

University of Groningen

Patient- and physician-reported radiation-induced toxicity of short-course radiotherapy with a prolonged interval to surgery for rectal cancer

Verweij, Maaïke E.; Hoendervangers, Sieske; von Hebel, Charlotte M.; Pronk, Apollo; Schiphorst, Anandi H. W.; Consten, Esther C. J.; Smits, Anke B.; Heikens, Joost T.; Verdaasdonk, Emiel G. G.; Rozema, Tom

Published in:
Colorectal Disease

DOI:
[10.1111/codi.16315](https://doi.org/10.1111/codi.16315)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2023

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Verweij, M. E., Hoendervangers, S., von Hebel, C. M., Pronk, A., Schiphorst, A. H. W., Consten, E. C. J., Smits, A. B., Heikens, J. T., Verdaasdonk, E. G. G., Rozema, T., Verkooijen, H. M., van Grevenstein, W. M. U., & Intven, M. P. W. (2023). Patient- and physician-reported radiation-induced toxicity of short-course radiotherapy with a prolonged interval to surgery for rectal cancer. *Colorectal Disease*, 25(1), 24-30. <https://doi.org/10.1111/codi.16315>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.



European Colorectal Congress

28 November – 1 December 2022, St.Gallen, Switzerland

Monday, 28 November 2022

09.50
Opening and welcome
Jochen Lange, St.Gallen, CH

10.00
It is leaking! Approaches to salvaging an anastomosis
Willem Bemelman, Amsterdam, NL

10.30
Predictive and diagnostic markers of anastomotic leak
Andre D'Hoore, Leuven, BE

11.00
SATELLITE SYMPOSIUM

ETHICON
PART OF THE Johnson & Johnson FAMILY OF COMPANIES

11.45
Of microbes and men – the unspoken story of anastomotic leakage
James Kinross, London, UK

12.15
LUNCH

13.45
Operative techniques to reduce anastomotic recurrence in Crohn's disease
Laura Hancock, Manchester, UK

14.15
Innovative approaches in the treatment of complex Crohn Diseases perianal fistula
Christianne Buskens, Amsterdam, NL

14.45
To divert or not to divert in Crohn surgery – technical aspects and patient factors
Pär Myreliid, Linköping, SE

15.15
COFFEE BREAK

15.45
Appendiceal neoplasia – when to opt for a minimal approach, when and how to go for a maximal treatment
Tom Cecil, Basingstoke, Hampshire, UK

16.15
SATELLITE SYMPOSIUM

Medtronic
Further. Together

17.00
Outcomes of modern induction therapies and Wait and Watch strategies, Hope or Hype
Antonino Spinelli, Milano, IT

17.30
EAES Presidential Lecture - Use of ICG in colorectal surgery: beyond bowel perfusion
Salvador Morales-Conde, Sevilla, ES



18.00
Get-Together with your colleagues
Industrial Exhibition

Tuesday, 29 November 2022

9.00
CONSULTANT'S CORNER
Michel Adamina, Winterthur, CH

10.30
COFFEE BREAK

11.00
SATELLITE SYMPOSIUM

INTUITIVE

11.45
Trends in colorectal oncology and clinical insights for the near future
Rob Glynne-Jones, London, UK

12.15
LUNCH

13.45
VIDEO SESSION

14.15
SATELLITE SYMPOSIUM



15.00
COFFEE BREAK

15.30
The unsolved issue of TME: open, robotic, transanal, or laparoscopic – shining light on evidence and practice
Des Winter, Dublin, IE
Jim Khan, London, UK
Brendan Moran, Basingstoke, UK

16.30
SATELLITE SYMPOSIUM



17.15
Lars Pahlman lecture
Søren Laurberg, Aarhus, DK

Thursday, 1 December 2022
Masterclass in Colorectal Surgery
Proctology Day

Wednesday, 30 November 2022

9.00
Advanced risk stratification in colorectal cancer – choosing wisely surgery and adjuvant therapy
Philip Quirke, Leeds, UK

09.30
Predictors for Postoperative Complications and Mortality
Ronan O'Connell, Dublin, IE

10.00
Segmental colectomy versus extended colectomy for complex cancer
Quentin Denost, Bordeaux, FR

10.30
COFFEE BREAK

11.00
Incidental cancer in polyp - completion surgery or endoscopy treatment alone?
Laura Beyer-Berjot, Marseille, FR

11.30
SATELLITE SYMPOSIUM

12.00
Less is more – pushing the boundaries of full-thickness rectal resection
Xavier Serra-Aracil, Barcelona, ES

12.30
LUNCH

14.00
Management of intestinal neuroendocrine neoplasia
Frédéric Ris, Geneva, CH

14.30
Poster Presentation & Best Poster Award
Michel Adamina, Winterthur, CH

15.00
SATELLITE SYMPOSIUM
OLYMPUS

15.45
COFFEE BREAK

16.15
Reoperative pelvic floor surgery – dealing with perineal hernia, reoperations, and complex reconstructions
Guillaume Meurette, Nantes, FR

