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ORIGINAL ARTICLE

Evaluation of Hematological/Pathological Prognostic Factors and Oncological Outcomes of Patients with Locally Advanced Rectal Cancer Treated with Neoadjuvant Radiotherapy

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OBJECTIVE

In this study, we aimed to present our results of overall survival (OS), progression-free survival (PFS) and local control (LC) in approximately five years of follow-up of the patients with locally advanced rectal cancer who underwent neoadjuvant radiotherapy (RT) and to investigate both the pathological and hematological parameters that affect the survival.

METHODS

A total of 76 patients with a pathologic diagnosis of rectum adenocarcinoma and clinical stage I- IVA who underwent neoadjuvant RT between August 2014 and March 2019 were evaluated retrospectively in this study. Eighty-five percent of the patients received 45/50 Gy doses of RT concomitantly with oral capecitabine. Fifty-eight patients (78.4%) underwent surgery. The median time between the completion of RT and surgery was 65 days.

RESULTS

The median follow-up was 25 months. The 2-year OS, PFS and LC rates were 85%, 83.7% and 85.2%, respectively. Positive radial surgical margin was a significant prognostic factor for OS and PFS, but not for LC. The factor affecting OS, PFS and LC was adverse tumor histology (undifferentiated). The prolongation of the time from completion of RT to surgery caused OS and LC to deteriorate. Local control significantly decreased in patients without concomitant chemotherapy. Among all the hematological parameters (e.g. albumin, WBC, platelet, neutrophil, CA 19-9), only pre RT Hb levels significantly correlated with OS but not with PFS. CEA's response to neoadjuvant treatment (NAT) significantly increased OS and PFS.

CONCLUSION

Adverse tumor histology, the prolonged time from completion of RT to surgery, CEA's response to NAT and pre RT Hb levels were essential factors that affect survival.

Keywords: Hematologic factors; neoadjuvant radiotherapy; outcome; prognostic factors; rectal cancer.

Introduction

Colorectal cancer is a significant health problem nowadays, and approximately 1 million patients worldwide are diagnosed with colorectal cancer every year.[1] A decrease in mortality due to advances in surgical techniques and the use of combined adjuvant therapies is noteworthy.[2] Surgery is the main treatment for rec-

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tal cancer, especially with the implementation of total mesorectal excision (TME); local control and survival were increased.[3,4] Systemic metastasis is an important problem in rectal cancer, as well as local recurrence. Therefore, adjuvant therapies are needed. While radiotherapy (RT) was implemented postoperatively in the previous decades, after the 2000s, the CAO/ARO/A10-94 study of the German Rectal Cancer Group demonstrated the superiority of preoperative RT.[5] Compared to postoperative treatment, preoperative chemoradiotherapy (CRT) has shown significant regression in tumor stage ("downstaging"), increased local control, less acute-late toxicity, and increased sphincter preservation rates in distal tumors. However, there was no difference in overall survival (OS) between both randomization arms. The German study, after its publication, was widely accepted all over the world and preoperative CRT replaced postoperative CRT in patients with locally advanced rectal cancer (LARC). Two large randomized trials have shown an increase in pathological complete response (pCR) and local control rates by adding concomitant chemotherapy (CT) to preoperative RT.[6,7]

Currently, the standard treatment of LARC is fluoropyrimidine-based concomitant neoadjuvant chemoradiotherapy (CRT) and surgery with total mesorectal excision.[8,9] Preoperative radiotherapy (RT) has been exhibited to be linked with better accordance and lower risk of complications than postoperative RT.[10] Neoadjuvant CRT enhances local control, allows downstaging, tumour regression and sphincter protection. Many large studies have demonstrated parameters, such as yp T/N, pCR, tumor-regression grading (TRG), as prognostic factors.[11-14]

In this study, we aimed to present our results of overall survival (OS), progression-free survival (PFS), local control in approximately five years of follow-up of patients with LARC who underwent neoadjuvant RT and to determine the pathological parameters affecting survival. Our secondary aim was to establish the relationship between hematologic parameters (albumin, WBC, hemoglobin, platelet, neutrophil, CA 19-9, CEA) with OS and PFS before and after RT.

