# Locally recurrent rectal cancer: improving radiation treatment

Piqeur, F.

# Chapter 1

## Introduction and thesis outline

Rectal cancer affects up to 3000 patients each year in the Netherlands.[1] Following the introduction of total mesorectal excision (TME) and the use of (chemo)radiotherapy in advanced rectal cancer, local control for patients with primary rectal cancer has improved significantly. In both intermediate and advanced disease, neoadjuvant treatment is used to increase the chances of a radical surgical resection (R0) and decrease the chance of local recurrences.[2] For patients with intermediate disease, short-course radiotherapy, consisting of 5 fractions of 5Gy (5x5Gy), can be considered. In case of advanced disease, neoadjuvant treatment is recommended, consisting of either 5x5Gy followed by consolidation chemotherapy, or full course chemoradiotherapy (CRT) (25x2Gy or 28x1.8Gy), combined with twice daily capecitabine. In the past decades, the use of radiotherapy in the primary setting has expanded with the introduction of organ-preservation strategies.[3]

The incidence of locally recurrent rectal cancer (LRRC), defined as recurrent disease within the small pelvis after partial or total mesorectal excision, has decreased following improvements in primary cancer treatment, but 6-12% of patients will still develop LRRC.[4–6] At LRRC diagnosis, 40-60% of patients will present with distant metastases.[7–9] The diagnosis and management of LRRC patients is highly complex and usually requires a multimodal approach by an experienced multidisciplinary team. LRRC management is complicated due to heterogeneity of patient presentation and previous treatment. Due to the loss of anatomical boundaries, LRRC can present in numerous different locations, such as the pelvic side wall, the anastomosis, or in the presacral area. Previous TME surgery also means that in LRRC, structures beyond the mesorectum are involved by definition.

The variation in primary rectal cancer treatment means some patients presenting with LRRC will previously have undergone extensive neoadjuvant treatment followed by surgery, whereas others will develop recurrent disease after surgery alone.
These variables greatly complicate standardization of recommendations. Not all modalities can be used in all patients, and it is questionable whether tumour biology after such varying primary treatment pathways is comparable between patients.

After LRRC diagnosis, the first obstacle often faced in LRRC management is staging. Due to the distortion or loss of normal anatomical plans and boundaries (i.e., the mesorectal fascia) after primary surgery, local recurrences can present anywhere within the small pelvis.[10,11] Although the CT-thorax abdomen is effective for the diagnosis of distant metastases

and may help identify progression of tumour in the small pelvis, its soft-tissue discrimination is insufficient for LRRC staging. The gold standard modality for LRRC staging is therefore the T2-weighted MRI, with additional diffusion-weighted imaging (DWI).[10–15] The MRI has proven pivotal in adequate staging, as it is highly sensitive, specific and accurate in regard to LRRC.[16–19] An FDG-18 PET-CT is not formally recommended in each (suspected) LRRC, but is often used as a trouble-shooter in cases of clinical doubt, for example in patients in which a LRRC is suspected, but no suspicious lesion can be seen on CT.[12,14,19–21] However, there are still concerns regarding the risk of false positives due to infectious or inflammatory causes, as well as false negatives, mainly in low cell-density mucinous tumours.
Even with the modalities mentioned at hand, staging can remain challenging. Differentiation between postoperative (inflammatory) changes, fibrosis and tumour requires extensive radiological expertise. These uncertainties not only influence adequate staging at baseline but can also cause challenges in several different aspects of LRRC treatment, such as surgery and radiotherapy planning.

A second obstacle lies in establishing the intent of treatment. In the Netherlands, there is general consensus that patients with non-metastatic, (borderline) resectable LRRC are deemed eligible for curatively intended treatment.[22] For patients with evident irresectable disease or extensive metastatic disease, there is a general consensus that palliative or best-supportive care is the most appropriate treatment. However, many patients will fall in a grey area between these two clear clinical scenarios, due to patient or disease characteristics. For example, to date, there is no consensus on how to define oligometastatic disease in LRRC, and general definitions of oligometastatic disease can also vary significantly.[23] Therefore, it is difficult to determine up-front which patients with low-burden metastatic disease will or will not benefit from curatively intended treatment, further complicating recommendations.

For now, treatment with curative intent for LRRC in the Netherlands generally consists of neoadjuvant CRT followed by surgery.[22] This involves either full-course CRT (25x2Gy or 28x1.8Gy) in patients who are radiotherapy naive, or chemo reirradiation (15x2Gy) in patients who have previously received (chemo)radiotherapy for their primary tumour. In both cases, radiotherapy is combined with twice-daily concomitant capecitabine. The ratio of RT-naive versus reirradiation patients with a local recurrence is approximately 30:70.[24]

