Asian Journal of Current Research in Clinical Cancer
ISSN: 3062-4444
2022, Volume 2, Issue 2, Page No: 22-32

Available online at: www.galaxypub.co/page/journals

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Low miR-19b Expression Predicts Improved Therapeutic Response and Prognosis in Locally Advanced Rectal Cancer

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Received: 12 April 2022; **Revised:** 01 August 2022; **Accepted:** 03 August 2022

ABSTRACT

For individuals diagnosed with locally advanced rectal cancer (LARC), neoadjuvant chemoradiotherapy (CRT) using 5-fluorouracil (5-FU) followed by total mesorectal excision remains the therapeutic standard. Despite its widespread use, a considerable proportion of patients exhibit limited or no response to this treatment, which negatively influences prognosis and exposes them to unnecessary toxicities and surgical postponements. Consequently, the discovery of dependable biomarkers capable of forecasting CRT response has become a pressing clinical objective. Among the microRNAs implicated in colorectal cancer (CRC), microRNA-19b (miR-19b) is known to exert oncogenic effects, modulate sensitivity to 5-FU, and influence patient outcomes. Nevertheless, its relevance in LARC has not been fully explored. In this study, we report that aberrant miR-19b expression is frequent in LARC, and reduced levels of this molecule are significantly correlated with smaller post-CRT tumor size ($p = 0.003$), lower pathological stage ($p = 0.003$), and absence of disease recurrence ($p = 0.001$). Remarkably, diminished miR-19b expression also predicts a more favorable response to neoadjuvant CRT ($p < 0.001$), along with prolonged overall ($p = 0.003$) and event-free survival ($p = 0.023$). Multivariate models identified miR-19b as an independent determinant of both treatment efficacy and clinical outcome, suggesting that this microRNA may serve as a promising prognostic and predictive biomarker for LARC management.

Keywords: MicroRNA-19b, Rectal cancer, Biomarker, Chemoradiotherapy, Prognosis

How to Cite This Article: Virtanen M, Laine S, Niemi O. Low miR-19b Expression Predicts Improved Therapeutic Response and Prognosis in Locally Advanced Rectal Cancer. Asian J Curr Res Clin Cancer. 2022;2(2):22-32. https://doi.org/10.51847/XQJMHQjiaW

Introduction

Colorectal cancer (CRC) remains one of the most prevalent malignancies in Western countries and represents the third leading cause of cancer-related mortality. In Spain alone, over 44,000 new cases are diagnosed annually, with approximately 15,000 deaths attributed to the disease each year [1]. Rectal cancer accounts for nearly one-third of all CRC cases. Anatomically, the rectum extends from the sigmoid colon, spanning approximately 12–15 cm, and terminates at the dentate line or anal verge [2].

Although several novel therapeutic modalities are currently under clinical investigation, the European Society for Medical Oncology (ESMO) recommends neoadjuvant chemoradiotherapy (CRT) with 5-fluorouracil (5-FU) — administered intravenously or orally as capecitabine — or alternatively, short-course preoperative radiotherapy (SCPRT) followed by total mesorectal excision (TME) as the standard treatment for locally advanced rectal cancer (LARC) [3]. Numerous studies have confirmed that this multimodal approach significantly improves local control and reduces recurrence compared to surgery alone or postoperative CRT [4, 5]. With this regimen, approximately 20% of patients achieve a pathological complete response (pCR), a subgroup that demonstrates superior overall survival (OS) and disease-free survival (DFS) [6, 7]. Conversely, patients who fail to reach pCR face a higher likelihood of local or distant relapse, with nearly 30% developing recurrent disease within a decade of initial therapy. Despite advances in treatment, distant metastasis continues to be the leading cause of death among LARC patients [8].

