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RESEARCH ARTICLE

The Effects of NT and Adjuvant Treatments on Anastomotic Leakage in Rectal Cancer

Neoadjuvan ve Adjuvan Tedavinin Rektum Kanseri Üzerindeki Etkileri

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ABSTRACT

Aim: Anastomosis leakage (AL) is a major complication following colorectal surgery. The present study aims to investigate the effects of adjuvant (AT) and neoadjuvant (NT) treatments on AL in surgical patients with rectal cancer.

Method: The study followed 319 patients (age >18 years) who were diagnosed with rectal cancer and underwent surgery with AT or NT treatment between January 1, 2010 and December 31, 2018. We evaluated demographic data, tumor stage, metastasis status, organ and lymph node involvement, surgery type, use of AT and NT, the presence of AL, mortality status, and serum carcinoembryonic antigen levels.

Results: A total of 179 (56.1%) patients were male, 140 (43.9%) were female (mean age =58.6±13.2 years). In terms of additional treatment, 48.6% (n=155) received AT and 51.4% (n=164) received NT. Data revealed that 13.1% (n=42) of the patients received only radiotherapy (RT), 10.6% (n=34) received only chemotherapy (CT), and 76.2% (n=243) received both RT and CT (CRT). Additionally, 23.5% (n=75) of the patients had AL. In terms of AL frequency, we found no difference between the patients receiving AT or NT (p=0.758). Additionally, RT and CT had no effect on the development of AL (p=0.827 and p=0.1, respectively). Finally, mortality was not higher in patients with AL.

Conclusion: In terms of AL development, we found no differences between patients receiving NT or AT and those using RT or CT alone or together. We recommend that these rectal cancer treatments should be continued because of their better local control, overall survival rate, and sphincter function preservation rates.

Keywords: Rectum cancer, radiotherapy, chemotherapy, anastomotic leakage

ÖZ

Amaç: Anastomoz kaçağı (AK) kolorektal cerrahi sonrası görülen önemli bir komplikasyondur. Bu çalışmada, rektum kanseri tanısıyla ameliyat edilen hastalarda, neoadjuvan (NT) ve adjuvan tedavinin (AT) AK üzerine etkilerini araştırmayı amaçladık.

Yöntem: Çalışmaya, 1 Ocak 2010 ve 31 Aralık 2018 tarihleri arasında, 18 yaşından büyük, rektum kanseri tanısı alan ve cerrahi operasyon ile birlikte AT veya NT tedavisi alan 319 hasta dahil edildi. Çalışmaya katılan hastaların demografik verileri, tümör evrelemesi, metastaz durumu, organ ve lenf nodu tutulumları, cerrahi tipi, aldıkları AT ve NT, AK varlığı, mortalite durumu ve serum karsinoembriyonik antijen düzeyleri değerlendirildi.

Bulgular: Hastaların 179'u (%56,1) erkek, 140'ı (%43,9) kadın ve yaş ortalaması 58,6±13,2 yıl idi. Çalışmaya dahil edilen hastaların %48,6'sının (n=155) AT, %51,4'ünün (n=164) ise NT aldığı saptandı. Hastaların %13,1'i (n=42) sadece radyoterapi (RT) aldığı, %10,6'sının (n=34) sadece kemoterapi (KT) aldığı, %76,1'inin (n=243) ise hem RT hem de KT (KRT) aldığı görüldü. Çalışmaya katılan hastaların %23,5'inde (n=75) AK tespit edildi. AT ve NT alan hastalar arasında AK sıklığı açısından fark görülmedi (p=0,758). Ayrıca RT ve KT'ninde AK gelişimi üzerine etkisi olmadığı belirlendi (sırasıyla; p=0,827 ve p=0,1). AK olan hastalarda mortalitenin artmadığı görülmüştür.

Sonuç: NT veya AT alan hastalar ve RT veya KT'nin tek başına veya birlikte kullanımı arasında AK gelişimi açısından fark bulunmamaktadır. Daha iyi lokal kontrol, genel sağkalım ve sfinkter fonksiyonu koruma oranları nedeniyle rektum kanseri tedavisinde bu tedavilerden vazgeçilmemelidir.

Anahtar Kelimeler: Rektum kanseri, radyoterapi, kemoterapi, anastomoz kaçağı

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Introduction

Colorectal cancer (CRC) is one of the most common and life-threatening cancers worldwide. Since the treatment for stage II and stage III CRC now involves a multidisciplinary structure of combined therapy rather than surgery alone, combined chemotherapy (CT) has become the preferred adjuvant (AT) therapy for stage III colon cancer.[1] Similarly, combined radiotherapy (RT) is also recommended for rectal cancer. Previous studies have shown reductions of local recurrence and improvement in survivability in locally advanced rectal cancer using combined AT RT and CT[2], while others report decreased recurrence rates using total mesorectal excision (TME).[3,4] Neoadjuvant (NT) chemoradiotherapy (CRT) has become the preferred treatment method in all stage II and III rectal cancers because of better outcomes compared with AT CRT, better patient tolerance, and downstaging in many cases, thus preventing permanent ostomy.[5]

