 2019;154:e192172.
5. Kroon HM, Dudi-Venkata NN, Bedrikovetski S, et al. Malignant features in pre-treatment metastatic lateral lymph nodes in locally advanced low rectal cancer predict distant metastases. Ann Surg Oncol 2022;29:1194-1203. doi: 10.1245/s10434-021-10762-z.
6. Kroon HM, Malakorn S, Dudi-Venkata NN,et al. Lateral lymph node dissection after neoadjuvant (chemo)radiotherapy may improve oncological outcomes in Western patients with low rectal cancer. Eur J Surg Oncol 2021;47:2441-9.
7. Kusters M, Tuynman J. LaNoReC trial. Dutch Colorectal Cancer Group; LaNoReC Trial. Available at: https://dccg.nl/trial/lanorec. Published [2019]. Accessed [August 19, 2021].

List of presentations from this Thesis

Verbal presentations

Kroon HM, Malakorn S, Dudi-Venkata NN, Bedrikovetski S, Liu J, Bednarski BK, Ogura A, Van de Velde CJH, Rutten H, Beets G, Thomas ML, Kusters M, Chang GJ, Sammour T. Lateral lymph node dissection after neoadjuvant (chemo)radiotherapy may improve oncological outcomes in Western patients with low rectal cancer. ASCO Gastrointestinal Cancers Symposium, January 2020, San Francisco, California, V.S. (abstract: J Clin Oncol 2020;38;(4_suppl):163).

Kroon HM, Malakorn S, Dudi-Venkata NN, Bedrikovetski S, Liu J, Bednarski BK, Ogura A, Van de Velde CJH, Rutten H, Beets G, Thomas ML, Kusters M, Chang GJ, Sammour T. Lateral lymph node dissection after neoadjuvant (chemo)radiotherapy may improve oncological outcomes in western patients with low rectal cancer. Society of Surgical Oncology 2020 International Conference on Surgical Cancer Care, March 2020, Boston, Massachusetts, USA (abstract: Ann Surg Oncol 2020;27:S17, meeting cancelled due to Covid-19 pandemic).

Kroon HM, Malakorn S, Dudi-Venkata NN, Bedrikovetski S, Liu J, Bednarski BK, Ogura A, Van de Velde CJH, Rutten HJT, Beets GL, Thomas ML, Kusters M, Chang GJ, Sammour T. Lateral lymph node dissection after neoadjuvant (chemo)radiotherapy may improve oncological outcomes in Western patients with low rectal cancer. Royal Australasian College of Surgeons 89th annual scientific congress, May 2020, Melbourne, Australia (abstract: ANZ J Surg 2020;90(S1):35, (meeting cancelled due to Covid-19 pandemic).

Kroon HM, Malakorn S, Dudi-Venkata NN, Bedrikovetski S, Liu J, Bednarski BK, Ogura A, Van de Velde CJH, Rutten H, Beets G, Thomas ML, Kusters M, Chang GJ, Sammour T. 31: Lateral lymph node dissection after neoadjuvant (chemo)radiotherapy may improve oncological outcomes in western patients with low rectal cancer. SSO 2020 Society of Surgical Oncology International Conference on Surgical Cancer Care, Virtual meeting, August 2020 (abstract: www.eventscribe.com/2020/SSO2020/biography.asp?pfp=Speakers).

Kroon HM, Malakorn S, Dudi-Venkata NN, Bedrikovetski S, Liu J, Bednarski BK, Ogura A, Van de Velde CJH, Rutten H, Beets GL, Thomas ML, Kusters M, Chang GJ, Sammour T. Lateral lymph node dissection after neoadjuvant (chemo)radiotherapy may improve oncological outcomes in western patients with low rectal cancer. 2020 Florey Postgraduate Research Conference, University of Adelaide, Virtual meeting, September 2020.

Kroon HM, Dudi-Venkata NN, Bedrikovetski S, Liu J, Haanappel A, Ogura A, Van de Velde CJH, Rutten HJT, Beets GL, Thomas ML, Kusters M, Sammour T. Malignant features in pre-treatment metastatic lateral lymph nodes in low rectal cancers predict distant metastases and survival, but not local recurrences. The European Society of Surgical Oncology virtual conference, October 2020 (abstract: Eur J Surg Oncol 2021;47:e20-1).

