Introduction and outline of this thesis

Introduction

Although the incidence of colorectal cancer decreases in the United States and seems to stabilize in The Netherlands, it remains the third most common malignancy among women and men in most Western countries.[1,2] Rectal cancer accounts for approximately one third of the total number of colorectal cancer patients and differs substantially from colon cancer. Generally, rectal malignancies are located under the peritoneal reflection, are closely related to the surrounding vital structures and are fixed within the pelvis. Colon malignancies are located intraperitoneally and are less often related to structures nearby. This factor makes rectal cancer different than colon cancer with different surgical and therapeutic options.

The treatment of rectal cancer has improved drastically in the last 3 decades, leading to improved outcomes. Historically, the outcome of rectal cancer has been poorer than the outcome of colon cancer. However, due to advancements in the treatment of rectal cancer the long-term outcome is now similar to colon cancer.[3,4] The main advancement is the introduction of a surgical technique, called total mesorectal excision (TME). Sir Bill Heald first described the TME-technique in 1979[5] and first long-term outcome of a large cohort of rectal cancer patients treated by this procedure was published in 1986.[6] This technique comprises a complete removal of the lymph node bearing mesorectum along with its intact enveloping fascia. This procedure has two advantages attributing to an improved long-term outcome. Firstly, the TME technique leads to a higher number of complete resections by leaving the visceral fascia intact. Secondly, TME leads to a complete removal of all possible regional lymph node metastases, which could potentially evolve into local recurrences.[7] Before the introduction of TME, local recurrence rates were reported up to 45%.[8-10] Currently, the local recurrence rate rarely exceeds 10% after rectal cancer surgery. Although no randomized controlled trials are available, it is highly likely that TME is the main cause of the decreased local recurrence rate and a prolonged overall survival after rectal cancer surgery.[11]

Simultaneously with the introduction of the TME technique, radiotherapy made its entry in rectal cancer management. The first high quality meta-analysis was published in 1989 demonstrating an improvement in local control without a beneficial effect on the overall survival.[12] Since then, many randomized trials have been executed on the effect of radiotherapy. The 'Dutch TME trial' and the German trial CAO/ARO/AIO-94 were one of the most important studies. The Dutch TME trial showed that even with TME surgery a short-course radiotherapy (5x5 Gy) leads to an improved local control.[11] The CAO/ARO/AIO-94 trial demonstrated that pre-operative radiotherapy resulted in a lower local recurrence rate compared to post-operative radiotherapy.[13] This has led to the current practice only to administer radiotherapy in a neo-adjuvant manner. The last important advancement concerning radiotherapy was combining it with concurrent chemotherapy. It

was shown that radiotherapy with concurrent chemotherapy as a radiosensitizer improves local control without an effect on survival benefit.[14,15]

The third major advancement in the treatment of rectal cancer is the quality of rectal cancer imaging. Two decades ago a digital rectal examination was standard of care to determine the extensiveness of the rectal malignancy. The introduction of Magnetic Resonance (MR) imaging has greatly improved rectal cancer staging. First single center series exploring the use of MR imaging in rectal cancer staging were published in the 80s,[16,17] but MR-imaging became standard of care in the first decade of the 21th century. The accuracies of tumor staging, nodal staging and circumferential resection margin involvement are superior compared to computed Tomographic scans (CT) or endoscopic ultrasound sonography (EUS).[18-20] Moreover, the Mercury trial has showed that MR imaging could accurately assess the completeness of the surgical resection margins and that MR imaging was accurately reproducible in multiple centers.[21] These factors have led to the recommendation to use MR imaging for pre-operative local staging in all guidelines.