Anastomotic leakage (AL) is defined as a defect of the intestinal wall in the anastomosis region (including the sutures and staple lines of the neorectal reservoirs), leading to transition between the intra- and extraluminal compartments.[6] It is a crucial and potentially life-threatening postoperative complication following colorectal surgery, causing around one-third of deaths after surgery.[7] Although AL mortality can be prevented if managed well [8], patients with AL who undergo treatment and survive have increased perioperative morbidity and lower survival in the long term.[9,10,11]

Based on numerous studies focusing on the predisposing factors for AL, the leak is thought to be caused by a large spectrum of both preventable and unavoidable factors.[12] Even with perioperative management (Enhanced Recovery After Surgery) and the improvement and optimization of surgical techniques (minimally invasive surgery), AL frequency has remained high (8%-20%) over time.[12,13,14,15] Among many local and general factors causing AL[16] is the patient's exposure to CT and/or RT. While some studies showed that NT RT or CRT did not increase AL development.[17,18,19,20,21,22] A study with a five-year follow-up period comparing the use of AT and NT CRT detected AL in 11% of the NT CRT arm and 12% of the AT CRT arm, with no differences found between the two groups.[5] Thus, the present study aims to investigate the effects of NT and AT therapies on AL in patients with rectal cancer who underwent surgery.

Materials and Methods

Patient Selection

We conducted retrospective file scans of patients with rectal cancer who underwent surgery between January 1, 2010 and December 31, 2018, in Trakya University General Surgery Department. The study included patients who were older than 18 years, were diagnosed with rectal cancer, underwent surgery in our clinic, and were given AT or NT by the radiation oncology and medical oncology clinics. We obtained patient data from the central and oncology clinic archives. Patients were grouped according to AT or NT status. We recorded demographic data, tumor stage, metastasis status, organ and lymph node involvement, surgery type, use of AT and NT, the presence of AL, mortality, and serum carcinoembryonic antigen (CEA) levels from patient files. The patients had 2-8 years of follow-up.

Chemotherapy and Radiotherapy Protocols

Surgery was performed according to TME principles. While RT and CT were generally applied together as AT or NT, RT or CT was administered alone in some patients. A total of 50.4 Gy (single dose of 1.8 Gy) RT was applied to the tumor and pelvic lymph nodes for five weeks as per protocol.[23] For CT, 5-fluorouracil (5-FU) was administered in a 120-hour continuous infusion at a dose of 1,000 mg/m^2/day in the first and fifth weeks of RT. Four cycles of 5-FU were additionally administered as bolus injection at a dose of 500 mg/m^2/day in 5 consecutive days for 4 weeks. Unlike in NT, an additional 5.4 Gy of RT was administered to the tumor bed for 3 days in AT. Surgical treatment was performed 4-6 weeks after completing the concurrent use of NT CT and RT, while the remaining four cycles of 5-FU were started 3-4 weeks after surgery. Alternatively, surgical treatment was performed first and AT started 1-2 weeks after surgery.

Approach to Anastomotic Leaks

We used the following AL grading system recommended by Rahbari et al.[6]: grade A does not require a therapeutic intervention, grade B requires active intervention without laparotomy, and grade C requires laparotomy. Based on literature, CT scan was performed for diagnosis when a leak was suspected, followed by contrast enema and endoscopy, then reoperation.[24] where the anastomosis was usually removed, and a permanent stoma was created. If possible, anastomosis was fixed in grade A and B leaks, with or without drainage and/or antibiotic treatments.[25,26]

Statistical Analysis

We used the Statistical Package for the Social Sciences (SPSS) package program version 22 for data analysis. We investigated the normality of the distribution of the data using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Mean ± standard deviation or median (minimum-maximum) was used for continuous variables, and frequency and percentage (%) were used for categorical variables. We used the Mann-Whitney U test to compare categorical

variables that were not normally distributed as well as continuous variables obtained in laboratory measurements. We used Pearson's chi-square test for comparisons between categorical variables. We used the McNemar test for comparisons between dependent categorical variables. The level of statistical significance was accepted as $p \leq 0.05$.

Results

The average age of the patients was 58.6±13.2 (range: 27-85) years. In total 179 (56.1%) patients were male. The mean body weight of the patients was 74.52±13.7 kg.

We found that 48.6% (n=155) of the patients received AT while 51.4% (n=164) received NT. Furthermore, 13.2% (n=42) received only RT, 10.7% (n=34) received only CT, and 76.2% (n=243) received both. In terms of NT use (n=164), 18 (11.0%) received only RT, 21 (12.8%) received only CT, and 125 (76.2%) received both. In terms of AT use (n=155), 25 (16.1%) received only RT, 12 (7.7%) receivd only CT, and 118 (76.1%) received both (Table 1).

We found that 16.3% (n=52) of the patients underwent anterior resection, 73.0% (n=233) had low anterior resection, and 10.7% (n=34) received a very low anterior resection.

