Lateral lymph nodes in rectal cancer

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Chapter 11

Summary

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This thesis provides insights into the multidisciplinary knowledge, awareness and treatment of lateral lymph nodes (LLNs) in rectal cancer. Part I addresses the differences in the treatment of patients with rectal cancer and LLNs between various cultures, and examines the differences in terminology currently used by various specialities. Part II assesses the variation in knowledge and awareness of radiologists for LLNs, and Part III focusses on the prognostic implications of LLNs and the various treatment paradigms adhered to for this population.

Part I – Interpretations of the significance and treatment of lateral lymph nodes
The articles in chapters 2 and 3 offer an overview of the current knowledge regarding lateral nodal disease. A broad description of the discrepancies between traditionally Eastern and Western approaches to the treatment of LLNs is provided in chapter 2. This review discusses the current knowledge regarding the definitions of LLNs and their oncological implications. According to Japanese studies and the recent Lateral Node Consortium study, the Lateral Lymph Node Dissection (LLND) procedure, may be beneficial for patients with (persistently) enlarged LLNs. The LLND procedure is described in detail, as well as the possible risks and procedural variation due to a lack of experience in the West. The article in chapter 3 continues in more detail regarding how Western and Eastern, primarily Japanese, have traditionally differed in their approach in treating patients with rectal cancer and suspicious LLNs. This is most evident in their differing use of neoadjuvant treatment and application of the (prophylactic) lateral lymph node dissection (LLND). Western physicians have largely relied on (chemo)radiotherapy to adequately sterilize the lateral compartments and avoided the LLND, while Japanese clinicians adopted the prophylactic LLND for all patients with rectal cancer beneath the peritoneal reflection, to remove all lymphatic tissue possibly containing malignant LLNs. Important recent research advocates for a combination of these paradigms in the adoption of the selective LLND for 'high-risk' patients. The most recent research suggests that this 'high-risk' is linked to the short-axis diameter of LLNs, and their anatomical location.

The results in Chapter 4 focus on inter-physician variation. Various research, per discipline, is discussed to establish the foundation of knowledge within that specialty. These data help explain why each speciality; radiology, radiation-oncology and surgery, act and treat in a certain way. This article establishes that common terminology used for patients with LLNs, are used differently between specialties. This can cause miscommunication. For example, surgeons referring to the 'internal iliac compartment' mean a completely different region of the pelvis than when a radiation-oncologist refers to the 'internal iliac compartment'. Furthermore, these results establish that there is a lack of research within disciplines regarding LLNs, which is limiting. At the end of chapter 4, detailed guidelines per specialty

were created to aid in the diagnostics and treatment process. These guidelines are subject to the available data and may change with increased evidence.

Part II – Variation in knowledge and awareness of radiologists regarding lateral lymph nodes

It is of vital importance that suspicious LLNs are correctly identified. The articles described in chapters 5 and 7 explored how often LLNs are stated in MRI reports. The article in chapter 5 was a single-centre study and investigated 202 patients who were treated for locally advanced rectal cancer (T3+, or N+) in one tertiary centre between 2012 and 2020. In total, only 44% of primary MRI reports mentioned the presence of LLNs. In the cases where lateral lymph nodes (LLNs) were mentioned, only one (1%) specified a short-axis size, anatomical location, whether malignant features were, or were not present and if the node was suspicious of malignancy. Only 33% of cases which mentioned LLNs in the primary MRI report, also described their presence in multidisciplinary meeting reports, while 40% of restaging MRI reports failed to report on the visible LLN(s) mentioned in the primary MRI report. It was established that reporting increased with nodal stage (N0, N1 and N2; p=.010) and over time (2018-2020 versus 2012-2018, p=.042).

The training of radiologists who participated in the Snapshot Rectal Cancer 2016 before commencing with the study is described in chapter 6. Radiologists were asked to complete a short questionnaire and then examine the MR-images of three patients with LLNs. For each case, radiologists scored the size and anatomical location of this LLN and whether they thought it was malignant. After the two-hour training, provided by two expert radiologists, participants were asked to score the same three cases again, plus an additional three cases. The results in chapter 6 show that although the initial consensus for malignancy is high (>95%), consensus regarding anatomical location is initially low (around 46-64%), but improves significantly after training (75-85%). Furthermore, the range and standard deviation of size measurements also reduced after training and were closer to an expert reference value.

The article in chapter 7 describes a similar investigation as carried in chapter 5, but on a population-scale with data from the Snapshot Rectal Cancer 2016 study after training (chapter 6). This national, cross-sectional study investigated primary MRI reports of 1096 patients who underwent rectal cancer surgery in the Netherlands in 2016 and had at least a clinical T3 stage tumour or higher, located ≤8cm of the anorectal junction. Similar to the single-centre study, only 51% of cases reported the presence or absence of LLNs in their primary MRI reports. Of the 127 patients who were identified during MRI re-review to have enlarged (≥7mm) LLNs, 41% were not originally mentioned in the primary MRI report. Furthermore, the present-day re-review found that 73% would now be classified into a different anatomical compartment compared to the original report, and 42% would be

categorised into a different size category (<7/≥7mm). Results from chapter 7 also found that reporting of LLNs occurred significantly more often in academic/teaching hospitals compared to non-teaching (p=.006) and more often in medium/high volume centres compared to low volume centres (p<.001).

