Original article

Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer

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Background: **Neoadjuvant chemoradiotherapy (CRT) has been proven to increase local control in rectal cancer, but the optimal interval between CRT and surgery is still unclear. The purpose of this study was to analyse the influence of variations in clinical practice regarding timing of surgery on pathological response at a population level.**

Methods: **All evaluable patients who underwent preoperative CRT for rectal cancer between 2009 and 2011 were selected from the Dutch Surgical Colorectal Audit. The interval between radiotherapy and surgery was calculated from the start of radiotherapy. The primary endpoint was pathological complete response (pCR; pathological status after chemoradiotherapy (yp) T0 N0).**

Results: **A total of 1593 patients were included. The median interval between radiotherapy and surgery was 14 (range 6–85, interquartile range 12–16) weeks. Outcome measures were calculated for intervals of less than 13 weeks (312 patients), 13–14 weeks (511 patients), 15–16 weeks (406 patients) and more than 16 weeks (364 patients). Age, tumour location and R0 resection rate were distributed equally between the four groups; significant differences were found for clinical tumour category (cT4: 17·3, 18·4, 24·5 and 26·6 per cent respectively; $P = 0{\cdot}010$) and clinical metastasis category (cM1: 4·4, 4·8, 8·9 and 14·9 per cent respectively; $P < 0{\cdot}001$). Resection 15–16 weeks after the start of CRT resulted in the highest pCR rate (18·0 per cent; $P = 0{\cdot}013$), with an independent association (hazard ratio 1·63, 95 per cent confidence interval 1·20 to 2·23). Results for secondary endpoints in the group with an interval of 15–16 weeks were: tumour downstaging, 55·2 per cent ($P = 0{\cdot}165$); nodal downstaging, 58·6 per cent ($P = 0{\cdot}036$); and (near)-complete response, 23·2 per cent ($P = 0{\cdot}124$).**

Conclusion: **Delaying surgery until the 15th or 16th week after the start of CRT (10–11 weeks from the end of CRT) seemed to result in the highest chance of a pCR.**

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Introduction

Neoadjuvant chemoradiotherapy (CRT) has become the standard of care for patients with locally advanced rectal cancer. Several randomized trials have shown that preoperative radiotherapy is more effective than postoperative radiotherapy, and that preoperative CRT results in better local control than long-course radiotherapy alone or postoperative CRT[1]. Furthermore, a randomized trial demonstrated that adding oxaliplatin to conventional CRT with 5-fluorouracil (5-FU) or capecitabine did not result in a significant increase in pathological complete response (pCR)[2].

One of the unresolved questions concerning preoperative CRT for rectal cancer is the timing of surgery. Traditionally, the interval between the end of CRT and surgery was 4–6 weeks. Conflicting results from small observational studies have been published on the association between pCR and time interval between radiotherapy and surgery[3–11]. The process of tumour regression takes

some time, as illustrated in a recent study by Dhadda and colleagues[12], who calculated the tumour volume-halving time. The interval to surgery was independently associated with the percentage tumour regression. Waiting for the highest degree of pathological response is clinically relevant as this increases the chance of R0 resection. Furthermore, a local excision or 'wait and see' policy is increasingly being considered for patients with a (near)-complete response, and timing is an important aspect in such decision-making[13,14].

All patients undergoing resection for colorectal cancer in the Netherlands are registered in a national database, the Dutch Surgical Colorectal Audit (DSCA; http://www.dsca.nl), which was started in 2009. The purpose of this study was to analyse the influence of variations in clinical practice regarding the timing of total mesorectal excision (TME) after CRT for rectal cancer on pathological response at a population level.

Methods

Of all patients who underwent TME surgery for primary rectal cancer between 1 January 2009 and 31 December 2011, an estimated 90 per cent were registered in the DSCA on 1 March 2012. All 92 Dutch hospitals in which rectal cancer surgery is performed participate in the DSCA. Data entry for the DSCA is web-based. The completeness and accuracy of data registration are validated on a yearly basis by comparing the data with registrations in the Netherlands Cancer Registry. Patients undergoing local transanal excision or resection of locally recurrent rectal cancer were not included in the database during the study period.

