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Lokal İleri Evre Rektum Tümörlerinde Neoadjuvan Kemoradyoterapinin Lokal Kontrol ve Hastalıksız Sağkalım Üzerine Etkisi

Effect of Neoadjuvant Chemoradiation on Local Control and Disease-Free Survival in Locally Advanced Rectal Neoplasms

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Özet

Amaç: Lokal ileri rektum kanserlerinde tedavinin temelini cerrahi oluştuşturmakla beraber neoadjuvan kemoradyoterapi (KRT) ile lokal ileri rektum kanserlerinde tümör boyutunda küçülmeye bağlı küratif rezeksiyon ve sfinkter koruyucu cerrahi yapılabilirliğinin arttığı bildirilmiştir. Bu çalışmanın amacı, neoadjuvan KRT aldıktan sonra cerrahi tedavi yapılan hastalarda rekürrens, hastalıksız /hastalıklı sağkalım ve buna etki eden faktörlerin araştırılmasıdır.

Yöntem: Ocak 2007- Mayıs 2012 tarihleri arasında lokal ileri rektum kanseri tanısı konularak neoadjuvan KRT sonrası ameliyat edilmiş olan 18 yaş üstü 79 hastanın dosya kayıtları; demografik, klinik, radyolojik ve patolojik veriler açısından retrospektif olarak incelendi.

Bulgular: Çalışmaya 27(%34.2) kadın, 52(%65,8) erkek olmak üzere toplam 79 hasta katılmış olup ortalama yaş 60,82±5' dir. Neoadjuvan KRT sonrası tam regresyon oranı %15,18'dir. Hastaların ortalama takip süresi, 26 ay (3-59 ay aralığında) olarak saptandı. Takip süresince 28 (%35,44) hastada tümör rekürrensi saptanmış olup bunun 12 tanesi lokal, 17 tanesi sistemik rekürrensti. Takip süresince hastaların hayatta kalımı %.83,54 idi. Hastalıksız sağ kalım ise %.72,15 idi. Hastaların büyük çoğunluğunda evre gerilemesi ve tümör boyutlarında küçülme sağlandı.

Sonuç: Hiperfraksiyone RT mezorektumun sınırlarını sterilize eder ve tümör hücre kalıntılarının gelişmesini engeller. Bu durum lokal nüks ihtimalini azaltır ve muhtemelen tümör hücrelerinin uzak organlara giderek metastaz yapmasını da engellemiş olur. Neoadjuvan KRT sonrası yapılacak ideal ameliyat tekniği Total mezorektal eksizyon' dur. Cevaplanması gereken önemli soru ise KRT sonrası ideal ameliyat zamanlamasının ne olduğudurÇalışmamızda olgu sayısının az olması ve takip süresinin kısa olması nedeni ile uzun dönem neoadjuvan kemoradyoterapi uygulanan lokal ileri rektum kanserli hastalarda nüks, sağkalım/ hastalıksız sağkalımın uzun dönem takip sonuçlarının anlaşılması için başka çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Lokal ileri rektum kanseri, neadjuan kemoradyoterapi, hastalıksiz sağkalım.

Abstract

Objective: Although surgery comprises the basis for the treatment of locally advanced rectal cancer, the feasibility of curative resection and sphincter-sparing surgery depending on the reduction in tumour size has been reported to increase with neoadjuvant chemoradiation (CRT) in patients with locally advanced rectal cancer. The aim of this study was to investigate recurrence, survival with disease/disease-free survival and factors affecting them in patients who underwent surgery after receiving neoadjuvant CRT.

Method: The files of 79 patients aged older than 18 years who were diagnosed with locally advanced rectal cancer and underwent surgery after receiving neoadjuvant CRT between January 2007 and May 2012 were retrospectively analysed in terms of demographics and clinical, radiological and pathological data.

Results: A total of 79 patients, among whom 27 (34.2%) were females and 52 (65.8%) were males, were included in the study, and the mean age was 60.82±5 years. The complete regression rate after neoadjuvant CRT was 15.18%. The average follow-up period of the patients was 26 months (range: 3–59 months). During the follow up, tumour recurrence was detected in 28 (35.44%) patients, among whom 12 had local recurrence and 17 had systemic recurrence; the survival rate of the patients was 83.54%. The disease-free survival rate was 72.15%. In most of the patients, stage regression and the reduction of tumour size were achieved.

