How to prevent local recurrence in enlarged lymphnodes

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Session XVIII: Multimodality Therapy for Rectal Cancer
No conflict of interests
Lymphatic drainage from rectum

No lymph nodes in presacral area

Connections between mesorectal and extramesorectal lymph nodes

Tumour recurrence might arise from lateral lymph nodes

(Kusters et al., Br J Surg, 2010)
Two directions of spread

- High tumors: along superior rectal artery up to inferior mesenteric artery
- Tumors below the peritoneal reflection: along the middle rectal artery to
  - Internal iliac nodes
  - Obturator nodes
Western surgeons

- Lateral lymph node positivity is already metastasized disease..
- Chemoradiotherapy is enough to sterilize these nodes..
- We would not cure these patients with a lateral lymph node dissection anyway...

Asian surgeons

- Lateral lymph node positivity is local disease..
- Chemoradiotherapy is not enough to sterilize all these nodes..
- We can cure these patients with a lateral lymph node dissection.
What if lymph nodes are enlarged?
What if lymph nodes are enlarged?

Pre-treatment size, lateral recurrence after CRT + TME!

Kim, Ann Surg Onc 2008
Lateral sidewall recurrence 2014, after APR after 5x5 Gray preop RTH in 2005
PET before neoadjuvant treatment
Oxford cohort

- 127 patients in 5 years with cT3/T4 tumors up to 8cm from the AV
Short-axis

33% short-axis
>10mm
p = 0.03

10% short-axis
<10mm
Oxford cohort

- Malignant features in this series not significantly associated with lateral local recurrence
Eindhoven cohort

• Of a total of 432 cT3/4 rectal cancers in 5 years: **192** patients with tumors up to 8cm from AV

• Lateral nodes reviewed on MRI: 5-year lateral LR rate
  - < 10mm: 8%  \( p = 0.04 \)

*Original article*

**Prognostic implications of MRI-detected lateral nodal disease and extramural vascular invasion in rectal cancer**

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Eindhoven cohort

- mrEMVI evaluated by different, mrEMVI-trained radiologist: 5-year distant metastasis rate
  - EMVI-: 26%
  - EMVI+: 43%

\[ p = 0.02 \]
Eindhoven cohort

Uni- and multi-variate analyses: independent entities

**Lateral nodal disease**

More lateral recurrences vs mrEMVI

More metastases
First hypothesis

- Lateral nodal recurrence occurs despite the use of nCRT
- Size seems to predict this more than other features, lateral nodes might behave differently than mesorectal nodes
- Lateral nodal disease is NOT associated with metastases. mrEMVI is!
- A small subgroup of patients might benefit from more extensive neoadjuvant and/or surgical management
Creating evidence
Lateral Lymphnode consortium

- Retrospective review of all low cT3/T4 primary tumors
- 12 centers worldwide
- +1200 patients operated in 5 years
- re-review of MRI’s with a standardized protocol
Creating evidence
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

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Patients

- 1216 patients from 12 centers between 2009-2013, follow-up till Jan. 2017
  - 64% male, 36% female
  - 76% cT3, 24% cT4
  - 79% n(C)RT

- LLND’s performed in 142 patients (12%)
  - 44 (31%) no neoadjuvant treatment
  - 98 (69%) after n(C)RT
LLND

- Two types:
  - **Prophylactic**: instead of n(C)RT, irrespective of nodal involvement (Nagoya)
  - **Indicated**: combined with n(C)RT, generally in nodes larger than 7mm or with malignant features (CIH, Toranomon, Karolinska, MSKCC)
- Different than sampling lateral lymph node(s): dissection of whole internal iliac and obturator compartment!
Results

• Only 6% R1 resections..
• 10.0% 5-year local recurrence rate
• 5.5% 5-year lateral local recurrence rate
• About 50% of patients with lateral LR had no metastases at/before local recurrence diagnosis

• Short-axis vs lateral local recurrence in patients with n(C)RT + TME
35% 5-year lateral local recurrence rate

6% of all patients have nodes $\geq 10\text{mm}$
16% of all patients have nodes $\geq 7$mm

19.5% 5-year lateral local recurrence rate

$p = 0.045$
n(C)RT+ LLND-

p = 0.217

Lateral nodal disease does not result in more metastases!
Effect of LLND on local recurrence

- Selecting only patients who had nodes $\geq 7$mm:

  \[ n(C)RT + TME \]

  vs

  \[ n(C)RT + TME + LLND \]

- In 53% of LLND’s after n(C)RT pathologically positive nodes
Effect of LLND in $\geq 7$mm nodes

Lateral local recurrence reduced by LLND!

19.5% LLND-  
$p = 0.042$

5.7% LLND+
Lateral Nodal Features on Restaging Magnetic Resonance Imaging Associated With Lateral Local Recurrence in Low Rectal Cancer After Neoadjuvant Chemoradiotherapy or Radiotherapy

Atsushi Ogura, MD1,2,3; Tsuyoshi Konishi, PhD5,9; Geerard L. Beets, PhD5; Chris Cunningham, MD9; Julio Garcia-Aguilar, PhD9; Henrik Iversen, PhD7; Shigeo Toda, MD8; In Kyu Lee, PhD9; Hong Xiang Lee, BS10; Keisuke Uehara, PhD2; Peter Lee, MS11,12; Hein Putter, PhD13; Cornelis J. H. van de Velde, PhD1; Harm J. T. Rutten, PhD14,15; Jurriaan B. Tuynman, PhD16; Miranda Kusters, MD, PhD16; for the Lateral Nocle Study Consortium

Re-staging after n(C)RT

- $\frac{3}{4}$ of patients underwent re-staging MRI after n(C)RT

- In 7% of patients with nodes $\geq 7$mm, they disappeared completely: 0% lateral LR

- In 29% of patients with nodes $\geq 7$mm they shrunk to $\leq 4$ mm: still 0% lateral LR!

- In nodes $>4$ mm at restaging: increased risk of LR

JAMA surgery 2019, A Ogura e.a., in press
Location of enlarged lateral node

- Enlarged external iliac nodes only lead to distant metastases, not to local recurrence.
- Enlarged obturator nodes are more common than internal iliac nodes.
- However, internal iliac nodes are less likely to shrink to $\leq 4\text{mm}$ (27%) and behave more aggressively: 52% lateral local recurrence rate in persistent internal nodes!
Re-staging after n(C)RT

- Mainly in internal iliac nodes that are pre $\geq 7\text{mm en post} >4\text{mm}$
- $52\%$ LLND-$9\%$ LLND+
- $p = 0.007$
Location of enlarged lateral node

- In obturator nodes even in $\leq 6\text{mm}$: no recurrences
- Likelihood to shrink: 62% (27% in internal iliac)
- Lateral local recurrence in $>6\text{mm}$: 18% 5-year rate (52% in internal iliac)
Discussion points

• Different behaviour of enlarged nodes per site
• Limitations of a retrospective study (no radiation fields were verified)
• LLND seems to be associated with a lower lateral local recurrence rate
• Are all these nodal structures lymphnodes? Or are they intravascular and intralymphatic tumor deposits, which may behave differently
• Do we need more extended preoperative imaging? Is there a role for PET?
Discussion points (continued)

- LLND for persisting enlarged nodes will be rare. Is there a role for a centralized approach?
- How to avoid unnecessary LLND and its subsequent risk of neurological damage.
- Definitely we need a prospective trial
LaNoReC trial

• Lateral Nodal Recurrence in Rectal cancer
  – Central review of MR imaging
  – Registration of radiotherapy volume incl boost
  – Standardized LLND with video analysis

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