Lateral Lymphadenectomy in Rectal Cancer

- What is the best parameter for its indication? -

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COLOSOS 2024, Toronto, 10/26-27,2024

Conflict of Interest

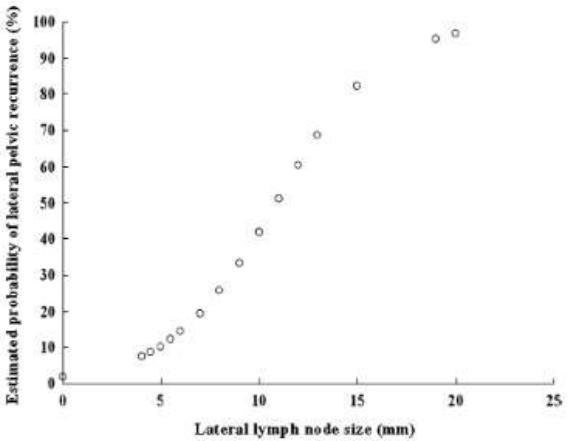
Lecture fee: Medtronic

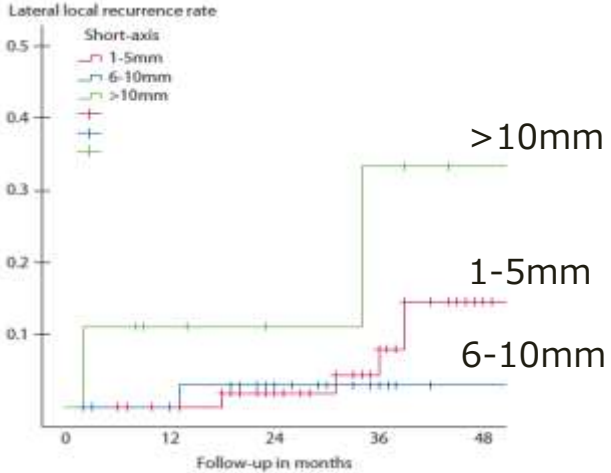
Consultant: Johnson & Johnson

nCRT does NOT control lateral nodal disease

Baseline enlarged lateral nodes

→ High local recurrence after nCRT + TME





Baseline lateral node ≥5 mm:
27% lateral local recurrence
>80% of LR occurred in lateral area

Kim, ASO 2008

Baseline lateral node >10 mm:
33% lateral local recurrence

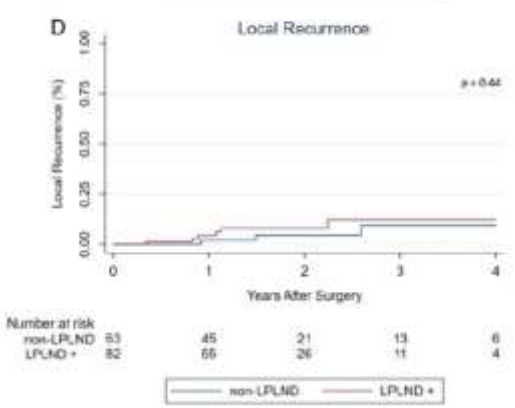
Kusters, DCR 2017

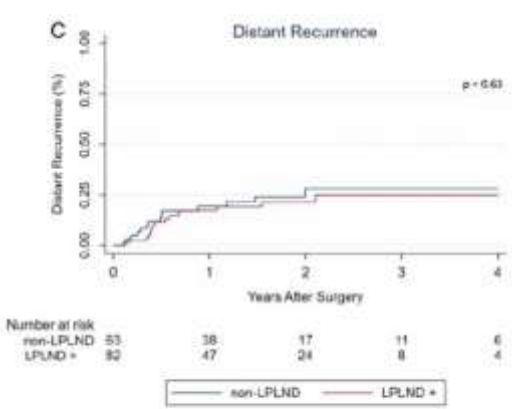
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

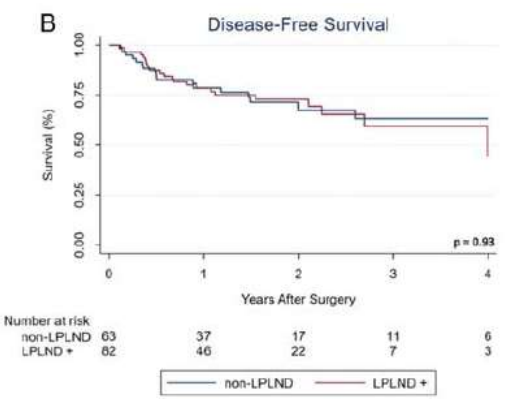
TNT Does NOT Eliminate Lateral Nodal Disease

cStage II-III rectal cancer with baseline enlarged lateral node (N=158)

- LPLND 56 % (N=88)
- yp-lateral N+: 19.0 % (N=30)
- No increase in distant/local recurrences with LPLND compared to c-lateral-N negative pts

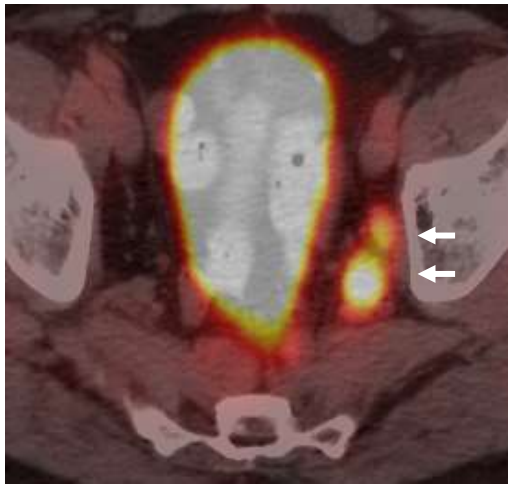


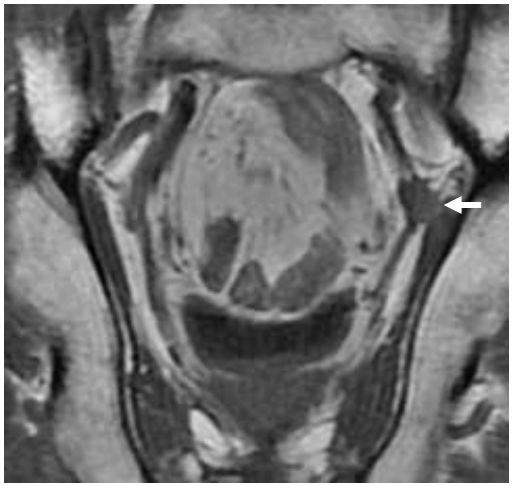




Peacock, Konishi, Chang, Ann Surg 2022

- Lateral node is the major site of local rec. after nCRT + TME alone
- >80% of local rec. in cStage II-III low rectal cancer occurs in lateral area





Kim, ASO 2008

Importance of Proper Indication for LPLND

Inappropriate indication may result in “no oncologic benefits”

J Gastrointest Surg (2011) 15:1368–1374
DOI 10.1007/s11605-011-1533-7

ORIGINAL ARTICLE

Clinically Enlarged Lateral Pelvic Lymph Nodes Do Not Influence Prognosis after Neoadjuvant Therapy and TME in Stage III Rectal Cancer

Sekhar Dharmarajan · Dandan Shuai · Alyssa D. Fajardo · Elisa H. Birnbaum · Steven R. Hunt · Matthew G. Mutch · James W. Fleshman · Anne Y. Lin

Int J Colorectal Dis (2017) 32:333–340
DOI 10.1007/s00384-016-2711-6

ORIGINAL ARTICLE

Extended lymphadenectomy for locally advanced and recurrent rectal cancer

Panagiotis A. Georgiou[1,2] · S. Mohammed Ali[1,2] · Gina Brown[3] · Shahnawaz Rasheed[1,2] · Paris P. Tekkis[1,2]

Extended lymphadenectomy versus conventional surgery for rectal cancer: a meta-analysis

Panagiotis Georgiou, Emile Tan, Nikolaos Gouvas, Anthony Antoniou, Gina Brown, R John Nicholls, Paris Tekkis

