Long-term patient-reported outcomes after high-dose chemoradiotherapy for non-surgical management of distal rectal cancer

Organ preservation in rectal cancer

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Conflict of interest

The authors report no conflicts of interest

SUMMARY

Previous evidence suggests that organ preservation after chemoradiotherapy for low rectal cancer might be a safe strategy for select patients. Data on functional outcome and quality of life is sparse, however. Based on prospectively collected data and with long follow-up, we report excellent functional outcome and good quality of life scores after high-dose chemoradiotherapy, using validated patient reported questionnaires.

ABSTRACT

Background: Surgery is standard treatment for rectal cancer, but neoadjuvant chemoradiotherapy (CRT) may result in clinical complete response (cCR) in select patients, allowing for non-surgical management (NSM). Prospective studies of NSM strategies are sparse however, and long-term data on quality of life (QoL) are limited. We conducted a single-arm phase II trial of high-dose CRT for NSM of distal rectal cancer; we report secondary long-term patient-reported outcomes (PROs), local regrowth and overall survival (OS) in patients managed non-surgically.

Methods: Fifty-one patients with resectable, T2 or T3, N0–N1, low adenocarcinoma received 65Gy (IMRT, brachytherapy boost) and oral tegafur-uracil. Patients with cCR 6 weeks after treatment (clinical examination, MRI, biopsy) were referred for observation, and followed closely with clinical examinations, endoscopies, PET-CTs, and PROs for 5 years. Overall colorectal cancer specific QoL and specific symptom scores were evaluated at baseline and in follow up, and compared between timepoints. Local regrowth was estimated using cumulative incidence; overall survival using Kaplan-Meier estimates.

Results: Forty patients achieved cCR after treatment; 29 were in follow-up at 24m, 21 at 36m, 20 at 60m. PRO questionnaire completion rates were 90% at 24 months, 100% at 36m, and 85% at 60m, respectively, for patients still in follow-up. Average QoL score did not differ between baseline (median 11.1) and 24m (13.7), 48m (11.1,) or 60m (6.9). Only rectal bleeding deteriorated from baseline, with bowel and bladder related symptom scores otherwise unchanged in follow-up. At median follow-up of 5.0 years, local regrowth rate and OS were 31% (95 CI 15%-47%) and 85% (95 CI 75%-97%), respectively.

Conclusion: Long term follow-up after NSM of distal rectal cancer showed excellent general colorectal cancer QoL and local symptom scores. Our study results indicate that high dose CRT followed by organ preservation might be an alternative to standard treatment.

INTRODUCTION

The last decades have seen a steady improvement in survival for patients with colorectal cancer.[1] Development of surgical procedures, treatment centralization, and the introduction of neoadjuvant chemoradiotherapy (CRT) have all been essential in this development.[2] Specifically, the introduction of total mesorectal excision (TME) in the 1980s has had major impact on outcomes. However, despite the improved survival rates, TME surgery is still associated with postoperative complications and long term impairment of quality of life, especially when combined with neoadjuvant treatment.[3,4]

More recently, it has become apparent that non-surgical management (NSM) might be an option in select patients who achieve clinical complete response (cCR) after CRT.[5] This organ preserving approach was initially promoted by Habr Gama et al.[6], with several subsequent publications demonstrating promising outcomes.[5,7,8,9] This has primarily been practiced as an "opportunistic" treatment strategy in patients with locally advanced rectal cancer undergoing standard neoadjuvant CRT, however. Prospective studies of dedicated NSM strategies have been sparse, especially for early rectal cancers. Consequently, there has been a lack of long-term longitudinal follow-up data on functional outcome and quality of life, especially using patient reported outcome (PRO) measures.

We here report long-term outcomes after high dose CRT followed by an organ preserving approach for low rectal cancer, focusing on PROs at baseline and during follow-up.

METHODS

Patients

We conducted a prospective trial in a single Danish tertiary cancer center, with a thorough description of the trial protocol to be found in the primary study publication.[5] Briefly, patients interested in organ preservation were referred from surgical departments throughout Denmark, and were enrolled in the trial prior to chemoradiotherapy. Patients were eligible if they had primary resectable T2-T3 adenocarcinoma of the rectum, within 6 cm of the anal verge, with no or limited lymph node involvement (1-3 mesorectal lymph nodes in the proximity of the tumor only) and planned for abdominoperineal resection. Diagnosis and stage were confirmed with pelvic MRI, transrectal ultrasound imaging, CT of thorax and abdomen, PET-CT, endoscopy with biopsy, and clinical examination.