Materials and Methods

A total of 76 patients with a pathologic diagnosis of rectum adenocarcinoma and clinical stage I- IVA who underwent neoadjuvant RT between August 2014 and March 2019 at the Radiation Oncology Clinic of Gaziosmanpaşa University Faculty of Medicine were evaluated in this study retrospectively.

Pelvic MRI, colonoscopy and 18F-FDG PET CT were performed for evaluation of the clinical stage before the neoadjuvant treatment decision. After neoadjuvant treatment, re-evaluation MRI and colonoscopy were carried out before surgery. Eighty-five percent of the patients received 45/50 Gy doses of radiotherapy concomitantly with oral capecitabine. The treatment details of the patients are summarized in Table 1.

The diagnosis date was accepted as the initial date for the OS and PFS. The final check-in date for the OS is the last control date for patients experiencing and the date of exitus for dying patients, for PFS is the first event date for patients with recurrence and distant metastasis and the last control date for patients without recurrence. Patients with incomplete file information received palliative treatment and postoperative adjuvant RT were excluded from this study.

Statistical Analysis

SPSS version 20 was used in the calculation of statistical data. Descriptive statistics for continuous (quantitative) variables were expressed as "mean", "standard deviation", "minimum-maximum and median" values, while categorical variables are expressed as number (n) and ratio (%). Nonparametric tests were used. The categorical demographic characteristics of the patients were computed using Chi-square and Fisher's exact test. Kaplan Meier was used for univariate survey analysis and the log-rank test was used for comparison. In multivariate analyses, a cox regression test was used. Spearman's rank correlation test was used for univariate correlation analysis. Statistically, the significant limit was accepted as less than 0.05.

Results

The data of 76 patients who underwent neoadjuvant CRT for curative purposes in our hospital were evaluated retrospectively. The median follow-up was 25 months (range, 3-57 months). While 58 patients (78.4%) underwent surgery, 16 patients (21.6%) did not undergo surgery for various reasons (e.g., patient rejection, decompensated comorbid disease, age, medically inoperable). The median time between completion of RT and surgery was 65 days (range, 10-389 days). Three patients had a complete pathological response to neoadjuvant therapy (NAT). A total of 13 patients died, nine patients had a local recurrence, and 30 had distant metastasis (10 patients initially M1a). Although 25 patients (33%) were located in the lower rectum, there were 11 patients who underwent APR. Sphinc-

Table 1 Patient characteristics and treatment details

Age	
Median (Range)	64 (42-86)
Gender	
Female	27 (35.5%)
Male	49 (64.5%)
Seconder malignancy	
No	70 (92.1%)
Yes	6 (7.9%)
Performans status	
Ecog 0	19 (25%)
Ecog 1	46 (60.5%)
Ecog 2	10 (13.2%)
Ecog 3	1 (1.3%)
Tumor localization	
Upper	26 (34.2%)
Medium	23 (30.3%)
Lower	25 (32.9%)
Rectosigmoidal	1 (1.3%)
Transrectal	1 (1.3%)
Anal sphincter involvement	
Yes	2 (2.6%)
No	74 (97.4%)
Inguinal LN involvement	
Yes	1 (1.3%)
No	75 (98.7%)
RT technique	
IMRT	73 (95.5%)
3D-conformal	3 (4.5%)
RT boost application	
Sequential	3 (4.5%)
SIB	73 (95.5%)
RT doses	
25 Gy (5X5 Gy)	5 (6.6%)
45 Gy/50 Gy	65 (85.5%)
45 Gy/50.4 Gy	2 (2.6%)
45 Gy/54 Gy	3 (3.9%)
41.4 Gy/46 Gy	1 (1.3%)
Pre-Treatment clinical stage	
Stage II	6 (7.9%)
Stage III	60 (78.9%)
Stage IVa	10 (13.2%)
Post-Treatment clinical stage	
cCR	3 (4.1%)
Stage 1	10 (13.5%)
Stage II	31 (41.9%)
Stage III	30 (40.5%)
Pathological Stage	
pCR	3 (5.6%)
Stage 1	11 (20.4%)
Stage II	20 (37%)
Stage III	18 (33.3%)
Stage IVa	2 (3.7%)
Metastas status	
Mo	66 (86.8%)
M1a	10 (13.2%)
Concomitant CT	
Oral capecitabine	64 (84.2%)
Infusional 5FU	4 (5.3%)
Bolus FUFA	1 (1.3%)
No implemented	7 (9.2%)
Surgery status	
Yes	60 (78.4%)
No	16 (22.6%)
Operation type	
LAR	46 (78.9%)
APR	11 (17.5%)
Total colectomy	1 (1.8%)
Pelvic excentration	1 (1.8%)
Pathological differentiation	
Good	15 (27.8%)
Moderately	37 (68.5%)
Poor	2 (3.7%)
LVI	
Yes	7 (12.3%)
No	50 (87.7%)
PNI	
Yes	11 (19.3%)
No	46 (80.7%)
ECE	
Yes	3 (5.3%)
No	54 (94.7%)
Radial surgical margin	
Negative	51 (89.5%)
Positive	6 (10.5%)
Adjuvant CT	
Yes	46 (63%)
No	27 (37%)

