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Original Article

Tumour regression after radiotherapy for rectal cancer – Results from the randomised Stockholm III trial

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ABSTRACT

Background and purpose: Neoadjuvant radiotherapy (RT) in rectal cancer induces tumour regression with a possible complete response (pCR). The optimal fractionation and timing to surgery is not established. The Stockholm III trial randomly assigned 840 patients to 5 × 5 Gy surgery within one week (SRT), 5 × 5 Gy with surgery after 4–8 weeks, and 2 Gy × 25 with surgery after 4–8 weeks (LRT-delay). The aim of this substudy was to assess tumour regression and correlation to survival.

Material and methods: All available microscopy slides were assessed by one pathologist, blinded to treatment, regarding tumour regression, graded according to the Dworak system (TRG), TNM-stage and other standard histopathology characteristics. Patients' data were collected from the Swedish ColoRectal Cancer Registry. Outcomes were TRG, pCR-rates, overall survival (OS) and time to recurrence (TTR).

Results: 318, 285 and 94 patients were included in the SRT, SRT-delay and LRT-delay groups. Median follow up was 5.7 years. There were significantly lower tumour stages after SRT-delay. pCR was seen in 1 (0.3%), 29 (10.4%) and 2 (2.2%) patients in SRT, SRT-delay and LRT-delay, respectively. The pCR and Dworak grade 4 were associated with superior survival. pCR vs no-pCR Hazard Ratio (95% Confidence Interval) OS: 0.51 (0.26–0.99) $p = 0.046$, TTR: 0.27 (0.09–0.86) $p = 0.027$.

Conclusion: SRT-delay induces pCR in about 10% of the patients and is in this aspect superior to 25 × 2 Gy. A complete tumour response, TRG 4 using the Dworak system, or a pCR, is associated with superior OS and TTR.

Preoperative radiotherapy (RT) in rectal cancer is widely used with the primary aim of reducing rates of local recurrences [1,2]. Another effect of RT is downstaging or tumour regression, more efficiently achieved after chemoradiotherapy (CRT) [3]. This may increase the possibility to resect primarily non-resectable tumours and to include patients with a clinical complete response (cCR) in watch-and-wait programs as an organ-preserving strategy. Tumour regression after short-course RT with 5 × 5 Gy (SRT) was initially described when delaying surgery at least 10 days [4,5]. More recent studies have shown that pathologic complete responses (pCR) are possible to achieve even after SRT if the interval between the end of RT and surgery is delayed for at least 4 weeks [6–9]. Neither the optimal course of RT, or CRT, nor the timing to surgery to achieve maximal regression is determined, and the relationship between regression and time is probably not linear [10–13]. Outcomes after near complete response are conflicting, and the regression effect on lymph nodes might be essential [13–20].

The Stockholm III trial randomly allocated 840 patients to SRT, with immediate or delayed surgery or to long-course RT (LRT). After a minimum follow-up of two years, it was concluded that a delay to surgery after SRT appears oncologically safe, with few post-operative complications [21]. An interim analysis of the trial, on about two-thirds of the patients randomised to the two SRT regimens showed a 12% chance of pCR after SRT with delayed surgery [6]. The aim of this sub-analysis of the Stockholm III trial is to anal-

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yse tumour regression in the whole trial and correlate regression to survival.

Methods

The Stockholm III trial (clinicaltrials.gov NCT00904813), a randomised multicentre study has previously been described in detail [21,22]. In short, between 1998 and 2013, 840 patients were randomised between three different RT courses, 5 × 5 Gy and surgery within one week (SRT), 5 × 5 Gy and surgery after 4–8 weeks (SRT-delay) or 25 × 2 Gy during 5 weeks, without concomitant chemotherapy, and surgery after 4–8 weeks (LRT-delay). In total, 18 Swedish hospitals participated. Inclusion criteria were patients with biopsy proven adenocarcinoma of the rectum, defined as a tumour ≤15 cm from the anal verge, without signs of distant metastases, and judged to be primarily resectable by an abdominal procedure. Exclusion criteria were a polyp cancer, severe cardiovascular comorbidities and previous RT to the pelvis. Standard surgery was total mesorectal excision (TME), performed by anterior resections (AR), abdomino-perineal excisions (APE) or Hartmann's procedure. The primary endpoint in the trial was time to local recurrence and secondary endpoints included overall survival (OS) and cumulative incidence of distant metastases. Other endpoints were postoperative complications, radiation toxicity and early mortality. After a protocol amendment in 1999, "downstaging" or tumour regression was introduced as a secondary endpoint, which is the main outcome to be analysed in the present study.

Delay to surgery

According to the study protocol, patients randomised to SRT should undergo surgery within one week after end of RT. Patients randomised to SRT-delay or LRT-delay should have surgery performed within 4–8 weeks after last given radiation fraction. This results in a range of the time from the first fraction to surgery (overall treatment time, OTT) of 7–13 days, 33–63 days and 53–91 days in the SRT, SRT-delay and LRT-delay groups, respectively, depending on weekends, holidays and other logistic reasons. In the present study, patients were grouped and analysed as treated, based on the RT they de-facto received and the true interval between start of RT and surgery, in the groups specified above. Patients with OTTs in between the pre-specified groups were considered as protocol violations and excluded from the groups. For the analyses of tumour regression over time, all patients that received 5 × 5 Gy were categorised in intervals of two weeks, i.e also including patients with "protocol-violations". In the survival analyses in relation to tumour regression, all patients receiving 5 × 5 Gy or 2 × 25 Gy were pooled and analysed together.