We investigated perineural invasion in 83.1% (n=265) of the patients and detected it in 16.6% (n=44). We also investigated lymphatic invasion in 84.9% (n=271) and found it in 16.6% (n=44). Meanwhile, we detected AL in 23.5% (n=75) of the patients. Unfortunately, 90 (28.2%) patients died.

The average age of the deceased patients was 58.68±0.87 years, while the average age of survivors was 58.4±1.39 years. We found no significant differences between the ages of survivors and those who died (p=0.871). Likewise, we found no statistically significant difference in terms of body weight between the survivors and those who died (p=0.822). A total of 50 (55.6%) male patients and 40 (44.4%) female patients died. Still, we found no significant differences between the sexes of the survivors and those who died (p=0.900).

Among the survivors and deceased patients, there were no differences in terms of TNM stage, surgery type, preoperative and postoperative CEA levels, anastomosis leaks, RT and/or CT use, and perineural and lymphatic invasions (Table 2).

Similarly, there were no differences in terms TNM stage, surgery type, preoperative and postoperative CEA levels, anastomosis leak, mortality, and perineural and lymphatic invasions among patients receiving AT or NT (Table 3).

When the average age and body weight of the patients were compared in terms of the presence of AL, we found no significant difference between the ages of those with and without AL (p=0.227). However, the average body weight of patients with AL was lower than that of patients without AL (p=0.042). Similarly, when sex distribution of the patients was compared, we found no significant difference between those with and without AL.

Table 4 shows the predictive factors to AL development. In univariate analysis, the relationship between gender, age, weight, surgery type, laparoscopic surgery, tumor size, lymph node involvement, NT or AT use, perineural involvement, lymphatic invasion, RT or CT use, and AL were examined. We found a relationship (p=0.021) between N2 lymph node involvement and AL. Also, we observed that RT, CT, or CRT did not have statistically significant effects on AL development.

Finally, we found no significant differences between postoperative and preoperative serum CEA levels in patients receiving AT and NT, in patients who survived and died, and in patients with and without AL (p>0.001) (Table 5).

Discussion

Based on our findings, we found no difference in terms of AL development between patients receiving NT and AT. We also found no difference between the uses of CRT and either RT or CT alone as NT or AT in terms of AL development. However, in patients with AL, we observed more frequent N2 lymph node involvement and lower body weight. Development of AL did not affect mortality in patients.

Presently, colorectal cancer accounts for approximately 10% of cancer-related mortality in Western countries.[27] New treatments for primary and metastatic colorectal cancer include laparoscopic surgery, radiotherapy, and NT, and palliative CT. Every method used in cancer treatments has its own side effects and complications, and these are additive in combined therapy. The appearance of AL at the suture line of the bowel folds after tumor removal is one of the most feared surgical complications. The AL incidence is 1%-19% and complications cause 6%-22% of postoperative

Table 1. The treatment options applied as adjuvant and NT therapy

	AT (n=155)	NT (n=164)
Only chemotherapy	7.7% (n=12)	12.8% (n=21)
Only radiotherapy	16.1% (n=25)	10.9% (n=18)
Chemotherapy + radiotherapy	76.1% (n=118)	76.2% (n=125)

AT: Adjuvant therapy, NT: Neoadjuvant therapy

Table 2. The comparison between patients who survived and patients who died in terms of TNM staging, type of surgery, preoperative and postoperative CEA levels, anastomosis leak, radiotherapy and/or chemotherapy, perineural invasion, and lymphatic invasion

Variables	Survival (n=229)	Mortality (n=90)	p
AL			
No (n=244)	76.0% (n=174)	77.8% (n=70)	0.734
Yes (n=75)	24.0% (n=55)	22.2% (n=20)	
CEA			
Preoperative >10 (n=238)	73.8% (n=169)	76.7% (n=69)	0.045
Preoperative <10 (n=81)	26.2% (n=60)	23.3% (n=21)	
Postoperative >10 (n=133)	41.9% (n=96)	41.1% (n=37)	
Postoperative <10 (n=186)	58.1% (n=133)	58.9% (n=53)	0.946
T1 (n=22)	7.4% (n=17)	5.6% (n=5)	
T2 (n=16)	5.7% (n=13)	3.3% (n=3)	0.578
T3 (n=112)	33.2% (n=76)	40.0% (n=36)	
T4 (n=169)	53.7% (n=123)	51.1% (n=46)	
N0 (n=120)	37.6% (n=86)	37.8% (n=34)	
N1 (n=93)	29.3% (n=67)	28.9% (n=26)	
N2 (n=60)	19.7% (n=45)	16.7% (n=15)	0.862
Nx (n=46)	13.5% (n=31)	16.7% (n=15)	
M0 (n=289)	90.8% (n=208)	90% (n=81)	
M1 (n=30)	9.2% (n=21)	10% (n=9)	0.819
Anterior resection (n=52)	15.7% (n=36)	17.8% (n=16)	
Low anterior resection (n=233)	73.8% (n=169)	71.1% (n=64)	0.880
Very low anterior resection (n=34)	10.5% (n=24)	11.1% (n=10)	
Perineural invasion (n=44)	14.4% (n=33)	12.2% (n=11)	0.679
Lymphatic invasion (n=72)	23.6% (n=54)	20.0% (n=18)	0.655
Radiotherapy	89.1% (n=204)	90% (n=81)	0.811
Yes (n=285)	10.9% (n=25)	10% (n=9)	
No (n=34)			
Chemotherapy	85.6% (n=196)	90% (n=81)	0.294
Yes (n=86)	14.4% (n=33)	10% (n=9)	
No (n=14)			

