Long-term effects and quality of life after treatment for rectal cancer

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Chapter 1

General introduction and outline

Epidemiology

Cancer of the bowel is the second most prevalent type of cancer in males (15.8% of male cancers) and the third in females (13.0% of female cancers). The number of newly diagnosed rectal cancer patients in the Netherlands is growing every year.[1,2] In 1990, rectal cancer was found in 1730 patients, whereas 4357 rectal cancers were found in 2014. Since the highest incidence is found in patients over 60 years[2], the raising number of newly diagnosed rectal cancer patients is partly due to aging of the population. In addition, since colorectal cancer is, worldwide, most observed in North America, Oceania and Europe, lifestyle factors associated with a westernizing environment like obesity and physical inactivity are pointed out as important risk factors as well.[3]

Moreover, population screening led to more cancers being diagnosed at an earlier stage, resulting in improved survival; the one-year survival of patients with screening-detected tumours was 95.9% versus 79.6% in patients, who were not invited for screening.[4]

Besides the possibility to detect cancers in an earlier stage, outcome after treatment has improved, due to more advanced treatment techniques. All these developments have resulted in more patients surviving their rectal cancer; 51% of patients diagnosed between 1989-1993 were still alive at 5 years after diagnosis, whereas this percentage was 65% after 5 years for patients diagnosed between 2008-2012.[2] The increasing number of rectal cancer survivors, emphasizes the need for knowledge of health-related quality of life (HRQL) and treatment-related side effects, like sexual and bowel dysfunctioning.

Staging and prognosis

Rectal cancer is diagnosed by performing a colonoscopy, followed by histological confirmation of a tumour tissue biopsy. In the Netherlands, the staging of rectal tumours is based on the fifth Tumour Node Metastasis (TNM) staging system[5], which classifies tumour infiltration depth in surrounding tissue (T stage), lymph node involvement (N stage) and the presence of metastasis (M stage).[5] To assess the clinical TNM stage preoperatively, endorectal ultrasound is used to evaluate T stage in superficial (T1-2) tumours, whereas magnetic resonance imaging (MRI) is used to assess the T and N stage of the more extensive tumours., MRI is also used to determine invasion or proximity to the mesorectal fascia and sphincter complex and the presence of extra-mural vascular invasion. Metastases of rectal cancer are most frequently found in the liver or lungs. About as much as 23% of the newly diagnosed Dutch colorectal cancer patients in 2012 presented with metastasis at diagnosis.[6] To rule out metastasis at diagnosis, the use of computed tomography (CT) and a radiograph of the lungs are currently recommended. If CT is not able to confirm or exclude the presence of a metastasis, FDG PET-CT can be used.[1]

The pathological TNM stage (table 1 and figure 1) of the tumour plays an essential role in predicting the patients' prognoses, in particular the nodal status. Neo-adjuvant (preoperative) treatment can lead to downsizing and downstaging of the tumour, resulting in an improved pathological TNM stage and prognosis. Prognoses based on rectal cancer stage are displayed in figure 2, in which 10-year survival rates of rectal cancer patients in the Dutch population are shown.[2]

Table 1. Pathological staging system

TNM			Stage
TIS	N0	M0	0
T1-2	N0	M0	I
T3	N0	M0	IIa
T4	N0	M0	IIb
T1-2	N1	M0	IIIa
T3-4	N1	M0	IIIb
T1-4	N2	M0	IIIc
T1-4	N0-2	M1	IV

