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Interval to surgery after neoadjuvant treatment for colorectal cancer

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Abstract

The current standard treatment of low-lying locally advanced rectal cancer consists of chemoradiation followed by radical surgery. The interval between chemoradiation and surgery varied for many years until the 1999 Lyon R90-01 trial which compared the effects of a short (2-wk) and long (6-wk) interval. Results showed a better clinical tumor response (71.7% vs 53.1%) and higher rate of positive and pathologic tumor regression (26% vs 10.3%) after the longer interval. Accordingly, a 6-wk interval between chemoradiation and surgery was set to balance the oncological results with the surgical complexity. However, several recent retrospective studies reported that prolonging the interval beyond 8 or even 12 wk may lead to significantly higher rates of tumor downstaging and pathologic complete response. This in turn, according to some reports, may improve overall and disease-free survival, without increasing the surgical difficulty or complications. This work reviews the data on the effect of different intervals, derived mostly from retrospective analyses using a wide variation of treatment protocols. Prospective randomized trials are currently ongoing.

reserved.

Key words: Rectal cancer; Chemoradiation therapy; Neoadjuvant; Surgery; Interval to surgery; Colorectal cancer

Core tip: The traditional 6-wk interval between chemoradiation and surgery in the treatment of rectal cancer was based primarily on a single publication. There has been a trend in recent years to prolong this interval based on studies showing that it may be advantageous in terms of tumor downstaging and pathologic complete response, without increasing surgical difficulty or complications. The data so far are derived largely from retrospective studies using a wide variation of treatments. Further investigations with a higher level of evidence are required to definitively resolve this issue.

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INTRODUCTION

Colorectal cancer is the fourth most common malignancy in the United States and the second most frequent cause of cancer-related death^[1]. Approximately 50% of rectal cancers are diagnosed at the locally advanced stage, with metastatic spread to the lymph nodes in two-thirds of these cases^[2]. The standard treatment of rectal cancer is curative surgical resection, combined with preoperative chemoradiation therapy (CRT) for T3 and/or node-positive tumors of the mid/low rectum (located 12 cm from the anal verge), and additional adjuvant therapy if indicated^[3-7]. Local recurrence rates following CRT and surgery

are less than 10%, especially when modern surgical techniques such as total mesorectal excision are used^[8]. Studies have shown that the addition of CRT has a beneficial effect on tumor downstaging and pathologic complete response (pCR)^[9,10], with improved tumor resectability, possibly increased sphincter preservation rates^[11,12], and maybe even increased overall survival rates^[13]. Recent evidence suggests that CRT-induced tumor regression may allow for a “watch and wait” approach that avoids surgery altogether in selected patients^[14].

Several strategies have been suggested to improve the response to CRT, including better patient selection^[15], case-personalized approach with specific genetic fingerprinting^[16,17], variations in the radiation and chemotherapy regimens^[18-20], and additional chemotherapy during a “rest interval” after CRT^[21]. In recent years, researchers have directed attention to optimizing the CRT-surgery interval^[22], which remains controversial^[22]. Ideally, the most favorable interval should facilitate maximal tumor regression, defined by maximal tumor downstaging and downsizing, with minimal risk of deterioration in the surgical results, defined by low short-term morbidity in mainly relation to perineal and anastomotic complications and better long-term oncological and functional outcomes.

Early trials conducted from the 1970s to the late 1990s used a broad range of CRT-surgery intervals with widely varying results^[23-27]. The 1999 Lyon R90-91 trial^[28] was the first to specifically address this issue. A cohort of 201 patients with rectal cancer were prospectively randomized to undergo surgery at 2 or 6 wk after completion of radiotherapy. The longer-interval group was found to have a better tumor response and improved pathological downstaging, with similar rates of complications and survival to the shorter-interval group. The authors concluded that 2 wk may be too short a time to achieve maximum benefits of radiation-induced tumor regression. As a consequence of this study, surgery at 6 wk after completion of radiotherapy became the standard of care. However, later data suggested that the response to CRT in patients with rectal cancer is time-dependent, and complete tumor regression may take months^[29]. Thus, the interval between CRT and surgery should be sufficient to attain greater tumor regression and to permit the acute radiation effects of tissue swelling and local inflammation to dissipate before surgery. At the same time, a too-long interval poses a risk of tumor progression during the wait for surgery, with a higher rate of distant metastasis. Furthermore, the accelerated repopulation of tumor cells that are not completely eradicated could lead to multidrug resistance. These drawbacks may explain the reported lack of change in survival in patients with rectal cancer despite the improvements in local control^[30]. Others have raised concerns that delaying surgery beyond 6 to 8 wk from CRT could also increase the technical operative risk due to radiation-induced pelvic fibrosis, thereby increasing the rate of surgical complications^[31] and locoregional recurrence^[32,33].

