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Original Article

Organ preservation following short-course radiotherapy for rectal cancer

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Abstract

Background: Non-operative management of rectal cancer is increasingly being used in selected patients. Most reports include patients treated with chemoradiotherapy (CRT) before inclusion into a Watch & Wait (W&W) programme. The aim of this study was to report outcomes from a single-centre W&W programme involving a large cohort of patients.

Methods: Patients treated with chemoradiotherapy (CRT) or short-course radiotherapy (SCRT) with or without chemotherapy, between 2008 and 2020, who showed signs of a clinical complete response (cCR) were reviewed. Patients were assessed using digital rectal examination, flexible endoscopy, carcinoembryonic antigen measurement, MRI, and CT imaging, discussed at the multidisciplinary tumour board meeting, and followed up in a dedicated W&W programme as from 2015. Outcomes including regrowth and 3-year survival (time to regrowth or death) were prospectively evaluated.

Results: Of 142 patients who were assessed, 88 fulfilled the criteria for cCR. Treatment before cCR included CRT, SCRT with chemotherapy, and SCRT alone in 16 (18 per cent), 28 (32 per cent), and 44 (50 per cent) patients, respectively. Patients treated with CRT and SCRT with chemotherapy had more advanced clinical T- and N-stage, compared with patients treated with SCRT alone (clinical T-stage > 2: 81 per cent and 89 per cent *versus* 47 per cent, respectively; clinical N-stage > 0: 75 per cent and 93 per cent *versus* 68 per cent, respectively). Overall rate of regrowth was 19 per cent, with 31 per cent, 21 per cent, and 14 per cent following CRT, SCRT with chemotherapy, and SCRT alone, respectively. Uni- and multivariable analyses evaluating the clinical parameters revealed no statistically significant associations with risk of local regrowth. All but one patient with regrowth underwent salvage surgery. The 3-year survival rate (death with regrowth as competing risk) was 93 per cent, with no significant difference between treatment groups.

Conclusion: In this cohort of W&W patients, the vast majority received SCRT with or without chemotherapy and results consistent with previous W&W reports were obtained. No statistically significant differences in terms of regrowth rate were obtained when comparing CRT, SCRT with chemotherapy, and SCRT alone. SCRT can induce sustained cCR and may precede a W&W strategy.

Introduction

Since the early studies on non-operative management in 2004[1], organ preservation for rectal cancer patients has developed to become an option in a selected group of patients. The International Watch & Wait Database (IWWD) was established in 2014, and four years later, outcomes in 1009 registered patients were reported[2]. According to the study, chemoradiotherapy (CRT) was delivered for 91 per cent of patients in whom a clinical complete response (cCR) was detected. Conventional fractionated CRT, with or without intensification, has been an integral part of the Brazilian experience of organ preservation[3] and was also part of the schedule in the ACOSOG Z6041 trial in the USA on clinically staged T2N0 rectal cancer[4], as well as in the OnCoRe project in the UK[5]. In addition, studies where CRT was combined with additional chemotherapy have shown an increase in pathological complete response rates in patients undergoing resection[6].

Preoperative short-course radiotherapy (SCRT) delivered as 5 × 5 Gy has been extensively studied, and is an effective and tolerable treatment in rectal cancer[7–9]. Initially, SCRT was followed by immediate surgery in the week after completion of radiotherapy, and absence of a time interval did not allow time for tumour regression. However, some recent studies have shown that tumour regression, and even pathological complete response, can also be achieved with SCRT if surgery is delayed by at least 4 weeks. The Stockholm III trial showed that pathological complete response was obtained in 10.4 per cent of patients in whom surgery was delayed by 4–8 weeks after completion of SCRT[10]. In the recent RAPIDO trial, pathological complete response was observed in 28 per cent of patients receiving

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the experimental arm consisting of SCRT followed by six cycles of capecitabine and oxaliplatin, compared to 14 per cent in the arm with conventional fractionated CRT[11]. These results indicate that SCRT with or without additional chemotherapy could play an important role also in non-operative management of rectal cancer.

A formal, centralized Watch & Wait (W&W) programme was established in 2015 at Karolinska University Hospital in Stockholm, Sweden. The aim of this study was to evaluate the oncological outcomes in rectal cancer patients enrolled in the W&W programme who received SCRT.

