ORIGINAL ARTICLE

Survival of Young Versus Late-Onset Post Neoadjuvant Treatment Pathologic Node Negative Rectal Cancer: A Retrospective Study from Two Tertiary Hospitals in Thailand

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Background: Although pathological node-negative (ypN0) status is associated with favorable outcomes in rectal cancer patients, recurrence still occurs.

Objective: To compare the clinical stage, tumor biology, treatment response, and survival outcomes between ypN0 young-onset rectal cancer (YORC) and late-onset rectal cancer (LORC) patients and identified factors associated with recurrence.

Materials and Methods: The present study was a retrospective cohort study included 159 ypN0 rectal cancer patients treated between 2013 and 2019 at two tertiary centers in Thailand. Patients were categorized into YORC, younger 50 years, and LORC at 50 years or older groups. Clinical and pathological characteristics, treatment response, disease-free survival (DFS), and overall survival (OS) were analyzed. Prognostic factors for recurrence were identified via Cox proportional hazards regression.

Results: Among 159 patients, 32 (20.1%) had YORC and 127 (79.9%) had LORC. YORC patients presented a greater prevalence of poorly differentiated, mucinous, and signet-ring cell histology. No significant differences were observed in 5-year DFS (p=0.072) or 5-year OS (p=0.127), although YORC patients demonstrated a trend toward earlier recurrence at 303 versus 406 days. Independent risk factors for recurrence included lateral lymph node involvement (adjusted HR 3.341, p=0.011), positive resection margins (adjusted HR 6.519, p=0.004), and a lower number of harvested lymph nodes with less than 12 (adjusted HR 1.099, p=0.007).

Conclusion: There were no statistically significant differences in OS or DFS between ypN0 YORC and LORC patients. However, optimizing lymph node retrieval and positive resection margin remain essential, and closer follow-up may be beneficial for YORC patients given their trend toward earlier recurrence.

Keywords: Young adult; Rectal cancer; Recurrence; Survival; Lymph nodes; ypN0; Retrospective

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Colorectal cancer (CRC) remains a leading global health concern, being a primary cause of cancer-related mortality in men and a significant contributor among women[1]. The incidence of young-onset colorectal cancer (YO-CRC) has been increasing, particularly in Western countries[2-4], with annual growth rates of approximately 1% to 2%[1]. Nearly 25% of new rectal cancer cases now occur in individuals under 50 years of age[5].

While colon and rectal cancers share similarities, they present distinct biological characteristics, treatment responses, and prognostic outcomes[6]. Although several studies have explored differences between YO-CRC and late-onset colorectal cancer (LO-CRC)[7-14], investigations specifically targeting young-onset rectal cancer (YORC) are limited[15]. Emerging findings suggest that YORC presents unique biological and pathological features compared with those of colon and late-onset rectal cancer (LORC), yet its impact on recurrence and survival

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remains unclear[5].

Locally advanced rectal cancer is typically managed through neoadjuvant chemoradiotherapy (CRT) or total neoadjuvant therapy (TNT) before surgery[16]. Achieving pathological negative-node (ypN0) status posttreatment is generally associated with improved survival[17]; however, recurrence still occurs in a subset of patients[18]. Understanding recurrence patterns in ypN0 rectal cancer patients is essential for refining treatment strategies and improving long-term patient outcomes.

YORC has a distinct response to neoadjuvant therapy, with higher rates of pathological complete response (pCR)[19]. Nonetheless, recurrence remains a concern, indicating the need to explore additional prognostic indicators beyond ypN0 status, such as tumor regression grade, molecular alterations, immune response, and patient age.

The present study aimed to compare the clinical stage, tumor biology, treatment response, disease-free survival (DFS), and overall survival (OS) between ypN0 YORC and LORC patients. Additionally, it seeks to explore factors associated with recurrence, offering insights into prognostic markers that could inform treatment and follow-up strategies.

Materials and Methods

The present study was a retrospective cohort study analyzed electronic medical records from Vajira Hospital and Maharaj Nakorn Chiang Mai Hospital in Thailand, following the STROBE reporting guidelines[20]. Patient data were collected from individuals diagnosed with rectal cancer between January 2013 and December 2019. The data were accessed on July 20, 2024.