IMRT: Intensity modulated radiotherapy; SIB: Simultaneous integrated boost; cCR: Clinical complete response; pCR: Pathological complete response; LAR: Low anterior resection; APR: Abdominopelvic resection; CT: Chemotherapy, LVI: Lymphovascular invasion; PNI: Perineural invasion; ECE: Extracapsular expansion

ter protection was achieved in 56% of the patients with the lower rectum. The radial surgical margin was positive in six patients. Because of postoperative complications or patient incompatibility, 37% of the patients could not receive adjuvant CT. The demographic data and treatment details of the patients are summarized in Table 1.

Parameters Affecting Overall Survival

The median OS was 26 months (range, 3-57 months). The 2-year OS rate was 84.7%. When the factors af-

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fecting OS are evaluated, no significant relationship was found with the following factors: age (p=0.25), gender (p=0.84), family history (p=0.13), tumor localization (p=0.67), anal sphincter involvement (p=0.54), inguinal lymph node (LN) involvement (p=0.54), clinical stage before NAT (p=0.84), clinical stage after NAT (p=0.33), pathological stage (p=0.12), RT dose escalation above 50.4 Gy (total dose 50.4 Gy vs 54 Gy) (p=0.49), sequential interstitial boost (SIB) or sequential boost technique (p=0.72), RT technique (IMRT vs 3D) (p=0.70), concomitant CT status (p=0.27), lymphovascular invasion (LVI) status (p=0.94), presence of extracapsular extension (ECE) (p=0.50), tumor size in pre-treatment colonoscopy (p=0.70) and tumor size in post-treatment colonoscopy (p=0.90). On the other hand, poorly differentiated tumor (p<0.001), perineural invasion (PNI) positivity (p=0.032), radial surgical margin positivity (p=0.034), no response to PET CT after NAT (p=0.011), no adjuvant CT (p=0.002) significantly reduces OS (Fig. 1).

There is a weak but significant negative correlation between the time from completion of RT to surgery and OS (CC (r):-327). OS decreased significantly with prolonged the time from completion of RT to surgery (p=0.014). When the time between completion of RT and surgery was grouped as less than 60 days and 60 days or more; the median OS was 33 months (range, 7.2-50.6 months) and 24 months (range 5-74 months) in patients whose interval time was fewer than 60 days and 60 days or more, respectively. The patients whose interval time was fewer than 60 days had higher OS, but the difference was not significant (p=0.54). This difference may become significant when the follow-up time is prolonged.

Among all the hematological parameters, only pre-RT hemoglobin level (p=0.050) and CEA response to NAT (p=0.049) were significantly correlated with OS. Median OS was 33 months (range, 7-57 months) and 18 months (range, 2-51 months) in the patient with a CEA response to NAT and no response, respectively.

Parameters Affecting Progression-Free Survival

The median PFS was 19 months (range, 1.2-57.4 months). The 2-year overall (systemic+local) control rate was 56.4%. The 2-year local PFS was 83.7%. When the factors affecting PFS were evaluated, no significant relationship was found with the following factors: age (p=0.41), gender (p=0.23), family history (p=0.41), tumor localization (p=0.50), anal sphincter involvement (p=0.73), inguinal LN involvement (p=0.35), sequen-