Methods

Patients

The W&W programme involves a centrally managed outpatient clinic serving primarily the Stockholm region (population of 2.4 million), although it also includes patients referred from other hospitals in Sweden. All patients referred were prospectively entered into a hospital-based register. Patients who achieved cCR were also entered into the Swedish W&W register and the IWWD. Between 2008 and 2014, a small number of patients had been introduced into a W&W policy before initiation of the formal W&W programme; for these patients, some variables in the local register were completed retrospectively. Therefore, for the purpose of this study, the locally managed hospital register was searched for data from 1 January 2008 to 31 October 2020. In cases of missing data or uncertainties, a chart review was performed. This study was conducted in accordance with STROBE guidelines and approved by the Swedish Ethical Review Authority (Dnr: 2012/1882 31–3, 2016/100–321, and 566–16).

Neoadjuvant therapy and restaging

In brief, all rectal cancer patients underwent clinical assessment and MRI before discussion at a multidisciplinary tumour board meeting. Based on parameters, including T- and N-stage, distance to the mesorectal fascia, extramural vascular invasion, and tumour height, tumours were grouped as low risk, intermediate risk, or high risk (*Table S1*)[12]. Patients in the low-risk group were recommended surgery alone; patients with intermediate-risk tumours were recommended preoperative SCRT, and those with locally advanced tumours were recommended CRT. Of note, the W&W programme is based on the premise that there should be no changes in terms of the indications for neoadjuvant treatment (that is, 'preoperative treatment' in accordance with national guidelines)[12]. During the study period, the RAPIDO trial was under way and patients with locally advanced tumours were randomized to either CRT or SCRT followed by chemotherapy[11]. When accrual to RAPIDO was complete (June 2016), a non-randomized rectal cancer trial (LARCT-US, ClinicalTrials.gov NCT03729687) was initiated in Sweden. This trial, which is still recruiting, applies the same inclusion criteria as those in the RAPIDO trial. However, only four cycles of capecitabine and oxaliplatin are administered in the interval between SCRT and surgery.

Initial response evaluation using clinical examination, MRI, and CT was performed at 6–10 weeks after completion of radiotherapy (20–22 weeks for RAPIDO patients) at the primary treating hospital.

W&W programme

All patients included in the W&W programme were diagnosed with a biopsy-proven rectal adenocarcinoma and underwent both pretherapeutic MRI staging and restaging MRI to evaluate the tumour after neoadjuvant treatment.

Patients showing signs of potential cCR were referred for assessment at Karolinska University Hospital. The outpatient clinic was managed by two senior colorectal surgeons, and assessment included digital rectal examination (DRE), flexible endoscopy performed by a specialist endoscopist, carcinoembryonic antigen (CEA) measurement, and local review of all MRI and CT imaging, including a discussion at the multidisciplinary tumour board meeting.

The following criteria were mandatory for being assessed as having cCR: no evidence of tumour remaining or metastatic lymph nodes on MRI; only scarring found on flexible endoscopy; telangiectasia or white mucosa; and no palpable tumour on clinical examination, including DRE. Patients with a very good response as evidenced on MRI or endoscopically, albeit not fulfilling all criteria for cCR, were considered as having 'near' cCR. For these patients, one or two additional assessments (including MRI, endoscopy, and DRE) at 4- to 6-week interval were performed before a final decision was made on whether they achieved cCR or not.

Follow-up assessment consisted of clinical examination including DRE, CEA measurement, endoscopy, and MRI every 3 months for 2 years and thereafter every 6 months until 5 years after termination of radiotherapy. Between 5 and 10 years, assessments were undertaken annually only. In addition, CT of the abdomen and thorax was performed at 1 and 3 years.