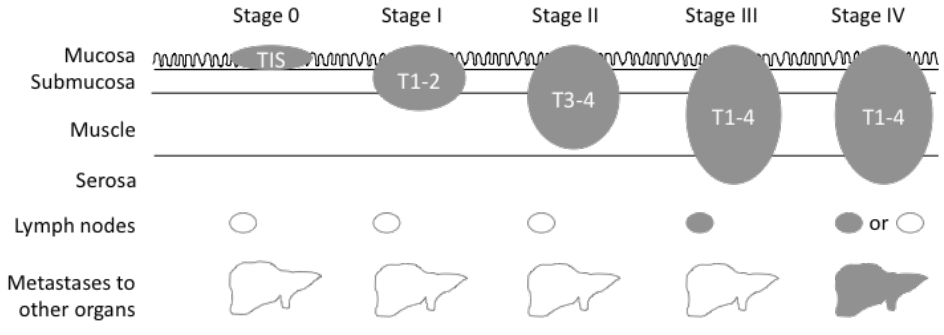

Figure 1. Pathological TNM Stage

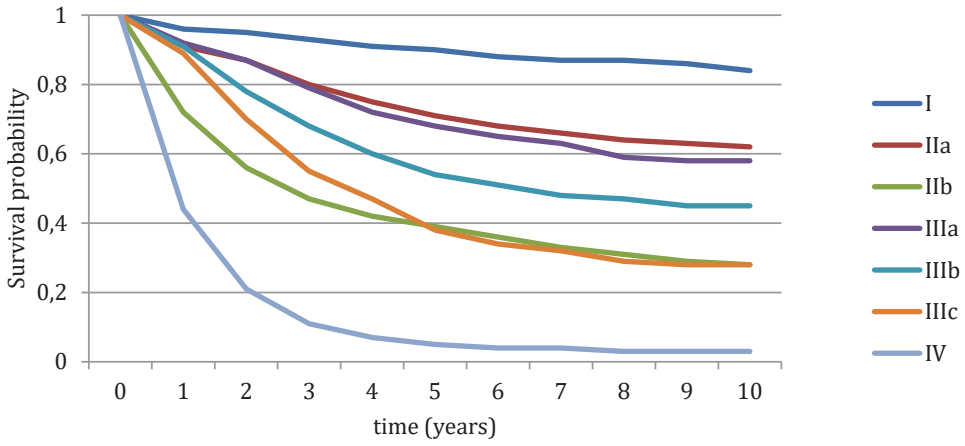

Figure 2. Survival by pathological TNM Stage[2]

Besides TNM stage, an important prognostic indicator for local and distant recurrence of rectal cancer is involvement of the circumferential resection margin (CRM).[7,8] The CRM is a surgically created margin that is assessed by the pathologists who can measure the distance between the tumour tissue and that margin. This margin can either be defined by the primary tumour or by an involved lymph node. According to the Dutch guidelines a CRM ≤1mm is considered positive.[1] Generally, a larger distance of tumour tissue from the mesorectal fascia, indicates a better prognosis,[8] whereas a tumour positive CRM indicates the presence of residual (microscopic) disease.

Treatment

Surgery

The first curative operation for rectal cancer was performed in 1908.[9] This radical abdominoperineal resection (APR) led to a decrease in local recurrence rates from almost 100% to 29%.[9] It became the standard treatment for rectal cancer patients. In the following century, treatment for rectal cancer developed enormously, ultimately resulting in the Total Mesorectal Excision (TME). With this technique a radical resection is achieved by a sharp dissection in the pelvis around the integral mesentery. The fatty lymphovascular tissue and the mesorectum surrounding the rectum are resected en bloc. Due to the

sharp dissection, the pelvic autonomic nerves are more presevered than with conventional surgery.[10] The intact mesorectum ensures a negative CRM in the majority of the patients.[8] Currently, most patients treated according to the TME principles undergo a low anterior resection (LAR) or an APR depending on the tumour location. In LAR the patients' sphincter is preserved, therefore the continuity of the bowel can be restored and no, or only a temporary, colostomy is needed. Low-lying rectal tumours require removal of the sphincters-complex with an APR, which consequently results in an end-colostomy.

Radiotherapy

Historically, in view of the high local recurrence rate in the pre-TME era, pre- or postoperative radiotherapy was applied frequently. Several randomised trials have defined the role of radiotherapy in the management of rectal cancer.[11-16]

In the randomized Swedish Rectal Cancer Trial increased local control was achieved by short-course radiotherapy prior to conventional surgery; a total dose of 25 Gy in 5 fractions followed by surgery within one week led to a local recurrence rate of 9%, compared to 26% in the surgery only group. Moreover, 13 years after treatment the overall survival was higher in the irradiated versus non-irradiated patients (38% vs. 30%).[11] To evaluate the role of radiotherapy after TME surgery, the Dutch TME trial was initiated. Between January 1996 and December 1999, a total of 1861 patients were randomly allocated to short-course pre-operative radiotherapy (PRT) followed by TME surgery or to TME surgery alone. PRT consisted of 5 fractions of 5 Gy delivered during 5-7 days. Surgery was performed according to the TME technique. Surgeons were trained at workshops and symposiums, watched educational videotapes, and were monitored by instructor surgeons. Moreover, pathologists were taught to determine the CRM following the protocol of Quirke et al.[7,12] When compared to results of conventional surgery, the standardized TME surgery resulted in a decrease of the local recurrence rate to 11%. The additional PRT reduced the local recurrence rates even further to 5% (figure 3). However, PRT did not translate into an improved overall survival; 48% after PRT+TME *vs.* 49% after TME (figure 4).[12,17] In contrast, in a subgroup analysis of patients with stage III tumours and a negative CRM, a significant improved overall survival was found (10-year survival 50% after TME+PRT and 40% after TME), as a result of a large benefit in local control after PRT.[17] This finding indicates that microscopic tumour tissue can still be present after adequate TME surgery and that PRT eradicates these remaining cancer cells in most cases.[18] Another strategy to reduce the risk