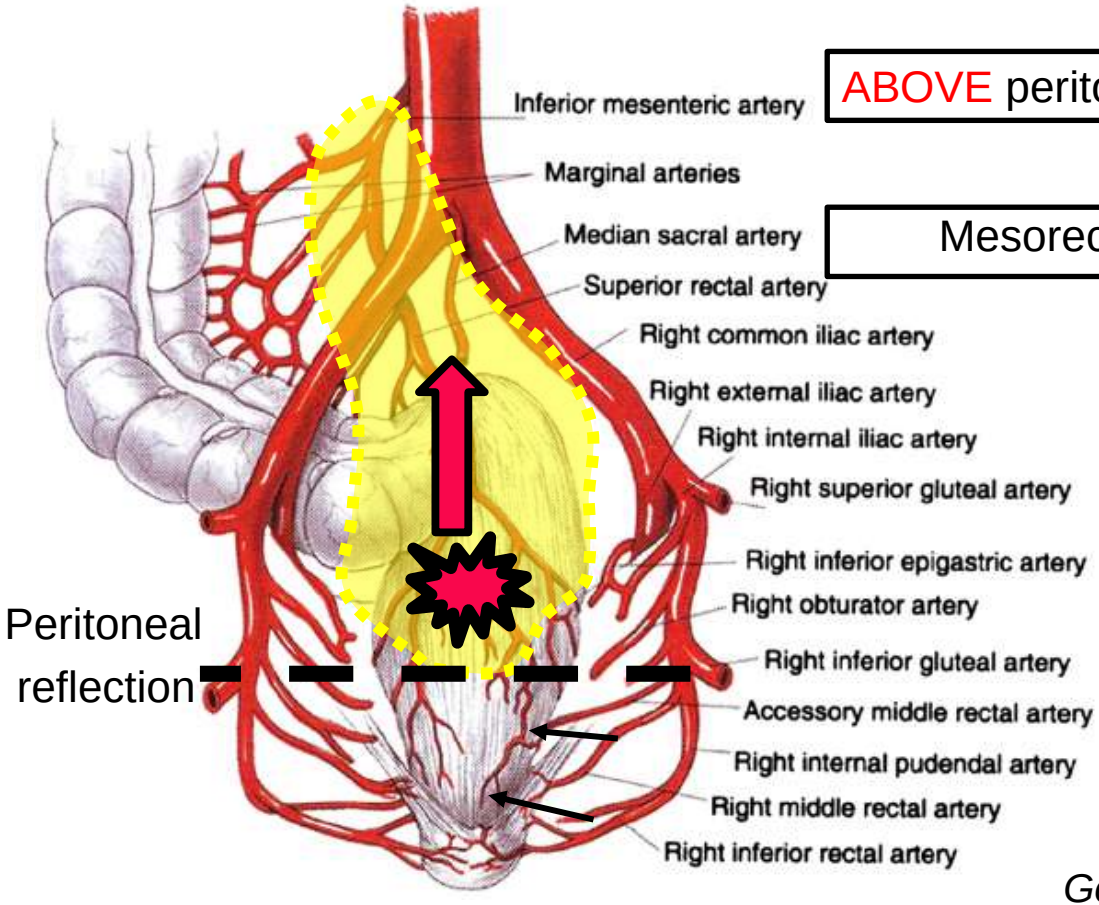
Original article

Relevance of magnetic resonance imaging-detected pelvic sidewall lymph node involvement in rectal cancer

MERCURY Study Group*

Primary Tumor

Lymphatic Drainage of the Rectum



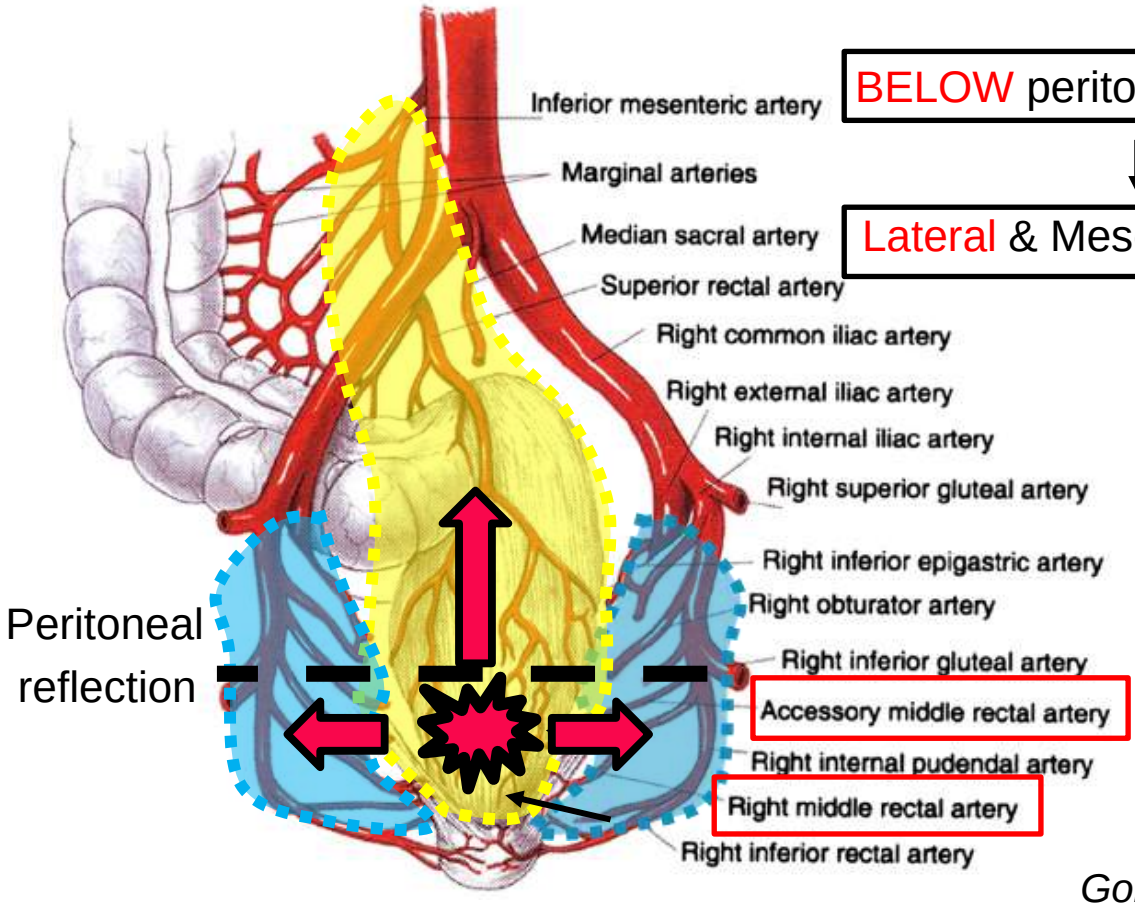
ABOVE peritoneal reflection

↓

Mesorectal spread

Gordon PH, 2007

Lymphatic Drainage of the Rectum

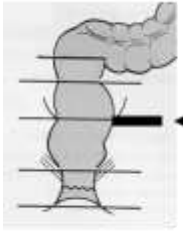


BELOW peritoneal reflection

↓

Lateral & Mesorectal spread

Gordon PH, 2007



Intraperitoneal (Ra)

Extraperitoneal (Rb)

TME only

TME + LPLND

(JSCCR database 1991-8)

		Overall No.	LND No.	LND %	Lateral LN mets. No.	Lateral LN mets. %
Ra	T1	138	5	3.6%	0	0.0%
	T2	149	18	12.1%	0	0.0%
	T3	230	58	25.2%	4	1.7%
	T4a	181	59	32.6%	7	3.9%
	T4b	15	8	53.3%	0	0.0%
	Total	713	148	20.8%	11	1.5%
RaRb+Rb	T1	234	37	15.8%	2	0.9%
	T2	372	218	58.6%	20	5.4%
	T3	350	230	65.7%	28	7.7%
	T4a	412	319	77.4%	75	18.0%
	T4b	59	48	81.4%	17	28.8%
	Total	1,427	852	59.7%	142	9.8%

