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Does total regression of primary rectal cancer after preoperative chemoradiotherapy represent "no tumor" status?

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Purpose: Insistence that total regression of primary tumor would not represent long-term oncologic outcomes has been raised. Therefore, this study aimed to evaluate the outcomes of these patients after preoperative chemoradiotherapy (PCRT) and radical surgery and to evaluate the associated risk factors.
Methods: We included 189 patients with rectal cancer who showed total regression of the primary tumor after PCRT, followed by radical resection, between 2001 and 2012. Recurrence-free survival (RFS) was calculated using the Kaplan-Meier method, and the results were compared with 77 patients with Tis rectal cancer who received only radical resection. Factors associated with RFS were evaluated using Cox regression analysis.
Results: Sphincter-saving resection was performed for 146 patients (77.2%). Adjuvant chemotherapy was administered to 168 patients (88.9%). During the follow-up period, recurrence occurred in 17 patients (9%). The 5-year RFS was 91.3%, which was significantly lower than that of patients with Tis rectal cancer without PCRT (P = 0.005). In univariate analysis, preoperative CEA and histologic differentiation were associated with RFS. However, no factors were found to be associated with RFS.
Conclusion: RFS was lower in patients with total regression of primary rectal cancer after PCRT than in those with Tis rectal cancer without PCRT, and it would not be considered as the same entity with early rectal cancer or "disappeared tumor" status.
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Key Words: Rectal neoplasm, Chemoradiotherapy, Total regression, Recurrence

INTRODUCTION

Preoperative chemoradiotherapy (PCRT) has been widely used as a standard treatment for patients with locally advanced rectal cancer: to downstage primary cancer, improve the rate of sphincter preservation, and reduce local recurrence [1,2]. PCRT results in a varying range of tumor responses, and these heterogeneous responses have resulted in ongoing and active research regarding analysis and evaluation of clinical stages, oncological outcomes, prognoses, and proper treatment after PCRT. Surgical treatment options after PCRT continues to be a subject of ongoing debate, particularly regarding the choice of local excision rather than radical resection for patients who are good responders or closed follow-up with nonoperative

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management (wait-and-watch strategy) for patients who are complete clinical responders [3-6].

Scientific interest in attractive alternatives to radical resection is increasing for several reasons. First, many published studies have reported a trend toward a favorable prognosis for patients with a pathologic complete response [7-10]. Second, locoregional treatment of early rectal cancer, which is associated with high rates of 5-year survival, has been found to lead to identical oncological outcomes as radical surgery, which is the long-standing gold standard treatment. Furthermore, compared with radical surgery, locoregional treatment is actually associated with better outcomes in terms of postoperative morbidity, mortality, and quality of life [11].

However, despite these promising outcomes, there has been ongoing controversy regarding whether the "no residual viable tumor cells status" of advanced rectal cancer after PCRT is the equivalent of early rectal cancer status or of "no cancer" status. Additionally, persistent nodal involvement and recurrence are sometimes observed despite total regression (TR) of the primary lesion.

For this reason, identifying the long-term prognosis of TR after PCRT and comparing it with that of early rectal cancer will provide a better understanding of the oncologic status of TR. This may lead to further improvement in the diagnosis and treatment of this group. Thus, the aim of this study is to evaluate the long-term oncologic outcome of patients with TR of the primary tumor after PCRT and to evaluate the factors associated with recurrence.

METHODS

Study design and patients

We included patients with rectal cancer who were treated with PCRT and radical resection before being diagnosed with TR of primary tumor between 2001 and 2012 in our center The response of the primary tumor to PCRT was determined using the tumor regression grade system, as suggested by the Gastrointestinal Pathology Study Group of the Korean Society of Pathologists [12], and the pathologic stage after radical resection was determined according to the 7th American Joint Committee on Cancer staging system. Tumor response assessments using the tumor regression grade system were performed by a dedicated pathologist who specializes in colorectal malignancy.

