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Original Article

Comparison of 5-Year Oncological Outcomes of Locally Advanced Rectal Cancer Patients Treated with Radiotherapy versus Without Radiotherapy: A Real-World Single-Center Retrospective Study

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Abstract

Background and Objective: Most oncologists treat rectal cancer following NCCN guidelines. Chemoradiotherapy (RT) is preferred for patients with suspected or proven T3-4 disease and/or regional node involvement. RT may result in tumor shrinking, reduce risk of local recurrence in the pelvis, and has been standard of care in North America for locally advanced rectal cancer. Because access to radiation is limited in Thailand, half of the patients deny being referred to radiation centers due to long waiting times and expenses. A transabdominal resection without radiotherapy (RT) was inevitable, but it observed favorable results. This study aimed to compare the long-term oncological outcomes of locally advanced rectal cancer patients who received RT with those who did not receive RT.

Materials and Methods: This retrospective study reviewed data of patients with clinical stage T3-4 rectal cancer who underwent curative resection, received RT, and those without RT from 1 January 2014 to 31 December 2019 in Trang Hospital. The survival and disease status of patients were updated as of 31 July 2024.

Results: Of 54 rectal cancer patients who underwent curative transabdominal resection (mean age 61.57 ± 10.8 years, male 51.9%), 26 patients (48.1%) received RT, and 28 patients (51.9%) did not receive RT. The median follow-up time was 68.5 months (range, 5-113 months). There was no statistical difference between the RT group and the no RT group in 5-year disease-free survival (72.1% vs.88.5%; $P = 0.320$) and 5-year overall survival rates (68.8% vs. 82.1%; $P = 0.242$). The 5-year local recurrence rate was higher in the RT group, but there was no statistically significant difference (21.7% vs. 4.0%; $P = 0.147$).

Conclusion: In rectal cancer patients who were eligible for curative transabdominal resection, receiving or not receiving RT offered comparable long-term oncological outcomes. Omitting RT is an option when radiotherapy is unavailable.

Keywords: Rectal cancer, Omission of radiotherapy, Long-term outcome

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Introduction

Colorectal cancer is the third most frequently diagnosed cancer in Thailand[1] and globally,[2] with rectal cancer accounting for approximately 31% of cases. 5-10% of rectal cancer patients present with locally advanced disease at the time of diagnosis.[2] The treatment of locally advanced rectal cancer (LARC) is challenging, requiring multimodality approaches and varying across countries. Most oncologists in Thailand treat rectal cancer by following the guidelines of the National Comprehensive Cancer Network (NCCN). Neoadjuvant chemoradiotherapy (CRT) is preferred for patients with suspected or proven T3-4 disease and/or regional node involvement and has been the standard of care in North America for LARC.[3,4] The use of RT or Short-course preoperative radiotherapy (SCPRT) aims to result in tumor shrinking, downstaging, and reducing the risk of local recurrence (LR) in the pelvis.[3-5]

On the other hand, in Scandinavian countries, these patients underwent surgery without any neoadjuvant therapy.[6] Consistent with some paraphrase in the European Society for Medical Oncology (ESMO) guideline, it is stated that standard total mesorectal excision (TME) should achieve a curative resection, and downsizing is not necessary if the surgeon routinely carries out good-quality TME and removes the mesorectal nodes en bloc.[7] The introduction of the TME technique is the most important in the surgical management of rectal cancer. The TME led to a significant reduction in local recurrence rates and a significant improvement in survival outcomes of rectal cancer patients.[8,9]

In Thailand, where access to radiotherapy is limited, approximately half of the patients in the study region declined referral to a radiation center because of several individual reasons, including the desire to stay in their local area, concerns about family separation, financial issues related to travel and living expenses in another province, and long waiting times at the radiation center, etc. For these patients, performing a transabdominal resection with the TME technique without the standard treatment of RT was an inevitable issue. However, favorable outcomes were observed in real-world clinical practice; however, there was no report of the long-term oncological outcomes of LARC patients who omit RT in real-world situations. This study aimed to compare the long-term oncological outcomes of locally advanced rectal cancer patients who received RT with those who did not receive RT.

