Locally recurrent rectal cancer: improving radiation treatment

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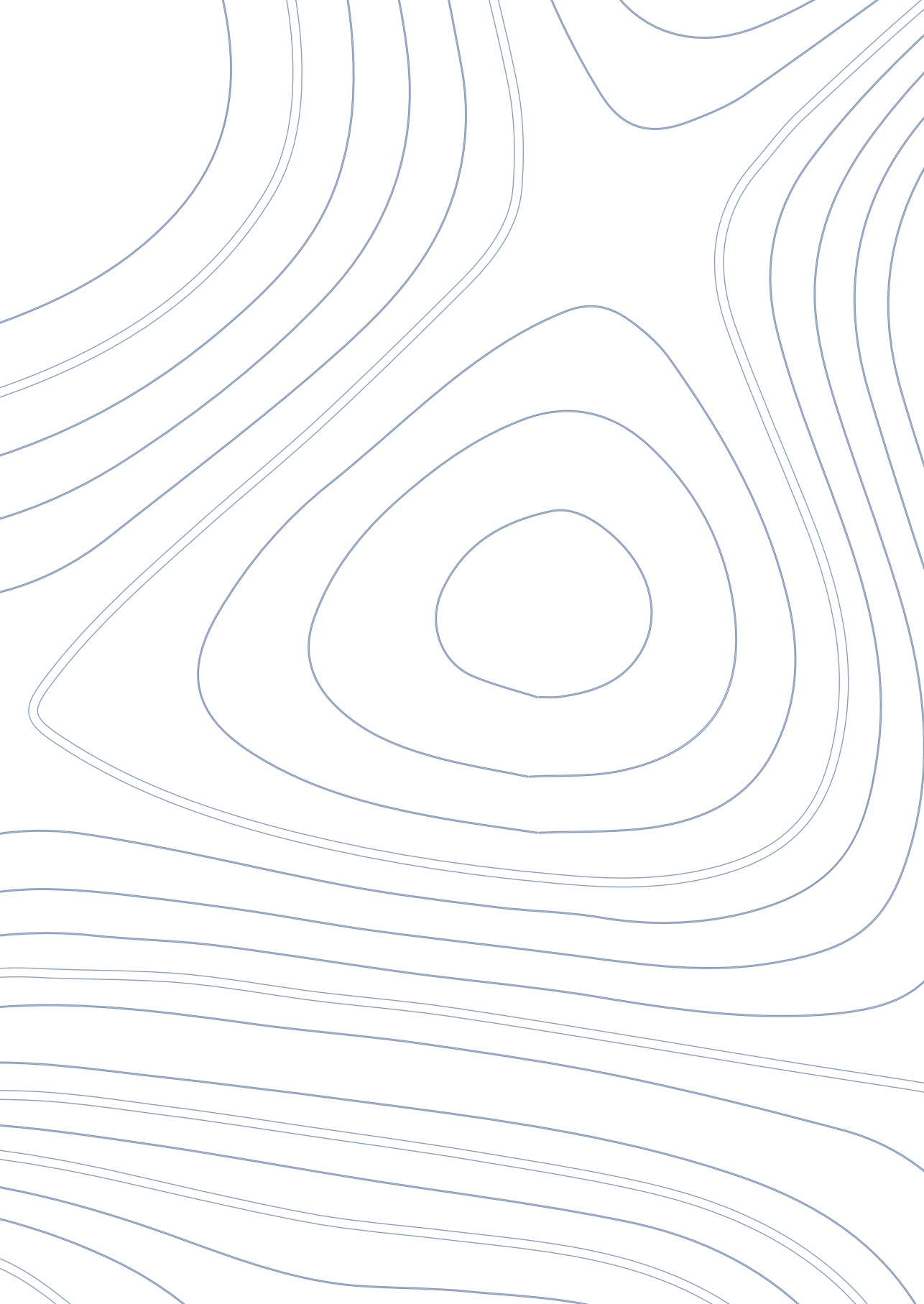
Part IV