Patients who were treated with local excision (n = 34), who had indeterminate tumor regression grade of primary tumor (n = 15), or who could not be assessed for recurrence status (n = 14) were excluded. A final total of 189 patients who were diagnosed with ypT0 of resected primary tumor (PCRT group) were included in our analysis (Fig. 1). For comparison of oncologic outcomes, 77 patients diagnosed with Tis rectal cancer after radical resection without PCRT (Tis group) were also analyzed.

This study was conducted with the approval of the Institutional Review Board for Human Research of Asan Medical Center (approval number: 2017-0791) in accordance with the Helsinki Declaration. Due to the retrospective nature of the study, informed consent was waived off.

PCRT, adjuvant treatment, and surgical resection

Preoperative radiotherapy consisted of 25 fractions at a dosage of 45–50 Gy administered to the entire pelvis, followed by a 5.4-Gy boost in 3 fractions to the primary tumor. For concurrent chemotherapy, 2 cycles of intravenous 5-fluorouracil (375 mg/m^2/day) and leucovorin (20 mg/m^2/day) were delivered in bolus over 3 days during the first and fifth weeks of radiation therapy. Alternatively, oral capecitabine (1,650 mg/m^2/day) was administered twice per day during radiotherapy. Surgery was performed 6–8 weeks after completing PCRT according the principle of total mesorectal excision.

Adjuvant chemotherapy, followed by radical resection, is recommended for all medically fit patients with PCRT. The usual adjuvant treatment comprised four cycles of 5-fluorouracil and leucovorin monthly or 6 cycles of capecitabine. Oxaliplatin regimens were delivered at the discretion of the attending physician.

Postoperative surveillance

All patients received postoperative follow-up examinations, which consisted of a physical examination, serum carcinoembryonic antigen measurement, chest radiography, and ab-

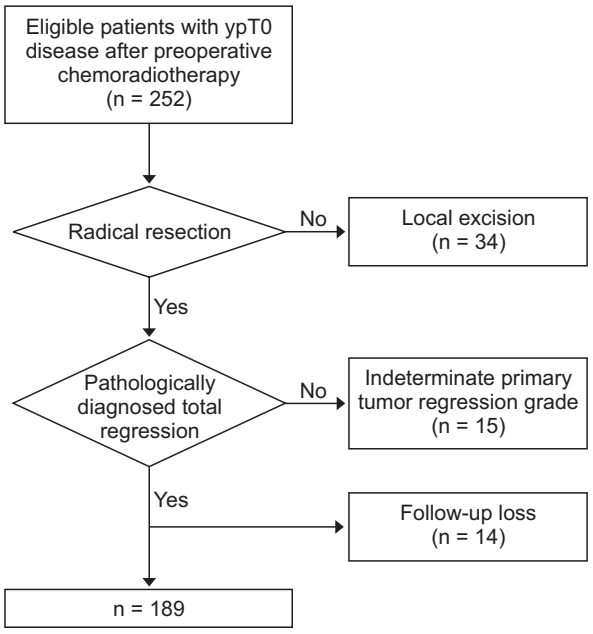

Fig. 1. CONSORT (consolidated standards for reporting of trials) diagram.

dominal, pelvic, and chest computed tomography every 3–6 months. Most patients underwent colonoscopy at 6–12 months postoperatively and every 2–3 years thereafter. Recurrence was determined according to the radiological or histopathologic findings. Local recurrence was defined as the presence of a suspicious lesion in the areas contiguous to the bed of the primary rectal resection or the site of anastomosis, and distant metastasis was defined as the presence of any recurrence in a distant organ or dissemination to the peritoneal surface. Recurrence-free survival (RFS) was measured from the date of surgery to the date of the first recurrence event or death.

Statistical analysis

The primary endpoint was RFS, which was calculated using the Kaplan-Meier method and compared using the log-rank test. Multivariable Cox proportional hazard analysis was used to test the effects of potential risk factors for RFS. A P-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA).