TME surgery, neoadjuvant radiotherapy and improved imaging modalities have brought a great quality improvement in rectal cancer management, resulting in improved local control and improved overall survival after rectal cancer surgery. Currently, the treatment has shifted towards a more personalized approach, depending on the local tumor stage. Early stages of rectal cancer require a different treatment strategy than the more advanced stages of rectal cancer. For example, early stage rectal cancer (T1-2N0) can be treated safely by performing surgery alone without neo-adjuvant radiotherapy.[22] Moreover, these patients may be offered organ-sparing procedures resulting in a lower morbidity rate.[23] Presently, there is even evidence that surgery can be omitted in highly selected patients in case of a complete clinical response after neo-adjuvant chemoradiotherapy. Several single center series have suggested that this so called 'watch and wait' approach is safe.[24,25]

The more advanced stages (e.g. locally advanced rectal cancer), on which the current thesis focuses, require a different approach. Locally advanced rectal cancer (LARC) is associated with higher local recurrence rates and poorer overall survival rates compared to the less advanced stages.[26] Therefore, LARC requires a multimodality approach with optimal staging, neo-adjuvant therapy and 'tailor-made' surgery to improve outcome. The circumferential resection margin (CRM) is often at risk and standard TME-surgery would lead to incomplete resections. Incomplete resections are detrimental for oncological outcome.[27] Neo-adjuvant (chemo-)radiotherapy is an essential part of the treatment of LARC, because it leads to lower local recurrence rates and tumor shrinkage (e.g. downstaging). Downstaging may render initially unresectable rectal malignancies into resectable tumors and thereby facilitating a complete resection.[14,15,22] Despite the downstaging effect of neo-adjuvant (chemo-)radiotherapy, a more radical

surgical approach, such as extralevatory abdominoperineal resections and partial or total exenterations, are often necessary to achieve complete resection magins.[28] These 'beyond TME' procedures are technically demanding with high complication and morbidity rates and may benefit from an experienced surgical team.[29]

Despite the advancements in primary rectal cancer treatment, 6-10% of the patients still develop a local recurrence.[11,14] Locally recurrent rectal cancer (LRRC) is usually accompanied by severe progressive pain, a poor quality of life and a poor overall survival. The treatment of LRRC is challenging. It is a heterogeneous disease varying from small central anastomotic recurrences to large pre-sacral or lateral recurrences with bony involvement of the sacrum or pelvis. A complete surgical resection is the only chance on durable local control and overall survival.[30] Several institutes across the world have explored the possibilities of the surgical treatment of LRRC and showed encouraging local control and overall survival rates when LRRC is treated in a multimodality manner.[31-33] The surgical treatment is technically demanding. Pelvic exenterative surgery is often necessary to achieve complete surgical margins but comes with a high complication and morbidity rate.[34]

The first chapters of this thesis focus on local staging. Previously mentioned, local staging is an essential part of high quality rectal cancer treatment. The accuracy of rectal cancer staging has greatly improved since the introduction of MR imaging. Unfortunately, the use of neo-adjuvant (chemo-)radiotherapy has confronted us with a new problem. Potentially, (chemo-)radiotherapy provides us the opportunity to perform less radical surgery due to the downstaging effect. However, the grade of downstaging differs per person and it seems useful to reassess the local tumor extent after (chemo-) radiotherapy. Unfortunately, the accuracy of MR imaging after (chemo-)radiotherapy is poor and this questions the usefulness of local restaging.[35,36] Fibrosis and local reactions caused by the radiotherapy makes it difficult to differentiate between viable tumor and non-malignant tissue. To improve restaging accuracy, it could be useful to add Dynamic Contrast Enhanced (DCE) sequences to MRI restaging. DCE may be helpful to differentiate between malignant and non-malignant tissue due to different contrast enhanced patterns. **In chapter 2** of this thesis we evaluated whether the addition DCE sequences resulted in an improved tumor, nodal staging and assessment of CRM involvement.