Part III – Prognostic implications and treatment of lateral lymph nodes

The final three chapters cover the prognostic implications of LLNs and their treatment in 2016. These chapters are based on data from the Snapshot Rectal Cancer 2016 study and focus on the features of LLNs seen on MRI related to oncological outcomes (chapter 8), the individual radiotherapy patterns of LLNs according to standard radiotherapy practice (chapter 9) and the various surgical procedures performed in 2016 for LLNs (chapter 10).

The article described in chapter 8 evaluated the 891 patients from the Snapshot Rectal Cancer 2016 study with at least a clinical T3 tumour, located ≤8cm from the anorectal junction, who received some form of neoadjuvant radiotherapy (short-course radiotherapy or chemoradiotherapy). In total, 314 (35%) patients had at least one visible LLN. Patients with visible LLNs had significantly higher 4-year local recurrence (LR) rates (16.4% versus 7.0%, p<.001) and 4-year ipsi-lateral local recurrence (LLR) rates (8.8% versus 0%, p<.001), compared to those without LLNs, respectively. Enlarged (≥7mm) LLNs (n=122) also resulted in higher 4-year LR (20.8%, 13.1%, 0%, p<.001) and LLR (14.7%, 4.4%, 0%, p<.001) rates, versus those with smaller or no LLNs, respectively. Both visible LLNs and enlarged LLNs remained independently associated with LR during multivariable analysis (visible LLNs: HR 1.787 (CI 95% 1.130-2.827), p=.013, enlarged LLNs: HR 1.948 (CI 95% 1.085-3.495), p=.041).

Enlarged LLNs did not result in higher rates distant metastases after multivariable analysis (HR 1.270, CI 0.881-1.830, p=.395) though initially associated with higher rates during univariate analysis (36.4% 24.4%, p=.021) and did not worsen rates of overall survival (71.1%, 79.4%, 78.3%, p=.071). Additionally, enlarged LLNs with at least one malignant feature present (heterogeneity, irregular border, round shape or loss of fatty centre) were found to have a 4-year LLR rate of 17.0% (versus 5.6% when malignant features were absent, p=.189). Intermediate LLNs (5-7mm) with at least one malignant feature also resulted in a higher 4-year LLR rate of 8.2%, compared to 2.1% when malignant features were absent (p=.561), though not statistically significant.

One of the most important assumptions in research concerning LLNs, is that they are irradiated fully when patients undergo some form of neoadjuvant radiotherapy. This was investigated the article shown in chapter 9, during which individual radiotherapy doses of internal iliac and obturator LLNs were examined. Patients in Chapter 9 were a subset from chapter 8 with the same inclusion criteria, but all had at least one LLN present of

at least 5mm, short-axis diameter. This resulted in a total of 223 patients. Sixty-one LLNs (27%) had an individual gross tumour volume (GTV) delineation and 181/223 (81%) were located inside the clinical target volume (CTV). In total, 91% received >95% of the originally planned irradiation dose. However, although 91% of patients with LLNs received >95% of the planned radiotherapy dose, these patients still resulted in a 4-year LLR rate of approximately 13%. A very small sample of seven patients received a dose-escalation ('boost') up to 60Gy and resulted in a 4-year LLR rate of 29% (2/7 developed a LLR after 4 years). Sub-analyses of only patients receiving CRT, which is the current, recommended treatment when LLNs are present, or only patients with enlarged LLNs (≥7mm short-axis), resulted in similar results.

The 64 patients who underwent an additional surgical procedure in 2016 due to a suspicious LLN were examined in the manuscript described in chapter 10. This surgery was in 81% (52/64) of cases the solitary removal of only the suspicious LLN ('node-picking'), while the remaining 19% (12/64) was the removal of a certain area ('partial regional node dissection' (PRND)). The overall 4-year LR and LLR rates for all 64 patients were 26.3% and 14.6%, respectively. Forty-eight of the 64 patients (75%) had LLNs measuring ≥7mm. For these patients, 4-year LR and LLR rates were 25.6% and 19.1%, respectively. These 48 patients were compared via multivariable analysis to 110 similar patients who also had enlarged LLNs, but only underwent total mesorectal excision surgery. No significant differences in 4-year LR or LLR rates were found (LR 25.6% vs. 20.0%, p=256, LLR 19.1% vs. 13.0%, p=.138, respectively), but with a trend towards higher LR and LLR rates after additional LLN surgery (LR HR 1.790 [CI 95% 0.822-3.898], LLR HR 1.709 [CI 95% 0.693-4.213]). This may be due to tumour spill, leaving micro-metastases behind, or a result of removing the wrong individual LLN or area.