The purpose of the present review was to summarize the current data on the optimal timing of surgical resec-

tion after CRT for rectal cancer.

EFFECT OF PROLONGED CRT-SURGERY INTERVAL ON ONCOLOGICAL OUTCOME

Tumor regression and rate of pCR

The time elapsed from after preoperative CRT is one of the factors affecting the process of T or N stage reduction. Foster *et al*^[22] systematically reviewed 15 studies, each based on different neoadjuvant treatment indications and regimens and different CRT-surgery intervals. Four of the 9 studies that evaluated the effect of a prolonged interval on tumor regression reported a significant improvement. Most of the studies did not apply a histologically based tumor regression grade to estimate the degree of postoperative tumor regression and fibrosis^[34], although proven to be of prognostic significance^[35]. The only randomized study among these publications was the Lyon R90-01 trial^[28] in which the longer-interval group had significantly higher rates of a positive clinical tumor response (71.7% *vs* 53.1%) and pathologic tumor regression (26% *vs* 10.3%) than the shorter-interval group ($P < 0.05$ for both factors). They also had a nonsignificantly higher rate of pCR (13.8% *vs* 7.1%).

The Dutch surgical colorectal audit is the most recent published study to address the CRT-surgery interval in terms of tumor regression^[36]. A total of 1593 patients with rectal cancer were evaluated. The results showed that delaying surgery by 10-11 wk from the end of CRT was associated with the highest chance of a pCR. Accordingly, in a study of predictive factors of pCR, Kalady *et al*^[37] concluded that an extended interval between completion of neoadjuvant therapy and surgery was the single most important determinant. This finding was in line with the study of Garcia-Aguilar *et al*^[38] which analyzed the impact of both prolonging the CRT-surgery interval and adding resting-period chemotherapy. Rates of tumor downstaging and pCR significantly increased after longer intervals to surgery (18% *vs* 25%).

Using another approach, Perez and co-workers^[39] investigated changes in labeled fluoro-2-deoxy-d-glucose uptake on positron emission tomography/computed tomography (PET/CT) imaging, at baseline and 6 and 12 wk after CRT. The maximal standard uptake value (SUVmax) was measured at 1 and 3 h at each time point. The authors found that patients with an increase in early SUVmax were less likely to have significant tumor downstaging, suggesting that the variation in PET/CT SUVmax at 6 wk might serve as a criterion for selecting patients who may be expected to benefit from a longer CRT-surgery interval.

A few studies of the impact of the CRT-surgery interval included an analysis of nodal regression^[40-44]. No significant impact of a longer interval was found. The Lyon R90-01 trial, however, yielded a significant effect of a longer interval on nodal regression in patients with N2 disease^[28]. Similar results were noted in the Dutch colorectal surgery^[36] audit in which surgery was per-

formed 15-16 wk from the start of CRT. Others found that nodal retrieval is time-dependent, with a negative correlation after longer post-CRT time^[45]. Thus, it is possible that lymph nodes have a more rapid response to CRT which may override the effect of prolonging the CRT-surgery interval^[46].

Surgical margins

The status of the resection margins, including the distal mucosal and mesorectal margins, and specifically, the circumferential margins, is one of the most important factors determining disease recurrence after surgery^[47,48]. Neoadjuvant CRT has been associated with reduced rates of local recurrence and tapering of the recommended margins^[49]. Among the studies that examined the effect of a prolonged CRT-surgery interval on resection margin clearance^[41,44], one found microscopically involved margins (R1) in 2% of patients who underwent surgery before 44 d from CRT and in 1% of patients who underwent surgery later^[44]. Another reported a similar rate of positive circumferential resection margins (2.8%) with short (< 41 d) or longer intervals^[41]. In neither was the effect of a prolonged interval on resection margins significant. This was true of other studies as well^[22].

