Locally advanced and locally recurrent rectal cancer

IMPACT PARAGRAPH

This thesis focused on patients with locally advanced rectal cancer (LARC) and locally recurrent rectal cancer (LRRC). LARC is an advanced stage of rectal cancer, in which the tumour grows beyond the wall of the rectum or shows other characteristics of locally advanced disease, such as involvement of the locoregional lymph nodes. In patients with LRRC, the tumour has recurred in the pelvis after previous successful treatment of rectal cancer.

Both LARC and LRRC require neoadjuvant treatment (i.e. treatment prior to surgery) followed by surgery. The current standard of neoadjuvant treatment consist of chemoradiotherapy, i.e. irradiation of the pelvis combined with oral chemotherapy. Surgical resection for LARC and, especially LRRC, is often an extended procedure involving the resection of multiple pelvic structures and/or organs. A total pelvic exenteration (i.e., resection of the rectum, bladder and reproductive organs) requiring reconstructive surgery is not uncommon. Not surprisingly, these surgeries are accompanied with a high postoperative morbidity rate and a profound impact on the quality of life.

In patients with LARC, distant metastases are a major concern with it being the most important cause of death in these patients. Although the rate of LRRC has decreased over the past decades owing to improvements in the treatment of primary rectal cancer, the prognosis for patients with LRRC is still poor, as only 30% of these patients are alive at 5 years after diagnosis.

This illustrates there is still much to gain in this specific population. In this thesis we therefore aimed to improve the treatment of patients with LARC and LRRC, with the purpose to ultimately improve their quality of life and long-term surgical as well as oncological outcomes.

The treatment of LARC and LRRC requires a multimodality approach. A surgical oncologist, medical oncologist, radiation oncologist, and radiologist are therefore all essential in the treatment of these patients. Depending on the need and type of reconstructive surgery other specialist are also involved. The results of the studies included in this thesis provide relevant knowledge applicable in the clinical decision-making of all of these physicians.

Among other things, we concluded that in elderly patients with LARC and LRRC there is still a need for improvement in order to achieve similar long-term outcomes to that

in younger patients and there is a need for better patients selection or better pre-, peri-, and postoperative care in these patients. With regard to patient selection we also observed that the presence of distant metastases in patients with LRRC requires a personalised approach giving the worse prognosis in this specific group. Furthermore, we observed that, to improve long-term outcomes in LARC and LRRC, achieving tumour response by means of neoadjuvant treatment is essential, and that in the assessment of this response after neoadjuvant treatment an MRI alone is not sufficient in LRRC. Besides, we found that a urostomy formed with a part of the colon is a good alternative for a urostomy formed with a part of the small intestine given the lower postoperative morbidity, and that intraoperative radiotherapy using a brachytherapy (HDR-IORT) appears more effective when compared with intraoperative radiotherapy using electron beam radiotherapy (IOERT) in patients with LARC and LRRC with microscopically residual tumour.

The above mentioned findings also resulted in new research questions and ideas. For example, a peri-and postoperative protocol adjusted to the specific challenges and needs of patients with LARC and LRRC was developed; whether this will improve morbidity and mortality will be evaluated. Moreover, the IOERT procedure was optimised in order to improve outcomes.

As such, these results are not just of interest for the treating physicians, but also for the patients themselves as these results support improvement of treatment and outcomes.

In the second part of this thesis, we investigated whether the addition of induction chemotherapy (i.e. intravenous chemotherapy administered prior to the chemoradiotherapy) could aid in improving the outcomes of patients with LARC and LRRC. Retrospective data showed promising results, but were inconsistent and therefore no definitive recommendations could be made regarding the use of induction chemotherapy. However, it did result in the awarding of two grants, enabling us to further research this. The MEND-it study will prospectively evaluate the additional value of induction chemotherapy in patients with LARC; the PelvEx II study is designed for patients with LRRC.

The PelvEx II study randomises patients with LRRC into two treatment groups: a) induction chemotherapy followed by chemoradiotherapy and surgery and b) chemoradiotherapy and surgery. This study not only aims to find an answer to the question whether induction chemotherapy is a valuable addition to the treatment of patients with LRRC, but also aims to improve the quality of care of these patients in general.

Firstly, we aim to do so by centralisation of care in so called expert centres. This will guarantee expertise of the treating physicians, which will hopefully result in the delivery of care that better meets the needs of the patient and its disease.

Moreover, with this study we also aim to develop uniform guidelines for the delivery of radiotherapy and the assessment of imaging in LRRC. Through the international involvement within this study, these guidelines will have a worldwide platform for implementation.

In spite of the absence of conclusive evidence of its value, treatment incorporating induction chemotherapy is increasingly being used worldwide. However, this is a long and intensive treatment regimen that is associated with treatment-related morbidity and inevitable costs. Therefore, a well-designed study to evaluate this treatment regimen is required.

From a patient perspective the effectiveness of a treatment is obviously of utmost importance. In addition, improvement in the quality of life and manageable side effects of treatment are also highly important. Within the PelvEx II study all of these aspects of treatment will be studied. In such way, the results of this study will show whether treatment with induction chemotherapy is a beneficial treatment from a patients perspective.

On the other hand, from a societal perspective, it is also desirable to offer the appropriate care to the right patients in order to ensure targeted use of resources. Therefore, the PelvEx study will also study the cost-effectiveness and cost-utility of both treatment regimens provided within the study.