Preliminary results of a cohort study of induction chemotherapy-based treatment for locally recurrent rectal cancer

Original article

Preliminary results of a cohort study of induction chemotherapy-based treatment for locally recurrent rectal cancer

D. M. G. I. van Zoggel[1], S. J. Bosman[1], M. Kusters[1,5], G. A. P. Nieuwenhuijzen[1], J. S. Cnossen[2], G. J. Creemers[3], G. van Lijnschoten[4] and H. J. T. Rutten[1,6]

Departments of [1]Surgery, [2]Radiotherapy and [3]Medical Oncology, Catharina Hospital, and [4]PAMM, Pathology Department, Eindhoven, [5]Department of Surgery, Leiden University Medical Centre, Leiden, and [6]GROW School of Oncology and Developmental Biology, Maastricht University, Maastricht, The Netherlands

Correspondence to: Professor H. J. T. Rutten, Department of Surgery, Catharina Ziekenhuis, Michelangelolaan 2, 5623 EJ Eindhoven, The Netherlands (e-mail: harm.rutten@cze.nl)

Background: **A significant number of patients treated for locally recurrent rectal cancer have local or systemic failure, especially after incomplete surgical resection. Neoadjuvant treatment regimens in patients who have already undergone preoperative (chemo)radiotherapy for the primary tumour are limited. The objective of the present study was to evaluate the influence of a neoadjuvant regimen incorporating induction chemotherapy (ICT) in patients with locally recurrent rectal cancer who had preoperative (chemo)radiotherapy for the primary cancer or an earlier local recurrence.**

Methods: **Patients were treated with a sequential neoadjuvant regimen including three or four cycles of 5-fluorouracil and oxaliplatin-containing chemotherapy. When no progressive disease was found at evaluation, neoadjuvant treatment was continued with chemoradiation therapy (CRRT) using 30 Gy with concomitant capecitabine. If there was a response to ICT, the patient was advised to continue with systemic chemotherapy after CRRT as consolidation chemotherapy while waiting for resection. These patients were compared with patients who received CRRT alone in the same time interval.**

Results: **Of 58 patients who had ICT, 32 (55 per cent) had surgery with clear resection margins, of whom ten (17 per cent) exhibited a pathological complete response (pCR). The remaining 26 patients had 23 R1 and three R2 resections. In 71 patients who received CRRT, a similar rate of R0 (35 patients) and R1 (36) resection was found ($P = 0{\cdot}506$), but only three patients (4 per cent) had a pCR ($P = 0{\cdot}015$).**

Conclusion: **The incorporation of ICT in neoadjuvant regimens for locally recurrent rectal cancer is a promising strategy.**

Paper accepted 14 August 2017

Published online 23 November 2017 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.10694

Introduction

Despite better preoperative and surgical treatment of rectal cancer, the incidence of locally recurrent rectal cancer remains approximately 5–10 per cent[1]. Unlike primary rectal cancer, local recurrence is not confined to a well defined surgical compartment, and multicompartment exenterative procedures are often required to achieve clear resection margins[2–4].

Preoperative treatment is used to downsize the tumour and facilitate surgical resection. However, because most patients have received preoperative (chemo)radiotherapy for their primary rectal cancer, the possible modalities in recurrent disease are limited. Whether these patients can be reirradiated safely is still debated[5]. Despite the fact that chemoradiation therapy (CRRT) cannot be considered standard therapy in the management of patients with previously irradiated locally recurrent rectal cancer, it has been demonstrated[6–9] that reirradiation with a limited dose of 30–39 Gy and concomitant chemotherapy can be applied safely and effectively in locally recurrent disease.

Even after reirradiation, incomplete resection remains a problem in a significant number of patients. The most important positive prognostic factor for recurrent rectal cancer appears to be radical resection with clear margins (R0)[4,10,11]. Early development of metastatic disease is quite common when local recurrence has occurred[12]. Even after