Follow-up

Data on tumour- and patient characteristics, type of surgery, recurrences and death have been collected in the Swedish ColoRectal Cancer Registry (SCRCR), used as an electronic clinical registration form. Data were reported by the local physician at surgery and at follow-up on 1, 3 and 5 years after surgery, or if an event had occurred. Data on survival, local- and distant recurrences were collected from the SCRCR with 2018–03-31 as last day of follow-up, when all patients had been followed for at least 5 years. To assure that all data were up-to-date, participating hospitals were asked to make an extra report if patients were in between the ordinary reporting intervals. Data on preoperative staging was not available for analyses in the present study. Reporting MRI-stage was not stated in the initial study protocol and has not routinely been reported to the SCRCR until ≥2007. Further, the clinical T-stage

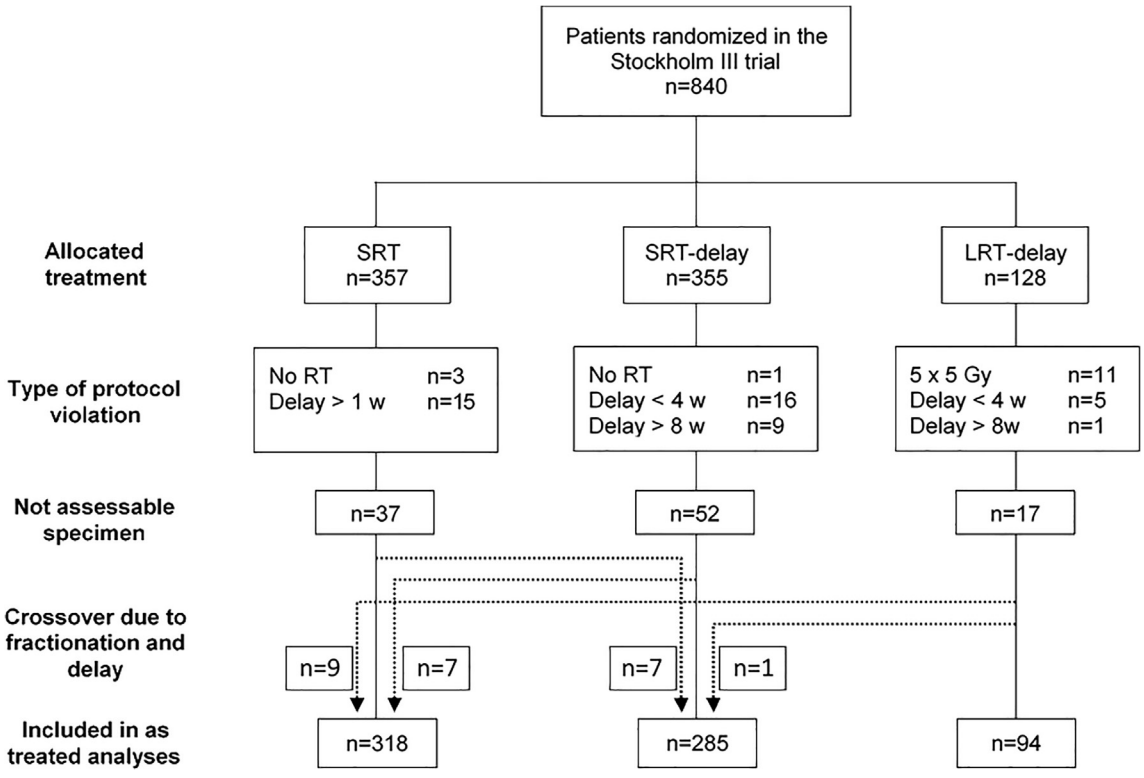

Fig. 1. Flowchart of included patients in the as treated comparison. Crossover was possible when both fractionation and waiting interval matched another group. RT radio therapy, SRT short course radiotherapy, 5 × 5 Gy with surgery within one week, SRT-delay 5 × 5 Gy with delayed surgery for 4–8 weeks, LRT-delay long course 25 × 2 Gy and surgery after 4–8 weeks.

variable in the registry has been shown not to be robust, with as low as 35% completeness [23].

