Original article

Tumour regression in the randomized Stockholm III Trial of radiotherapy regimens for rectal cancer

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Background: **The Stockholm III Trial randomized patients with primary operable rectal cancers to either short-course radiotherapy (RT) with immediate surgery (SRT), short-course RT with surgery delayed 4–8 weeks (SRT-delay) or long-course RT with surgery delayed 4–8 weeks. This preplanned interim analysis examined the pathological outcome of delaying surgery.**

Methods: **Patients randomized to the SRT and SRT-delay arms in the Stockholm III Trial between October 1998 and November 2010 were included, and data were collected in a prospective register. Additional data regarding tumour regression grade, according to Dworak, and circumferential margin were obtained by reassessment of histopathological slides.**

Results: **A total of 462 of 545 randomized patients had specimens available for reassessment. Patients randomized to SRT-delay had earlier ypT categories, and a higher rate of pathological complete responses (11·8 *versus* 1·7 per cent; $P = 0·001$) and Dworak grade 4 tumour regression (10·1 *versus* 1·7 per cent; $P < 0·001$) than patients randomized to SRT without delay. Positive circumferential resection margins were uncommon (6·3 per cent) and rates did not differ between the two treatment arms.**

Conclusion: **Short-course RT induces tumour downstaging if surgery is performed after an interval of 4–8 weeks.**

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Introduction

Preoperative radiotherapy (RT) is recommended to many patients with rectal cancer as it leads to a reduced local recurrence rate[1–6] and, in some studies[7,8], improved overall survival. RT can induce downsizing and/or downstaging of the primary tumour and may increase sphincter preservation, although this is controversial[9]. A conventional, long-course RT schedule (approximately 50 Gy over 6 weeks) combined with chemotherapy (CRT) induces tumour downstaging when surgery has to be delayed owing to the acute reaction caused by the treatment[8,10]. In contrast, it had been thought that hypofractionated, short-course RT (25 Gy in 1 week) did not induce downstaging[11]. However, two large trials[4,12] found tumour regression after a short delay (less than 1 week). In addition, in three retrospective[13–15] and one prospective[16] studies, short-course RT induced downstaging if surgery was delayed for more than 4 weeks.

In 1998, the Stockholm Colorectal Cancer Study Group initiated the Stockholm III Trial to address the issues of fractionation and timing to surgery, with local recurrence rate as the primary endpoint. The multicentre randomized trial has recruited patients with primary resectable rectal cancers to one of three preoperative RT regimens: short-course RT with surgery within a week (SRT), short-course RT with surgery delayed for 4–8 weeks (SRT-delay) and long-course RT with surgery delayed for 4–8 weeks (LRT-delay). The trial closed for further inclusion in February 2013. The aim of this second preplanned interim analysis was to compare the pathological outcomes in the two short-course RT randomization arms after 500 included patients, with a special focus on T and N categories, involved resection margins and tumour regression.

Methods

The Stockholm III Trial

The Stockholm III Trial (ClinicalTrials.gov registration number NCT00904813) has been described previously[17]. The trial included patients with a primary rectal cancer, defined as an adenocarcinoma within 15 cm of the anal verge, and judged to be resectable. The patients were scheduled for an open abdominal procedure. Exclusion criteria were previous RT to the abdominal or pelvic regions, signs of severe ischaemic disease or symptoms of severe arteriosclerosis.

After giving informed consent, patients were randomized to SRT, SRT-delay or LRT-delay. A hospital could choose to participate in the three-arm (SRT, SRT-delay or LRT-delay) or the two-arm (SRT or SRT-delay) comparison.