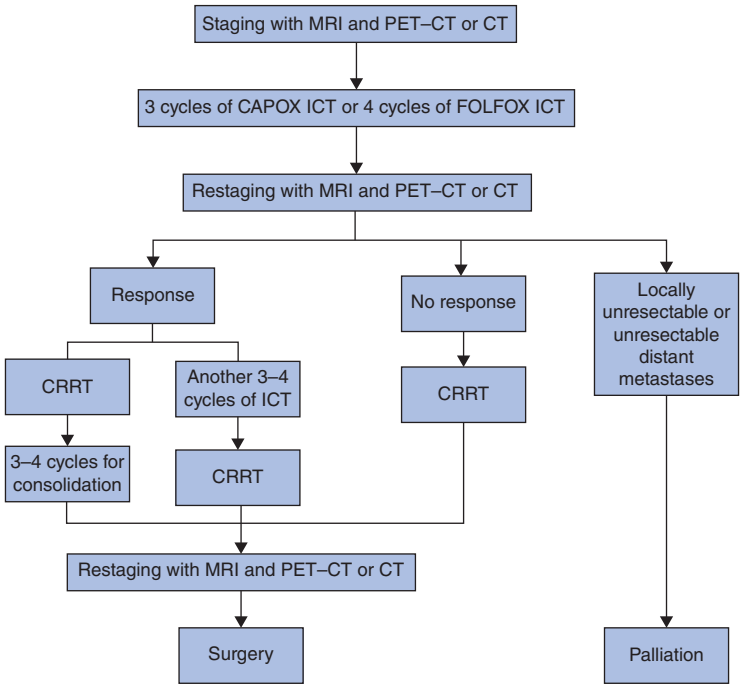


Fig. 1 Treatment flow chart for induction chemotherapy (ICT). Thirteen patients had ICT and consolidation therapy, 15 had all (full-course) chemotherapy cycles before chemoradiation therapy (CRRT) and 30 had only ICT and no consolidation therapy (for exact type of chemotherapy see *Table S1*, supporting information). Fourteen patients entered the palliative path. CAPOX, capecitabine and oxaliplatin; FOLFOX, leucovorin, fluorouracil and oxaliplatin

successful treatment of local recurrence, development of systemic disease remains the principal cause of death[13]. This finding indicates the importance of administering systemic chemotherapy early in the treatment.

The use of induction chemotherapy (ICT) as part of the preoperative management of patients with locally recurrent rectal cancer may offer several advantages. First, systemic treatment might improve resectability by a significant downsizing and downstaging effect, as shown in primary colorectal cancer[14,15]. Second, ICT may lead to an increased rate of pathological complete response (pCR) and thus possibly better overall survival. Finally, it might prevent early metastatic disease or offer the best palliative treatment in the meantime, and prevent extensive surgical morbidity.

Methods

Details of all patients with locally recurrent rectal cancer who underwent a resection at Catharina Hospital, a national tertiary referral centre for locally recurrent rectal cancer, between January 2010 and December 2016 were collected in a prospective database and reviewed retrospectively. A cohort of patients who had undergone reirradiation were selected, including those who had full-course radiotherapy for either their primary tumour or a previous local recurrence. Patients with unresectable distant metastatic disease at presentation were excluded. At the start, these patients were deemed unresectable with regard to achieving clear margins; later, more 'regular' patients with locally recurrent disease were also selected. Patients who did not receive ICT but only concurrent CRRT, were used to compare the primary endpoints of pCR, clear margin (R0) rate, overall survival (OS), local recurrence-free survival (LRFS) and metastasis-free survival (MFS).

Treatment and imaging regimen

The general treatment regimen for the ICT group (*Fig. 1*) consisted of three cycles of CAPOX (capecitabine and oxaliplatin) or four cycles of FOLFOX (leucovorin, fluorouracil and oxaliplatin), after which tumour response was evaluated by MRI and/or PET–CT. The presence of systemic disease was evaluated with CT or PET-CT. Referring hospitals were advised to administer three cycles before CRRT. When a good response was noted, continuation of chemotherapy with three cycles

Table 1 Patient and neoadjuvant treatment characteristics for all resected patients