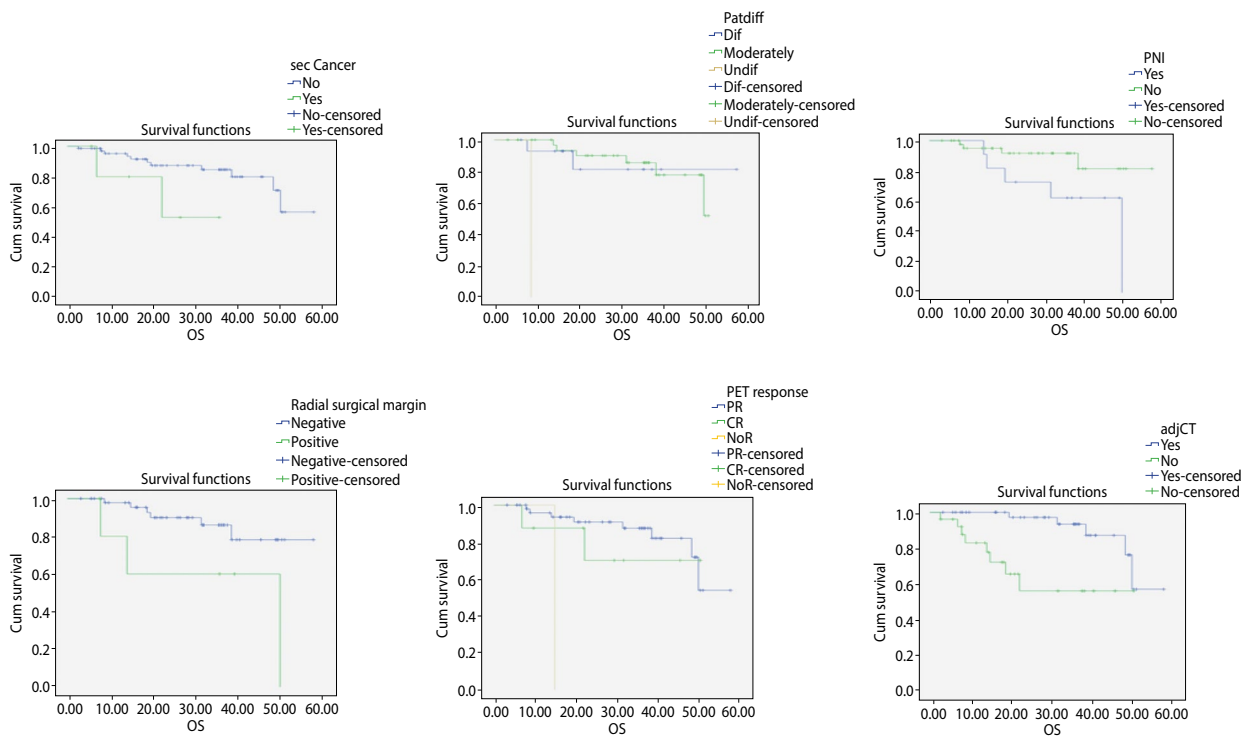

Fig. 1. Parameters that significantly affect OS.

tial interstitial boost (SIB) or sequential boost technique (p=0.48), RT technique (IMRT vs 3D) (p=0.46), concomitant CT status (p=0.11), LVI status (p=0.11), presence of ECE (p=0.077), tumor size in pre-treatment colonoscopy (p=0.53), tumor size in post-treatment colonoscopy (p=0.94), no response to PET CT after NAT (p=0.24), PNI positivity (p=0.065), clinical stage after NAT (p=0.066) and surgery status (p=0.82).

Conversely, poorly differentiated tumor (p<0.001), the clinical stage before NAT (p=0.028), radial surgical margin positivity (p=0.034) and pathological stage (p<0.001) were significantly associated with PFS (Fig. 2).

Among the hematological parameters, only pre/post-RT CEA levels were significantly negatively correlated with PFS. When the relationship between CEA response to NAT and PFS was examined, median PFS was 23.1 months (range, 2-57 months) and 14 months (range, 2-50 months) in the patient with CEA response and no response, respectively (p=0.025).