CEA: Carcinoembryonic antigen, AL: Anastomosis leakage

mortality[28,29,30,31,32] or about one-third of deaths after colorectal surgery.[7] Gessler et al.[33] reported that the AL rate was 10% in patients operated on for colorectal cancer and 18.8% in rectal resections. Additionally, other studies have observed that mortality is higher in AL after rectal resection with rates reaching up to 22%-50%.[7,34,35] Therefore, the risk factors causing AL should be well defined in order to treat it effectively once it develops.

Previous studies have associated AL with male sex, advanced age, lower anastomosis, malignant disease, high American Society of Anesthesiologists (ASA) score, long surgical time, emergency surgery, preoperative RT, perioperative blood loss, and transfusion.[30,36,37,38,39,40,41,42,43] One study showed that male sex and rectal cancer were independent risk factors for both early and late AL. For early AL, younger age, increased body mass index (BMI), laparoscopic surgery, emergency surgery, and lack of guided ileostomy were deemed risk factors, while the Charlson Comorbidity Index, high ASA scores, additional resection due to tumor growth, and preoperative RT were deemed risk factors for late AL. Several studies have discovered higher AL frequency in males than in females, probably due to differences in pelvic anatomy[29,44,45], while others found no difference between the sexes in terms of AL.[46,47,48] Many of the surgical-related risk factors for early AL reflect surgical difficulty. One study showed that laparoscopic surgery was an independent risk factor for early AL.[22] whereas others found no difference in terms of AL between laparoscopic surgery and open

Table 3. The comparison between patients who were treated with adjuvant therapy and patients who were treated with NT therapy in terms of TNM staging, type of surgery, preoperative and postoperative CEA levels, anastomosis leak, mortality, perineural invasion, and lymphatic invasion

Variables	AT (n=155)	NT (n=164)	p
AL (n=70)	42.8% (n=30)	57.2% (n=40)	0.758
CEA			
Preoperative >10 (n=238)	76.8% (n=119)	72.5% (n=119)	0.999
Preoperative <10 (n=81)	23.2% (n=36)	27.4% (n=45)	
Postoperative >10 (n=133)	36.8% (n=57)	46.3% (n=76)	
Postoperative <10 (n=186)	63.2% (n=98)	53.6% (n=88)	0.206
T1 (n=22)	54.5% (n=12)	45.5% (n=10)	
T2 (n=16)	56.3% (n=9)	43.8% (n=7)	0.758
T3 (n=112)	50% (n=56)	50% (n=56)	
T4 (n=169)	46.2% (n=78)	53.8% (n=91)	
N0 (n=120)	48.3% (n=58)	51.7% (n=62)	
N1 (n=93)	45.2% (n=42)	54.8% (n=51)	0.208
N2 (n=60)	60.0% (n=36)	40.0% (n=24)	
Nx (n=46)	41.3% (n=19)	58.7% (n=27)	
M0 (n=289)	47.8% (n=138)	52.2% (n=151)	0.352
M1 (n=30)	56.7% (n=17)	43.3% (n=13)	
Anterior resection (n=52)	51.9% (n=27)	48.1% (n=25)	
Low anterior resection (n=233)	48.1% (n=112)	51.9% (n=121)	0.866
Very low anterior resection (n=34)	47.1% (n=16)	52.9% (n=18)	
Perineural invasion (n=44)	18% (n=28)	9.7% (n=16)	0.758
Lymphatic invasion (n=72)	51.4% (n=37)	48.6% (n=35)	0.700
Survival (n=229)	48.9% (n=112)	51.1% (n=117)	0.856
Mortality (n=90)	47.8% (n=43)	52.2% (n=47)	

CEA: Carcinoembryonic antigen, AL: Anastomosis leakage, AT: Adjuvant therapy, NT: Neoadjuvant therapy

surgery.[49,50] In two separate studies, AL frequencies in patients with low anterior resection were 10%[8] and 11%.[51] Those studies that included patients who underwent anterior resection, low anterior resection, or very low anterior resection found no difference between these types of surgeries in terms of AL development. However, AL was detected in 23.5% of our patients, which was slightly higher than the rates in the literature. Mortality rate in AL patients was 28.2%, suggesting that AL development did not increase mortality. In addition, our univariate analysis showed that sex, age, tumor size, perineural involvement, and lymphatic invasion did not have significant effects on AL development. Although stage 3-4 rectal cancer and poorly differentiated or mucinous adenocarcinoma were shown as independent risk factors for early AL in one study[21], this was not the case in another study.[22] In fact, we observed a relationship between N2 lymph node involvement (stage 3C and 4 rectal cancer) and AL, similar to the study by Shin et al.[21]