Preoperative radiotherapy

In patients randomized to short-course RT (SRT and SRT-delay), a total dose of 25 Gy was given over 5–7 consecutive days using a four-field box technique, including the primary tumour and the primary and secondary lymph nodes in the pelvis. No individual tumour target was drawn in the few first years of the study, but this has become more common with time. After the first few years the anal canal was included in the target volume only if an abdominoperineal resection was planned. Otherwise, the lower limit of the beams was 3–4 cm above the anal verge or at least 5 cm below the lowest part of the visible tumour. The upper beam limit was initially typically at mid-L5, or 1–1·5 cm above the promontory. In more recent years it was individualized. The dorsal limit of the lateral beams was behind the sacrum, and the anterior limit was sufficiently ventral to cover the obturator nodes, the entire mesorectum with tumour extension and the internal iliac nodes. The lateral limits of the anterior–posterior beams extended 1–1·5 cm outside the pelvic rim. In patients randomized to LRT-delay the same target and technique was used, but with a daily fraction of 2 Gy in 25 fractions over 5 weeks, giving a total dose of 50 Gy. All treatments were given with high-energy photons (8–20 Gy). Appropriate shielding of non-target volumes was prescribed. Individual three-dimensional dose planning of the tumour target volume and multileaf collimators were used at all hospitals during the latter part of the study, but not during the early years.

Surgery

Patients underwent anterior resection, abdominoperineal resection or Hartmann's procedure. The standard operation included total mesorectal excision, defined as removal of the rectum with the entire mesorectum by sharp dissection along the mesorectal fascia down to the pelvic floor. According to the protocol, patients randomized to the SRT group were to undergo surgery 1–7 days after the completion of RT. During the later phase of the study, it was stressed that it was preferable to carry out surgery within 1–4 days[17,18]. In the two other groups (SRT-delay and LRT-delay) the surgery was undertaken 28–56 days after the completion of RT. Bowel preparation, and antiseptic and antithrombotic prophylaxis were administered according to local routines.

Follow-up

Data on all patients with rectal cancer are reported continuously to the Swedish Rectal Cancer Register by the Regional Oncology Centres. The information in the register includes clinical patient characteristics, details of preoperative assessment, preoperative therapy, surgery and perioperative complications, the pathologists' and surgeons' assessments of clearance of primary tumours, postoperative mortality and morbidity, histopathology and follow-up data on recurrences, metachronous metastases and cause of death. The Stockholm Regional Oncology Centre is responsible for the study database, which is validated continuously[19].

Interim analyses of the Stockholm III Trial

Data from an interim analysis of the Stockholm III Trial after the first 303 randomized patients have been reported previously[17]. A second interim analysis was preplanned with the aim of comparing the downstaging and downsizing effects of the preoperative short-course RT schedules after 500 included patients. The present study reports the findings regarding pathological tumour downstaging in the SRT and SRT-delay arms. The LRT-delay arm is not included in this interim analysis because it was expected that too few patients would have been included in the three-arm randomization at this time. No formal power calculation for the analyses of the endpoints in the second interim analysis was done.

Present study

The present study identified patients randomized to the SRT and SRT-delay arms from the trial start in October 1998 to November 2010. Demographic data, allocated treatment arm, RT received and surgical data were extracted from the Swedish Rectal Cancer Register. The specimens were originally dissected, prepared

