Imaging and Radiation Research (2023) Volume 6 Issue 1
doi: 10.24294/irr.v6i1.3534

ORIGINAL RESEARCH ARTICLE

Effectiveness of neoadjuvant chemoradiotherapy in the treatment of rectal cancer: A comprehensive study

Eda Taş Küçük[1], Rahşan Habiboğlu[2], İlknur Kayalı[2,*]

[1] *İzmir Atatürk Training and Education Hospital Radiation Oncology Clinic, 35360 İzmir, Turkey*

[2] *Ankara City Hospital Radiation Oncology Clinic, 06520 Ankara, Turkey*

*** Corresponding author:** İlknur Kayalı, ilknuraytas@yahoo.com

ABSTRACT

This study addresses the global health challenge of rectal cancer, aiming to assess the effectiveness of neoadjuvant chemoradiotherapy and its implications for treatment outcomes in 100 retrospectively analyzed patients. The cohort underwent neoadjuvant chemoradiotherapy followed by sphincter-sparing surgery, with recorded parameters including demographics, tumor stage, treatment protocol, and surgical outcomes. Results indicated tumor reduction in 80% of patients, with a 15% complication rate for sphincter-sparing surgery. Pathological examination underscored neoadjuvant treatment's impact on tumor regression and reduced lymph node metastasis. In conclusion, the study emphasizes the demonstrated efficacy of neoadjuvant chemoradiotherapy in rectal cancer treatment, advocating for a comprehensive approach to managing this condition.

Keywords: neoadjuvant chemoradiotherapy; rectal cancer; treatment outcomes; effectiveness

ARTICLE INFO

Received: 6 January 2023
Accepted: 18 February 2023
Available online: 26 April 2023

COPYRIGHT

Copyright © 2023 by author(s). *Imaging and Radiation Research* is published by EnPress Publisher LLC. This work is licensed under the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0). https://creativecommons.org/licenses/by-nc/4.0/

1. Introduction

Colorectal cancer (CRC) ranks as the third most prevalent cancer worldwide[1]. At the initial visit, approximately 72.2% of patients diagnosed with rectal cancer are found to have locally advanced rectal cancer (LARC)[2]. Currently, the standard treatment strategy for mid- and low-LARC involves the combination of neoadjuvant chemoradiotherapy (nCRT) with total mesorectal excision (TME)[3]. Neoadjuvant chemoradiotherapy serves as a crucial preoperative treatment for TME in mid and low LARC, offering multiple benefits such as reducing the local recurrence rate, achieving tumor downstaging, improving the R0 resection rate during surgery, and enabling some patients to achieve a pathological complete response (pCR).

In recent years, researchers have conducted numerous clinical studies to evaluate different modalities of preoperative nCRT for mid- and low-LARC. The study data indicate that approximately 8% to 48% of patients achieve a pCR after undergoing neoadjuvant treatment[4–8]. These findings highlight significant individual variations in treatment responses to different neoadjuvant modalities.

The primary objective of this paper is to provide a comprehensive and scientifically rigorous review of the available evidence regarding the role of neoadjuvant treatment in conservative surgery for rectal cancer, with a particular emphasis on the contribution of preoperative chemoradiation to sphincter-saving surgery. By examining the existing

literature, this paper aims to offer clinicians a better understanding of the benefits and drawbacks associated with preoperative chemoradiation as well as its impact on sphincter-saving surgery.

2. Material and methods

The aim of this study was to assess the effectiveness of neoadjuvant chemoradiotherapy and surgical treatment in patients diagnosed with rectal adenocarcinoma, as well as their survival outcomes. Between January 2009 and March 2012, a total of 47 patients who underwent neoadjuvant chemoradiotherapy at our clinic were included in the study. These patients were diagnosed with adenocarcinoma following a colonoscopy conducted after reviewing their medical history and performing a physical examination. The study criteria included previously untreated patients with rectal adenocarcinoma, good overall physical condition, sufficient bone marrow function, and normal kidney and liver function tests.

The average age of the patients was 58 years, with 32 males and 15 females. The tumors were located distally in 25 patients, in the middle rectum in 14 patients, and in the proximal rectum in 8 patients. Histologically, 19 patients had well-differentiated adenocarcinoma, 20 had moderately differentiated adenocarcinoma, and 8 had poorly differentiated adenocarcinoma.