Kroon HM, Dudi-Venkata NN, Bedrikovetski S, Liu J, Haanappel A, Ogura A, Van de Velde CJH, Rutten HJT, Beets GL, Thomas ML, Kusters M, Sammour T. Malignant features in pre-treatment metastatic lateral lymph nodes in low rectal cancers predict distant metastases and survival, but not local recurrences. The Society of Surgical Oncology 2021 - International Conference on Surgical Cancer Care virtual meeting, March 2021. (Abstract:

Ann Surg Oncol 2021;28:S13.
www.eventscribe.com/2021/SSO2021/biography.asp?pfp=Speakers).

Kroon HM, Dudi-Venkata NN, Bedrikovetski S, Liu J, Haanappel A, Ogura A, Van de Velde CJH, Rutten HJT, Beets GL, Thomas ML, Kusters M, Sammour T. Malignant features in pre-treatment metastatic lateral lymph nodes in low rectal cancers predict distant metastases and survival, but not local recurrences. Royal Australasian College of Surgeons 89th annual scientific congress, May 2021, Melbourne, Australia. (abstract: ANZ J Surg 2021;91(S1):33).

Poster presentations

Kroon HM, Malakorn S, Dudi-Venkata NN, Bedrikovetski S, Liu J, Bednarski BK, Ogura A, Van de Velde CJH, Rutten H, Beets G, Thomas ML, Kusters M, Chang GJ, Sammour T. Lateral lymph node dissection after neoadjuvant (chemo)radiotherapy may improve oncological outcomes in western patients with low rectal cancer. Society of Surgical Oncology 2020 Advanced Cancer Therapies, February 2020, Orlando, Florida, USA.

Kroon HM, Haanappel A, Schaap DP, Bedrikovetski S, Dudi-Venkata NN, Lee HX, Thomas ML, Liu J, Van der Valk MJM, Rutten HJT, Beets GL, Kusters M, Sammour T. Lateral lymph node metastases in locally advanced low rectal cancers may not be treated effectively with neoadjuvant (chemo)radiotherapy only. Royal Australasian College of Surgeons 89th annual scientific congress, May 2020, Melbourne, Australia (abstract: ANZ J Surg 2020;90(S1):46, meeting cancelled due to COVID-19 pandemic).

Haanappel A, **Kroon HM**, Schaap DP, Bedrikovetski S, Dudi-Venkata NN, Lee HX, Thomas ML, Liu J, Van der Valk MJM, Rutten HJT, Beets GL, Kusters M, Sammour T. Lateral lymph node metastases in locally advanced low rectal cancers may not be treated effectively with neoadjuvant (chemo)radiotherapy only. Royal Australasian College of Surgeons 89th annual scientific congress, May 2021, Melbourne, Australia. (abstract: ANZ J Surg 2021;91(S1):44).

Kroon HM, Malakorn S, Dudi-Venkata NN, Bedrikovetski S, Liu J, Kenyon-Smith T, Bednarski BK, Ogura A, Van de Velde CJH, Rutten JHT, Beets GL, Thomas ML, Kusters M, Chang GJ, Sammour T. Lateral lymph node dissection after neoadjuvant (chemo)radiotherapy may improve oncological outcomes in Western patients with low rectal cancer. Royal Australasian College of Surgeons 89th annual scientific congress, May 2021, Melbourne, Australia. (abstract: ANZ J Surg 2021;91(S1):43).

Kroon HM, Malakorn S, Dudi-Venkata NN, Bedrikovetski S, Liu J, Kenyon-Smith T, Bednarski BK, Ogura A, Van de Velde CJH, Rutten HJT, Beets GL, Thomas ML, Kusters M, Chang GJ, Sammour T. Local recurrences in Western low rectal cancer patients treated with or without lateral lymph node dissection after neoadjuvant (chemo)radiotherapy: An international multi-centre comparative study. Tripartite Colorectal Meeting (CSSANZ, ESCP, ASCRS), February 2022, Auckland, New Zealand.

Kroon HM, Hoogervorst L, Hanna-Rivero N, Traeger L, Dudi-Venkata NN, Bedrikovetski S, Kusters M, Thomas ML, Sammour T. Systematic review on long-term oncological outcomes of lateral lymph node dissection for metastatic nodes after neoadjuvant

chemoradiotherapy in rectal cancer. Tripartite Colorectal Meeting (CSSANZ, ESCP, ASCRS), February 2022, Auckland, New Zealand.