Local staging mainly determines the optimal treatment in rectal cancer management. However, detecting distant metastases is at least as important in order to offer patients optimal treatment. Approximately 20% of the patients are diagnosed with synchronous distant metastases at presentation.[37] These patients can, in case of limited metastatic disease, be offered resection of both metastases and primary tumor. If this is not the case, these patients should be referred for palliative care. Fortunately, most patients present without distant metastases and are candidates for curative surgery. In case of

LARC, patients are scheduled for neo-adjuvant (chemo-)radiotherapy and planned for surgery approximately 8-12 weeks after ending (chemo-)radiotherapy. The duration of a long course of (chemo-)radiotherapy is approximately 5 weeks and this means surgery is performed 4 to 5 months after initial staging. In this period new metastases may have developed or may become visible on imaging. This is particularly the case in LARC patients as these patients have the highest chance of developing distant metastases.[27,38,39] It could be of additional value to restage these patients by a thoraco-abdominal CT-scan after neo-adjuvant (chemo-)radiotherapy to identify patients with new distant metastases. This would have clinical impact, since these patients could be offered a different surgical approach or these patients could be spared surgery in case of extensive metastasized disease and be referred for palliative care. **In chapter 3**, we evaluated the benefit of restaging by thoraco-abdominal CT-scan after a long course (chemo-)radiotherapy for LARC.

Despite the poor accuracy of restaging techniques after (chemo-)radiotherapy, it is widely used. To evaluate the usefulness, we briefly reviewed the current literature to evaluate and question the potential benefit of restaging **in chapter 4**.

After optimal staging and neo-adjuvant therapy, patients with LARC are planned for the most suitable surgical procedure. The downstaging effect of neo-adjuvant therapy and beyond TME surgery may result in complete resections in the majority of the patients. However, due to the extensiveness of the local tumor some patients may still have involved circumferential resection margins (CRM). Involved CRMs leads to poor oncologic outcomes with high local recurrence rates and poor overall survival.[40] In an attempt to improve outcomes for these patients, several institutes across the world have implemented intra-operative radiotherapy (IORT) to their multimodality approach. The advantage of IORT is that a local radiotherapy boost can be administered at a specific area at risk, while other radiosensitive tissue, such as the small intestine and bladder, can be shielded from this radiation therapy. One single dose of IORT is considered to have a two to three times higher biological equivalent than fractioned radiotherapy. Therefore, a 10 Gy radiation dose may be able to eliminate microscopic remnants after a microscopically incomplete resection.[41,42] **In chapter 5**, we evaluated the effect of IORT in LARC on the local recurrence rate after neo-adjuvant (chemo-)radiotherapy and TME surgery.

The multimodality treatment of LARC results in improved oncological outcomes, whereas the benefit of a multimodality approach in early stage rectal cancer is limited. Moreover, the surgical treatment of early stage rectal cancer is considered to be technically less demanding. These factors render early stage and locally advanced rectal cancer to be considered as two different diseases. The most advanced stage (cT4) rectal cancer is relatively rare. In this stage radical surgical procedures are often necessary and these procedures are accompanied by high complication and morbidity rates. These

patients may potentially benefit the most from a dedicated and experienced (surgical) multidisciplinary team. Therefore, the benefit of treatment in dedicated high volume hospital may be more apparent in cT4 rectal cancer than in the more common cT1-3 rectal cancer. **In chapter 6**, we hypothesized that the effect of hospital volume in the treatment of cT4 rectal cancer was more important than in cT1-3 rectal cancer. We have analyzed the overall survival in a large population based study according to the hospital volume for cT4 and cT1-3 rectal cancer separately. A previous population based study did not find evidence that hospital volume regardless of the tumor stage was associated with a long-term overall survival in the Netherlands.[43]

Approximately 20% of the colorectal cancer patients are diagnosed with synchronous distant metastases.[44,45] Patients with limited metastatic disease can be treated with curative intent by a synchronous resection of primary tumor and metastases, by a 'liver first' approach or a resection of the metastases in a later stage.[46] Unfortunately, the majority of the patients is not suitable for a curative resection. For these patients, the best treatment strategy remains unclear. They can undergo a palliative resection of the primary tumor, which is frequently performed worldwide or they can be treated with palliative systemic therapy.[47] In case of disabling symptoms, there may be an indication for resection. In asymptomatic or mildly symptomatic tumors, the effect of primary tumor resection is questionable. Some advocate primary tumor resection, as it would lead to a prolonged survival. However, the studies suggesting a beneficial effect of primary tumor resection are often limited by selection bias. In these studies only patients in good clinical condition were considered candidates for surgery. High level evidence (e.g. randomized controlled trials) is lacking. Therefore, i**n chapter 7**, we reviewed the current evidence of primary tumor resection in stage IV colorectal cancer with unresectable metastatic disease.