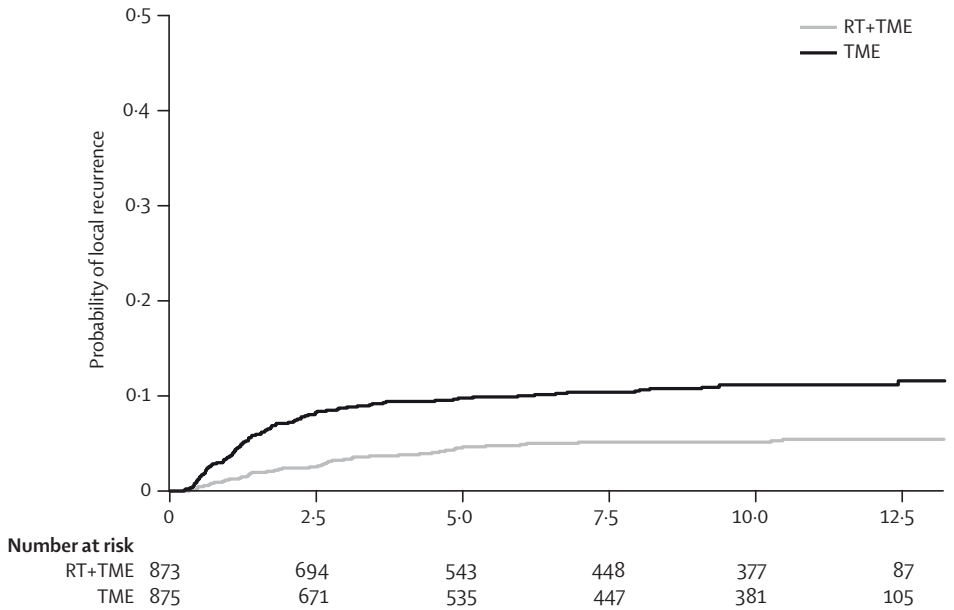

Figure 3. Local recurrence rates in the TME trial[17]

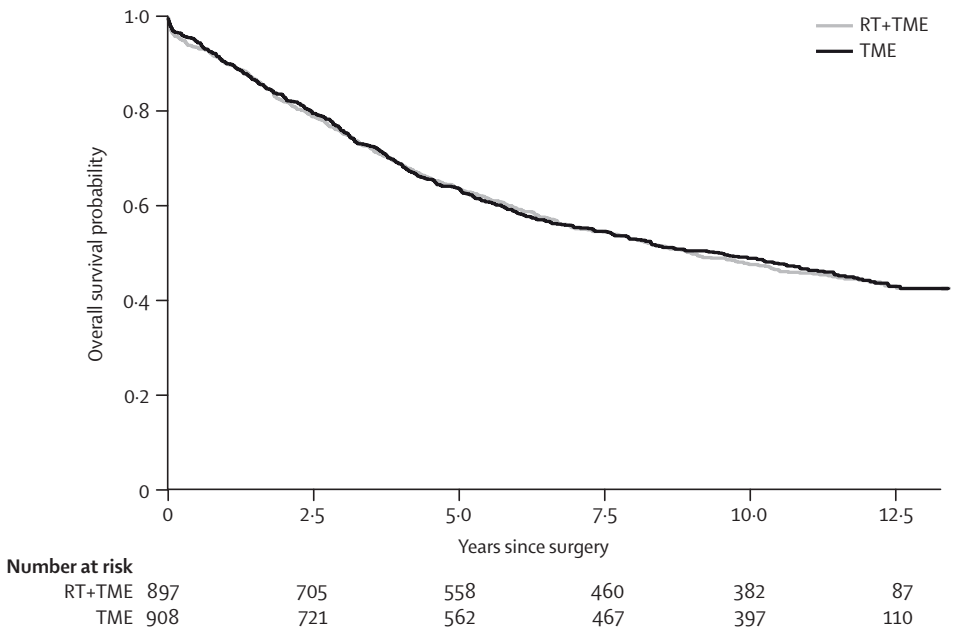

Figure 4. Overall survival in the TME trial[17]

of local recurrences is to provide selective postoperative chemoradiotherapy for patients with a positive CRM after TME surgery. In the CR07 trial this strategy was compared to preoperative PRT (5X5 Gy). In this large randomized controlled trial, including 1350 patients, less local recurrences and an improved disease-free survival were found after preoperative PRT, supporting the use of PRT.[13]