Given this scenario, the identification of reliable biomarkers capable of predicting prognosis and treatment response is of great clinical interest. Such markers could help stratify patients according to their likelihood of responding to CRT, allowing oncologists to tailor treatment strategies and avoid unnecessary toxicity, morbidity, and surgical delays in non-responders [9]. Although several prognostic and a few predictive molecular indicators have been explored, none have yet been validated for clinical use [10–12]. Consequently, the absence of robust pre-treatment predictors of pathological tumor response remains a critical limitation in the management of LARC.
MicroRNAs (miRNAs or miRs) are small, non-coding, single-stranded RNA molecules of approximately 19–25 nucleotides that regulate gene expression at the post-transcriptional level. They typically bind to complementary sequences within the 3′ untranslated region (UTR) of target messenger RNAs (mRNAs), leading to translational repression or degradation [13]. Depending on their targets, miRNAs may function either as oncogenes or tumor suppressors. Their diagnostic, prognostic, and predictive potential has been documented across numerous cancer types, including rectal cancer [14–16]. Moreover, miRNAs have been implicated in modulating drug resistance, suggesting their value in predicting tumor responsiveness to chemotherapy [17]. In rectal cancer, several miRNAs have shown promise as non-invasive biomarkers detectable in both tumor tissue and liquid biopsies [12]. Consequently, quantifying specific miRNAs or miRNA signatures in tissue samples or circulating fluids could enhance the stratification of LARC patients by predicted CRT response, thus optimizing clinical decision-making [18–21].
Among these molecules, miR-19b has garnered considerable attention due to its involvement in tumorigenesis across multiple cancer types through diverse molecular pathways. Overexpression of miR-19b has been associated with enhanced tumor growth and metastasis by targeting p53, resulting in decreased levels of its downstream effectors BAX and p21 [22]. It has also been shown to inhibit PTEN and activate the PI3K/AKT signaling cascade in malignancies such as Wilms tumor, multiple myeloma, renal carcinoma, and cholangiocarcinoma [23–25]. In non-small cell lung cancer (NSCLC), miR-19b promotes tumor proliferation by repressing the tumor suppressor PP2A through direct inhibition of its regulatory subunit PPP2R5E [26].
In colorectal cancer specifically, miR-19b expression has been reported to increase during the adenoma–carcinoma sequence, predominantly within epithelial cells in the transition from normal to neoplastic tissue [27]. Functional studies have revealed that miR-19b promotes CRC cell proliferation [28, 29], migration, and invasion [30], in part via c-MYC–driven repression of the pro-apoptotic protein BIM (Bcl2-like 11) [31]. At the therapeutic level, miR-19b overexpression confers resistance to key chemotherapeutic agents, including 5-FU and oxaliplatin. Jiang *et al*. demonstrated that miR-19b mediates oxaliplatin resistance through the suppression of SMAD4 [29], while other research has shown that exosomal miR-19b contributes to the development of oxaliplatin resistance in CRC cells [32]. Furthermore, miR-19b has been implicated in 5-FU resistance, with elevated expression levels observed in resistant CRC cell lines [33].
From a biomarker perspective, circulating serum miR-19b has been suggested as a diagnostic indicator for inflammatory bowel disease and colonic polyps [34]. Additionally, a six-miRNA signature including miR-19b has been proposed as a diagnostic tool for detecting advanced adenomas and CRC [35]. While Cruz-Gil *et al*. reported that miR-19b expression correlates with improved prognosis in CRC [36], most studies have identified its overexpression as a marker of poor outcome, including higher recurrence risk and shorter overall survival in CRC patients with liver metastases [37]. Multiple independent investigations have corroborated its association with adverse clinical outcomes [29, 30].
To date, evidence regarding miR-19b in rectal cancer remains scarce. The study by Molinari *et al*. examined the DNA copy number (DCN) of the MIR17HG gene—host to the miR-17-92a-1 cluster, which includes miR-19b—in 108 LARC cases. Although no direct link was found between MIR17HG DCN and CRT response, gene amplification correlated with non-responsiveness, suggesting that miRNAs within this cluster, including miR-19b, might play a role in therapy resistance [38]. The authors emphasized the necessity of assessing the expression levels of these miRNAs in LARC patient cohorts.
In light of these findings, the clinical relevance of miR-19b in LARC has not yet been defined. The present study addresses this gap by evaluating, for the first time, the expression profile of miR-19b and its prognostic and predictive significance in a cohort of 121 patients with LARC. Our results demonstrate that reduced miR-19b expression is a frequent molecular event associated with favorable clinicopathological features, improved survival outcomes, and enhanced sensitivity to 5-FU–based neoadjuvant CRT.