Conclusion: In summary, hyperfractionated radiotherapy sterilises the margins of the mesorectum and prevents the development of tumour cell remnants, thus reducing the likelihood of local recurrence and preventing tumour cells from metastasising to remote organs. The ideal surgical technique after neoadjuvant CRT is total mesorectal excision. The important question is the optimum time for surgery after CRT. Thus, further studies are required to understand the long-term follow-up results of recurrence and survival/disease-free survival in patients with locally advanced rectal cancer who received long-term neoadjuvant CRT.

Keywords: Locally advanced rectal neoplasms, neoadjuvant chemoradiation, disease-free survival.

Introduction

Colorectal cancers are the most common cancers of the gastrointestinal tract. Their rate among all cancer cases is 13%. Approximately 30% of colorectal cancers comprise rectal cancers (1). Total mesorectal excision (TME) is the basis of treatment of locally advanced rectal cancers (2). Locally advanced rectal cancer (LARC) is a condition that indicates the probability of being unable to be

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resected without leaving any microscopic or gross (macroscopic) disease behind due to adhesion to the local area or fixation on other organs of the tumour (3) (4) . The feasibility of curative resection and sphincter-sparing surgery depending on the reduction in tumour size has been reported to increase with neoadjuvant chemoradiation (CRT) in patients with locally advanced rectal cancer (5). Preoperative radiotherapy (RT) is said to be more effective than postoperative RT (6).

The aim of this study was to retrospectively analyse patients who received neoadjuvant CRT followed by TME, determine locoregional recurrence and disease-free survival rates, as well as factors that affect them, evaluate the results of the applied protocol and compare these results with those reported in the literature.

Table 1. Ratio of the T and N statuses of patients by preoperative (pre-CRT) and postoperative findings.

	Preoperative (%)	Postoperative (%)
T0	-	12 (15.2)
T1	-	2 (2.5)
T2	3 (3.79)	13 (16.5)
T3	69 (87.3)	48 (60.8)
T4	7 (8.86)	4 (5.1)
N0	30 (37.9)	51 (64.5)
N1	28 (35.4)	19 (24)
N2	21 (26.5)	9 (11.3)

Materials and Methods

Patients

The records of 79 patients older than 18 years of age who were diagnosed with LARC and underwent surgery after receiving neoadjuvant CRT between January 2007 and May 2012 at Kocaeli University, Faculty of Medicine,

Table 2. Pathological characteristics and tumour response to CRT (tumour regression status)

	Number	%
Differentiation		
Good	19	24.05
Moderate	45	56.96
Poor	3	3.79
No complete response	12	15.18
Is there lymphovascular invasion?		
Yes	5	6.32
No	74	93.67
Is there perineural invasion?		
Yes	3	3.79%
No	76	96.20%
Tumour regression grade (TRG)		
0	1	1.26%
1	13	16.45%
2	27	34.17%
3	27	34.17%
4	11	13.92%
Distal resection margin (cm)	3.46	
Circumferential surgical margin		
Negative	66	83.6
Positive	13	16.4%
T category		
T0	12	15.18%
T1	2	2.53%
T2	13	16.45%
T3	48	60.75%
T4	4	5.06%
Lymph node category		
N0	51	64.55%
N1	19	24.05%
N2	9	11.39%
Removed lymph node	784	
Average	9.92	
Involved lymph node	103	13.13%
Average	1.3	

Table 3. Postoperative pathological findings and their correlation with regression

Variable	Regression		Total
	≤50%	>50%	
Postoperative T stage			
T0	0	12 (30.76%)	12 (15.18%)
T1	0	2 (5.12%)	2 (2.53%)
T2	4 (10%)	9 (23.07%)	13 (16.45%)
T3	32 (80%)	16 (41.02%)	48 (60.75%)
T4	4 (10%)	0	4 (5.06%)
Postoperative N stage			
N0	22 (55%)	29 (74.35%)	51 (64.55%)
N1	12 (30%)	8 (20.51%)	20 (25.31%)
N2	6 (15%)	2 (5.12%)	8 (10.12%)
Postoperative differentiation			
No complete differentiation	0 (0%)	12 (30.76%)	12 (15.18%)
Poorly differentiated	2 (5%)	1 (2.56%)	3 (3.79%)
Moderately differentiated	31 (77.5%)	14 (35.89%)	45 (56.96%)
Well-differentiated	7 (17.5%)	12 (30.76%)	19 (24.05%)
Surgical margin			
Negative	28 (70%)	38 (97.43%)	66 (83.54%)
Positive	12 (30%)	1 (2.56%)	13 (16.45%)
Is there lymphatic invasion?			
No	39 (97.5%)	38 (97.43%)	77 (97.46%)
Yes	1 (2.5%)	1 (2.56%)	2 (2.53%)
Is there venous invasion?			
No	37 (92.5%)	39 (100%)	76 (96.20%)
Yes	3 (7.5%)	0 (0%)	3 (3.79%)
Is there neural invasion?			
No	37 (92.5%)	39 (100%)	76 (96.20%)
Yes	3 (7.5%)	0 (0%)	3 (3.79%)