The introduction of TME surgery and pelvic radiotherapy introduced a new problem of treating this new 'type' of LRRC. The optimal LCCR treatment includes neo-adjuvant (chemo-)radiotherapy to improve local control.[48] However, when the primary tumor has already been treated with radiotherapy, the radiation dose for LRRC treatment is limited. Additionally, previous TME-surgery makes complete resection of the local recurrence more demanding due to the fact that local recurrences after TME surgery may not be limited to an anatomical compartment. These factors render treatment of LRRC after TME surgery and previous radiotherapy more difficult. Furthermore it makes it questionable whether these patients still should be offered surgical treatment. **In chapter 8**, we have evaluated the outcome of LRRC in patients who received pelvic radiotherapy and TME surgery and compared it to the outcome of patients who did not receive previous pelvic radiotherapy.

In LRRC treatment, the single most important prognostic factor for overall survival and disease free survival is the resection margin status.[49] A complete resection (R0)

can lead to 5-year survival rates up to 60%, while incomplete resections (R1/2) lead to significantly poorer outcomes.[50,51] All efforts should be made to achieve a R0-resection by tumor downstaging by neo-adjuvant therapy and performing more radical surgery. In primary rectal cancer, it is unclear whether to consider 1mm or 2mm as an involved resection margin. Some authors plea to consider margins less or equal to 1mm to be involved, while others advice to consider margins less or equal to 2mm to be involved[27,52,53]. Nonetheless, there is consensus that close margins, either 1 or 2 mm, are associated with poorer oncological outcomes. If this is also the case in LRRC is unknown as it has never been evaluated. This may be important, because this could determine the extensiveness of the surgical resection and it may be helpful to inform patients more accurately after surgery about their prognosis. **In chapter 9**, we have evaluated the association between width of the tumor-free resection margin and the long term outcome after LRRC surgery.

Although surgical resection is the only durable option for long-term overall survival and local control, only 31-40% of the LRRC patients are considered to be suitable candidates for a curative surgical resection.[33,54] The majority of the patients have metastatic disease or an advanced local recurrence till such an extend that surgical resection is technically impossible or futile. These patients can be treated by pelvic radiotherapy in case of pain or may be offered chemotherapy which may prolong overall survival. Currently, a high number of patients diagnosed with LRRC have already received pelvic radiotherapy for the primary tumor. These patients represent an even more challenging group to treat palliatively. The radiation dose is limited and chemotherapy may not be as effective due to radiation induced fibrosis and scarring. The poorer response of chemotherapy in irradiated area has been previously demonstrated in recurrent cervical cancer. A meta-analysis found that the proportion of women who responded to treatment was significantly lower for recurrences within the pelvic field compared with disease outside of the pelvic radiotherapy field.[55] Whether this is also the case in LRRC is unknown and in **chapter 10**, we have evaluated the response of chemotherapy on the local recurrence in previously irradiated area and compared it to distant metastases outside the radiation field in that patient.

That study found that the proportion of women who responded to treatment was significantly lower for recurrences within the pelvic field compared with disease outside of the pelvic radiotherapy field

Due to the rarity of LRRC and the complexity of the optimal curative and palliative treatment, the treatment options for physicians in the Netherlands are relatively unknown. A multimodality approach can lead to a relatively good oncological outcome. On the other hand, even for patients with LRRC without curative options, there are several options to alleviate symptoms. In **chapter 11**, we have reviewed the current

literature to evaluate the outcome of the surgical treatment and explored the possibilities of both curative and palliative treatment of LRRC.

Summarizing, the treatment of rectal cancer has drastically improved over the last 3 decades. The treatment has shifted towards a more personalized treatment. LARC and LRRC represent a challenging group of patients who require a multimodality approach to achieve optimal oncological outcome. The current thesis aimed to further improve this multimodality treatment.

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