Experimental section

Patient samples

This study retrospectively included 121 patients diagnosed with locally advanced rectal cancer who were treated at University Hospital Fundación Jiménez Díaz (Madrid, Spain) between 2007 and 2017. Pretreatment tumor biopsies were collected through colonoscopy before any neoadjuvant chemoradiotherapy (CRT) was administered. All patients underwent neoadjuvant CRT followed by total mesorectal excision in accordance with European clinical guidelines, with preoperative staging performed using magnetic resonance imaging, transrectal ultrasound, and computed tomography scans. Only patients with histologically confirmed adenocarcinoma, operable disease, sufficient tissue for molecular analysis, available clinical follow-up, and no evidence of metastasis were included. Tumor staging was performed according to the 7th edition of the AJCC TNM classification for colorectal cancer. Informed consent for tissue storage and research use was obtained from all participants, and the study protocol was approved by the institutional ethics committee (approval number 2018/54).

Assessment of pathological response

Tumor regression was evaluated on the initial biopsy samples using the CAP TNM classification, 7th edition. Two pathologists, blinded to patient outcomes, independently assessed tumor regression according to the modified Ryan system, which categorizes response into four grades: complete response (no viable tumor cells), moderate response (small clusters or isolated tumor cells), minimal response (residual tumor dominated by fibrosis), and poor response (extensive viable tumor with minimal regression). Regression grades were compared with the corresponding primary tumor in line with current clinical guidelines.

RNA extraction

RNA was isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue using the RecoverAll Total Nucleic Acid Isolation Kit (Ambion, Thermo Fisher Scientific) following the manufacturer's protocol. RNA concentration and purity were measured with a NanoDrop spectrophotometer. FFPE specimens allowed long-term preservation while minimizing contamination risk.

miRNA quantification

For quantification, total RNA was reverse-transcribed using the TaqMan MicroRNA Reverse Transcription Kit (Applied Biosystems). Mature miR-19b levels were measured with TaqMan MicroRNA Assays (Applied Biosystems), and U6B served as an internal control. PCR reactions were run on an Applied Biosystems 7500 system with a preheating step of 95 °C for 10 minutes, followed by 45 cycles of 95 °C for 15 seconds and 60 °C for 1 minute. Relative expression levels were calculated using the ΔCT method.

Statistical analysis

All analyses were conducted with SPSS for Windows. Associations between miR-19b expression and clinical or pathological variables were examined using Chi-square or Fisher's exact tests as appropriate. The optimal cutoff for defining low miR-19b expression was determined using receiver operating characteristic (ROC) analysis, selecting the point that maximized sensitivity and specificity for predicting CRT response. A ΔCT value below 1.22 was considered indicative of miR-19b downregulation. Event-free survival (EFS) was defined as the interval from diagnosis to the first event, including local or distant recurrence, last follow-up, or death. Overall survival (OS) was calculated from the date of pathological diagnosis to the date of last contact or death. Kaplan–Meier curves were compared using log-rank or Breslow tests, depending on proportional hazards assumptions. Factors significant in univariate analyses were included in multivariate Cox proportional hazards models. The study followed REMARK guidelines for tumor marker prognostic studies.

Results and Discussion

Prevalence of low miR-19b expression and associations with clinical features

miR-19b expression was analyzed in 121 patients with complete follow-up information. The cohort comprised 73 men and 48 women, with a median age of 69 years (range 36–86). Low miR-19b expression was observed in 47 patients, accounting for 38.8% of the cohort. Reduced miR-19b levels were significantly associated with smaller tumors following CRT ($p = 0.003$) and earlier pathological stage ($p = 0.003$). There was a tendency for patients

with low miR-19b to exhibit lower tumor grade prior to CRT and fewer positive lymph nodes after treatment, although these trends did not reach statistical significance ($p = 0.103$ and $p = 0.216$, respectively). Detailed correlations between miR-19b expression and clinicopathological parameters are provided in **Table 1**.

