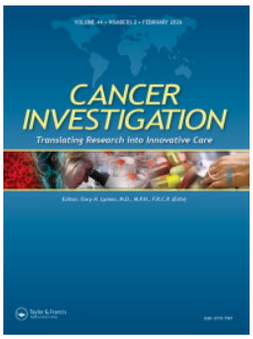

Cancer Investigation

ISSN: 0735-7907 (Print) 1532-4192 (Online) Journal homepage: www.tandfonline.com/journals/icnv20

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To cite this article: Mukremin Uysal, Sezer Saglam, İsmail Beypınar, Esra Kaytan Saglam, Elkhan Mammadov, Birol Ocak, Ozge Aybi, Rukiye Arıkan, Sefika Arzu Ergen, Pınar Gursoy, Abdullah Sakin, Vildan Kaya, Ercan Ozden, Tulay Eren, Atike Gokcen Demiray, Abdilkerim Oyman, Ali Murat Tatli, Haci Mehmet Turk, Ahmet Gulmez, Atakan Demir, Özkan Alan, Teoman Sakalar, Erdem Sen, Gokhan Ucar, Saadettin Kilickap, Ahmet Bilici, Didem Colpan Oksuz & Bulent Karabulut (2026) Long-Term Oncological Outcomes for Locally Advanced Rectal Cancer Patients with Pathological Complete Response After Neoadjuvant Chemoradiotherapy: A Turkish Oncology Group Study, Cancer Investigation, 44:2, 127-135, DOI: 10.1080/07357907.2025.2595536

To link to this article: https://doi.org/10.1080/07357907.2025.2595536

CANCER INVESTIGATION
2026, VOL. 44, NO. 2, 127–135
https://doi.org/10.1080/07357907.2025.2595536

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Long-Term Oncological Outcomes for Locally Advanced Rectal Cancer Patients with Pathological Complete Response After Neoadjuvant Chemoradiotherapy: A Turkish Oncology Group Study

Mukremin Uysal[a*], Sezer Saglam[b*], İsmail Beypınar[c], Esra Kaytan Saglam[d], Elkhan Mammadov[e], Birol Ocak[f], Ozge Aybi[g], Rukiye Arıkan[h], Sefika Arzu Ergen[i], Pınar Gursoy[j], Abdullah Sakin[k], Vildan Kaya[l], Ercan Ozden[m], Tulay Eren[n], Atike Gokcen Demiray[o], Abdilkerim Oyman[p], Ali Murat Tatli[q], Haci Mehmet Turk[r], Ahmet Gulmez[s], Atakan Demir[t], Özkan Alan[h], Teoman Sakalar[u], Erdem Sen[v], Gokhan Ucar[w], Saadettin Kilickap[g], Ahmet Bilici[e], Didem Colpan Oksuz[i] and Bulent Karabulut[j]

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ABSTRACT

The goal of this study was to look at the long-term survival outcomes and clinical characteristics of stage II/III locally advanced rectal cancer (LARC) patients who acquired pathological complete response (pCR) following neoadjuvant chemoradiotherapy (NCRT). The clinicopathological characteristics and treatment details of 277 LARC patients with pCR, relapse-free survival (RFS), overall survival (OS), and locoregional and systemic recurrence rates, were assessed. The 5-year RFS and OS rates were 85.6% and 90.9%. The rates of local and systemic recurrence were 3.6% and 7.9%. Our study confirmed the favorable results in survival in patients with LARC who achieved pCR

ARTICLE HISTORY
Received 1 April 2022
Revised 5 June 2022
Accepted 22 November 2025

KEYWORDS
Disease-free survival, Local recurrence, Local advanced rectal cancer, Neoadjuvant chemoradiation, Pathological complete response, Overall survival, Surgical outcome

Introduction

Colorectal cancer is the world's third leading cause of cancer mortality. Rectal cancer management has progressed substantially over the last several decades, and novel multimodality procedures have been created. Surgery, radiation (RT), and chemotherapy (CT) are three primary treatments that must be carefully integrated. Although combined therapy reduces locoregional recurrences, OS has not increased. Major randomized trials have revealed a higher 5-year OS rate with improved staging, better surgical technique, and the addition of RT (1–3).