	ICT + CRRT ($n = 58$)	CRRT alone ($n = 71$)	P‡
Age (years)*	64 (33–76)	65 (30–84)	0·297§
Sex ratio (M : F)	46 : 12	40 : 31	0·006
Stage of primary tumour†			0·080
0	1 (2)	1 (1)	
I	3 (5)	13 (19)	
II	13 (22)	19 (27)	
III	35 (60)	35 (50)	
IV	6 (10)	2 (3)	
(Neo)adjuvant treatment for primary tumour			0·697
None/chemotherapy alone‡	4 (7)	5 (7)	
Radiotherapy (5 × 5 Gy)	22 (38)	32 (45)	
Chemoradiotherapy	32 (55)	34 (48)	
History of metastasis§			0·276
No	40 (69)	55 (78)	
Yes	18 (31)	16 (23)	
Type of primary surgery			0·073
Hartmann procedure	3 (5)	2 (3)	
Rectosigmoid resection	2 (3)	0 (0)	
Low anterior resection	27 (47)	38 (54)	
Abdominoperineal/abdominosacral resection	23 (40)	22 (31)	
Total exenteration	3 (5)	2 (3)	
Other/unknown	0 (0)	7 (10)	
Local recurrence			0·570
First	51 (88)	65 (92)	
Second	6 (10)	4 (6)	
Third	1 (2)	2 (3)	

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Information on the primary tumour could not be retrieved for one patient in the chemoradiation therapy (CRRT) group. ‡These patients did receive full-course radiotherapy for a previous recurrence. §Metachronous or synchronous resectable metastases. ICT, induction chemotherapy. ‡χ^2 test, except §t test.

Table 2 Pathological responses of patients in induction chemotherapy and chemoradiation therapy-alone groups

	ICT + CRRT ($n = 58$)	CRRT alone ($n = 71$)	P*	Total ($n = 129$)
R0	32 (55)	35 (49)	0·506	67 (51·9)
pCR	10 (17)	3 (4)	0·015	13 (10·1)

Values in parentheses are percentages. ICT, induction chemotherapy; CRRT, chemoradiation therapy; R0, complete resection; pCR, pathological complete response. *χ^2 test.

of consolidation chemotherapy in the waiting time after CRRT was advised. Some patients received six cycles of chemotherapy before CRRT. If no response to the first three cycles was noted, consolidation chemotherapy was considered not to be useful when administered in the waiting period. CRRT consisted of 30–30·4 Gy in fractions of 2–1·8 Gy with concomitant capecitabine (825 mg/m^2 twice daily) in all patients.

Resectability and timing of surgery

The waiting period between radiotherapy and surgery was generally 8–10 weeks. The tumour was restaged with MRI 1 month after the last radiotherapy administration to determine response and local resectability, and metastatic disease was excluded by CT or PET–CT. All patients were discussed in a multidisciplinary board meeting, and two senior surgeons with 20 years of experience in recurrent rectal cancer surgery performed all resections, as described previously[16].

Pathology

All specimens were revised by a single pathologist trained as a total mesorectal excision pathologist, and with particular expertise in evaluating recurrent rectal cancer specimens using the Mandard classification[17]. pCR was defined as the absence of tumour residue (Mandard score 1). Margin status was classified as either microscopic (R1) or macroscopic (R2) tumour present in the resection margin, or a tumour-free resection margin (R0). Patients with a pCR were classified as R0, but were analysed as a separate group

to determine differences from R0 resections with and without pCR in survival curves.

Statistical analysis

To compare individual variables, *t* tests and χ^2 tests were used when appropriate. OS for resected patients was calculated as the time interval between the date of resection of the recurrence and the date of last follow-up or death. LRFS was calculated as the time interval between the date of recurrence resection and the date of histological or evident radiological presence of a local rerecurrence. MFS was calculated as the time interval between the date of recurrence resection and the date of histological or evident radiological presence of distant metastasis. OS, LRFS and MFS were estimated using the Kaplan–Meier method, with differences assessed with the log rank test.

Statistical analysis was performed using SPSS® version 23 for Windows® (IBM, Armonk, New York, USA). Sample size calculations were done with Power and Precision™ release 4.1 2012 (Biostat, Englewood, New Jersey, USA).

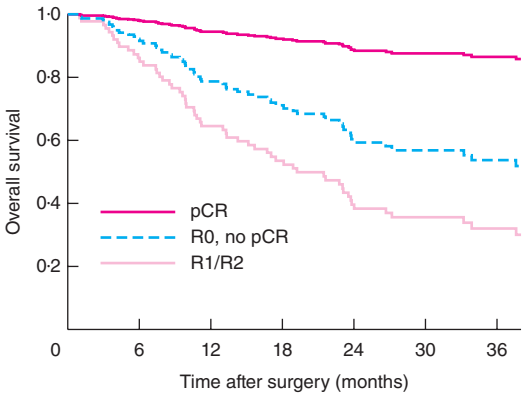
Results

During the selected time frame, ICT was incorporated into the multimodality management of 58 patients, and 71 patients received concurrent CRRT alone. Patient and neoadjuvant treatment characteristics are shown in *Table 1*. Apart from sex differences, there were no significantly different characteristics between the two groups.