Summary, general discussion,
future perspectives and appendices



Chapter 10

General discussion and future perspectives

GENERAL DISCUSSION

The treatment of locally recurrent rectal cancer (LRRC) remains a clinical challenge. The heterogeneous patient presentation, the invasive nature of disease and the differences in previous treatments amongst patients all complicate management significantly. The low incidence of LRRC also hampers collection of high-quality, prospective data. Hence, treatment is often based on low-grade retrospective evidence, local practice, or consensus statements.[1–3]

In the Netherlands, radiotherapy is often used as a neoadjuvant modality in the curative setting, in order to downstage tumour volume preoperatively, increase the chance of a radical (R0) surgical resection and improve local re-recurrence free survival (LrRFS).[4–6] For RT naive LRRC patients, full course CRT may improve overall survival (OS), but an OS benefit following reirradiation has not been reported.[6–8]

Despite the lack of an OS benefit, improving LrRFS remains an important goal of LRRC management. Complaints such as pain, fistulation and tumour mass effect due to local disease are common and detrimental to quality of life in LRRC patients.[9–11] Therefore, achieving local control in the palliative setting and preventing a re-recurrence in the curative setting is equally important as improving OS, warranting the use of reirradiation. However, many questions still remain unanswered regarding radiotherapy, and data to answer these questions is scarce. Questions such as optimal dose constraints, the potential for reirradiation beyond 30Gy, indications of radiotherapy for LRRC outside of the neoadjuvant or palliative setting, and the benefit of novel radiotherapy techniques remain. Given the lack of robust data and evidence-based guidelines steering clinical decision making for LRRC, this thesis aimed to benchmark the current treatment of LRRC, as well as improve radiotherapy for LRRC. The need for further research regarding radiotherapy in LRRC is evident, as well as the need for strong multidisciplinary collaboration in expert centres, working with and towards a common standard of care.

Advancing radiotherapy

Target volume delineation

The development of the first delineation guideline for LRRC with leading LRRC experts was important in standardizing radiotherapy for all patients included in the PelvEx II trial, which is investigating the benefit of induction chemotherapy prior to chemoradiotherapy and surgery for LRRC. To guarantee the validity of the trial, it is crucial that patients in both arms receive radiotherapy that adheres to a uniform standard of care, as the primary

outcome is the R0 resection rate, which is influenced by chemoradiotherapy. Guideline development was not only important in raising awareness for LRRC-specific delineation challenges, but also highlighted the lack of substantiating data to corroborate any recommendations made.

Substantial interobserver variation (IOV) in target volume delineation amongst radiation oncologists was found. While large IOV does not necessarily reflect the accuracy or quality of individual delineations, it does indicate a lack of consensus regarding appropriate target volumes. The observed IOV was hypothesized to stem from challenges in interpreting diagnostic imaging, complicating GTV delineation. Incorporating a dedicated radiologist in a multidisciplinary approach to delineation was therefore seen as a logical step in improving care.

Overall, improvement in IOV when delineating with radiologists' input was modest, although the effect varied considerably across cases. In some recurrences, such as solitary lymph node recurrences, there was little IOV amongst all participating radiologists and radiation oncologists. In cases with low up-front IOV, an improvement was not expected or necessary.
However, the varying effect in more complex recurrences was not expected. This could be attributed to the lack of a common definition for GTV, such as in tumours in fibrosis. IOV in these cases was high amongst both radiation oncologists and radiologists, as the IOV could largely be explained by either delineating the whole fibrosis as GTV, or only apparent tumour within fibrosis as GTV. IOV can then only be reduced if either approach is assigned based on consensus. In the literature, this consensus does not exist. In primary rectal cancer, substantial differences are found in something as seemingly simple as defining lateral lymph nodes.[12] In LRRC, where the complexity is much higher due to altered anatomy and heterogeneity of disease, it is inevitable that the definition of GTV also varies amongst clinicians. For radiation oncologists, the delineation guideline can help reduce these variations. For radiologists, no common staging or reporting system currently exists.[13]

The lack of substantiating data to support the delineation guideline was apparent. To address this, multidisciplinary case discussions were held, debating patients who suffered re-recurrences after intended curative treatment for LRRC. In over half of the discussed cases, at least one point of improvement to treatment could be noted. In the majority of

cases, this included adapting target volumes. Often, proposed adaptations fell in line with current delineation guideline recommendations; however, some new recommendations were proposed, as in recurrences located in an abscess. In some cases, an abscess around a local recurrence was not completely irradiated during LRRC treatment. Re-recurrences subsequently developed along the border of the previous abscess. This may indicate that this area was insufficiently treated, especially considering the potentially tumour-conducive micro-environment of an abscess and the circulating fluids within.[14,15] By discussing cases in which treatment failed, target volume recommendations can be improved. Of course, prospective validation of these hypotheses should be sought, but until then, these observations are used for further guideline development.