All available microscopy slides were retrieved from the eight local pathology departments that initially handled the original resection specimens. The slides were re-evaluated by one experienced GI-pathologist, blinded to allocated treatment. Factors that were reassessed were: T-stage, N-stage, tumour differentiation, distance to circumferential resection margin (CRM), perineural-(PN) and extra-mural vein invasion (EMVI). For assessment of tumour regression (TRG), the Dworak grading system was used: the Dworak regression grade 0 (TRG 0), no regression; grade 1 (TRG 1), dominant tumour mass with obvious fibrosis and/or vasculopathy; grade 2 (TRG 2), dominantly fibrotic changes with few tumour cells or groups (easy to find); grade 3 (TRG 3), very few (difficult to find microscopically) tumour cells in fibrotic tissue with or without mucous substance; grade 4 (TRG 4), no tumour

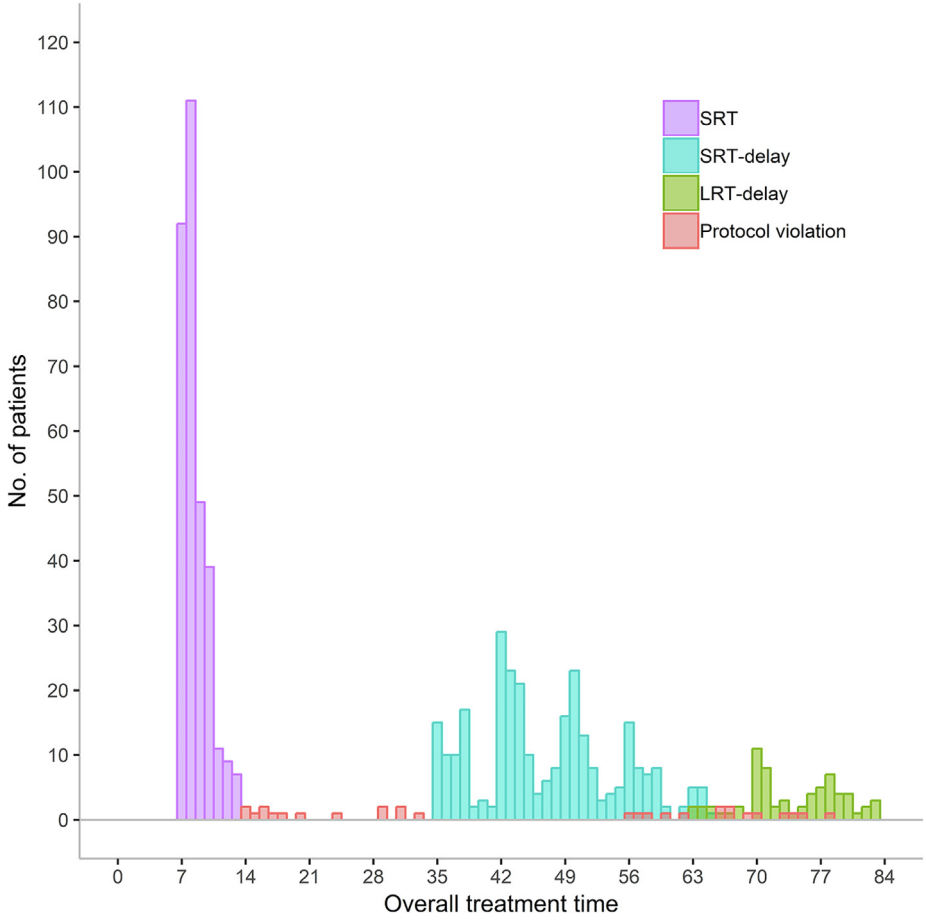

Fig. 2. Number of patients by overall treatment time, time between start of radiotherapy and surgery. Patients are categorised into groups based on the treatment they actually received – as treated. SRT short course radiotherapy, 5 × 5 Gy with surgery within in one week, SRT-delay 5 × 5 Gy with delayed surgery for 4–8 weeks, LRT-delay long course 25 × 2 Gy, Protocol violation due to incorrect waiting interval.

Table 1
Baseline patient characteristics and overall treatment time.

		SRT	SRT-delay	LRT-delay	*p*
n		318	285	94	
Sex	Male	188 (59.1%)	170 (59.6%)	58 (61.7%)	0.90
	Female	130 (40.9%)	115 (40.4%)	36 (38.3%)	
Age		66.8 (9.2)	67.2 (9.0)	66.1 (8.4)	0.59
ASA-score	1	58 (29.4%)	47 (25.8%)	16 (34.8%)	0.71
	2	113 (57.4%)	107 (58.8%)	26 (56.5%)	
	3	25 (12.7%)	28 (15.4%)	4 (8.7%)	
	4	1 (0.5%)	0 (0.0%)	0 (0.0%)	
Distance from anal verge		7.4 (3.8)	7.7 (3.7)	8.9 (3.4)	0.005
Type of operation	AR	195 (61.3%)	164 (57.5%)	73 (77.7%)	0.015
	Hartman	16 (5.0%)	12 (4.2%)	5 (5.3%)	
	APE	107 (33.6%)	108 (37.9%)	16 (17.0%)	
	Local excision	0 (0.0%)	1 (0.4%)	0 (0.0%)	
OTT, mean (SD)		8.4 (1.4)	47.0 (7.6)	78.0 (8.4)	<0.001

Numbers are number of patients (%) if not otherwise specified. ASA American Society of anesthesiologists. AR anterior resection. APE abdominoperineal excision. OTT overall treatment time or days from start of radiotherapy to surgery, SRT short course radiotherapy 5 × 5 Gy with surgery within one week, SRT-delay 5 × 5 Gy with surgery after 4–8 weeks, LRT long course RT 2 × 25 Gy with surgery after 4–8 weeks.

Table 2
Pathology outcomes.