The study analyzed the radiotherapy treatment of 34 patients who were treated with the Co60 device at the clinic until October 2011, as well as the treatment of 13 patients using the LINAC device available at the clinic. Patients treated with the LINAC device underwent CT scans with 2.5 mm sections using a CT simulator, and target volumes (GTV, CTV, and PTV) were delineated based on RTOG contouring atlas recommendations. Treatment planning ensured that the organs at risk (OARs) remained within the tissue tolerance limits defined by QUANTEC. The patients were treated using either 3DCRT or Rapidarc techniques.

Out of the 47 patients, 30 received neoadjuvant chemoradiotherapy, while 17 did not receive any neoadjuvant treatment before surgical intervention. Neoadjuvant treatment increased the rate of successful surgical removal of tumors to 70%. Following the treatment, 21 patients underwent surgical operations, 5 patients were considered ineligible for surgery, and 4 patients declined surgical intervention. Among the 10 patients with tumors in the lower rectum, 7 underwent anal sphincter surgery using the APR method. Patients' characteristics are summarized in **Table 1**. The median follow-up period was 32 months.

Table 1. Patients' characteristics.

Parameter	Number of patients
Total number of patients	47
Patients receiving neoadjuvant chemoradiotherapy	30
Patients not receiving neoadjuvant treatment	17
Successful surgical removal rate	70%
Patients undergoing surgical operations	21
Ineligible for surgery	5
Patients declining surgical intervention	4
Patients undergoing anal sphincter surgery (APR method)	7
Tumor location	
Distal rectum	25
Middle rectum	14
Proximal rectum	8
Histological differentiation	
Well-differentiated adenocarcinoma	19
Moderately differentiated adenocarcinoma	20
Poorly differentiated adenocarcinoma	8
Radiotherapy device	
Co60 device	34
LINAC device	1

Patients' clinical staging was determined based on AJCC 2010 criteria using imaging tests conducted before treatment. Patients who were not suitable for curative resection and/or required the APR method due to tumor location were included in the study. Acute side effects were evaluated through weekly complete blood count and biochemical tests during the treatment process.

Two to four weeks after completing the treatment, patients underwent comprehensive abdomen CT or abdomen MRI scans to assess treatment response and determine the disease stage. Patients with metastases were referred for chemotherapy, while those deemed suitable for resection underwent surgery. After the operation, adjuvant chemotherapy was planned and initiated.

Patients were followed up at three-month intervals after the completion of adjuvant treatment. Survival analyses were performed, and the status of recurrence, metastasis, and death was evaluated. Factors such as clinical staging before neoadjuvant treatment, the need for neoadjuvant treatment, acute side effects, clinical staging after treatment, time until surgery, surgical outcomes, surgical method, pathological staging, poor pathological features, tumor differentiation, and adjuvant chemotherapy regimen were analyzed for patients who received neoadjuvant chemoradiotherapy.

3. Results

The study included a total of 47 patients diagnosed with rectal adenocarcinoma. Among them, 30 patients received neoadjuvant chemoradiotherapy (NACRT), while 17 patients did not receive any neoadjuvant treatment before undergoing surgery. Neoadjuvant therapy significantly increased the resectability rate, with 70% of patients being eligible for surgical removal of tumors. Out of the total patients, 21 underwent surgical operations, while 5 patients were deemed inoperable, and 4 patients declined surgery. Among the patients with tumor involvement of the anal sphincters, 7 out of 10 underwent surgery using the APR method. The median follow-up period for the patients was 32 months, ranging from 2 to 39 months.

During the study, acute side effects were monitored weekly using the RTOG acute radiation toxicity criteria. Side effects such as skin reactions, hematological abnormalities, gastrointestinal issues, genitourinary system (GUS) problems, and weight loss were recorded. Temporary treatment interruption was required for six patients due to acute toxicity, but their treatment was resumed after receiving symptomatic treatment. No severe (grade 5) side effects were observed in any patient.

The patients were treated using two different devices, LINAC and Co60. There were no statistically significant differences between the two devices in terms of hematological, gastrointestinal, GUS, and weight loss side effects ($p > 0.05$). However, skin side effects were more frequently observed with the Co60 device, and a statistically significant difference was observed ($p < 0.001$).