According to the national guideline (http://www.oncoline.nl), CRT is advised in patients with clinical (c) T4 tumours, if a positive circumferential resection margin is expected, or if four or more lymph nodes are suspected to be tumour-positive on preoperative imaging (cN2). In addition, CRT is used for a subgroup of distal cT1–3 N0 tumours, aiming at local excision or a 'wait and see' policy in the event of a (near)-complete clinical response. Patients who eventually undergo TME surgery because of an unfavourable pathological response in the local excision specimen are included in the DSCA. For the purpose of the present analysis, these patients were excluded, because no separate pathological data were available for the two specimens. In addition, patients were excluded if the date of radiotherapy or pathological tumour node (pTN) stage was not registered. Missing data and additional variables of interest (end date of radiotherapy, CRT regimen) could not be retrieved retrospectively via chart review because patient identity and hospital are concealed in databases provided for research by the Dutch Institute of Clinical Auditing.

Among the 19 radiotherapy institutes in the Netherlands, the fractionation schedule was 25×2 Gy in 11 institutes and $28 \times 1{\cdot}8$ Gy in seven. In one institute, fractionation of $25 \times 1{\cdot}8$ Gy was followed by a boost of $3 \times 1{\cdot}8$ Gy. Capecitabine was administered at 825 mg/m^2 twice daily, either on weekdays only during radiation treatments or also at weekends, depending on local policy. In three centres a higher dose of capecitabine was administered (1000–1200 mg/m^2 twice daily). A few patients participated in clinical trials and received 5-FU with or without oxaliplatin instead of capecitabine. Full-dose systemic combination chemotherapy that had been given before surgery was defined as induction or interval chemotherapy based on a start date before or after the start of radiotherapy respectively.

The start date of radiotherapy and date of surgery are available in the DSCA database for the purpose of calculating time intervals. Therefore, the interval between CRT and surgery was calculated from start of radiotherapy. The waiting time from the end of CRT can be estimated by subtraction of 5 weeks (duration of a conventional CRT scheme) from the reported intervals, which facilitates comparison with published data.

The primary endpoint was a pCR (pathological status after chemoradiotherapy (yp) T0 N0). The pCR rate was calculated from the start of radiotherapy for each week in the period from 11 to 30 weeks, as well as for patients operated on before week 11 or after week 30. Two 2-week periods were clustered based on the four highest pCR rates, and two remaining time periods preceding and following these 4 weeks were defined. Secondary endpoints were (near) pCR (ypT0–1 N0), tumour downstaging (ypT less than cT), nodal downstaging (ypN less than cN), lymph node yield, overall complication rate within 30 days after rectal resection, and 30-day postoperative mortality. Clinical stage (cTN), as determined at the beginning of neoadjuvant treatment, was compared with pathological stage (ypTN) to evaluate differences in overall response between time interval groups. For the purpose of this analysis, 'response' was defined as ypTN less than cTN, 'stable disease' as ypTN equal to cTN, and 'progression' as ypTN greater than cTN.

Statistical analysis

χ^2 test, Fisher's exact test and one-way ANOVA were used to compare characteristics and outcome parameters between the groups. Multivariable logistic regression analysis was done to identify independent predictors of

a pCR. Statistical significance was defined as $P < 0{\cdot}050$. SPSS® software was used for statistical analysis (IBM, Armonk, New York, USA).

Results

Of 7249 patients registered with rectal cancer, 2203 had preoperative CRT. Five patients underwent transanal endoscopic microsurgery before the TME and were excluded. After exclusion of records with incomplete data on start date of radiotherapy (501) and ypT (104), 1593 patients remained for inclusion in the analysis. The cT status was available for 1491 (93·6 per cent) of 1593 patients.

The median interval between radiotherapy and surgery was 14 (range 6–85, interquartile range 12–16) weeks. The overall pCR rate was 13·5 per cent (215 of 1593 patients). The number of pCRs in relation to the interval between the start of CRT and surgery is shown in *Fig. 1*. The four highest pCR rates occurred in patients with an interval of 15 weeks (19·7 per cent), 16 weeks (15·7 per cent), 13 weeks (13·1 per cent) and 14 weeks (13·1 per cent). The cumulative pCR rate is plotted in *Fig. 2*. A plateau in the pCR rate appeared to be reached in week 17.

