Do enlarged lateral lymph nodes after CRT lead to preventable lateral local recurrences?

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Background:
Lateral nodal disease in rectal cancer is generally considered as metastasized disease in the West and it is often assumed that lateral local recurrence can be prevented by neoadjuvant (chemo)radiotherapy. Very recent literature however suggests that patients with enlarged lateral lymph nodes (>5mm on MRI), who had neoadjuvant chemoradiotherapy and standard TME, have an up to 80% local recurrence rate in the lateral compartment (Figure) 1-3. Of these local recurrences, 40% is not metastasized, suggesting that it is still localized disease. There are only data on size of the lymph nodes, not on heterogeneity, border irregularity or extramural vascular invasion (EMVI).

A recent Japanese article showed, if in patients with enlarged lateral nodes neoadjuvant chemoradiotherapy is combined with a lateral lymph node dissection, which resulted in 66% pN+ lateral lymph nodes, these patients have a 5-year overall survival of 80% 4. So, contrary to the ideas in the West that lateral nodal disease cannot be treated curatively or that neoadjuvant therapy is enough to sterilize the disease, the above mentioned literature strongly suggests we should reconsider our ideas.

Goal of this study:
To perform a retrospective multi-center pooled analysis to study all patients with low locally advanced rectal cancers in a 5-year period. All MRI’s are reviewed and the incidence of enlarged lateral lymph nodes and/or malignant features is studied. Then, factors that influence local recurrence are analysed, to see whether despite an R0 resection local regrowth occurs in the lateral compartment.

If this is shown to be high in Western patients, despite of neoadjuvant chemoradiotherapy including the full dose of radiotherapy on the lateral lymph node compartment, we should consider performing a lateral lymph node dissection (LLND) specifically in these patients. Further, we hope to elucidate the difference between lateral nodal disease and extra-mesorectal EMVI.

Patient inclusion:
From each center all patients with low, within 8cm of the anal verge (measured on MRI), locally advanced (cT3/T4) rectal cancer between Jan 2009 and Dec 2013 will be reviewed. Only patients without metastases at the time of rectal cancer diagnosis are included. Of these patients the MRI of the primary tumor will be reassessed and location will categorized (majority of the tumor above or at/below the peritoneal reflection, and whether the distal margin of the tumor is below the attachment of the levator attachment on the pelvic bone on sagittal MRI). Also the lateral lymph nodes in the lateral lymph node compartment (obturator/internal iliac/external iliac) will be evaluated and whether these are enlarged and/or presence of malignant features. Also the presence of extra-mesorectal EMVI will be evaluated.

Parameters:
TNM-stage, level according to peritoneal reflection, level according to levator attachment, CEA, node size of largest lateral node on MRI (in mm), irregular border/ internal heterogeneity of lateral nodes, side of enlarged lymph node (left/right/bilateral), presence of (extra-mesorectal) EMVI, dosage of radiotherapy on lateral compartment (by review of radiotherapy fields), if available: size of lymph node after neoadjuvant therapy, operation details (TME/extended resection/exenteration, LLND performed or not), local recurrence-free survival, metastases-free survival, overall and cancer-specific survival.
Endpoints:
Primary: lateral nodal regrowth on follow-up CT/MRI
Secondary: percentage of patient with (irresectable) metastases before/at local recurrence diagnosis, survival.

Participating centers:
Because the low incidence of these specific patients, we need as many centers as possible to participate. These centers have already agreed to participate:
- Catharina Hospital, Eindhoven, the Netherlands. Prof. Rutten, dr. Kusters
- Leiden University Medical Center, the Netherlands. Prof. van de Velde
- Antoni van Leeuwenhoek Hospital/Maastricht University, the Netherlands. Prof. Beets
- Memorial Sloan Kettering Cancer Center, New York, USA. Dr. Garcia-Aguilar, dr. Konishi
- Churchill Hospital, Oxford, UK. Dr. Cunningham, dr. Hompes
- Aarhus University Hospital, Arhus, Denmark. Prof. Laurberg, dr. Verwaal
- University Hospital of Geneva, Geneva, Switzerland. Dr. Buchs, dr. Ris, dr. Vitali
- Angelita & Joaquim Gama Institute, São Paulo, Brazil. Prof. Habr-Gama, dr. Perez
- Royal Prince Alfred Hospital, Sydney, Australia. Prof. Solomon, dr. Austin
- University Medical Center Ljubljana, Slovenia. Assoc. Prof. Tomažič, dr. Grosek
- Clinical Hospital Center Zemun, Belgrade, Serbia. Dr. Blazic
- Karolinska Institute, Stockholm, Sweden. Prof. Holm, Prof. Martling
- University of Otago, Christchurch, New Zealand. Prof. Frizelle

Joining the study
Please contact me by email: miranda.kusters@catharinaziekenhuis.nl and you will be provided with an excel/SPSS sheet with the required parameters. Each center can publish their own data first before we publish the pooled results.

Figure (from reference 1):
Estimated probability of lateral pelvic recurrence according to lateral lymph node size, after neoadjuvant chemoradiotherapy

![Figure 2](image-url)
References