Parameters Affecting Local Control

The 2-year local control (LC) rate was 85.3%. When the factors affecting LC were evaluated, no significant relationship was found with the following factors: age (p=0.38), gender (p=0.78), family history (p=0.072), tumor localization (p=0.16), anal sphincter involvement (p=0.95), inguinal LN involvement (p=0.87), LVI status (p=0.87), PNI positivity (p=0.73), presence of ECE

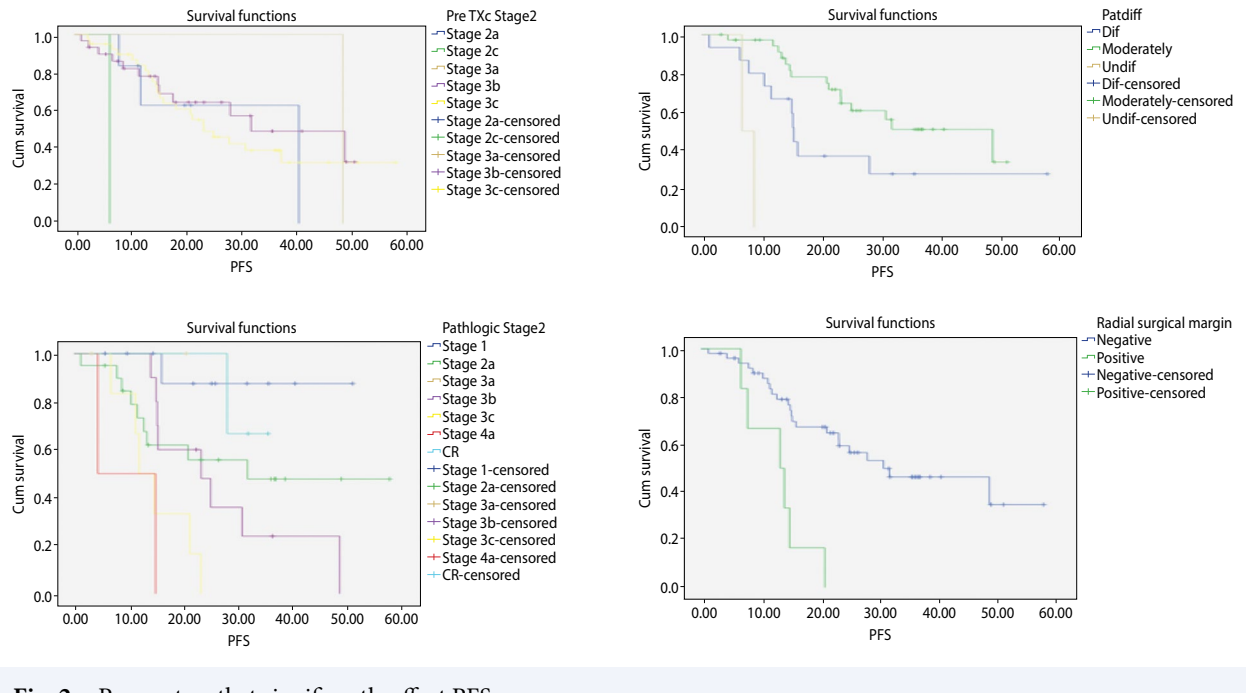

Fig. 2. Parameters that significantly affect PFS.

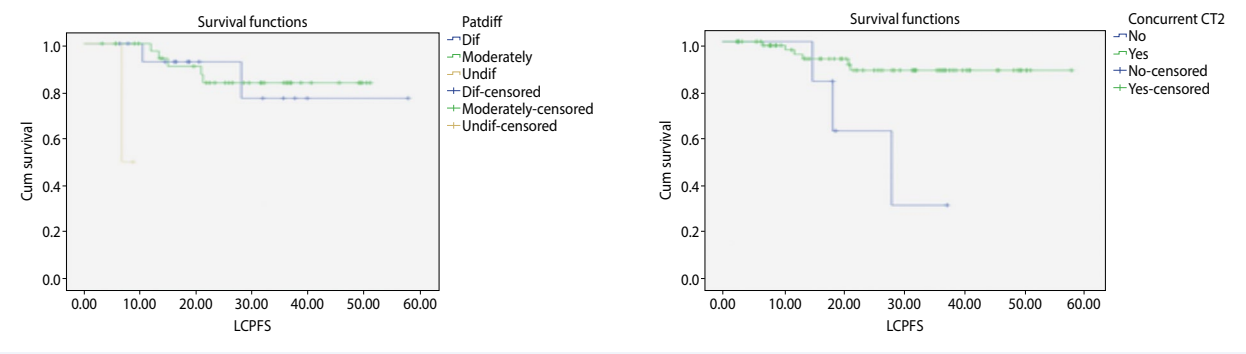

Fig. 3. Parameters that significantly affect LC.