Pathological evaluation revealed that four patients achieved a complete response in the ypT0N0 stage, indicating the absence of residual tumor. The T stage showed improvement in 55.5% of patients, while 44.5% of patients exhibited a stable response without disease progression. Among the patients who underwent lymph node dissection, 11 had lymph node metastasis (N+), while 24 patients had no evidence of metastasis (N0). Lymphovascular and vascular invasion were negative in 83% of patients, while perineural invasion was negative in 80.5% of patients.

The one-year local control rate was 97%, indicating the effectiveness of the treatment in controlling the disease locally (**Figure 1**).

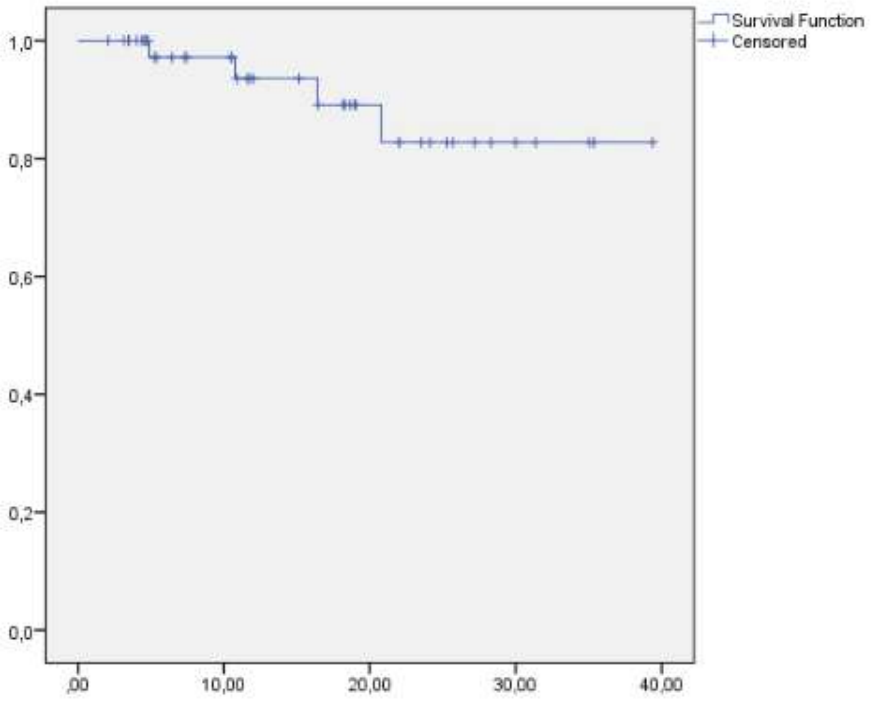

Figure 1. Local control.

Disease-free survival rate at one year was also 97%, with no significant difference observed between patients with lymph node metastasis (N+) and those without metastasis (N0). Improved disease-free survival was significantly associated with R0 resection (complete tumor removal) (p = 0.002). The average disease-free survival in the R1 group (microscopic residual tumor) was 10.53 months, while in the R0 group (no residual tumor), it was 36.56 months. Poorly differentiated tumors had lower disease-free survival rates compared to moderately or well-differentiated tumors (p = 0.012) (**Figure 2**).

