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

D. Pettersson¹, E. Lörinc², T. Holm¹, H. Iversen¹, B. Cedermark¹, B. Glimelius²,³ and A. Martling¹

Departments of ¹Molecular Medicine and Surgery, and ²Oncology and Pathology, Karolinska Institute, Stockholm, and ³Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden

Correspondence to: Dr D. Pettersson, Department of Surgery, Norrtälje Hospital, Box 905, SE-761 28 Norrtälje, Sweden (e-mail: david.pettersson@tiohundra.se)

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%; \(P = 0.001\)) and Dworak grade 4 tumour regression (10.1% versus 1.7%; \(P < 0.001\)) 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.

Presented in part to the European Society of Coloproctology, Vienna, Austria, September 2012

Paper accepted 20 February 2015

Published online in Wiley Online Library (www.bjs.co.uk). DOI: 10.1002/bjs.9811

Introduction

Preoperative radiotherapy (RT) is recommended to many patients with rectal cancer as it leads to a reduced local recurrence rate¹–⁸ and, in some studies⁷,⁸, improved overall survival. RT can induce downsizing and/or downstaging of the primary tumour and may increase sphincter preservation, although this is controversial⁹. 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 treatment⁸,¹⁰. In contrast, it had been thought that hypofractionated, short-course RT (25 Gy in 1 week) did not induce downstaging¹¹. However, two large trials⁴,¹² found tumour regression after a short delay (less than 1 week). In addition, in three retrospective¹³–¹⁵ and one prospective¹⁶ 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 previously17. 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 abdomino-perineal 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, abdominopереineal 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 days17,18. 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 continuously19.

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 previously17. 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
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)\textsuperscript{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\textsuperscript{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\textsuperscript{\textregistered} 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 (\( P = 0.947 \)). 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 (\( P = 0.534 \)). 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 (42-6)           |
| High (> 10 cm) | 56 (23-9)    | 49 (21-9)           |
| 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   |              |                     |      |
| yp0            | 4 (1-7)      | 27 (11-8)           | 0.001|
| yp1            | 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)             |      |
| ypV            | 11 (4-7)     | 11 (4-8)            |      |
| Tumour category|              |                     |      |
| ypT0           | 5 (2-1)      | 27 (11-8)           | <0.001|
| ypT1           | 12 (5-1)     | 27 (11-8)           |      |
| ypT2           | 74 (31-6)    | 60 (26-3)           |      |
| ypT3;§         | 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  |              |                     |      |
| ypN0           | 149 (63-7)   | 163 (71-5)          | 0.059|
| ypN1           | 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 (45-8)          |      |
| 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.

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. Short-course RT with a delay to surgery has been used outside trials for patients who were not suitable for CRT. Retrospective outcome analyses 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 possible 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, 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.

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. 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 studies29,30 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 time11. 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 previously13–15.

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 alone12. 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.

Acknowledgements

The authors thank H. Johansson (Department of Oncology and Pathology, Karolinska University Hospital, Stockholm) for help with statistical calculations, T. Singnomklao (Regional Cancer Centre, Stockholm) for help with the collection and validation of register data, and all members of the Stockholm Colorectal Cancer Study Group and hospitals outside the Stockholm/Gotland region for recruiting patients to the Stockholm III Trial and for providing support during the reassessment of pathological specimens: L. Blomqvist (Karolinska University Hospital, Stockholm); J. Dalén (St Göran’s Hospital, Stockholm); L. Franzén (Medilab, Stockholm); M. Goldinger (St Göran’s Hospital, Stockholm); M. Bragmark (Danderyds Hospital, Stockholm); G. Lindgren (Södertälje Hospital, Södertälje); N. Lundqvist (Norrtälje Hospital, Norrtälje); M. Machado (Ersta Hospital, Stockholm); Y. Raab (South Hospital, Stockholm); P. Nygren, Å. Berglund, L. Pålman (University Hospital, Uppsala); A. Nihlberg (Falun Hospital, Falun); R. Heuman (Mora Hospital, Mora); G. Lindmark (Helsingborg Hospital, Helsingborg); I. Syk (Skåne University Hospital, Malmö); G. Ljung (Mälarsjukhuset Hospital, Eskilstuna); O. Hallböök, (Linköping University Hospital, Linköping); P. Loftás (Vrinnevi Hospital, Norrköping); P. Gustavsson (Visby Hospital, Visby).