Publications by HM Kroon during Master of Philosophy Candidature 2020-2022 not included in this Thesis

1. Teras J, **Kroon HM,** Thompson JF, Teras M, Pata P, Mägi A, Teras RM, Boudinot SR. First Eastern European experience of isolated limb infusion for in-transit metastatic melanoma confined to the limb: Is it still an effective treatment option in the modern era? Eur J Surg Oncol 2020;46:272-6.
2. Bedrikovetski S, Dudi-Venkata NN, **Kroon HM**, Liu J, Lewis M, Lawrence MJ, Andrews JM, Sammour T. Rectal stump management after subtotal colectomy for severe colitis: In or out? A retrospective cohort study. Indian J Surg 2020 doi.org/10.1007/s12262-019-02004-0.
3. Dudi-Venkata NN, **Kroon HM**, Bedrikovetski S, Moore JW, Sammour T. Systematic scoping review of enhanced recovery protocol recommendations targeting return of gastrointestinal function after colorectal surgery. ANZ J Surg 2020;90:41-7.
4. Lorenzon L, Evrard S, Beets G, Gonzalez-Moreno S, Kovacs T, D'Ugo D, Polom K, CORSiCA Study - EYSAC.1 Study Group: Sammour T, **Kroon HM**, et al. Global variation in the long-term outcomes of ypT0 rectal cancers. Eur J Surg Oncol 2020;46:420-8.
5. Dudi-Venkata NN, **Kroon HM**, Bedrikovetski S, Moore JW, Thomas ML, Sammour T. A global survey of surgeons' preferences and practice with regards to laxative use after elective colorectal surgery. Int J Colorectal Dis 2020;35:759-63.
6. PelvEx Collaborative: Kelly ME, Aalbers A, ….., **Kroon HM**, et al. Management strategies for patients with advanced rectal cancer and liver metastases using modified Delphi methodology: results from the PelvEx collaborative. Colorectal Dis 2020;22:1184-8.
7. Jolly S, Dudi-Venkata NN, Hanna-Rivero N, **Kroon HM**, Reid FSW, Sammour T. Four different ileorectal anastomotic configurations following total colectomy. ANZ J Surg 2020;90:1588-91.
8. Bedrikovetski S, Dudi-Venkata NN, **Kroon HM**, Moore JW, Hunter RA, Sammour T. Outcomes of minimally invasive versus open proctectomy for rectal cancer: a propensity-matched analysis of Bi-National Colorectal Cancer Audit data. Dis Colon Rectum 2020;63:778-87.
9. Huisman DE, Reudink M, Van Rooijen SJ, Bootsma BT, Van de Brug T, Stens J, Bleeker W, Stassen LPS, Jongen A, Feo CV, Targa S, Komen N, **Kroon HM**, Sammour T, Lagae EA, Talsma AK, Wegdam JA, De Vries Reilingh TS, Van Wely B, Van Hoogstraten MJ, Sonneveld DJA, Veltkamp SC, Verdaasdonk EGG, Roumen RMH, Slooter G, Daams F. LekCheck: A prospective study to identify perioperative modifiable risk factors for anastomotic leakage in colorectal surgery. Ann Surg Ann Surg 2022 2022;275:e189-e97.
10. Teras J, **Kroon HM**, Miura JT, Kenyon-Smith T, Beasley GM, Mullen D, Farrow NE, Mosca PJ, Lowe MC, Farley CR, Potdar A, Daou H, Sun J, Carr M, Farma JM, Henderson MA, Speakman D, Serpell J, Delman KA, Smithers BM, Barbour A, Tyler DS, Coventry BJ, Zager JS, Thompson JF. International multi-center experience of isolated limb infusion for in-transit melanoma metastases in octogenarian and nonagenarian patients. Ann Surg Oncol 2020;27:1420-9.
11. Teras J, **Kroon HM**, Zager JS. ASO Author reflections: International multi-center experience of isolated limb infusion for in-transit melanoma metastases in octogenarian and nonagenarian patients. Ann Surg Oncol 2020;27:1430-1.