Inevitably, the guideline that was established will not be applicable to all LRRC, as the limited number of cases used can never completely reflect a heterogeneous disease as LRRC. To address this, the PelvEx II trial quality assurance (QA) programme was implemented. QA goals included ensuring homogeneous treatment within the PelvEx II trial and assessing guideline applicability in several types of local recurrences. This programme has provided valuable insights on how to improve target volume recommendations. It also highlighted some recurrence types that were not properly discussed in the first delineation guideline, such as high (nodal) recurrences after a partial mesorectal excision.

Ultimately, the goal of guideline development is to determine a standard of care and simplify delineation for radiation oncologists, especially those who do not often encounter LRRC. Based on the results in this thesis, it is pivotal that radiologists and radiation oncologists, but also surgeons agree on how to report, define and target LRRC in order to further improve. Radiologists are important in evaluating the extent of the tumour and their input can improve GTV delineations in up to a third of cases. This effect could however be larger if consensus on GTV definition is reached. For now, radiologists could facilitate target volume delineation by demarcating the extent of the tumour on MRI as clearly as possible, for example with arrows pointing to the tumour border in several plains and directions, and by detailing all involved or potentially involved organs and structures as clearly as possible. Surgeons provide important information on where surgical resection margins will be. These margins should always be incorporated within the CTV, as this is where an irradical resection may occur, which neoadjuvant therapy aims to prevent.[4,5,16]

Surgeons could therefore improve target volume delineation by discussing the surgical plan prior to radiotherapy treatment.

The overall effect of introducing a delineation guideline on quality of care should not be underestimated and guideline improvements have already been made based on results from several successive studies. In the future, many more questions regarding target volume delineation will likely arise. Target volume delineation in LRRC should therefore remain an area of research and guideline development should continue using PelvEx II data.

Dose escalation

One of the most prominent questions in LRRC radiotherapy is in regard to the dose of reirradiation. Reirradiation is used as a neoadjuvant treatment, to improve the chance of an R0 resection and improve LrRFS, but its effect is less than that of full course CRT.[4,6] This difference in efficacy may be caused by a lower and thus suboptimal reirradiation dose, by a higher incidence of radiation-insensitive tumours, or a combination of both. Either way, the key question in the neoadjuvant setting is whether further dose escalation could enhance oncological outcome.

Toxicity concerns have previously limited dose escalation of neoadjuvant reirradiation after the benchmark trial by Valentini et al., which employed hyperfractionated reirradiation up to 40Gy.[17] Fortunately, recent cohorts report low acute toxicity rates using conventional fractionation schedules.[7,18–22] Moreover, no difference in postoperative complications is seen when comparing patients irradiated prior to surgery to patients treated with up-front surgery.[23] Furthermore, advances in radiotherapy have enabled better sparing of organs at risk (OAR), suggesting that higher reirradiation doses can be explored. As of yet, dose-escalation in the neoadjuvant setting has not been researched in the Netherlands. This is because intraoperative radiotherapy is often used as an adjunct modality, adding a single-fraction boost of 10-16Gy to the at-risk margins during surgery, resulting in an EQD2 of over 40Gy (α/β=10), albeit to a small at-risk volume.[24,25] Hyperfractionated radiotherapy may aid in dose-escalation but is not the most patient-friendly option and it places a substantial burden on resources due to the twice-daily schedule. Dose-escalation with conventional fractionation to at least 40Gy may however be a feasible starting point for clinical trials, given the low acute radiotherapy toxicity reported following 30Gy.