Treatment

Patients were treated with long course radiotherapy (60 Gy in 30 fractions to the tumor and 50 Gy in 30 fractions to elective lymph nodes, delivered with simultaneous integrated boost) with concomitant chemotherapy (tegafur-uracil 300mg/m2). A high dose rate (HDR) brachytherapy boost (5 Gy) was delivered to the tumor in the final week of CRT; using an

endorectal applicator with dose prescribed 1cm from the applicator surface. Response to treatment was evaluated by MRI, digital rectal examination and endoscopy with tumor site biopsies 6 weeks after the end of CRT. Patients with insufficient response were referred to surgery, while those with no signs of remaining disease were allocated for watchful waiting (WW). This report focuses exclusively on outcomes for these latter patients.

Follow up

Patients included in the WW cohort were followed by clinical examination and endoscopy every 2 months the first year, every 3 months the second year, every 6 months the third year and 12 months the fourth and fifth year; with additional PET-CT thrice the first year, twice the second year, and once yearly thereafter.

Quality of life

Toxicity, functional outcome and quality of life (QoL) were evaluated with PRO measures using the QLQ-CR29 module from the European Organisation for Research and Treatment of Cancer (EORTC). EORTC developed the colorectal QoL module QLQ-CR38 for evaluation of new treatments. This was later revised to the shorter QLQ-CR29 and validated in an international study.[10] The QLQ-CR29 consists of 29 items; 12 items addressing gastrointestinal and urinary symptoms, 6 addressing mental health, separate modules addressing anorectal function for participants with or without stoma, and separate modules addressing sexual function in men and women. Overall QoL was assessed with an average, rescaled symptom score (all questions except for sexual function items, rescaled to 0-100, as per the standard EORTC questionnaire data analysis guideline). Items especially relevant for this patient group were selected for further analysis (question 31, 33, 36, 38, 49, 50, 52, 53**).**

Patients completed QLQ-CR29 before and after CRT, at 6 and 12 months, and every year thereafter. Questionnaires were completed by patients prior to clinical appointments in the clinic waiting area, and were distributed and collected by dedicated endoscopy nursing staff. Patients were followed for QoL up to 5 years after referral to observation, but left QoL follow-up if they underwent pelvic surgery (for local tumor regrowth or new primary cancer) or initiated systemic anticancer treatment (for either rectal cancer or new primary cancer). Patients treated with non-pelvic local treatment (surgery, radiotherapy) for rectal cancer recurrence or new primary cancer (e.g. lung resections) were kept on QoL follow-up.

Data analysis

Overall scores on the QLQ-CR29 symptom scales (i.e. per-patient average scores) were reported as group medians at relevant time points, and were assessed across time points using Wilcoxon signed-rank and rank-sum tests for paired and unpaired comparisons, respectively. For select individual symptom scores, descriptive reporting consisted of proportions and absolute numbers at each time point. For the estimate of cumulative

incidence of local tumor regrowth, local failure was recorded when biopsies confirmed tumor regrowth in the rectal wall, and patients were censored for local control in case of non-cancer death, new primary cancer, or uncontrolled metastatic disease. Overall survival was estimated using death from all causes as events, with survival tracked through the Danish national civil registration system. Standard actuarial estimates were used for both oncological outcome measures. Data cutoff for the current report was February 2019. The study is registered with ClinicalTrials.gov, and was approved by the regional scientific ethical committee for Southern Denmark . All patients provided oral and written informed consent for experimental treatment.

RESULTS

Between October 20, 2009, and December 23, 2013, 55 patients were enrolled on trial, with 51 patients found eligible for organ preservation strategy at baseline investigations prior to treatment. After high-dose chemoradiotherapy, 40 patients were classified as complete responders (sixteen T2N0, seven T2N1, seven T3N0, and ten T3N1) and selected for observation. Patients were predominantly men (80%), in good performance status, and with small tumors (Table 1).

Median follow up for local tumor regrowth was 60 months (IQR 42-72). Twelve patients had local regrowth, with eleven patients undergoing salvage TME surgery. One patient had metastatic disease at the time of detection. Cumulative local regrowth at 2 years was 25.2% (95% CI 10.4-37.9%); 25.2% (95% CI 10.4-38.1%) at 3 years and 30.9% (95% CI 14.6-47.0%) at 5 years (Figure 1). Seven patients developed distant metastases; four of these patients with a synchronous, biopsy verified, local regrowth of the rectal cancer. Metastases to the lung were found in six patients, while only one patient had metastasis to the liver. Six patients developed a new primary cancer (one prostate-, one upper gastrointestinal-, two breast and two pulmonary cancers). After a median follow up of 78 months (IQR 42-72) six patients died of metastatic disease (one synchronous with local regrowth, two after surgery) and one due to a new primary cancer. Overall survival at 2, 3 and 5 years were 100%, 95% (95% CI 88.6-100%), and 85% (95% CI 74.8-96.8%), respectively (Figure 1).

