ORIGINAL CONTRIBUTION

Complete Pathological Response After Neoadjuvant Long-Course Chemoradiotherapy for Rectal Cancer and Its Relationship to the Degree of T3 Mesorectal Invasion

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BACKGROUND: Many studies have shown significantly improved outcomes (reduced local recurrence and improved overall survival) for patients achieving a complete pathological response from neoadjuvant chemoradiotherapy.

OBJECTIVE: This study aimed to document the complete pathological response rate and outcomes in patients receiving preoperative long-course chemoradiotherapy stratified for the extent of T3 mesorectal invasion measured on preoperative imaging.

DESIGN: This is a retrospective study of prospectively collected data, of patients with rectal cancer in the Cabrini Monash University Department of Surgery colorectal neoplasia database, incorporating data from Cabrini Hospital and The Alfred Hospital, identifying patients entered between January 2010 and June 2014.

PATIENTS AND SETTINGS: One hundred eighteen patients with T3 rectal cancer met the selection criteria for the study; 26 achieved complete pathological response (22%).

MAIN OUTCOME MEASURES: Outcomes in terms of complete pathological response and oncological outcomes such as disease-free and overall survival were analyzed.

RESULTS: Patients with complete pathological response had significantly less preoperative invasion than those with no complete pathological response ($p < 0.001$). Depth of invasion was the only variable associated with complete pathological response ($p < 0.002$), and the likelihood of complete pathological response decreased by 35% for every millimeter of invasion. Complete pathological response was associated with increased disease-free survival ($p = 0.018$) and a lower risk of cancer progression ($p = 0.046$). Depth of invasion was associated with an increased risk of death after surgery; HR increased by 1.07 (95% CI, 1.00–1.15) for each 1-mm increase in invasion.

LIMITATIONS: This was a retrospective study with the usual limitations, although these were minimized through the use of a clinician-driven prospective database.

CONCLUSIONS: The smaller the degree of T3 invasion, the higher the chance of achieving complete pathological response (up to 35%), which is associated with improved disease-free and overall survival. A higher complete pathological response rate is observed in early T3 disease in comparison with more extensive T3 invasion.

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Complete pathological response (pCR), defined as the absence of viable tumor cells, may develop after neoadjuvant treatment for rectal cancer. Complete clinical response rates, defined as the absence of clinically detectable tumor, vary between 12% and 31%, with pCR rates reported between 11.4% and 27%.[1–6] A study examining the chemoradiotherapy arms of 7 randomized trials and 45 phase II trials demonstrated an overall pCR rate of 13.5.[7] Patients achieving a pCR from neoadjuvant chemoradiotherapy have significantly improved outcomes (with respect to both local recurrence and overall survival).[8–11]

Preoperative radiotherapy is indicated in locally advanced rectal cancer. Common indications for preoperative radiotherapy include T3/T4 and/or node-positive disease based on preoperative imaging, particularly MRI or endorectal ultrasonography. Patients who achieve a pCR after neoadjuvant treatment for rectal cancer rarely develop distant recurrence and have been demonstrated to have a 5-year overall survival rate of 93%.[4] Pooled analysis from several studies showed that pCR patients had a significantly better outcome than those patients with residual local disease.[12] The regimen of chemotherapy administered can also affect pCR rates, because higher pCR rates are seen in studies using a 2-drug chemoradiotherapy regime and/or the administration of 5-fluorouracil.[7] Variations in radiotherapy treatment affect outcomes. The long-course radiotherapy (LCRT) dose of <45 Gy is associated with lower pCR rates.[7,13]

A number of other clinical and histopathological factors can lead to poorer outcomes and lower pCR rates. Well-established indicators including poor histopathological features (angiolymphatic and/or perineural invasion) and positive nodal status increase the chances of local recurrence.[8] Genetic factors may influence the response to chemoradiotherapy and the pCR rate, although there is some debate as to the benefit of some biomarkers.[14–17]

The prognostic differences between T3 early invasion (≤5 mm) compared with more advanced invasion (>5 mm) have been demonstrated.[18] Local recurrence rates and 5-year survival rates were improved in T3 patients with early invasion.[18] These findings have been corroborated in numerous other studies stratifying data at 4 mm,[19,20] 5 mm,[21–25] and 6 mm.[26] We hypothesize that, in patients receiving preoperative LCRT, a higher pCR rate is observed in patients with early T3 disease compared with more extensive T3 invasion.