Patient identification was based on the ICD-10 code C20, malignant neoplasm of the rectum. Inclusion criteria were patients aged over 20 years who underwent neoadjuvant CRT or TNT followed by curative surgery and confirmed ypN0 status. The exclusion criteria included individuals with concomitant inflammatory bowel disease or known hereditary CRC syndromes such as Lynch syndrome, or microsatellite instability-high (MSI-H) tumors, although comprehensive molecular screening was not universally available (Figure 1).

The CRT protocols used in the hospitals included either long-course radiotherapy concurrent with capecitabine or 5-fluorouracil/leucovorin (5-FU/LV) or short-course radiotherapy, whereas the TNT protocols consisted of either induction chemotherapy followed by CRT or CRT followed by consolidation

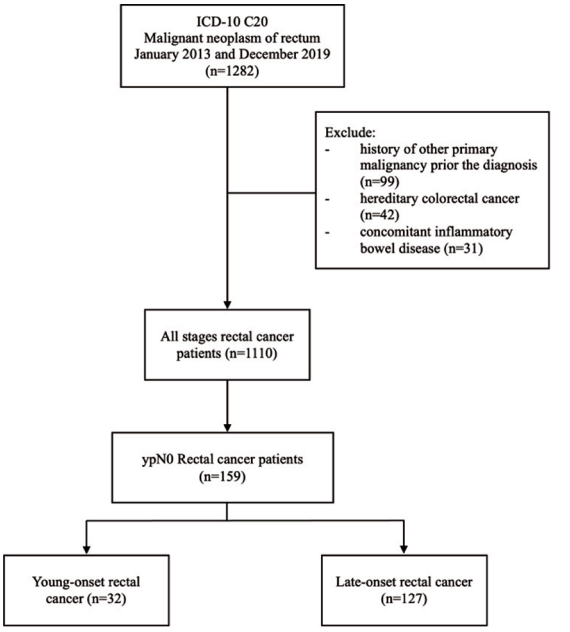

Figure 1. Flow diagram of patient selection showing inclusion of rectal cancer patients with ypN0 status and classification into young-onset and late-onset groups.

chemotherapy. The specific treatment protocol was determined by a multidisciplinary team (MDT) discussion, which included surgeons, medical oncologists, radiation therapists, pathologists, and radiologists. The follow-up protocol adhered to the National Comprehensive Cancer Network (NCCN) guidelines, incorporating computed tomography (CT) imaging every three to six months for the first two years, then annually, alongside carcinoembryonic antigen (CEA) monitoring and scheduled colonoscopies.

Data collection included demographic and clinical characteristics recorded at the time of diagnosis, prior to any treatment. The variables collected were patient age, presence of comorbidities, CEA levels, tumor height from the anal verge, tumor location as determined by MDT discussion, and tumor staging on the basis of CT or magnetic resonance imaging (MRI). Tumor height from the anal verge was measured preoperatively during diagnostic rigid proctoscopy, flexible sigmoidoscopy, or digital rectal examination performed by colorectal surgeons as part of the MDT assessment before initiating neoadjuvant therapy, or from pelvic MRI when determined appropriate by the MDT. The same measurement approach was applied to all patients to ensure consistency across the cohort. Lateral pelvic lymph node status was assessed according to the

lateral pelvic lymph node lexicon criteria[21]. Lateral pelvic lymph nodes were considered positive if they exhibited a short-axis of 7 mm or more, irregular or spiculated margins, or heterogeneous signal intensity on T2-weighted MRI. When lateral pelvic lymph node dissection was performed, pathological confirmation was used when available, otherwise, lateral pelvic lymph node status was recorded based on MRI findings at diagnosis. YORC was defined as a diagnosis of rectal cancer in patients under the age of 50, according to the American Gastrointestinal Association (AGA) definition[22].

For survival analysis, vital status and dates of death were retrieved from the government civil registration database, with follow-up data updated as of December 2024. Recurrence status was categorized into locoregional recurrence and metastatic recurrence, defined as evidence of disease on the basis of imaging studies by CT, MRI, or positron emission tomography (PET), or pathological reports.