The vast majority of patients in follow-up completed QoL assessment, with completion rates of 90% at 24 months, 95% at 36 months, 100% at 48 months, and 85% at 60 months; although some individual items (especially for bowel function) had slightly lower data compliance (Table A1, supplementary material, online only). Patient-reported functional outcome was generally stable throughout the period without worsening of symptoms in follow-up, relative to baseline (Figure 2). Faecal continence was excellent, with only two patients reporting severe (“quite a bit” or “very much”) faecal incontinence at 24 months. No patients reported faecal incontinence at 48 and 60 months. Bowel movement was good: no patients reported symptoms during night, while severe bowel movement during daytime was

reported by 4 (17%) out of 24 at 24 months, and 2 (13%) out of 15 at 48 months and 2 (13%) out of 16 at 60 months. Rectal bleeding was the only reported toxicity which seemed to deteriorate, especially at the 2-year time-point; with 21 (81%) out of 26 patients reporting bleeding of any severity and 7 (27%) reporting "quite a bit" or "very much" at 24 months. Twelve patients (60%) reported bleeding of any severity at 48 months and seven (49%) at 60 months; although only 4 (20%) and 2 (12%) patients reported severe symptoms at 48 and 60 months, respectively. Bleeding was manageable, although two patients needed blood transfusions, and another small subset of patients were treated with argon beaming or formaldehyde application. See Table A1 in the supplementary material for full data for eight select symptom scores related to bladder and bowel function (questions 31, 33, 36, 38, 49, 50, 52, 53 on QLQ-CR29).

Overall scores on the QLQ-CR29 symptom scales (all questions except for number 56 for men and 58 for women) showed little variation over time. Median score at baseline (n=38) was 9.7 (IQR 6.9-14.3), median score at 2 years (n=26) was 13.7 (IQR 5.9-19.1), at 4 years (n=21) was 10.1 (IQR 5.6-16.7) and at 5 years (n=17) was 6.9 (IQR 5.6-11.1). The overall score at 5 years was significantly better than at baseline (p=0.05) on unpaired group comparison, with all other time-points demonstrating no statistically significant change from baseline.

The median per patient change in QoL symptom score compared to baseline was 0.3 (IQR -4.2-8.3) at 24 months (n=24), -1.8 (IQR -4.9-7.0) at 48 months (n=19) and -3.0 (-4.5-2.8) at 60 months (n=16) (Figure 3). None of these were significantly different from zero on paired comparisons.

DISCUSSION

We here report unique data for prospectively collected long-term PROs after high dose CRT followed by an organ preserving approach. We found little variation over time in overall scores on the QLQ-CR29 symptom scales. Although the overall symptom score apparently improved in long term follow-up (significant at 5 years), the individual change in QoL compared to baseline was not significant at any time-point. Patient reported functional outcome was generally stable through the period and specific functional scores did not deteriorate except for rectal bleeding. Faecal continence was excellent with no patients reporting symptoms at long term follow-up (4 and 5 years).

We found a local regrowth rate of 25.2% at 3 years and 30.9% at 5 years, which is consistent with previous publications on patients with rectal cancer offered "opportunistic" watch and wait. A recent publication from the International Watch and Wait Database (IWWD) reported on outcomes from 880 patients, with a regrowth rate of 25.2% at 2 years[11], in line with a large literature-based meta-analysis[9]. There is generally a lack of long-term data beyond three years; but our 5-year local regrowth rate of 31% is comparable to the 31% reported at 5 years

of follow up by Habr-Gama et al[12]. It is encouraging that the high initial response rate does indeed appear to translate into high rate of overall local control without excess local tumor regrowth.

These publications provide a growing body of evidence that an organ preserving approach seems oncologically safe, and that salvage surgery is still an option in patients with local regrowth without comprising long-term outcome. It consequently becomes paramount to demonstrate that patients offered non-surgical management also achieve good long term QoL and rectal function. This is especially vital for rectal cancer patients where CRT is not part of the standard treatment strategy, and when intensified treatment regimens are used as part of a dedicated organ preservation approach.