The study was supported financially by the Swedish Research Council, the Swedish Cancer Society and the Stockholm Cancer Society. Financial support was also provided through the regional agreement on medical training and clinical research (ALF) between the Stockholm County Council and Karolinska Institute.

Disclosure: The authors declare no conflict of interest.
References

1. Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg 2007; 246: 693–701.

2. Kapiteijn E, Marijnen CA, 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: 638–646.

3. Pahlman L, Glimelius B. Pre- or postoperative radiotherapy in rectal and rectosigmoid carcinoma. Report from a randomized multicenter trial. Ann Surg 1990; 211: 187–195.

4. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial [see comments]. N Engl J Med 1997; 336: 980–987 [published erratum appears in N Engl J Med 1997; 336: 1539].

5. Martling A, Holm T, Johansson H, Rutqvist L, Cederman B. The Stockholm II trial on preoperative radiotherapy in rectal carcinoma. Cancer 2001; 92: 896–902.

6. Cederman B, Johansson H, Rutqvist LE, Wilking N. The Stockholm I trial of preoperative short term radiotherapy in operable rectal carcinoma. A prospective randomized trial. Stockholm Colorectal Cancer Study Group. Cancer 1995; 75: 2269–2275.

7. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 850 patients from 22 randomised trials. Lancet 2001; 358: 1291–1304.

8. Glimelius B, Grönberg H, Järhult J, Wallgren A, Cavallin-Stähle E. A systematic overview of radiation therapy effects in rectal cancer. Acta Oncol 2003; 42: 476–492.

9. Bujko K, Nowacki MP, Nasirowska-Guttmejer A, Michalski W, Bebenek M, Pudelko M et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radioter Oncol 2004; 72: 15–24.

10. Glimelius B, Holm T, Blomqvist L. Chemotherapy in addition to preoperative radiotherapy in locally advanced rectal cancer – a systematic overview. Rev Recent Clin Trials 2008; 3: 204–211.

11. Marijnen CA, Nagtegaal ID, Klein Kranenbarg E, Hermans J, van de Velde CJ, Leer JW et al. No downstaging after short-term preoperative radiotherapy in rectal cancer patients. J Clin Oncol 2001; 19: 1976–1984.

12. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 2009; 373: 811–820.

13. Hatfield P, Hingorani M, Radhakrishna G, Cooper R, Melcher A, Crellin A et al. Short-course radiotherapy, with elective delay prior to surgery, in patients with unresectable rectal cancer who have poor performance status or significant co-morbidity. Radioter Oncol 2009; 92: 210–214.

14. Radu C, Berglund A, Pahlman L, Glimelius B. Short-course preoperative radiotherapy with delayed surgery in rectal cancer – a retrospective study. Radioter Oncol 2008; 87: 343–349.

15. Pettersson D, Holm T, Iversen H, Blomqvist L, Glimelius B, Martling A. Preoperative short-course radiotherapy with delayed surgery in primary rectal cancer. Br J Surg 2012; 99: 577–583.

16. Pac R, Kulig J, Richter P, Gach T, Szura M, Kowalska T. Randomized clinical trial on preoperative radiotherapy 25 Gy in rectal cancer – treatment results at 5-year follow-up. Langenbecks Arch Surg 2012; 397: 801–807.

17. Pettersson D, Cederman B, Holm T, Radu C, Pahlman L, Glimelius B et al. Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. Br J Surg 2010; 97: 580–587.

18. Fokstuen T, Holm T, Glimelius B. Postoperative morbidity and mortality in relation to leukocyte counts and time to surgery after short-course preoperative radiotherapy for rectal cancer. Radioter Oncol 2009; 93: 293–297.