		SRT	SRT-delay	LRT-delay	*p*-value
N		318	285	94	
ypStage	ypStage 0‡	4 (1.3%)	35 (12.3%)	3 (3.2%)	<0.0001
	ypStage I	86 (27.0%)	100 (35.1%)	27 (28.7%)	
	ypStage II	107 (33.6%)	72 (25.3%)	36 (38.3%)	
	ypStage III	109 (34.3%)	68 (23.9%)	24 (25.5%)	
	ypStage IV	4 (1.3%)	4 (1.4%)	2 (2.1%)	
	ypStage x†	8 (2.5%)	6 (2.1%)	2 (2.1%)	
ypT-stage	ypT0	4 (1.3%)	30 (10.5%)	3 (3.2%)	<0.0001
	ypTis	2 (0.6%)	6 (2.1%)	2 (2.1%)	
	ypT1	13 (4.1%)	34 (11.9%)	6 (6.4%)	
	ypT2	100 (31.4%)	78 (27.4%)	27 (28.7%)	
	ypT3	188 (59.1%)	124 (43.5%)	54 (57.4%)	
	ypT3 a/b	135 (42.5%)	90 (31.6%)	37 (39.4%)	
	ypT3 c/d	50 (15.7%)	33 (11.6%)	12 (12.8%)	
	ypT3 x	3 (0.9%)	1 (0.4%)	5 (5.3%)	
	ypT4	11 (3.5%)	13 (4.6%)	2 (2.1%)	
	ypT4a	3 (0.9%)	5 (1.8%)	1 (1.1%)	
	ypT4b	6 (1.9%)	4 (1.4%)	1 (1.1%)	
	ypTx †	2 (0.6%)	4 (1.4%)	0 (0.0%)	
ypN-stage	ypN0	199 (62.6%)	211 (74.0%)	66 (70.2%)	0.046
	ypN1	76 (23.9%)	48 (16.8%)	15 (16.0%)	
	ypN2	37 (11.6%)	23 (8.1%)	11 (11.7%)	
	ypNx †	6 (1.9%)	3 (1.1%)	2 (2.1%)	
EMVI+	Yes	124 (39.0%)	75 (26.3%)	35 (37.2%)	0.005
	No	192 (60.4%)	204 (71.6%)	59 (62.8%)	
	N/A	2 (0.6%)	6 (2.1%)	0 (0.0%)	
PN+	Yes	67 (21.1%)	25 (8.8%)	13 (13.8%)	<0.0001
	No	249 (78.3%)	254 (89.1%)	81 (86.2%)	
	N/A †	2 (0.6%)	6 (2.1%)	0 (0.0%)	
Differentiation*	Adenoma	1 (0.3%)	4 (1.6%)	0 (0.0%)	0.028
	High	15 (4.8%)	24 (9.4%)	6 (6.6%)	
	Moderate	251 (79.7%)	201 (78.8%)	79 (86.8%)	
	Low	22 (7.0%)	10 (3.9%)	0 (0.0%)	
	Mucinous	25 (7.9%)	16 (6.3%)	5 (5.5%)	
	Signet ring	1 (0.3%)	0 (0.0%)	1 (1.1%)	
	N/A †	1 (0.3%)	4 (1.6%)	0 (0.0%)	
CRM	>1 mm	228 (92.3%)	193 (96.0%)	66 (94.3%)	0.26
	≤ 1 mm	19 (7.7%)	8 (4.0%)	4 (5.7%)	
	N/A †	71	84	24	
Dworak	TRG 0	29 (9.1%)	20 (7.0%)	4 (4.3%)	<0.0001
	TRG 1	233 (73.3%)	124 (43.5%)	42 (44.7%)	
	TRG 2	50 (15.7%)	92 (32.3%)	37 (39.4%)	
	TRG 3	2 (0.6%)	16 (5.6%)	7 (7.4%)	
	TRG 4	4 (1.3%)	29 (10.2%)	3 (3.2%)	
	N/A†	0 (0.0%)	4 (1.4%)	1 (1.1%)	
pCR		1 (0.3%)	29 (10.4%)	2 (2.2%)	<0.0001

Numbers are n (%) if not otherwise specified. EMVI extramural vascular invasion, Pn perineural invasion, CRM circumferential resection margin, pCR pathological complete response (T0N0). N/A not assessable. *ypT0 not included. †Not included in statistical calculation. ‡ Includes ypT0 and ypTis, SRT short course radiotherapy 5 × 5 Gy with surgery within one week, SRT-delay 5 × 5 Gy with surgery after 4–8 weeks, LRT long course RT 2 × 25 Gy with surgery after 4–8 weeks.

cells, only fibrotic mass (total regression or complete response) [24]. ypStage was calculated according to the AJCC 8th edition, ypStage 0 includes T0 and Tis [25]. pCR was defined as no signs of viable tumour or metastatic nodes (ypT0N0). Only specimens possible to assess for both T- and N-stage were included in the calculation of ypStages and pCR-rates. Previous publications have shown that patients with pCR have improved survival and few recurrences compared to patients with no-pCR [26,27]. However, the optimal tumour regression grading system in respect of predicting survival and cancer relapse is not determined. One remaining issue is if patients with near-complete response have similar outcomes compared to patients with complete pCR [16,28]. Consequently, we reclassified the Dworak regression grade into TRG 0–2, TRG 3 and TRG 4, in the survival analyses. Estimation of CRM-rates included only specimens that were possible to assess regarding CRM, either as the distance from primary tumour or from metastatic lymph nodes. A distance of ≤1 mm to CRM was deemed as positive margin.