Few studies so far have paid attention to functional outcome after chemoradiotherapy followed by NSM. It is well-established that patients receiving conventional tri-modality treatment may suffer from low anterior resection syndrome (LARS). Forty-six percent report major LARS even after 14 years, and patients who received (chemo-)radiation generally score worse compared to patients treated with surgery, except for incontinence for flatus. Patients with major LARS also report worse scores on EORTC-QLQ questionnaires.[3] To date few studies have collected long-term PROs in rectal cancers managed with a watch and wait strategy, and none have done so prospectively with baseline measures. The limited data available indicate that an organ-preserving approach may provide better functional outcomes. In a matched controlled study by Hupkens et al., better QoL and fewer defecation (major LARS; WW 35.9% vs. TME 66.7%) and urinary tract problems were seen in patients followed with observation compared to patients who underwent TME.[13] Others have examined the combination of chemoradiotherapy and transanal endoscopic microsurgery (TEM) compared to TME. One prospective trial reports good functional outcome and QoL after TEM using the Faecal Incontinence Severity Index (FISI) and Functional Assessment of Cancer Therapy - Colorectal (FACT-C) questionnaires.[14] However, comparison of WW patients with patients undergoing TEM by the Habr-Gama group favored the first procedure in regard to symptoms and QoL.[8,15]

We report good functional outcome, with excellent continence after 5 years, with no patients reporting incontinence at late follow-up. Van der Sande et al. report a tendency towards decreased rectal function for patients receiving higher radiation dose to the anal canal.[16] Given the distal position of the cancers included in the study and the very high tumor doses, with resulting high doses potentially delivered to the anal canal, it is possibly surprising that general bowel and rectal symptoms did not deteriorate relative to baseline. Only rectal bleeding symptoms deteriorated, but – as discussed in the primary trial publication - this may likely be explained by the brachytherapy boost, delivering very high radiation doses to the rectal mucosa. Bleeding was manageable with either argon beaming or formaldehyde; however two patients did require blood transfusions. The ongoing multicenter WW2 trial uses external beam boost only, to avoid this complication. The trial is expected to close Oct

2019, with enrollment of 105 patients planned. Patients are treated with 50.4Gy/28 fractions to elective lymph nodes and 62Gy/28 fractions with concomitant boost to the tumor volume. Concomitant capecitabine 825mg/m2 x 2 is given on treatment days. Long-term side effects are registered by means of CTCAE, LARS score and EORTC QLQ-C30 and QLQ-CR29.

When developing future radiotherapy-based organ-preservation strategies, one might have to consider new organs at risk in treatment optimization. These will not traditionally have been on the radar for rectal cancer radiotherapy planning. To do so will require careful collection of toxicity and functional outcome data, to develop dose constraints and optimization objectives. Another aspect to be considered, for patient selection and treatment optimization, is the group of patients who are candidates for rectal sparing surgical procedures up-front, such as ultra-low resection. These patients might lose the opportunity for organ preservation in case of local regrowth requiring APR after initial non-surgical approach.

The current trial used PROs as the primary instrument for measurement of long-term treatment-related toxicity. Reporting of PROs is sparse in the rectal cancer radiotherapy literature, in spite of evidence suggesting that relying on clinician-reported outcomes results in underestimation of symptoms. Gilbert et. al reviewed all phase 2 and 3 randomized controlled trials for resectable rectal cancer receiving preoperative chemotherapy or chemoradiation[17]. Grade >3 bowel toxicities were reported at rates from 1.4 to 9%. Faecal incontinence and diarrhea were reported at rates of approximately 9%. Using PROs, faecal incontinence rates varied between 8 and 50% for solid stools and from 24 to 72% for liquid stools. None of the studies of clinician-reported outcomes mentioned sexual dysfunction, which was reported at rates of 70-80% and 41-52% in men and women, respectively, with PROs. Studies of clinician-reported outcomes seemed to exclusively focus on severe adverse symptoms, and different symptoms related to one organ were grouped as one. This can lead to an underestimation of symptoms; and even mild grade symptoms may be experienced as serious by patients in their impact on daily living.

We observed very high questionnaire completion rate in our study, supporting the robustness of the reported results. Questionnaire administration relied on dedicated clinical staff, however, and might not be sustainable in standard clinical practice. Gilbert et al. report higher response rates when electronic PROs were used instead of paper-based, which should be explored further, as this might also alleviate logistical challenges with paper-based forms. Another strength of the current study is the prospective nature, with baseline scores available for nearly all patients. This reduces confounding of other conditions which might be present prior to treatment, including general age-related functional problems.