In general, local recurrences occurred within the first 3 years after resection of the primary tumour, with a median interval of 32 (range 5–201) months for first recurrences and of 17 (range 8–52) months between previous recurrence surgery and index surgery for second and third recurrences. Of the 58 patients in the ICT group, ten required a dose reduction during ICT and six during their CRRT. Four patients in this group were hospitalized during ICT, and one patient during CRRT. In the CCRT-only group, one patient required dose reduction, and four had to be hospitalized. Postoperative complications (Clavien–Dindo grade III–IV) were comparable between groups: 13 (22 per cent) in the ICT group and 19 (27 per cent) in the CRRT group ($P = 0{\cdot}715$).

Clear margin and pathological complete response rates

Patients who received ICT had a similar R0 resection rate to those who had CRRT alone (55 *versus* 49 per cent respectively; $P = 0{\cdot}506$), but exhibited a significantly increased pCR rate (17 *versus* 4 per cent; $P = 0{\cdot}015$) (*Table 2*). The remaining 26 patients in the ICT arm had 23 R1 and three R2 resections, and the 36 remaining in the CRRT-alone arm all had an R1 resection.



No. at risk

pCR	13	12	6	5	4	2	1
R0, no pCR	54	47	34	28	20	14	13
R1/R2	62	45	35	28	20	15	10

Fig. 2 Kaplan–Meier curve for overall survival in all resected patients based on pathological outcome. pCR, pathological complete response; RO, complete resection; R1/R2, microscopic/macroscopic tumour present in the resection margin. $P = 0{\cdot}012$ (log rank test)

Overall survival

The 3-year OS rate for the 129 patients was 44 per cent (median survival 27 months), 92 per cent in patients who had a pCR, 54 per cent in those with an R0 resection but no pCR, and 32 per cent in patients who had an R1/R2 resection ($P = 0{\cdot}012$) (*Fig. 2*).

In the ICT group, patients who had a pCR were all alive at the end of follow-up, whereas those with R0 but no pCR or margin-positive patients had a median survival of 23 months ($P = 0{\cdot}039$). There were only three R2 resections in the ICT group, and none in the CRRT group; therefore, no separate analyses for resection state were performed. In the CRRT group, only three patients achieved a pCR, so the numbers were too small to perform statistical comparisons; however, one patient with a pCR died from another cause at 10 months.

Local and distant recurrence

The 3-year LRFS rate was 41 per cent (median survival 20 months), 89 per cent at 24 months in patients who had a pCR, 65 per cent in those with R0 but no pCR, and 25 per cent for patients with an R1/R2 resection ($P < 0{\cdot}001$). The 3-year MFS rate was 45 per cent (median survival 28 months), 60 per cent in patients who had a pCR, 60 per

cent for R0 but no pCR, and 25 per cent for patients with an R1/R2 resection ($P = 0{\cdot}010$).

Discussion

This study has demonstrated high pCR rates in patients with locally recurrent rectal carcinoma after a new sequential neoadjuvant regimen consisting of ICT followed by CRRT. This is comparable to pCR rates described after chemoradiotherapy in locally advanced primary rectal cancer[18,19]. Furthermore, pCR exhibited a strong relationship with OS, LRFS and MFS. This is an important finding as the treatment options for this group of patients are limited. Thus, new treatment options should focus on increasing the pCR rate. To date, only case reports[20–22] have described pCR in locally recurrent rectal cancer.

In subgroup analyses of the ICT and CRRT groups, the benefit of a pCR was apparent only in the ICT group. This finding might reflect a systemic effect, reducing the development of systemic micrometastasis and improving not only local, but also distant recurrence rates. These are, however, speculations, as these trends could not be demonstrated by survival differences in the two groups. This lack of statistical significance might be due to a power problem; hence, these data need to be interpreted with caution.