Preoperative chemoradiotherapy (CRT), followed by total mesorectal excision (TME) and postoperative adjuvant CT, is increasingly being

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utilized to treat newly diagnosed locally advanced rectal cancer (LARC). This trimodal therapy was well-known for lowering the risk of local recurrence, improving surgical outcomes, providing long-term and disease-free survival (DFS), and increasing pathological complete response (pCR). The absence of tumor cells in the resected specimen and lymph nodes (ypT0N0) is linked with greater local control, OS rate, and DFS, all of which contribute to a better prognosis (4–6). The rate of patients with pCR following neoadjuvant CRT ranges from 8 to 27% (7,8).

Previous research has revealed that patients who had preoperative CRT had much lower rates of local failure and toxicity than those who received postoperative CRT (9). LARC patients who obtained pCR of primary tumor after preoperative CRT had good long-term oncological outcomes, with an OS of more than 90% and an estimated local recurrence rate of 2% (10). As a result of these findings, preoperative CRT has become the standard therapy for patients with cT3-4 and/or node-positive rectal cancer.

In a systemic review and meta-analysis of 18 studies using NCRT in rectal cancer, small tumor size, close localization to the anal border, clinical lymph node negativity, and more than 8 weeks until surgery, were concluded to be potential predictive factors for pCR (11).

Hence, the purpose of this study was to assess long-term oncological outcomes in LARC patients (cT2N+, T3-4; N0/+) who had a pCR in the surgery conducted after NCRT and to identify clinicopathological variables that may impact the survival rate.

Material & methods

Study population

The patients who were diagnosed with LARC stage II-III (cT2N+, T3-4, N0M0) and who attained a pCR after NCRT at multiple institutions were enrolled in this study. Eight non-surgical patients included this study because of whose complete response was confirmed by radiological and rectoscopic biopsy. Patients who were newly diagnosed with stage I (T1-2N0), M1 disease and without pCR with LARC stage II-III after NCRT were excluded from the study. This study was conducted retrospectively at multiple institutions using a total all of 277 LARC patients who had a pCR post-CRT and was approved by the Ethics Committee of the Afyonkarahisar University of Health Sciences Faculty of Medicine (AFSUKAEK NO: 2019/174) and was conducted following the ethical principles stated in the "Declaration of Helsinki". The informed consent was waived owing to retrospective nature of the study.

Assessments

All medical records for all LARC patients were reviewed for 12 months, and the data on patient demographics (such as age and sex), clinical tumor status, clinical nodal status, tumor localization, histology, pretreatment CEA and CA19-9 levels, histologic grade, the interval between NCRT and surgery, RT dose, chemotherapeutic agents, tumor progression, and survival rates were recorded.

The radiotherapy dose was 45–50 Gy in 25 fractions over 6 weeks for long term radiotherapy, and 25 Gy/daily/5 fractions for short term radiotherapy.

Reassessment consisted of rectoscopy and various imaging modalities according to each institution's policy. Radiological scans and rectoscopy of all patients were performed one week before surgery for reevaluation after NCRT. Clinical complete response, defined as no signs of residual tumor at reassessment with radiological and rectoscopic biopsy after neoadjuvant therapy.

Statistical analyses

A descriptive statistical analysis was performed. Descriptive data were presented as either means or median for continuous variables, while frequencies and percentages were reported for categorical variables. Relapse-free survival (RFS) and Overall survival (OS) were determined using the Kaplan–Meier method, and survival curves were compared via the log-rank test. RFS and OS were calculated in months from the start of chemoradiation to the date of relapse (RFS) and death or

the last follow-up (OS). All statistical analyses were performed using the SPSS statistical software (Statistical Package for The Social Sciences, version 22.0, SPSS Inc, Chicago, IL, USA). $p < 0.05$ was considered to indicate statistical significance.

Results

Clinicopathological and treatment characteristics

A total of 277 patient cohort comprising 163 men (58.85%) and 114 women (41.15%). The mean age of the patients was 58 (age range: 28–93) years. Table 1 summarizes the demographic, clinicopathological, and therapeutic features of LARC patients with pCR. T3 tumors and clinically positive lymph nodes were identified in 203 (76.3%) and 194 (72.4%) of the patients, respectively. In 39.6% of tumors, the distance to the anal verge was ≤5 cm. Only 77 patients (39.1%) achieved a radiologically complete response following NCRT, according to radiological response and rectoscopic assessment. The specificity of radiological imaging in predicting the pathological complete response after neoadjuvant CRT was 28%. Overall, 202 patients (93.1%) received long-course RT as part of NCRT, whereas 202 patients (75.1%) received concurrent capecitabine and 61 patients (22.7%) received 5-FU. The vast majority of patients (n = 215) (78.5%) did not receive CT between chemoradiation and surgery. The median duration between finishing NCRT and undergoing surgery was 10.3 weeks (range: 2–72 weeks) (Figure 1). The most frequent surgical method done in 207 patients (75.5%) was low anterior resection, with a median number of lymph nodes removed of 12 (range: 1–52). Eight patients (%2.9), whose complete response was confirmed by radiological and rectoscopic biopsy, did not undergo surgery because they refused surgery. In 182 patients, adjuvant CT was delivered (67.7%).