With the intention to keep the patient burden as low as possible and encourage high completion rates, only one PRO questionnaire was administered. There is no doubt that our results in terms of QoL and anorectal function could have been strengthened by administration of further questionnaires besides the QLQ-CR29. The scale in the QLQ-CR29 is graded from “not at all” to “very much”, which is subject to individual interpretation, while e.g.

the faecal incontinence severity index (FISI) has specific questions regarding objective symptoms, such as frequency. However, the FISI score lacks assessment of impact of symptoms on patients' overall wellbeing. The low anterior resection syndrome (LARS) score, which was still under development at the time of design of the current trial, also focuses on bowel symptoms; and has by now been extensively validated.[18] The Functional Assessment of Cancer Therapy - Colorectal (FACT-C) questionnaire includes items on psychological impact and might thus have an advantage in terms of assessing emotional aspects of QoL.[19] The fecal incontinence quality of life (FIQL) scale focuses as well on the impact symptoms may have on daily living.[20] Any future studies in this space should consider administering at least a subset of these questionnaires. The challenge remains, however, that the questionnaire instruments summarized here have all been developed for the post-operative setting, and they may not be valid for assessment of functional outcome after non-surgical management.

The study limitations include the small patient numbers and the non-standard treatment regimen. Secondarily, for patients who had regrowth and were referred to surgery, we have no PRO data after salvage surgery. These patients might have experienced additional morbidity not captured here. Given the high questionnaire completion rate, and the absence of severe functional problems in follow-up, the current data supports the safety in terms of functional outcome of a (chemo-)radiotherapy-based organ preservation approach in distal rectal cancers. This should also hold for standard, less intense, treatment regimens. Conversely, the risk of patient selection bias in the current trial can impact the generalizability of the conclusions. Patients enrolled on the trial presumably had a preference for organ preservation; one could suspect that these patients might have a greater acceptance of side effects in order to avoid surgery and this might influence the QoL results. Men were overrepresented in our study, as would be expected for a rectal cancer cohort reflecting patients in general clinical practice. The data from the currently study may thus be less representative for women. In a similar vein, sexual function scores have not been reported here – they were not the focus of the current publication, and had in general a very low individual item completion rate.

In conclusion, our study demonstrates good long-term oncological outcomes after CRT followed by organ preservation, in line with the existing literature. We demonstrate excellent functional outcome, with good rectal continence. Importantly, these data are based on prospectively collected PROs, providing a unique contribution to the very sparse literature on QoL after CRT followed by organ preservation – evidence suggests that the use of PROs gives a more diverse picture of treatment complications. Our study indicates that high dose CRT followed by organ preservation might be an excellent alternative to standard treatment in terms of patient reported functional outcome. While we await high level evidence from randomized trials comparing watch and wait with standard surgical treatment (e.g. the STAR-TREC trial), existing literature and our results might help guide treatment decisions for patients where surgery is not desirable.

REFERENCES

1. Ait Ouakrim D, Pizot C, Boniol M, et al. Trends in colorectal cancer mortality in Europe: retrospective analysis of the WHO mortality database. *Bmj*. 2015:h4970. doi:10.1136/bmj.h4970

2. Engelmann B, Andersen F, Jensen LH, Vestermark LW, Eriksen JR. DCCG.DK's NATIONALE RETNINGSLINIER FOR DIAGNOSTIK OG BEHANDLING AF KOLOREKTAL CANCER - Indikationer for adjuverende kemoterapi til patienter med kolon eller rektumcancer i UICC stadium II. 2017;1.2:1-16. https://dccg.dk/wp-content/uploads/2017/08/2017_Adj_kemo_stadium_-II_cancer.pdf.

3. Chen TYT, Wiltink LM, Nout RA, et al. Bowel function 14 years after preoperative short-course radiotherapy and total mesorectal excision for rectal cancer: Report of a multicenter randomized trial. *Clin Colorectal Cancer*. 2015;14(2):106-114. doi:10.1016/j.clcc.2014.12.007

4. van Heinsbergen M, Janssen-Heijnen ML, Leijtens JW, Slooter GD, Konsten JL. Bowel dysfunction after sigmoid resection underestimated: Multicentre study on quality of life after surgery for carcinoma of the rectum and sigmoid. *Eur J Surg Oncol*. 2018;44(8):1261-1267. doi:10.1016/j.ejso.2018.05.003

5. Appelt AL, Pløen J, Harling H, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: A prospective observational study. *Lancet Oncol*. 2015;16(8):919-927. doi:10.1016/S1470-2045(15)00120-5

6. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: Long-term results. *Ann Surg*. 2004;240(4):711-718. doi:10.1097/01.sla.0000141194.27992.32

7. Lai CL, Lai MJ, Wu CC, Jao SW, Hsiao CW. Rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy, surgery, or "watch and wait." *Int J Colorectal Dis*. 2016;31(2):413-419. doi:10.1007/s00384-015-2460-y