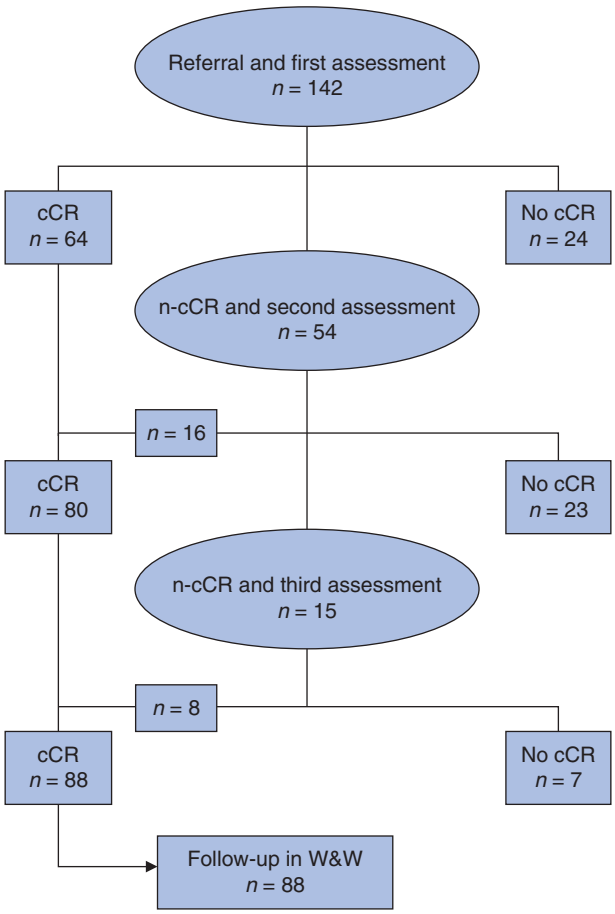

Fig. 1 Study flow chart

cCR, clinical complete response; n-cCR, near clinical complete response; W&W, Watch & Wait.

Table 1 Baseline characteristics of study patients

	All patients	CRT	SCRT + chemo	SCRT
n	88	16	28	44
Age median (range, years)	65 (30–94)	60 (41–78)	64 (45–75)	68 (30–94)
Age				
≤ 65 years (%)	43 (49)	10 (63)	17 (61)	16 (36)
> 65 years (%)	45 (51)	6 (37)	11 (39)	28 (64)
Sex				
Female (%)	34 (39)	7 (44)	11 (39)	16 (36)
Male (%)	54 (61)	9 (56)	17 (61)	28 (64)
Initial MRI T-stage (%)				
T1–2*	29 (33)	3 (19)	3 (11)	23 (52)
T3†	48 (55)	10 (62)	18 (64)	20 (45)
T4	11 (13)	3 (19)	7 (25)	1 (2)
Initial MRI N-stage (%)				
N0	20 (23)	4 (25)	2 (7)	14 (32)
N1	37 (42)	7 (44)	10 (36)	20 (45)
N2	31 (35)	5 (31)	16 (57)	10 (23)
Initial M-stage				
M0	82 (93)	13 (81)	25 (89)	44 (100)
M1	6 (7)	3 (19)	3 (11)	0
Tumour height‡ (cm) median (range)	6 (0–15)	3 (0–12)	4 (2–12)	7 (2–15)
Follow-up (weeks) median (range)	144 (19–648)	152 (61–648)	136 (26–340)	144 (19–575)

*Refers to all T1, T2, and T1–2 grouped together. †Refers to all T2–3 and T3 grouped together. ‡Refers to 0–3 cm grouped as 0 cm, 'low' or 'distal' grouped as 2 cm, 3–4 cm grouped as 3 cm, and 4–5 cm grouped as 4 cm. CRT, chemoradiotherapy; SCRT, short-course radiotherapy.

Table 2 Assessment of clinical response

	All patients	CRT	SCRT + chemo	SCRT
n	88	16	28	44
Time interval from completion of RT to first-evaluation MRI (weeks), median (range)	8 (2–45)	7 (6–45)	17 (4–32)	7 (2–22)
Time interval from completion of RT to cCR (weeks), median (range)	18 (5–58)	15 (7–58)	22 (5–43)	14 (9–53)
Assessment* for determining cCR				
cCR at first assessment (%)	64 (73)	11 (69)	22 (78)	31 (70)
cCR at second assessment (%)	16 (18)	4 (25)	5 (18)	7 (16)
cCR at third assessment (%)	8 (10)	1 (6)	1 (4)	6 (14)

*Refers to assessment including digital rectal examination, flexible endoscopy, MRI, and carcinoembryonic antigen measurement. CRT, chemoradiotherapy; SCRT, short-course radiotherapy; RT, radiotherapy; cCR, clinical complete response.