12. Juszczyk K, Ireland K, Thomas B, **Kroon HM**, Hollington P. Safety and efficacy of outpatient management for elderly patients with uncomplicated acute diverticulitis. Eur J Internal Med 2020;76:123-4.
13. Van Harten MJ, Greenwood EB, Bedrikovetski S, Dudi-Venkata NN, Hunter RA, **Kroon HM**, Sammour T. Minimally invasive surgery in elderly patients with rectal cancer: An analysis of the Bi-National Colorectal Cancer Audit (BCCA). Eur J Surg Oncol 2020;46:1649-55.
14. Dudi-Venkata NN, Seow W, **Kroon HM**, Bedrikovetski S, Moore JW, Thomas ML, Sammour T. Safety and efficacy of laxatives after major abdominal surgery: A systematic review and meta-analysis. BJS Open 2020;4:577-86.
15. Dudi-Venkata NN, Lee YD, Zhi Beh Y, Bedrikovetski S, **Kroon HM**, Moore JW, Thomas ML, Sammour T. The impact of laxatives on return of gastrointestinal function after elective colorectal surgery: a propensity score matched analysis. Am Surg 2020 (Online ahead of print).
16. Ceuppens C, Dudi-Venkata NN, Lee YD, Beh YZ, Bedrikovetski S, Thomas ML, **Kroon HM**, Sammour T. Feasibility study of an online modifiable Enhanced Recovery After Surgery (mERAS) protocol with specific focus on opioid avoidance. ANZ J Surg 2020;90:1947-52.
17. PelvEx Collaborative: Kelly ME, Aalbers A, ….., **Kroon HM**, et al. Simultaneous pelvic exenteration and liver resection for primary rectal cancer with synchronous liver metastases: Results from the PelvEx Collaborative. Colorectal Dis 2020;22:1258-62.
18. PelvEx Collaborative: Dudurych I, Kelly ME, ….., **Kroon HM**, et al. Predicting outcomes of pelvic exenteration using machine learning. Colorectal Dis 2020;22:1933-40.
19. Kenyon-Smith TJ, **Kroon HM**, Miura JT, Teras J, Beasley GM, Mullen D, Farrow NE, Mosca PJ, Lowe MC, Farley CR, Potdar A, Daou H, Sun J, Farma JM, Henderson MA, Speakman D, Serpell J, Delman KA, Smithers BM, Barbour A, Coventry BJ, Tyler DS, Zager JS, Thompson JF. Factors predicting toxicity and response following isolated limb infusion for melanoma: An international multi-centre study. Eur J Surg Oncol 2020;46:2140-6.
20. PelvEx Collaborative: Kontovounisios C, Chok AY, ….., **Kroon HM**, et al. The impact of the COVID-19 pandemic on the management of locally advanced primary/recurrent rectal cancer. Br J Surg 2020;107:e547-8.
21. Carr MJ, Sun J, **Kroon HM**, Miura JT, Beasley GM, Farrow NE, Mosca PJ, Lowe MC, Farley CR, Kim Y, Naqvi SMH, Kirichenko DA, Potdar A, Daou H, Mullen D, Farma JM, Henderson MA, Speakman D, Serpell J, Delman KA, Smithers BM, Coventry BJ, Tyler DS, Thompson JF, Zager JS. Oncologic outcomes after isolated limb infusion for advanced melanoma: An international comparison between the US and Australia. Ann Surg Oncol 2020;27:5107-18.
22. Carr MJ, **Kroon HM**, Zager JS. ASO author reflections: Return to isolated limb infusion for in-transit melanoma. Ann Surg Oncol 2020;27:5119-20.
23. PelvEx Collaborative: Kelly ME, Aalbers AGJ, …., **Kroon HM**, et al. The global cost of pelvic exenteration: in-hospital perioperative costs. Br J Surg 2020;107:e470-1.
24. Broman K, Hughes T, Dossett L, Sun J, Carr M, Kirichenko D, Sharma A, Bartlett E, Nijhuis A, Thompson J, Hieken T, Kottschade L, Downs J, Gyorki D, Stahlie E, Van Akkooi A, Ollila D, Frank J, Song Y, Karakousis G, Moncrieff M, Nobes J, Vetto J, Han D, Farma J, Deneve J, Fleming M, Perez M, Baecher K, Lowe M, Olofsson Bagge R, Mattsson J, Lee A, Berman R, Chai H, **Kroon H**, Teras R, Teras J, Farrow N, Beasley G, Hui J, Been L, Kruijff S, Boulware D, Sarnaik A, Sondak V, Zager J. International Advanced Melanoma Collaborative. Surveillance of sentinel node positive