RESULTS

Clinicopathologic characteristics of patients

A total of 189 patients with TR of the primary tumor were included. Among them, 107 (56.6%) were men, and the mean age at diagnosis was 57.3 ± 11.1 years. The distribution of sex and age at diagnosis in the PCRT group were similar to that in the Tis group. Preoperative CEA levels were within normal range in 93.7% of the PCRT group and in 98.7% of the Tis group,

Table 1. Clinicopathologic characteristics of all patients

Characteristic	TR after PCRT (n = 189)	Tis without PCRT (n = 77)	P-value
Age (yr)	57.3 ± 11.1	59 ± 10.4	0.223
Sex			0.758
Male	107 (56.6)	42 (54.5)	
Female	82 (43.4)	35 (45.5)	
Pre-PCRT CEA			
Normal range	151/182 (83.0)	-	
Increased	28/182 (15.4)	-	
Unchecked	3/182 (1.6)	-	
Preoperative CEA			0.190
Normal range	177 (93.7)	76 (98.7)	
Increased	6 (3.2)	1 (1.3)	
Unchecked	6 (3.2)	0 (0)	
No of harvested LNs	14.2 ± 6.2	13.2 ± 7.4	0.269
N stage			0.040
N0	179 (94.7)	77 (100)	
N1	10 (5.3)	0 (0)	
Histologic grade			<0.001
Well	58 (30.7)	60 (77.9)	
Moderate	94 (49.7)	15 (19.5)	
Poor	15 (7.9)	0 (0)	
Mucinous	2 (1)	0 (0)	
Unknown	20 (10.7)	2 (2.6)	
Total harvested LNs	14.6 ± 6.4	13.5 ± 7.5	0.223
Lymphovascular invasion			0.026
Absent	189(100)	75 (97.4)	
Present	0 (0)	2 (2.6)	
Perineural invasion			<0.001
Absent	189 (100)	76 (98.7)	
Present	0 (0)	1 (1.3)	
Operation			<0.001
Abdominoperineal resection	43 (22.8)	0 (0)	
Sphincter-saving resection	146 (77.2)	77 (100)	
Adjuvant chemotherapy	168 (88.9)	0 (0)	<0.001
Follow-up duration (mo)	67.2 ± 31.8	71.5 ± 36.4	0.338

Values are presented as mean ± standard deviation or number (%).
TR, total regression; PCRT, preoperative chemoradiotherapy; LN, lymph node.

Table 2. Recurrence in patients treated with preoperative chemoradiotherapy

Patient	Sex	Age (yr)	Pretreatment CEA (ng/dL)	Preoperative CEA (ng/dL)	Surgery	Adjuvant chemo-therapy	1st metastatic organ	ypN stage	Time to recurrence (mo)	Follow-up (mo)
1	Female	46	5.4	4.4	uLAR	Yes	Lung	N0	8	59
2	Female	49	2	3.1	LAR	Yes	Lung,	N2a	5	20
3	Male	64	1.8	1.7	LAR	Yes	Lung, liver, bone, distant LNs	N0	64	65
4	Female	72	1	1.6	LAR	Yes	Bone	N0	49	65
5	Male	74	1	1.2	LAR	No	Liver, distant LNs	N0	5	15
6	Male	50	2.5	0.4	LAR	Yes	Brain, distant LNs	N0	105	115
7	Female	66	0.8	1.4	ISR	Yes	Lung	N0	21	61
8	Male	39	46	17.3	APR	Yes	Lung, liver	N1a	10	21
9	Female	53	4.3	4.0	APR	Yes	Lung	N0	22	30
10	Male	62	4.6	3.9	APR	Yes	Brain	N0	16	85
11	Male	40	1.9	1.8	APR	Yes	Lung	N0	39	16
12	Male	60	1.5	1.8	APR	Yes	Distant LNs	N0	7	89
13	Male	48	0.9	1.1	APR	Yes	Lung	N0	30	50
14	Male	39	6.2	1.1	uLAR	No	Anastomosis	N0	12	63
15	Female	38	0.3	1.5	uLAR	Yes	Lung	N0	6	119
16	Female	60	9.4	10.0	LAR	Yes	Lung, distant LNs	N0	9	54
17	Male	52	1.9	1.2	LAR	Yes	Liver	N0	6	31