Study outcomes

Outcomes evaluated included tumour regrowth and 3-year survival rate.

Statistics

Statistical comparisons of proportions were performed by the chi-square test. Median follow-up time was calculated using the reverse Kaplan–Meier method. Survival time was calculated from the date of completion of radiotherapy to tumour regrowth or death. For patients with no regrowth who were still alive, survival time was calculated from the date of completion of radiotherapy to the common closing date of 31 October 2020. Cumulative incidence functions were used to graphically display the probability of regrowth, taking into account the competing risk of mortality. Competing risk regression was used to estimate the effect of clinical parameters on time to failure. Results of these regression models are presented as subhazard ratios (sHRs), together with 95 per cent confidence intervals. *P*-values using these models refer to the Wald test.

Results

Between 2008 and 2014, 10 patients were assigned to a W&W policy before initiation of the formal W&W programme. From 2015, 132 patients were assessed at the outpatient clinic as part of the W&W programme. Of these 142 patients, 88 were found to have achieved cCR (*Fig. 1*). Median follow-up after completion of radiotherapy was 144 weeks (range: 19–648).

Of the 88 patients with cCR, 72 (82 per cent) had received SCRT (44 SCRT alone, and 28 SCRT followed by chemotherapy). Baseline characteristics of all patients are presented in *Table 1*. Among patients treated with either CRT or SCRT with chemotherapy, the proportion of locally advanced tumours (that is, advanced T- or N-stage) was significantly higher, compared to that of patients who had received SCRT alone.

In accordance with treatment protocols, time interval between completion of radiotherapy and first response evaluation with MRI was longer for patients treated with SCRT followed by chemotherapy (*Table 2*). This prolonged interval was reflected in terms of both time interval from completion of radiotherapy to

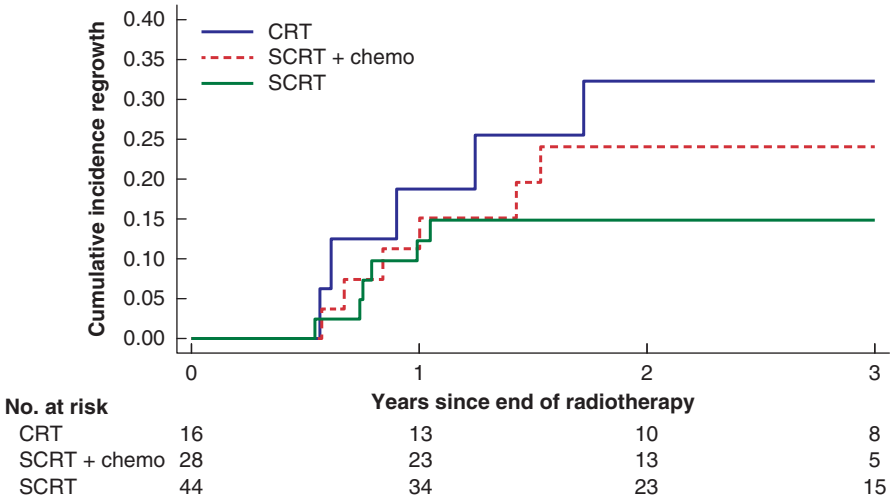

Fig. 2 Cumulative incidence of regrowth (with death as competing risk) in relation to initial therapy

CRT, chemoradiotherapy; SCRT, short-course radiotherapy. $P = 0.398$ (log rank test).

Table 3 Regrowth

	All patients	CRT	SCRT + chemo	SCRT
n	88	16	28	44
Regrowth				
No (%)	71 (81)	11 (69)	22 (79)	38 (86)
Yes (%)	17 (19)	5 (31)	6 (21)	6 (14)
Time to regrowth (weeks), median (range)	43 (27–90)	47 (27–90)	44 (30–80)	40 (28–55)

cCR and the proportion of patients having cCR at the first assessment (78 per cent *versus* 70 per cent *versus* 69 per cent for SCRT with chemotherapy, SCRT alone, and CRT, respectively). *Table 2* and *Fig. 1* show that around one-third of patients initially were found to have achieved 'near' cCR and about 1 in 10 needed three sequential assessments before achieving cCR.