In patients not eligible for surgery, due to frailty, tumour characteristics or preference, reirradiation may be used for palliation, local control, or even as an alternative to surgery. Chung et al. performed reirradiation up to 50Gy, showing an in-field progression-free survival of 49% and OS of 55% at 2-years without surgery.[26] However, a relatively high late severe toxicity rate of 41% was reported, compared to 25% reported in a reirradiation meta-analysis.[22] Achieving dose-escalation without increasing toxicity is therefore key. In the United Kingdom, a hypofractionated approach with Stereotactic Ablative Radiotherapy (SABR) is being studied for selected cases within this population. SABR is characterized by a high biological effective dose (BED) and a steep dose fall of towards surrounding (healthy) tissues. In general, smaller tumours (<5cm) with enough distance to surrounding (critical) OAR are eligible for SABR. Relatively small margins are used, adding only a 5mm margin to the GTV, thereby minimizing the target volume. Dose-escalation is performed in an isotoxic manner, meaning the radiation dose is tailored to the tolerance of surrounding OAR rather than the target volume.[27,28] By doing so, it is hoped that dose-escalation can be achieved, without exceeding a pre-defined OAR tolerance threshold. In a planning study, median EQD2 increased from 43 to 61Gy, which could have a significant effect on oncological outcome.[28] Toxicity data and oncological outcomes of this approach are awaited, as this may become a valid alternative to conventional reirradiation in patients opting out of surgery.

Although dose-escalation in reirradiation seems feasible based on recent cohorts and technical advances, it is possible that no oncological benefit will be found. Patients undergoing reirradiation have already demonstrated poor tumour biology and some degree of radiotherapy resistance. Future research should therefore focus on understanding the dose-response relationship in reirradiation and uncovering the underlying mechanisms of potential radiation resistance, as well as researching the safety of dose-escalation in both neoadjuvant and non-operative settings.

Implementation of novel modalities

Another point of discussion is the use of novel radiotherapy modalities in LRRC irradiation, such as the MR-linac, which may reduce side effects and facilitate dose escalation. The MR-linac enables more precise target volume delineation due to the MRI's superior soft-tissue visualization.[29–31] The MR-linac could prove valuable in reducing toxicity or escalating radiotherapy dose, by reducing planning target volume (PTV) margins and facilitating a boost to the GTV. In primary rectal cancer, such an approach has been studied.[32] The

MR-linac allows for compensation of inter- and intrafraction variation and a reduction of delineation uncertainty, which is accounted for in the PTV.[33–35] By reducing PTV margins, toxicity is reduced.[36–39] This could facilitate dose-escalation, for example by a boost to the GTV, which results in more pathologic tumour response in primary rectal cancer.[40,41] It is highly likely that a similar effect can be achieved in LRRC. An increased pathologic tumour response correlates to a superior oncological outcome in LRRC.[42–45]
The benefit of an MR-linac may however not be as large as in primary rectal cancer, as recurrences are often fixated within the small pelvis.[46,47] Therefore, accounting for tumour motion may only result in a minimal PTV reduction. Moreover, more precise target volume delineation may also be facilitated by implementing a diagnostic MRI in radiotherapy treatment position for each patient. This approach already improves image comparability and reduces registration errors that may occur when using a standard diagnostic MRI.[48] Additionally, the workflow of an MR-linac can consume up to an hour per fraction compared to ten minutes per fraction on a conventional linac.[49] Lastly, the availability of the MR-linac is limited and its use may therefore be more justified in other tumour sites. Although an MR-linac workflow for LRRC holds potential, this approach may not be warranted just yet, and should be studied prospectively.

Other potentially beneficial modalities include proton and carbon-ion radiotherapy. Proton radiotherapy's unique dose distribution properties allow for more precise radiotherapy, enabling higher doses while better sparing OAR.[50–53] Similarly, carbon-ion radiotherapy's steep Bragg peak and higher linear energy transfer may provide the benefit of better targeting relatively radiotherapy-resistant tumours, such as in LRRC reirradiation.[54–58] However, the significantly higher costs and limited availability of these advanced modalities may restrict their widespread adoption. Additionally, the low toxicity rates currently reported with chemo reirradiation for LRRC suggest that the boundaries of conventional radiotherapy have not yet been fully explored, making the immediate use of more expensive and less accessible techniques questionable. A Danish reirradiation trial for LRRC is currently investigating the feasibility and efficacy of dose-escalation up to 60 Gy using proton radiotherapy in patients with irresectable local disease. Its results will provide necessary information on whether or not proton radiotherapy could be of additional benefit, and whether steep dose-escalation could be feasible and beneficial for palliative patients.