Based on the primary outcome analysis, patients were divided into four groups according to the interval between the start of CRT and resection: less than 13 weeks, 13–14 weeks, 15–16 weeks and more than 16 weeks. Patient, tumour and treatment characteristics of these groups are shown in *Table 1*. Significant differences were found for cT ($P = 0{\cdot}010$) and cM ($P < 0{\cdot}001$). The percentage of patients with cT4 disease increased from 17·3 to 26·6 per cent with increasing time interval from

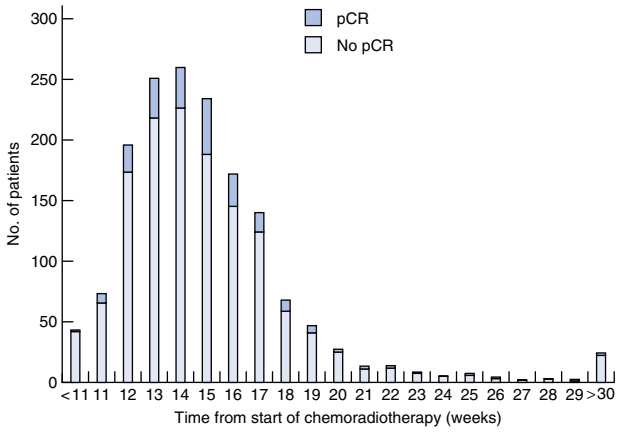

Fig. 1 Number of patients showing a complete pathological response (pCR) in relation to time from start of chemoradiotherapy

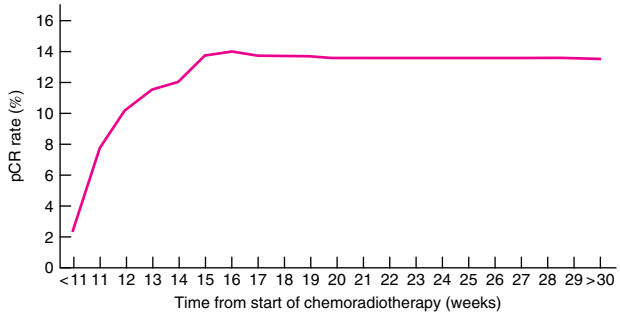

Fig. 2 Cumulative complete pathological response (pCR) rate

the start of CRT. A similar trend was observed for distant metastases: 4·4 per cent of patients who underwent surgery before week 13 had cM1 disease, compared with 14·9 per cent of those who had surgery after more than 16 weeks. Consequently, the use of induction or interval systemic chemotherapy ($P < 0{\cdot}001$) as well as extended resections for locally advanced disease ($P = 0{\cdot}005$) or additional resections for metastatic disease ($P < 0{\cdot}001$) increased significantly with increasing time between CRT and surgery.

Primary and secondary outcomes for each group are shown in *Table 2*. The pCR rate was significantly higher in patients with an interval of 15–16 weeks between CRT and surgery (18·0 per cent) compared with the other time intervals (10·3, 13·1 and 11·8 per cent for less than 13 weeks, 13–14 weeks and more than 16 weeks respectively; $P = 0{\cdot}013$). If a small tumour remnant (ypT1 N0) was combined with pCR (ypT0 N0), the highest response rate was also found for patients with a 15–16-week interval week (23·2 per cent), although this was not significantly different from the rate in the other three groups ($P = 0{\cdot}124$). Comparing pathological findings with clinical status based on imaging, again the highest percentage downstaging was found in patients with an interval of 15–16 weeks, which was significant for N status but not for T category. Response rates based on combined TN stage did not differ significantly among the four time interval groups (*Table 2*). No statistically significant differences in lymph node yield and 30-day morbidity or mortality rates were observed.