Table 1. Demographic, clinicopathological, and treatment characteristics of patients with pCR (n = 277).

Demographics			
Age (year), median (range)	58 (28–93)		
		n	%
Gender	Female	114	41.2
	Male	163	58.8
Clinicopathological characteristics			
Clinical T stage	2	32	12.0
	3	203	76.3
	4	31	11.7
Clinical node stage	Negative	74	27.6
	Positive	194	72.4
Grade	Well	55	20.0
	Moderate	101	37.1
	Poor	18	6.6
	Unknown	98	36.0
Distance to anal canal	≤5cm	109	39.6
	6–10	130	47.3
	≥11	30	10.9
	Undetermined	6	2.2
Treatment characteristics			
Receiving chemotherapy before NCRT	Yes (FOLFOX)	9	3.4
	No	258	96.6
Type of radiotherapy	Short-course	15	6.9
	Long-course	202	93.1
Concurrent chemotherapy	Capecitabine	202	75.1
	5-FU	61	22.7
	None	6	2.2
Chemotherapy between NCRT and surgery	No	215	78.5
	Yes	59	21.5
Preop clinical imaging	MRI	153	61.2
	CT	41	16.4
	PET-CT	2	0.8
	None	54	21.6
Clinical response for NCRT	Complete response	77	39.1
	Partial response	114	57.9
	Stable disease	5	2.5
	Progressive disease	1	0.5
Type of surgery	None*	8	2.9
	LAR	207	75.5
	APR	59	21.1
Number of lymph nodes harvested, median (range)		12 (1–52)	
Adjuvant chemotherapy	No	87	32.3
	Yes	182	67.7
Type of adjuvant chemotherapy	Capecitabine	72	39.6
	CAPOX	82	45.0
	FOLFOX	14	7.7
	FUFA	14	7.7

CRT: Chemoradiation; CT: Chemotherapy; RT: Radiotherapy; XELOX: Oxaliplatin and capecitabine; FOLFOX: Oxaliplatin and infusion 5-FU; FUFA: 5-Fluorouracil and Folinic Acid; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; PET-CT: Positron Emission Tomography–Computed Tomography; LAR: Low Anterior Resection Surgery; APR: Abdominoperineal Resection Surgery.
*Eight non-surgical patients included this study because of whose complete response was confirmed by radiological and rectoscopic biopsy.

Oncological outcomes

The incidences of locoregional and systemic recurrence were 3.6 and 7.9%, respectively. The median relapse-free survival (RFS) and OS were not attained after a median follow-up of 42 months (range: 5–144 mo). The RFS rates after three and five years were 89.3% and 85.6%, respectively. The 3-year and 5-year OS rates were 95.0 and 90.9%, respectively (Figure 2, Table 2). Albeit median survival times were not reached, OS rate was significantly higher in patients without vs. with recurrence ($p < 0.001$), and there was no significant difference between local and distant recurrence ($p = 0.74$) (Table 3).