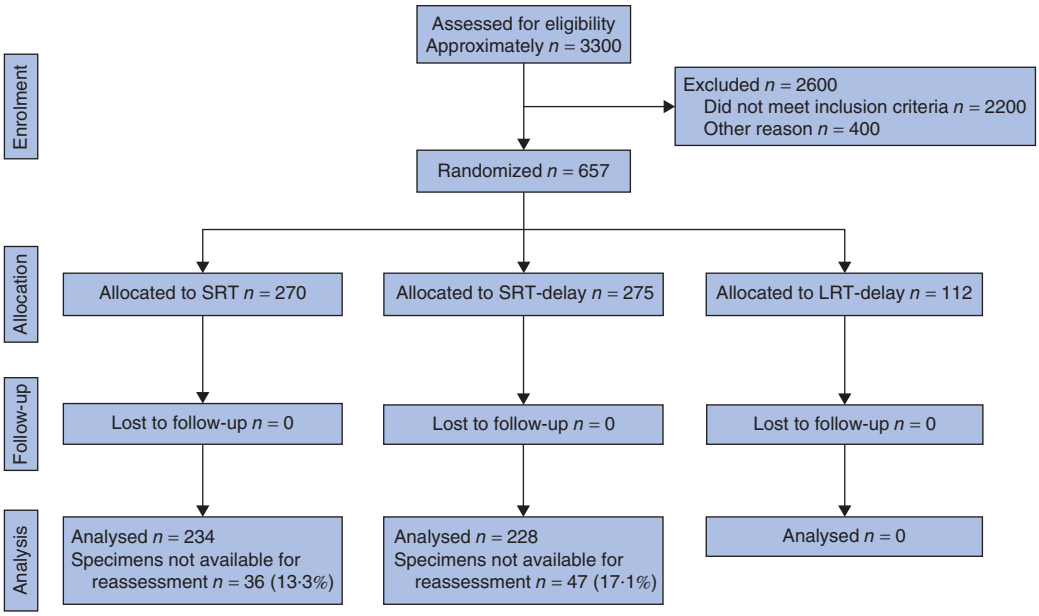

Fig. 1 Flow diagram of randomization to the Stockholm III Trial, and patient selection to the present study of the trial arms with short-course radiotherapy (RT) with immediate surgery (SRT) and short-course RT with surgery delayed 4–8 weeks (SRT-delay). The trial arm with long-course RT and surgery delayed 4–8 weeks (LRT-delay) was not analysed in the present study

and assessed by eight different pathology departments according to local routines. For the present study, all available slides were retrieved for blinded reassessment by one pathologist. If the reassessment was impaired by technical difficulties, such as damaged slides or pale staining, the stage or circumferential resection margin (CRM) was recorded as not assessable. Patients for whom single whole-mount sections of the tumour were missing were excluded from the analysis of CRM. The TNM staging system (6th edition)[20,21] was used for staging.

At pathological assessment, the CRM was defined as positive if the tumour involved the CRM or was 1 mm or less from the margin. It was judged to be negative if the distance from the tumour to the margin exceeded 1 mm.

The Dworak system[22] was used for the assessment of tumour regression: grade 0, no regression; grade 1, dominant tumour mass with obvious fibrosis and/or vasculopathy; grade 2, dominantly fibrotic changes with few tumour cells or groups (easy to find); grade 3, very few (difficult to find microscopically) tumour cells in fibrotic tissue with or without mucous substance; grade 4, no tumour cells, only fibrotic mass (total regression or response).

Statistical analysis

Differences in distribution between the randomization arms regarding pathological outcomes of treatment were tested using Fisher's exact test or the Mann–Whitney *U* test. All analyses were carried out using Stata® version 11.2 (StataCorp LP, College Station, Texas, USA).

Results

From October 1998 to November 2010, 657 patients were randomized in the Stockholm III Trial; 112 were randomized to the LRT-delay arm and were not analysed in the present study. Some 462 of 545 specimens were available for reassessment in the present study (*Fig. 1*). Clinical characteristics and surgical data are shown in *Table 1*.

RT was delivered according to the protocol in all 234 patients in the SRT group and in 226 (99·1 per cent) of 228 in the SRT-delay group ($P = 0{\cdot}947$). The overall treatment time (OTT; time from start of RT to surgery) was according to protocol in 221 (94·4 per cent) of 234 patients (range 6–98, mean 10, median 8, i.q.r. 3 days) and 198 (86·8 per cent) of 228 patients (range 7–428, mean 47, median 45, i.q.r. 13 days) respectively ($P = 0{\cdot}534$). Reasons for protocol violations in the SRT-delay group were a longer OTT in 16 patients and a shorter OTT than prescribed in the trial protocol in 14 patients.

Pathological outcomes are summarized in *Table 2*. There were statistically significant differences in distributions between the randomization arms regarding tumour stage and ypT category; both were lower in patients randomized

Table 1 Demographics and surgery

	SRT ($n = 234$)	SRT-delay ($n = 228$)
Age (years)*	67 (35–89)	67 (40–88)
Sex ratio (M : F)	147 : 87	138 : 90
Tumour height		
Low (< 6 cm)	88 (37·6)	82 (36·0)
Medium (6–10 cm)	90 (38·5)	97 (42·5)
High (> 10 cm)	56 (23·9)	49 (21·5)
Type of surgery		
Anterior resection	143 (61·1)	129 (56·6)
Abdominoperineal resection	78 (33·3)	87 (38·2)
Hartmann's procedure	13 (5·6)	12 (5·3)

Values in parentheses are percentages unless indicated otherwise; *values are median (range). SRT, short-course radiotherapy and immediate surgery; SRT-delay, short-course radiotherapy with surgery delayed 4–8 weeks.