Peritoneal reflection

Above

Below

Watanabe T, Int J Clin Oncol. 2018

Lateral LN in T3-4 low rectal cancer below peritoneal reflection

- 15-20% in T3-4 rectal cancer below PR

Ueno, Ann Surg 2007
Kobayashi, DCR 2009,
Akiyoshi Ann Surg 2012

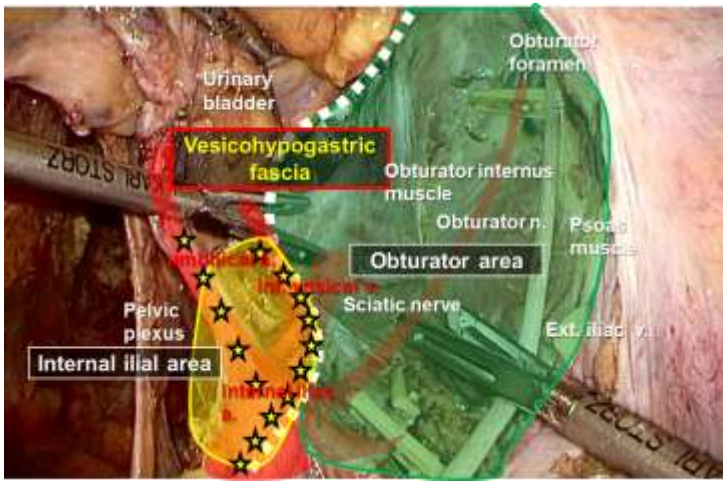
- Higher risk in lower tumors

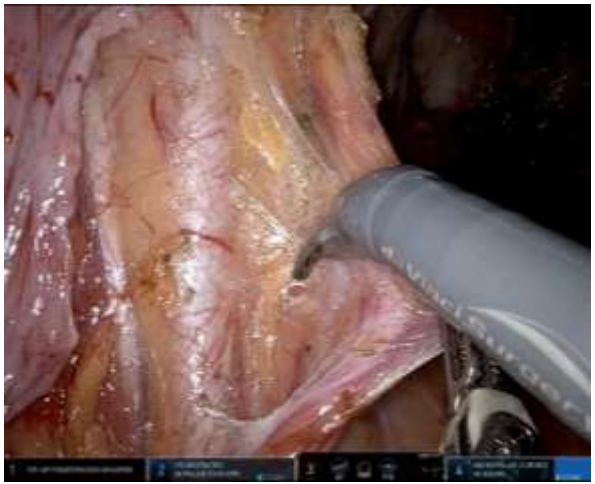
Distance from AV (cm)	LPLN mets (%)	Odds Ratio	P
6.1-8.0	11 %	Ref	
4.1-6.0	13 %	1.4	0.564
2.1-4.0	26 %	4.7	0.003
0-2.0	42 %	9.9	<.001