Table 1. Association between clinical and molecular parameters and miR-19b expression levels in a cohort of 121 locally advanced colorectal cancer (LARC) patients.

	No. Cases	**No. miR-19b Low (%)**	**No. miR-19b High (%)**	**p**
MiR-19b	121	47 (38.8)	74 (61.2)	
Gender	121	47	74	0.605
Male	73	27 (37)	46 (63)	
Female	48	20 (41.7)	28 (58.3)	
Age	121	47	74	0.562
<60	40	17 (42.5)	23 (57.5)	
≥60	81	30 (37)	51 (63)	
ECOG [1]	121	47	74	0.831
0	81	32 (39.5)	49 (60.5)	
1–2	40	15 (37.5)	25 (62.5)	
Clinical stage pre-CRT [2]	121	47	74	0.285
II	9	5 (55.6)	4 (44.4)	
III	112	42 (37.5)	70 (62.5)	
Grade pre-CRT	112	42	70	0.103
Low	40	19 (47.5)	21 (52.5)	
Moderate-High	72	23 (31.9)	49 (68.1)	
ypT [3]	121	47	74	0.003
0	16	13 (81.3)	3 (18.7)	
1	16	7 (43.8)	9 (56.2)	
2	38	12 (31.6)	26 (68.4)	
3	44	13 (29.6)	31 (70.4)	
4	4	0 (0)	4 (100)	
x	3	2 (66.7)	1 (33.3)	
ypN [4]	121	47	74	0.216
N0	91	38 (41.8)	53 (58.2)	
N1	26	9 (34.6)	17 (65.4)	
N2	4	0 (0)	4 (100)	
Pathological stage	121	47	74	0.003
yp0	16	13 (81.3)	3 (18.7)	
ypI	43	15 (34.9)	28 (65.1)	
ypII	32	10 (31.3)	22 (68.7)	
ypIII	30	9 (30)	21 (70)	

[1] ECOG = Eastern Cooperative Oncology Group; [2] CRT = Chemoradiotherapy; [3] ypT = tumor size after CRT; [4] ypN = pathological lymph node after CRT.

MiR-19b as a predictive biomarker for neoadjuvant CRT response in locally advanced rectal cancer

To explore whether miR-19b expression could serve as a predictive marker for preoperative chemoradiotherapy in LARC, we performed receiver operating characteristic (ROC) analysis. The results indicated that miR-19b

levels effectively differentiated patients who achieved a favorable pathological response from those who did not. The area under the ROC curve was calculated at 0.765 (95% confidence interval: 0.626–0.905; p = 0.001), demonstrating a robust discriminative capacity. Using the optimal threshold, miR-19b predicted treatment response with a specificity of 81.3% and a sensitivity of 66.7%, suggesting its potential utility for identifying patients likely to benefit from neoadjuvant CRT **(Figure 1)**.