For the statistical analyses, continuous variables were summarized as the means with standard deviations (SDs) or medians with interquartile ranges (IQRs), whereas categorical variables were summarized as frequencies with percentages. Statistical comparisons were performed via the paired t-test for parametric data and the Wilcoxon rank-sum test for nonparametric data. The chi-square test was used for hypothesis testing of categorical data, or Fisher's exact test was used when appropriate. Kaplan-Meier (K-M) survival analysis was utilized for the evaluation of DFS and OS. Cox proportional hazards regression analysis was used to determine the risk of recurrence, and hazard ratios (HRs) and adjusted HRs with 95% confidence intervals (CIs) were calculated. Factors included in the multivariable model were preselected on the basis of a literature review and those with a p-value of less than 0.2 in the univariable analysis. Statistical significance was defined as a p-value of less than 0.05. No imputation was performed for missing data. Statistical analyses were conducted via R Studio version 2023.06.0+421, utilizing the packages dplyr, epiDisplay, survival, survminer, and ggplot2.

The present study received approval from the Institutional Review Board (IRB) of Vajira Hospital and the Research Ethics Committee of Maharaj Nakorn Chiang Mai Hospital (approval numbers: COA 143/67 E and SUR-2567-0440). Informed consent was waived because of the retrospective design, which utilized anonymized electronic medical records without patient identification.

Table 1. Baseline demographic and clinical characteristics of young-onset (YORC) and late-onset (LORC) rectal cancer patients with ypN0 status

	YORC (n=32)	LORC (n=127)	p-value
Male; n (%)	17 (53.1)	87 (68.5)	0.102
Age (years); mean±SD	42.1±6.8	62.3±8	<0.001
BMI; median (IQR)	21.5 (19.7, 23.9)	23 (20.4, 25.7)	0.186
Presence of comorbidities; n (%)	6 (18.8)	70 (55.1)	<0.001
CEA level; median (IQR)	2.3 (1.7, 6.6)	4 (2.5, 12.4)	0.049
Level of tumor (cm); median (IQR)	5 (3, 8)	5 (4, 8)	0.158
Tumor location; n (%)			0.433
Upper	4 (12.5)	12 (9.4)	
Middle	8 (25.0)	47 (37.0)	
Lower	20 (62.5)	68 (53.5)	
Clinical T stage; n (%)			0.35
cT2	8 (25.0)	18 (14.3)	
cT3	21 (65.6)	94 (74.6)	
cT4a	0 (0.0)	5 (4.0)	
cT4b	3 (9.4)	9 (7.1)	
Clinical N stage; n (%)			0.175
cN0	9 (28.1)	22 (17.5)	
cN+	23 (71.9)	104 (82.5)	
EMVI positive; n (%)	2 (11.8)	8 (11.4)	1
Lateral LN positive*; n (%)	4 (23.5)	18 (25.7)	1
TNT status; n (%)			0.831
None	29 (90.6)	112 (88.2)	
Consolidation	2 (6.2)	11 (8.7)	
Induction	1 (3.1)	4 (3.2)	
Operation; n (%)			0.92
LAR	13 (40.6)	59 (46.5)	
CAA†	8 (25.0)	29 (22.8)	
APR	11 (34.4)	39 (30.7)	
Approach; n (%)			0.239
Open	8 (25.0)	46 (36.2)	
Laparoscopy	24 (75.0)	75 (59.1)	
TaTME	0 (0.0)	6 (4.7)	

YORC=young-onset rectal cancer; LORC=late-onset rectal cancer; SD=standard deviation; BMI=body mass index; IQR=interquartile range; CEA=carcinoembryonic antigen; c=clinical; EMVI=extramural vascular invasion; LN=lymph node; TNT=total neoadjuvant therapy; LAR=low anterior resection; CAA=coloanal anastomosis; APR=abdominoperineal resection; TaTME=transanal total mesorectal excision

* Refers to radiological lymph node status on pretreatment MRI, † Refers to ultra-LAR or intersphincteric resection

Results

Patient characteristics

One hundred fifty-nine ypN0 rectal cancer patients were included in the analyses, with 32 (20.1%) classified as YORC and 127 (79.9%) as LORC. The mean age was significantly lower in the YORC group at 42.1±6.8 years, than in the LORC group, at 62.3±8.0 years (p<0.001). There was no