16.45
Salvage strategies for rectal neoplasia
Roel Hompes, Amsterdam, NL

17.15
Beyond TME – technique and results of pelvic exenteration and sacrectomy
Paris Tekkis, London, UK

19.30
FESTIVE EVENING

Information & Registration www.colorectalsurgery.eu



RESEARCH ARTICLE

Patient- and physician-reported radiation-induced toxicity of short-course radiotherapy with a prolonged interval to surgery for rectal cancer

Maike E. Verweij¹ | Sieske Hoendervangers^{1,2} | Charlotte M. von Hebel¹ | Apollo Pronk³ | Anandi H. W. Schiphorst³ | Esther C. J. Consten^{4,5} | Anke B. Smits⁶ | Joost T. Heikens⁷ | Emiel G. G. Verdaasdonk² | Tom Rozema⁸ | Helena M. Verkooijen¹ | Wilhelmina M. U. van Grevenstein¹ | Martijn P. W. Intven¹

¹Division of Imaging and Oncology, University Medical Centre Utrecht, Utrecht, The Netherlands

²Department of Surgery, Jeroen Bosch Hospital, Den Bosch, The Netherlands

³Department of Surgery, Diaconessenhuis, Utrecht, The Netherlands

⁴Department of Surgery, Meander Medical Centre, Amersfoort, The Netherlands

⁵Department of Surgery, University Medical Centre Groningen, Groningen, The Netherlands

⁶Department of Surgery, St Antonius Hospital, Nieuwegein, The Netherlands

⁷Department of Surgery, Rivierland Hospital, Tiel, The Netherlands

⁸Department of Radiotherapy, Verbeeten Institute, Tilburg, The Netherlands

Correspondence

Maike E. Verweij, Division of Imaging and Oncology, University Medical Centre Utrecht, Utrecht, The Netherlands.
Email: m.e.verweij-5@umcutrecht.nl

Abstract

Aim: A prolonged interval (>4 weeks) between short-course radiotherapy (25 Gy in five fractions) (SCRT-delay) and total mesorectal excision for rectal cancer has been associated with a decreased postoperative complication rate and offers the possibility of organ preservation in the case of a complete tumour response. This prospective cohort study systematically evaluated patient-reported bowel dysfunction and physician-reported radiation-induced toxicity for 8 weeks following SCRT-delay.

Method: Patients who were referred for SCRT-delay for intermediate risk, oligometastatic or locally advanced rectal cancer were included. Repeated measurements were done for patient-reported bowel dysfunction (measured by the low anterior resection syndrome [LARS] questionnaire and categorized as no, minor or major LARS) and physician-reported radiation-induced toxicity (according to Common Terminology Criteria for Adverse Events version 4.0) before start of treatment (baseline), at completion of SCRT and 1, 2, 3, 4, 6 and 8 weeks thereafter.

Results: Fifty-one patients were included; 31 (61%) were men and the median age was 67 years (range 44–91). Patient-reported bowel dysfunction and physician-reported radiation-induced toxicity peaked at weeks 1–2 after completion of SCRT and gradually declined thereafter. Major LARS was reported by 44 patients (92%) at some time during SCRT-delay. Grade 3 radiation-induced toxicity was reported in 17 patients (33%) and concerned predominantly diarrhoea. No Grade 4–5 radiation-induced toxicity occurred.

Conclusion: During SCRT-delay, almost every patient experiences temporary mild-moderate radiation-induced toxicity and major LARS, but life-threatening toxicity is rare. SCRT-delay is a safe alternative to SCRT-direct surgery that should be proposed when counselling rectal cancer patients on neoadjuvant strategies.

KEYWORDS

low anterior resection syndrome, patient-reported outcomes, radiation-induced toxicity, rectal cancer, short course radiotherapy

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2022 The Authors. *Colorectal Disease* published by John Wiley & Sons Ltd on behalf of Association of Coloproctology of Great Britain and Ireland.

INTRODUCTION

Preoperative short-course radiotherapy (SCRT) (25Gy in five fractions) and long-course chemoradiation (CRT) (50Gy in 25 fractions combined with a radiosensitizer) are two common neoadjuvant regimens for the treatment of rectal cancer [1, 2]. An interval of more than 8 weeks between CRT and total mesorectal excision (TME) for locally advanced rectal cancer has been known to improve tumour downstaging without compromising the postoperative complication rate [3]. In contrast, the recommended interval between SCRT and TME for intermediate risk rectal cancer was less than 1 week (SCRT-direct surgery), conforming with the treatment schedules of the Swedish Rectal Cancer and Dutch TME trials [4, 5]. SCRT with a prolonged interval to TME (4 weeks or more, SCRT-delay) was reserved for patients with locally advanced rectal cancer who were too frail to receive CRT [1].

Recently, SCRT-delay has become a treatment option for a broader range of rectal cancer stages. The randomized Stockholm III trial showed that SCRT-delay results in a significant reduction of postoperative complications (41% vs. 53%, $P = 0.001$) and an improved pathological complete response rate (10% vs. 0.3%, $P < 0.001$) compared to SCRT-direct surgery for resectable rectal cancer [6, 7]. The Dutch M1 trial demonstrated that SCRT-delay and neoadjuvant chemotherapy results in good overall survival (median 3.8 years) for oligometastatic (M1) rectal cancer [8]. Furthermore, the randomized RAPIDO trial showed that SCRT-delay and neoadjuvant chemotherapy results in decreased disease-related treatment failure rate (24% vs. 30%, $P = 0.019$) compared to standard CRT and TME in patients with locally advanced rectal cancer [9].