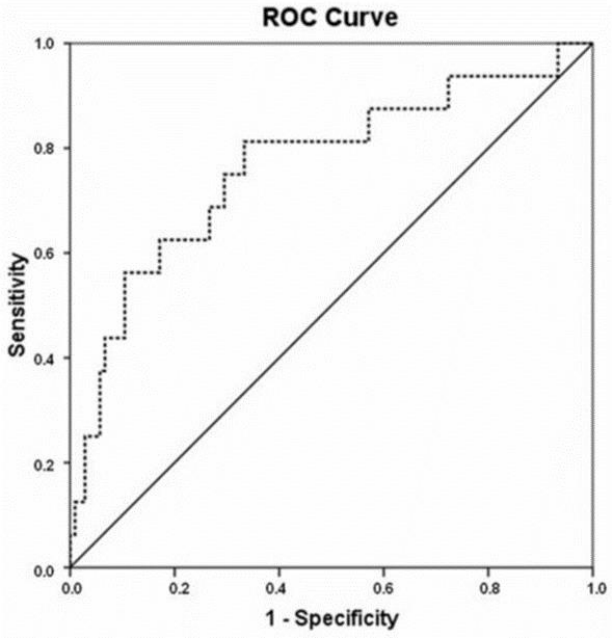


Figure 1. Receiver operating characteristic (ROC) curve to assess the usefulness of miR-19b to discriminate response to neoadjuvant chemoradiotherapy (CRT) in LARC. The dashed line is the coordinated point of the ROC curve. The solid line represents the reference diagonal line.

Analysis revealed a significant relationship between miR-19b expression and pathological response to preoperative CRT ($p < 0.001$). Notably, only 20.6% of patients who did not achieve a favorable response exhibited low levels of miR-19b **(Table 2)**.

Table 2 summarizes the correlation between miR-19b expression and treatment response, highlighting the distribution of low and high miR-19b levels across responder and non-responder groups.

Table 2. Association between miR-19b expression levels and pathological response to neoadjuvant CRT in LARC patients.

Response to NCRT [1]	No. Cases	Responders [2] (%)		Non-Responders [3] (%)		p
MiR-19b Expression	**121**	**58**		**63**		**<0.001**
Low	47	24		(72.3)		13
High	74	34	(32.4)	50	(67.6)	

[1] NCRT: neoadjuvant chemoradiotherapy; [2] Responders. Moderate or complete pathological response; [3] Non-Responders: poor or minimal pathological response.

In concordance with these data, we also observed a strong association between miR-19b expression and recurrence in our cohort, and miR-19b downregulation was found only in 11.5% of those cases that developed recurrence **(Table 3)**.

Table 3. Association between patient relapse and miR-19b expression levels in LARC patients.

Recurrence	No. Cases	Yes (%)	No (%)	p
MiR-19b Expression	121	26	95	0.001
Low	47	3	(6.4)	44

High	74	23	(31.1)	51	(68.9)

Importantly, multivariate logistic regression analysis was conducted incorporating all available clinical and pathological variables assessed prior to neoadjuvant CRT. The results indicated that pre-treatment miR-19b expression independently predicted pathological response in patients with locally advanced rectal cancer. Specifically, lower miR-19b levels were associated with a markedly reduced likelihood of non-response, with an odds ratio of 0.18 (95% confidence interval: 0.06–0.57; p = 0.003) **(Table 4)**.

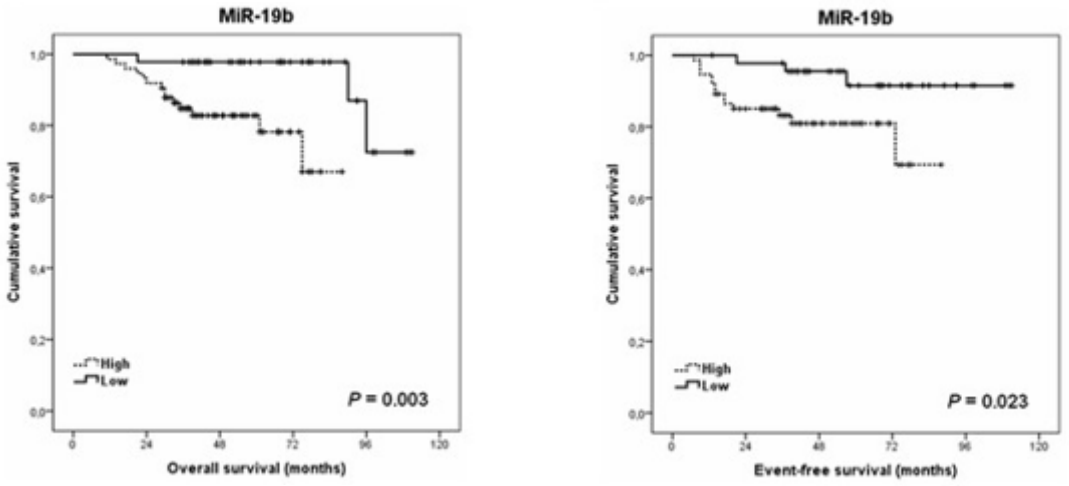
Table 4. Univariate and multivariate logistic analyses for pathological response in the cohort of 121 LARC patients.