Table 2. Pathological tumor characteristics of young-onset (YORC) and late-onset (LORC) rectal cancer patients with ypN0 status

	YORC (n=32)	LORC (n=127)	p-value
pCR; n (%)	9 (28.1)	22 (18.2)	0.567
Tumor differentiation; n (%)			0.235
WD	14 (43.8)	64 (51.6)	
MD	13 (40.6)	52 (41.9)	
PD/mucinous/signet	5 (15.6)	8 (6.5)	
Presence of LVI; n (%)	3 (9.4)	17 (13.9)	0.768
Presence of PNI; n (%)	6 (18.8)	13 (10.7)	0.232
Resection margin; n (%)			0.49
Negative	29 (90.6)	116 (94.3)	
Positive distal margin	0 (0.0)	2 (1.6)	
Positive circumferential margin	3 (9.4)	5 (4.1)	
Harvested LN (no.); median (IQR)	6 (3, 11)	10 (5, 13)	0.023

YORC=young-onset rectal cancer; LORC=late-onset rectal cancer; pCR=pathologic complete response; WD=well-differentiated; MD=moderate-differentiated; PD=poor-differentiated; LVI=lymphovascular invasion; PNI=perineural invasion; LN=lymph node; IQR=interquartile range

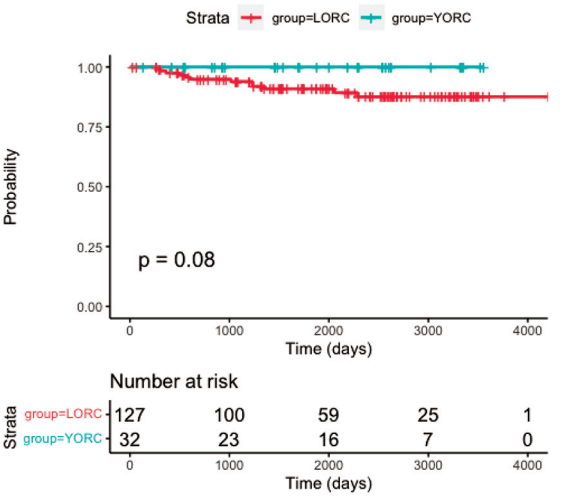

Figure 2. Kaplan-Meier overall survival curves comparing young-onset (YORC) and late-onset (LORC) rectal cancer patients with ypN0 status.

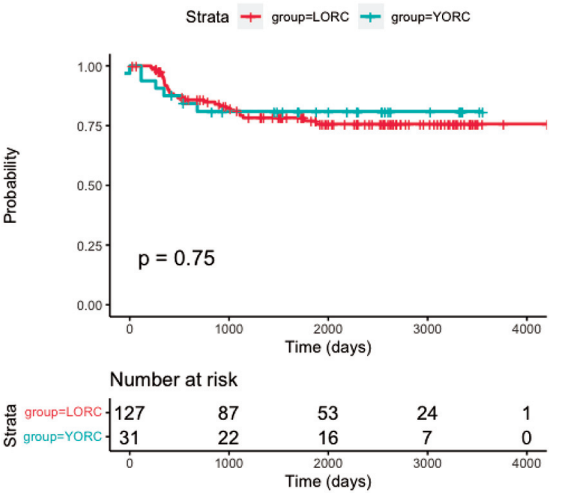

Figure 3. Kaplan-Meier disease-free survival curves comparing young-onset (YORC) and late-onset (LORC) rectal cancer patients with ypN0 status.

significant difference in body mass index (BMI) between the groups (p=0.186). The presence of comorbidities was significantly greater in the LORC group at 55.1% versus 18.8% (p<0.001). The median CEA level was significantly greater in the LORC group at 4.0 versus 2.3 (p=0.049). The tumor location did not differ significantly between the groups (p=0.433). Clinical stages were not significantly different in terms of T stage (p=0.35) or N stage (p=0.175). Similarly, the rates of extramural vascular invasion (EMVI) positivity (p=1.000) and lateral lymph node positivity (p=1.000) were comparable between the groups, as shown in Table 1.