Statistical methods

Outcome of primary interest of this study was tumour regression and other outcomes were OS and TTR. Distribution of patient and tumour characteristics between the groups were compared using χ^2-test, Fisher's exact or Kruskal–Wallis' test, where applicable. For the calculation of p-values of differences in T-stage, N-stage, EMVI+, PN+, differentiation and TRG, missing values were not included. The Kaplan–Meier method was used to calculate survival curves. Events defining TTR were local recurrence or distant metastases. Both TTR and OS were calculated from the day of randomisation to date of event or last follow-up. Differences in survival curves were calculated using the log-rank test. For survival estimations all patients, independent of fractionation, with assessable specimens regarding, T-stage, N-stage and the Dworak regression grade were pooled and included in the analyses; patients with local excision were excluded from analyses. Since TRG is dependent on the interval between RT and surgery, we calculated OS

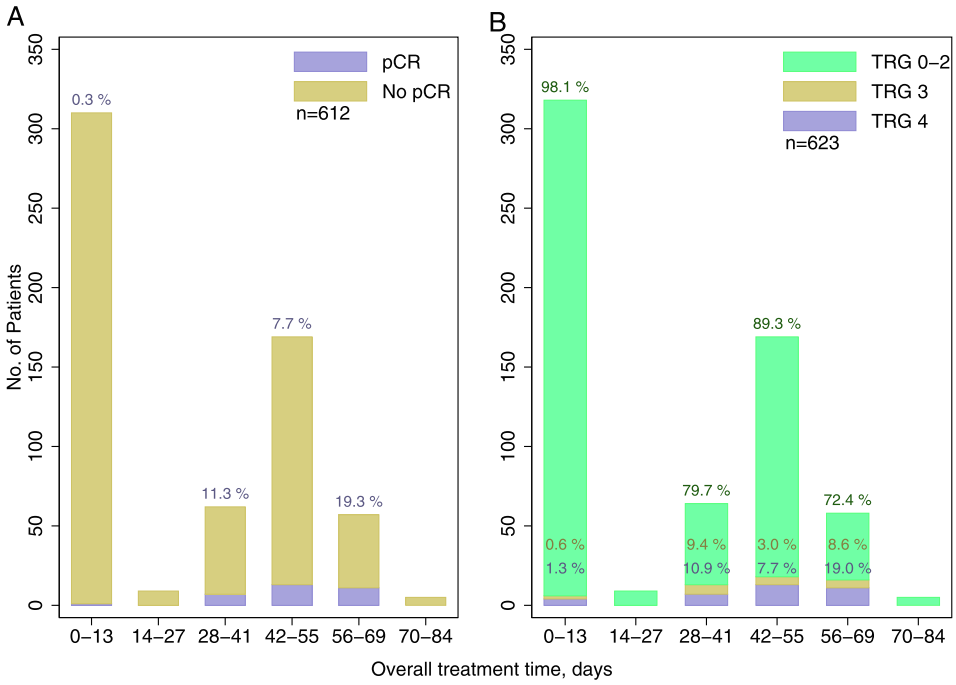

Fig. 3. Tumour regression after SRT (5 × 5 Gy) by overall treatment time in 2-week intervals. pCR pathologically graded complete response. A Proportion of pathologically graded complete responses. B Proportion of morphological tumour regression according to Dworak. TRG, tumour regression grade.