The effects of NT RT or CRT on AL development are controversial. A prospective study showed that short-term NT RT does not increase AL risks.[17] In while another prospective study showed that NT CRT therapy was a risk factor for AL in patients undergoing laparoscopic surgery with change in the direction of stoma. However, the same study could not demonstrate NT CRT therapy as a risk factor for AL in all patients undergoing low anterior resection due to cancer.[18] Similarly, other studies showed that preoperative RT or CRT are a risk factor for late AL.[19,20,21,22] However, in a study comparing AT and NT CRT, no difference was found between the two groups in terms of AL development[5] Likewise, our study found no difference in AL between patients who received CRT and patients who received CT or RT as NT. We also found no difference in AL between patients who received CT and RT as CRT and AT.

Although serum CEA increased in 17%-47% of patients with colorectal cancer[52,53], its sensitivity is not high enough to be

Table 4. The comparison between patients who had anastomosis leakage and those who did not have in terms of TNM staging, laparoscopic surgery, tumor size, lymph node involvement, type of surgery, RT and/or CT, NT or AT, perineural invasion, and lymphatic invasion.

Variables	No AL (n=244)	AL (n=75)	p
CEA			
Preoperative >10 (n=238)	77.7% (n=185)	22.3% (n=53)	0.111
Preoperative <10 (n=81)	72.8% (n=59)	27.2% (n=22)	
Postoperative >10 (n=133)	84.2% (n=112)	15.8% (n=21)	0.589
Postoperative <10 (n=186)	71.0% (n=132)	29.0% (n=54)	
T1 (n=22)	86.4% (n=19)	13.6% (n=3)	0.057
T2 (n=16)	81.2% (n=13)	18.8% (n=3)	
T3 (n=112)	83.0% (n=93)	17.0% (n=19)	
T4 (n=169)	70.4% (n=119)	29.6% (n=50)	
N0 (n=120)	84.2% (n=101)	15.8% (n=19)	0.021
N1 (n=93)	72.0% (n=67)	28.0% (n=26)	
N2 (n=60)	65.0% (n=39)	35.0% (n=21)	
Nx (n=46)	80.4% (n=37)	19.6% (n=9)	
M0 (n=289)	77.2% (n=223)	22.8% (n=66)	0.379
M1 (n=30)	70.0% (n=21)	30.0% (n=9)	
Anterior resection (n=52)	73.1% (n=38)	26.9% (n=14)	0.774
Low anterior resection (n=233)	76.8% (n=179)	23.2% (n=54)	
Very low anterior resection (n=34)	79.4% (n=27)	20.6% (n=7)	
Laparoscopic surgery			
Yes (282)	75.5% (n=213)	24.5% (n=69)	0.266
No (37)	83.8% (n=31)	16.2% (n=6)	
Perineural invasion (n=44)	75.0% (n=33)	25.0% (n=11)	0.633
Lymphatic invasion (n=72)	75.0% (n=54)	25.0% (n=18)	0.555
Radiotherapy			
Yes (n=285)	77.2% (n=220)	22.8% (n=65)	0.391
No (n=34)	70.6% (n=24)	29.4% (n=10)	
Chemotherapy			
Yes (n=277)	87.3% (n=213)	85.3% (n=64)	0.660
No (n=42)	12.7% (n=31)	14.7% (n=11)	
NT with RT and CT (n=125)	75.8% (n=94)	77.5% (n=31)	0.827
NT with either RT or CT (n=39)	24.2% (n=30)	22.5% (n=9)	
AT with RT and CT (n=118)	79.2% (n=95)	65.7% (n=23)	0.1
AT with either RT or CT (n=37)	20.8% (n=25)	34.3% (n=12)	

CEA: Carcinoembryonic antigen, AL: Anastomosis leakage, AT: Adjuvant therapy, NT: Neoadjuvant therapy

used as a screening test. Nevertheless, serum CEA levels may have a prognostic value for rectal cancer as prognosis worsens in patients with the same stage of the disease but with CEA values higher than 5 ng/mL.[54] In our study, the CEA cut-off value was accepted as 10 ng/mL since our biochemistry laboratory used different reference values. Our data on high mortality rate in patients with higher CEA levels are consistent with the literature. The absence of relationships between preoperative and postoperative CEA levels, as well as postoperative CEA levels and survival, confirms that serum CEA levels cannot be used as a screening test because of the lack sensitivity.