uLAR, ultra-low anterior resection; LAR, low anterior resection; ISR, intersphincteric resection; APR, abdominal perineal resection; LN, lymph node.

with no significant difference between the 2 groups.

Sphincter-preserving resection was performed for 146 patients (77.2%) in the PCRT group, which was a much lower rate than that in the Tis group.

In the PCRT group, 10 patients (5.3%) had pathologically diagnosed metastatic lymph nodes (LNs). Seven patients had 1 metastatic LN and 3 patients had 2 or more metastatic LNs. Moderately differentiated histology was the most common differentiation type in both groups. Adjuvant chemotherapy was administered to 168 patients (88.9%) of the PCRT group (Table 1).

Recurrence

The mean follow-up duration was 67.2 ± 31.8 months. There was no recurrence in the Tis group. Tumor recurrence was observed in 17 patients (9%) of the PCRT patients. Among them, 10 were male and 7 were female. Single-site recurrence developed in 12 patients (66.7%). The most common recurrence site was lung (55.6%) followed by distant LNs (29.4%) and liver (23.5%). Sixteen patients had distant metastases, with only 1 patient showing evidence of local recurrence.

Adjuvant chemotherapy was given for 15 patients among all patients with recurrences. Among the 17 patients who developed recurrence in the PCRT group, 2 had LN metastases when the primary tumor resection was done. The mean recurrence-free interval (time interval from surgery to diagnosis of recurrence) was 56 ± 33.2 months. The recurrence developed within one year in 8 of the 17 patients (47.1%), and the latest recurrence developed after 105 months (Table 2).

RFS and associated factors in patients with TR after PCRT

The 5-year RFS in patients with TR of primary rectal cancer after PCRT (91.3%) was significantly lower than that of patients with Tis rectal cancer without PCRT (100%) (Fig. 2).

Univariate analysis showed that RFS was significantly associated with post-PCRT CEA (P = 0.045) and histologic differentiation (P = 0.046). However, multivariable analysis did not show any factor independently associated with recurrence (Table 3).

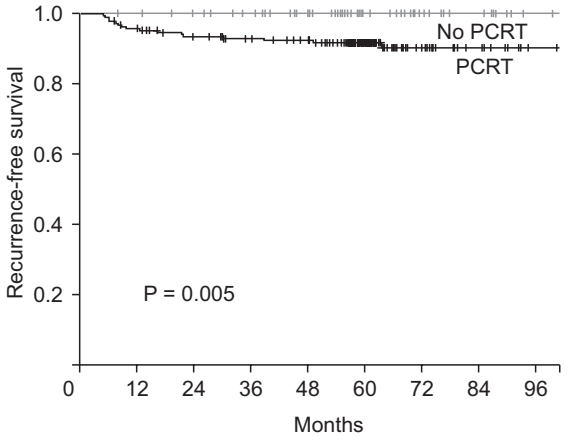

Fig. 2. Recurrence-free survival (RFS) in patients with total regression of primary tumor after preoperative chemoradiotherapy (PCRT), and those with Tis rectal cancer without PCRT (No PCRT).