Besides time interval to surgery, cT category was the only potential predictor of pCR in univariable analysis. A pCR was achieved in 12 per cent of patients with cT1 tumours (3 of 25), 21·0 per cent (22 of 105) for cT2, 14·5 per cent (150 of 1038) for cT3 and 10·5 per cent (34 of 323) for cT4 ($P = 0{\cdot}052$). In multivariable logistic regression analyses, an interval of 15–16 weeks after the start of CRT was independently associated with a higher pCR rate, in comparison with an interval of less than 15 weeks or more

Table 1 Patient, tumour and treatment characteristics for four groups based on interval between start of chemoradiotherapy and surgery

	< 13 weeks (*n* = 312)	13–14 weeks (*n* = 511)	15–16 weeks (*n* = 406)	> 16 weeks (*n* = 364)	*P*‡
Age (years)*	63 (31–85)	63 (35–87)	64 (26–85)	64 (18–93)	0·400§
Sex ratio (M : F)	200 : 112	327 : 184	244 : 162	229 : 135	0·613
Body mass index (kg/m^2)*	25·6 (15·6–43·0)	25·9 (15·6–43·4)	25·7 (15·5–46·9)	25·8 (15·1–43·2)	0·818§
Imaging of pelvis (*n* = 1524)	*n* = 303	*n* = 493	*n* = 386	*n* = 342	0·057
CT	11 (3·6)	7 (1·4)	12 (3·1)	19 (5·6)	
MRI	290 (95·7)	484 (98·2)	370 (95·9)	322 (94·2)	
Distance from anal verge (cm) (*n* = 1469)	*n* = 286	*n* = 475	*n* = 376	*n* = 332	0·204
0–5	140 (49·0)	221 (46·5)	183 (48·7)	181 (54·4)	
6–10	101 (35·3)	188 (39·6)	128 (34·0)	106 (31·9)	
>10	45 (15·7)	66 (13·9)	65 (17·3)	45 (13·6)	
Clinical tumour category (*n* = 1491)	*n* = 278	*n* = 483	*n* = 384	*n* = 346	0·010
cT1	6 (2·2)	3 (0·6)	6 (1·6)	10 (2·9)	
cT2	17 (6·1)	35 (7·2)	28 (7·3)	25 (7·2)	
cT3	207 (74·5)	356 (73·7)	256 (66·7)	219 (63·3)	
cT4	48 (17·3)	89 (18·4)	94 (24·5)	92 (26·6)	
Clinical node category (*n* = 1428)	*n* = 272	*n* = 459	*n* = 374	*n* = 323	0·073
cN0	74 (27·2)	105 (22·9)	68 (18·2)	68 (21·1)	
cN1	125 (46·0)	216 (47·1)	179 (47·9)	140 (43·3)	
cN2	73 (26·8)	138 (30·1)	127 (34·0)	115 (35·6)	
Clinical metastasis category (*n* = 1408)	*n* = 273	*n* = 457	*n* = 369	*n* = 309	< 0·001
cM0	261 (95·6)	435 (95·2)	336 (91·1)	263 (85·1)	
cM1	12 (4·4)	22 (4·8)	33 (8·9)	46 (14·9)	
No. of examined lymph nodes*	12·3 (0–46)	11·9 (0–57)	11·4 (0–37)	11·7 (0–50)	0·099§
No. of positive lymph nodes*	1·6 (0–42)	1·2 (0–24)	1·1 (0–24)	1·3 (0–20)	0·201§
Lymph node ratio*†	0·12 (0–1)	0·10 (0–1)	0·10 (0–1)	0·12 (0–1)	0·198§
Preop. systemic chemotherapy (*n* = 1258)	*n* = 259	*n* = 403	*n* = 319	*n* = 277	< 0·001¶
Induction	0	5 (1·2)	3 (0·9)	4 (1·4)	
Interval	0	1 (0·2)	11 (3·4)	23 (8·3)	
Extended resection for T4 (*n* = 1512)	32 of 280 (11·4)	61 of 495 (12·3)	63 of 388 (16·2)	72 of 349 (20·6)	0·005
Additional resection for M1 (*n* = 1528)	4 of 296 (1·4)	13 of 493 (2·6)	24 of 387 (6·2)	27 of 352 (7·7)	< 0·001
Completeness of resection (*n* = 1555)	*n* = 302	*n* = 499	*n* = 397	*n* = 357	0·649¶
R0	284 (94·0)	471 (94·4)	374 (94·2)	328 (91·9)	
R1	14 (4·6)	25 (5·0)	20 (5·0)	26 (7·3)	
R2	4 (1·3)	3 (0·6)	3 (0·8)	3 (0·8)	

Values in parentheses are percentages unless indicated otherwise;*values are mean (range). †Number of positive lymph nodes/total number of lymph nodes. CT, computed tomography; MRI, magnetic resonance imaging. ‡χ^2 test, except §one-way ANOVA and ¶Fisher's exact test.