Ueno M, BJS 2005

Lateral Lymph Node

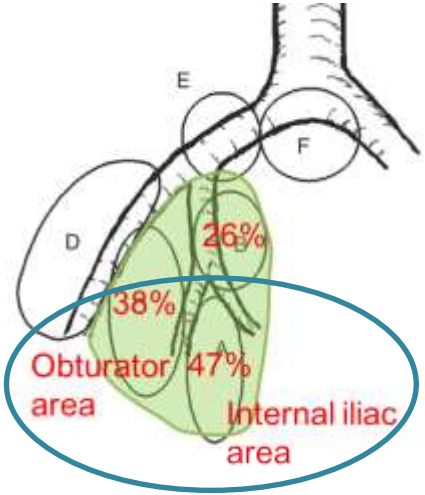
Anatomical Location



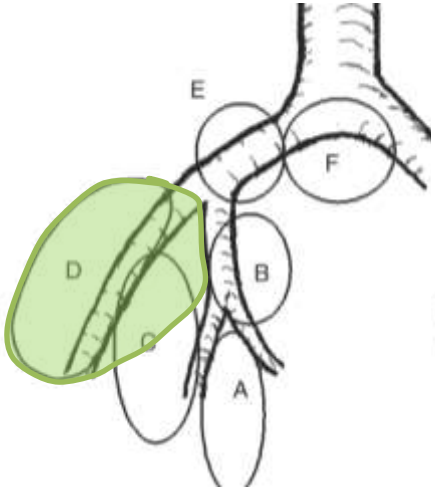


Different Distribution from GYN/URO

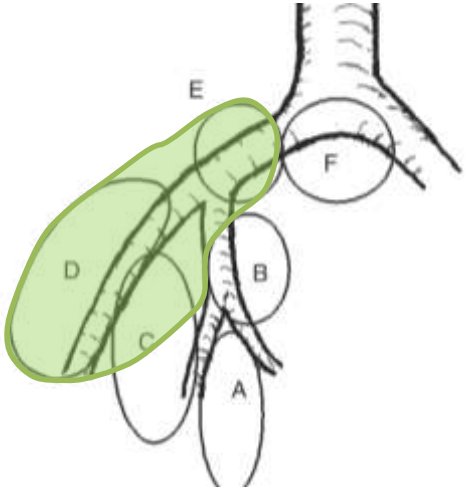
Rectal Cancer



Prostate Cancer

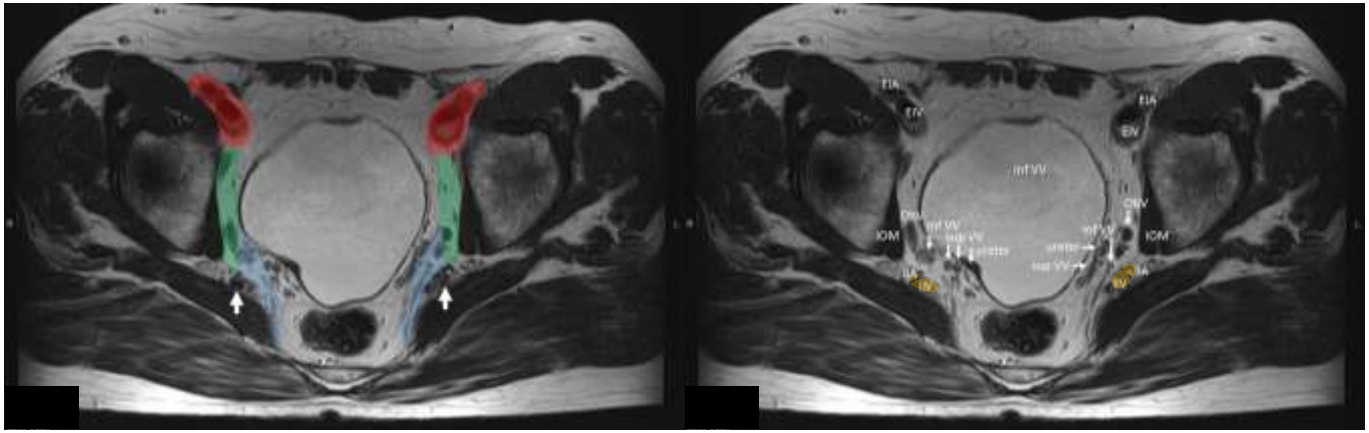


Cervical Cancer



Kobayashi, DCR 2009
Karim, Urol Oncol 2013
Cibula, Ginecol Oncol 2010

MRI anatomy of lateral area

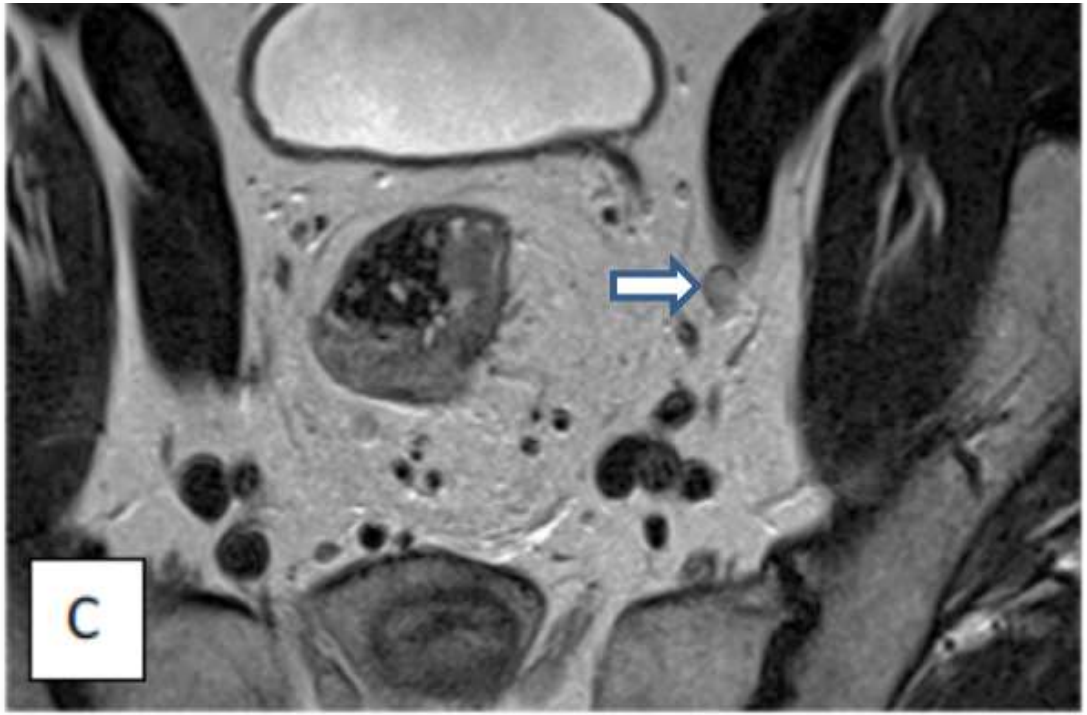


External iliac area

Obturator area

Internal iliac area

Ignore a Long-stretched Junctional LN at Ext. Iliac Vein



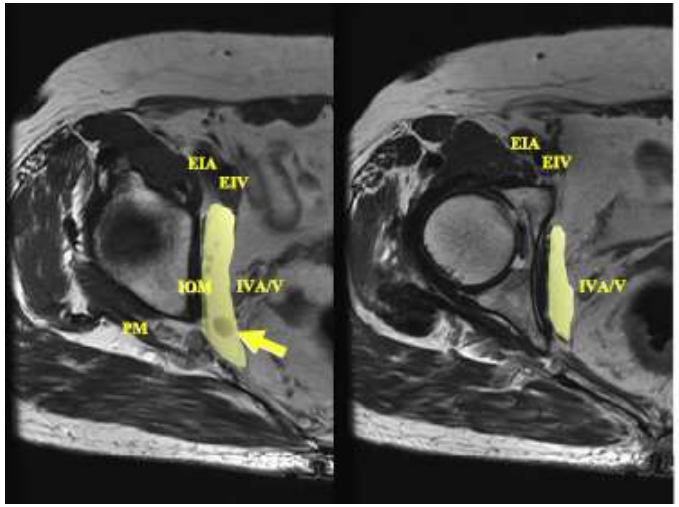
Sluckin, European Radiology 2022
Sluckin, DCR 2024

Importance of DISTAL Lateral Compartment

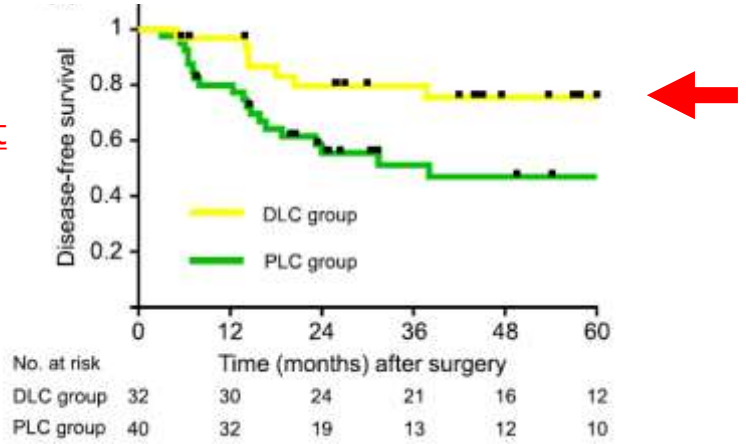
Oncologic impact of lateral lymph node metastasis at the distal lateral compartment in locally advanced low rectal cancer after neoadjuvant (chemo)radiotherapy

Takashi Akiyoshi [a,*], Tomohiro Yamaguchi [a], Makiko Hiratsuka [b], Toshiki Mukai [a], Yukiharu Hiyoshi [a], Toshiya Nagasaki [a], Masashi Ueno [c], Yosuke Fukunaga [a], Tsuyoshi Konishi [d]

[a] Gastroenterological Center, Department of Gastroenterological Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan
[b] Department of Diagnostic Imaging, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan
[c] Department of Gastroenterological Surgery, Toranomon Hospital, Tokyo, Japan
[d] Department of Colon and Rectal Surgery, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA



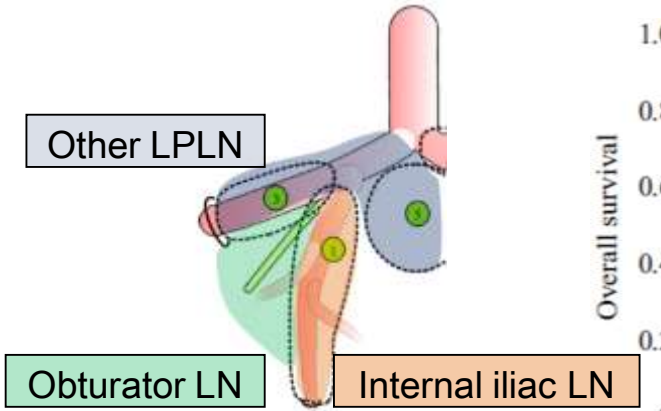
- nCRT + TME + selective LPLND (n=718)
- 44 % of lateral LN metastasis occurred in distal compartment
- Better DFS after LPLND than proximal compartment

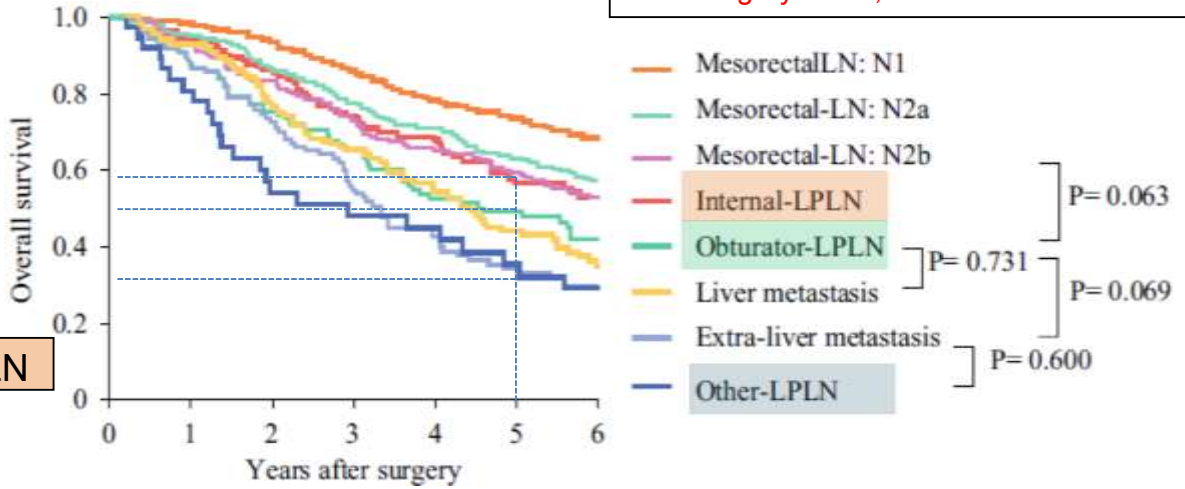


Akiyoshi, Konishi, EJSO 2021

Oncologic outcomes of LPLND (Surgery Alone)

- Japanese nationwide registry
- pT3-4 low rectal cancer below PR
- 2003-2011 (n=3,487)
- LPLND 45 % (n=1,530)
- Surgery alone, without CRT





- Internal iliac LN
- Obturator LN
- Other LPLN = systemic disease

JSCCR Guideline

→ Regional (D3) ... 50-60% OS

→ Distant (M) ... <30% OS

Chen, Ann Surg Onc 2022

Lateral Lymph Node

Baseline Size

Multidisciplinary treatment and LPLND

Global evidences for “West + East”

- International multicenter study (12 centers, 7 countries)
- cT3-4 rectal cancer ≤8cm from anal verge, 2009-13 (n=1,216)

Ogura, Konishi, JCO 2018
Ogura, Konishi, JAMA Surg 2019
Schaap, Konishi,BJS 2021

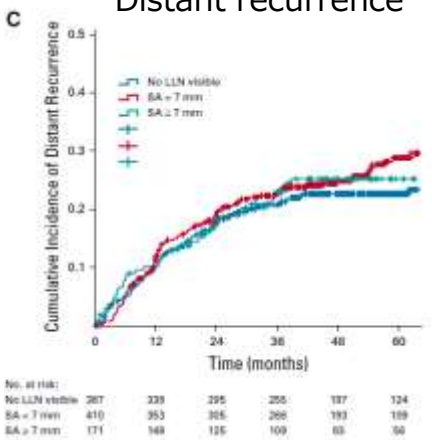
Enlarged Lateral Nodes

- Increased LR with nCRT + TME
- No increase in distant mets

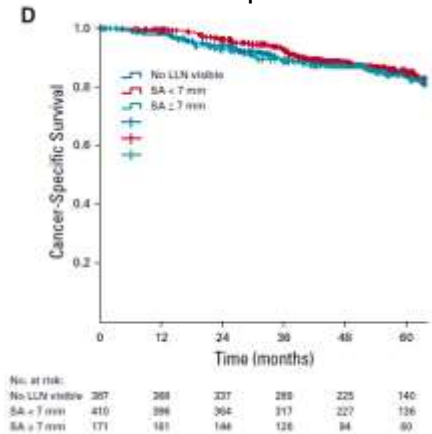
Lateral local recurrence after nCRT + TME

