Organ preservation in rectal cancer

APPENDICES

Summary

The aims of this thesis are: 1] to evaluate if magnetic resonance imaging (MRI) alone can accurately identify patients who have substantial residual disease after neoadjuvant chemoradiation (CRT) that requires immediate surgery, and if these findings are reproducible amongst radiologists with various expertise levels; 2] to evaluate the pooled prevalence of lymph nodes after CRT according to increasing depth of residual tumour in the rectal wall and to assess the impact of post-CRT lymph nodes metastases on long-term oncological outcomes; 3] to evaluate the current watch-and-wait (W&W) follow-up schedule and to propose improvements to make the follow-up schedule more efficient; 4] to evaluate the oncological and functional outcomes of a W&W approach in older patients; 5] to evaluate if distant metastasis occur later in W&W patients than in patients treated with CRT and total mesorectal excision (TME) by comparing metastasis and detection; and 6] to give an overview of current and new imaging technologies for prediction and assessment of response. The introduction *(chapter 1)* summarizes the currently available evidence and status with regard to these aims.

Part I: Patient selection and follow-up

Chapter 2 evaluates whether radiologists with variable levels of expertise are able to correctly identify those patients with substantial residual disease who require immediate surgery using a simplified three-categorized MRI response evaluation system. This may facilitate more selective use of endoscopy which is particularly interesting for low volume centres with limited access to endoscopy. Although there was not a perfect agreement between readers, radiologists correctly identified the 20% of poor responders who have substantial residual disease at histopathology and who require surgery without the need for endoscopy to evaluate response. Also, almost all complete responders were appointed to the good or intermediate response group. In total, by this approach 80% of the patients are referred for additional endoscopy to evaluate luminal response and decide on their eligibility for organ preserving therapy.

Chapter 3 describes a large pooled analysis of individual patient data from historical cohorts that evaluated the prevalence of lymph node metastases according to ypT-stage in patients with locally advanced rectal cancer treated with CRT and TME. Similar as in the primary setting, the risk of lymph node metastases increases with increasing T-stage: 7% for ypT0, 12% for ypT1, 17% for ypT2, 40% for ypT3 and 46% for ypT4. In addition, the presence of malignant lymph nodes was a strong predictor for poor long-term disease-free survival and overall survival in patients with ypT0-2 disease (HRs of 2.05-2.45) and in the total cohort (HRs of 2.08-2.26). These outcomes can be used in clinical practice to discuss the risk of lymph node metastases after local excision or when considering organ preservation according to the depth of residual tumour in the rectal wall.

Chapter 4 proposes a more efficient follow-up schedule by constructing a theoretical comparison of the occurrence and detection of local regrowth in the current follow-up schedule with four other hypothetical follow-up schedules. The new proposed follow-

up schedule reduces the number of examinations from 24 to 20. Endoscopy should be performed more frequently in the first two years because most regrowths occur within two years (98%), are located in the lumen (94%) and are visible on endoscopy (88%). After two years the schedule can be deintensified to yearly follow-up with endoscopy and MRI. It is likely that the proposed follow-up schedule will result in better efficiency and lower burden for patients.

Part II: Oncological outcomes

Chapter 5 evaluates the outcome of a W&W policy in older patients. W&W appears to be a safe alternative in older patients with a non-regrowth disease-free survival of 91%, overall survival of 97% and overall pelvic control of 98%. In addition, most patients avoided surgery and a permanent stoma with a colostomy-free rate of 93% and had reasonable anorectal and urinary function with good continence, no or minor Low Anterior Resection Syndrome Score and moderate urinary problems.

Chapter 6 compares the time pattern of distant metastasis from two large datasets of individual patient data: one dataset with 1642 W&W patients from the International Watch-and-Wait Database and the other dataset containing 2401 patients treated with CRT and surgery. The risk to develop metastases in W&W patients is low (3-year distant metastasis-free rate 92%) compared to patients treated with CRT and surgery (3-year distant metastasis-free rate 82%). Even though during the entire follow-up period W&W patients have a lower risk for distant metastases compared to operated patients, a significant interaction effect was found for follow-up time and distant metastasis: the risk for distant metastases was lower during early follow-up (HR of 0.27, 95%CI 0.12-0.60) than during later follow-up (HR 0.66, 95%CI 0.53-0.83) in W&W patients. So, although the risk to develop distant metastasis in W&W patients is low, they develop metastases later and the hypothesis is that there is a small risk that metastases originate from local regrowths.

Part III: Recent advanced imaging technologies

Chapter 7 gives an overview of current MR imaging techniques for response prediction and assessment of response and gives insight in which advanced imaging techniques will probably be valuable in future research and clinical practice. New functional imaging biomarkers (i.e. derived from diffusion weighted imaging or dynamic contrast enhanced MRI) capture changes in tumour perfusion and microstructure before they appear on morphological imaging. Many studies show that the combination of functional and morphological data has the highest accuracy in prediction and assessment of response, with other functional imaging biomarkers on the horizon. A recent promising advance is radiomics, which uses computer algorithms to find associations between quantitative features (i.e. pre-defined general purpose features such as intensity distribution, tumour shape and heterogeneity) and clinical outcome. Several studies have evaluated radiomics based on MRI of rectal tumours, with promising results in response prediction and post-neoadjuvant therapy assessment of response. However, due to various methodological

problems, the generalizability is hampered and, more studies are needed before it can be adopted into clinical practice.

Chapter 8 evaluates the accuracy of deep learning models based on endoscopic images acquired during response evaluation to identify complete responders. The diagnostic performance of different open access deep learning networks was evaluated. In addition, the diagnostic performance of clinical features were combined with endoscopic image features. The outcomes of the different models were compared with the reference standard: complete response (sustained complete response ≥2 years or ypT0 at histopathology) or residual disease (local regrowth) during follow-up or ypT1-4 at histopathology). Findings show that deep learning has a modest accuracy to detect complete responders and the combined models achieved the highest performance (AUC 0.76-0.83) compared to models that were built on clinical features (AUC 0.71-0.74) or endoscopic images only (AUC 0.71-0.79). Overall, EfficientNet-B2 achieved the highest performance amongst the different combined models with an AUC of 0.83 , an accuracy of 0.75, a sensitivity of 0.77 and specificity of 0.75.