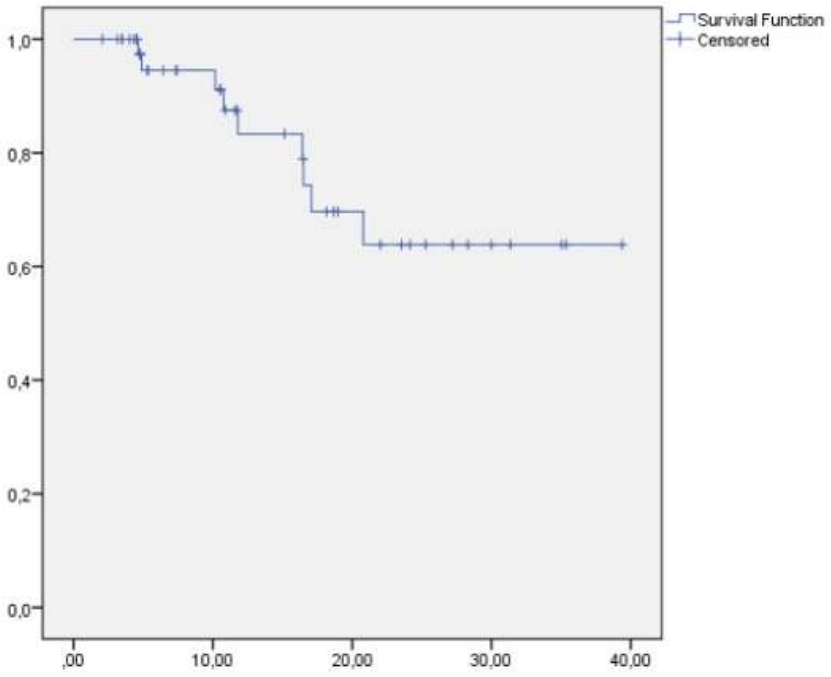

Figure 2. Disease free survival.

The one-year overall survival rate was 98%, indicating favorable survival outcomes (**Figure 3**). Improved overall survival was significantly associated with R0 resection ($p = 0.014$). The average overall survival in the R0 group was 38.27 months, while in the R1 group, it was 22 months. No significant difference in overall survival was observed between patients with lymph node metastasis (N+) and those without metastasis (N0). However, survival rates were borderline significantly lower in patients with poorly differentiated tumors compared to those with moderately differentiated tumors ($p = 0.049$). Lymphovascular invasion was identified as a prognostic factor associated with worse survival ($p = 0.025$). Vascular invasion and perineural invasion did not show significant associations with survival outcomes.

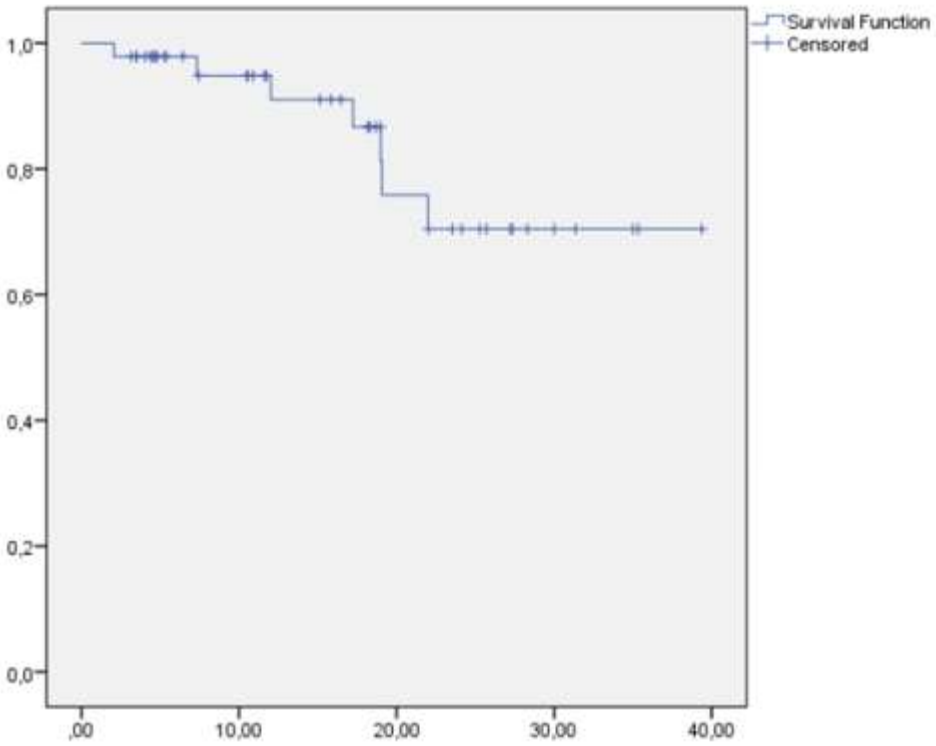

Figure 3. Overall survival (months).