Given the high number of positive CRMs after TME surgery for large or irresectabel tumours, neo-adjuvant treatment is used to achieve downsizing and thereby downstaging of the tumour leading to a negative CRM. This can be accomplished by using preoperative long-term chemoradiotherapy (CRT), which is most often a combination of radiotherapy (45-50 Gy in daily fractions of 1.8-2.0 Gy) and oral capecitabine (825-1000 mg/m^2 for 5-7 days a week) followed by TME surgery after 8-12 weeks.[1] The addition of chemotherapy to long course radiation was investigated in the FFCD 9203, the EORTC 22921 trial and in a study performed by Braendengen et al. These randomised trials reported more downsizing and downstaging of the tumour, facilitating surgical resection with a negative CRM, resulting in an increased local control.[19-21] In the comparison of CRT and short-course PRT in two randomised trials, more downstaging and downsizing of the tumour after chemoradiotherapy was found, but this did not translate in a lower recurrence rate or an improvement of overall survival.[22,23] Currently, both CRT and short-course PRT are considered as standard treatment schedules, which are advocated in different parts of the world.[24]

Adverse treatment effects

Unfortunately, all curative treatment options for rectal cancer come at a price. Adverse events of surgery, and (chemo)radiotherapy are categorized into short- and long-term adverse events. Short-term adverse events occur during treatment, within 6 weeks after surgery or within 90 days after radiotherapy. Usually, patients recover from these,[25] whereas long-term adverse events are long-lasting and can remain for the rest of a patients live.

Measuring adverse effects

Different classification systems have been developed for clinicians to uniformly assess side effects. For example, to evaluated side effects after radiotherapy the

RTOG/EORTC Acute and Late Radiation Morbidity Scoring Scheme[26] and the LENT-SOMA score[27] are used. The Common Terminology Criteria for Adverse Events (CTCAE)[28] were originally used in the field of medical oncology, however nowadays also the other oncological specialists use this scale. Despite these scales, interpretation of low grade toxicity is not universally. For example, for low grade toxicity it is difficult to decide if the gastrointestinal function is altered or not. In spite of this, it must be noted that clear definitions are included for high grade toxicity leading to more universal and specific reporting of these more serious adverse events.

Furthermore, a substantial discrepancy exists between the perspective of the physician and the patient's experience. For example, for rectal cancer patients treated with sphincter-preserving surgery, physicians overestimated the impact of liquid fecal incontinence and frequent bowel movements on health-related quality of life and underestimated the influence of urgency and clustering.[29] Moreover, physicians underestimate the patient's degree of bother,[30] and the frequency of reporting adverse events by clinicians is consistently lower.[31] Therefore, symptoms and functioning reported by patients self are more representative compared to physicians' grading systems.

During the last decades the value of patient reported symptoms and HRQL is recognized and tools are developed to study these. The EORTC Quality of Life Department played a major role in enhancing research into HRQL of cancer patients. In 1987 this group developed the QLQ-C36. This questionnaire, containing 36 items, is cancer specific, multidimensional, easy to use for self-administration by patients, and applicable in several cultural settings. After a revision of this questionnaire, the QLQ-C30 was established in 1992.[32] The QLQ-C30 is a general cancer HRQL-questionnaire composed of 30 items, that can be combined in a global health status scale, functional scales, symptoms scales and a few single-item scales (table 2).[33] Several supplemental modules are designed in addition to the QLQ-C30 questionnaire to provide more detailed information for different tumour types. The QLQ-CR38 was designed to evaluate HRQL of colorectal cancer patients.[34,35] In 2007 the QLQ-CR38 was revised, resulting in a shorter questionnaire, the QLQ-CR29.[36,37] The core questionnaire and the additional modules are validated in many languages. With the development of these standardized questionnaires the EORTC strongly stimulates uniform HRQL research and also supports comparison of trial populations with general populations, since normative data for the QLQ-C30 are available for several countries.[38]

Table 2. QLQ-C30[33]

Items	Example of question on which item is based
Global health status	How would you rate you overall health during the past week?
Functional scales	
Physical functioning	Do you have any trouble taking a long walk?
Role functioning	Were you limited in doing either your work or other daily activities?
Emotional functioning	Did you worry?
Cognitive functioning	Have you had difficulty remembering things?
Social functioning	Has your physical condition or medical treatment interfered with your family life?
Symptom items	
Fatigue	Did you need to rest?
Nausea and vomiting	Have you felt nauseated?
Pain symptoms	Have you had pain?
Dyspnoea	Were you short of breath?
Insomnia	Have you had trouble sleeping?
Appetite loss	Have you lacked appetite?
Constipation	Have you been constipated?
Diarrhoea	Have you had diarrhoea?
Financial difficulties	Has you physical condition or medical treatment caused you financial difficulties?