Materials and Methods

This retrospective study reviewed the data of patients with clinical stage T3-4 rectal cancer at Trang Hospital from January 1, 2014, to December 31, 2019. The inclusion criteria were patients who underwent curative resection at Trang Hospital. Tumor histology was confirmed through preoperative endoscopic biopsies. The patients underwent preoperative staging with contrast-enhanced CT imaging. The rectal MRI was not conducted due to limited resources and financial issues. The exclusion criteria were patients who underwent palliative resection (stage IV disease), emergency surgery, rectosigmoid lesion, malignant lesions arising on a polyp, and those denied surgery.

The patients were divided into two groups: those treated with RT and those without RT. The decision to exclude radiation therapy from the standard treatment protocol was purely dependent on the individual patient's reasons since the beginning of the treatment planning. The patients who accepted to undergo treatment with RT were referred to receive RT at Songklanagarind University Hospital and were subsequently referred back for surgery at Trang Hospital. The patients who denied RT undergo standard total mesorectal excision (TME) at Trang Hospital. The postoperative adjuvant chemotherapy (FOLFOX4) was recommended for all patients who denied RT. However, the decision to receive chemotherapy was based on the patient's own decision.

The characteristic, pathological, and oncological data were retrieved for analysis. The survival and disease status of the patients were followed up until July 31, 2024. The follow-up period was defined as the time, in months, from the date of surgery to the last healthcare interaction or time of death. The long-term outcomes were 5-year disease-free survival (DFS), 5-year overall survival (OS), and local recurrence rate (LR). DFS was defined as survival free from disease recurrence or death from any cause. OS was defined as survival free from death from any cause. LRs were identified based on their location in the pelvis, regardless of the mode of detection.

The data were summarized as counts, frequencies (%), and means ± standard deviations (SD). The population characteristics were compared using the chi-square test, Fisher's exact test, or t-test, as appropriate. The outcomes of both groups were evaluated using the chi-square and Fisher's exact test for categorical variables and the *t*-test for continuous variables. Survival was analyzed

using the Kaplan-Meier method and compared with the log-rank test. The Cox proportional-hazards model was used to calculate hazard ratios (HR) and 95% confidence intervals (CI). Statistical significance was attributed to a p-value < 0.05. The statistical software SPSS v.26.0 (IBM, New York, USA) was used for statistical analyses. Institutional Review Board approval was obtained for this study.

Results

From 1 January 2014 to 31 December 2019, A total of 121 patients underwent rectal cancer surgery at Trang Hospital during this period. Of the 54 eligible clinical T3-T4 rectal cancer patients who underwent curative transabdominal resection were included in the final analysis. The mean age of all patients was 61.57 ± 10.8 years. There were 26 patients (48.1%) who received RT and 28 patients (51.9%) underwent surgery without receiving RT. 18 patients (64.3%) of the without RT group received post-operative FOLFOX regimen as adjuvant chemotherapy. Most of the tumors were located at 5-10 cm from the anal verge (70.4%). 51.9% of patients were male, and no statistically significant difference between genders. The received RT group had better prognostic factors than the non-received RT group, as younger age, smaller tumor size, lower T stage, but tumor location closer to the anal verge, as shown in Table 1. Most of the histological tumor type was well-differentiated adenocarcinoma, which was found in 44 of all 54 patients (81.5%). The other surgical and pathological outcomes are in Table 2.

The overall median follow-up time for the entire study was 68.5 months (range, 5-113 months). The mean follow-up period was 66.9 ± 26.2 months. There was no statistical difference in LR and distant metastasis between the groups, as shown in Table 3.