Table 3. Factors associated with recurrence-free survival in patients treated with preoperative chemoradiotherapy

Variable	Univariate		P-value	Multivariate		P-value
	HR	95% CI		HR	95% CI	
Adjuvant chemotherapy	1.14	0.261–4.988	0.862	-	-	
Pre-PCRT CEA						
Normal	1	-	-	-	-	-
Increased	1.057	0.303–3.688	0.931	-	-	-
Preoperative CEA			0.045			0.173
Normal	1	-		-	-	
Increased	4.567	1.034–20.161		4.639	0.509–42.262	
ypN stage			0.246			
ypN0	1	-		1	-	0.668
ypN+	2,402	0.547–10.549		0.606	0.061–5.990	
Histologic grade			0.046			0.085
G1	1	-		1	-	
G2	3.274	1.022–10.492		2.973	0.861–10.280	
Sex			0.875			-
Male	1	-		-	-	
Female	0.925	0.352–2.432	-	-	-	
Age	0.981	0.939–1.025	0.387	-	-	-

HR, hazard ratio; CI, confidence interval; PCRT, preoperative chemoradiotherapy.

DISCUSSION

Our findings showed that the PCRT group had a lower RFS than did the Tis group, suggesting that TR after PCRT may not represent "no tumor" status even with tumor-confined mucosa.

We compared the oncologic outcome of the Tis tumor with that of the TR after PCRT to determine the oncologic status of the regression of primary tumor. This may provide indirect evidence to answer the clinical question of whether TR of the primary tumor can be considered as "no tumor" status.

Evaluating the oncologic status of TR after PCRT is important for determining appropriate surgical strategies after PCRT in this subgroup of patients. Rectal cancer confined within submucosa has been known to have good oncologic outcomes, and 5-year RFS has been reported to exceed 95% in most studies [7,13,14]. As a result of these favorable oncologic outcomes for this group of patients, local excision for early rectal cancer has increased steadily over time [15-17]. These strategies have influenced the surgical approach for "significantly regressed" cases of rectal cancer after neoadjuvant chemoradiotherapy which tumor cell was located within submucosa.

To date, many studies have demonstrated significant favorable oncologic outcomes in patients with prominent regression of the primary tumor after PCRT [8,9,18,19], including significant superiority in RFS and local control of patients whose tumor showed a TR or near-TR compared with those in other regression groups [3,9,20]. Based on these findings, interest in organ-preserving surgery in patients who show a good response to PCRT has increased, in an effort to avoid morbidity and functional derangement associated with radical resection.

However, organ-preserving treatment for ypT0-1 disease after PCRT has resulted in controversial findings in many studies in terms of oncologic outcomes. Multicenter trials that include patients with cT2N0 rectal cancer treated with PCRT showed a 5-year DFS of 79.3% after local excision [4]. In this study, 49% of patients had ypT0 or Tis disease, and oncologic outcome was not in the expected range considering the proportion of patients with regressed disease. Another research reported a wide range of oncologic outcomes after local excision for rectal cancer after PCRT. Pathologically confirmed TR was reported in 30.2%–64% of patients; local recurrence among patients with less than ypT1 disease was 2%–11.1% [4,5,6,21]; and the 10-year disease free survival was reported to be 89.5% for patients with TR after radical resection [10]. However, there is a lack of studies on long-term oncologic outcomes of patients with TR after PCRT.

Although patients with TR after PCRT have been included in many studies in which they were treated as patients with early rectal cancer, their "pretreatment tumor status" should be considered. Although surgical strategies progressed in patients who had good response to PCRT according to their posttreatment primary TR, we still administered adjuvant chemotherapy according to their initial clinical tumor stage regardless of the final pathologic stage. Treatment irrespective of post-treatment tumor status might be caused by a lack of evidence of the long-term oncologic outcome in this group of patients. Thus, there is a need to evaluate the long-term oncologic outcomes of patients with TR after PCRT and compare with oncologic outcomes of patients with initial early rectal cancer.

Several studies have compared patient outcomes stratified by pathologic stage between patients treated with PCRT or not. It may not seem logical to compare oncologic outcomes according to the pathologic stages of patients treated with PCRT and those without PCRT, because the pathologic staging system was originally developed from results of patients not treated with neoadjuvant treatment. However, stage-stratified comparisons may help in understanding the objective oncologic status of certain subgroups of patients based on the generally accepted system.