8. Martens MH, Maas M, Heijnen LA, et al. Long-term outcome of an organ preservation program after neoadjuvant treatment for rectal cancer. *J Natl Cancer Inst*. 2016;108(12):1-10. doi:10.1093/jnci/djw171

9. Renehan AG, Malcomson L, Emsley R, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): A propensity-score matched cohort analysis. *Lancet Oncol*. 2016;17(2):174-183. doi:10.1016/S1470-2045(15)00467-2

10. 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. *Eur J Cancer*. 2009;45(17):3017-3026. doi:10.1016/j.ejca.2009.08.014

11. van der Valk MJM, Hilling DE, Bastiaannet E, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *Lancet*. 2018;391(10139):2537-2545. doi:10.1016/S0140-6736(18)31078-X

12. Habr-Gama A, Gama-Rodrigues J, São Julião GP, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: Impact of salvage therapy on local disease control. *Int J Radiat Oncol Biol Phys*. 2014;88(4):822-828. doi:10.1016/j.ijrobp.2013.12.012

13. Hupkens BJP, Martens MH, Stoot JH, et al. Quality of life in rectal cancer patients after chemoradiation: Watch-and-wait policy versus standard resection - A matched-controlled study. *Dis Colon Rectum*. 2017;60(10):1032-1040. doi:10.1097/DCR.0000000000000862

14. Garcia-aguilar PJ, Renfro LA, Chow OS, et al. Local Excision : Results of a Multicenter Phase 2. 2016;16(15):1537-1546. doi:10.1016/S1470-2045(15)00215-6.ORGAN

15. Habr-Gama A, Lynn PB, Jorge JMN, et al. Impact of Organ-Preserving Strategies on Anorectal Function in Patients with Distal Rectal Cancer Following Neoadjuvant Chemoradiation. *Dis Colon Rectum*. 2016;59(4):264-269. doi:10.1097/DCR.0000000000000543

16. van der Sande ME, Hupkens BJP, Berbée M, et al. Impact of radiotherapy on anorectal function in patients with rectal cancer following a watch and wait programme. *Radiother Oncol*. 2019;132:79-84. doi:10.1016/j.radonc.2018.11.017

17. 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. *Int J Radiat Oncol Biol Phys*. 2015;92(3):555-567. doi:10.1016/j.ijrobp.2015.02.021

18. Juul T, Ahlberg M, Biondo S, et al. International validation of the low anterior resection syndrome score. *Ann Surg*. 2014;259(4):728-734. doi:10.1097/SLA.0b013e31828fac0b

19. Ward WL, Hahn EA, Mo F, Hernandez L, Tulsky DS, Cella D. Reliability and Validity of the Functional Assessment of Cancer Therapy-Colorectal (FACT- C) Quality of Life Instrument Author (s): Wendy L . Ward , Elizabeth A . Hahn , Fei Mo , Lesbia Hernandez , David S . Tulsky and David Cella Published by : Springer Stable URL : https://www.jstor.org/stable/4035813 REFERENCES Linked references are available on JSTOR for this article : You may need to log in to JSTOR to access the linked references . Reliability and validity of the Functional Assessment of Cancer Therapy-Colo- rectal (FACT-C) quality of life instrument. 2019;8(3):181-195.

20. McLeod RS. Fecal Incontinence Quality of Life Scale:Quality of Life Instrument for Patients with Fecal Incontinence. *Dis Colon Rectum*. 2000;43(1):16-17.