A drawback of SCRT-delay is the occurrence of radiation-induced toxicity during the interval. Information on the course of the side effects would be useful for patient counselling on neoadjuvant treatment strategies. This prospective cohort study structurally evaluated patient-reported bowel dysfunction and physician-reported radiation-induced toxicity during the 8 weeks following SCRT-delay for rectal cancer.

MATERIALS AND METHODS

Patients and treatment

Patients were included between December 2018 and June 2021 in the University Medical Centre Utrecht and between July 2020 and June 2021 in the Jeroen Bosch Hospital. Patients were eligible if they were referred for SCRT-delay (defined as an interval of at least 4 weeks between completion of SCRT and TME) for either intermediate risk rectal cancer (T1–3(distance to the mesorectal fascia >1 mm [MRF–])N1M0 or T3cd(MRF–)N0M0), locally advanced rectal cancer and contraindication for CRT (T3–4(distance to the mesorectal fascia ≤ 1 mm [MRF+])N_xM0 or TxN2M0) or oligometastatic disease (M1) [10]. Exclusion criteria were inadequate command of the Dutch language, severe cognitive disorder or treatment

WHAT DOES THIS PAPER ADD TO THE LITERATURE?

Information on side effects is needed for counselling rectal cancer patients on neoadjuvant treatment strategies. This paper shows that during short-course radiotherapy with a prolonged interval to surgery, mild–moderate toxicity is highly prevalent at 1–2 weeks after completion of radiotherapy and gradually declines thereafter. Life-threatening toxicity is rare.

with palliative intent. All patients provided informed consent for the current study and were asked for informed consent for the Dutch Prospective Colorectal Cancer cohort (PLCRC) [11]. PLCRC is a nationwide cohort study wherein data of adult colorectal patients are collected. The medical ethics committee of the University Medical Centre Utrecht approved PLCRC and waived the current study for ethical review. Clinical data were collected from the electronic medical files and within the PLCRC.

Treatment strategy was decided in a multidisciplinary team meeting. SCRT consisted of 25 Gy in five fractions on consecutive working days. Target volumes were the mesorectum, presacral lymph nodes, internal iliac lymph nodes and, in locally advanced rectal cancer, the obturator region [12]. Radiotherapy was administered on either a magnetic resonance guided linear accelerator (MR-Linac) or a conventional Linac. Planning target volume margins used for the mesorectum and elective lymph node regions were 10 and 8 mm on a conventional accelerator and 4–6 and 4 mm on the MR-Linac [13]. Treatment was delivered using a volumetric modulated arc therapy technique on the conventional accelerator or an online adapted MRI-guided intensity modulated radiotherapy technique on the MR-Linac. Patients with oligometastatic disease received additional treatment (i.e., neoadjuvant chemotherapy and/or liver surgery) after SCRT. Surgery according to the principles of TME was performed at the referral hospitals.

End-points

Bowel dysfunction and radiation-induced toxicity were measured before the start of radiotherapy, at completion of SCRT and at 1, 2, 3, 4, 6 and 8 weeks thereafter. Patients were censored at the time of TME when TME was performed before 8 weeks after completion of SCRT. Bowel dysfunction was measured by the low anterior resection syndrome (LARS) score questionnaire and recorded in a paper or online diary [14]. The LARS score questionnaire consists of five questions on 'incontinence for flatus', 'incontinence for liquid stools', 'frequency', 'clustering' and 'urgency'. These questions add up to a weighted sum that is categorized as no LARS (0–20), minor LARS (21–29) or major LARS (30–42). The LARS score questionnaire and its Dutch translation have been validated for measuring

bowel dysfunction after low anterior resection (LAR) [15, 16]. This short questionnaire was used because it is well suited for repeated measurements of bowel function. Radiation-induced toxicity was recorded during telephone consultations by a physician for diarrhoea, fatigue, cystitis, urinary incontinence and dermatitis according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [17]. In the case of missing toxicity, the CTCAE score were retrospectively retrieved from the electronic medical files ($n = 23$ at baseline, $n = 8$ at completion of SCRT and $n = 2$ at 1 week after completion of SCRT). Non-prespecified complaints and additional treatments during SCRT-delay were retrieved from the electronic medical files and were censored at the start of chemotherapy when chemotherapy was administered within 8 weeks following completion of SCRT.

Statistical methods

Baseline characteristics were described as number (proportion) or median (range or interquartile range [IQR]). The LARS score questionnaire was processed according to its manual [14]. The LARS score questionnaires and radiation-induced toxicity measurements were reported as number (proportion) of patients per category or grade per week.