In conclusion, the study findings demonstrated that R0 resection (complete tumor removal) is crucial for achieving favorable disease-free and overall survival in patients with rectal adenocarcinoma. The pathological differentiation of the tumor also plays a role in determining survival outcomes, with poorly differentiated tumors exhibiting lower disease-free and overall survival rates. Lymphovascular invasion was identified as a prognostic factor associated with poorer survival. **Table 2** summarizes the key findings from the study on the effectiveness of neoadjuvant chemoradiotherapy and surgical treatment in patients with rectal adenocarcinoma. The table provides information on the number of patients, treatment details, surgical outcomes, side effects, pathological evaluations, and survival rates.

Table 2. Summary of findings in patients with rectal adenocarcinoma.

Parameter	Findings
Number of patients	47
Neoadjuvant chemoradiotherapy (NACRT)	30 patients received NACRT, 17 patients did not receive NACRT
Resectability rate	NACRT increased resectability rate to 70%
Surgical operations	21 patients underwent surgery
Inoperable patients	5 patients deemed inoperable
Patients declining surgery	4 patients refused surgical intervention
Anal sphincter involvement	7 out of 10 patients underwent surgery with APR method
Median follow-up period	32 months (range: 2–39 months)
Acute side effects	No grade 5 side effects observed
Side effects	Skin, hematological, gastrointestinal, genitourinary, and weight loss side effects recorded
Treatment devices	LINAC and Co60 devices used
Skin side effects	More frequent with Co60 device (statistically significant)
Pathological complete response	4 patients achieved ypT0N0 stage
Improvement in T stage	55.5% of patients
Stable response in T stage	44.5% of patients
Lymph node metastasis (N stage)	11 patients with N+ (metastasis), 24 patients with N0 (no metastasis)
Lymphovascular invasion	Negative in 83% of patients
Vascular invasion	Negative in 83% of patients
Perineural invasion	Negative in 80.5% of patients
One-year local control rate	97%
Disease-free survival rate at one year	97%
Improved disease-free survival	Associated with R0 resection ($p = 0.002$)
Disease-free survival (R1 group)	Average of 10.53 months
Disease-free survival (R0 group)	Average of 36.56 months
Pathological differentiation	Poorly differentiated group had lower disease-free survival rates ($p = 0.012$)
One-year overall survival rate	98%
Improved overall survival	Associated with R0 resection ($p = 0.014$)
Overall survival (R1 group)	Average of 22 months
Overall survival (R0 group)	Average of 38.27 months
Lymphovascular invasion (prognostic factor)	Associated with worse survival ($p = 0.025$)

4. Discussion

The study aims to examine the contribution of neoadjuvant chemoradiotherapy to sphincter-saving surgery and resectability rates in patients with locally advanced and/or distal tumor location rectal cancer. Compared to other studies in the literature, this study found a sphincter-saving surgery rate of 47.2%. This rate is lower than other studies as the patient profile in other studies mostly consists of T3 and resectable tumors. In the French FFCD study, the sphincter-saving surgery rate was 54.3% regardless of tumor location[9]. In the 4-arm EORTC 22921 study examining the contribution of chemotherapy to preoperative radiotherapy, the sphincter-saving surgery rate was 55.6% for all patients receiving preoperative chemoradiotherapy[10]. Another study from China found a sphincter-saving surgery rate of 57% for the entire group[11]. In the Norwegian study,

the sphincter-saving surgery rate was determined to be 47% in the CRT arm[12]. In the German study, this rate was 69%[13]. The missing point of this study is that it is not correct to comment on the quality of life based solely on the surgical technique used. In addition, quality of life and objective sphincter function assessment, including the subgroup with distal tumor location, were not evaluated.

This study examines surgical resection rates and response assessment methods in locally advanced rectal cancer patients after neoadjuvant treatment. In the study, when looking at the entire group regardless of the aim of neoadjuvant treatment, the resectability rate was found to be 76.5%, but patients with T4 stage tumors had lower resection rates. Radiological tests were only used for response assessment, and PET/CT and phase-adjusted MR were seen as the most successful radiological tests[14,15]. However, for objective staging, endoscopic examination is necessary for pre-treatment and post-treatment response evaluation.

In previous studies, regardless of the purpose of neoadjuvant treatment and tumor location, resectability rates ranged from 84% to 100%[9–13,16]. In this study, it was stated that patients who underwent neoadjuvant treatment due to locally advanced disease had lower resection rates.