Baseline Lateral LN size	N (%)	5-yr lateral LR	p-value
Short axis			<0.0001
< 5 mm	316 (65)	4.6%	
≥ 6 mm	171 (35)	**15.9%**	
≥ 7 mm	118 (24)	**19.5%**	
≥ 8 mm	77 (16)	**25.5%**	
≥ 9 mm	62 (13)	**30.3%**	
≥10 mm	46 (9)	**35.6%**	

Distant recurrence



Cancer-specific survival

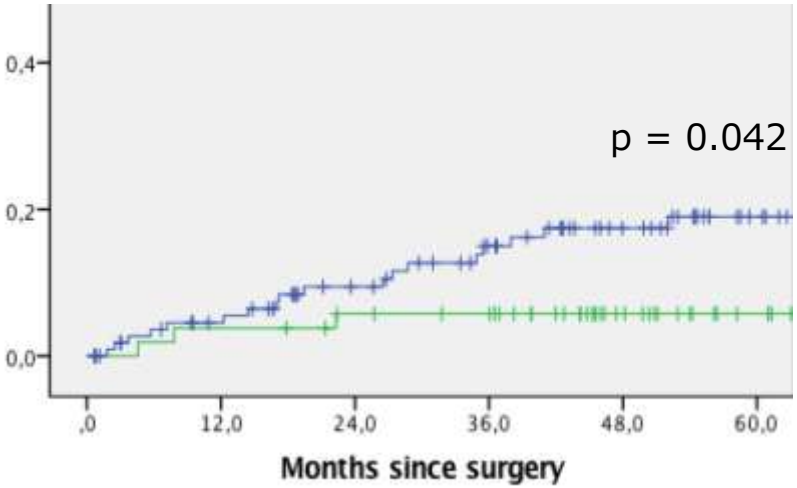


Ogura, Konishi, JCO 2019

Local recurrence with/out LPLND

(Baseline lateral nodes≧7mm)

	5-yr overall LR	P	5-yr lateral LR	P
		.005		.042
nCRT + TME	25.6 %		19.5 % ← Majority of LR	
nCRT + TME + LPLND	5.7 %		5.7 %	



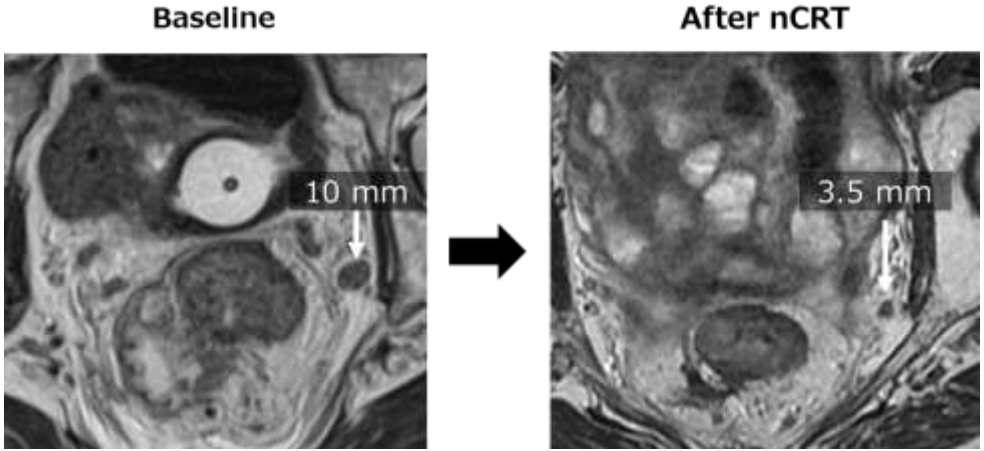
nCRT + TME

nCRT + TME + LPLND

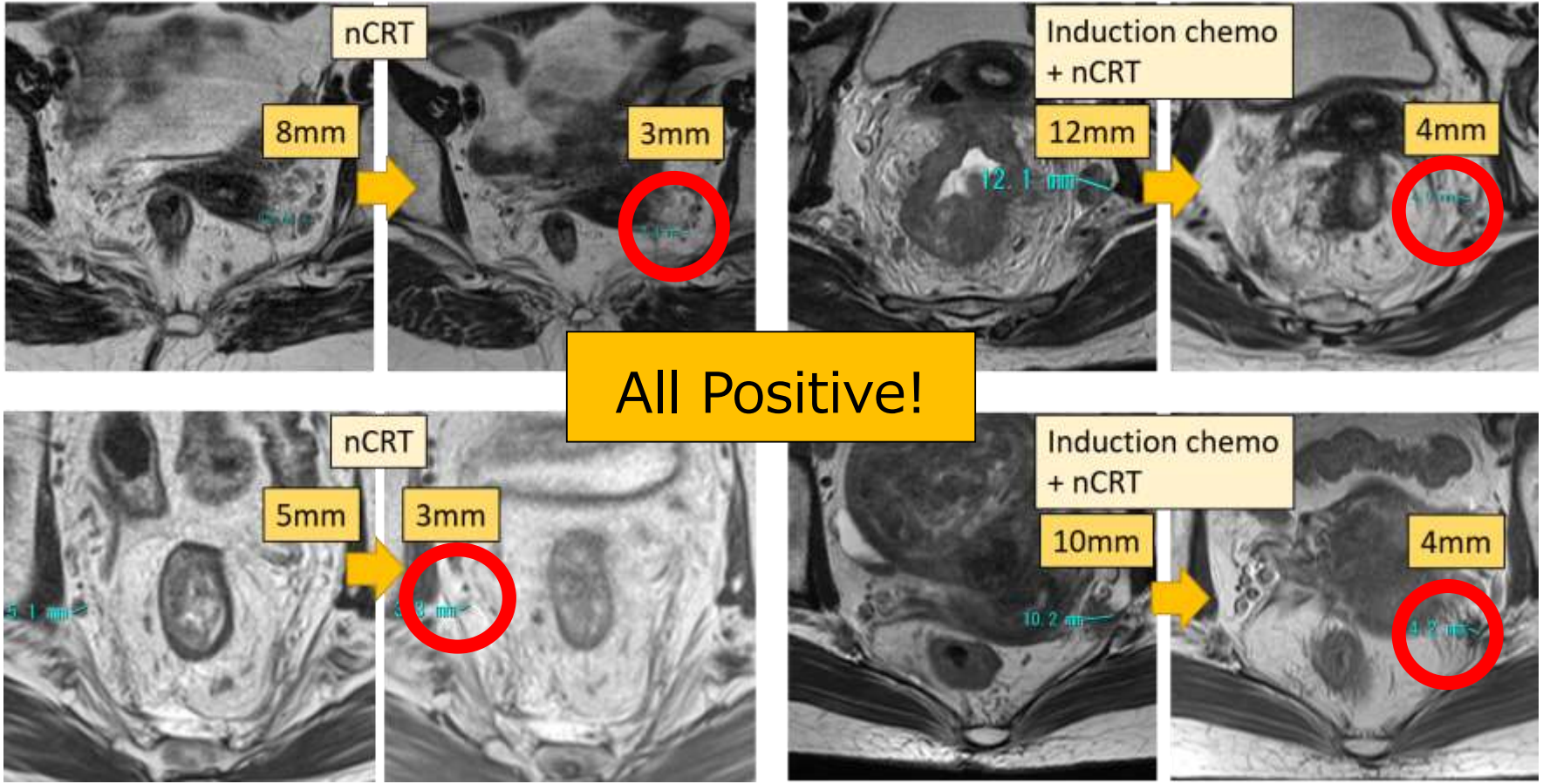
Ogura, Konishi, JCO 2018

Lateral Lymph Node

Response to Neoadjuvant therapy



Residual Cancer in Responsive Lateral Nodes



Systematic review of lateral node mets after nCRT

Significant rates of residual cancer in RESPONSIVE LN!