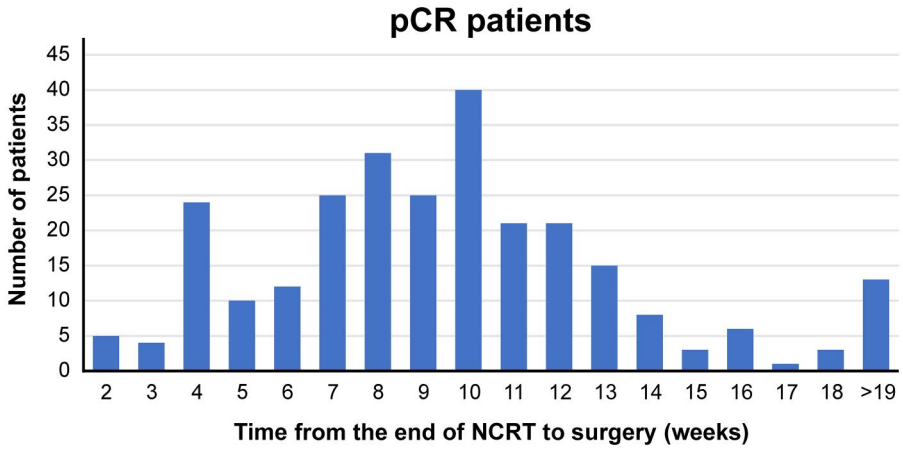

Figure 1. The interval between NCRT and Surgery (median: 10.3 weeks; range: 2–72 weeks).

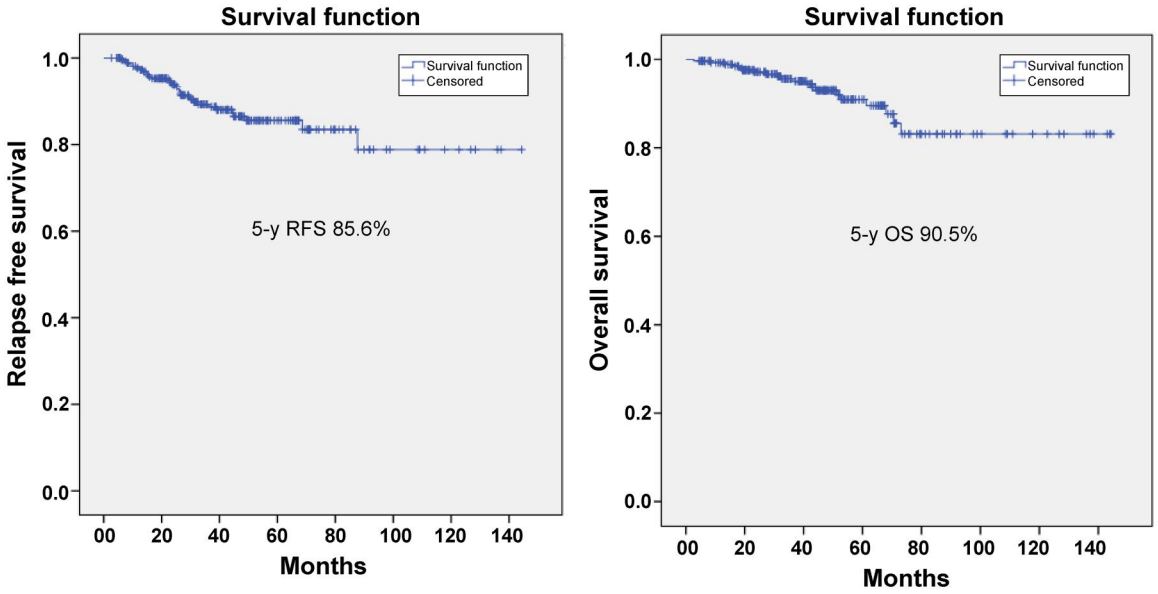

Figure 2. The survival plots for RFS and OS.

Table 2. Oncological outcomes of the study subjects.

Recurrence	n(%)
Total	32(11.5)
Local	10(3.6)
Distant	22(7.9)
Missing	11
Survival	%
Time to relapse (months)	NR
3-year RFS rate (%)	89.3
5-year RFS rate (%)	85.6
Overall survival (months)	NR
3-year OS rate (%)	95.0
5-year OS rate (%)	90.9

RFS: Relapse free survival, OS: Overall survival.

The difference in time from NCRT to surgery (≥8 vs. <8 weeks) did not affect 3- (98.7% vs. 90.4%) or 5-year (92.6% vs. 87.5%) OS rates (p = 0,801, Figure 3, Table 3). Furthermore, extending the time between NCRT and surgery for 12 weeks did not affect survival, with 5-year OS rates of 96.0% and 89.6% in patients operated before and after 12 weeks of CRT (p = 0.83), respectively.

Recurrence occurred in only 2 of 8 patients who did not have surgery (one of them was local and the other was distant organ recurrence). One of the relapsed patients died, the other is still alive.

Clinicopathological variables and their impact on 5-year RFS rates

The number of lymph nodes extracted, the use of adjuvant CT or CT between NCRT-surgery, the distance to the anal verge and CEA and CA-19-9 levels did not affect 5-year RFS rates. There was no statistical difference between those who

Table 3. The 3- and 5-year OS rates according to the recurrence status and time from CRT to surgery.