This study aims to document the relationship between the degree of invasion on pCR rate and outcomes in the cohort of patients having preoperative LCRT.

MATERIALS AND METHODS

A retrospective review of rectal cancer cases in the prospectively maintained Cabrini Monash University Department of Surgery colorectal neoplasia database, incorporating data from Cabrini Hospital and The Alfred Hospital, Melbourne, Australia, identified patients entered between January 2010 and June 2014.[27] Patients were subject to selection criteria: they had undergone a preoperative, pretreatment MRI, had been diagnosed with T3 adenocarcinoma, had completed neoadjuvant LCRT, and had had surgery for rectal cancer. Those patients who had a preoperative endorectal ultrasonography, were diagnosed with T1, T2, or T4 disease, had undergone short-course radiotherapy, or had not received chemotherapy or radiotherapy were excluded. Three patients were excluded because they had received a different chemotherapy regime because of an additional primary cancer. Patients were also excluded because they had either too-short or too-long an interval between chemoradiotherapy and surgery outside typical treatment parameters (4–14 weeks). Patients that had minor variations in their radiotherapy or chemotherapy treatments, for example, the last 3 chemotherapy treatment days were missed, were included. Patient follow-up data were collected up to June 2015, so that all patients had at least 12 months follow-up (with the exception of 4 patients who died within 8 months of surgery) up to a maximum of more than 5 years for patients who underwent surgery in early 2010. No patients were lost to follow-up.

All MRI scans were reviewed by an independent radiologist with significant experience in rectal MRI using the 3-plane T2 sequences for the measurement of invasion into the mesorectum or perirectal tissues beyond the muscularis propria in accordance with previously validated criteria.[28] The radiologist was blinded to the outcome of patients to postchemoradiotherapy staging. Nodular and irregular spiculated extension was measured in millimeters from the estimated line of muscularis penetration, perpendicular to the bowel wall. Thin, smooth, well-defined spicules, not definite for tumor extension, were not measured.

Pathological tumor staging was assessed according to the guidelines of the American Joint Committee on Cancer by an independent pathologist.[29] Complete pathological response was defined as the absence of detectable viable tumor cells in the specimen.[29]

Data were analyzed with the Student *t* tests, χ^2 tests, Fisher exact tests, Kruskal-Wallis equality of populations test, Kaplan-Meier survival estimates, log-rank tests (to determine equivalence), Cox regression (to determine HRs), and logistic regression (Stata 13, StataCorp LP, College Station, TX). A p value of <0.05 was considered statistically significant.

Ethics approval for this study was granted by Cabrini Human Research Ethics Committee (Reference no. 03-09-12-13).

RESULTS

Of a total of 1677 patients treated for colorectal cancer in the colorectal neoplasia database, there were 118 patients with rectal cancer (79 men (66.9%), 39 women (33.1 %)) who conformed to the selection criteria and were evaluated in this study. Twenty-six patients demonstrated a post-surgical pathological stage of ypT0N0 indicating a pCR outcome (pCR rate, 22.03 %). The clinicopathological characteristics and treatment events of the patients, stratified by pCR outcome, are summarized in Table 1. Mean follow-up period of the patients was 36.8 ± SEM 1.4 (median, 36.9; range, 0.2–65) months. Mean age of all patients at surgery was 61.5 years.