Table 1 Characteristics of rectal cancer patients

Characteristic	Receive RT Group (N = 26)	Not receive RT Group (N = 28)	p-value
Age: years, Mean ± SD	58.42 ± 10.8	64.5 ± 10.2	0.038
Gender: n (%)			0.586
Male	12 (46.2)	16 (57.1)	
Female	14 (53.8)	12 (42.9)	
Tumor distance from anal verge; cm			
Mean ± SD	5.32 ± 2.5	8.14 ± 2.3	< 0.000
Rectal tumor location, n (%)			0.040
< 5 cm from the anal verge	8 (30.8)	2 (7.1)	
5-10 cm from the anal verge	17 (65.4)	21 (75.0)	
> 10 cm from the anal verge	1 (3.8)	5 (17.9)	
Clinical T category, n (%)			0.024
T3	22 (84.6)	18 (64.3)	
T4	4 (15.4)	10 (35.7)	
Diameter of tumor: cm, Mean ± SD	3.6 ± 2.7	5.3 ± 1.8	0.008

Table 2 Surgical and pathological outcomes

Characteristic	Receive RT group (N= 26)	Not receive RT group (N=28)	*p*-value
Type of surgery, n (%)			0.02
Abdominal perineal resection	6 (23.1)	1 (3.6)	
Low anterior resection	18 (69.2)	17 (60.7)	
Laparoscopic low anterior resection	2 (7.7)	7 (25.0)	
High anterior resection	0	3 (10.7)	
Tumor Histological Type, n (%)			1.000
Well differentiated	22 (84.6)	22 (78.6)	
Moderately differentiated	4 (15.4)	5 (17.9)	
Mucinous carcinoma	0	1 (3.6)	
Pathological T category, n (%)			0.045
pT0	3 (11.5)	0	
pT1	2 (7.7)	0	
pT2	5 (19.2)	4 (14.3)	
pT3	13 (50.0)	14 (50.0)	
pT4	3 (11.5)	10 (35.7)	
Pathological Ncategory, n (%)			0.243
N0	16 (61.5)	17 (60.7)	
N1	6 (23.1)	10 (35.7)	
N2	4 (15.4)	1 (3.6)	
Lymphovascular invasion, n (%)			
Yes	3 (11.5)	7 (25.0)	0.298
No	23 (88.5)	21 (75.0)	
Circumferential Resection Margin positive, n (%)	0	0	

Table 3 Oncological outcomes of patients

Characteristic	Receive RT group (N = 26)	Not receive RT group (N = 28)	*p*-value
Location of Recurrence, n (%)			0.246
Liver	1 (4.0)	0	
Lung	0	2 (7.7)	
Lung and liver	1	0	
Local recurrence	5 (19.2)	2 (7.1)	0.243
Lung and local recurrence	3 (12.0)	0	
Liver and local recurrence	1 (4.0)	1 (3.8)	
Follow-up, months			0.138
Mean ± SD	61.4 ± 27.3	72.0 ± 24.5	

For long-term oncological outcomes, the 5-year disease-free survival (DFS) rate was 72.1% (95% CI, 0.545-0.897) in the RT group and 88.5% (95% CI, 0.761-1.000) in the group without RT. Although there was no statistically significant difference in 5-year DFS between the two groups ($P = 0.320$), the HR of 1.78 (95% CI, 0.563-5.617) indicates a numerically higher risk of disease recurrence in the RT group.

The 5-year overall survival (OS) rate was 68.8% (95% CI, 0.508-0.868) in the RT group and 82.1% (95% CI, 0.680-0.962) in the group without RT. There was no statistically significant difference in 5-year OS rates between the two groups ($P = 0.242$). The HR for death in the RT group, compared with the group without RT, was 1.84 (95% CI, 0.653-5.169). There was no statistically significant difference in mortality rates between the two groups.

The 5-year local recurrence (LR) rate was 21.7% (95% CI, 0.047-0.387) in the RT group and 4.0% (95% CI, 0.000-0.116) in the without RT group. This difference was not statistically significant ($P = 0.147$). Although there was a numerically higher risk of local recurrence in the RT group, the HR was 3.16 (95% CI, 0.612-16.329), indicating no statistically significant difference in risk between the two groups. All survival curves are demonstrated in Figures 1, 2, and 3.