Intraoperative radiotherapy

Intraoperative radiotherapy (IORT) is used in LRRC to improve LrRFS, although the evidence is limited and often confounded by different nCRT schedules and mixed locally advanced and recurrent rectal cancer cohorts.[24,59,60] Nevertheless, IORT is frequently considered as an additional modality to improve local control given the significant morbidity associated with local failure.[9–11,24] Inaccurate IORT dose-reconstruction after surgery may have previously hindered proper data collection and research. This is partly due to the ad-hoc placement of IORT, which is based on the surgeon's assessment of where an incomplete resection may have occurred. Another reason is the substantial anatomical change that occurs between the preoperative and postoperative setting, which can lead to a mismatch between the planned and delivered IORT location. As a result, it can be challenging to determine whether a subsequent tumour re-recurrence develops within the area treated by IORT. The introduction of intraoperative navigation may offer a potential solution to these issues, by facilitating IORT dose reconstruction during or following surgery.[61–64] This combination of IORT and intraoperative navigation may facilitate and accelerate research in the field of IORT.

Overall, many questions still stand in regard to radiotherapy for LRRC. Many steps to improve quality of radiotherapy have already been taken and the potential for further improvements is clear. The mere fact that there is a heightened awareness regarding the potential as well as the pitfalls of radiotherapy for LRRC is a significant step forward. Aforementioned opportunities in relation to target volume delineation, dose-escalation, and the possible introduction of novel techniques such as intraoperative navigation and the MR-linac can all contribute to better radiotherapy for LRRC.

Improving patient selection

Careful patient selection is critical in the management of LRRC. Patients selected for treatment with curative intent undergo intensive treatment, consisting of nCRT, sometimes preceded by induction chemotherapy, and extensive multicompartmental resections.[1–3,16,65–67] Surgical procedures are associated with high postoperative morbidity and mortality, reflected in a high postoperative complication rate and a significant and prolonged impact on quality of life (QoL).[9–11,23,68] Therefore, selecting the right patients for curative treatment is essential to prevent unnecessary treatment.

On the other hand, patients selected for palliative treatment have a significantly lower OS than patients selected for a curative treatment and can also suffer a decreased QoL due

to issues such as tumour mass effect and pain.[9,69,70] Moreover, local palliative treatments such as radiotherapy often only relieve symptoms for a limited amount of time.[71,72] Withholding curative treatment in patients who may have benefited from a curative approach can therefore also be detrimental to OS and QoL.

In current practice, patients with non-metastatic and resectable local disease are often deemed eligible for curative treatment, while patients with metastatic or unresectable disease receive palliative care. However, this approach fails to consider individual patient or tumour-specific factors. Therefore, more sophisticated methods are needed to select and monitor patients throughout their treatment.

Neoadjuvant therapy provides a window of opportunity for patient selection. On the one hand, it provides time for clinicians to observe the biological behaviour of the local recurrence. If the local recurrence is progressive despite neoadjuvant treatment and becomes irresectable, or if distant metastases develop, this is a reason to not perform surgery. There is no oncological benefit of surgery if a macroscopically irradical resection is expected when compared to non-operative management.[73] OS of LRRC patients presenting with synchronous metastases is known to be worse compared to patients without (a history of) metastases, even in highly selected cohorts from tertiary referral centres.[74] It is therefore likely that the differences in outcome are even larger, as patients with extensive local or distant disease are usually not presented at tertiary expert MDTs.

Monitoring tumour response could also help to select excellent responders for a watch-and-wait (W&W) strategy, as in primary rectal cancer. In chapter 8, it is concluded that achieving a pathological complete response after neoadjuvant therapy is predictive of superior oncological outcomes, even compared to patients in whom an R0 resection is achieved.[45,75,76] In these patients, surgery could be avoided if it does not have an additional effect on oncological outcome. In near-complete responders, dose-escalation to maximize local control may be justified if surgery and thus its potential complications can be omitted, even if this would entail an increase in radiotherapy toxicity. However, selection for a W&W approach relies heavily on accurate identification of a (near-)complete tumour response in LRRC, which is difficult due to altered anatomy, postoperative fibrosis hampering MRI-based follow-up and the inability for endoscopic follow-up in a majority of patients.