There were no significant differences between those patients achieving pCR and no pCR in any measured variables, including age, sex, LCRT treatment variables, and surgical procedure type (Table 1). The mean number of days between LCRT completion and surgery was not significantly different for pCR and no-pCR patients ($p = 0.89$). Four patients had an interval of less than 42 days or 6 weeks from LCRT completion to surgery (30, 36, 37, and 39 days), whereas the interval from LCRT completion to surgery of the remaining 22 pCR patients ranged from 42 to 77 days (mean, 60.4 days; median, 59.5).

Table 2 summarizes the tumor characteristics of the patients achieving pCR and no-pCR outcomes. There were no significant differences in variables such as rectal cancer site, distance of tumor from anal verge, preoperative nodal status, or tumor type. Tumor pathology such as tumor type, differentiation, and lymphovascular invasion were collected after surgical resection of the rectum.

The main focus of this study was the relationship between the degree of pretreatment of T3 mesorectal invasion and the outcome of pCR so that further analyses were undertaken to examine this. Patients in this study who achieved pCR had significantly less invasion than those with no pCR ($p < 0.001$; Table 2; Figure 1). The range of T3 invasion in all patients was 1 to 31 mm. The maximum depth of invasion beyond the muscularis propria achieving pCR was 12 mm in a tumor 10 cm from the anal verge.

Patients were assigned to groups according to the degree of invasion to examine whether there was a relationship with greater depth of invasion and a pCR outcome rather than by using a single cutoff. When patients were stratified by the degree of T3 invasion and their outcome (pCR or no pCR), it was clear that the greater the degree of T3 invasion, the lower the rate of pCR. Of the patients with ≤5 mm T3 invasion, 35.1% achieved pCR, 12.5 % achieving pCR with 6- to 9-mm T3 invasion, and 6.1% achieving pCR of those patients having ≥10 mm of T3 invasion (Figure 2).

The association of depth of invasion and pCR outcome was confirmed with logistic regression univariate analysis. Less T3 mesorectal invasion was associated with a higher likelihood of pCR (OR, 0.74; 95 % CI, 0.62–0.90; $p < 0.002$). With the use of the depth of invasion as a predictor value, and pCR as the outcome variable, it was calculated that the likelihood of achieving a pCR outcome was decreased by approximately 35% for every millimeter of invasion. Predictor variables, preoperative N stage, interval between LCRT completion and surgery, distance of tumor from anal verge, and procedure type, were not significantly associated with a pCR outcome.

TABLE 1. Clinicopathological characteristics and treatment events of patients defined by pCR outcome

	pCR	*No pCR*	
	n = 26	*n= 92*	*p*
Age, y			
Mean (SEM)	61.2 (±2.2)	61.6 (±1.4)	0.90[a]
Sex, n (%)			
Male	15 (57.7)	64 (69.6)	0.26[b]
Female	11 (42.3)	28 (30.4)	
Long-course chemotherapy, n (%)			
Oxaliplatin	0 (0)	2 (2.2)	0.18[b]
5-Fluorouracil	23 (88.5)	85 (92.4)	
Capecitabine	2 (7.7)	3 (3.3)	
Xeloda	2[c] (7.7)	1 (1.1)	
Not recorded	0 (0)	1 (1.1)	
Radiation dose, Gy[d]			
Median	50.4	50.4	0.15[a]
Range	50.4–54	40–50.4	
Interval between LCRT and surgery, days			
Mean (SEM)	56.6 (±2.7)	57.0 (±1.6)	0.89[a]
Median (range)	55 (30–77)	58 (24–99)	
Procedure type, n (%)			
Abdominoperineal resection	4 (15.4)	15 (16.3)	0.63[e]
Coloanal anastomosis	3 (11.5)	4 (4.3)	
Proctocolectomy	1 (3.9)	2 (2.2)	
Ultralow anterior resection	15 (57.7)	57 (62.0)	
Low anterior resection	3 (11.5)	10 (10.9)	
Other	0 (0)	4 (4.3)	
Local recurrence, n (%)			
Yes	0 (0)	1 (1.1)	0.78[e]
No	26 (100)	91 (98.9)	
Distant metastasis, n (%)			
Yes	1 (3.8)	22 (23.9)	0.015[e]
No	25 (96.2)	70 (76.1)	
Alive, n (%)			
Yes	26 (100)	79 (85.9)	0.032[d]
No	0 (0)	13 (14.1)	