Another questionnaire used in this thesis, is recently developed in Denmark to evaluate bowel function: the Low Anterior Resection Syndrome Score. This brief questionnaire composed of five questions measures the broad spectrum of symptoms related to the low anterior resection syndrome (LARS) like urgency, clustering and frequent bowel movements (table 3).[39]

Table 3. LARS Score[39]

Incontinence for flatus
Incontinence for liquid stool
Frequency of bowel movement
Clustering of stools
Urgency

Factors associated with surgery

Several surgical complications have been reported, such as infection and bleeding, but also anastomotic leakage after LAR, which is associated with high morbidity and mortality rates.[40] Furthermore, mortality rates are increased by a higher age at surgery and pre-existent comorbidity, especially cardiac and vascular disease.[41]

Urinary dysfunction is a long-term side effect. In the TME trial 38.1% of the patients reported urinary incontinence at five years after surgery, whereas 72.0% of these patients reported a normal urinary function before the resection.[42] Although urinary incontinence is a multifactorial problem, it was found to be mainly caused by surgery due to nerve damage.[42] This nerve damage also plays a role in sexual problems after rectal cancer treatment. In particular, an APR with extensive surgery in the narrow lower part of the pelvis, is shown to be a risk factor for male erectile dysfunction.[43-45] Other risk factors for sexual dysfunction in males are blood loss, anastomic leakage, radiotherapy and the presence of a stoma, whereas risk factors in females consist of radiotherapy and having a stoma. The finding that the presence of a stoma is a risk factor is indicative of the multidimensional aspects of sexual dysfunctioning, including psychological components.[46]

Until recently, it was assumed that patients with a stoma (after APR) would have a decreased health-related quality of life (HRQL) compared to patients without a stoma. Nevertheless, a Cochrane review was not able to draw firm conclusions concerning the better HRQL after LAR compared to APR surgery.[47] A possible explanation is the reduced HRQL of patients with major Low Anterior Resection Syndrome (LARS).[48]

This syndrome, arising after a LAR, consists of a combination of faecal incontinence, urgency and clustering. It is a result of the decreased maximal distension of the neo-rectum after resection,[49] in which a higher pressure develops even if only small faecal volumes are involved. This reduced capacity to act as a reservoir results in a higher stool frequency and clustering. Furthermore, the network of nerve endings in the anal canal, which differentiate liquid and solid stools from flatus, are partially compromised during the resection, adding to the development of faecal incontinence. Radiotherapy is an important risk factor for LARS and is described in more detail below.

Factors associated with radiotherapy

Short-term side effects of radiotherapy are mainly caused by cell death in highly proliferative tissues such as the mucosa or skin. This results in symptoms comparable with inflammatory effects, such as diarrhoea or a skin reaction. The majority of these symptoms resolve spontaneously during the first 6 weeks after treatment.[25]

Short-term side effects are more pronounced after chemoradiation. This is partly explained by the fact that adverse event are being obscured by the surgery following immediately after short-course radiation. In addition, chemotherapy adds systemic side effects such as leucopenia, nausea and vomiting,[25] and has effect on the mucosa as well.

The long-term side effects after radiotherapy are mainly caused by damage to the microvasculature and the formation of fibrosis in irradiated tissues. Subsequently the functioning of the supporting nerves, blood and lymph vessels is impaired, causing decreased functioning of the specific organ.[47] Compared to surgery alone, bowel and sexual functioning are decreased in irradiated rectal cancer patients.[50] Fibroses reduces the compliance of the remaining rectum, leading to an even more reduced capacity,[51] supporting a higher stool frequency and clustering. Furthermore, radiotherapy might also impair the myenteric plexus of the internal anal sphincter, which damages impuls conduction of the sacral and pudendal nerve.[52] Together with the fibrosis, this may lead to a weaker pelvic floor and anal sphincter and consequently resulting in more faecal leakage. With regard to the sexual dysfunction, radiotherapy may lead to fibrosis in female internal genitals and to atrophy and adhesions of the vagina as well.[53] The ovaries may also be impaired, resulting in a permanent menopause or in ovarian failure, which is associated with vaginal dryness and dyspareunia.[54] In males fibroses caused by radiotherapy might result in neuro- and vascular toxicity. Especially vascular toxicity of the cavernous arteries may lead to erectile dysfunction.[55] Furthermore, radiation can also lead to dry ejaculation as a result of damage to the seminal vesicles and to permanent testicular dysfunction resulting in increased the levels of gonadotropine and decreased testosteron levels.[56]