Two studies have investigated response assessment in LRRC. Voogt et al. compared the use of the MRI tumour regression grade (mrTRG) to the pathological tumour regression grade (pTRG).[75] A high positive predictive value (PPV) for a major pathological response (pTRG 1-2) is achievable when evaluation is done by an expert radiologist. However, overestimation of response was seen in 17% of cases, which is a clear risk when selecting patients for a watch-and wait strategy. Van Zoggel et al. demonstrated that a PPV of 63% can be achieved for a major pathological response with an F18-FDG PET/CT but reported overestimation in 23% of cases.[76] Improving response assessment, potentially by combining T2-weighted MRI with DWI and an F18-FDG PET/CT, with new liquid biopsy biomarkers such as ctDNA should be a research priority given its potential implications for a W&W appraoch.[77]

The importance of patient selection is also reflected in Chapter 9. In up to 60% of patients undergoing surgical treatment for LRRC, a re-recurrence will occur.[16,23,73] In these patients, treatment options are often even more limited than in LRRC, as options may be exhausted. Even so, long-term survival following curative treatment is achievable and factors beyond metastases and resectability seem to play a role in patient selection. For example, the interval between LRRC surgery and re-LRRC presentation influenced treatment intent in re-LRRC patients. In patients treated with curative intent, the median interval was 16.1 months, whereas in patients treated with palliative intent, the interval was only 11.3 months. An interval between LRRC and rLRRC of less than 12 months was associated with a poor 3y OS of only 30%. It is likely that this short interval reflects poor tumour biology.
Apparently, clinicians already consider different clinical characteristics when choosing the most optimal patient approach. However, data that can confirm the prognostic value of these characteristics is lacking. Future research should therefore focus on prospectively confirming clinical characteristics as prognostic factors, as well as identifying new prognostic factors. Prospective data generated from the PelvEx II trial will facilitate this.

Standardizing and centralizing LRRC care

It is clear that multidisciplinary collaboration and expertise are pivotal in improving LRRC care. Two LRRC guidelines have been developed and endorsed by a multidisciplinary team of experts. Close collaboration between radiologists and radiation oncologists has demonstrated the ability to enhance LRRC delineations. Multidisciplinary discussions have facilitated the formation of new hypotheses regarding LRRC target volumes. The

benefit of expert peer-review in LRRC delineation has been proven. These steps emphasize the value of multidisciplinary input and close collaboration amongst disciplines involved in LRRC treatment.

Currently, treatment is often centred around surgical expertise and there are no volume or expertise requirements for radiotherapy. This may hamper consistent, high-quality radiotherapy. Given the low incidence of LRRC, individual radiation oncologists have limited exposure to LRRC cases. During PelvEx II QA, nearly half of LRRC delineations were edited prior to nCRT, even though a delineation guideline was provided. A recent systematic review of radiotherapy QA measures in clinical trials showed that learning curves can rapidly diminish, even after benchmarking or peer review, and even in less complex primary cancer settings.[78] This, in combination with the low incidence and complexity of LRRC, makes it unlikely that individual radiation oncology departments will be able to develop sufficient LRRC-specific expertise.

Consequently, further centralizing LRRC-expertise into multidisciplinary expert teams, similar to those in the PelvEx II trial, may prove essential. Expert centres would be in charge of staging, restaging, determining indication and type of treatment, reviewing or performing target volume delineation and performing surgery. A minimum of 10 patients per year to define an expert centre is currently used in the PelvEx II trial but given the absence of a learning curve in LRRC delineation after ten cases, this norm may have to be increased. Patients could be referred back to local centres for the majority of care, as long as patients are discussed regularly in expert MDT-meetings. By doing so, patients can be certain that their individual treatment is up to the highest standards of care, whilst receiving care nearby, thereby enhancing care and collaboration in a physician- and patient-friendly manner.