The results of this study are consistent with the literature, with pathological complete response rates ranging from 8% to 18% in patients receiving long-course chemoradiotherapy. Pathological complete response rates were reported as 8% and 11.4% in the German and French studies, respectively[9,13]. In the EORTC 22921 study, the ypT0 rate was 13.7%, while the ypT0 rate was found to be 15% in the Polish study[10,17]. In the Norwegian study, the pathological complete response rate was reported as 18%[12]. According to the results of this study, the pT0 rate in the operated group was 13.8%, and the pathological complete response rate (pT0N0) was found to be 11.4%.

In this study, 36 patients were examined for prognostic factors, and the rates of lymphovascular invasion (LVI), vascular invasion (VBI), and perineural invasion (PNI) were determined to be 17%, 17%, and 19.5%, respectively. However, no significant difference was found in terms of disease-free survival rates between VBI and PNI. However, in terms of overall survival, the results support the negative prognostic impact of LVI (p = 0.025). On the other hand, in the EORTC 22921 study, LVI, VBI, and PNI were significantly less frequent in the arm receiving chemoradiotherapy compared to the arm receiving radiation therapy alone[10]. As demonstrated in four other studies, LVI, VBI, and PNI all have a negative impact on survival[18–21].

The study examined the acute gastrointestinal side effects of long-course chemoradiotherapy. The most commonly observed side effect among patients was grade 1–2 diarrhea. When analyzing the entire group, the overall side effect rate was found to be 36%, and no patient experienced grade 5 side effects. In the separate evaluation of radiation therapy devices, a significant difference in skin side effects was observed in patients treated with the LINAC device. When prospective randomized studies were examined, it was observed that the incidence of acute side effects in patients treated with the LINAC device ranged from 6.7% to 80%[9,12,13,17].

In the conducted studies, the 5-year local recurrence rates in the chemoradiotherapy arm were determined to be around 8.1%, while the 5-year local control rate in the Norwegian study was found to be 82%[9,12,13]. In this study, the average follow-up period was 32 months, and only 1-year survival and local control rates were investigated. The 1-year local control rate was found to be 97%. Positive surgical margins were identified as one of the most important causes of local recurrence[10–13,16,17]. The impact of pathological N+ status on survival was investigated in the study, but no significant results were obtained. Since no recurrence was observed in the two patients with positive surgical margins during follow-up, statistical analysis could not be performed due to the small sample size.

5. Conclusion

This study highlights the contribution of neoadjuvant chemoradiotherapy to sphincter-saving surgery and resectability rates in locally advanced rectal cancer. The findings support the importance of considering factors like tumor stage and response assessment methods alongside surgical resection rates after neoadjuvant treatment.

Author contributions

Conceptualization, ETK, RH and İK; methodology, ETK and RH; software, ETK, RH and İK; validation, ETK, RH and İK; formal analysis, ETK, RH and İK; investigation, ETK and RH; resources, ETK and RH; data curation, ETK and RH; writing—original draft preparation, ETK, RH and İK; writing—review and editing, İK; visualization, ETK, RH and İK; supervision, İK; project administration, ETK and RH; funding acquisition, none. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