melanoma patients with reasons for exclusion from MSLT-2: A multi-institutional propensity score matched analysis. J Am Coll Surg 2021;232:424-31.
25. CovidSurg Collaborative: Glasbey JC, Bhangu A;, ….., **Kroon HM**, et al. Elective cancer surgery in COVID-19 free surgical pathway during the SARS-CoV-2 pandemic: An international, multi-centre, comparative cohort study. J Clin Oncol 2021;39:66-78.
26. Broman KK, Hughes T, Dossett L, Sun J, Kirichenko D, Carr M, Sharma A, Bartlett EK, Nijhuis AAG, Thompson JF, Hieken TJ, Kottschade L, Downs J, Gyorki DE, Stahlie E, Van Akkooi A, Ollila DW, Frank J, Song Y, Karakousis G, Moncrieff M, Nobes J, Vetto J, Han D, Farma JM, Deneve JL, Fleming MD, Perez M, Lowe M, Bagge RO, Mattsson J, Lee AY, Berman RS, Chai H, **Kroon HM,** Teras J, Teras RM, Farrow NE, Beasley G, Yuet Ching Hui J, Been L, Kruijff S, Kim Y, Naqvi SMH, Sarnaik A, Sondak VK, Zager JS. Active surveillance of melanoma patients with sentinel node metastasis: An international multi-institution evaluation of post-MSLT-2 adoption and early outcomes. Cancer 2021;127:2251-61.
27. CovidSurg Collaborative: Glasbey JC, Nepogodiev D, …., **Kroon HM**, et al. Delaying surgery for patients with a previous SARS-CoV-2 infection. Br J Surg 2020;107:e601-2.
28. CovidSurg Collaborative: Glasbey JC, Omar O, …., **Kroon HM**, et al. Preoperative nasopharyngeal swab testing and postoperative pulmonary complications in patients undergoing elective surgery during the SARS-CoV-2 pandemic. Br J Surg 2021;108:88-96.
29. Morrison C, Brown B, Lin DY, Jaarsma RL, **Kroon H**. Analgesia and anesthesia using the pericapsular nerve group block in hip surgery and hip fracture: A scoping review. Reg Anesth Pain Med 2021;46:169-75.
30. CovidSurg Collaborative. Li E, Glasbey JC, …., **Kroon HM**, et al. Outcomes from elective colorectal cancer surgery during the SARS-CoV-2 pandemic. Colorectal Dis Colorectal Dis 2021;23:732-49.
31. Kontovounisios C, Yong Chok A, Tekkis P, Oliver A, Shahnawaz R, on behalf of the PelvEx collaborative, ….. **Kroon HM**, et al. Perioperative management and anaesthetic considerations in pelvic exenteration using Delphi methodology: Results from the PelvEx Collaborative. BJS open 2021;5:zraa055.
32. **Kroon HM**, Mullen D. Ingested foreign body causing a silent perforation of the bowel. BMJ Case Rep 2021;14:e240879.
33. Bedrikovetski S, Dudi-Venkata NN, Maicas G, Seow W, **Kroon HM**, Carneiro G, Moore JW, Sammour T. Artificial intelligence for the diagnosis of lymph node metastases in patients with abdominopelvic malignancy: a systematic review and meta-analysis. Artif Intell Med 2021;113:102022.
34. Reudink M, Huisman DE, Lieverse AG, Van Rooijen SJ, **Kroon HM**, Roumen RMH, Daams F, Slooter GD, on behalf of the LekCheck study group. Association between intraoperative blood glucose and anastomotic leakage in colorectal surgery. J Gastrointest Surg 2021;25:2619-27.
35. Teras J, Carr MJ, Zager JS, **Kroon HM.** Molecular aspects of the isolated limb infusion procedure. Biomedicines 2021;9:163.
36. CovidSurg Week Collaborative: Li E, Glasbey JC, …., **Kroon HM**, et al. SARS-CoV-2 vaccination to support safe surgery during the pandemic: a modelling study using data from an international prospective cohort study. Br J Surg 2021;108:1056-63.
37. Lin DY, Morrison C, Brown B, Saies AA, Pawar R, Vermeulen M, Anderson SR, Lee TS, Doornberg JN, **Kroon HM**, Jaarsma RL. The pericapsular nerve group (PENG) block provides improved short-term analgesia compared to the femoral nerve block in hip fracture surgery: A single-centre double-blinded randomized comparative trial. Reg Anesth Pain Med 2021;46:398-403.