Tumor characteristics

The pCR was observed in 28.1% of YORC patients compared with 18.2% of LORC patients, although this difference was not statistically significant (p=0.567) (Table 2). The tumor differentiation patterns were similar across the groups (p=0.235), however, poor differentiation (PD)/mucinous/signet ring cell histology tended to be more prevalent in the YORC group at 15.6% versus 6.5%. The presence of lymphovascular invasion (LVI) (p=0.768) and perineural invasion (PNI) (p=0.232) did not significantly differ between the two cohorts. Negative resection margins were achieved by more than 90% of both groups (p=0.490). However, a significantly lower median number of lymph nodes were harvested in YORC at 6 (IQR 3, 11) than in LORC at 10 (IQR 5, 13) (p=0.023).

Survival and recurrence outcomes

K-M survival analysis revealed no significant difference in OS between the YORC and the LORC groups (p=0.08). The OS curve (Figure 2) revealed a trend toward better survival in the YORC group, although statistical significance was not reached. Similarly, DFS did not differ significantly between the two cohorts (p=0.75). The DFS K-M curve (Figure 3) revealed a slightly shorter time to recurrence in YORC patients than in LORC patients,

Table 3. Survival and recurrence outcomes of young-onset (YORC) and late-onset (LORC) rectal cancer patients with ypN0 status

	YORC (n=32)	LORC (n=127)	p-value
Follow-up times (days); median (IQR)	1,942 (951.5, 2,610.8)	1,919 (1,140.5, 2,689.5)	0.909
Vital status; n (%)			0.127
Alive	32 (100)	115 (90.6)	
Die	0 (0.0)	12 (9.4)	
Recurrent status; n (%)			1
None	26 (81.2)	100 (78.7)	
Local recurrence	3 (9.4)	14 (11.0)	
Liver metastasis	1 (3.1)	3 (2.4)	
Lung metastasis	2 (6.2)	7 (5.5)	
Intraabdominal LN metastasis	0 (0.0)	1 (0.8)	
Carcinomatosis	0 (0.0)	1 (0.8)	
Adrenal gland metastasis	0 (0.0)	1 (0.8)	
Time to recurrence (days); median (IQR)	303 (151.8, 483.5)	406 (345, 939)	0.072

YORC=young-onset rectal cancer; LORC=late-onset rectal cancer; IQR=interquartile range; LN=lymph node

but the difference remained non-significant. These findings suggested that while survival trends might vary, both groups presented comparable long-term outcomes.

The median follow-up period was similar between YORC and LORC, with both at 5.3 years (p=0.909) (Table 3). The 5-year OS trended to be greater in the YORC group, with all patients remaining alive at the last follow-up, whereas 12 deaths (9.4%) occurred in the LORC group (p=0.127). Recurrence rates were comparable (p=1.000), with 81.2% of YORC patients and 78.7% of LORC patients being recurrence-free. Local recurrence was observed in 9.4% and 11% of the YORC and LORC patients, respectively. Distant metastases, including those in the liver at 3.1% versus 2.4%, lung at 6.2% versus 5.5), intra-abdominal lymph nodes at 0% versus 0.8%, and adrenal glands at 0% versus 0.8%, did not differ significantly between the groups. The median time to recurrence was slightly shorter in the YORC group at 303 days than in the LORC group at 406 days, although this difference did not reach statistical significance (p=0.072).

Prognostic factors and Cox regression analysis

Univariable and multivariable Cox regression analyses were performed to identify prognostic factors influencing DFS among ypN0 rectal cancer patients. Variables with a p-value of less than 0.20 in the univariable Cox regression analysis were considered for inclusion in the multivariable model. In addition, clinically important factors were included regardless of their univariable significance as forced entry, specifically, group with YORC versus LORC, TNT status, pathological T stage (pT), and resection margin status. The final multivariable Cox regression model was therefore constructed using both statistically and clinically relevant variables. According to the multivariable analysis, lateral lymph node positivity was independently associated with poorer prognosis (adjusted HR 3.341, 95% CI 1.314 to 8.496, p=0.011). Positive resection margins significantly increased the risk of recurrence and mortality (adjusted HR 6.519, 95% CI 1.841 to 23.085, p=0.004). Additionally, the number of harvested lymph nodes was a significant predictor, with fewer than 12 harvested nodes associated with worse outcomes (adjusted HR 1.099, 95% CI 1.026 to 1.178, p=0.007). Other factors, including age, tumor location, clinical T and N stage, EMVI, PNI, and pCR did not reach statistical significance as independent prognostic markers, as shown in Table 4.