Table 2 Outcome parameters in relation to interval between start of chemoradiotherapy and surgery

	< 13 weeks	13–14 weeks	15–16 weeks	> 16 weeks	d.f.	*P**
pCR (ypT0 N0)	32 of 312 (10·3)	67 of 511 (13·1)	73 of 406 (18·0)	43 of 364 (11·8)	3	0·013
pCR and near pCR (ypT0–1 N0)	57 of 312 (18·3)	91 of 511 (17·8)	94 of 406 (23·2)	63 of 364 (17·3)	3	0·124
Tumour category downstaging (ypT < cT)	132 of 278 (47·5)	244 of 483 (50·5)	212 of 384 (55·2)	167 of 346 (48·3)	3	0·165
Node category downstaging (ypN < cN)	128 of 272 (47·1)	245 of 459 (53·4)	219 of 374 (58·6)	169 of 323 (52·3)	3	0·036
cTN *versus* ypTN					6	0·472
Response (ypTN < cTN)	165 of 261 (63·2)	299 of 446 (67·0)	248 of 356 (69·7)	206 of 317 (65·0)		
Stable disease (ypTN = cTN)	75 of 261 (28·7)	123 of 446 (27·6)	87 of 356 (24·4)	85 of 317 (26·8)		
Progression (ypTN > cTN)	21 of 261 (8·0)	24 of 446 (5·4)	21 of 356 (5·9)	26 of 317 (8·2)		
Any complication within 30 days of operation	116 of 311 (37·3)	178 of 506 (35·2)	168 of 403 (41·7)	142 of 359 (39·6)	3	0·220
30-day mortality	8 of 312 (2·6)	4 of 511 (0·8)	4 of 406 (1·0)	5 of 364 (1·4)	3	0·183†

Values in parentheses are percentages. pCR, pathological complete response; ypT/N, pathological tumour/node status after chemoradiotherapy; cT/N, clinical tumour/node category.*χ^2 test, except †Fisher's exact test.

Table 3 Multivariable logistic regression analysis of factors predicting a pathological complete response

	Hazard ratio	*P*
Clinical tumour category		
cT1 and cT2	1·00 (reference)	
cT3 and cT4	0·66 (0·41, 1·04)	0·076
Interval between CRT and surgery (weeks)		
< 15 or > 16	1·00 (reference)	
15 or 16	1·63 (1·20, 2·23)	0·002

Values in parentheses are 95 per cent confidence intervals. CRT, chemoradiotherapy.

than 16 weeks (hazard ratio 1·63, 95 per cent confidence interval 1·20 to 2·23; $P = 0·002$). cT category did not reach statistical significance in multivariable analysis (*Table 3*).

Discussion

Based on differences in clinical practice regarding the timing of TME surgery among 92 Dutch hospitals, in this study the pCR rate after neoadjuvant CRT for rectal cancer was related to the interval between CRT and surgery, in both univariable and multivariable analysis. The highest pCR rates were observed in patients operated on 15 or 16 weeks after the start of CRT, corresponding to approximately 10–11 weeks from the end of CRT. This is longer than usually reported in literature; the interval to surgery was shorter than 10 weeks in all 16 studies included in a recent systematic review of CRT for rectal cancer[15]. Response rates after 16 weeks are difficult to interpret, because of the small number in each week and another clinical setting, including metastatic disease being treated with systemic chemotherapy, sometimes with palliative intent.

To date, the only randomized trial to examine the time interval to surgery is the Lyon R90-01 trial, published in 1999[16]. A total of 210 patients with rectal cancer were randomized between surgery after a short (less than 2 weeks) or long (6–8 weeks) interval from the end of preoperative radiotherapy (total dose 39 Gy in 13 fractions). The longer interval was associated with a significantly higher proportion of patients with ypT0–1 disease, but not pCR. This 6–8-week interval has become routine practice after CRT for rectal cancer.