Prognosis

Both tumor downstaging and pCR are correlated with a better oncological outcome after CRT for rectal cancer^[50,51]. Some studies reported an improved prognosis after a longer CRT-surgery interval^[42,52]. Tulchinsky *et al*^[52] compared patients operated on at an interval of more or less than 7 wk after CRT. The longer-interval group had a significantly higher overall survival rate (93% *vs* 81%) and significantly lower distant metastasis rate (6% *vs* 19%) than the shorter-interval group. However, there was no between-group difference in local recurrence rate. Similarly, Coucke *et al*^[42] demonstrated that delaying surgery for more than 5 d after hyperfractionated accelerated radiotherapy (41.6 Gy/26 Fx *bid*) led to a significantly higher rate of overall survival (69% *vs* 47% for < 5 d, $P = 0.002$), disease-free survival (62% *vs* 41%, $P = 0.0003$), and cancer-specific survival (82% *vs* 57%, $P = 0.0007$) at a median follow-up of 39 mo. In this study, too, there was no difference in local control rate between the groups. de Campos-Lobato *et al*^[53] found a significant 3-year local recurrence benefit for delaying surgery for more than 8 wk after CRT (10.5% *vs* 1.2%), and Wolthuis *et al*^[54] reported significantly improved 5-year cancer-specific survival (91% *vs* 83%) and recurrence-free survival (73% *vs* 83%) when CRT-surgery intervals were prolonged. Pach *et al*^[55] randomized 154 patients to receive preoperative short-course radiation and surgery after 7 d *vs* surgery after 4-6 wk. Long CRT-surgery interval was associated with more tumor downstaging and tumor regression. Nevertheless, survival was similar in the two groups. On analysis of the oncological results of the Lyon R90-01 trial after a median follow-up of 6.3 years (range 6.1-7.2 years), Glehen *et al*^[56] failed to find any significant between-group differences. These results were supported by a Korean study in

which 397 patients were randomized to undergo surgery 28-41 or 42-59 d after long-course CRT^[41]. Rates of local and distal recurrence and of overall survival were similar in the two groups. By contrast, a retrospective multivariate analysis of 102 patients with low rectal cancer demonstrated that delaying surgery beyond 16 wk from rectal cancer diagnosis had a negative impact on overall and metastasis-free survival (OR = 2.59; 95%CI: 1.33-5.79, $P = 0.005$)^[57]. A long interval between radiation therapy and surgery (6-8 wk) was not recommended for patients who may not benefit from tumor downstaging by sphincter preservation.

Table 1 reviews the literature on the effect of a prolonged CRT-surgery interval on oncological outcome^[28,36,38,40-44,49-52,54-62].

EFFECT OF A PROLONGED CRT-SURGERY INTERVAL ON SURGICAL OUTCOME

Sphincter preservation

The benefit of preoperative CRT in increasing the sphincter preservation rate in patients with low-lying rectal cancer is controversial. The German CAO/ARO/AIO 94 Preoperative *vs* Postoperative Rectal Trial^[11] reported that the preoperative administration of CRT led to a higher rate of sphincter preservation in clinical candidates for abdominoperineal resection. By contrast, a systematic review and meta-analysis of trials comparing preoperative radiation with preoperative chemoradiation showed that although preoperative CRT significantly increased the rate of pCR ($P < 0.001$), this did not translate into a higher rate of sphincter preservation ($P = 0.29$)^[63]. The original Lyon R90-01 trial^[28] suggested that extending the interval from CRT to surgery from 2 to 6 wk led to a trend of reduced rates of abdominoperineal resection in the longer-interval group. Yet in neither this study nor others that investigated sphincter preservation rates by CRT-surgery interval were the findings statistically significant^[22,28,36].

Surgical difficulty and complications

Neoadjuvant radiotherapy for rectal cancer increases postoperative complications, predominantly because of an increased risk of anastomotic leaks and delayed perineal wound healing after abdominoperineal resection^[31,64]. Delaying surgery after CRT is based on the rationale that it will allow more time for resolution of the acute inflammatory response to radiotherapy. At the same time, however, it could make dissection in the narrow pelvis more complex owing to the establishment of post-radiation fibrosis^[58]. Garcia-Aguilar *et al*^[38] examined the surgical difficulty and complication rate in 144 patients who underwent total mesorectal excision at 6 or 11 wk after CRT. The longer-interval group also received 2 cycles of modified FOLFOX-6 during the late resting period. There were no significant between-group differences in operative time, blood loss, or rates of diverting