19. Jörgen F, Johansson R, Damber L, Lindmark G. Validity of the Swedish Rectal Cancer Registry for patients treated with major abdominal surgery between 1995 and 1997. Acta Oncol 2013; 52: 1707–1714.

20. Sobin LH, Wittekind C. International Union Against Cancer TNM Classification of Malignant Tumours (6th edn). John Wiley & Sons: New York, 2002.

21. Greene FL, Fleming ID, Fritz A, Balch CM, Haller DG, Morrow M (eds). AJCC Cancer Staging Manual (6th edn). Springer: New York, 2002.

22. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorectal Dis 1997; 12: 19–23.

23. Graf W, Dahlberg M, Osman MM, Holmberg L, Pahlman L, Glimelius B. Short-term preoperative radiotherapy results in down-staging of rectal cancer: a study of 1316 patients. Radioter Oncol 1997; 43: 133–137.

24. Glimelius B, Beets-Tan R, Blomqvist L, Brown G, Nagtegaal I, Pahlman L et al. Mesorectal fascia instead of circumferential resection margin in preoperative staging of rectal cancer. J Clin Oncol 2011; 29: 2142–2143.

25. Maas M, Nelemans PJ, Valentinini V, Das P, Rödel C, Kuo L et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010; 11: 835–844.

26. Rödel C, Martus P, Papadopoulos T, Füzlesi L, Klimpfinger M, Fietkau R et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol 2005; 23: 8688–8696.

27. Gerard JP, Conroy T, Bonnetain F, Bouche O, Chapet O, Closson-Dejardin MT et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3–4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006; 24: 4620–4625.
28 Bosset J-F, Calais G, Mineur L, Maingon P, Stojanovic-Rundic S, Bensadoun R-J et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *Lancet Oncol* 2014;15: 184–190.

29 Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006; 93: 1215–1223.

30 Bujko K, Bujko M. Point: short-course radiation therapy is preferable in the neoadjuvant treatment of rectal cancer. *Semin Radiat Oncol* 2011; 21: 220–227.

31 Valentini V, Aristei C, Glimelius B, Minsky BD, Beets-Tan R, Borras JM et al. Multidisciplinary Rectal Cancer Management: 2nd European Rectal Cancer Consensus Conference (EURECA-CC2). *Radiother Oncol* 2009; 92: 148–163.

32 Glimelius B, Tiret E, Cervantes A, Arnold D; ESMO Guidelines Working Group. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; 24(Suppl 6): vi81–vi88.

**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. 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.

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

D. C. Winter
**Editor, BJS**

---

1 Verseveld M, de Graaf EJ, Verhoef C, van Meerten E, Punt CJ, de Hingh IH, Nagtegaal ID, Nuyttens JJ, Marijnens CA, de Wilt JH; CARTS Study Group. Chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery (CARTS study). *Br J Surg* 2015; 102: 853–860.

2 Faria S, Kopek N, Hijal T, Liberman S, Charlebois P, Stein B, Meterissian S, Meguerditchian A, Fawaz Z, Artho G. Phase II trial of short-course radiotherapy followed by delayed surgery for locoregionally advanced rectal cancer. *Colorectal Dis* 2014; 16: O66-70.

3 Smith FM, Waldron D, Winter DC. Rectum-conserving surgery in the era of chemoradiotherapy. *Br J Surg* 2010; 97: 1752–1764.

4 Leong KJ, Beggs A, James J, Morton DG, Matthews GM, Bach SP. Biomarker-based treatment selection in early-stage rectal cancer to promote organ preservation. *Br J Surg* 2014; 101: 1299–1309.

5 Sloothaak DA, Geijsen DE, van Leersum NJ, Punt CJ, Buskens CJ, Bemelman WA, Tanis PJ; Dutch Surgical Colorectal Audit. Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. *Br J Surg* 2013; 100: 933–939.