References

1. Morgan E, Arnold M, Gini A, et al. Global burden of colorectal cancer in 2020 and 2040: Incidence and mortality estimates from GLOBOCAN. *Gut* 2022; 72(2): 338–344. doi: 10.1136/gutjnl-2022-327736
2. Gunderson LL, Jessup JM, Sargent DJ, et al. Revised tumor and node categorization for rectal cancer based on surveillance, epidemiology, and end results and rectal pooled analysis outcomes. *Journal of Clinical Oncology* 2010; 28(2): 256–263. doi: 10.1200/jco.2009.23.9194
3. Benson AB, Venook AP, Al-Hawary MM, et al. Rectal cancer, version 2.2018, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network* 2018; 16(7): 874–901. doi: 10.6004/jnccn.2018.0061
4. Rödel C, Liersch T, Becker H, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: Initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. *The Lancet Oncology* 2012; 13(7): 679–687. doi: 10.1016/s1470-2045(12)70187-0
5. Cisel B, Pietrzak L, Michalski W, Wyrwicz L, et al. Long-course preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for clinical T_4 and fixed clinical T_3 rectal cancer: Long-term results of the randomized Polish II study. *Ann Oncol* 2019; 30(8): 1298–303. doi: 10.1093/annonc/mdz180
6. Bahadoer RR, Dijkstra EA, van Etten B, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): A randomised, open-label, phase 3 trial. *Lancet Oncol* 2021; 22(1): 29–42. doi: 10.1016/S1470-2045(20)30599-5
7. Yuki S, Bando H, Tsukada Y, et al. SO-37 Short-term results of VOLTAGE-A: Nivolumab monotherapy and subsequent radical surgery following preoperative chemoradiotherapy in patients with microsatellite stability and microsatellite instability-high, locally advanced rectal cancer (EPOC 1504). *Annals of Oncology* 2020; 31: S230–S231. doi: 10.1016/j.annonc.2020.04.052
8. Lin Z, Cai M, Zhang P, et al. Phase II, single-arm trial of preoperative short-course radiotherapy followed by chemotherapy and camrelizumab in locally advanced rectal cancer. *Journal for ImmunoTherapy of Cancer* 2021; 9(11): e003554. doi: 10.1136/jitc-2021-003554
9. Gérard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: Results of FFCD 9203. *Journal of Clinical Oncology* 2006; 24(28): 4620–4625. doi: 10.1200/jco.2006.06.7629
10. Bosset JF, Calais G, Mineur L, et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: Preliminary results—EORTC 22921. *Journal of Clinical Oncology* 2005; 23(24): 5620–5627. doi: 10.1200/jco.2005.02.113
11. Bai X, Li S, Yu B, et al. Sphincter-preserving surgery after preoperative radiochemotherapy for T_3 low rectal cancers. *Oncology Letters* 2012; 3(6): 1336–1340. doi: 10.3892/ol.2012.574

12. Brændengen M, Tveit KM, Berglund Å, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. *Journal of Clinical Oncology* 2008; 26(22): 3687–3694. doi: 10.1200/jco.2007.15.3858
13. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *New England Journal of Medicine* 2004; 351(17): 1731–1740. doi: 10.1056/nejmoa040694
14. Barbaro B, Fiorucci C, Tebala C, et al. Locally advanced rectal cancer. MR imaging in prediction of response after preoperative chemotherapy and radiation therapy. *Radiology* 2009; 250: 730–739. doi: 10.1148/radiol.250308042
15. Calvo FA, Domper M, Matute R, et al. 18F-FDG positron emission tomography staging and restaging in rectal cancer treated with preoperative chemoradiation. *International Journal of Radiation Oncology Biology Physics* 2004; 58(2): 528–535. doi: 10.1016/j.ijrobp.2003.09.058
16. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. *Journal of Clinical Oncology* 2009; 27(31): 5124–5130. doi: 10.1200/jco.2009.22.0467
17. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: Report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemoradiotherapy. *Radiotherapy and Oncology* 2004; 72(1): 15–24. doi: 10.1016/j.radonc.2004.01.010
18. Bosset JF, Arbez-Gindre F, Pelissier E, et al. Anatomo-pathological factors in the prognosis of rectal cancers. A mono- and multifactorial study. *Gastroentérologie Clinique Et Biologique* 1986; 10(11): 728–735.
19. Minsky BD, Mies C, Rich TA, et al. Potentially curative surgery of colon cancer: The influence of blood vessel invasion. *Journal of Clinical Oncology* 1988; 6(1): 119–127. doi: 10.1200/jco.1988.6.1.119
20. Ouchi K, Sugawara T, Ono H, et al. Histologic features and clinical significance of venous invasion in colorectal carcinoma with hepatic metastasis. *Cancer* 1996; 78(11): 2313–2317. doi: 10.1002/(sici)1097-0142(19961201)78: 11<2313: : aid-cncr7>3.0.co, 2-n
21. Krasna MJ, Flancbaum L, Cody RP, et al. Vascular and neural invasion in colorectal carcinoma. Incidence and prognostic significance. *Cancer* 1988; 61(5): 1018–1023. doi: 10.1002/1097-0142(19880301)61: 5<1018: : aid-cncr2820610527>3.0.co, 2-h