Although there has been relative consensus regarding the indication of CRT for LRRC, there has been a lack of awareness regarding radiotherapy delivery, exampled by the absence of LRRC delineation guidelines. In primary rectal cancer, national and international guidelines have been formulated specifying treatment details, such as areas to be incorporated in target volumes and margins to be used.[25] No such guidelines exist for LRRC, introducing even more heterogeneity in LRRC management. For surgery, similar issues are present. Although there is consensus that surgery should be performed for patients with resectable disease in a curative setting, there are no guidelines on how extensive the performed surgery should be, other than that a radical surgical resection (R0-resection) should be aimed for.[13] Additionally, there is no clear consensus on when or how to perform additional intra-operative radiotherapy (IORT), meaning its use is often dependent on availability.[12,13,26–28]

In recent years, the use of induction chemotherapy for LRRC has increased. A handful of retrospective cohorts have suggested that the use of induction chemotherapy can influence tumour response rate.[29–32] More pathological complete responses were seen in patients receiving induction chemotherapy followed by CRT, compared to patients only receiving CRT. However, so far, this has not translated into an overall survival benefit, and toxicity has not yet properly been investigated, meaning its place in LRRC treatment is still unknown.[24]

A last obstacle is that robust data to base treatment decisions on are lacking for LRRC. Only a handful of (non-randomized) prospective trials are available for this population of patients. The data that are available often stem from retrospective cohorts and consensus statements, that are subject to biases. Therefore, there is an evident need for robust, high-level, prospective data to steer clinical decision making in this complex patient population.

Due to all the aforementioned factors, LRRC management has proven to be a clear clinical challenge. Fortunately, two prospective phase-3 randomized controlled trials for LRRC patients have been initiated in recent years, namely the PelvEx II and the GRECCAR-15 trial.[33,34] Both trials include patients with (borderline) resectabel LRRC, without distant metastases. The biggest difference in trial population is that the GRECCAR-15 trial only included patients that have previously undergone radiotherapy for primary rectal cancer. The GRECCAR-15 trial was investigating the benefit of reirradiation after induction

chemotherapy but before surgery, whereas the PelvEx II trial is investigating the benefit of induction chemotherapy prior to CRT or chemo reirradiation and surgery. Unfortunately, the GRECCAR-15 trial has recently been closed due to slow accrual.

Ultimately, prospective randomized controlled trials as well as two prospective single arm reirradiation trials, will increase the availability of high-level evidence in the coming years.[35,36] Additionally, the PelvEx II trial has made it a clear goal to establish strong research networks, to facilitate multidisciplinary collaboration and accelerate related research. Within the PelvEx II trial, several initiatives have been taken to ensure uniformity in radiological reporting, radiotherapy treatment delivery and surgical resections, some of which are highlighted within this thesis.



An important step towards improving treatment for LRRC in general, is to reach a clear consensus on how to approach these patients. The aim of this thesis was therefore to achieve standardization of LRRC care and to further improve quality of care, with a specific focus on radiotherapy. The first part of this thesis addresses efforts to standardize LRRC care. The second part of this thesis focusses on improving quality of radiotherapy for LRRC patients. The last part of this thesis describes oncological outcomes for LRRC.

**Chapter 2** describes the development of a radiotherapy manual for LRRC. Several meetings were held with an expert radiologist, expert radiation oncologists and expert colorectal surgeons to discuss and standardize radiotherapy treatment for LRRC, based on consensus.
**Chapter 3** details the national guideline for LRRC treatment that was developed based on an extensive narrative literature review, to further standardize LRRC care. This guideline incorporates recommendations for LRRC diagnosis, patient selection, and treatment and advocates for centralization of expertise in dedicated referral centres.
To investigate where delineation variations for radiotherapy may occur, a multidisciplinary delineation study was performed (**Chapter 4**). This delineation study provides insight into when delineation variations occur and can aid in tailoring radiotherapy treatment recommendations to specific recurrence types. Moreover, it investigates the clinical benefit of a multidisciplinary approach to radiotherapy delineation, incorporating a radiologist to the clinical workflow.
As substantiating data for the delineation guideline are lacking, a retrospective analysis of local re-recurrences was performed in **Chapter 5**. This in-depth analysis of individual cases provide insights into where local treatment for LRRC may have failed, and forms

hypotheses on how to further improve treatment, hopefully eventually improving local control.

Within the PelvEx II trial, prospective peer-review of all CRT delineations for trial patients is performed. In **Chapter 6**, preliminary results and "lessons learnt" from this quality assurance programme are described. By doing so, the initially instated radiotherapy guideline can be continuously improved.

As described, radiotherapy is also used intraoperatively for LRRC treatment. In **Chapter 7**, a retrospective analysis is performed, to compare postoperative complications before and after IORT dose escalation. This was implemented to improve local control by escalating the dose of IORT on potentially involved resection margins. However, it is important to ensure that further dose escalation can be performed safely.

In **Chapter 8**, oncological outcome of patients with a pathological complete response following neoadjuvant radiotherapy is described and compared to LRRC patients without a complete response. This retrospective analysis has established a pathological complete response as an additional prognostic factor for oncological outcome.

Lastly, in **Chapter 9**, oncological outcomes of patients with re-recurrent rectal cancer are evaluated, highlighting the importance of careful patient selection.

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