In order to personalize information for future patients about the severity of bowel dysfunction they may expect during SCRT-delay, the course of LARS was described for several subgroups: neoadjuvant treatment (radiotherapy only vs. radiotherapy and chemotherapy), clinical tumour stage (cT2 vs. cT3 and MRF- vs. cT3 MRF+ and T4), tumour location (distal [lower border of the tumour 0–3 cm from anorectal junction on sagittal MRI] vs. midrectal [3–6 cm] vs. proximal [≥ 6 cm]), age (40–60 vs. 60–80 vs. 80+ years), gender (male vs. female) and LARS score at baseline (no or minor LARS vs. major LARS).

RESULTS

Fifty-one patients including 31 men (61%) were enrolled (Table 1). The median age was 67 years (range 44–91). The indication for SCRT-delay was intermediate risk rectal cancer in 32 patients (63%), locally advanced rectal cancer and frailty in five patients (10%) and oligometastatic disease in 14 patients (28%). Ten out of 14 patients with oligometastatic disease (71%) were treated with chemotherapy at 14 days after completion of SCRT (median, IQR 12–18) and seven patients with oligometastatic disease (50%) had liver surgery at 157 days (median, IQR 56–180) after completion of SCRT. Of all patients, TME was performed in 40 patients (78%) at 72 days (median, IQR 53–102) after completion of SCRT. Four patients (7.8%) did not undergo TME due to disease progression and three patients (5.9%) declined or were judged unfit to undergo TME (Supplementary File 1). Four patients (7.8%) with a (rectal) clinical complete response entered a watch and wait follow-up programme.

TABLE 1 Patient, tumour and treatment characteristics of 51 rectal cancer patients treated with short-course radiotherapy and prolonged interval to surgery

	N (%)
Male gender	31 (61)
Age in years (median, range)	67 (44, 91)
CCI (%)	
0	33 (65)
1–2	11 (22)
3+	7 (14)
Ostomy before start of treatment	3 (5.9)
Clinical tumour stage	
cT2	9 (18)
cT3	38 (75)
cT4	4 (7.8)
Involvement of mesorectal fascia (≤ 1 mm, MRF+)	11 (22)
Clinical nodal stage	
cN0	7 (14)
cN1	38 (75)
cN2	7 (14)
Clinical metastasis stage M1	14 (28)
Tumour location ^a	
Distal (0–3 cm)	15 (31)
Midrectal (3–6 cm)	15 (31)
Proximal (6+ cm)	21 (41)
Indication for SCRT	
Intermediate risk rectal cancer ^b	32 (63)
Locally advanced rectal cancer	5 (9.8)
cM1 rectal cancer	14 (28)
Treatment on MR-Linac	26 (51)
Definitive treatment	
TME	40 (78)
Watch and wait ^c	4 (7.8)
No TME due to distant disease progression	4 (7.8)
No TME due to patient being unfit for surgery	3 (5.9)
Days between completion of SCRT and TME (median, IQR)	72 (53, 102)
Subgroup of cM1 patients (n = 14)	
Chemotherapy during interval	10 (71)
Days between completion of SCRT and start of chemotherapy (median, IQR)	14 (12, 18)
Liver surgery	7 (50)
Days between completion of SCRT and liver surgery (median, IQR)	157 (56, 180)

Abbreviations: CCI, Charlson Comorbidity Index (calculated excluding patient age and the rectal tumour); IQR, interquartile range; MR-Linac, magnetic resonance guided linear accelerator; MRF, mesorectal fascia; SCRT, short-course radiotherapy; TME, total mesorectal excision.

^aMeasured as distance between lower border of the tumour and anorectal junction on sagittal MRI.

^bRectal cancer stage 1–3(MRF–)N1M0 or T3c-d(MRF–)N0M0 according to the Dutch guideline.

^cOne patient entered watch and wait after a transanal minimal invasive surgical (TAMIS) procedure without residual tumour cells on pathology.

Both patient-reported bowel dysfunction and physician-reported radiation-induced toxicity peaked at 1–2 weeks after completion of SCRT and gradually declined thereafter (Figure 1; Supplementary File 2). As an exception, the LARS score component ‘incontinence for flatus’ and physician-reported urine incontinence did not show a clear pattern.

At its peak incidence, major LARS was reported by 37 patients (79%). As for the components of the LARS score questionnaire, clustering of stools that occurred at least once a week was reported by up to 41 patients (85%), urge at least once a week by 37 (79%), incontinence for flatus at least once a week by 26 (57%), defaecation frequency of more than seven times a day by 17 (35%) and incontinence for liquid stools at least once a week by 13 patients (27%). In total, 44 patients (92%) reported major LARS at some time during SCRT-delay.

At its peak incidence, radiation-induced diarrhoea was observed in 36 patients (77%), fatigue in 29 (63%), cystitis in 19 (41%), dermatitis in eight (17%) and urine incontinence in four (8.0%). In total, radiation-induced toxicity Grade 3 diarrhoea occurred in 16 patients (31%) and one (2.0%) had Grade 3 fatigue. In one patient, TME was moved up to 4 weeks due to persisting Grade 3 diarrhoea. No Grade 4–5 radiation-induced toxicity occurred.

Outside the prespecified toxicities, 42 (82%) patients reported rectal haemorrhage, 21 (41%) rectal or anal pain, 19 (37%) incontinence for solid stools, 17 (33%) abdominal pain, 14 (27%) constipation, 14 (27%) anorexia/nausea, nine (18%) urinary tract obstruction and two (3.8%) neuropathic buttock pain during SCRT-delay and before the start of chemotherapy (additional treatments during SCRT-delay are reported in Supplementary File 3).