pCR = complete pathological response; LCRT = long-course chemoradiotherapy.
[a]Unpaired 2-tailed *t* test.
[b]χ^2 test.
[c]One patient received 5-fluorouracil then Xeloda.
[d]All pCR patients received 50.4 Gy except 1 patient who received 54 Gy in 25 fractions; 1 no-pCR patient received 40 Gy, 2 received 45 Gy, and 1 received 48 Gy.
[e]Fisher exact test.

TABLE 2. Tumor characteristics defined by pCR outcome

	pCR	*No pCR*	
	n = 26	*n= 92*	*p*
Rectal cancer site, n (%)			
Upper third 13–18 cm	0 (0)	1 (1.1)	0.86[a]
Middle third 7–12 cm	16 (61.5)	52 (56.5)	
Lower third 0–6 cm	10 (38.5)	39 (42.4)	
T3 invasion, mm, median (range)	4.4 (1–12)	8.7 (2–31)	<0.001[b]
Distance from anal verge, cm, mean (SEM)	7.2 (±0.6)	7.1 (±0.3)	0.86[a]
Preoperative nodal status, n (%)			
N0	13 (50.0)	29 (31.5)	0.34[c]
N1	7 (26.9)	37 (40.2)	
N2	4 (15.4)	20 (21.7)	
Nx	2 (7.7)	6 (6.5)	
Tumor type, n (%)			
Adenocarcinoma	26 (100)	82 (89.1)	0.38
Adenocarinoma mucinous	0	9 (9.8)	
Adenocarcinoma signet	0	1 (1.1)	
Differentiation, n (%)			
Poor	0	17 (18.5)	–
Moderate	0	69 (75.0)	
Well	0	4 (4.3)	
Not recorded	0	2 (2.2)	
Lymphovascular invasion, n (%)			
Yes	0	27 (29.3)	–
No	26 (100)	65 (70.6)	

pCR = complete pathological response.
[a]Unpaired 2-tailed *t* test.
[b]Kruskal-Wallis equality of populations test.
[c]Fisher exact test. Nodal status as determined by preoperative MRI. N0 = no regional node metastases; N1 = metastasis in 1 to 3 regional lymph nodes; N2 = metastasis in 4 or more regional lymph nodes; Nx = regional lymph nodes cannot be assessed.

With the use of the same stratification of patients for the degree of invasion (≤5, 6–9, ≥10 mm), the relationship between residual disease and the depth of invasion was examined. It was found that the greater the degree of T3 invasion, the higher the rate of patients with residual disease postoperatively (ypT stage). The distribution of the percentages of patients with T3 invasion ≤5, 6–9, and ≥10 mm in relation to final ypT stage are shown in Figure 3 and Table 3.

The postoperative oncological outcomes and survival of the patients were examined. One no-pCR patient developed local recurrence 6 months after surgery (Table 1). Patients who achieved pCR had a significantly lower rate of distant metastasis (3.8% vs 23.9%, $p = 0.015$; Table 1). A log-rank test of distant metastasis outcomes showed a significantly higher rate of metastasis in no-pCR patients ($p = 0.02$). Analysis of follow-up data for disease-free survival showed a significantly higher rate for those patients achieving pCR ($p = 0.018$; Figure 4). Cox regression univariate analyses for disease-free survival showed no association between disease progression and age, sex, depth of T3 invasion, distance of tumor from anal verge, or interval between LCRT completion and surgery (Table 4). However, an outcome of pCR was associated with a lower risk of cancer progression ($p = 0.046$; Table 4). There was no