Study Limitations

Our study has some limitations due to its single-centered and retrospective nature. We also excluded patients

Table 5. Change in serum CEA levels in the postoperative period compared with the preoperative period in patients with and without anastomosis leakage, in patients who survived and who died, and in patients receiving adjuvant therapy and patients receiving NT therapy

		Postoperative CEA <10	Postoperative CEA >10	p
AL	**Preoperative CEA <10 (n=59)**	54.2% (n=32)	45.8% (n=27)	0.111
Yes	**Preoperative CEA >10 (n=185)**	54.0% (n=100)	46.0% (n=85)	
No	**Preoperative CEA <10 (n=22)**	63.6% (n=14)	36.4% (n=8)	0.589
	Preoperative CEA >10 (n=53)	75.5% (n=40)	24.5% (n=13)	
Survival	**Preoperative CEA <10 (n=60)**	10.0% (n=6)	90.0% (n=54)	0.045
	Preoperative CEA >10 (n=169)	53.2% (n=90)	46.7% (n=79)	
Mortality	**Preoperative CEA <10 (n=69)**	65.2% (n=45)	34.8% (n=24)	0.946
	Preoperative CEA >10 (n=21)	38.1% (n=8)	61.9% (n=13)	
AT	**Preoperative CEA <10 (n=36)**	27.8% (n=10)	72.2% (n=26)	0.999
	Preoperative CEA >10 (n=119)	73.9% (n=88)	26.0% (n=31)	
NT	**Preoperative CEA <10 (n=45)**	17.8% (n=8)	82.2% (n=37)	0.206
	Preoperative CEA >10 (n=119)	57.1% (n=68)	42.9% (n=51)	

CEA: Carcinoembryonic antigen, AL: Anastomosis leakage, AT: Adjuvant therapy, NT: NT therapy

undergoing abdominopelvic resection and those undergoing emergency surgery from the study. Additionally, early and late AL discrimination was not performed in patients with AL. Furthermore, we had no data regarding interventions performed on patients who developed AL. On the other hand, our study's strength lies in its high number of patients (n=319), reflecting 10-year clinical data with 2-8 years of follow-up.

Conclusion

In conclusion, we found no difference in terms of AL development between patients receiving NT and patients receiving AT. The use of RT, CT, or CRT as NT or AT did not increase the risk of AL. Additionally, mortality did not increase in patients with AL. We recommend the continued use of these treatments for rectal cancer because of better local control, overall survival, and sphincter function protection rates.

Ethics

Ethics Committee Approval: Trakya University Faculty of Medicine Scientific Research Ethics Committee (no: 18/13, date: 06.11.2019)

Peer-review: Internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: N.A., İ.E.C, İ.C., Concept: N.A., İ.E.C, Design: N.A., İ.E.C, Data Collection or Processing: N.A., İ.E.C, Analysis or Interpretation: N.A., İ.E.C, Literature Search: N.A., İ.E.C, Writing: N.A., İ.E.C

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References

1. Liu FQ, Cai SJ. Adjuvant and perioperative neoadjuvant therapy for colorectal cancer. Zhonghua Wei Chang Wai Ke Za Zhi 2019;22:315-320.
2. Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW, Kubista TP, Poon MA, Meyers WC, Mailliard JA, Twito D, Morton RF, Veeder MH, Witzig T, Cha S, Vidyarthi SC . Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 1991;324:709-715.
3. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? Br J Surg 1982;69:613-616.
4. Heald RJ, Karanjia ND. Results of radical surgery for rectal cancer. World J Surg 1992;16:848-857.
5. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R; German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-1740.
6. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, Holm T, Wong WD, Tiret E, Moriya Y, Laurberg S, den Dulk M, van de Velde C, Büchler MW. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery 2010;147:339-351.
7. Alberts JC, Parvaiz A, Moran BJ. Predicting risk and diminishing the consequences of anastomotic dehiscence following rectal resection. Colorectal Dis 2003;5:478-482.
8. Harris LJ, Phillips BR, Maxwell PJ, Isenberg GA, Goldstein SD. Outcomes of low anterior resection anastomotic leak after preoperative chemoradiation therapy for rectal cancer. Am Surg 2010;76:747-751.