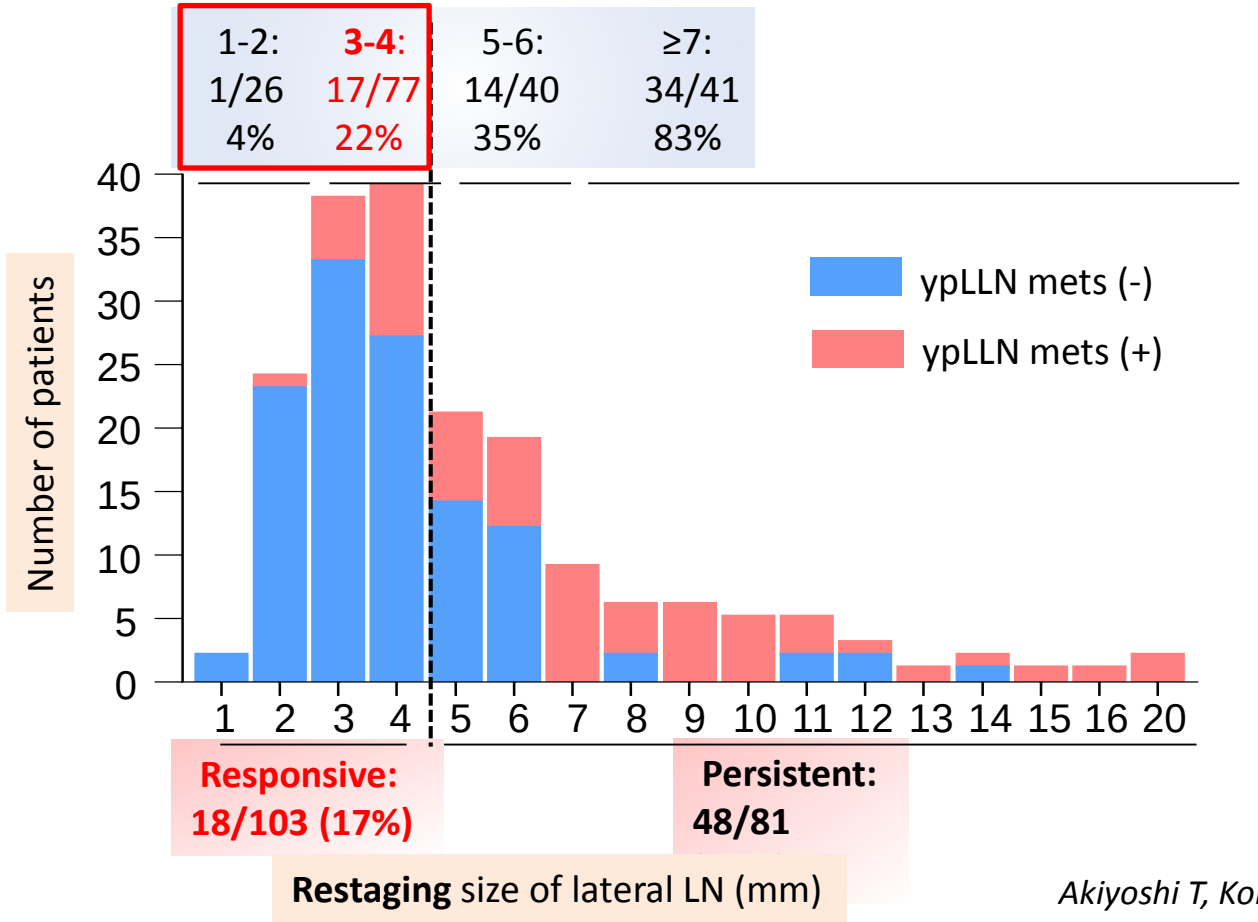
- Systematic review of 11 studies, N=462
- Baseline suspicious lateral LNs
- yp-lateral N+: Responsive nodes: 0-20.4%
  Persistent nodes: 25-83%

Author	Total N	Responsive N	%	**yp-lateral N+**	%
Oh	66	30	45.5	0	0
Akiyoshi	77	49	63.6	10	20.4
Ishihara	31	11	35.5	1	9.1
Kim	53	30	56.6	5	16.7
Kim	57	33	57.9	3	9.1
Total	284	153	35.5-63.6	16	10.5

Atef, WJS 2019

JAPANESE FOUNDATION FOR CANCER RESEARCH

Residual lateral LN mets by restaging size (Baseline ≥5mm, n = 184)



Akiyoshi T, Konishi T. EJSO 2021

Predictive Parameters for Residual Lateral LN

TABLE 2 Factors associated with lateral pelvic lymph node metastasis

Factor	n	Univariate analysis			Multivariate analysis		
		LPLN metastasis			OR	95 % CI	P value
		Negative	Positive	P value			
Sex				0.1276			0.0192
Male	55	36 (65 %)	19 (35 %)		1		
Female	22	10 (45 %)	12 (55 %)		5.616	1.315–28.942	
Age (years)				1			
≤60	33	20 (61 %)	13 (39 %)				
>60	44	26 (59 %)	18 (41 %)				
Location of tumor from AV (mm)				0.0608			0.2005
40–80	33	24 (73 %)	9 (27 %)		1		
≤40	44	22 (50 %)	22 (50 %)		2.469	0.619–10.831	
Pretreatment CEA (ng/ml)				0.8161			
≤5	44	27 (61 %)	17 (39 %)				
>5	33	19 (58 %)	14 (42 %)				
Clinical T stage				0.7587			
T2–3	64	39 (61 %)	25 (39 %)				
T4	13	7 (54 %)	6 (46 %)				
Histologic type				0.6800			
Well/moderate	71	43 (61 %)	28 (39 %)				
Mucinous/poor/signet	6	3 (50 %)	3 (50 %)				
Induction systemic chemotherapy				0.0484			
Yes	17	14 (82 %)	3 (18 %)		1		
No	60	32 (53 %)	28 (47 %)		9.235	1.241–106.947	0.0047
Short-axis diameter of LPLN before CRT (mm)				<0.0001			
<8	49	39 (80 %)	10 (20 %)		1		
≥8	28	7 (25 %)	21 (75 %)		9.188		
Border irregularity of LPLN				0.2818			
No	58	37 (64 %)	21 (36 %)				
Yes	19	9 (47 %)	10 (53 %)				0.0668
Mixed signal intensity of LPLN				<0.0001			
No	42	35 (83 %)	7 (17 %)		1		
Yes	35	11 (31 %)	24 (69 %)		3.924	0.909–18.420	
Short-axis diameter of LPLN after CRT				<0.0001			0.1356
Responsive (≤5 mm)	49	39 (80 %)	10 (20 %)		1		
Persistant (>5 mm)	28	7 (25 %)	21 (75 %)		3.113		
LPLN reduction (%)				0.7805			
≤60	61	37 (61 %)	24 (39 %)				
>60	16	9 (47 %)	7 (53 %)				

AV anal verge, CEA carcinoembryonic antigen, LPLN lateral pelvic lymph node, CRT chemoradiotherapy

Baseline size: Best predictive

Baseline malignant features: Marginally predictive

Post-treatment size: NOT predictive

Akiyoshi, Konishi, ASO 2015

Consideration of Tumor Location for Cut-off Size

Baseline size

Cutoff value	Sensitivity[a]	Specificity[b]	Positive predictive value[c]	Negative predictive value[d]
Initial, 5 mm	100% (36/36)	14.5% (10/69)	37.9% (36/95)	100% (10/10)
Initial, 6 mm	100% (36/36)	24.6% (17/69)	40.9% (36/88)	100% (17/17)
Initial, 7 mm	94.4% (34/36)	34.8% (24/69)	43.0% (34/79)	92.3% (24/26)
Initial, 8 mm	94.4% (34/36)	47.8% (33/69)	48.6% (34/70)	94.3% (33/35)
Initial, 9 mm	88.9% (32/36)	50.7% (35/69)	48.5% (32/66)	89.7% (35/39)
Initial, 10 mm	83.3% (30/36)	66.7% (46/69)	56.6% (30/53)	88.5% (46/52)

Post-treatment restaging size

Cutoff value	Sensitivity[a]	Specificity[b]	Positive predictive value[c]	Negative predictive value[d]
Post-CRT, 4 mm	95.2% (20/21)	17.9% (10/56)	30.3% (20/66)	90.9% (10/11)
Post-CRT, 5 mm	90.5% (19/21)	28.6% (16/56)	32.2% (19/59)	88.9% (16/18)
Post-CRT, 6 mm	81.0% (17/21)	44.6% (25/56)	35.4% (17/48)	86.2% (25/29)
Post-CRT, 7 mm	81.0% (17/21)	66.1% (37/56)	47.2% (17/36)	90.2% (37/41)
Post-CRT, 8 mm	71.4% (15/21)	82.1% (46/56)	60.0% (15/25)	88.5% (46/52)
Post-CRT, 10 mm	33.3% (7/21)	94.6% (53/56)	70.0% (7/10)	79.1% (53/67)

- Multicenter retrospective study in Korea
- TME + LPLND (n=105, 2015-20)

- Baseline size had better sensitivity, specificity, PPV, NPV
- Best cut-off size was different between mid vs low rectal cancer
- Smaller cut-off size for low tumors

Baseline, ≥8mm for AV >5 cm, ≥6mm for AV ≤5 cm

Criteria	Total (N=105)	LPLN+ (N=36)	LPLN- (N=69)
+	77 (73%)	36 (34%)	41 (39%)
-	28 (27%)	0	28 (27%)

Bae, DCR 2023

Longer waiting eliminates residual disease?