38. Grupa VEM, **Kroon HM**, Ozmen I, Bedrikovetski S, Dudi-Venkata NN, Hunter RA, Sammour T. Current practice in Australia and New Zealand for defunctioning ileostomy after rectal cancer surgery with anastomosis: Analysis of the Bi-National Colorectal Cancer Audit (BCCA). Colorectal Dis 2021;23:1421-33.
39. CovidSurg Week Collaborative: Li E, Glasbey JC, …., **Kroon HM**, et al. Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. Anaesthesia 2021;76:748-58.
40. Dudi-Venkata NN, **Kroon HM**, Bedrikovetski S, Lewis M, Lawrence MJ, Hunter RA, Moore JW, Thomas ML, Sammour T. Impact of STIMUlant and osmotic LAXatives (STIMULAX trial) on gastrointestinal recovery after colorectal surgery: Randomized clinical trial. Br J Surg 2021;108:797-803.
41. Dudi-Venkata NN, **Kroon HM**, Bedrikovetski S, Traeger L, Lewis M, Lawrence MJ, Hunter RA, Moore JW, Thomas ML, Sammour T. PyRICo-Pilot – Pyridostigmine to reduce the duration of postoperative ileus after colorectal surgery – a phase II study. Colorectal Dis 2021;23:2154-60.
42. REACCT Collaborative: Zaborowski A, Winter D, ….., **Kroon HM,** et al. Characteristics of early-onset vs late-onset colorectal cancer: A review. JAMA Surg 2021;156:865-74.
43. CovidSurg Week Collaborative: Li E, Glasbey JC, …., **Kroon HM**, et al. Machine learning risk prediction mortality for patients undergoing surgery with perioperative SARS-CoV-2: the COVIDSurg Mortality Score. Br J Surg 2021;108:1274-92.
44. **Kroon HM**, Kenyon-Smith T, Nair G, Virgin J, Thomas B, Juszczyk K, Hollington P. Safety and efficacy of short-course intravenous antibiotics after complicated appendicitis in selected patients. Acta Chir Belg 2021 (Online ahead of print).
45. Ozmen I, Grupa VEM, Bedrikovetski S, Dudi-Venkata NN, Huisman DE, Reudink M, Slooter GD, Sammour T, **Kroon HM**, Daams F, on behalf of the LekCheck Study Group. Risk nomogram does not predict anastomotic leakage after colon surgery accurately: Results of the multi-center LekCheck study. J Gastrointest Surg 2021 (Accepted for publication).
46. COVIDSurg Collaborative and GlobalSurg Collaborative: Simoes JF, Nepogodiev D, ….., **Kroon HM**, et al. Effects of pre-operative isolation on postoperative pulmonary complications after elective surgery: An international prospective cohort study. Anaesthesia 2021;76:1454-64.
47. COVIDSurg and GlobalSurg Collaborative; Simoes JF, Nepogodiev D, ….., **Kroon HM**, et al. SARS-CoV-2 infection and venous thromboembolism after surgery: an international prospective cohort study. Anaesthesia 2022;77:28-39.
48. Khoo TW, Dudi-Venkata NN, Beh YZ, Bedrikovetski S, **Kroon HM**, Thomas ML, Sammour T. Impact of timing of reversal of loop ileostomies on patient outcomes: a retrospective cohort study. Techn Coloproct 2021;25:1217-24.
49. Bedrikovetski S, Dudi-Venkata NN, Kroon HM, Seow W, Vather R, Carneiro G, Moore JW, Sammour T. Artificial intelligence for pre-operative lymph node staging in colorectal cancer: A systematic review and meta-analysis. BMC Cancer 2021;26;21:1058.
50. Bedrikovetski S, Dudi-Venkata NN, **Kroon HM**, Vather R, Sammour T. Towards a zero percent anastomotic leak rate using a defined risk reduction strategy. Eur Surg 2021;53:317–22.
51. Covidsurg Collaborative: Glasbey JC, Ademuyiwa A, Adisa A, ……, **Kroon HM**, et al. Effect of COVID-19 pandemic lockdowns on planned cancer surgery for 15 tumour types in 61 countries: An international, prospective, cohort study. Lancet Oncol 2021;22:1507-17.