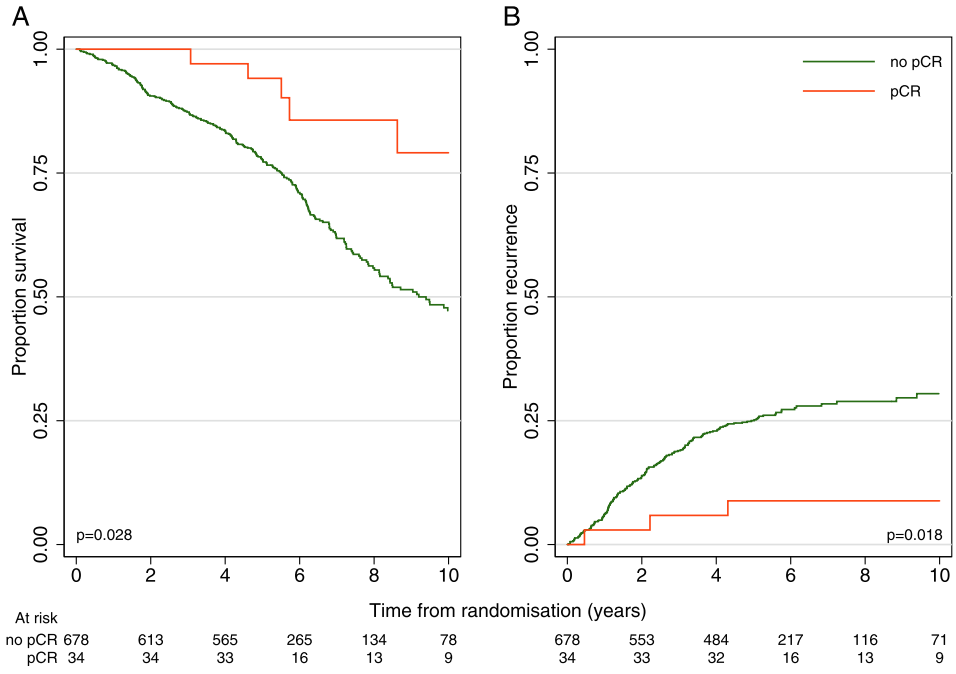

Fig. 4. Kaplan–Meier's estimates by pCR, pathologically graded complete response, all patients with assessable ypT and ypN stages. A Overall survival. B Time to recurrence.

and TTR restricted to patients in the groups with a delay to surgery (SRT-delay and LRT-delay), as a sensitivity analysis. Cox regression was used to calculate hazard ratios (HR). Proportional hazards assumption was tested on the basis of Schoenfeld's residuals. Covariates in the adjusted Cox models were older age dichotomised to <75 or ≥75 years, type of surgery (AR, APE or Hartmann) and distance from anal verge (low, medium, high); these variables were considered as possible confounders and chosen based on the assumption that age, type of surgery and tumour height may affect, prognosis and survival. P-values ≤0.05 were considered statistically significant. STATA v. 14 (STATA corp, Texas, USA) and R v. 3.5.1 (The R foundation for Statistical Computing) were used for statistical calculations and graphs.

Results

Between October 1998 and January 2013, a total of 840 patients were randomised in the Stockholm III trial, distributed as 357, 355 and 128 to SRT, SRT-delay and LRT-delay, respectively. Patients

Table 3
Overall survival and time to recurrence.

	no pCR (ref.)	pCR crude HR	*p*	pCR adjusted HR	*p*
n	678	34		34	
OS HR (95% Ci)	1.0	0.48 (0.25;0.93)	0.030	0.51 (0.26;0.99)	0.046
TTR HR (95% ci)	1.0	0.28 (0.09;0.87)	0.028	0.27 (0.09;0.86)	0.027
	TRG0-2 (ref.)	TRG 3 crude HR	p	TRG 3 adjusted HR	p
n	661	25		25	
OS HR (95% Ci)	1.0	0.72 (0.34;1.53)	0.401	0.81 (0.38;1.72)	0.578
TTR HR (95% ci)	1.0	0.82 (0.36;1.85)	0.631	0.83 (0.37;1.88)	0.661
	TRG0-2 (ref.)	TRG 4 crude HR	p	TRG 4 adjusted HR	p
n	661	38		38	
OS HR (95% Ci)	1.0	0.36 (0.18;0.72)	0.004	0.38 (0.19;0.77)	0.008
TTR HR (95% ci)	1.0	0.24 (0.08;0.74)	0.013	0.24 (0.08;0.74)	0.013
	TRG 3 (ref.)	TRG 4 crude HR	p	TRG 4 adjusted HR	p
n	25	38		38	
OS HR (95% Ci)	1.0	0.36 (0.11;1.15)	0.085	0.47 (0.13;1.69)	0.248
TTR HR (95% ci)	1.0	0.30 (0.07;1.20)	0.089	0.38 (0.09;1.61)	0.193

Adjusted model include older age, sex and type of surgery. HR Hazard ratio, TRG 0–4 Dworak's regression grade 0–4, OS overall survival, TTR time to recurrence.

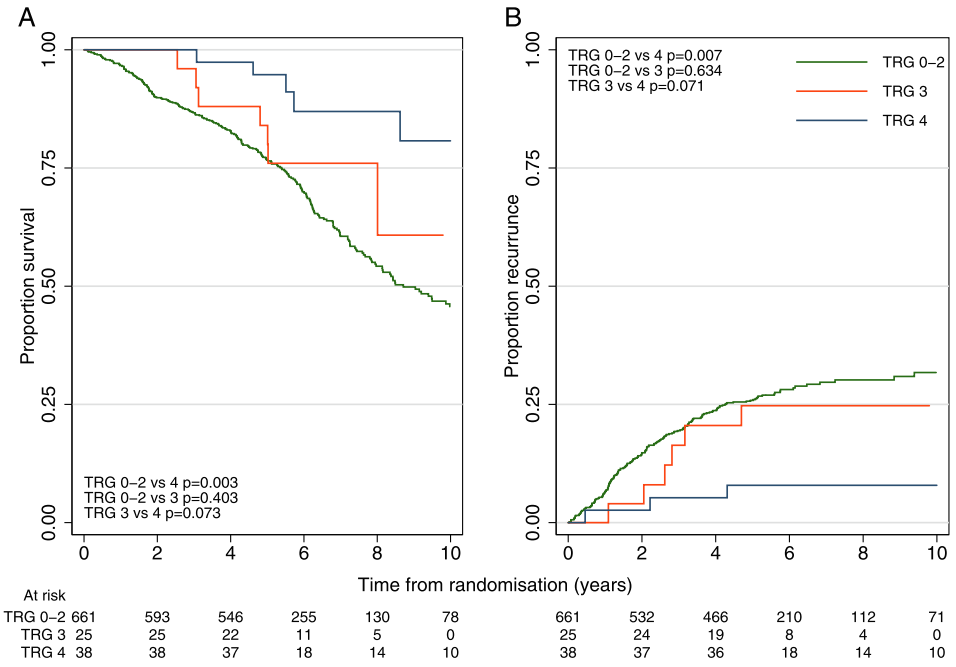

Fig. 5. Kaplan–Meier's estimates by regression grade according to Dworak, all patients with assessable tumour regression. TRG, tumour regression grade. p is log-rank test A Overall survival. B Time to recurrence.