Response [1] vs. Non-Response [2]		
	OR [3] (95% CI [4])	**p**
Gender, Male vs. Female	1.227 (0.558 to 2.98)	0.611
Age, < 60 vs. ≥60	0.778 (0.714 to 1.925)	0.587
Clinical stage pre-CRT [5], II vs. III	1.210 (0.709 to 2.064)	0.485
Grade pre CRT, Low vs. Moderate/High	1.021 (0.492 to 2.119)	0.956
ECOG [6], 0 vs. 1–2	1.174 (0.484 to 2.850)	0.722
miR-19b, High vs. Low	0.166 (0.071 to 0.390)	<0.001

[1] Response: moderate or complete pathological response; [2] Non-response: poor or minimal pathological response; [3] OR: odds ratio; [4] CI: confidence interval; [5] CRT: chemoradiotherapy; [6] ECOG: Eastern Cooperative Oncology Group.

MiR-19b expression determines outcome in locally advanced rectal cancer patients

To further assess the clinical relevance of miR-19b in locally advanced rectal cancer, we analyzed its association with patient outcomes. All 121 cases in the cohort were included in the survival analyses, as complete follow-up information was available for each patient. Remarkably, patients exhibiting low miR-19b expression experienced substantially longer overall survival compared with those displaying higher expression levels (median OS: 105 versus 75 months, p = 0.003) **(Figure 2a)**. In addition, reduced miR-19b levels were associated with significantly prolonged event-free survival, with a median EFS of 105 months compared to 73 months in the high-expression group (p = 0.023) **(Figure 2b)**.



a) b)

Figure 2. Clinical impact of miR-19b in LARC patient outcomes. Kaplan-Meier analyses for (a) overall and (b) event-free survival.

Figure 2 depicts the influence of miR-19b expression on patient survival in locally advanced rectal cancer, with Kaplan–Meier curves comparing overall survival **(Figure 2a)** and event-free survival **(Figure 2b)** between low and high miR-19b groups.

To explore prognostic factors, Cox regression analyses were carried out. In univariate models, poorer outcomes were linked to higher pathological stage (hazard ratio 3.48, 95% confidence interval 1.13–10.73; p = 0.03), the presence of positive lymph nodes (HR 3.75, 95% CI 1.44–9.73; p = 0.007), and elevated miR-19b levels (HR 0.085, 95% CI 0.011–0.656; p = 0.018). When these variables were included in a multivariate analysis, reduced miR-19b expression emerged as an independent predictor of improved overall survival, indicating a strong protective effect in patients treated with neoadjuvant CRT (HR 0.093, 95% CI 0.012–0.727; p = 0.024) **(Table 5)**.

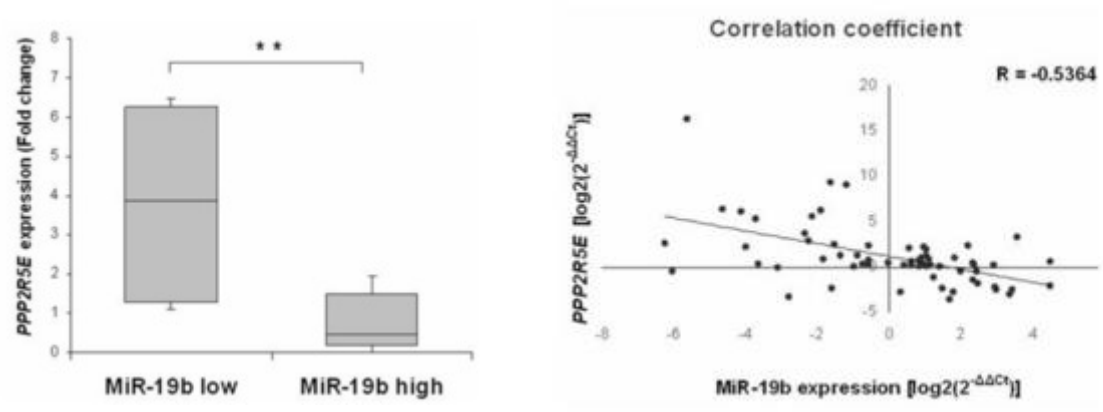
Table 5. Univariate and multivariate Cox analyses in the cohort of 121 LARC patients.