In the present study, patients with TR after PCRT had favorable oncologic outcomes. However, the RFS of patients with TR after PCRT was "lower" than that of the initial Tis tumor. In this study, recurrence occurred in 9% of patients with TR, which is similar to findings of previous reports [4,5,6,10,21]. The most common distant metastasis site was the lung (58.8%), and recurrence occurred within 1 year after the operation in approximately half of the recurrence cases. We attempted, but were unable, to identify risk factors associated with recurrence in the TR after PCRT group. Typically, LN metastasis is suspected as a major associated factor of recurrence in patients treated with PCRT [10,22-24], even in patients who show a good response to PCRT [23,24]. Local recurrence rate occurred in only 1 patient among 17 patients with recurrences in the present study. Patients with TR after PCRT had low LN metastasis incidence and no chance of circumferential resection margin involvement which were important risk factors of local recurrence in rectal cancer. These may result in low local recurrence rate. In the present study, recurrence occurred in 20% of patients with metastatic LN and in 8.3% of patients without LN metastasis in the TR after PCRT group. However, LN metastasis was not found with multivariate analysis to be an independent risk factor of RFS. This could be the result of the small number of patients with LN metastasis among patients with TR in this study, as only 5.3% of patients with TR had LN metastasis. Future studies of are needed to evaluate the influence of LN metastasis on recurrence in a larger cohort of patients with TR after PCRT.

In many cases, the degree of LN metastasis has been known to correlate with cancer stage [25]. Patients with TR after PCRT had <10% of LN metastasis. If LN metastasis was not an

independent risk factor for recurrence in these patients, organ-preserving treatment would be accepted more easily. However, as LN metastasis has been determined as a critical risk factor for RFS, it is important to emphasize appropriate diagnosis for identifying metastatic LN before determining surgical treatment, and to use care in deciding to omit radical resection [25].

In the present study, 88.9% of patients with TR after PCRT received adjuvant chemotherapy. Considering the lack of evidence whether adjuvant chemotherapy is beneficial for patients with good response to PCRT, it is quite high rate. The current recommendation to use adjuvant chemotherapy after PCRT is based on the belief that the risk of recurrence is high in patients with clinical stage II or III rectal cancer, and that this is not modified by PCRT and surgery. During study period, we adapted the current concept of adjuvant chemotherapy after PCRT in our institution, and all patients who are planned to receive PCRT was informed that they have to receive adjuvant chemotherapy regardless of final pathologic results ahead of PCRT start. We thought that institutional treatment strategy and notice of adjuvant chemotherapy before PCRT were responsible for high compliance to adjuvant chemotherapy.

There are some limitations to our study. We performed a retrospective single-center database study, which may have introduced an inherent bias. Furthermore, we did not include local excision after TR, so it may not be possible to analyze the overall oncologic outcomes of the TR group after PCRT. However, comparison between patients who have undergone radical resection can provide valuable analysis of the different outcomes within the same surgical treatment group. Additionally, we compared oncologic outcomes in the PCRT group with those in the Tis group, and it is not actual comparison with no-tumor status. Tis tumor, however, would not recur theoretically and it might be represent oncologically most favorable tumor. Although the statistical power of our analysis was limited by the abovementioned reasons, this study would show indirectly the oncologic status of TR after PCRT.

Based on the results of this study, TR after PCRT is different from Tis in terms of oncologic outcomes. Further large-scale studies should be performed to assess the long-term oncologic outcomes of patients with TR after PCRT. It is clear that additional investigations are needed to better understand the oncologic status of patients with TR. To ensure proper treatment for patients who show a good response after PCRT, evaluation of the factors associated with recurrence and survival and a better understanding of advanced diagnostic criteria before surgical treatment are necessary.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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