adhering to allocated treatment were 338 (94.6%) in SRT, 328 (92.4%) in SRT-delay and 112 (87.5%) in LRT-delay. Protocol violations consisted of other radiation fractionations or different time intervals than allocation prescribed. For the as treated comparison, 318, 285 and 94 patients were included in the SRT, SRT-delay and LRT-delay groups, respectively. Reasons of protocol violation and flow-chart for the current study are presented in Fig. 1. Distribution of patients in the as-treated groups and patients with protocol violation over OTT is presented in Fig. 2. The 33 excluded patients from the as-treated groups had no significant differences in age, gender distribution, type of surgery or tumour distance from anal verge, but had a higher proportion of ASA scores 3 and 4 compared to the included patients. In total, 730 (86.9%) of 840 specimens were available for reassessment, the proportion of missing slides was not statically significantly different between the three randomisation arms (data not shown). Sixty-five specimens were not possible to retrieve from the local pathology department and 45 specimens could not be assessed due to technical reasons or missing slides. Baseline patient characteristics did not differ between the as-treated groups except that in the LRT-delay group, tumours were located at a longer median distance from anal verge, with a subsequently higher proportion of ARs (Table 1).

There were significantly lower ypT-stages in the SRT-delay group compared to the other groups. Both the frequency of PN+ and EMVI+ were lower in SRT-delay compared to SRT and LRT-delay. The CRM was not assessable in 179 (25.7%) of 697 of the patients. A distance to CRM of $\leq$1 mm was seen in 31 (6.0%) of 518 of the patients, without significant difference between the groups. After SRT with immediate surgery, TRG 0–2 was seen in 312 of 318 (98.1%). The highest proportion of pCR was seen in SRT-delay (Table 2). When grouping patients receiving 5 $\times$ 5 Gy in 2 week intervals based on OTT, it was noted that it requires at

Table 4
Pathology outcomes and number of events by Dworak's regression grade.

	TRG 0	TRG 1	TRG 2	TRG 3	TRG 4
N	55	421	186	25	38
ypTstage					
T0	0 (0)	0 (0)	0 (0)	0 (0)	38 (100)
Tis	5 (9.1)	3 (<1%)	1 (<1)	0 (0)	0 (0)
T1	4 (7.2)	19 (4.5)	19 (10.4)	12 (48)	0 (0)
T2	14 (25.5)	132 (31.5)	58 (31.7)	11 (44)	0 (0)
T3	30 (54.5)	249 (59.4)	101 (55.1)	2 (8)	0 (0)
T4	2 (3.6)	16 (3.8)	4 (2.2)	0	0 (0)
ypNStage					
N0	34 (61.8)	272 (64.6)	130 (69.9)	23 (92)	34 (89.5)
N1	12 (21.8)	98 (23.3)	34 (18.3)	2 (8)	2 (5.3)
N2	9 (16.4)	44 (10.5)	20 (10.8)	0 (0)	0 (0)
N/A	0 (0)	7 (1.7)	2 (1.1)	0 (0)	2 (5.3)
CRM $\leq$ 1 mm	3 (7.7)	24 (7.2)	6 (3.9)	0	0
EMVI+	21 (38.2)	162 (38.7)	61 (32.8)	2 (8)	0 (0)
Perineural invasion	6 (10.9)	77 (18.4)	27 (14.5)	0 (0)	0 (0)
Events					
Local recurrence	4 (7.2)	15 (3.6)	6 (3.2)	1 (4)	0 (0)
Distant metastasis	14 (25.5)	117 (27.8)	39 (21.0)	5 (20)	3 (7.9)
Death	26 (47.3)	189 (45.9)	69 (37.1)	7 (28)	8 (21.1)

All patients with assessable tumour stage. CRM circumferential resection margin, EMVI extramural vascular invasion. Death is any cause of death. TRG Tumour regression grade according to Dworak.

least 3 weeks of delay after the end of RT to achieve pCR; a pCR was achieved in only one patient with a shorter waiting time than 3 weeks (Fig. 3).

Median follow-up time was 5.7 years (ICQ 4.9–14.3). Seven hundred and twelve patients were included in the survival analyses based on pCR and 724 patients in the pooled analyses by the Dworak regression grades. Patients with pCR had statistically significantly better outcomes for both OS and TTR, compared to patients with no pCR (Fig. 4). Differences in HR of OS and TTR remained statistically significant after adjusting for covariates in the Cox model (Table 3).