Table 1 Effect of chemoradiotherapy-surgery intervals on oncological outcome

Ref.	Year	CRT-surgery interval	Pts (n)	pCR	LR	OS
Francois <i>et al</i> ^[28] + Glehen <i>et al</i> ^[56]	1999	2/6-8 wk	201	7%/14% NS	13%/10%	69%/66%
Stein <i>et al</i> ^[43]	2003	4-8/10-14	33	21%/14%	NA	NA
Moore <i>et al</i> ^[44]	2004	≤ 44 d <	155	12%/19%	NA	NA
Coucke <i>et al</i> ^[42]	2006	≤ 5 d <	250	NA	10%/7%	47%/69% ²
Supiot <i>et al</i> ^[57]	2006	≤ 6 wk <	102	NA	16%	NA
Tran <i>et al</i> ^[40]	2006	≤ 8 wk <	48	6%/9%	0%/9%	NA
Dolinsky <i>et al</i> ^[60]	2007	≤ 6-8 wk <	107	Same (P = 0.8)	11%	NA
Veenhof <i>et al</i> ^[62]	2007	2/6-8 wk ¹	108	0%/12%	7%/2%	64%/77%
Habr-Gama <i>et al</i> ^[61]	2008	≤ 12 wk <	250	10%/6% ⁴	NA ³	NA
Lim <i>et al</i> ^[41]	2008	28-41/42-56 d	397	13.8%/15%	8.2% ³	NA
Tulchinsky <i>et al</i> ^[52]	2008	≤ 7 wk <	132	17%/35% ²	6%/4%	81%/93%
Kerr <i>et al</i> ^[59]	2008	Median 76 d (6-215 d)	189	15.90%	21%	NA
de Campos-Lobato <i>et al</i> ^[53]	2011	≤ 8 wk <	177	16%/31% ²	10.5%/1.2%	NA
Garcia-Aguilar <i>et al</i> ^[38]	2011	6/11 wk	136	18%/25% ²	NA	NA
Evans <i>et al</i> ^[58]	2011	≤ 6-8 wk <	95	5%/12%/17% ²	NA	NA
Wolthuis <i>et al</i> ^[54]	2012	≤ 7 wk <	356	16%/28% ²	6%/3%	NA
Pach <i>et al</i> ^[55]	2012	7-10 d/4-5 wk ¹	154	0%/10.4% ²	1.5%/7%	63%/73%
Sloothaak <i>et al</i> ^[36]	2013	≤ 8 wk/8-9/10-11/11 <	1593	10%/13%/18% ² /11%	NA	NA

¹Short-course chemoradiotherapy (CRT); ²Statistically significant difference; ³Local and systemic recurrence; ⁴Pts with complete clinical response who were not operated were excluded. pCR: Pathological complete response; LR: Local recurrence; OS: Overall survival; NA: Not available.

stoma, sphincter preservation, and R0 resection. Additionally, the proportion of patients who acquired any postoperative complications was similar in both groups (40%), with no significant difference in rate of anastomotic leaks. Surgeons participating in that study reported more widespread fibrosis in the longer-interval group. However, they were not blinded to the treatment protocol and ultimately rated surgical difficulty similarly (on a scale of 1-10) for both groups. Other authors, however, reported a longer operative time when the CRT-surgery interval was longer, which may reflect increased surgical difficulty^[40,52]. Nonetheless, extending the CRT-surgery interval did not increase the complication rate^[22]; indeed, one study noted significantly higher rates of anastomotic leak and perineal wound complications in patients in the shorter-interval (< 44 d) arm^[59].

CONCLUSION

The traditional 6-wk CRT-surgery interval used for years in the treatment of rectal cancer was based primarily on a single study showing its oncological benefit compared to a 2-wk interval, which was apparently too short to yield significant post-radiation changes. Recent studies that sought to further improve outcome in patients with locally advanced, low-lying rectal tumors found that prolonging the interval beyond 6 wk was advantageous, mainly in terms of tumor downstaging and pCR rates, without increasing surgical difficulty or complications. These findings appear to have prompted a recent trend towards increasing the time from neoadjuvant CRT to surgery. However, the data available so far derive largely from retrospective studies that applied different CRT protocols and different CRT-surgery intervals, with no consideration of the effect of variability in preoperative staging. Further investigations with a higher level of evidence are required to definitively resolve this issue.

Several centers are currently conducting prospective randomized control studies to determine the optimal interval between CRT and surgery. The multicenter Swedish Stockholm III trial^[65] that is testing different regimens of radiotherapy will be completed in 2018. Participants are divided into 3 groups: short-course CRT followed by surgery one week later; short-course CRT followed by surgery 4-8 wk later; and long-course CRT followed by surgery 4-8 wk later. The study will include an estimated 840 patients. An interim analysis of 303 patients showed that short-course CRT and surgery at 7-11 d was associated with a trend for more complications^[66]. In another study begun in 2009 in the United Kingdom, patients are randomized to undergo CRT and surgery after 6 or 12 wk. The final cohort will include 218 patients at the end of recruitment^[67]. Also from the United Kingdom, the STARRCAT Trial: Surgical Timing after Radiotherapy for Rectal Cancer^[68], is a one-year pilot study assessing the same variables in addition to quality of life outcome. The findings will have important implications for the treatment of patients with rectal cancer.

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