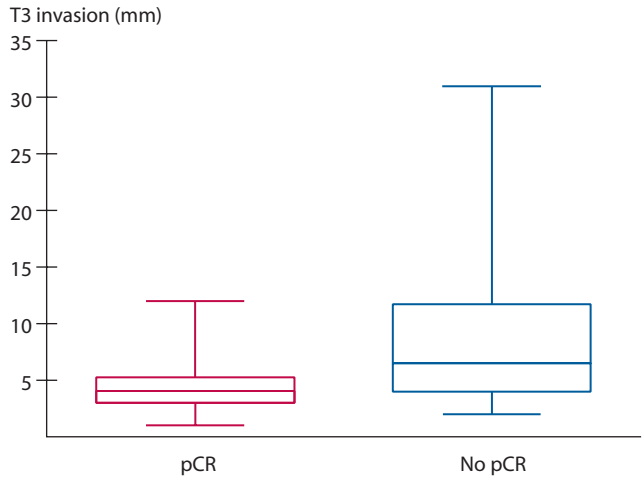

FIGURE 1. The extent of T3 mesorectal invasion in pCR and no-pCR outcomes in LCRT-treated patients. pCR patients: median, 4; range, 1–12; n = 26 (mean ± SEM, 4.4 mm ± 0.5). No pCR patients: median, 7; range, 2–31; n = 92 (mean ± SEM, 8.7 mm ± 0.6). Unpaired 2-tailed *t* test: $p < 0.001$. pCR = complete pathological response; LCRT = long-course chemoradiotherapy.

association between cancer-related death and age, sex, T3 invasion, distance from anal verge, interval between LCRT and surgery, or pCR outcome.

Patients not achieving pCR had a significantly higher rate of death following surgery (14.1% vs 0%, $p = 0.032$; Table 1). Cox regression univariate analyses of follow-up data for overall survival showed no association between overall survival and age, sex, distance of tumor from anal verge, and interval between LCRT completion and surgery (Table 5). Because there were no deaths in the pCR group, it was not possible to calculate a HR for pCR outcome. Significantly, however, the depth of T3 invasion was associated with an increased risk of postoperative death; the HR increased by 1.07 (95% CI, 1.00–1.15) for each 1-mm increase in the depth of mesorectal invasion (Table 5).

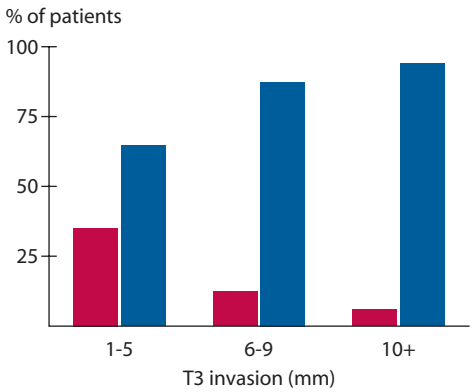

FIGURE 2. Percentage distribution of LCRT-treated patients dependent on T3 mesorectal invasion (millimeters) ≤5 mm, 6–9 mm, ≥10 mm, and outcome (pCR or no pCR). pCR (red columns) ≤5 mm 35.1% (20 cases), 6 to 9 mm 12.5% (4 cases), ≥10 mm (2 cases). No pCR (blue columns) ≤5 mm 64.9 % (37 cases), 6 to 9 mm 87.5 % (28 cases), ≥10 mm 93.9% (33 cases). pCR = complete pathological response; LCRT = long-course chemoradiotherapy.