In the meantime, a standardized radiological reporting protocol should be developed, incorporating information essential to radiation oncologists, such as a description of each (possibly) involved structure and clear demarcations of the tumour. Surgeons could detail their expected surgical approach and define where they anticipate the closest resection margins prior to delineation, as this impacts both GTV and CTV. Lastly, radiation oncologists should discuss delineations with colleagues at high-volume expert centres. The PelvEx II trial has already demonstrated how easily peer-review can be implemented in a manner that does not cause treatment-delay and does not require data transfers. Although these

are all relatively simple interventions, the combined effect in improving quality of care could be substantial.

All in all, significant improvements have been made in LRRC care. Although LRRC remains a complex and multidisciplinary challenge, the evolving understanding of patient selection, the standardization and centralization of expertise, and the further development of radiation treatment all provide hope for improved outcomes in this patient population.

FUTURE PERSPECTIVES

Ultimately, the implementation of an expert-centre structure for all patients with LRRC will improve care substantially and should be a priority. The steps that have already been taken, such as mandatory peer-review for PelvEx II trial delineations, should be continued and expanded for other LRRC patients. New efforts to further standardize, centralize and improve the quality of treatment and patient selection are essential.

Currently, ESTRO is developing a radiotherapy guideline for LRRC, covering radiotherapy indications, treatment planning recommendations, dose constraints, dose summation strategies, as well as the indications of novel techniques. This comprehensive guideline will greatly aid in internationally benchmarking LRRC radiotherapy and identifying additional research areas that require further exploration.

One of the major issues in LRRC is the lack of robust data to draw conclusions from. The PelvEx II and the (no longer recruiting) GRECCAR-15 trial will aid in providing high-quality, prospective data.[66,79] Both trials however only include(d) selected patients. Therefore, gathering comprehensive data of all LRRC patients in LRRC research centres is important. A new data-collecting initiative that aims to collect data on all LRRC-patients treated in- and outside of the PelvEx II trial is currently under construction. The aim is to gather clinical data, imaging, radiotherapy plans, tissue and liquid biopsies and create a large international LRRC data- and biobank. This will hopefully provide the knowledge that can be used to generate new research hypotheses, confirm others and improve care for LRRC patients.

LRRC knowledge is limited overall, but especially in the palliative setting. Importantly, palliative patients may be excellent candidates for dose-escalation trials in LRRC, with the goal of maximizing local control. In patients deemed ineligible for surgery, either due

to frailty, irresectable disease, or preference, definitive radiotherapy may be a valuable treatment alternative. Several cohorts have proven its feasibility in both RT naive and reirradiation LRRC patients, reporting progression free survival and overall survival rates similar to patients undergoing surgery.[26,80,81] When considering a reported 3-year OS of 20% in palliative patients overall, definitive radiotherapy could become a valid alternative and should therefore be explored in clinical trials.[70]

In the meantime, an additional data-collecting initiative for patients undergoing palliative radiotherapy is also being initiated, providing insight into which doses and schedules are used in palliative (re-)irradiation in the Netherlands. Once treatment variations have been established, efficacy of different schemes on oncological outcome can retrospectively be evaluated. In a "pick-the-winner" fashion, promising radiotherapy schedules could be researched prospectively. As an added benefit, the applicability of our delineation guideline could be evaluated in a palliative population.

Currently, we do not have enough data to support a W&W strategy in LRRC, in part due to the clinical doubts regarding the accuracy of determining a complete response through imaging. However, there are patients that will opt out of surgery, given the high morbidity and mortality associated with it, or patients in whom surgery is omitted for other reasons such as (new) comorbidities. Careful registration and follow-up, for example with three-monthly MRIs and CTs, of patients in whom surgery is omitted will hopefully help in determining the role of W&W in the future, provide valuable information on longevity of tumour response, and shape further research on this topic.

In conclusion, centralization and standardization of LRRC care as well as continuous clinical research is of the utmost importance for LRRC patients. Ongoing and future trials, as well as large-scale data-collecting initiatives will aid in further optimizing treatment for this challenging patient group. In the meantime, every effort should be made to provide patients with optimal treatment through rigorous and continuous multidisciplinary collaboration.

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