The largest retrospective cohort study on this topic analysed waiting time after CRT in 397 patients; the pCR rate after a 4–6-week interval was similar to that after a 6–8-week wait (14 and 15 per cent respectively)[10]. In contrast, a significantly different pCR rate was found when an interval to surgery of at least 8 weeks from the end of CRT was compared with a shorter interval in a cohort of 242 patients: 30 *versus* 16 per cent[11]. The 8-week cut-off point was determined from a receiver operating characteristic (ROC) curve. In multivariable analyses, including sex, age, body mass index, radiotherapy dose and cTN stage, interval to surgery was the only predictor of pCR. Three smaller cohort series could not demonstrate a significant association between pCR and interval to surgery[4,7,8]. There were probably specific reasons for planning resection at shorter or longer intervals in these non-prospective studies. For instance, a large bulky tumour showing a partial response at first evaluation may be a reason for postponing resection, whereas progressive disease would necessitate early surgery. Such confounding factors may have contributed to the conflicting results.

This national audit allowed a multi-institutional analysis of a large number of patients, but the present study also had several limitations. Data were collected retrospectively, although validation with the Netherlands Cancer Registry confirmed accurate registration in the DSCA. Exclusion of patients with incomplete data could have introduced selection bias. Moreover, there is no information in the DSCA on patient-tailored approaches or institutional protocols with time intervals different from the 6–8 weeks advised in the current Dutch guideline. For example, post-CRT response evaluation by magnetic resonance imaging (MRI) is not registered in the DSCA. Finally, patients who did not proceed to surgery after CRT because of treatment-related toxicity, an inadequate response or disease progression are not recorded by the DSCA. More advanced disease was evident on pre-CRT imaging with longer time intervals to surgery. Nonetheless, pCR rates among patients with an interval of 15–16 weeks from the start of CRT were significantly greater than those in patients who had a shorter interval. The percentage of patients with a higher ypT than cT did not differ between the groups. This finding does not indicate a potential risk of tumour progression during waiting. These results should be confirmed by randomized clinical trials. Two such trials are currently accruing patients: one at the National Institutes of Health with intervals ranging from 6 to 24 weeks, and the Surgical Timing After Radiotherapy for Rectal Cancer (STARRCAT) trial, which is comparing 6- *versus* 12-week intervals from the end of CRT.

Waiting for the highest degree of tumour regression after CRT is of clinical relevance, as this will optimize the chance of an R0 resection. Furthermore, after waiting for a complete response, a subgroup of patients with excellent long-term survival can be better identified[15,17]. This may have implications for the surgical management. Transanal resection of residual mucosal abnormalities or watchful waiting after a complete clinical response have shown promising results, but adequate patient selection

for these treatments is challenging[13,14]. Pathological evaluation of tumour regression in rectal cancer has not been standardized, and a uniform definition of pCR, and protocol for sectioning and staining are lacking[18,19]. The observed overall pCR rate of 13·5 per cent in the present analysis is comparable to the mean pCR rate of 15·6 per cent in a recent meta-analysis of 12 studies comprising 1913 patients, although the pCR rates in the individual studies ranged between 10 and 26 per cent[17].

Response monitoring may be helpful for tailoring patient management regarding timing of surgery, with, for example, identification of progressive disease requiring early surgery. Monitoring the tumour response, however, is difficult. Morphological and size-related criteria generally lack sufficient accuracy for discriminating responders from non-responders[20]. Despite its shortcomings, MRI tumour regression grade appeared to be predictive of long-term outcome and may help in adapting treatment planning[21]. The value of functional imaging modalities such as diffusion-weighted MRI for response assessment during and soon after CRT is being evaluated[22].

The pCR rate may be further increased by induction chemotherapy or interval chemotherapy. In the Netherlands, this is applied on an incidental basis, mainly for M1 disease (*Table 1*). Initial studies have shown promising results[23,24]. The pCR rate increased from 18 to 25 per cent by adding two courses of FOLFOX (folinic acid–fluorouracil–oxaliplatin) chemotherapy after CRT and delaying surgery from 6 to 11 weeks after CRT in a randomized clinical trial[24]. Further delay of resection has been associated with decreasing lymph node retrieval[25], but this could not be confirmed in the present analysis. Radiation-induced fibrosis may result in a more difficult dissection after a longer waiting period, but no association with postoperative morbidity has been reported[4,6,9,10].

The present data suggest that delaying surgery until the 15th or 16th week after the start of CRT (week 10 and 11 after a 5-week CRT regimen) results in the highest chance of a pCR in patients with rectal cancer.

Disclosure

The authors declare no conflict of interest.

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