9. Nesbakken A, Nygaard K, Lunde OC. Outcome and late functional results after anastomotic leakage following mesorectal excision for rectal cancer. Br J Surg 2001;88:400-404.
10. Akyol AM, McGregor JR, Galloway DJ, Murray G, George WD. Recurrence of colorectal cancer after sutured and stapled large bowel anastomoses. Br J Surg 1991;78:1297-1300.
11. Peeters KC, Tollenaar RA, Marijnen CA, Klein Kranenbarg E, Steup WH, Wiggers T, Rutten HJ, van de Velde CJ; Dutch Colorectal Cancer Group. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg 2005;92:211-216.
12. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Br J Surg 2015;102:462-479.
13. Borstlap WAA, Musters GD, Stassen LPS, van Westreenen HL, Hess D, van Dieren S, Festen S, van der Zaag EJ, Tanis PJ, Bemelman WA. Vacuum-assisted early transanal closure of leaking low colorectal anastomoses: the CLEAN study. Surg Endosc 2018;32:315-327.
14. Trencheva K, Morrissey KP, Wells M, Mancuso CA, Lee SW, Sonoda T, Michelassi F, Charlson ME, Milsom JW. Identifying important predictors for anastomotic leak after colon and rectal resection: prospective study on 616 patients. Ann Surg 2013;257:108-113.
15. Vermeer TA, Orsini RG, Daams F, Nieuwenhuijzen GA, Rutten HJ. Anastomotic leakage and presacral abscess formation after locally advanced rectal cancer surgery: Incidence, risk factors and treatment. Eur J Surg Oncol 2014;40:1502-1509.
16. Vasiliu EC, Zarnescu NO, Costea R, Neagu S. Review of risk factors for anastomotic leakage in colorectal surgery. Chirurgia (Bucur) 2015;110:319-326.
17. Kapiteijn E, Kranenbarg EK, Steup WH, Taat CW, Rutten HJ, Wiggers T, van Krieken JH, Hermans J, Leer JW, van de Velde CJ. Total mesorectal excision (TME) with or without preoperative radiotherapy in the treatment of primary rectal cancer. Prospective randomised trial with standard operative and histopathological techniques. Dutch ColoRectal Cancer Group. Eur J Surg 1999;165:410-420.
18. Marijnen CA, Kapiteijn E, van de Velde CJ, Martijn H, Steup WH, Wiggers T, Kranenbarg EK, Leer JW; Cooperative Investigators of the Dutch Colorectal Cancer Group. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 2002;20:817-825.
19. Lim SB, Yu CS, Kim CW, Yoon YS, Park IJ, Kim JC. Late anastomotic leakage after low anterior resection in rectal cancer patients: clinical characteristics and predisposing factors. Colorectal Dis 2016;18:135-140.
20. Morks AN, Ploeg RJ, Sijbrand Hofker H, Wiggers T, Havenga K. Late anastomotic leakage in colorectal surgery: a significant problem. Colorectal Dis 2013;15:e271-e275. doi: 10.1111/codi.12167.
21. Shin US, Kim CW, Yu CS, Kim JC. Delayed anastomotic leakage following sphincter-preserving surgery for rectal cancer. Int J Colorectal Dis 2010;25:843-849.
22. Sparreboom CL, van Groningen JT, Lingsma HF, Wouters MWJM, Menon AG, Kleinrensink GJ, Jeekel J, Lange JF; Dutch ColoRectal Audit group. Different risk factors for early and late colorectal anastomotic leakage in a nationwide audit. Dis Colon Rectum 2018;61:1258-1266.
23. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, Becker H, Raab HR, Villanueva MT, Witzigmann H, Wittekind C, Beissbarth T, Rödel C. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012;30:1926-1933.
24. Hirst NA, Tiernan JP, Millner PA, Jayne DG. Systematic review of methods to predict and detect anastomotic leakage in colorectal surgery. Colorectal Dis 2014;16:95-109.
25. Blumetti J, Chaudhry V, Cintron JR, Park JJ, Marecik S, Harrison JL, Prasad LM, Abcarian H. Management of anastomotic leak: lessons learned from a large colon and rectal surgery training program. World J Surg 2014;38:985-991.
26. Sirois-Giguere E, Boulanger-Gobeil C, Bouchard A, Gagné JP, Grégoire RC, Thibault C, Bouchard P. Transanal drainage to treat anastomotic leaks after low anterior resection for rectal cancer: a valuable option. Dis Colon Rectum 2013;56:586-592.
27. Kuipers EJ, Grady WM, Lieberman D, Seufferlein T, Sung JJ, Boelens PG, van de Velde CJ, Watanabe T. Colorectal cancer. Nat Rev Dis Primers 2015;1:15065
28. Rickert A, Willeke F, Kienle P, Post S. Management and outcome of anastomotic leakage after colonic surgery. Colorectal Dis 2010;12:e216-e23. doi: 10.1111/j.1463-1318.2009.02152.x.
29. Rullier E, Laurent C, Garrelon JL, Michel P, Saric J, Parneix M. Risk factors for anastomotic leakage after resection of rectal cancer. Br J Surg 1998;85:355-358.
30. Buchs NC, Gervaz P, Secic M, Bucher P, Mugnier-Konrad B, Morel P. Incidence, consequences, and risk factors for anastomotic dehiscence after colorectal surgery: a prospective monocentric study. Int J Colorectal Dis 2008;23:265-270.
31. Yeh CY, Changchien CR, Wang JY, Chen JS, Chen HH, Chiang JM, Tang R. Pelvic drainage and other risk factors for leakage after elective anterior resection in rectal cancer patients: a prospective study of 978 patients. Ann Surg 2005;241:9-13
32. Hyman N, Manchester TL, Osler T, Burns B, Cataldo PA. Anastomotic leaks after intestinal anastomosis: it's later than you think. Ann Surg 2007;245:254-258.
33. Gessler B, Eriksson O, Angenete E. Diagnosis, treatment, and consequences of anastomotic leakage in colorectal surgery. Int J Colorectal Dis 2017;32:549-556.
34. Karanjia ND, Corder AP, Holdsworth PJ, Heald RJ. Risk of peritonitis and fatal septicaemia and the need to defunction the low anastomosis. Br J Surg 1991;78:196-198.
35. Scott N, Jackson P, al-Jaberi T, Dixon MF, Quirke P, Finan PJ. Total mesorectal excision and local recurrence: a study of tumour spread in the mesorectum distal to rectal cancer. Br J Surg 1995;82:1031-1033.
36. Krarup PM, Jorgensen LN, Andreasen AH, Harling H. A nationwide study on anastomotic leakage after colonic cancer surgery. Colorectal Dis 2012;14:e661-e667. doi: 10.1111/j.1463-1318.2012.03079.x.
37. Boccola MA, Buettner PG, Rozen WM, Siu SK, Stevenson AR, Stitz R, Ho YH. Risk factors and outcomes for anastomotic leakage in colorectal surgery: a single-institution analysis of 1576 patients. World J Surg 2011;35:186-195.
38. Pommergaard HC, Gessler B, Burcharth J, Angenete E, Haglind E, Rosenberg J. Preoperative risk factors for anastomotic leakage after resection for colorectal cancer: a systematic review and meta-analysis. Colorectal Dis 2014;16:662-671.
39. Matthiessen P, Hallbook O, Andersson M, Rutegard J, Sjodahl R. Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis 2004;6:462-469.
40. Kruschewski M, Rieger H, Pohlen U, Hotz HG, Buhr HJ. Risk factors for clinical anastomotic leakage and postoperative mortality in elective surgery for rectal cancer. Int J Colorectal Dis 2007;22:919-927.
41. Konishi T, Watanabe T, Kishimoto J, Nagawa H. Risk factors for anastomotic leakage after surgery for colorectal cancer: results of prospective surveillance. J Am Coll Surg 2006;202:439-444.
42. Komen N, Dijk JW, Lalmahomed Z, Klop K, Hop W, Kleinrensink GJ, Jeekel H, Ruud Schouten W, Lange JF. After-hours colorectal surgery: a risk factor for anastomotic leakage. Int J Colorectal Dis 2009;24:789-795.