ORIGINAL ARTICLES

Predictive Factors of Pathologic Complete Response After Neoadjuvant Chemoradiation for Rectal Cancer

Matthew F. Kalady, MD,† Luiz Felipe de Campos-Lobato, MD,* Luca Stocchi, MD,* Daniel P. Geisler, MD,* David Dietz, MD,* Ian C. Lavery, MD,* and Victor W. Fazio, MD**

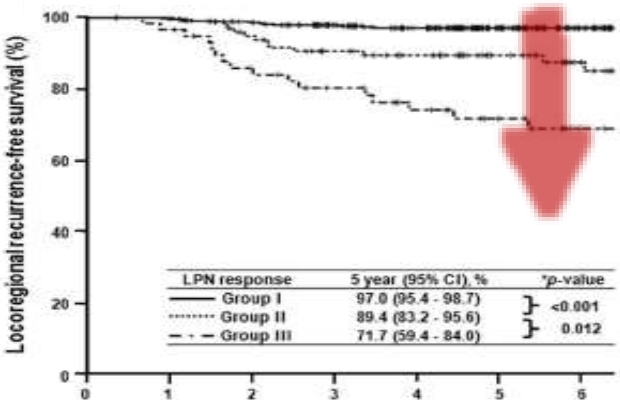
Is lateral pelvic node dissection necessary after preoperative chemoradiotherapy for rectal cancer patients with initially suspected lateral pelvic node?

Min Ju Kim, MD, Sung Chan Park, MD, Tae Hyun Kim, MD, Dae Yong Kim, MD, Sun Young Kim, MD, Ji Yeon Baek, MD, Hee Jin Chang, MD, Ji Won Park, MD, and Jae Hwan Oh, MD, Goyang, Republic of Korea

Korea, 2001-09
cT3-4 M0 mid/low rectal cancer
nCRT + TME **without LPLND**
N=580

- Lateral nodal recurrence was a major cause of LR (71%, 29/41)
- 45% of lateral recurrence had no distant mets (= regional!)
- "Responsive" nodes had higher local recurrence than "Normal" nodes (HR 3.6)

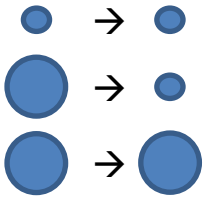
Local recurrence free survival



Normal lateral LN 3.0% (N=423, 73%)

Responsive lateral LN 10.6% (N=98, 17%)

Persistent lateral LN 28.3% (N=59, 10%)



Kim MJ, Oh JH. Surgery 2016

Ann Surg Oncol (2020) 27:3525–3533
https://doi.org/10.1245/s10434-020-08481-y

Annals of SURGICAL ONCOLOGY

ORIGINAL ARTICLE – COLORECTAL CANCER

Oncological Impact of Lateral Lymph Node Dissection After Preoperative Chemoradiotherapy in Patients with Rectal Cancer

Min Jung Kim, M.D.[1,2], George J. Chang, M.D., M.S.[3], Han-Ki Lim, M.D.[4], Mi Kyung Song, Ph.D.[5], Sung Chan Park, M.D.[4], Dae Kyung Sohn, M.D., Ph.D.[4], Hee Jin Chang, M.D., Ph.D.[4], Dae Yong Kim, M.D., Ph.D.[4], Ji Won Park, M.D.[1,2], Seung-Yong Jeong, M.D., Ph.D.[1,2], and Jae Hwan Oh, M.D., Ph.D.[4]

Korea, National Cancer Center, 2001-16

cT3-4 M0 mid/low rectal cancer

Treatment change

2001-09

nCRT + TME without LLND

→

2010-

nCRT + TME **+ LLND (≥5mm BASELINE)**

Responsive LLN

N = 97

	Local recurrence	
	HR (95%CI)	P
TME only	1	
LLND	**0.10 (0.01-0.94)**	**0.04**

Kim MJ, Chang GJ, Oh TH. ASO 2020

Post-treatment Size and Lateral Local Recurrence

(International Lateral Node Study Consortium)

Baseline ≥7mm

Restaging Size	Obturator		Internal iliac	
Short axis	N (%)	5-yr lateral LR	N (%)	5-yr lateral LR
≤ 2 mm	7 (13)	**0%**	2 (6)	**0%**
≤ 3 mm	11 (20)	**0%**	6 (19)	**0%**
≤ 4 mm	20 (36)	**0%**	7 (22)	**0%**
≤ 5 mm	26 (46)	**0%**	9 (28)	**12.5%**
≤ 6 mm	35 (63)	**0%**	12 (38)	**20.5%**
≤ 7 mm	41 (73)	**4.9%**	18 (56)	**21.2%**

- ✓ Subpopulation analysis of only 61% of the initial cohort
- ✓ Shrinkage ≤4 mm occured only in 30% of the cases, 22% in internal iliac nodes

Ogura, Konishi, JAMA Surg 2019

National Data from the Netherland in a Trained Setting

Prognostic Implications of Lateral Lymph Nodes in Rectal Cancer: A Population-Based Cross-sectional Study With Standardized Radiological Evaluation After Dedicated Training

Tania C. Sluckin, M.D.[1,2,3] • Eline G.M. van Geffen, M.D.[1,2,3]
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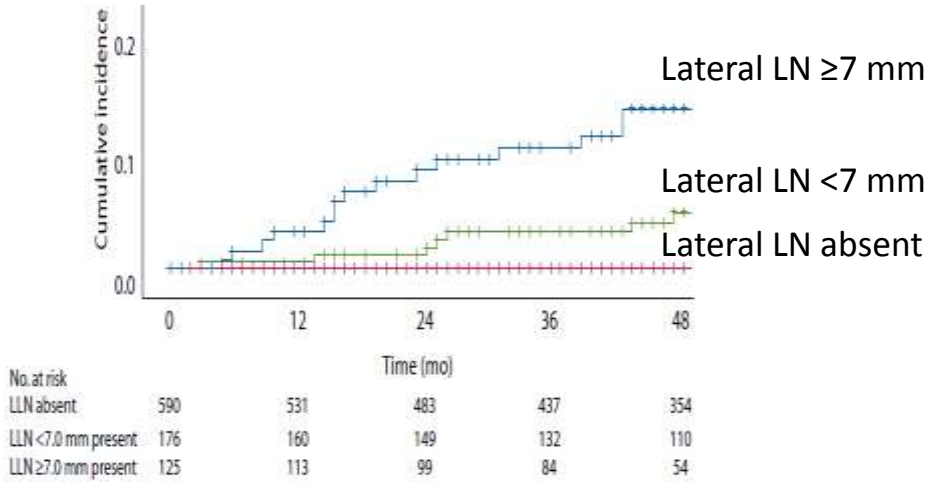
Regina G.H. Beets-Tan, M.D., Ph.D.[5,6,7,8] • Corrie A.M. Marijnen, M.D., Ph.D.[9,10]
Pieter J. Tanis, M.D., Ph.D.[2,3,11,12] • Miranda Kusters, M.D., Ph.D.[1,2,3]
On behalf of the Dutch Snapshot Research Group

- Dutch population-based cross-sectional study
- cT3-4, ≤8 cm from ARJ, nCRT (n=894, 2016)
- 96 % had no additional surgery for lateral LN



- Enlarged ≥7 mm lateral LN (baseline)
  - ➢ independent predictor of LR
  - ➢ No impact on OS
- Downsizing had no impact on lateral LR
- Majority of baseline-enlarged lateral LN remained enlarged after nCRT (63% int. iliac, 42% obturator)

Slunkin, DCR 2024

Current controversies in TNM for the radiological staging of rectal cancer and how to deal with them: results of a global online survey and multidisciplinary expert consensus