Table 2 Pathological outcomes

	SRT ($n = 234$)	SRT-delay ($n = 228$)	P¶
Tumour stage			0·001
ypT0	4 (1·7)	27 (11·8)	
ypI	69 (29·5)	76 (33·3)	
ypII	71 (30·3)	53 (23·2)	
ypIII	74 (31·6)	55 (24·1)	
ypIV	5 (2·1)	6 (2·6)	
ypx†	11 (4·7)	11 (4·8)	
Tumour category			< 0·001
ypT0	5 (2·1)	27 (11·8)	
ypT1	12 (5·1)	27 (11·8)	
ypT2	74 (31·6)	60 (26·3)	
ypT3‡			
ypT3ab	88 (37·6)	67 (29·4)	
ypT3cd	41 (17·5)	26 (11·4)	
ypT3x	3 (1·3)	1 (0·4)	
ypT4‡			
ypT4a	1 (0·4)	5 (2·2)	
ypT4b	3 (1·3)	3 (1·3)	
ypTx†	7 (3·0)	12 (5·3)	
Node category			0·059
ypN0	149 (63·7)	163 (71·5)	
yp N1	52 (22·2)	41 (18·0)	
ypN2	28 (12·0)	19 (8·3)	
ypNx†	5 (2·1)	5 (2·2)	
Tumour regression*			< 0·001
Grade 0	17 (7·3)	15 (6·6)	
Grade 1	165 (70·5)	104 (45·6)	
Grade 2	41 (17·5)	64 (28·1)	
Grade 3	2 (0·9)	11 (4·8)	
Grade 4	4 (1·7)	23 (10·1)	
Grade x†	5 (2·1)	11 (4·8)	
Circumferential resection margin§	$n = 170$	$n = 150$	1·000#
Positive (≤ 1 mm)	11	9	
Negative (> 1 mm)	159	141	

Values in parentheses are percentages. *Dworak regression grading system. SRT, short-course radiotherapy and immediate surgery; SRT-delay, short-course radiotherapy with surgery delayed 4–8 weeks. †Not included in statistical analysis; ‡subcategorization not used in statistical analysis; §142 patients with missing data excluded from analysis. ¶Mann–Whitney U test, except #Fisher's exact test.

to SRT-delay. Node status did not differ significantly between the groups. There were differences in the rate of complete pathological response: 11·8 per cent in the SRT-delay arm compared with 1·7 per cent for SRT. There was also a significant difference in tumour regression grade according to Dworak between the two groups ($P < 0·001$). Thirty-four patients (14·9 per cent) in the SRT-delay group had grade 3 or 4 tumour regression compared with six (2·6 per cent) in the SRT arm.

Patients without single whole-mount sections of the tumour were excluded from the analysis of CRM; 170 (72·6 per cent) of 234 patients were analysed in the SRT arm, and 150 (65·8 per cent) of 228 in the SRT-delay arm ($P = 0·499$). CRM positivity and node status again did not differ significantly between the treatment arms. The median (range) total number of examined lymph nodes in the SRT and SRT-delay groups were 11 (0–56) and 12 (0–39) respectively, and did not differ between the groups ($P = 0·733$).

Discussion

The present interim analysis comparing pathological outcomes between the two arms of short-course RT in the randomized Stockholm III Trial showed that patients in the SRT-delay group had a lower tumour stage (ypTNM stage), a lower ypT category, a higher rate of complete pathological response and a greater degree of tumour regression than patients in the SRT group. This effect is not seen with traditional short-course RT with surgery within a week unless surgery is postponed[23]. Short-course RT with a delay to surgery has been used outside trials for patients who were not suitable for CRT. Retrospective outcome analyses[13–15] of these patients have indicated a downstaging and downsizing effect similar to that seen here.

In primary resectable rectal cancer, without an involved or threatened mesorectal fascia indicating the risk of a positive CRM, tumour regression *per se* is not an important endpoint after RT. However, more advanced cT3 lesions with a threatened margin, or cT4 tumours demonstrated on preoperative MRI[24], may require tumour regression (downstaging) to allow radical surgery. Several studies have indicated a better prognosis in patients who have shown significant tumour regression after CRT, especially in those with a pathological complete response[25,26].