	Univariate OS [1] Analysis				**Multivariate OS Cox Analysis**			
	HR [3]	**95% CI [2]**		**p**	**HR**	**95% CI**		**p**
		Lower	**Upper**			**Lower**	**Upper**	
Gender				0.816				-
Male	1.000							
Female	0.888	0.326 to 2.418			-	-		
Age				0.225				-
<60	1.000							
≥60	2.167	0.621 to 7.564			-	-		
Pathological stage				0.030				0.490
0-I	1.000				1.000			
II-III	3.484	1.131 to 10.732			1.635	0.405 to 6.607		
ypT [4]				0.139				-
0–2	1.000							
3–4	2.120	0.783 to 5.741			-	-		
ypN [5]				0.007				0.105
N-	1.000				1.000			
N+	3.747	1.443 to 9.729			2.658	0.814 to 8.677		
ECOG [6]				0.454				-
0	1.000							
1–2	1.450	0.548 to 3.836			-	-		
MiR-19b				0.018				0.024
High	1.000				1.000			
Low	0.085	0.011 to 0.656			0.093	0.012 to 0.727		

[1] OS: overall survival; [2] CI: confidence interval; [3] HR: hazard ratio; [4] ypT: tumor size after chemoradiotherapy (CRT); [5] ypN: pathological lymph node after CRT; [6] ECOG: Eastern Cooperative Oncology Group.

Cox proportional hazards regression was also conducted for event-free survival to examine potential prognostic factors. In univariate analyses, worse outcomes were associated with advanced pathological stage (hazard ratio 3.52; 95% confidence interval 1.15–10.81; p = 0.028), positive lymph node status (HR 4.05; 95% CI 1.55–10.52; p = 0.004), and higher miR-19b expression (HR 0.26; 95% CI 0.073–0.91; p = 0.035). When these factors were entered into a multivariate model, only miR-19b expression remained statistically significant (HR 0.27; 95% CI 0.074–0.965; p = 0.044), indicating that reduced miR-19b levels independently predict longer event-free survival in this cohort.

In addition, the potential functional relevance of the miR-19b/PPP2R5E axis in LARC was investigated. PPP2R5E expression could be quantified in 63 patients with sufficient tissue available. Notably, patients exhibiting low miR-19b expression displayed significantly elevated PPP2R5E levels ($p < 0.001$) **(Figure 3a)**. Furthermore, analysis across the cohort revealed a significant inverse correlation between miR-19b and PPP2R5E expression **(Figure 3b)**, supporting a potential regulatory relationship between the two molecules in locally advanced rectal cancer.



a) b)

Figure 3. Evaluation of the miR-19b/PPP2R5E axis in LARC; (a) Box-plot showing PPP2R5E levels in LARC patients with low and high miR-19b expression; ** $p < 0.001$; (b) Scatter plot showing the negative correlation between miR-19b and PPP2R5E expression in 63 LARC patients.

As expected, high PPP2R5E and low miR-19b expression were significantly associated in our series of LARC patients ($p < 0.001$), and PPP2R5E was also able to predict response to neoadjuvant CRT ($p = 0.022$).