In only two patients who were both treated with SCRT alone, therapeutic interventions were performed, in addition to radiotherapy, to achieve cCR. One patient underwent transanal endoscopic microsurgery (TEMS), and the other had contact radiotherapy (Papillon technique).

Tumour regrowth

During follow-up, regrowth was detected in 17 patients (19 per cent) (*Table 3*). Median time from completion of radiotherapy to regrowth was 43 weeks, with no statistically significant differences between treatment groups. All regrowths were detected within 2 years of completion of radiotherapy. Initial T-stage in patients with regrowth was T1–2 in four patients, T3 in 10 patients, and T4 in three patients. Regrowth occurred in five patients (31 per cent) after CRT, seven patients (25 per cent) after SCRT and chemotherapy, and six patients (14 per cent) after SCRT alone. Cumulative 3-year risk of regrowth (with death as competing risk) among patients treated with CRT, SCRT with chemotherapy, and SCRT alone is presented in *Fig. 2*. Uni- and multivariable analyses on risk of local regrowth are presented in *Table 4*.

One patient who was treated with SCRT alone developed extensive systemic lymph node dissemination (M1), with no signs of locoregional regrowth. Another patient, initially treated with SCRT and chemotherapy, was diagnosed with a metachronous distal sigmoid cancer and subsequently underwent an intersphincteric abdominoperineal excision, with histopathology of the rectal specimen showing ypT0N0.

Salvage surgery

Of the 17 patients with local regrowth, 16 underwent salvage surgery. One patient who did not undergo surgery had initially been treated with CRT and achieved cCR locally, but developed multiple pulmonary metastases during the course of neoadjuvant therapy. Subsequently, asymptomatic local regrowth was detected alongside progressive metastatic disease and the decision was made to not operate. The salvage surgical procedures performed and the type of approach are presented in *Table 5*. Clear resection margins (R0) were achieved in 15 patients, and one patient had an R1 resection with an involved margin towards the vagina. Among the 16 patients who had surgery, two (both with an R0 resection) developed distant metastases, of whom one also had locoregional recurrence.

Survival

At the last follow-up assessment, 82 patients were alive and the estimated 3-year survival rate (death with regrowth as competing risk) was 93 per cent (95 per cent c.i. 83 to 98). In the cohort of 88 patients, 17 eventually had a rectal resection (16 patients because of regrowth and one due to a metachronous tumour as detailed above), yielding an organ preservation rate of 81 per cent.

Discussion

The majority of patients included in this study on non-operative management of rectal cancer were treated with SCRT with or without chemotherapy. The overall regrowth rate of 19 per cent, with all but one being salvageable, and the estimated 3-year survival rate exceeding 90 per cent are consistent with other reports in the literature that included mostly patients treated with

Table 4 Uni- and multivariable analyses on risk of regrowth

	Univariable sHR	*P*-value	Multivariable sHR	*P*-value
Sex				
Female	1.0 (ref)		1.0 (ref)	
Male	1.18 (0.44–3.19)	0.745	1.35 (0.48–3.80)	0.575
Age (years)				
< 65	1.0 (ref)		1.0 (ref)	
≥ 65	0.91 (0.35–2.35)	0.845	1.01 (0.35–2.91)	0.989
T-stage				
T1–2	1.0 (ref)		1.0 (ref)	
T3–4	1.57 (0.50–4.89)	0.435	1.34 (0.34–5.36)	0.675
N-stage				
N0	1.0 (ref)		1.0 (ref)	
N1–2	0.84 (0.28–2.58)	0.767	0.73 (0.22–2.45)	0.615
Initial therapy				
CRT	1.0 (ref)		1.0 (ref)	
SCRT + chemo	0.71 (0.22–2.25)		0.72 (0.22–2.37)	
SCRT	0.44 (0.14–1.45)	0.399	0.47 (0.11–2.00)	0.594

sHR, subhazard ratio; CRT, chemoradiotherapy; SCRT, short-course radiotherapy.