Another long-term concern after radiotherapy treatment, especially for patients with a young age at diagnosis, is the development of a second cancer. A second cancer is a new primary cancer that originates in a primary site or tissue and is not an extension, nor a recurrence, nor a metastasis.[57] The existing literature is conflicting about the relation of radiotherapy for the treatment of rectal cancer and the development of second cancers. An increased risk of developing a second cancer after radiotherapy was found in a study based on the Uppsala trial and Swedish Rectal Cancer Trial,[58] however a study based on the Surveillance,

Epidemiology and End Results (SEER) Registry found no differences in second cancer risk after rectal cancer treatment.[59] Moreover, in a large study, including 647 672 SEER Registry patients with different primary cancers, only 8% of the second cancers were found to be attributable to radiotherapy.[60]

Aims and outline of this thesis

The aim of this thesis was to evaluate long-term effects after radiotherapy for rectal cancer. Previous studies, which investigated treatment-related effects until 5 years, reported more bowel and sexual dysfunction in irradiated patients compared to patients who underwent surgery alone.[54,61-63] Only a few studies assessed HRQL after 5 years, demonstrating still more bowel dysfunction after radiation up to 10 years after the diagnosis of rectal cancer. [52,64-66] In **chapter 2** HRQL is assessed at 14 years after rectal cancer treatment in the TME trial, in which patients were randomly allocated to PRT followed by TME or TME alone. Furthermore, to provide an outline for patients on what to expect of their HRQL until 14 years after treatment, a comprehensive longitudinal overview is given in **chapter 3**. Since these chapters are based on long-term data of the TME trial, no patients who underwent chemoradiotherapy were included. Like short-course radiotherapy, long-course chemoradiotherapy decreased local recurrence rates, without leading to a benefit in overall survival.[13,17,19,67-69] This fact underlines the necessity of knowledge of long-term treatment related effects and HRQL after chemoradiotherapy as well. Therefore, patient reported HRQL of chemoradiotherapy is compared to short-course radiotherapy in **chapter 4**. In these chapters patients in all treatment groups reported bowel dysfunction. Therefore, bowel function of TME trial patients was assessed more in detail in **chapter 5** using the LARS Score. In addition, the association of severe LARS with HRQL was examined.

Another long-term concern after radiotherapy is the development of second cancers. Since second cancers are scarce and develop after a long period, a large trial cohort with a long follow-up time is needed to study the risk of second cancers. For this purpose the TME trial, the PORTEC-1 (Post Operative Radiation Therapy in Endometrial Carcinoma 1)[70] and PORTEC-2[71] study were combined to create a large pooled trial cohort of patients randomised between treatment with or without radiotherapy. Results of this cohort including over 2500 patients are reported in **chapter 6**. Finally, in **chapter 7** a general discussion of the data presented in this thesis is provided.

References

1. Colorectaal carcinoom. Oncoline, beheerd door IKNL. © October 2015.
2. Nederlandse Kankerregistratie, beheerd door IKNL © October 2015.
3. Center MM, Jemal A, Smith RA, Ward E. Worldwide variations in colorectal cancer. *CA* 2009; 59(6): 366-78.
4. Morris EJ, Whitehouse LE, Farrell T, et al. A retrospective observational study examining the characteristics and outcomes of tumours diagnosed within and without of the English NHS Bowel Cancer Screening Programme. *British journal of cancer* 2012; 107(5): 757-64.
5. Sobin LH, Wittekind Ch.; editors. UICC TNM Classification of malginant tumours. 5th ed. New York: John Wiley & Sons; 1997: 66-9.
6. Elferink MAG, Vlugt van der M, Meijer GA, Lemmens VEPP, Dekker E. Colorectaal Carcinoom in Nederland. *Ned Tijdschr Geneesd* 2014; 158(A7699): 1-6.
7. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. *Lancet* 1986; 2(8514): 996-9.
8. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? *Journal of clinical oncology* 2008; 26(2): 303-12.
9. Miles EW. A method of performing abdomino-perineal excision for carcinoma of the rectum and of the terminal portion of the pelvic colon *Lancet* 1908; 2: 1812-3.
10. Heald RJ. A new approach to rectal cancer. *British journal of hospital medicine* 1979; 22(3): 277-81.
11. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *Journal of clinical oncology* 2005; 23(24): 5644-50.
12. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *The New England journal of medicine* 2001; 345(9): 638-46.
13. Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 2009; 373(9666): 811-20.
14. Wong RK, Tandan V, De Silva S, Figueredo A. Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma. *Cochrane database of systematic reviews* 2007; (2): Cd002102.
15. De Caluwe L, Van Nieuwenhove Y, Ceelen WP. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. *Cochrane database of systematic reviews* 2013; (2): Cd006041.
16. McCarthy K, Pearson K, Fulton R, Hewitt J. Pre-operative chemoradiation for non-metastatic locally advanced rectal cancer. *Cochrane database of systematic reviews* 2012; 12: Cd008368.

17. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *The lancet oncology* 2011; 12(6): 575-82.
18. Marijnen CA, Glimelius B. The role of radiotherapy in rectal cancer. *European journal of cancer* 2002; 38(7): 943-52.
19. Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *Journal of clinical oncology* 2006; 24(28): 4620-5.
20. Bosset JF, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *The lancet oncology* 2014; 15(2): 184-90.
21. Braendengen M, Tveit KM, Berglund A, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. *Journal of clinical oncology* 2008; 26(22): 3687-94.
22. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. *Journal of clinical oncology* 2012; 30(31): 3827-33.
23. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *The British journal of surgery* 2006; 93(10): 1215-23.
24. Glynne-Jones R, Tan D, Moran BJ, Goh V. How to Select for Preoperative Short-course Radiotherapy, While Considering Long-course Chemoradiotherapy or Immediate Surgery, and Who Benefits? *European Oncology & Haematology* 2014; 10(1): 17-24.
25. Ooi BS, Tjandra JJ, Green MD. Morbidities of adjuvant chemotherapy and radiotherapy for resectable rectal cancer: an overview. *Diseases of the colon and rectum* 1999; 42(3): 403-18.
26. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *International journal of radiation oncology, biology, physics* 1995; 31(5): 1341-6.
27. Rubin P, Constine LS, Fajardo LF, Phillips TL, Wasserman TH. RTOG Late Effects Working Group. Overview. Late Effects of Normal Tissues (LENT) scoring system. *International journal of radiation oncology, biology, physics* 1995; 31(5): 1041-2.
28. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, June 2010, National Institutes of Health, National Cancer Institute.
29. Chen TY, Emmertsen KJ, Laurberg S. Bowel dysfunction after rectal cancer treatment: a study comparing the specialist's versus patient's perspective. *BMJ open* 2014; 4(1): e003374.
30. Rodriguez LV, Blander DS, Dorey F, Raz S, Zimmern P. Discrepancy in patient and physician perception of patient's quality of life related to urinary symptoms. *Urology* 2003; 62(1): 49-53.
31. Gilbert A, Ziegler L, Martland M, et al. Systematic Review of Radiation Therapy Toxicity Reporting in Randomized Controlled Trials of Rectal Cancer: A Comparison of Patient-Reported Outcomes and Clinician Toxicity Reporting. *International journal of radiation oncology, biology, physics* 2015; 92(3): 555-67.
32. Bjordal K, Kaasa S. Psychometric validation of the EORTC Core Quality of Life Questionnaire, 30-item version and a diagnosis-specific module for head and neck cancer patients. *Acta oncologica* 1992; 31(3): 311-21.
33. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 1993; 85(5): 365-76.
34. Sprangers MA, Velde te A, Aaronson NK, Hopwood P, Haes de HC, Kuchler Th. The construction of a Colorectal Cancer Module. *EORTC Study Group on Quality of Life* 1992.
35. Sprangers MA, te Velde A, Aaronson NK. The construction and testing of the EORTC colorectal cancer-specific quality of life questionnaire module (QLQ-CR38). European Organization for Research and Treatment of Cancer Study Group on Quality of Life. *European journal of cancer* 1999; 35(2): 238-47.
36. Whistance RN, Conroy T, Chie W, et al. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer. *European journal of cancer* 2009; 45(17): 3017-26.
37. Gujral S, Conroy T, Fleissner C, et al. Assessing quality of life in patients with colorectal cancer: an update of the EORTC quality of life questionnaire. *European journal of cancer* 2007; 43(10): 1564-73.
38. Fayers PM. Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. *European journal of cancer* 2001; 37(11): 1331-4.
39. Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. *Annals of surgery* 2012; 255(5): 922-8.
40. den Dulk M, Noter SL, Hendriks ER, et al. Improved diagnosis and treatment of anastomotic leakage after colorectal surgery. *European journal of surgical oncology* 2009; 35(4): 420-6.
41. van Gestel YR, Lemmens VE, de Hingh IH, et al. Influence of comorbidity and age on 1-, 2-, and 3-month postoperative mortality rates in gastrointestinal cancer patients. *Annals of surgical oncology* 2013; 20(2): 371-80.
42. Lange MM, Maas CP, Marijnen CA, et al. Urinary dysfunction after rectal cancer treatment is mainly caused by surgery. *The British journal of surgery* 2008; 95(8): 1020-8.