These results highlighted notable differences between ypN0 YORC and LORC, particularly regarding patient demographics and tumor biology. While YORC patients demonstrated a trend toward higher pCR rates and lower comorbidity burdens, no significant differences in recurrence or survival were observed. Importantly, lateral lymph node involvement, positive resection margins, and the number of harvested lymph nodes emerged as independent prognostic indicators, underscoring the importance of thorough surgical resection and nodal assessment in rectal cancer management.

Discussion

The incidence of YORC is increasing globally, reflecting an increasing trend across multiple

Table 4. Univariable and multivariable Cox regression analyses of prognostic factors for recurrence in ypN0 rectal cancer

Variables		Univariable			Multivariable		
		HRs	95% CI (upper to lower)	p-value	Adjusted HRs	95% CI (upper to lower)	p-value
Age	LORC	1.000	Reference	-	1.000	Reference	-
	YORC	0.938	0.387 to 2.272	0.887	0.428	0.091 to 2.015	0.283
Sex	Male	1.000	Reference	-			
	Female	0.821	0.391 to 1.725	0.603			
BMI	<18.5	1.000	Reference	-			
	18.5 to 22.9	1.395	0.404 to 4.819	0.599			
	23 to 24.9	1.158	0.277 to 4.846	0.841			
	≥25	1.184	0.326 to 4.306	0.797			
Presence of comorbidities	No	1.000	Reference	-			
	Yes	1.039	0.525 to 2.057	0.913			
CEA level (μg/mL)	≤5	1.000	Reference	-			
	>5	1.010	0.462 to 2.207	0.980			
Tumor location	Upper	1.000	Reference	-			
	Middle	2.862	0.366 to 22.362	0.316			
	Lower	4.255	0.574 to 31.573	0.157			
Clinical T stage	cT2	1.000	Reference	-			
	cT3	1.413	0.490 to 4.074	0.523			
	cT4	1.986	0.533 to 7.396	0.307			
Clinical N stage	cN–	1.000	Reference	-			
	cN+	0.887	0.385 to 2.044	0.778			
EMVI status	EMVI–	1.000	Reference	-	1.000	Reference	-
	EMVI+	2.334	0.784 to 6.949	0.128	2.850	0.835 to 9.731	0.095
Lateral LN status*	LLN–	1.000	Reference	-	1.000	Reference	-
	LLN+	2.832	1.190 to 6.740	0.019	3.341	1.314 to 8.496	0.011
TNT status	None	1.000	Reference	-	1.000	Reference	-
	TNT	0.864	0.264 to 2.834	0.810	2.104	0.211 to 20.962	0.526
Operation	LAR	1.000	Reference	-			
	CAA†	1.779	0.686 to 4.612	0.236			
	APR	2.669	1.168 to 6.101	0.020			
Approach	Open	1.000	Reference	-	1.000	Reference	-
	Lap/TaTME	0.497	0.251 to 0.985	0.045	0.714	0.253 to 2.017	0.524
pCR status	Yes	1.000	Reference	-	1.000	Reference	-
	No	3.650	0.873 to 15.263	0.076	1.945	0.401 to 9.444	0.409
Tumor differentiation	WD	1.000	Reference	-			
	MD	6.388	0.378 to 29.601	0.212			
	PD/mucinous/signet	3.482	0.316 to 38.411	0.308			
LVI status	LVI–	1.000	Reference	-			
	LVI+	1.287	0.495 to 3.341	0.605			
PNI status	PNI–	1.000	Reference	-			
	PNI+	1.270	0.489 to 3.300	0.623			
Resection margin	Margin–	1.000	Reference	-	1.000	Reference	-
	Margin+	7.896	3.527 to 17.676	<0.001	6.519	1.841 to 23.085	0.004
Harvested LN (no.)	≥12	1.000	Reference	-	1.000	Reference	-
	<12	0.515	0.253 to 1.048	0.067	1.099	1.026 to 1.178	0.007