Table 5 Regrowth and salvage surgery

	All patients	CRT	SCRT + chemo	SCRT
n	88	16	28	44
Salvage surgery				
Yes (%)	16 (94)	4	6	6
No (%)	1 (6)	1	0	0
Low anterior resection	5	1	3	1
Open	2			
Robotic	3			
Abdominoperineal excision	11	3	3	5
Open	5			
Robotic	6			
Resection margin status				
R0	15	3	6	6
R1	1	1	0	0
Recurrence after salvage surgery	2	0	2	0
Isolated locoregional recurrence	0			
Systemic recurrence	1			
Combined locoregional and systemic	1			

CRT, chemoradiotherapy; SCRT, short-course radiotherapy.

conventional fractionated CRT[5,13,14]. Therefore, this study suggests that SCRT with or without chemotherapy can induce sustained cCR and may precede a W&W strategy.

Preoperative SCRT for rectal cancer has been extensively studied in several randomized trials[7–11]. In addition to logistic and resource-related advantages, this regimen has a favourable toxicity profile in comparison with CRT[15]. Long-term health-related quality of life has been reported to be similar following SCRT and CRT[16]. Addition of chemotherapy to radiotherapy was not found to impact long-term quality of life in a randomized trial on locally advanced rectal cancer[17]. In the RAPIDO trial, where SCRT was combined with full-dose systemic chemotherapy in the time interval between radiotherapy and surgery, compliance was excellent, with 84 per cent of patients receiving at least 75 per cent of prescribed chemotherapy[18]. As reported in the Stockholm III trial and the RAPIDO trial, complete response can be achieved in 10–28 per cent of patients treated with SCRT with or without chemotherapy[10,11]. In addition to the other benefits of SCRT, compared to CRT, this study demonstrates that SCRT with or without chemotherapy may be used as part of an organ preservation strategy.

As patients in this study were treated in accordance with national guidelines, preoperative radiotherapy patients were included in this W&W programme based on incidental cCR, and not on a planned organ preservation strategy. Reliable predictive markers for cCR and the risk of regrowth are currently lacking, making an upfront non-operative strategy challenging. However, should such markers become available, SCRT with or without chemotherapy could be an option. Furthermore, as good outcomes for older patients on a W&W programme have been reported, SCRT could be an option for more frail patients[19]. The recently published TREC study reported favourable outcomes with a strategy including SCRT followed by planned TEMS[20]. Interestingly, almost one-third of randomized patients in the TREC study were complete responders to SCRT, with the authors suggesting the adoption of a W&W strategy with SCRT and selective use of TEMS. The ongoing STAR-TREC trial will provide further evidence of the role of SCRT in an organ preservation strategy[21].

Although our study findings indicate the regrowth rate to be higher following CRT than following SCRT with or without chemotherapy, one must bear in mind that patients were treated in accordance with national guidelines whereby patients with more advanced tumours were selected for CRT, rather than for SCRT alone. Indeed, the multivariable analysis indicates the initial T-stage as the main driver for regrowth risk, consistent with a recent study on the IWWD[13]. However, the reported regrowth rate of 14 per cent following SCRT alone in primarily non-advanced tumours suggests that this strategy could be an option also as part of an upfront non-operative rectal cancer management strategy for earlier-stage tumours. In such a setting, SCRT followed by chemotherapy may be an option for more advanced tumours. However, the dilemma of a failed upfront non-operative strategy in which an early rectal cancer patient undergoes both radiotherapy and major surgery still would remain for a proportion of patients.

Our study results on regrowth rate in patients mainly treated with SCRT compare favourably to recent IWWD data reporting a regrowth rate of 27 per cent[13]. In the UK OnCoRe project, the local regrowth rate was 34 per cent, although with a longer follow-up than in the current series[5]. In addition, the reported survival rate of 93 per cent is comparable to those reported in patients treated mainly with CRT[2,5]. Results presented are based on a well organized, centralized W&W programme that allows not only for

strict follow-up, but also for multidisciplinary cooperation, research, and experience gather.

Although this study is limited by its size, it included a relatively large cohort of patients who underwent SCRT before achieving cCR. The study strengths include prospective entry of patients into the register and meticulous patient follow-up. This study shows that SCRT could play a significant role in the era of organ-preserving rectal cancer management.

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Disclosure. The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

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