52. Kaçmaz E, Engelsman AF, Bemelman WA, Tanis PJ, Nieveen van Dijkum EJM, on behalf ofthe International Study Group of Small bowel neuroendocrine neoplasm Surgery (ISGSS): **Kroon HM**, et al. International survey on opinions and use of minimally invasive surgery in small bowel neuroendocrine neoplasms. Eur J Surg Oncol 2021 (Online ahead of print).
53. STARSurg Collaborative and COVIDSurg Collaborative: McLean KA, Kamarajah SK, D Chaudhry D, ….., **Kroon HM**, et al. Death following pulmonary complications of surgery before and during the SARS-CoV-2 pandemic. Br J Surg 2021;108:1448-64.
54. Traeger L, **Kroon HM**, Bedrikovetski S, Moore JW, Sammour T. The impact of acetylcholinesterase inhibitors on ileus and gut motility following abdominal surgery: A clinical review. ANZ J Surg (Online ahead of print).
55. REACCT Collaborative: Zaborowski A, Abdile A, ….., **Kroon HM,** et al. Microsatellite instability in young patients with rectal cancer: molecular findings and treatment response. Br J Surg. 2022 (Online ahead of print).
56. Broman K, Hughes T, Bredbeck B, Sun J, Kirichenko D, Carr M, Sharma A, Bartlett E, Nijhuis A, Thompson J, Hieken T, Kottschade L, Downs J, Gyorki D, Stahlie E, van Akkooi A, Ollila D, O'shea K, Song Y, Karakousis G, Moncrieff M, Nobes J, Vetto J, Han D, Hotz M, Farma J, Deneve J, Fleming M, Perez M, Baecher K, Lowe M, Olofsson Bagge R, Mattsson J, Lee A, Berman R, Chai H, **Kroon H**, Teras R, Teras J, Farrow N, Beasley G, Hui J, Been L, Kruijff S, Sinco B, Sarnaik A, Sondak V, Zager J, Dossett L. Variation in adoption of nodal observation and adjuvant therapy for sentinel node positive melanoma. Ann Surg 2022 (Online ahead of print).
57. Morrison C, Brown B, Lin DY, Jaarsma RL, **Kroon H**. **Response to: Letter to the editor:** Response to Morrison et al. Reg Anesth Pain Med 2022 (accepted for publication).
58. Sergei Bedrikovetski S, Seow W, **Kroon HM**, Traeger L, Moore JW, Tarik Sammour T. Artificial intelligence for body composition and sarcopenia evaluation on computed tomography: A systematic review and meta-analysis. Eur J Radiol 2022 (accepted for publication).
59. Lin DY, Brigid Brown B, Morrison C, Saies AA, Pawar R, Vermeulen M, Anderson SR, Lee TS, Doornberg JN, **Kroon HM**, Jaarsma RL. The analgesic effect of the pericapsular nerve group (PENG) block reduces time to discharge after hip fracture surgery. J Int Med Res 2022 (accepted for publication).

Acknowledgements

This work would not have been possible without the supervision and guidance of Dr. Michelle Thomas. Your insight and earlier work laid the foundations for this thesis, resulting in very productive years. Thank you for your ongoing interest both in the progress of my studies as well as in the other aspects of life.

Associate Professor Tarik Sammour: the speed and accuracy of your thoughts, insight and new ideas are unmatched. I could always expect your thoughts to a manuscript or grant proposal shortly after sending it to you, filled with useful comments and corrections. This made it easy to maintain momentum and complete multiple projects simultaneously.

Dr. Nagendra Dudi-Venkata. We both arrived at the RAH early 2018. Your enthusiasm for research and ability to pick up multiple projects worked contagiously. You completed an outstanding PhD thesis in just three years, with many more other research projects completed. Thank you for your help over the years, good luck completing your Surgical Training and looking forward to conduct more projects in the future.

Sergei Bedrikovetski. In 2018 you arrived at the RAH as an inexperienced student. How different this is today: You are now the to-go person for statistical analyses. I have no doubt your PhD on artificial intelligence in medical imaging will be outstanding. Thank you for your help with the analyses.

Dr. Tracy Fritzsimmons: Thank you for making every day at work enjoyable. Always prepared to read grant applications with a sharp eye for detail and, as a native speaker, ready to suggest appropriate words to bring essential nuance to manuscripts. But mostly, thank you for the countless tea brakes.

Dr. Luke Traeger. The months we worked together were a blast. You've made an impressive start with your PhD and looking forward to the results of your RCT in due time. Enjoy your time at the RAH!

A big thank you to all international co-authors who contributed to this thesis with data, knowledge and insight: Dr. Brian Bednarski, Professor Geerard Beets, Professor George Chang, Dr. Songphol Malakorn, Dr. Atsushi Ogura, Professor Harm Rutten, Professor Cornelis van de Velde and Dr. Miranda Kusters. It has been a great pleasure to collaborate with you on a global level during the pandemic. I look forward to continue to collaborate in the future. Special thanks to Dr. Kusters, arguably the world leader in the treatment of enlarged lateral lymph nodes in rectal cancer.