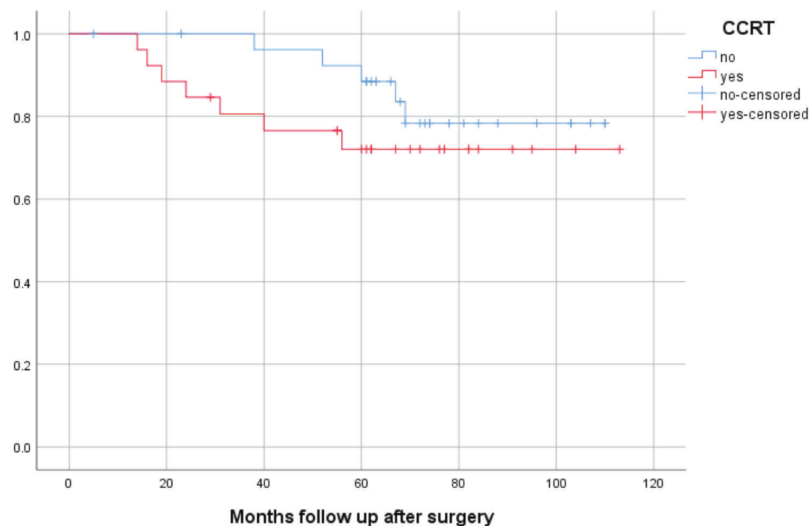

Figure 1 Kaplan-Meier curves show disease-free survival; differences between the RT group and the without RT group were assessed with the log-rank test ($p = 0.320$).

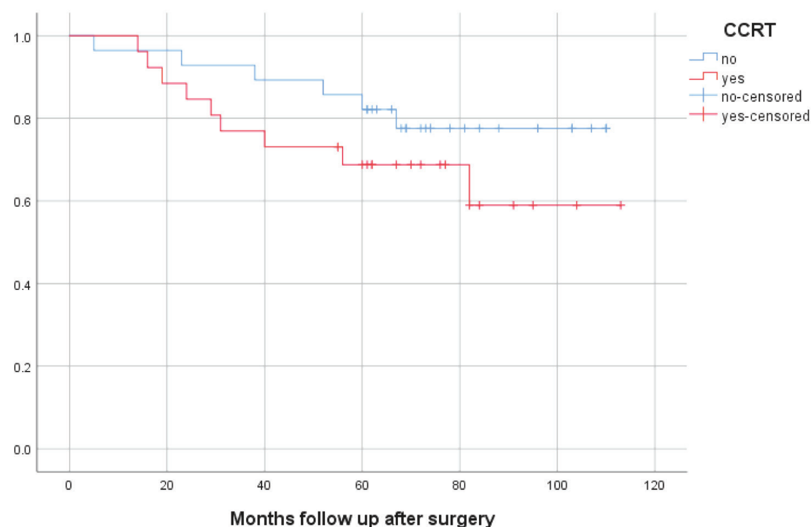

Figure 2 Kaplan-Meier curves show overall survival; differences between the RT group and the without RT group were assessed with the log-rank test ($p = 0.242$).

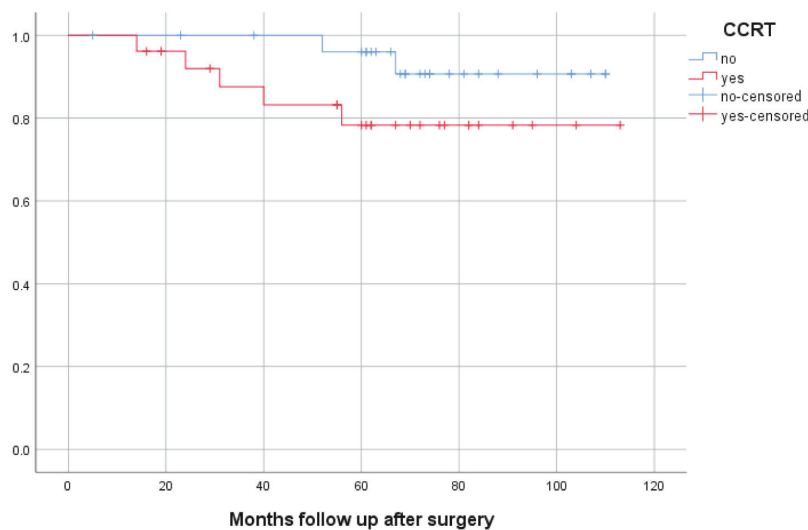

Figure 3 Kaplan-Meier curves show freedom from local recurrence; differences between the RT group and the without RT group were assessed with the log-rank test (p = 0.147).