FIGURES

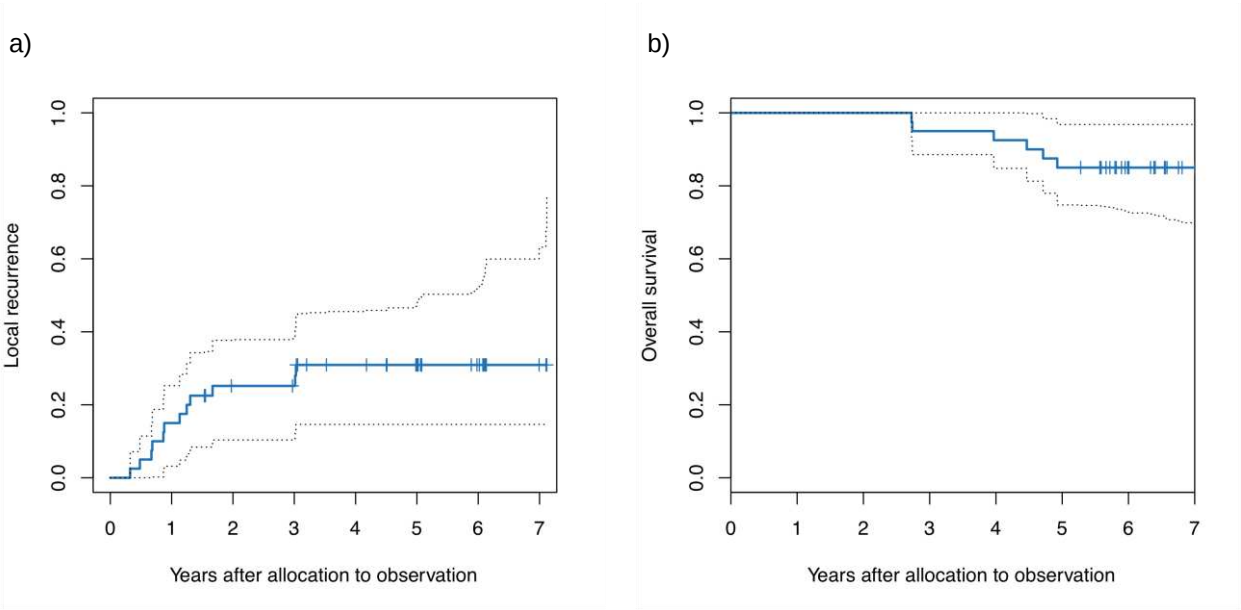

Figure 1: Local tumor regrowth and overall survival. Dotted lines indicate 95% confidence intervals on regrowth and survival estimates.