Current clinical management of locally advanced rectal cancer relies primarily on pre-treatment clinical parameters to guide decisions regarding neoadjuvant chemoradiotherapy. However, approximately 30% of patients do not benefit from preoperative CRT, resulting in delayed surgery and unnecessary exposure to treatment-related toxicity. Although several candidate biomarkers have been proposed to predict treatment response, none have yet been integrated into routine clinical practice. Therefore, identifying reliable predictors of both treatment response and prognosis remains an urgent challenge for optimizing patient management in LARC. In this study, we investigated the clinical significance of miR-19b and hypothesized that it could serve as a biomarker for predicting both patient outcomes and response to neoadjuvant CRT. Several lines of evidence support this hypothesis. While the role of miR-19b in rectal cancer has not been previously explored, multiple studies in colorectal cancer have linked its expression to patient prognosis, suggesting its potential relevance in LARC. Additionally, miR-19b has been reported to influence the sensitivity of colorectal cancer cells to 5-fluorouracil, the primary chemotherapeutic component of standard neoadjuvant regimens. Our previous work also indicated that inhibition of the phosphatase PP2A contributes to 5-FU resistance, with downregulation of the regulatory subunit PPP2R5E serving as a key mechanism. Interestingly, PPP2R5E has been validated as a direct target of miR-19b, pointing to a potential regulatory axis that could modulate chemotherapy sensitivity. Furthermore, prior genomic analyses demonstrated that amplification of MIR17HG, the host gene for miR-19b, correlates with poor response to neoadjuvant CRT, highlighting the clinical relevance of this miRNA in treatment resistance.

Our results showed that reduced miR-19b levels were associated with smaller post-treatment tumor size, earlier pathological stage, and a trend toward lower lymph node positivity. These observations align with prior findings in colorectal cancer, where higher miR-19b expression has been linked to lymph node involvement, distant metastasis, and recurrence. Consistently, patients with lower miR-19b expression in our cohort exhibited longer overall and event-free survival, and multivariate analyses confirmed its independent prognostic value. These findings reinforce reports from colorectal cancer studies that associate elevated miR-19b with poorer survival outcomes.

Beyond prognostic implications, our study demonstrates that miR-19b expression is a strong predictor of pathological response to neoadjuvant CRT. This observation raises the possibility that miR-19b may modulate tumor cell sensitivity to 5-FU, potentially through regulation of PPP2R5E and PP2A activity. Indeed, we observed an inverse correlation between miR-19b and PPP2R5E expression in patient samples, suggesting that higher miR-19b levels may suppress PPP2R5E, thereby influencing treatment response. Notably, PPP2R5E itself was also associated with CRT response in our cohort, supporting the clinical significance of this regulatory axis. These findings warrant further mechanistic studies to validate the role of miR-19b-mediated PP2A inhibition and to explore its therapeutic potential, particularly in light of recent reports highlighting PPP2R5E as a target for allosteric PP2A activators.

Several limitations of our study should be acknowledged. The retrospective design and the use of a single cohort of 121 patients limit the generalizability of our findings. Furthermore, potential ethnic or population-specific variations in miR-19b expression were not assessed. Validation in independent patient cohorts and evaluation in liquid biopsy samples would strengthen the evidence supporting miR-19b as a predictive biomarker. Additionally, comparing preoperative and postoperative miR-19b levels could provide insight into its role in disease progression.

Conclusion

In summary, our study demonstrates that miR-19b downregulation is a frequent event in locally advanced rectal cancer and identifies a patient subgroup with improved survival outcomes. Low miR-19b expression independently predicts longer overall and event-free survival and correlates with favorable pathological response to neoadjuvant CRT. These results highlight the potential of miR-19b as a predictive and prognostic biomarker in LARC. Future studies are required to elucidate the molecular mechanisms underlying its function, validate these findings in independent cohorts, and explore its utility in liquid biopsies to support clinical implementation.

Acknowledgments: None

Conflict of Interest: None

Financial Support: This research was funded by PI18/00382 and PI16/01468 grants from “Instituto de Salud Carlos III FEDER”. M.S-A. is supported by “Fundación Cristina Rábago de Jiménez Díaz”.

Ethics Statement: None

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