Department of General Surgery were analysed retrospectively. During preoperative staging, patients with a tumour identified as T3/T4 and/or N1/N2 on pelvic magnetic resonance imaging (MRI) taken after the rectum is filled with gel and/or with suspected tumour deposits in the mesorectum and a tumour that settled within the first 12 cm from the anal verge were recognised as locally advanced. All of the patients underwent long-term neoadjuvant CRT; after a break of 6 to 8 weeks on average, total mesorectal excision (TME) was performed. In addition, the medical records of patients were examined, and the findings from their physical examination, routine blood tests, carcinoembryonic antigen (CEA) levels and colonoscopic examinations were recorded. Furthermore, the length of the patient follow up, duration of the development of local/systemic recurrence and length of the disease-free survival were assessed. Patients whose neoadjuvant CRT could not be completed for any reason were excluded from the study.

Table 4. Surgical results and follow-up information

	Number	%
Surgical technique		
Sphincter-sparing	52	65.82
Abdominoperineal resection	27	34.17
Morbidity		
Anastomotic or other complications		
Rectovaginal fistula	1	1.26
Anastomotic leak	1	1.26
Pelvic abscess	0	
Separation of perineal wound	0	
Anastomotic stricture	0	
Enterovesical Fistula	2	2.53
Death during follow up	13	16.45
Tumour-related	11	13.92
Non-tumour related	2	2.53
Recurrence during follow up	28	35.44
Local	12	15.18
Anastomotic line	1	1.26
Pelvic cavity	11	13.92
Systemic	17	21.51
Lung	12	
Brain	1	
Liver	10	
Peritoneum	0	
Systemic lymph node	0	
Bone	1	
Adrenal gland	1	
Pancreas	1	

Treatment plan

Chemoradiotherapy: The radiotherapy (RT) area was planned such that it would encompass the primary tumour region and all of the regional lymph nodes; the upper margin was considered the L5-S1 vertebral range, the lower margin was considered the line passing 2 cm beneath the obturator foramen, and the procedure was conducted using a linear accelerator device. RT was applied to the patients as a total of 50.4 Gy in 25 fractions, including 1.8 Gy per session to the whole pelvis. The chemotherapeutic agent 5-fluorouracil (5-FU) was administered as a bolus for 4 days at the beginning of RT and 3 days before the end of RT.

Surgical technique:TME was performed on patients 6 to 8 weeks after CRT was completed.

Pathologic evaluation

After surgery, the specimens removed were examined by a single pathologist who had no knowledge of the clinical data of the patients in accordance with the TME specimen examination protocol, and tumour regression grading as defined by Drowak was evaluated (7). All of the blocks and preparations were checked, and parameters, including the histological type, grade, differentiation, depth of invasion, metastatic lymph node status, presence of tumour deposits, surgical margin (distal and circumferential margins), percentage of circumferential involvement of lumen, tumour diameter, distance of the tumour from the anal verge, lymphovascular invasion, and presence of perineural invasion were re-evaluated. The circumferential margin was considered positive if the tumour involving the mesorectum reached the fascia propria or was located <1 mm from it. The distal surgical margin was considered positive if the tumour was located <5 mm from the margin.