Discussion

The management of LARC in high-volume hospitals in Thailand, particularly for T3-4 disease and/or regional node involvement, has been standardized by guidelines such as those from the National Comprehensive Cancer Network (NCCN), which advocate for neoadjuvant chemoradiotherapy (nCRT) followed by curative resection.[3] This approach aims to achieve tumor downstaging, reduce local recurrence, and improve overall oncological outcomes.[3,5]

However, the optimal sequencing and necessity of each component, especially RT, are increasingly being re-evaluated globally, often driven by the desire to mitigate treatment-related morbidities and improve patient quality of life.[7,10] The effect of RT can damage the bowel, bone, sexual function, and fertility. This is associated with short-term and long-term toxic effects.[11-14] The omission of RT could improve patients' quality of life by reducing the temporary ostomy and side effects of RT, including the preservation of fertility, sexual function, bowel function, bone marrow resilience, and more.

Another important reason for investigating the outcome of skipping RT is the issue of healthcare access disparities. The global applicability of these guidelines is often challenged by real-world constraints, especially in this resource-limited study setting. And mainly in Thailand, where accessing comprehensive cancer care, particularly specialized treatments such as RT, is a significant challenge.[15,16]

This retrospective analysis reveals no statistically significant differences in the 5-year disease-free survival (DFS) and the 5-year overall survival (OS) between the two groups. The 5-year DFS was 72.1% in the RT group and 88.5% in the group without RT (P = 0.320), and the 5-year OS rates were 68.8% in the RT group and 82.1% in the group without RT (P = 0.242). The HR for death in the RT group, compared with the group without RT, was 1.84 (95% CI, 0.653-5.169). This result indicates a numerically higher risk of disease recurrence in the RT group but no statistically significant difference in risk between the groups.

The results of this study are inconsistent with evidence from old randomized controlled trials, which demonstrated a clear benefit of preoperative chemoradiotherapy in reducing local recurrence.[5,17]

However, these findings are consistent with a recent study from Helsinki, which suggests that the omission of neoadjuvant short-course radiotherapy before surgery does not compromise the 5-year oncological outcome compared to no radiotherapy.[6] Moreover, an updated result of the Chinese FOWARC study after a median follow-up of 10 years found no significant difference in long-term survival outcomes between the LARC with RT and without RT groups.[18]

The 5-year DFS of patients without RT at Trang Hospital was higher than that reported in previous chemoradiotherapy treatments (DFS of 73.9-78.6%),[4,19,20] and the 5-year OS of patients without RT at Trang Hospital was in

the range of previous reports (OS of 75-90.2%).[4,19,20] Upon Kaplan-Meier survival analysis, omitting RT did not have a statistically significant effect on patient survival.

The major benefit of pelvic radiation therapy that has been shown is a decrease in the risk of pelvic recurrence.[3,5] The RAPIDO randomized trial used short-course RT, followed by neoadjuvant chemotherapy before surgery, compared with long-course CRT before surgery. This resulted in a reduction in disease-related treatment failure and metastasis. However, it is associated with an increased risk of LR (12% vs 8%) after 5 years.[21]

Peeters et al. found increased local control in irradiated patients, but no detectable improvement in overall survival. In their study, the 5-year LR risk of patients undergoing a complete local resection was 5.6% in the case of preoperative radiotherapy compared with 10.9% in patients undergoing TME alone ($P < 0.001$). The 5-year OS rates were 64.2% and 63.5%, respectively ($P = 0.902$).[22] Surprisingly, in contrast, the 5-year OS (82.1%) and LR (4.0 %) in the group without RT of this study appear more favorable compared to the RT group of the previous literature (1.6 % - 10%).[4,9,19,21,22]