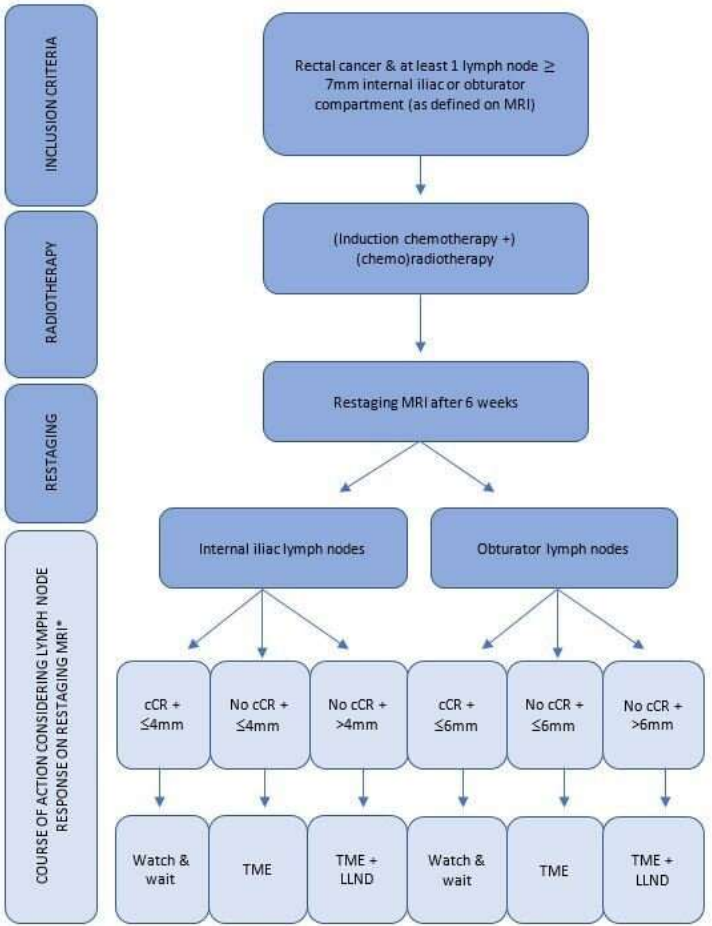
added benefit for lateral nodal staging [27]. Considering the current level of evidence, the panel agreed that for primary staging, the ≥ 7-mm threshold may for now be adopted, although further validation is obviously needed. The panel did not support the proposed size thresholds after chemoradiotherapy as the evidence provided was considered too preliminary. Reasons for concern included under-investigation of confounding effects (e.g., varying intervals between neoadjuvant treatment and radiological re-assessment/surgery, varying radiation volumes/doses).

Doenja, Konishi, Eur Radiology 2022

Dutch Prospective Study

- LANOREC Study

- National prospective registration study
- Predefined treatment protocol
- Startup cadaver workshops
- Monthly online technical feedback



THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Decision of LPLND is complex

Magnetic Resonance Imaging Directed Surgical Decision Making for Lateral Pelvic Lymph Node Dissection in Rectal Cancer After Total Neoadjuvant Therapy (TNT)

Oliver Peacock, BMBS, PhD, Naveen Manisundaram, MD,* Sandra R. Dibrito, MD, PhD,* Youngwan Kim, MD, PhD,* Chung-Yuan Hu, MPH, PhD,* Brian K. Bednarski, MD,* Tsuyoshi Konishi, MD, PhD,* Nir Stanietzky, MD,† Raghunandan Vikram, MD,† Harmeet Kaur, MD,† Melissa W. Taggart, MD,‡ Arvind Dasari, MD,§ Emma B. Holliday, MD,‖ Y Nancy You, MD, MHSc,* and George J. Chang, MD, MS*¶*

Multiple MDT factors affect on indication for LPLND

- Lateral LN
  - Baseline size
  - Baseline malignant features
  - Response to TNT
- Primary tumor
  - Baseline size
  - Baseline malignant characteristics (T, N, EMVI, etc)
  - Response to TNT (cCR)
- Patient factors
  - Surgical risk

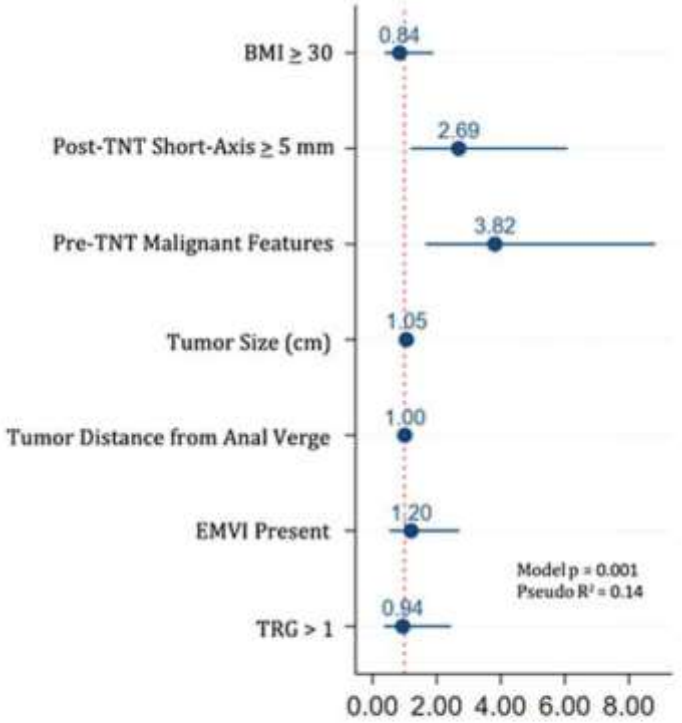


FIGURE 3. Multivariable analysis for factors affecting decision making for LPLND versus non-LPLND.

Peacock, Konishi, Ann Surg 2022

Counter-Debate

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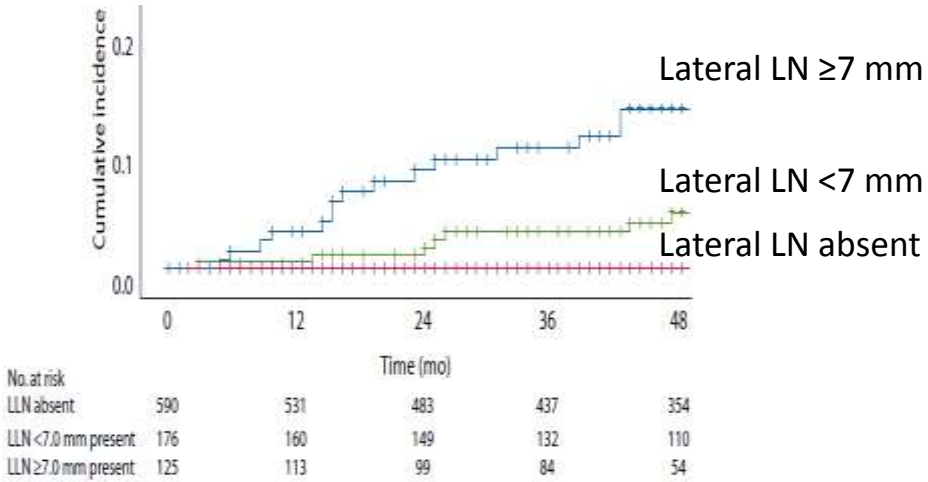

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Slunkin, DCR 2024

Counter-Debate

- 3,057 rectal cancer in 2016
- 1,109 cT3-4, ≤8 cm
- 122 ≥7 mm lateral LN
- 23 lateral LR, of which 16 developed DM
- A very small group of patients...

No.					
LLN					
LLN ≥7.0 mm present	125	113	99	84	54

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Slunkin, DCR 2024

Counter-Debate

LLN is a minor issue!

- OPRA cohort (N=324)
- 57 had visible LLN+, of which 3 had LLND
- 30 LLN disappeared after TNT
- Lateral LN recurrence was rare 3.5 % in LLN+
- Similar local rec or distant rec between
    - LLN+ vs. LLN-
    - LLN ≥7 mm vs LLN <7 mm
- Lateral LN dissection likely benefits few pts

Beets Ann Surg 2024

Counter-Debate

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Data reliability?

- Special cohort with extremely high cCR >50 %
- ypN+ only 8.3 %
- MRI reviewed by untrained radiologists
- LLN+ is not clinically relevant

Beets Ann Surg 2024

Take Home Notes: Indication for Lateral Node Dissection

- Primary tumor
  - T3-4 mid-low rectal cancer below peritoneal reflection

Take Home Notes: Indication for Lateral Node Dissection

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  - T3-4 mid-low rectal cancer below peritoneal reflection
- Lateral LN
  - Location: internal iliac /obturator areas
  - Baseline 7mm (short axis) is a reasonable cut-off
  - Baseline vs restaging size... controversial
  - Low-located primary tumor may need a smaller cut-off
  - Malignant feature may support diagnosis

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  - T3-4 mid-low rectal cancer below peritoneal reflection
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  - Baseline 7mm (short axis) is a reasonable cut-off
  - Baseline vs restaging size... controversial
  - Low-located primary tumor may need a smaller cut-off
  - Malignant feature may support diagnosis
- Comprehensive MDT decision
  - Training across the depts (surgeons, radiologists, rad. Oncologist...)

Thank you

tkonishi@mdanderson.org