HRs=hazard ratios; CI=confidence interval; YORC=young-onset rectal cancer; LORC=late-onset rectal cancer; BMI=body mass index; CEA=carcinoembryonic antigen; c=clinical; EMVI=extramural vascular invasion; LN=lymph node; TNT=total neoadjuvant therapy; LAR=low anterior resection; CAA=coloanal anastomosis; APR=abdominoperineal resection; Lap=laparoscopy; TaTME=transanal total mesorectal excision; pCR=pathologic complete response; WD=well differentiation; MD=moderate differentiation; PD=poor differentiation; LVI=lymphovascular invasion; PNI=perineural invasion; LN=lymph node

* Refers to radiological lymph node status on pretreatment MRI, † Refers to ultra-LAR or intersphincteric resection

populations. O'Connell et al. analyzed data from the Surveillance, Epidemiology, and End Results (SEER) registry spanning between 1973 and 1999 and reported a significant annual increase of 75% in rectal cancer incidence among young patients[23]. This upward trend has been well documented in Western countries[24] and is increasingly evident in Eastern populations as well. For example, Nath et al. examined data from a tertiary care center in India between 2003 and 2007 and reported that rectal cancer in individuals younger than 40 years accounted for up to 35.5% of cases, indicating a marked increase compared with previous reports[25]. More recent studies further highlight this trend, with one reporting that one in four newly diagnosed rectal cancer cases occurs in individuals under the age of 50[5]. Consistent with these findings, the present study revealed a YORC-to-LORC ratio of 1 to 4, underscoring the alarming increase in incidence among younger patients.

When the tumor characteristics of YORC and LORC patients were compared, the present study revealed no statistically significant differences. However, there was a non-significant trend for YORC patients to present with more advanced clinical T stages, including cT4b, whereas other characteristics, including clinical lymph node positivity, EMVI status, and the presence of lateral lymph nodes, were not significantly different.

Previous reports, such as that by Nath et al. (2009), demonstrated higher pathological T and N stages in YORC patients, suggesting more unfavorable tumor biology in younger adults[25]. Although the present study data did not show statistically significant differences, the direction of the findings was consistent with prior literature[26], showing a higher, but non-significant, prevalence of poorly differentiated, mucinous, and signet-ring cell histology in YORC. This may imply potential biological differences that warrant further investigation using larger cohorts. Similarly, a large retrospective study utilizing the U.S. National Cancer Data Base reported that biological factors may underlie variations in treatment response between YORC and LORC[27].

Although the present study revealed a higher pCR rate in YORC, at 28.1%, than in LORC, at 18.2%, this difference was not statistically significant. This finding is particularly noteworthy, as some studies suggest that younger patients may have lower pCR rates than older patients do[28]. Importantly, the present study included only patients with ypN0 rectal cancer, which may have influenced the observed differences in pCR rates compared with the previous studies that reported pCR rates across all cases of locally advanced rectal cancer.

The choice between short- and long-course CRT in the present study was determined by MDT consensus, considering tumor stage, distance from the anal verge, and patient comorbidities or treatment tolerance. In this cohort, more than 85% of patients received long-course CRT, suggesting that treatment heterogeneity had a limited influence on outcomes. Notably, positive circumferential resection margins (CRM) were observed in both CRT regimens at comparable rates, indicating that CRM involvement was driven by tumor-related factors rather than the type of preoperative CRT administered.

The present study revealed no significant differences in OS or DFS between YORC and LORC. However, the observed trend toward a shorter time to recurrence in YORC patients at 303 versus 406 days ($p=0.072$) suggests the potential influence of more aggressive tumor biology and pretreatment tumor status, despite the ypN0 designation. The shorter median time to recurrence in YORC was unlikely to be related to CRM positivity, as the incidence of local recurrence remained slightly lower than in LORC. This pattern may suggest a potential association with lateral pelvic node involvement rather than surgical margin status. Despite the significantly higher rate of comorbidities in LORC patients, this factor did not appear to adversely affect oncologic outcomes, as both DFS and OS were comparable between the two groups. The impact of comorbidities may have been mitigated by patient selection and MDT-guided treatment planning, which ensured that all included cases were fit for curative-intent therapy.