		3-year OS rate (%)	5-year OS rate (%)	p value
Recurrence	None	97.4	96.6	<0.001
	Local	80.0	68.6	p = 0.74
	Distant	85.7	56.7	
Interval between CRT and surgery	≥8 weeks (n = 173)	98.7	92.6	0.108
	<8 weeks (n = 96)	90.4	87.5	

OS: Overall survival; CRT: Chemoradiotherapy.

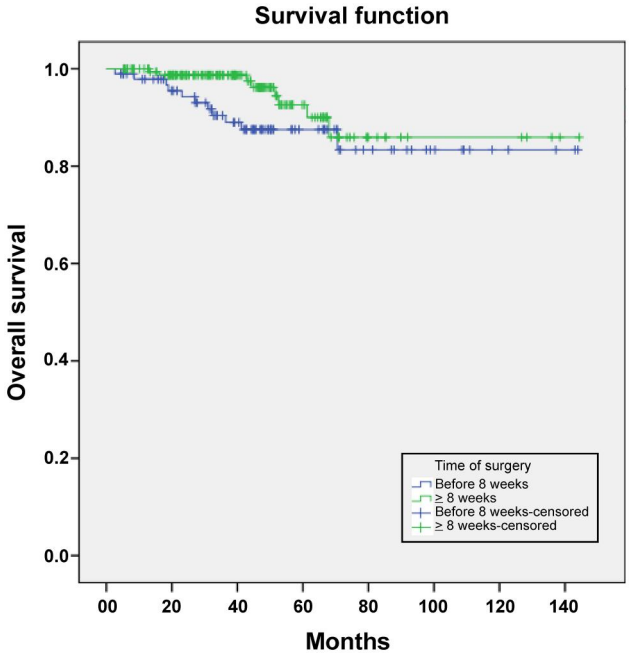

Figure 3. The Kaplan–Meier curves for OS according to the time of surgery.

received adjuvant chemotherapy and those who did not (Table 4).

Discussion

Our findings indicated good oncological outcomes with a 5-year OS rate of 90.9%, making this one of the largest scale trials in LARC patients with pCR. Given the significantly lower survival rates (60%–70%) observed in patients with non-pCR, these findings imply that pCR is the intended end-result in NCRT and support the idea of raising pCR rate as the major aim of LARC treatment (12). Furthermore, our findings are consistent with those of Maas et al. who found that the 5-year RFS (83.3%) and 5-year OS (87.6%) rates in LARC patients (Stage I–III) with pCR after NACRT significantly higher after a median of 48 months of follow-up (range: 0–277 months) (5). The authors also mentioned that the 5-year risk of local recurrence was 2.8% in the pCR group and 9.7% in the no-pCR group, with an unadjusted HR of 0.33 ($p < 0.001$). In contrast to Maas et al study, only stage II and III LARC patients were enrolled in our study, and the local recurrence rate was 3.6%, which is higher than the one reported by Maas et al., possibly due to the inclusion of only stage II and III patients and higher clinical T4 (9% vs 11.7%) and clinical node positivity (59% vs 72.4%) rates in our study population (5).

The impact of local recurrence or distant metastases on LARC patients' post-NCRT survival with pCR is unclear. The Istanbul R-01 trial was the first to show that patients with local recurrence following NCRT had a considerably lower survival rate than those with metastatic disease (37.7% vs. 80.3%, respectively) (13). Although patients with local recurrence had a slightly better 5-year survival rate than those with distant metastases in our research, there was no statistically significant difference between the two groups (68.61% vs. 56.7%, $p = 0.74$). This appears to be connected to the fact that all of our LARC patients had pCR, highlighting the importance of pCR in OS.

Previous research has yielded inconclusive findings on the best timing for surgery following NCRT to enhance pCR. Prolonging the period before surgery is thought to enhance tumor regression and pCR rates while decreasing perioperative problems and surgical morbidity (14–19). The major reason for delaying CRT and surgery is the delayed lysis of tumor cells following acute DNA damage with NCRT because tumor cells remain morphologically intact immediately after RT (20). The Lyon Trial R90-01 is the first prospective study to compare short (2 weeks) and long (6–8 weeks) intervals after NCRT and finds that the long-interval group has significantly better clinical tumor response (53.1% vs. 71.7%) and pathologic downstaging (10.3% vs. 26%), but no significant difference in terms of

Table 4. Clinicopathological features and their impact on 5-year RFS rates.