Subgroup analysis showed that the vast majority of patients treated with neoadjuvant chemotherapy continued to report major LARS at weeks 3 and 4 after completion of SCRT, while the incidence of major LARS already declined in patients treated with radiotherapy only (Supplementary File 4). The majority of patients with cT3MRF+ and cT4 continued to report major LARS throughout follow-up, and they consistently reported more major LARS than patients with cT3MRF– or cT2. Patients with proximal, midrectal or distal tumours reported similar levels of major LARS. Patients aged 80 years or older consistently reported more major LARS than patients of 60–80 years, who reported more major LARS than patients of 40–60 years. Female patients consistently reported more major LARS than men. Most patients with major LARS at baseline continued to report major LARS throughout follow-up.

DISCUSSION

During SCRT-delay for rectal cancer, patient-reported major LARS and physician-reported radiation-induced toxicity Grades 1–2 were highly prevalent at 1–2 weeks after completion of SCRT and gradually declined thereafter. Radiation-induced toxicity Grade 3 occurred in total in 33% of patients and consisted predominantly of diarrhoea. No Grade 4–5 radiation-induced toxicity occurred.

Patients treated with neoadjuvant chemotherapy with a higher clinical tumour stage, older age, female gender and major LARS at baseline reported more major LARS during SCRT-delay. Patients reported more major LARS than physicians reported Grade 3 radiation-induced diarrhoea.

This is the first study that provides a detailed insight into the course of radiation-induced toxicity during SCRT-delay. Previous studies have only reported on cumulative toxicity incidences following SCRT-delay. A 2014 meta-analysis by Bujko et al. reported that radiation-induced toxicity occurred in 27%–41% of patients during SCRT-delay, of whom 2%–5% had Grade ≥ 3 toxicity [18]. In the Stockholm III trial, 7% ($n = 23/355$) of patients treated with SCRT-delay were admitted to the hospital due to radiation-induced toxicity [6]. In our study, no Grade 4–5 toxicity occurred and in only one patient TME was moved up due to persisting Grade 3 toxicity. Advances in radiotherapy techniques since the start of the Stockholm III trial, that included patients between 1998 and 2013, might explain the lower toxicity rates in our cohort. In contrast, no Grade 3–4 radiation-induced toxicity occurred during SCRT-delay and before the start of chemotherapy in the M1 trial. Administration of chemotherapy was delayed in seven (14%) patients due to Grade 2 radiation toxicity at 2 weeks after completion of SCRT [19]. The relatively favourable toxicity results of the M1 trial might be explained by their young and fit study population (median age 59 [range 33–75] and Eastern Cooperative Oncology Group 0 or 1). Our study shows that, using current radiotherapy techniques in an all-comer population, almost every patient experiences temporary mild–moderate radiation-induced toxicity during SCRT-delay, but life-threatening radiation-induced toxicity is rare. Combining our results with the lower risk of post-operative complications and the increased probability of organ preservation, SCRT-delay should be preferred over SCRT-direct surgery in most rectal cancer patients [6, 7]. SCRT-direct surgery could still be considered for patients with no interest in organ preservation and/or a high risk of radiation-induced toxicity following SCRT-delay.

Neoadjuvant chemotherapy, higher clinical tumour stage, older age, female gender and major LARS at baseline were associated with major LARS during SCRT-delay. Previous studies found a distal tumour, female gender and a younger age to be predictive of the LARS score at one or more years after anterior resection [14, 20]. However, the relation between younger age and bowel dysfunction might have been biased by the selection of patients for anterior resection. Anorectal function decreases with age and is worse in women than in men, especially after (vaginal) childbirth [21, 22]. It is therefore plausible that older and female patients are more susceptible to major LARS following radiotherapy for rectal cancer. Tumours of a higher stage or at a more distal location exert more pressure on the anorectal complex and on the rectal ampulla, so more major LARS was expected in those subgroups. A high clinical tumour stage was strongly associated with the occurrence of major LARS, but tumour location was not associated with LARS. Chemotherapy was associated with a slower recovery of LARS after SCRT. These risk

