Rectal cancer treatment

SUMMARY

For years, the standard treatment of rectal cancer included total mesorectal excision (TME), in intermediate or locally advanced rectal cancer preceded by neoadjuvant (chemo)radiotherapy. In a substantial part of patients, however, a pathological complete response (pCR) following neoadjuvant (chemo)radiotherapy was found in the resection specimen. Subsequently, Watch-and-Wait emerged as non-operative treatment option for rectal cancer patients with a clinical complete response (cCR) after neoadjuvant therapy. Although, there is increasingly more knowledge on Watch-and-Wait and organ-preserving treatment strategies, there are still some remaining clinical challenges. This theses addresses the following challenges: 1. to provide prospective data on long-term quality of life and functional outcome of a large patient cohort followed by Watch-and-Wait; 2. to evaluate the oncological outcome of stage IV rectal cancer patients managed by Watch-and-Wait; 3. to give an overview of the terminology, features, and criteria used in literature to describe a near-complete response and to establish an expert-based consensus on the definition of a near-complete response; and 4. to evaluate the short-term oncological and functional outcome of older or inoperable rectal cancer patients treated with contact x-ray brachytherapy (CXB) and to present the features and patterns observed on endoscopy and MRI after treatment with CXB.

Part I: Watch-and-Wait

Chapter 2 provides prospective data on long-term quality of life and functional outcome, including bowel, urinary, and sexual function of rectal cancer patients followed by Watch-and-Wait. These real-world data indicate that patients followed by Watch-and-Wait who do not require additional surgery report a good quality of life with limited variation over time. Major bowel dysfunction is observed in about a quarter of patients at all time-points. Male patients report moderate urinary dysfunction and severe erectile dysfunction in 18% and 32% at 24 months. In female patients, sexual satisfaction and overall sexual function decreases during follow-up. Patients after additional local excision report comparable quality of life scores, however, more major bowel dysfunction (56%) is observed at 24 months. Patient after TME score significant worse on several quality of life subscales. These data are essential in daily clinical practice for shared decision making and to counsel patients on what to expect following Watch-and-Wait.

In *chapter 3* the clinical and oncological outcome of a selected group of stage IV rectal cancer patients managed by Watch-and-Wait following a (near-)complete response after pelvic radiotherapy is evaluated. After a median follow-up period of 35 months, local regrowth is observed in 40.5% of patients, with no differences between clinical complete and near-complete responders. The corresponding 2-year local regrowth rate of 39.9% is on the high side compared to the regrowth rate in non-metastasized rectal cancer patients. The 2-year organ-preserving rate and colostomy-free rate are 77.1% and 88.1%, respectively. The 2-year and 5-year overall survival rates are 92.0% and 67.5%.

Although a relatively high regrowth rate is observed, TME and a permanent colostomy are avoided in the majority of patients. Therefore, Watch-and-Wait can be considered as alternative for TME in a selected group of stage IV rectal cancer patients with a (near-)complete response following pelvic radiotherapy.

Part II: The definition of a near-complete response

The systematic review in *chapter 4* gives an overview of the terminology, features, and criteria used in literature to describe a near-complete response after (chemo)radiotherapy for rectal cancer. In literature, patients with a near-complete response are either selected for Watch-and-Wait or for additional local excision aiming at organ-preservation. The majority of studies use the term 'near-complete response', additionally, terminology such as 'major response' or 'potential complete response' are used. A variety of criteria and features is used to define a near-complete response. The most common features with digital rectal examination (DRE) and endoscopy are minor irregularities or a smooth induration with DRE, and a small flat ulcer on endoscopy. On MRI, studies used features, TNM criteria, and mrTRG to define a near-complete response. The variety in criteria and features used for a near-complete response can partly be explained by the difference in treatment strategies patients are selected for. In the future, a more uniform, evidence-based, and reproducible definition of a near-CR is required for patient care and research purposes.

Chapter 5 provides an expert-based consensus on the definition of a near-complete response following chemoradiotherapy for rectal cancer. A three-tier categorization of a near-complete response based on the likelihood of the response to evolve into a cCR is established. In addition to this three-tier categorization, the clinical experts recommend: (1) the definition near-complete response should be used temporarily in the first six months from end of neoadjuvant chemoradiotherapy, after this interval the response should have resolved in either a cCR or incomplete response; (2) although the response on endoscopy is most decisive, the response should be based on three modalities, DRE, endoscopy, and MRI including T2W-MRI and DWI; (3) the lymph node status should be taken into account when deciding whether or not there is a near-complete response; and (4) biopsies are not always needed when a near- complete response is found, particularly as false-positive and false-negative biopsies have been reported. The provided three-tier categorization of a near-complete response should be used in further studies to find a larger evidence base for the predictive values for successful organ-preservation.

Part III: Contact x-ray brachytherapy as organ-preserving treatment strategy

In *chapter 6* the short-term oncological and functional outcome of older or inoperable rectal cancer patients treated with CXB to avoid TME are evaluated. After a median follow-up period of 13 months, local control of the tumour is observed in 68% of patients. The corresponding 12 months organ-preservation rate, progression-free survival, and overall survival are 88%, 78%, and 100%, respectively. At 3 months of follow-up, a transient decrease in quality of life and bowel function is observed,

however, this decrease is generally restored later during follow-up. Although, side-effects shortly after treatment are reported, patients' experience with CXB is positive. As CXB is well-tolerated and can provide a good control of the local tumour, CXB can be considered as alternative option to avoid TME in older or inoperable rectal cancer patients.

Chapter 7 presents the features on endoscopy and MRI after treatment with CXB for rectal cancer. Early in follow-up the response evaluation can be obscured by treatment-related features, such as an irregular ulcer on endoscopy and a more diffuse "reactive" signal on DWI. Therefore, the distinction between a cCR and residual tumour after CXB generally can be made after six months of follow-up. Features indicative for residual tumour are a tumour mass on endoscopy, a focal tumour signal on T2W-MRI, and a mass-like high signal on DWI. These features are in general not seen in patients with a cCR. Early recognition of these features is important, to refer patients who will not develop a cCR for TME as early as possible. The results presented in chapter 7 can help clinicians in daily practice to interpret the features observed on endoscopy and MRI after treatment with CXB for rectal cancer.