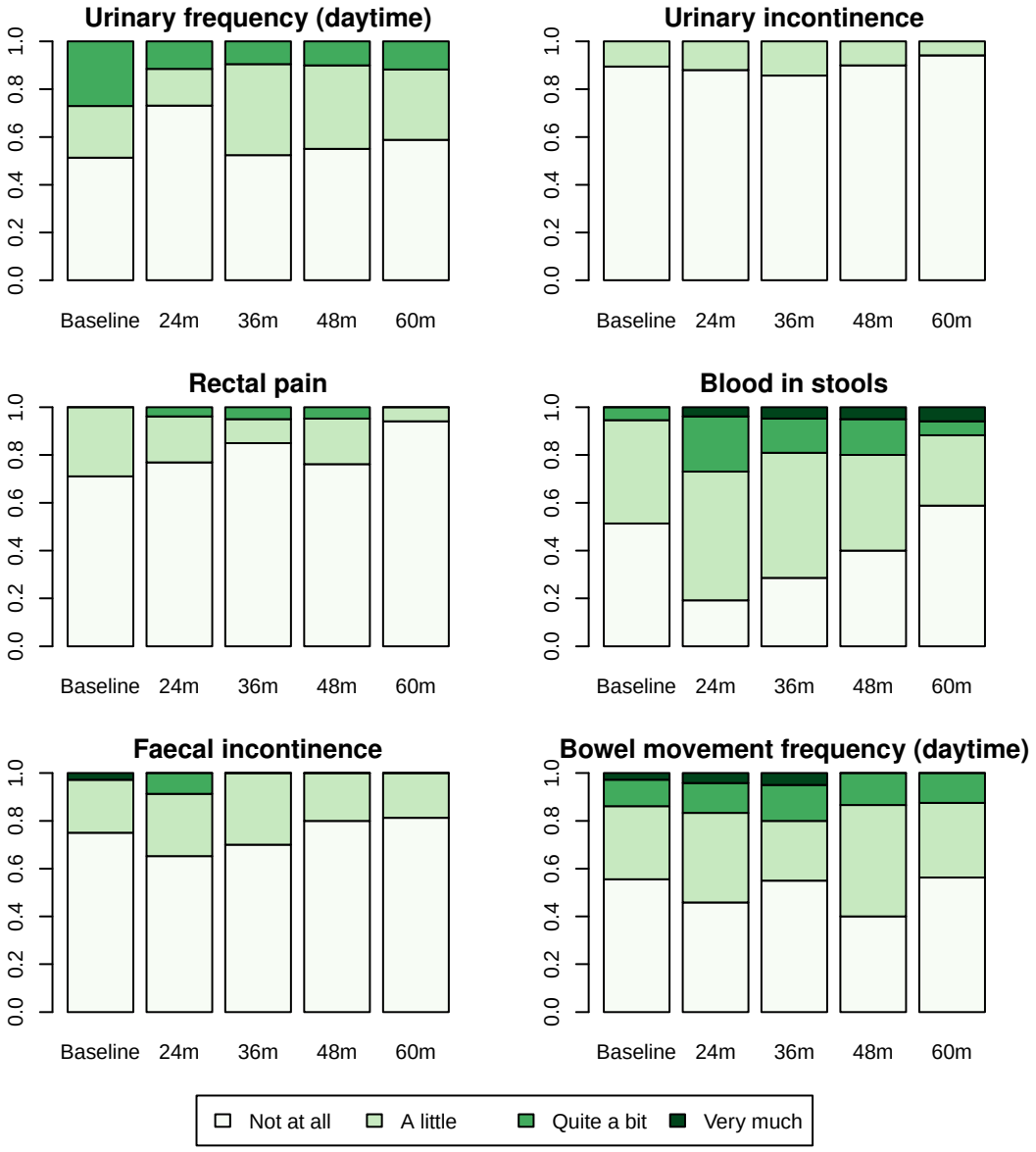

Figure 2: Selected patient-reported symptoms at baseline and during follow up, reported as proportions of patients with data available at each time point. For number of patients assessed at each time point, please see the Appendix (supplementary materials, online only)

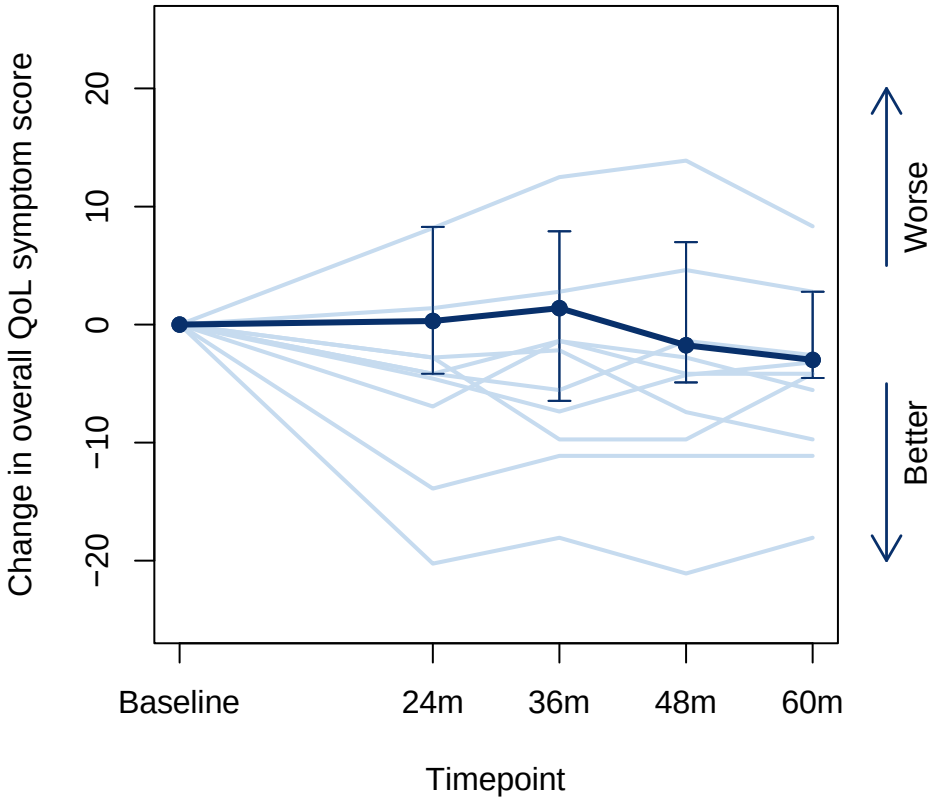

Figure 3: Change in average symptom score on EORTC-CR29 over time. Change in average score has been calculated for each patient relative to their baseline score. Dark blue points and lines represent median value for the whole population; bars are interquartile ranges (IQR). Light blue lines are values for individual patients (only patients with data for all timepoints included for clarity).

TABLES

	Population (n=40)
Sex	
Men	32
Women	8
Age [years]	68 (61-77)
Performance status	
0	34
1	4
ND	2
Disease stage	
T2N0	16
T2N1	7
T3N0	7
T3N1	10
Tumor size [cm][1]	
Diameter	2.7 (2.0-3.4)
Length	3.4 (2.6-4.3)
Distance from sphincter [cm]	4.8 (4.0-5.1)
Radiotherapy treatment volumes [cm^3]	
CTV-T	47 (34-60)
PTV-T	173 (139-201)
CTV-N	629 (575-671)
PTV-N	1372 (1278-1476)

Table 1: Patient characteristics. All data for continuous measures represent medians, with interquartile range in brackets.
[1]Tumor measurements were performed on MRI on the T2 weighed sequences