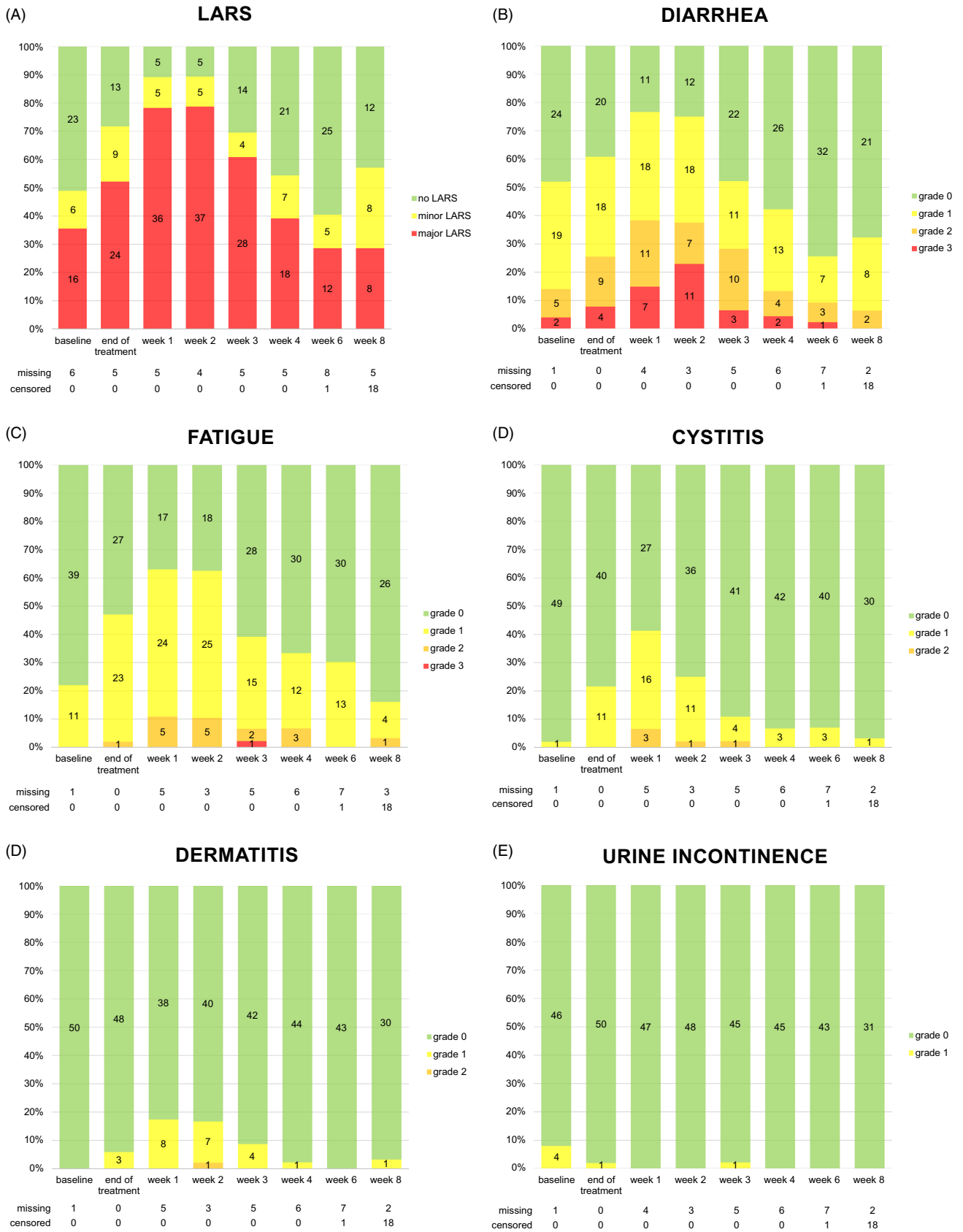


FIGURE 1 (A)–(F) Patient-reported bowel dysfunction measured by the low anterior resection syndrome (LARS) score and physician-reported radiation-induced toxicity according to CTCAE during short-course radiotherapy and prolonged interval to surgery (SCRT-delay) for rectal cancer ($n = 51$). Patients were censored at the time of TME when TME was scheduled within 8 weeks after completion of SCRT.

factors should be considered when counselling patients on LARS during SCRT-delay.

Patient-reported LARS and physician-reported radiation-induced diarrhoea showed similar patterns, but a considerable proportion of patients reported major LARS when physicians reported diarrhoea Grade 0, 1 or 2. This difference is probably due to the extensiveness of the LARS score questionnaire compared to diarrhoea according to the CTCAE grading system [14]. When interpreting the LARS score, it should be acknowledged that major LARS has a prevalence of 15% in a reference population [23, 24]. Also, it is well known that physicians consistently report lower frequency and severity of toxicity than patients do in direct reports [25]. Our study once again shows the importance of collecting patient-reported outcomes for measuring the impact of a treatment.

The LARS score questionnaire has been validated for measuring bowel dysfunction after LAR [14–16, 26]. Here, the LARS score questionnaire was used to measure bowel dysfunction following radiotherapy for rectal cancer, an indication for which it has not been specifically validated. That the LARS score questionnaire does not cover all radiation-induced bowel symptoms is illustrated by the high prevalence of rectal haemorrhage (82%), rectal pain (41%) and incontinence for solid stools (37%) in our study. However, major LARS has been correlated with poor quality of life in a reference population, indicating that the LARS score questionnaire is of value outside of the LAR population [23]. Other studies have used the LARS score questionnaire in patients who had not been treated with LAR, that is, patients on a watch-and-wait strategy [27–29]. Future research could focus on the development and validation of a simple questionnaire like the LARS score questionnaire for measuring bowel dysfunction following radio(chemo)therapy for rectal cancer.

In this study, toxicity was only recorded for diarrhoea, fatigue, cystitis, urine incontinence and dermatitis during 8 weeks following completion of SCRT. Adverse events during the remaining duration of chemotherapy were not recorded. Because of these choices, it was unfortunately not possible to compare our results to trials that reported the cumulative incidence of toxicity of SCRT-delay and neoadjuvant chemotherapy together (such as the RAPIDO trial).