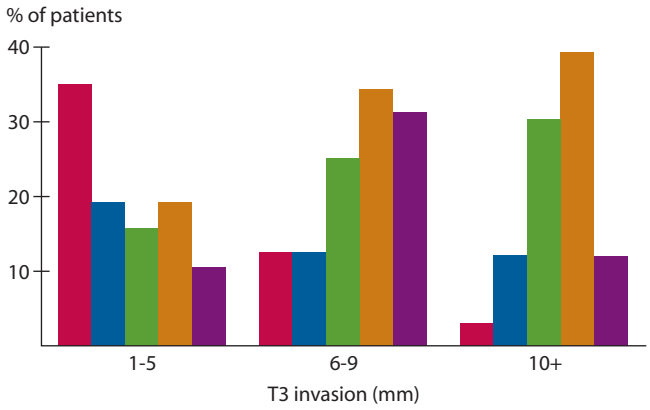

FIGURE 3. Distribution of LCRT patients determined by T3 mesorectal invasion (millimeters) and final ypT stage. pCR (red columns), ypT1 (blue columns), ypT2 (green columns), ypT3 (orange columns), ypT4 (purple columns). LCRT = long-course chemoradiotherapy.

DISCUSSION

The pCR rate of 22.03% achieved in this study is comparable to previously published findings.[1,2,4–7] Contemporary LCRT and a longer delay to surgery have resulted in higher reported pCR rates in published series (21%–24%),[4–6] compared with older reports pre-2000 (11%–13%).[30,31] These rates are now at a level that is a clinical entity that can be aimed for as part of clinical decision making, rather than seen as an uncommon but desirable outcome.

In this study, the degree of pretreatment T3 invasion in LCRT patients achieving pCR was significantly lower than patients with no pCR ($p < 0.001$). Complete pathological response rates following LCRT for ≤5 mm T3 invasion were 35.1%, 6- to 9-mm T3 invasion 12.5%, and for ≥10 mm T3 invasion, 6.1%. Logistic regression analyses confirmed that the degree of invasion was a predictor variable in achieving pCR. The likelihood of achieving pCR was reduced by approximately 35% for every millimeter of invasion. These results support the hypothesis that, in patients receiving preoperative LCRT, a higher pCR rate is observed in patients with early T3 disease compared with more extensive T3 mesorectal invasion.

A pCR outcome was associated with a lower risk of cancer progression, and the depth of invasion was associated with an increased risk of death where the HR increased by 1.07 with every millimeter of mesorectal invasion. This is the first time that overall survival has been shown to be associated with the degree of invasion in this manner. Previous studies have shown that when patients who have T3 rectal cancer are stratified with a cutoff in invasion, those patients with less invasion have improved outcomes. Invasion of ≤5 mm is a factor for reduced local recurrence,[25] whereas patients with invasion of <4 mm have significantly better cancer survival rates and disease-free survival rates.[19] In addition, the overall survival rate in patients with <6 mm invasion was significantly higher than those patients with ≥6 mm.[26]

The ideal time interval between LCRT and surgery in patients who have rectal cancer has been the subject of recent debate.[32,33] In our hospitals, there is now a tendency to wait longer from LCRT completion to surgery compared with a decade ago. In this study, the mean number of days from LCRT to surgery was 56.9 days or approximately 8 weeks. The suggested minimum interval between LCRT and surgery is 8 weeks with any adverse impact unlikely unless the interval is more than 10 to 14 weeks.[34] Moreover, extending the interval between LCRT and surgery is well tolerated and may increase the pCR rate.[5] There was no significant difference between the pCR rate of those patients having <44 days and those with >44 days between chemoradiotherapy and surgery.[1] In this study, the interval between LCRT and surgery had no effect on pCR rate, disease-free survival, or overall survival. There was no correlation between downstaging depending on the number of days between LCRT completion and surgery. A downstaging effect from preoperative therapy was observed in 61.0% (72/118) of patients. Previous studies have shown lower pCR rates in patients receiving less than 45 Gy.[7,13] In this study, one no-pCR patient received 40 Gy, whereas all other patients received more than 45 Gy. The effect of achieving pCR on long-term outcomes was not affected by T or N stage, or distance from the anal verge, or the type of surgery.[12] Similarly, in this study there was no association of a preoperative positive nodal status with an outcome of achieving pCR. A number of additional factors were not associated with a pCR outcome; sex, age at time of surgery, surgical procedure, tumor type, or distance of tumor from anal verge. These findings corroborate the findings of Garcia-Aguilar et al,[9] where pCR was not related to age, sex, tumor size, stage, grade, and distance from the anal verge.