Patients with specimens assessed as TRG 4 had better OS and TTR compared to patients with TRG 0–2. (Fig. 5). Cox regression models comparing TRG 0–2 with TRG 3 and TRG 4 showed that TRG 4 has significantly better OS and TTR compared to the Dworak grade 0–2. There were no statistically significant differences when comparing TRG 0–2 with TRG 3 or TRG 3 with TRG 4, in neither the unadjusted nor adjusted models (Table 3). The results remained stable in the sensitivity analyses including only patients with a delay to surgery (SRT-delay and LRT-delay) (Supplementary Fig. 1). Pathology graded outcomes in TRG 3 were more similar to TRG 4 than TRG 0-2. (Table 4).

Discussion

In the present substudy of the Stockholm III trial we found lower postoperative stages, higher frequency of pCR and higher TRG after SRT-delay compared to SRT and LRT-delay. Patients with pCR or TRG 4 had longer OS and TTR. A near complete tumour regression (TRG 3) was not associated with the same survival gain as a complete tumour regression (TRG 4).

Among the strengths of the present study is the large randomised patient cohort, with little discrepancies in patient characteristics between the allocated treatments. Since tumour regression has not been reported to the SCRCR, all available specimens were reassessed by one pathologist blinded to treatment. However, there are some limitations. In about 13% of the patients, the pathology specimen or slides were missing or not assessable. However, since there was no difference in the proportion missing between the treatment groups this resulted in a non-differential misclassification. Only one pathologist evaluated the slides. It is known that there is variability in the evaluation, particularly in the separation between Dworak 2 and 3, but it is not our belief that this would have changed the results of this entirely blinded evaluation [29,30]. The long recruitment period in the Stockholm III trial could naturally affect the results; today patients are probably better preoperatively staged, the delivery of the RT has improved, and the surgical technique has been further optimised. These differences over time would however most likely only dilute the results, since recruitment to all arms went on during the whole trial period. Most patients were also included during the last 6 years of the recruitment period.

In the present study, TRG 4 and pCR were virtually only seen after an OTT exceeding 4 weeks, which confirmed the findings in the interims analysis [6]. Previous studies found that the time needed to induce downstaging or tumour regression after 5×5 Gy was at least 10 days between start of RT and surgery [4,5]. TRG 4 and pCR after SRT-delay were significantly higher compared to after LRT. Previous trials exploring 5×5 Gy with immediate surgery vs. CRT (LRT with concomitant chemotherapy) have shown similar oncological outcomes, but for obvious reasons with a higher frequency of tumour regression after CRT [31–34]. Retrospective studies analysing tumour regression after SRT-delay vs CRT have concluded a higher probability for pCR after CRT [10,35]. Since complete data on pre-operative staging were missing, the interpretation and generalisability of the data might be somewhat troublesome. Only about half of the patients included in the Stockholm III trial had potential information on preoperative staging in the SCRCR (patients included >2007). Some 85% of the patients were reported to have cStage II or III (data not published). Further, patients eligible for randomisation were mainly considered as having "bad" tumours, more advanced tumours (T4, MRF +) have been treated outside the study, in accordance with Swedish national care programs [36]. In the present study no conclusions on the optimal waiting time regarding maximum regression could be drawn after categorising OTT in two-week intervals in the present study. This was also seen in the French GRECCAR-6 trial, where no increase in pCR rates were seen after 11 compared to 7 weeks after CRT, but retrospective studies indicate a relationship [8,11,12,37,38].

We found that outcomes in patients with TRG 3 were more like in patients with lower grades of tumour regression (TRG 0–2) regarding OS and TTR, but histopathology features were more similar compared to TRG 4. Previous studies show contradictive results regarding if downstaging per-se is beneficial or if a pCR has to be achieved to truly indicate a low risk of recurrence [14,16–18]. In the present study, only the primary tumours were assessed regarding regression; lymph nodes were categorised as metastatic or not. In two patients (5.3%) with TRG 4, metastatic nodes (ypN1) were found, indicating that a complete tumour regression cannot predict complete lymph node regression in all cases. Results from other studies are conflicting regarding the predictive value of tumour regression on nodal regression and the subsequent prognostic value [15,39–41].

In the minimum 2-year follow up the Stockholm III trial it was concluded that the OS and recurrence-free survival were similar in SRT and SRT-delay [21]. This indicates that there is a low risk in delaying surgery for 4–8 weeks after SRT in patients with tumours with limited or no response to radiation. Adjuvant chemotherapy was not routinely used after rectal cancer surgery in Sweden during the inclusion of the patients in the Stockholm III trial; thus, it is not possible to evaluate whether a delay will result in more systemic recurrences due to less effects of an adjuvant treatment initiated 4–8 weeks later than if surgery had been done immediately [42]. The effect of delaying surgery in patients with no tumour regression (TRG 0) could not be analysed in this study due to the small number of patients. Other studies show conflicting outcomes for patients with no tumour regression compared to poor or intermediate response after CRT [14,17,18].

In conclusion, 5×5 Gy in one week with a delay of surgery between 4 and 8 weeks induces pCR in about 10 per cent of the patients and is in this respect superior to 2 Gy $\times$ 25 in five weeks. A very good RT response in the tumour, TRG 4 using the Dworak system, or a pCR, is associated with superior OS and TTR.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.03.016.

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