Similar R0 margin rates were observed in patients who underwent ICT and those who had CRRT alone. However, there is a need to clarify why the ICT was initiated. ICT was formerly administered exclusively to patients with unresectable locally recurrent rectal cancer. In several cases, remarkable results were observed: many lesions became resectable, and some patients even had a pCR. After observing favourable results in this poor category of patients, this regimen was expanded to patients with locally recurrent rectal cancer and better prognostic features. The ICT group thus consisted of surgically unfavourable recurrent cases and could hamper any comparison. However, the finding that ICT results in more pCRs and similar R0 resection rates in these unfavourable cases demonstrates that it has a definite role in intensifying the response of neoadjuvant treatment in previously irradiated patients with locally recurrent rectal cancer. Studies of ICT in recurrent rectal cancer are not available, but the findings here are in line with the results of studies on primary locally advanced rectal cancer, which demonstrated a higher response rate after ICT before chemoradiotherapy and also seemed to translate into a better outcome[23,24]. Further radiological guidelines are required to enable categorization of 'resectable' *versus* 'irresectable' disease, such that similar groups of patients can be compared to demonstrate a difference in R0 resection rate.

A major advantage of a neoadjuvant treatment regimen including ICT is the avoidance of possible overtreatment in patients with progressive systemic disease. This regimen enables the possibility of observing oncobiological behaviour of the recurrent disease, and unnecessary surgery might be prevented in patients with progressive distant disease. Response to this treatment could also be used as a selection criterion for further procedures. Good responders not developing metastases may be better candidates for this extensive surgery, whereas those who exhibit local progression or even develop metastases during chemotherapy could be spared unnecessary morbidity and mortality, and undergo the best palliative treatment in the meantime.

One of the major drawbacks of this study is that it was not designed as a prospective study to achieve a complete response. Negative selection bias on the basis of more or less unfavourable conditions may have influenced the results. The accidental finding that most of these patients could undergo an R0 resection and unexpectedly showed a high pCR rate is hypothesis-generating, and requires further validation in future studies. To show an increase in the pCR rate following ICT from 5 to 15 per cent (two-tailed $\alpha = 0{\cdot}05$ and power of 80 per cent), the number of patients in each arm would need to be 140. A difference of 15 per cent in the R0 resection rate, which is the strongest predictor of oncological outcome, would also require 140 patients per arm. To demonstrate a 10 per cent increase in the DFS rate at 3 years, more than 700 patients would be required in each study arm, which is an unrealistic number for a study with such a heterogeneous group as patients with locally recurrent rectal cancer. Alternative study designs, such as a matched case–control study, would require a relatively small cohort of patients to undergo the intervention.

Disclosure

The authors declare no conflict of interest.

References

1 van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T *et al.*; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011; **12**: 575–582.
2 Sasikumar A, Bhan C, Jenkins JT, Antoniou A, Murphy J. Systematic review of pelvic exenteration with *en bloc* sacrectomy for recurrent rectal adenocarcinoma: R0 resection predicts disease-free survival. *Dis Colon Rectum* 2017; **60**: 346–352.
3 Harris CA, Solomon MJ, Heriot AG, Sagar PM, Tekkis PP, Dixon L *et al.* The outcomes and patterns of treatment