Previous studies have shown that a pCR outcome is the most favorable outcome for a patient with rectal cancer, but why do some patients achieve pCR, whereas other patients do not respond to or even progress their disease

TABLE 3. Percentage distribution of LCRT-treated patients determined by T3 mesorectal invasion (millimeter) and final ypT stage

T3 mesorectal invasion	*pCR (cases)*	*ypT1 (cases)*	*ypT2 (cases)*	*ypT3 (cases)*	*ypT4 (cases)*
≤5 mm	35.1 (20)	19.3 (11)	15.8 (9)	19.3 (11)	10.5 (6)
6–9 mm	12.5 (4)	12.5 (4)	25.0 (8)	34.4 (11)	31.3 (1)
≥10 mm	6.1 (2)	12.1 (4)	30.3 (10)	39.4 (13)	12.1 (4)

pCR = complete pathological response; LCRT = long-course chemoradiotherapy.

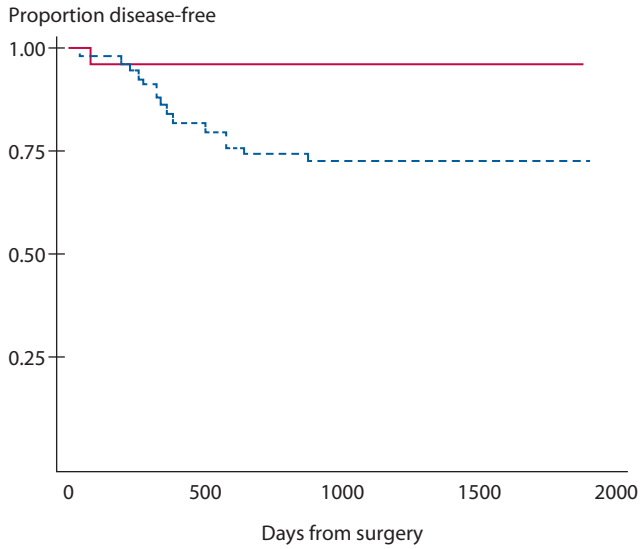

FIGURE 4. Disease-free survival according to pCR outcome. Disease-free survival rate in pCR patients (continuous red line, 96.2%) and no-pCR patients (dotted blue line, 74.0 %). Number of patients at 0 days (pCR 26, no pCR 92), at 500 days (pCR 25, no pCR 75), at 1000, 1500, and 2000 days (pCR 25, no pCR 68). Log-rank test for equality of survivor functions $p = 0.018$. pCR = complete pathological response.

after LCRT? A pCR outcome may be an indication of favorable biological tumor characteristics with fewer propensities for local or distant recurrences and improved overall survival than for patients with residual disease.[12] There is a possibility that this was the case in the patients achieving pCR in this study. Patients that were ypT3/4 could represent a different population of cancers that either did not respond to LCRT (35 patients) or progressed during or after LCRT (11 patients). The heterogeneity of patients with rectal cancer when treated preoperatively suggests that treatment options should be tailored according to tumor response to therapy.[13] There is much debate as to the predictive nature of biomarkers for response to chemotherapy and the outcome of patients who have rectal cancer, with some studies contradicting others. Low expression of p53 and/or high expression of VEGF, p21, and Ki67 demonstrated a higher pCR rate,[15] and p21 positive

TABLE 4. Cox regression analysis of factors affecting disease-free survival

Predictor variable	*HR*	*SE*	*p*	*95% CI*	
Sex	0.76	0.34	0.55	0.32	1.84
Distance from anal verge, cm	0.98	0.06	0.80	0.86	1.12
Age at surgery	0.98	0.02	0.23	0.95	1.01
Preoperative N stage	1.16	0.32	0.60	0.67	2.00
Depth of invasion, mm	1.05	0.03	0.09	0.99	1.11
Days between LCRT and surgery	1.00	0.01	0.70	0.98	1.03
pCR	0.13	0.13	0.046	0.02	0.96

pCR = complete pathological response; LCRT = long-course chemoradiotherapy.