43. Jestin P, Pahlman L, Gunnarsson U. Risk factors for anastomotic leakage after rectal cancer surgery: a case-control study. Colorectal Dis 2008;10:715-721.
44. Law WI, Chu KW, Ho JW, Chan CW. Risk factors for anastomotic leakage after low anterior resection with total mesorectal excision. Am J Surg 2000;179:92-96.
45. Lipska MA, Bissett IP, Parry BR, Merrie AE. Anastomotic leakage after lower gastrointestinal anastomosis: men are at a higher risk. ANZ J Surg 2006;76:579-585.
46. Alves A, Panis Y, Trancart D, Regimbeau JM, Pocard M, Valleur P. Factors associated with clinically significant anastomotic leakage after large bowel resection: multivariate analysis of 707 patients. World J Surg 2002;26:499-502.
47. Telem DA, Chin EH, Nguyen SQ, Divino CM. Risk factors for anastomotic leak following colorectal surgery: a case-control study. Arch Surg 2010;145:371-376; discussion 376.
48. Kumar A, Daga R, Vijayaragavan P, Prakash A, Singh RK, Behari A, Kapoor VK, Saxena R. Anterior resection for rectal carcinoma - risk factors for anastomotic leaks and strictures. World J Gastroenterol 2011;17:1475-1479.
49. Bonjer HJ, Deijen CL, Abis GA, Cuesta MA, van der Pas MH, de Lange-de Klerk ES, Lacy AM, Bemelman WA, Andersson J, Angenete E, Rosenberg J, Fuerst A, Haglind E; COLOR II Study Group. A randomized trial of laparoscopic versus open surgery for rectal cancer. N Eng J Med 2015;372:1324-1332.
50. Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, Haglind E, Påhlman L, Cuesta MA, Msika S, Morino M, Lacy AM; COlon cancer Laparoscopic or Open Resection Study Group (COLOR). Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 2005;6:477-484.
51. Rodriguez-Ramirez SE, Uribe A, Ruiz-Garcia EB, Labastida S, Luna-Perez P. Risk factors for anastomotic leakage after preoperative chemoradiation therapy and low anterior resection with total mesorectal excision for locally advanced rectal cancer. Rev Invest Clin 2006;58:204-210.
52. Tarantino I, Warschkow R, Schmied BM, Güller U, Mieth M, Cerny T, Büchler MW, Ulrich A. Predictive value of CEA for survival in stage i rectal cancer: a population-based propensity score-matched analysis. J Gastrointest Surg 2016;20:1213-1222.
53. Probst CP, Becerra AZ, Aquina CT, Tejani MA, Hensley BJ, González MG, Noyes K, Monson. Watch and wait?--elevated pretreatment CEA is associated with decreased pathological complete response in rectal cancer. J Gastrointest Surg 2016;20:43-52; discussion 52.
54. Lee JH, Kim DY, Kim SH, Cho HM, Shim BY, Kim TH, Kim SY, Baek JY, Oh JH, Nam TK, Yoon MS, Jeong JU, Kim K, Chie EK, Jang HS, Kim JS, Kim JH, Jeong BK. Carcinoembryonic antigen has prognostic value for tumor downstaging and recurrence in rectal cancer after preoperative chemoradiotherapy and curative surgery: a multi-institutional and case-matched control study of KROG 14-12. Radiother Oncol 2015;116:202-208.