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(p=0.85), tumor size in pre-treatment colonoscopy (p=0.74), tumor size in post-treatment colonoscopy (p=0.85), sequential interstitial boost (SIB) or sequential boost technique (p=0.65), RT technique (IMRT vs 3D) (p=0.75), adjuvant CT status (p=0.18), clinical stage before NAT (p=0.23) and clinical stage after NAT (p=0.31), pathological stage (p<0.078).

Undifferentiated histology (p<0.001), no concomitant CT (p=0.007), and prolonged the time between completion of RT and surgery (p=0.038) significantly reduced local control (Fig. 3).

Discussion

In this study, we retrospectively examined 76 patients who underwent neoadjuvant RT from a single center. The 2-year OS, PFS and LC rates were 85%, 83.7%, 85.2%, respectively. Positive radial surgical margin was a significant prognostic factor for OS and PFS, but not for LC. The factor affecting OS, PFS, LC was adverse tumor histology (undifferentiated). The prolongation of the time from completion of RT to surgery caused OS and LC to deteriorate. yp T/N stage affected PFS, no adjuvant CT and no PET CT response to NAT adversely affected OS. Local control significantly decreased in patients without concomitant CT. Among all the hematological parameters (e.g. albumin, WBC, platelet, neutrophil, CA 19-9), only pre RT Hb levels significantly correlated with OS but not with PFS. CEA response to NAT significantly increased OS and PFS.

Neoadjuvant standard long course-RT (LC-RT), a total dose of 50 Gy, is administered with concurrent CT and is more commonly preferred in the USA and European countries. Short-term RT (SC-RT) is administered at 5x5 Gy doses, more commonly used in Sweden, Netherlands, Poland and the UK without concurrent CT in patients with moderate risk for local recurrence. Short-term RT was preferred concerning less postoperative complications due to the ability to perform surgery one week after RT.[15] In a recently published Stockholm III randomized non-inferiority study, 840 LIRC patients randomized to SC-RT–surgery (a week after RT) (n=318), SC-RT and delay surgery (4-8 weeks after RT) (n=285), LC-RT and delay surgery (4-8 weeks after RT) (n=94) arms. At a minimum 2-year follow-up, SC-RT- delay surgery was found to be safe oncologically with a low postoperative complication ratio.[16] In the long-term, 5-year follow-up of this study, the tumor stage after NAT was significantly lower, so the best treatment response in the SCRT-delay surgery arm. pCR was seen in one (0.3%), 29 (10.4%), two (2.2%) patients in SC-RT (surgery after a week), SC-RT-delay surgery, LCRT-delay surgery groups, respectively. pCR and Dworak grade 4 were interrelated with superior survival. As a result of the Stockholm III study, SC-RT achieved pCR in 10% of patients with delayed surgery after 4-8 weeks. Consequently, survival (OS) and time to recurrence (TTR) improved in the SC-RT delay surgery arm.[17] In the aforementioned study, pCR was 2.2% in the LC-RT-delay surgery arm. In our study, the pCR rate also was 3.9%.

Outcomes of delay surgery after SC-RT were demonstrated in a randomized controlled trial.[16] However, the time of surgery after LC-RT is still controversial. Prolonged surgery (over eight weeks) after LC-RT increases the possibility of complete response, unfortunately, increases the likelihood of postoperative complications and positive resection margin.[18-20] The ESMO guideline recommends surgery within 4-12 weeks after LC-RT and 7-10 days after SC-RT.[21] Is it possible to maximize downstaging and thereby increase sphincter protection rates by extending the waiting period until surgery? In a Dutch study of 1593 patients with LARC, the findings showed that pCR rates gradually increased as the interval between RT-surgery prolonged and reached the maximum level after 10-11 weeks from completion of RT.[22] Similar results are demonstrated in the "American National Cancer" database (n=17255). It was illustrated that there was a statistically significant difference in pCR rates when the time from completion of RT to surgery was fewer than six weeks and more than eight weeks. The pathological complete response peaked 10-11 weeks after completion of RT.[23] A recent prospective randomized study investigated the effect of prolonged RT-surgery interval on cCR and surgical morbidity. Patients with LARC were randomized into two groups as follows: surgery 6 and 12 weeks after RT completion. cCR and surgical morbidity were compared. Longer interval time did not increase cCR and even more surgical morbidity was reported. [24] Longer intervals after RT may amplify pCR rates, but the prolongation of the time to surgery leads to the lateness in the use of postoperative adjuvant CT, which may increase the risk of systemic metastasis and elevate cell repopulation. In the present study, as the time from neoadjuvant CRT to surgery was elongated, OS and local control were significantly impaired. When the time between completion of RT and surgery is grouped as less than 60 days and 60 days or more; the median OS was 33 months (range, 7.2-50.6 months) and 24 months (range, 5-74 months) in patients whose interval time is less than 60 days and 60 days or more, respectively.