Variables		N	5-year RFS rate (%)	p value
Clinical lymph nodes				0.58
	Node negative	74	88.7	
Number of lymph nodes harvested	Less than 12	118	83.6	0.37
	12 and more	118	88.1	
Adjuvant chemotherapy	Yes	182	84.7	0.25
	No	86	88.7	
Oxaliplatin-based adjuvant chemotherapy	Yes	96	79.2	0.26
	No	86	89.1	
Chemotherapy between CRT-surgery	Yes	59	85.0	0.84
	No	213	85.7	
Distance to anal verge	≤5cm	109	84.6	0.82
	6–10	129	90.0	
	≥11	30	83.6	
CA19-9	Normal <36	183	87.1	0.61
	High ≥36	12	79.5	
CEA	Normal < 7	144	91.2	0.35
	High ≥ 7	46	73.2	

local relapse (15). Although Akgün et al. did not disclose any data on long-term local recurrence and OS findings, they did show a substantial rise in disease regression and pCR rate with an extension of the time between NCRT and surgery (14). The authors discovered that LC-CRT fails to produce the benefits previously observed in NCRT trials in the Istanbul R-01 and Greccar 06 investigations (13,21). Dhadda et al. demonstrated that pCR after NCRT can be extended up to the 20th week (22). Our findings suggested that the pCR can be extended between the 6th and 12th weeks.

The predictive effect of imaging on pathological complete response is controversial. The MRI and other radiological scans were not successful in predicting pCR, indicating its relationship with poor sensitivity (range: 39%–82%) and a 22% success rate reported in other investigations (23–25). In our study, pCR was determined to be 39.2% on radiological imaging after NCRT. This indicates that the specificity is 28%.

The utility of adjuvant CT in these patients is still controversial; it has not been specifically addressed for the LARC group with pCR (26). Two retrospective clinical studies have found that adjuvant CT improves survival in patients with pCR (27,28). According to Morris et al., adjuvant CT, used in 32% of patients, was linked with an increased 5-year survival rate ($p < 0.01$) (27). Furthermore, 50% with pCR were given adjuvant therapy in a research done by the Turkish Society for Radiation Oncology Group (TROD) (29). The rate of adjuvant CT in our research was considerably greater (66.8%) than that reported in the literature. Despite this, there was no statistically significant difference in survival between those who received and those who did not get oxaliplatin-based therapy, according to our findings.

The pCR was considered to be an independent predictor of survival (30). As a result, the primary focus of rectal cancer research in the next years should be on identifying robust biomarkers that predict pCR and increasing its rate. Currently, existing indicators for predicting complete clinical or pCR response are insufficient. Recent research has shown favorable outcomes for circulating tumor cell (ctDNA) serial tracking, as well as NCRT or a predictive genotype signature for pCR in predicting pCR (31,32). Furthermore, total neoadjuvant therapy (TNT) is increasingly being utilized to enhance the rate of complete response, with studies showing that TNT can raise pCR rates by up to 30%–40% (33,34). Furthermore, Zhu et al. observed that adding weekly irinotecan to CRT increases the pCR rate by 15% compared to the single capecitabine arm (15% in the control and 30% in the experimental groups; risk ratio, 1.96; 95% CI, 1.30 to 2.97; $p < 0.001$) (35).

There are numerous limitations to our study. The primary drawback of this study is that it is retrospective. Despite the large number of patients included in the research, only pCR patients were included, therefore no comparison with non-pCR patients could be performed. Furthermore, as a consequence of the favorable prognosis of pCR patients, the median survival

durations were insufficient to provide convincing data about the survival rate in LARC patients with pCR following NCRT. Finally, our data corroborated the excellent prognosis of LARC patients who achieved pCR following NCRT, underlining the importance of LC-CRT in increasing pCR in LARC malignancies. The higher survival rates were consistent with previous research. In this situation, the main aspects of future research should be discovering novel therapeutic techniques to enhance the pCR rate in LARC patients, as well as potential markers that will predict pCR.

Acknowledgements

Uysal M., Saglam S., Beypinar I., and Karabulut B were involved in the conception and design of the study. All authors were involved in acquisition, analysis and interpretation of data. All authors have read and approved the final manuscript.

Disclosure statement

The authors report there are no competing interests to declare.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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