Even among ypN0 patients, recurrence rates remained substantial, with 21.3% in LORC patients and 18.8% in YORC patients. However, studies specifically investigating recurrence patterns in YORC remain limited. In contrast to the present study findings, You et al. (2011) reported a significantly higher distant recurrence rate in younger patients, or patients younger than 50 years old, at 24.6% than in older patients at 13.9% ($p<0.001$), whereas no significant difference was observed in locoregional recurrence[26]. These discrepancies highlight the need for further investigation into the unique biological and clinical characteristics of YORC.

The objective of the present study was not only to investigate potential differences in tumor biology between ypN0 YORC and LORC but also to explore

factors associated with recurrence in ypN0 rectal cancer patients. The authors found that lateral lymph node involvement, positive resection margins, and a lower lymph node yield, with less than 12 nodes, were associated with recurrence. The prognostic implications of a reduced lymph node yield should be carefully considered, as it remains unclear whether this finding reflects biological differences such as lower nodal involvement in YORC, or surgical/pathological factors such as variations in lymph node retrieval techniques. Furthermore, the lack of a significant impact of pCR and tumor differentiation on survival outcomes suggests that once ypN0 status is achieved, surgical and nodal factors may have a greater influence on prognosis than initial tumor biology does.

The lower lymph node yield observed in YORC may have several explanations. First, younger patients often present with a more robust immune response and fibrotic reaction following CRT, which can obscure nodal identification during pathological examination[29]. Second, the neoadjuvant treatment itself induces nodal atrophy and fibrosis, thereby reducing the number of retrievable nodes regardless of patient age[30,31]. Finally, variations in surgical technique, specimen handling, and pathological diligence across institutions may also contribute to lower nodal counts[32]. Although the prognostic relevance of total lymph node yield after neoadjuvant therapy remains controversial, an inadequate count of less than 12 nodes may still reflect the thoroughness of mesorectal excision and pathological assessment[33], both of which could influence DFS.

While the present study offered meaningful observations, limitations should be acknowledged. The small sample size of 159 ypN0 patients may limit the statistical power of subgroup analyses, particularly in comparisons between young-onset and late-onset patients. Additionally, as a retrospective study, inherent selection biases and data collection limitations must be considered, emphasizing the need for prospective validation in larger cohorts. Another important limitation is the lack of molecular data in the study country, as the absence of genomic and transcriptomic profiling restricts the ability to fully understand the biological mechanisms underlying recurrence in ypN0 patients. Furthermore, the American Society of Anesthesiologists (ASA) physical status scores were not consistently recorded in both hospital databases; therefore, the presence of comorbidities was used as a surrogate indicator of baseline health. This may have limited the precision of perioperative risk assessment. Moving forward, prospective studies with larger sample sizes, molecular profiling, and standardized follow-up protocols will be valuable in refining risk assessment and optimizing posttreatment management in ypN0 YORC patients.

Conclusion

In conclusion, the present study revealed that ypN0 YORC and LORC patients shared comparable pathological characteristics, with only numerical, though not statistically significant, differences observed in certain tumor features. These trends may warrant confirmation in larger prospective cohorts. Despite the absence of significant differences in DFS and OS between the two groups, recurrence remained a clinical concern in both. The observed trend toward earlier recurrence in YORC highlights the potential value of more intensified surveillance, particularly during the first postoperative year, with clinical and biomarker assessments to enable early detection and timely management of treatable recurrence. Furthermore, ensuring adequate lymph node retrieval remains a critical quality indicator in rectal cancer surgery and may influence long-term oncologic outcomes.

What is already known about this topic?

Pathological ypN0 status in rectal cancer is associated with favorable prognosis, yet recurrence still occurs and the influence of young age on recurrence risk remains unclear.

What does this study add?

This study demonstrates that while ypN0 YORC patients exhibit more aggressive tumor histology, their survival outcomes are comparable to late-onset patients, and recurrence is primarily driven by surgical and pathological factors such as lymph node retrieval, resection margins, and lateral lymph node involvement.

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Conflicts of interest

The authors declare no conflict of interest.

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