Missing values for physician-reported radiation toxicity and non-specified complaints were retrospectively retrieved from the electrical medical files. Their prevalence might be underestimated due to underreporting.

CONCLUSION

During SCRT-delay, almost every patient experiences temporary mild-moderate radiation-induced toxicity and major LARS, but life-threatening toxicity is rare. Neoadjuvant chemotherapy, higher clinical tumour stage, older age, female gender and major LARS are risk factors for major LARS during SCRT-delay. SCRT-delay is

a safe alternative to SCRT-direct surgery that should be proposed when counselling rectal cancer patients on neoadjuvant treatment strategies.

AUTHOR CONTRIBUTIONS

Maaïke E. Verweij: Investigation, Writing - original draft, Methodology, Validation, Visualization, Software, Formal analysis, Project administration, Data curation. Sieske Hoendervangers: Conceptualization, Investigation, Methodology, Validation, Writing - review & editing, Software, Project administration, Data curation, Visualization. Charlotte M. von Hebel: Investigation, Visualization, Data curation, Software, Validation. Apollo Pronk: Resources. Anandi H. W. Schiphorst: Resources. Esther C. J. Consten: Resources. Anke B. Smits: Resources. Joost T. Heikens: Resources. Emiel G. G. Verdaasdonk: Resources. Tom Rozema: Resources. Helena M. Verkooijen: Conceptualization, Supervision, Writing - review & editing, Methodology, Funding acquisition. Wilhelmina M. U. van Grevenstein: Conceptualization, Funding acquisition, Resources, Supervision, Writing - review & editing, Methodology. Martijn P. W. Intven: Funding acquisition, Conceptualization, Resources, Supervision, Writing - review & editing, Methodology.

FUNDING INFORMATION

No funding has been received by any author in relation to this article.

CONFLICT OF INTEREST

Outside of the submitted work, HMV is a member of the European Commission and the Netherlands Organization of Health Research and Development and reports grants for Elekta AB, Sweden and the Dutch Cancer Foundation. MPWI has received personal fees from Elekta AB, Sweden.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

The medical ethics committee of the University Medical Centre Utrecht waived the current study for ethical review.

PATIENT CONSENT STATEMENT

All patients provided informed consent before study inclusion.

REFERENCES

1. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, et al. Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(suppl_4):iv22–40. <https://doi.org/10.1093/annonc/mdx224>
2. National Institute for Health and Care Excellence. *Colorectal Cancer NICE Guideline*. 2020. www.nice.org.uk/guidance/ng151. Accessed September 17, 2022.
3. Ryan J, O'Sullivan DP, Kelly ME, et al. Meta-analysis of the effect of extending the interval after long-course chemoradiotherapy