43. Hendren SK, O'Connor BI, Liu M, et al. Prevalence of male and female sexual dysfunction is high following surgery for rectal cancer. *Annals of surgery* 2005; 242(2): 212-23.
44. Heald RJ, Karanjia ND. Results of radical surgery for rectal cancer. *World journal of surgery* 1992; 16(5): 848-57.
45. Santangelo ML, Romano G, Sassaroli C. Sexual function after resection for rectal cancer. *American journal of surgery* 1987; 154(5): 502-4.
46. Lange MM, Marijnen CA, Maas CP, et al. Risk factors for sexual dysfunction after rectal cancer treatment. *European journal of cancer* 2009; 45(9): 1578-88.
47. Pachler J, Wille-Jorgensen P. Quality of life after rectal resection for cancer, with or without permanent colostomy. *Cochrane database of systematic reviews* 2012; 12: Cd004323.
48. Emmertsen KJ, Laurberg S. Impact of bowel dysfunction on quality of life after sphincter-preserving resection for rectal cancer. *The British journal of surgery* 2013; 100(10): 1377-87.
49. Varma JS, Smith AN, Busuttil A. Correlation of clinical and manometric abnormalities of rectal function following chronic radiation injury. *The British journal of surgery* 1985; 72(11): 875-8.
50. Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. Late adverse effects of radiation therapy for rectal cancer - a systematic overview. *Acta oncologica* 2007; 46(4): 504-16.
51. Ziv Y, Zbar A, Bar-Shavit Y, Igov I. Low anterior resection syndrome (LARS): cause and effect and reconstructive considerations. *Techniques in coloproctology* 2013; 17(2): 151-62.
52. Pollack J, Holm T, Cedermark B, Holmstrom B, Mellgren A. Long-term effect of preoperative radiation therapy on anorectal function. *Diseases of the colon and rectum* 2006; 49(3): 345-52.
53. Grigsby PW, Russell A, Bruner D, et al. Late injury of cancer therapy on the female reproductive tract. *International journal of radiation oncology, biology, physics* 1995; 31(5): 1281-99.
54. Bruheim K, Tveit KM, Skovlund E, et al. Sexual function in females after radiotherapy for rectal cancer. *Acta oncologica* 2010; 49(6): 826-32.
55. Morgentaler A. Male impotence. *Lancet* 1999; 354(9191): 1713-8.
56. Bruheim K, Svartberg J, Carlsen E, et al. Radiotherapy for rectal cancer is associated with reduced serum testosterone and increased FSH and LH. *International journal of radiation oncology, biology, physics* 2008; 70(3): 722-7.
57. International rules for multiple primary cancers (ICD-0 third edition). *European Journal of Cancer prevention* 2005; 14: 307-8.
58. Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. Occurrence of second cancers in patients treated with radiotherapy for rectal cancer. *Journal of clinical oncology* 2005; 23(25): 6126-31.

59. Kendal WS, Nicholas G. A population-based analysis of second primary cancers after irradiation for rectal cancer. *American journal of clinical oncology* 2007; 30(4): 333-9.
60. Berrington de Gonzalez A, Curtis RE, Kry SF, et al. Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. *The lancet oncology* 2011; 12(4): 353-60.
61. Bruheim K, Guren MG, Dahl AA, et al. Sexual function in males after radiotherapy for rectal cancer. *International journal of radiation oncology, biology, physics* 2010; 76(4): 1012-7.
62. Peeters KC, van de Velde CJ, Leer JW, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients--a Dutch colorectal cancer group study. *Journal of clinical oncology* 2005; 23(25): 6199-206.
63. Stephens RJ, Thompson LC, Quirke P, et al. Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: data from the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 randomized clinical trial. *Journal of clinical oncology* 2010; 28(27): 4233-9.
64. Pollack J, Holm T, Cedermark B, et al. Late adverse effects of short-course preoperative radiotherapy in rectal cancer. *The British journal of surgery* 2006; 93(12): 1519-25.
65. Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. *Journal of clinical oncology* 2005; 23(34): 8697-705.
66. Thong MS, Mols F, Lemmens VE, et al. Impact of preoperative radiotherapy on general and disease-specific health status of rectal cancer survivors: a population-based study. *International journal of radiation oncology, biology, physics* 2011; 81(3): e49-58.
67. Local recurrence rate in a randomised multicentre trial of preoperative radiotherapy compared with operation alone in resectable rectal carcinoma. Swedish Rectal Cancer Trial. *The European journal of surgery* 1996; 162(5): 397-402.
68. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *The New England journal of medicine* 2006; 355(11): 1114-23.
69. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *Journal of clinical oncology* 2012; 30(16): 1926-33.
70. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. *Lancet* 2000; 355(9213): 1404-11.
71. Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. *Lancet* 2010; 375(9717): 816-23.