The proportion of pathological complete responses in the SRT-delay arm in the present study is at the same level as those reported in studies on CRT[9,27,28]. The Stockholm III Trial will not answer whether the tumoricidal effect differs between short-course RT and CRT, as

chemotherapy is not included in the trial. However, two other medium-sized randomized studies[29,30] did not find any difference in local recurrence rates after SRT or CRT, indicating that the effects on local control are similar. Final results from the Stockholm III Trial will probably give an answer to the relative cell kill effect of short-course RT and LRT-delay (50 Gy without concurrent chemotherapy). However, in this report comparison between short-course RT and LRT-delay was not feasible as some hospitals participating in the trial randomized only between SRT and SRT-delay, but not LRT-delay. Hence, too few patients had been included in the LRT-delay arm to allow an interim analysis.

The retrospective reassessment of pathology is one limitation of this study. The standards and routines of specimen preparation, assessment and reporting have gradually improved over time[31]. During the early years of the trial some pathology laboratories had routines that might be considered substandard today. Owing to the lack of single whole-mount sections or few regular slides from the tumour, the pathology could not always be reassessed adequately, and so data were missing for some patients, especially regarding the CRM. However, there was no difference in the proportion of missing CRM data between the randomization arms; the missing data contribute mainly to loss of power, but do not introduce selection bias. The reassessment of specimens by a single pathologist, blinded to the original pathology report, is the strength of this study. Thus, there was no introduction of information bias between the treatment arms in the partly subjective evaluation of tumour stage and regression grading.

With a difference in tumour stage, T category and tumour regression grade between the two groups, a difference in the positive CRM rate might also have been expected, although this was not observed. The proportion of involved CRMs in the reassessed specimen was low in both arms. The likely reason for this is that patients with locally advanced T3 tumours involving the mesorectal fascia or T4 tumours, judged with present terminology as unresectable, were not eligible and therefore not included. Downstaging *per se* is not important in primary resectable tumours. However, the downstaging effect of hypofractionated RT may be important in locally advanced unresectable tumours (often cT4). The use of SRT-delay in these locally advanced tumours when the patient is not fit for CRT has been reported previously[13–15].

The inclusion of some patients with early tumours in the present study is also illustrated by the fact that about 30 per cent of patients in the SRT arm had stage I disease. Early tumours, besides cancer in a polyp, were not an exclusion criterion in the trial protocol. However, there has been a gradual shift during the study towards exclusion of these tumours, especially in the upper and mid rectum, owing to the low risk of local recurrence after surgery alone[32]. In many hospitals there was a lack of appropriate pretreatment local tumour staging with MRI in the early years of the study, and the use of high-standard MRI protocols in all hospitals has been achieved only recently. Pretreatment clinical staging was not recorded in the Swedish Rectal Cancer Register before 2008 and so there is insufficient information on pretreatment cT category and threatened or involved mesorectal fascia to assess whether there were any differences between the groups before RT. An ongoing analysis within the Stockholm III Trial of MRI images before and after RT (correlated with pathological outcome) will provide information on this matter.

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Editor's comments

The Swedes have proved to be evidence ambassadors once again. If radiotherapy alone achieves downstaging (and even complete response) after an interval of only 4–8 weeks then why use chemoradiotherapy (CRT) regimens at all? One week of external beam radiation is accessible, fiscally responsible, and safe compared with 5-fluorouracil-based long-course CRT (6 weeks). Would that it were that simple. Yes, as many as 40 per cent of the Dutch CARTS study experienced grade 3 toxicity with mortality in two of 55 patients[1]. However, there was an adequate response in 30 of 47 patients undergoing subsequent (after 6–8 weeks) transanal excision of the tumour site such that organ preservation was possible. Short-course radiotherapy with long interval (8 weeks) achieved only 10 per cent complete response in a Canadian phase II study of similar size[2].

Rectum-preserving approaches to multidisciplinary care represent the new frontier for this decade[3]. The question is: how do we get there? Whether it is short-course radiotherapy alone or CRT, molecular biology will assist tailored treatment[4] and delaying as long as 11 weeks after radiotherapy may be optimal in selected patients[5]. *BJS* is committed to channelling the highest quality data to shape practice in the field.

D. C. Winter
Editor, *BJS*

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