Banwell VC et al.[25] reported a study in well-selected patients with stage I-III rectal cancer, which aimed to demonstrate similar oncologic outcomes with surgery alone without neoadjuvant therapy. LC-RT (n=91) was administered concurrently with capecitabine to the highest risk group of patients for local recurrence (cT4, N2, clinical fixity, extra-mesenteric nodal disease), while in the patients with the moderate risk for local recurrence (T3, suspected mesorectal lymph node or intramesenteric extramural vascular invasion) SC-RT (n=90) (5x5 Gy) was applied. Finally, only surgery (n=240) was performed to cT1-T3a and cN0 disease. The 5-year local recurrence was 10.8%, 3.3%, and 18.7% in the surgery alone, SC-RT and LC-RT groups, respectively. Distant metastasis (DM) was highest in the SC-RT group (13.8% surgery alone, 25.6% SC-RT, 15.4% LC-RT). The risk of local recurrence was low in patients selected for SC-RT, although distant metastasis most developed in this patient group. In multivariate analysis, the most powerful predictive factor affecting all parameters, such as OS, PFS, DM local recurrence, is adverse tumor biology. Positive circumferential radial margin (CRM) is an independent predictor for DM, OS and PFS, while not for local recurrence.[25] As in the aforementioned study, in our study, the positive radial margin was the factor affecting OS and PFS, but not for local recurrence too. Similarly, in the CR07 trial, a positive CRM was not independently predictive of local recurrence.[26]

Kim M et al.[27] presented 14-year oncologic outcomes of 580 LARC patients who underwent neoadjuvant CRT followed by TME in a single center. A total of 111 patients (23.7%) achieved pCR, while the other 469 patients demonstrated residual disease. However, the pretreatment CEA level and cT (clinical T) stage were less in patients with pCR than the patients with residual disease. Pathologic stage after CRT was the most statistically significant independent predictor of OS (HR, 6.97 [95% confidence interval, 3.16–15.39] for stage III vs. stage 0) and DFS (HR, 7.30 [95% confidence interval, 3.63–14.67] for stage III vs. stage 0).[27] Similarly, in the present study, we demonstrated that the pathological T stage affects PFS.

Baqar et al.[28] investigated the prognostic value of preoperative CEA levels for 5-year OS and disease-free survival (DFS) in 623 patients with rectal cancer. As a result, the 5-year OS and DFS rates were 85% and 86% for patients with low CEA levels, 73% and 79% for patients with high CEA levels, respectively.[28] Franco et al.[29] assessed the prognostic role of hemoglobin levels in 161 patients with anal cancer who underwent CRT. In multivariate analysis, pre-treatment Hb level was significantly correlated with OS (p=0.001) but not with PFS (p=0.12).[29] In our study, similar results were obtained among all the hematological parameters, only pre RT Hb levels significantly correlated with OS but not with PFS. PFS and local control (LC) were significantly increased in patients with low pre-RT CEA.

There are several limitations to this study. Firstly, the number of patients from the single-center is low, and it is a retrospective study. Secondly, we did not compare toxicity profiles or quality of life owing to data limitations. Finally, the patients who underwent both short and long course RT were included in this study.

Conclusion

Neoadjuvant CRT is an effective and standard treatment used for long years to increase local control in LARC. Adverse tumor histology, the prolonged time from completion of RT to surgery, CEA response to NAT, pre-RT Hb levels were essential factors affecting survival. The optimal timing of surgery of LARC after neoadjuvant CRT is still controversial.

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Conflict of Interest: No conflict of interest.

Ethics Committee Approval: This study was approved by the Institutional Ethics Committee of Gaziosmanpaşa University.

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