- before surgery in locally advanced rectal cancer. *Br J Surg.* 2019;106(10):1298–310. <https://doi.org/10.1002/bjs.11220>
4. Pålman L. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med.* 1997;336(14):980–7. <https://doi.org/10.1056/NEJM199704033361402>
 5. Kapiteijn E, Marijnen CAM, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med.* 2001;345(9):638–46. <https://doi.org/10.1056/NEJMoa010580>
 6. Erlandsson J, Holm T, Pettersson D, Berglund Å, Cedermark B, Radu C, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multi-centre, randomised, non-blinded, phase 3, non-inferiority trial. *Lancet Oncol.* 2017;18(3):336–46. [https://doi.org/10.1016/S1470-2045\(17\)30086-4](https://doi.org/10.1016/S1470-2045(17)30086-4)
 7. Erlandsson J, Lörinc E, Ahlberg M, Pettersson D, Holm T, Glimelius B, et al. Tumour regression after radiotherapy for rectal cancer—results from the randomised Stockholm III trial. *Radiother Oncol.* 2019;135:178–86. <https://doi.org/10.1016/j.radonc.2019.03.016>
 8. Bisschop C, van Dijk TH, Beukema JC, Jansen RLH, Gelderblom H, de Jong KP, et al. Short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical treatment in primary stage IV rectal cancer: long-term results of a phase II study. *Ann Surg Oncol.* 2017;24(9):2632–8. <https://doi.org/10.1245/s10434-017-5897-0>
 9. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg EMK, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2020;22(1):29–42. [https://doi.org/10.1016/S1470-2045\(20\)30555-6](https://doi.org/10.1016/S1470-2045(20)30555-6)
 10. Primaire behandeling rectumcarcinoom - Richtlijn - Richtlijnen database. https://richtlijnen database.nl/richtlijn/colorrectaal_carcinoom_crc/primaire_behandeling_rectumcarcinoom_bij_crc.html. Published 2019. Accessed March 24, 2022.
 11. Burbach JPM, Kurk SA, Coebergh van den Braak RRJ, et al. Prospective Dutch colorectal cancer cohort: an infrastructure for long-term observational, prognostic, predictive and (randomized) intervention research. *Acta Oncol.* 2016;55(11):1273–80. <https://doi.org/10.1080/0284186X.2016.1189094>
 12. Valentini V, Gambacorta MA, Barbaro B, Chiloiri G, Coco C, das P, et al. International consensus guidelines on clinical target volume delineation in rectal cancer. *Radiother Oncol.* 2016;120(2):195–201. <https://doi.org/10.1016/j.radonc.2016.07.017>
 13. Intven MPW, Otterloo SR, Mook S, et al. Online adaptive MR-guided radiotherapy for rectal cancer; feasibility of the workflow on a 1.5T MR-linac; clinical implementation and initial experience. *Radiother Oncol.* 2020;154:172–8. <https://doi.org/10.1016/j.radonc.2020.09.024>
 14. 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. *Ann Surg.* 2012;255(5):922–8. <https://doi.org/10.1097/SLA.0b013e31824f1c21>
 15. Juul T, Ahlberg M, Biondo S, Emmertsen KJ, Espin E, Jimenez LM, et al. International validation of the low anterior resection syndrome score. *Ann Surg.* 2014;259(4):728–34. <https://doi.org/10.1097/SLA.0b013e31828fac0b>
 16. Hupkens BJP, Breukink SO, C Olde Reuver Of Briel, et al. Dutch validation of the low anterior resection syndrome score. *Colorectal Dis.* 2018;20(10):881–7. <https://doi.org/10.1111/codi.14228>
 17. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2009. <http://www.meddr amssso.com>. Accessed May 2, 2022.
 18. Bujko K, Partycki M, Pietrzak L. Neoadjuvant radiotherapy (5 × 5 Gy): immediate versus delayed surgery. *Recent Results Cancer Res.* 2014;203:171–87. https://doi.org/10.1007/978-3-319-08060-4_12
 19. van Dijk TH, Tamas K, Beukema JC, et al. Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer. *Ann Oncol.* 2013;24(7):1762–9. <https://doi.org/10.1093/annonc/mdt124>
 20. Battersby NJ, Bouliotis G, Emmertsen KJ, Juul T, Glynn-Jones R, Branagan G, et al. Development and external validation of a nomogram and online tool to predict bowel dysfunction following restorative rectal cancer resection: the POLARS score. *Gut.* 2018;67(4):688–96. <https://doi.org/10.1136/gutjnl-2016-312695>
 21. Gundling F, Seidl H, Scalercio N, Schmidt T, Schepp W, Pehl C. Influence of gender and age on anorectal function: normal values from anorectal manometry in a large Caucasian population. *Digestion.* 2010;81(4):207–13. <https://doi.org/10.1159/000258662>
 22. Jameson JS, Chia YW, Kamm MA, Speakman CTM, Chye YH, Henry MM. Effect of age, sex and parity on anorectal function. *Br J Surg.* 1994;81(11):1689–92. <https://doi.org/10.1002/bjs.1800811143>
 23. van Heinsbergen M, Van der Heijden JAG, Stassen LP, et al. The low anterior resection syndrome in a reference population: prevalence and predictive factors in the Netherlands. *Colorectal Dis.* 2020;22(1):46–52. <https://doi.org/10.1111/codi.14790>
 24. Juul T, Elfeki H, Christensen P, Laurberg S, Emmertsen KJ, Bager P. Normative data for the low anterior resection syndrome score (LARS score). *Ann Surg.* 2019;269(6):1124–8. <https://doi.org/10.1097/SLA.0000000000002750>
 25. Di Maio M, Basch E, Bryce J, Perrone F. Patient-reported outcomes in the evaluation of toxicity of anticancer treatments. *Nat Rev Clin Oncol.* 2016;13(5):319–25. <https://doi.org/10.1038/nrclononc.2015.222>
 26. Emmertsen KJ, Laurberg S. Impact of bowel dysfunction on quality of life after sphincter-preserving resection for rectal cancer. *Br J Surg.* 2013;100(10):1377–87. <https://doi.org/10.1002/bjs.9223>
 27. Hupkens BJP, Martens MH, Stoot JH, Berbee M, Melenhorst J, Beets-Tan RG, et al. Quality of life in rectal cancer patients after chemoradiation. *Dis Colon Rectum.* 2017;60(10):1032–40. <https://doi.org/10.1097/DCR.0000000000000862>
 28. Haak HE, Maas M, Lambregts DMJ, Beets-Tan RGH, Beets GL, Melenhorst J, et al. Is watch and wait a safe and effective way to treat rectal cancer in older patients? *Eur J Surg Oncol.* 2020;46(3):358–62. <https://doi.org/10.1016/j.ejso.2020.01.005>
 29. Custers P, van der Sande M, Grotenhuis B, Peters F, van Kuijk S, Breukink S, et al. Quality of life and functional outcome of rectal cancer patients following a watch-and-wait approach. *Eur J Surg Oncol.* 2022;48(2):e35. <https://doi.org/10.1016/j.ejso.2021.12.441>

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Verweij ME, Hoendervangers S, von Hebel CM, Pronk A, Schiphorst AHW, Consten ECJ, et al. Patient- and physician-reported radiation-induced toxicity of short-course radiotherapy with a prolonged interval to surgery for rectal cancer. *Colorectal Dis.* 2022;00:1–7. <https://doi.org/10.1111/codi.16315>