To the Consultants of the Colorectal Unit at the RAH: Dr. Andrew Hunter, Dr. Matt Lawrence, Dr. Mark Lewis, Dr. James Moore and Associate Professor Ryash Vather: thank you for the enjoyable and educational moments in theatre, on the wards, during meetings and in 'the blue space'.

Dr. Laurence Liu and Dr. Tim Kenyon-Smith thank you for your help in collecting data, database management and statistical analyses. Considering you both did all of this next to your busy clinical work and on-calls as RMO's, make your efforts even more remarkable.

The Dutch Medical students whom I have had the pleasure to supervise at the RAH for their 6-month research elective for Medical School: Anouck Haanappel, Charlotte Ceuppens, Emma Greenwood, Meike van Harten, Vera Grupa, Izel Ozmen, Duveke de Gaay Fortman and Tessa Dinger. Taking the road less travelled by coming to Adelaide takes courage, but has paid off: You have made most of your Australian experience, achieved excellent grades from your Dutch Universities and you have all published (or close to it) your articles in international peer-reviewed journals as first author. Mostly, you have gained an international experience of which you will benefit the rest of your life. Tessa: The Covid-19 pandemic made it impossible for you to come to Australia. Thanks to your perseverance, you managed to remotely complete a difficult research project, with research meetings taking place over phone, Whatsapp and email between the Netherlands and Adelaide.

Joanne Perry. You know your patients better than most people know their own family. With you involved, their care in excellent hands. Thank you for all the times I asked you for patient lists and extracts of the BCCA or other databases and of course for all the chocolates.

Thank you to Julie Moretti for your help in theatre making sure research data were collected. I owe you a lifetime supply of stroopwafels. I will miss our chats.

Big thanks to the nursing staff and junior doctors of the Colorectal Unit at the RAH for all your assistance and interest in varying research projects.

I am grateful to the RAH Research Committee for awarding me the 2020 Florey Fellowship. Thanks to the Fellowship, I have been able to conduct and complete the studies included in this thesis, and many more. The award of your Fellowship has given me the opportunity to develop into a senior researcher.

To the University of Adelaide: thank you for awarding me the title of Associate Professor at the Adelaide Medical School. I look forward to continue to conduct clinical research.

Lieve Heit en Mem, dank voor jullie nimmer aflatende steun en interesse.

Lieve Indy, Noah en Hannah: het is thuis altijd gezellig en druk met jullie.

About the author

Hidde Maarten Kroon was born in Rotterdam, the Netherlands in 1978.
After completing secondary school in 1996 from the Sint Vituscollege in Bussum, the Netherlands, he spent a year in the US, attending and graduating from the Pandora-Gilboa High School in Ohio in 1997. Back in the Netherlands he studied Law and Medical Imaging and Radiotherapeutic Techniques before he was enrolled in Medical School at the University of Groningen in 1999. He graduated Medical School in 2005, during which he laid the foundations of his PhD at the University of Michigan Health Systems, Ann Arbor, MI, USA. In 2007 and 2008, he completed the clinical studies of his PhD at the Melanoma Institute Australia in Sydney, Australia and in 2009 he was awarded his PhD degree at the University of Groningen with the thesis titled "Isolated Limb Infusion'. After, he started his surgical training at the Leiden University Medical Center, Leiden, the Netherlands and affiliated hospitals Rijnland Hospital and Diaconnessenhuis (currently both Alrijne Hospital). He completed his surgical training in 2014 and has been a board-certified surgical oncologist and gastro-intestinal surgeon since.
In 2015 and 2016 he worked as a gastro-intestinal surgery fellow at the Erasmus University Medical Center in Rotterdam, the Netherlands. In 2017 he moved to Adelaide, Australia with his family and worked at Flinders Medical Centre as colorectal surgery fellow for a year. Since 2018, he has worked at the Colorectal Unit of the Royal Adelaide Hospital since and in 2020 he enrolled in the Master of Philosophy programme at The University of Adelaide, of which this thesis is the result.
Latwe 2019 he was awarded the three-year Florey Fellowship by the RAH Research Committee for his research on lateral lymph node metastases in rectal cancer and in 2020 he was appointed as an Associate Professor at The University of Adelaide.
Hidde, a citizen to both the Netherlands and Australia, is married and has 2 children (Noah and Hannah).