failure after surgery for locally recurrent rectal cancer. *Ann Surg* 2016; **264**: 323–329.
4 Alberda WJ, Verhoef C, Schipper ME, Nuyttens JJ, Rothbarth J, de Wilt JH *et al.* The importance of a minimal tumor-free resection margin in locally recurrent rectal cancer. *Dis Colon Rectum* 2015; **58**: 677–685.
5 Beyond TME Collaborative. Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. *Br J Surg* 2013; **100**: E1–E33.
6 Bosman SJ, Holman FA, Nieuwenhuijzen GA, Martijn H, Creemers GJ, Rutten HJ. Feasibility of reirradiation in the treatment of locally recurrent rectal cancer. *Br J Surg* 2014; **101**: 1280–1289.
7 Mohiuddin M, Marks G, Marks J. Long-term results of reirradiation for patients with recurrent rectal carcinoma. *Cancer* 2002; **95**: 1144–1150.
8 Glimelius B. Recurrent rectal cancer. The pre-irradiated primary tumour: can more radiotherapy be given? *Colorectal Dis* 2003; **5**: 501–503.
9 van der Meij W, Rombouts AJ, Rutten H, Bremers AJ, de Wilt JH. Treatment of locally recurrent rectal carcinoma in previously (chemo)irradiated patients: a review. *Dis Colon Rectum* 2016; **59**: 148–156.
10 Dresen RC, Gosens MJ, Martijn H, Nieuwenhuijzen GA, Creemers GJ, Daniels-Gooszen AW *et al.* Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. *Ann Surg Oncol* 2008; **15**: 1937–1947.
11 Holman FA, Bosman SJ, Haddock MG, Gunderson LL, Kusters M, Nieuwenhuijzen GA *et al.* Results of a pooled analysis of IOERT containing multimodality treatment for locally recurrent rectal cancer: results of 565 patients of two major treatment centres. *Eur J Surg Oncol* 2017; **43**: 107–117.
12 van den Brink M, Stiggelbout AM, van den Hout WB, Kievit J, Klein Kranenbarg E, Marijnen CA *et al.* Clinical nature and prognosis of locally recurrent rectal cancer after total mesorectal excision with or without preoperative radiotherapy. *J Clin Oncol* 2004; **22**: 3958–3964.
13 Tanis PJ, Doeksen A, van Lanschot JJ. Intentionally curative treatment of locally recurrent rectal cancer: a systematic review. *Can J Surg* 2013; **56**: 135–144.
14 Bhatti ABH, Waheed A, Hafeez A, Akbar A, Syed AA, Khattak S *et al.* Can induction chemotherapy before concurrent chemoradiation impact circumferential resection margin positivity and survival in low rectal cancers? *Asian Pac J Cancer Prev* 2015; **16**: 2993–2998.
15 Fernandez-Martos C, Garcia Fadrique A, Glynne-Jones R. Optimal sequencing of neoadjuvant therapy (NAT) in rectal cancer: upfront chemotherapy *vs*. upfront chemoradiation. *Curr Colorectal Cancer Rep* 2017; **13**: 154–164.
16 Dresen RC, Kusters M, Daniels-Gooszen AW, Cappendijk VC, Nieuwenhuijzen GA, Kessels AG *et al.* Absence of tumor invasion into pelvic structures in locally recurrent rectal cancer: prediction with preoperative MR imaging. *Radiology* 2010; **256**: 143–150.
17 Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF *et al.* Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer* 1994; **73**: 2680–2686.
18 Cercek A, Goodman KA, Hajj C, Weisberger E, Segal NH, Reidy-Lagunes DL *et al.* Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. *J Natl Compr Canc Netw* 2014; **12**: 513–519.
19 de Campos-Lobato LF, Stocchi L, da Luz Moreira A, Geisler D, Dietz DW, Lavery IC *et al.* Pathologic complete response after neoadjuvant treatment for rectal cancer decreases distant recurrence and could eradicate local recurrence. *Ann Surg Oncol* 2011; **18**: 1590–1598.
20 Ishiba T, Ohtsukasa S, Kato S, Nagano H, Takamatsu S, Taki K *et al.* [A case of pathologically complete response of local recurrence in the mesorectum after multidisciplinary therapy.] *Gan To Kagaku Ryoho* 2013; **40**: 1993–1995.
21 Iwata N, Ishikawa T, Takahashi H, Baba H, Masuda D, Okazaki S *et al.* [A case of recurrent rectal cancer successfully treated for a long period with capecitabine plus oxaliplatin and bevacizumab therapy.] *Gan To Kagaku Ryoho* 2013; **40**: 2008–2010.
22 Yatsuoka T, Nishimura Y, Sakamoto H, Tanaka Y, Yamaguchi K. [A case of recurrent rectal cancer with paraaortic lymph node metastasis treated by FOLFIRI therapy leading to complete response.] *Gan To Kagaku Ryoho* 2011; **38**: 2057–2059.
23 Denost Q, Kontovounisios C, Rasheed S, Chevalier R, Brasio R, Capdepont M *et al.* Individualizing surgical treatment based on tumour response following neoadjuvant therapy in T4 primary rectal cancer. *Eur J Surg Oncol* 2017; **43**: 92–99.
24 Rouanet P, Rullier E, Lelong B, Maingon P, Tuech JJ, Pezet D *et al.*; GRECCAR Study Group. Tailored treatment strategy for locally advanced rectal carcinoma based on the tumor response to induction chemotherapy: preliminary results of the french phase II multicenter GRECCAR4 trial. *Dis Colon Rectum* 2017; **60**: 653–663.

Supporting information

Additional supporting information can be found online in the supporting information tab for this article.