TABLE 5. Cox regression analysis of factors affecting overall survival

Predictor variable	*HR*	*SE*	*p*	*95% CI*	
Sex	0.33	0.26	0.16	0.07	1.52
Distance from anal verge, cm	0.99	0.09	0.91	0.83	1.18
Age at surgery	1.02	0.02	0.52	0.97	1.06
Preoperative N stage	1.48	0.64	0.37	0.63	3.46
Depth of invasion, mm	1.07	0.04	0.048	1.0005	1.15
Days between LCRT and surgery	1.02	0.02	0.20	0.99	1.06
pCR	No deaths in pCR group. No convergence of estimates				

pCR = complete pathological response; LCRT = long-course chemoradiotherapy.

tumors, as well, were associated with tumor regression and a higher pCR rate.[35] Conversely, p21 and CD166 expression were associated with poor disease-free survival and non-pCR outcomes.[14] Low expression of p21 and the absence of EGFR expression were associated with improved overall survival and disease-free survival.[36] High EGFR expression in wild-type KRAS patients showed better survival rates than low EGFR expression and KRAS mutations.[16] However, a meta-analysis showed that KRAS mutations did not predict the efficacy of neoadjuvant chemoradiotherapy in rectal cancer.[17] More studies are needed to investigate the relationship between tumor characteristics and response to chemoradiotherapy and prognosis.[12] It is likely that, as the diagnosis and treatment of cancer moves to a molecular level, more tailored treatments for each patient depending on their tumor characteristics are likely in the future once a panel of reliable biomarkers has been established.

There are several limitations to this study, one of which is its retrospective analysis; however, the database was 100% complete with respect to clinician-led data fields.[27] The data were prospectively entered, with the exception that the measured degree of T3 invasion was by retrospective re-reporting of all MRI scans; however, the radiologist was blinded to final outcome. The study is not a large-scale randomized trial and consists of data from only 2 centers; however, the data obtained show a strong correlation between the degree of T3 invasion and pCR rate, which warrants further larger studies. Quality-of-life measures, functionality, or complications of chemoradiotherapy were not addressed.

A recent hot topic in rectal cancer has been investigation into the watch-and-wait approach of the omission of surgery for patients achieving pCR. The long-term oncological outcomes of this approach are still to be validated, especially given the clear and proven success of surgery in rectal cancer and the potential of losing a window to offer a curative resection.[37] Any success of a watch-and-wait approach will depend on accurate methods for assessing the response to chemoradiotherapy.[37]

CONCLUSIONS

Previous studies have stratified the degree of T3 invasion into groups with a cutoff of 4, 5, or 6 mm to examine patient outcomes in terms of recurrence and overall survival rather than pathological response.[18,24,25] This study stratifies a cohort of LCRT-treated patients with rectal cancer demonstrating that the degree of T3 invasion correlates in a statistically significant manner with the pCR rate; the lower the degree of T3 invasion, the higher the pCR rate. When follow-up data were considered, a no-pCR outcome was associated with the development of distant metastases after surgery, and a pCR outcome was associated with a lower risk of cancer progression. The depth of T3 invasion was a key predictor of patient outcome. Logistic regression analyses demonstrated that the likelihood of achieving a pCR in patients who have rectal cancer was reduced by 35% with every millimeter of T3 invasion; moreover, the chance of overall survival was reduced with every millimeter of T3 invasion. This further highlights that early diagnosis and intervention in patients who have rectal cancer is paramount in achieving the best clinical outcome of pCR, disease-free survival, and long-term survival.

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