The 5-year LR was numerically higher in the RT group (21.7%) compared to the group without RT (4.0%) in this study, although there was no statistical difference ($P = 0.147$); the HR was 3.16 (95% CI, 0.612-16.329); however, there was no statistically significant difference in risk of LR between groups. This could be attributed to several limitations, such as the small sample size, which increases the likelihood of random variation; unmeasured confounders, where patients with a higher inherent local recurrence risk may prefer RT; long waiting times to surgery[20]; or adherence to protocols in a real-world setting. The tumor location being "closer to the anal verge" in the RT group is known as an adverse prognostic factor for local recurrence and sphincter preservation, which could have driven the decision for RT and contributed to the numerically higher LR despite treatment. The low recurrence rate and high OS in this study may be due to the predominance of well-differentiated adenocarcinoma (81.5% overall). This pathologic finding suggests a favorable tumor biology in this cohort, which might be less dependent on intensive multimodal therapy. Furthermore, this study showed acceptable surgical oncological clearance demonstrated by all negative circumferential resection margins (CRM) (Table 2), although it enrolled patients with high-risk tumors (T4) and limited MRI staging, which are typically excluded from other trials.[4-6]

Additionally, the group without RT, where 64.3% received post-operative FOLFOX adjuvant chemotherapy, might have benefited from effective systemic therapy. This aggressive adjuvant chemotherapy could have compensated for the lack of RT, especially in a subset of patients with favorable tumor biology. This finding has recently been explored through the introduction of total neoadjuvant therapy (TNT), a novel approach for management in LARC.[23,24] The patients with locally advanced rectal cancer with tumors that respond to chemotherapy may safely omit radiation therapy before surgery, based on the findings of the PROSPECT trial and the study by Schrag et al. concluded that in locally advanced rectal cancer patients who were candidates for sphincter-sparing surgery, omission of the RT was noninferior to the current North American standard of neoadjuvant pelvic RT with similar outcomes in DFS and OS.[4]

While this study did not find a statistically significant difference in long-term oncological outcomes between the RT and without-RT groups, it's essential to interpret these findings in the context of the study's several limitations. The primary reason for the lack of statistical significance is likely due to low statistical power. The relatively small sample size may have prevented the detection of an actual difference between the groups, even if one exists in the larger population. This limitation is also reflected in the wide confidence intervals for the Hazard Ratios in this study. This broad range highlights a high degree of uncertainty surrounding our point estimate, indicating that the actual effect could be anywhere from protective to significantly harmful.

Another critical limitation to consider is selection bias, which is inherent in a retrospective study design. Patients who received RT and those who did not were not randomly assigned; instead, they were selected based on the patient's own decision in real-world situations. For example, patients who did not receive RT may have had less severe disease, a preference for upfront surgery, or limited access to radiotherapy due to geographic or financial constraints. This study did not conduct in-depth research to understand the rationale behind each patient's treatment decision. The unmeasured baseline differences could significantly influence the observed outcomes, confounding variables such as adjuvant chemotherapy or comorbidities, making a direct comparison between the groups challenging in real practice. It's crucial for future

research to address these limitations through larger, prospective studies or randomized controlled trials to provide a definitive answer on the role of RT in this patient cohort.

The accuracy of T staging was based on CT imaging alone, without a gold standard MRI, due to limited resources. Without an MRI, the accuracy of preoperative assessment of the CRM has always been a concern in real practice. The CRM is the surgical plane of the Total Mesorectal Excision (TME), and its involvement by the tumor is the most critical predictor of local failure. CT scans lack the soft-tissue resolution to visualize this fascial plane reliably. This diagnostic limitation may lead to a higher probability of incomplete surgical resection (an R1 resection) and, consequently, a higher incidence of local recurrence within the pelvis. However, this study demonstrated the surgical technique of R0 resection in all patients, without the need for MRI assessment.

Furthermore, being a single-center study, the generalizability of our findings to other institutions or broader patient populations with different healthcare systems, socioeconomic contexts, or treatment protocols is limited.

Despite these limitations, the study's findings provide valuable insights into the long-term oncological outcomes of LARC patients whose treatment decisions were influenced by these real-world practical limitations. They suggest that for some patients, perhaps those with more favorable biology, acceptable long-term oncological outcomes may still be achieved even in the absence of RT.

Conclusion

In locally advanced rectal cancer patients eligible for curative transabdominal resection, omitting RT may not compromise long-term oncological outcomes. This study found comparable long-term oncological outcomes between patients who received RT and those who did not. These findings suggest that RT omission could be a viable consideration, particularly in clinical settings with limited access to radiotherapy.

Conflicts of interest

The author declares that there is no conflict of interest.

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