Table 5. Relationship between tumour regression grade and type of surgery

Type of surgery/TRD	AAR (%)	APR (%)	p
0	-	100	0.344
1	84.6	15.4	
2	61.5	38.5	
3	66.7	33.3	
4	58.3	41.7	

Table 6. Analysis of factors affecting overall survival

Variable	Number of Patients	Mean survival of 26 months (%)	Univariate (P)	Multivariate (P)
Sex				
Male	52	82.7	0.584	
Female	27	85.2		
Surgical Technique				
Sphincter-sparing	52	82.7	0.791	
APR	27	85.2		
Differentiation				
Good	3	33.3		
Moderate	45	86.7	0.196	
Poor	19	78.9		
LVI				
Positive	2	50	0.0001	0.063
Negative	77	84.4		
PNI				
Positive	3	66.7	0.598	
Negative	76	84.2		
TRD				
1	14	78.6		
2	27	85.2		
3	27	81.5	0.853	
4	11	90.9		
SS				
Positive	13	69.2	0.228	
Negative	66	86.4		
Pathological T				
0	12	91.7		
1	2	50		
2	13	84.6	0.832	
3	48	83.3		
4	4	75		
Pathological N				
0	51	86.9		
1	19	78.9	0.320	
2	9	77.8		

PNI: perineural invasion, LVI: lymphovascular invasion, TRD: tumour regression grade, SS: circumferential margin.

Table 7. Analysis of factors affecting local recurrence

Variable	Number of Patients	Local Recurrence	Univariate (p)
Sex			
Male	52	19.2	0.165
Female	27	7.4	
Type of surgery			
Sphincter-sparing	52	15.4	0.947
APR	27	14.8	
Differentiation			
Good	3	8.3	0.624
Moderate	45	33.3	
Poor	19	28.3	
LVI			
Positive	2	-	0.544
Negative	77	15.6	
PNI			
Positive	3	33.3	0.372
Negative	76	14.5	
TRD			
0	0	0	0.328
1	14	38.5	
2	27	19.2	
3	27	3.7	
4	11	8.3	
SS			
Positive	13	15.2	0.983
Negative	66	15.4	
Pathological T			
0	12	8.3	0.118
1	2	-	
2	13	-	
3	48	18.8	
4	4	50	
Pathological N			
0	51	15.7	0.713
1	19	10.5	
2	9	22.2	

Postoperative follow-up and evaluation of recurrence

In accordance with a standard follow-up program, patients were followed up with physical examination, complete blood count, liver function tests, CEA and chest x-ray once every 3 months for the first 2 years, and then with whole abdominal computed tomography (CT) once every 6 months, followed by colonoscopy annually. Recurrence was detected pathologically and/or radiologically, and was classified as recurrence in the surgery area (local) or recurrence outside the surgery area in another organ (remote).

Table 8. Analysis of factors affecting systemic recurrence

Variable	Number of Patients	Systemic recurrence	Univariate (p)
Sex			
Male	52	19.2	0.492
Female	27	25.7	
Type of surgery			
Sphincter-sparing	52	23.1	0.640
APR	27	18.5	
Differentiation			
Good	3	16.7	0.738
Moderate	45	0	
Poor	19	48.5	
LVI			
Positive	2	-	0.453
Negative	77	22.1	
PNI			
Positive	3	33.3	0.812
Negative	76	21.1	
TRD			
0	1	100	0.328
1	14	7.7	
2	27	23.1	
3	27	25.9	
4	11	16.7	
SS			
Positive	13	30.8	0.375
Negative	66	19.7	
Pathological T			
0	12	16.7	0.501
1	2	50	
2	13	15.4	
3	48	20.8	
4	4	50	
Pathological N			
0	51	19.6	0.652
1	19	21.1	
2	9	33.3	

Statistical analysis

The SPSS 15.0 software package (SPSS, Chicago, IL, USA) was used to evaluate the data. Chi-squared test was used when assessing categorical variables, and p values less than 0.05 were considered to indicate significance. Multiple logistic regression was conducted for values found to be significant by univariate analysis.

Results

A total of 79 patients, of whom 27 (34.2%) were females and 52 (65.8%) were males, were included in the study. The mean age was 60.82 years (range: 25–83 years). The average distance between the tumour and anal verge was 6.19 cm (range: 0–15 cm), and the average segment length involved by the tumour was 5.14 cm (range: 0.5–15 cm). As a surgical technique, TME was applied to all of the patients. As resection and reconstruction, anterior resection, low anterior resection and abdominoperineal resection (Miles operation) were applied to 4 (5.06%), 48 (60.75), and 27 (41.79%) patients, respectively.

Staging

During clinical and radiological (pelvic MRI) preoperative staging, the tumours of patients were identified as follows: 3 (3.79%) as T2, 69 (87.3%) as T3, 7 (8.86%) as T4, 30 (37.9%) as N0, 28 (35.4%) as N1, 21 (26.5%) as N2, 76 (96.2%) as M0, 3 (3.79%) as M1. In the M1 cases, metastases were solitary in the liver, and metastasectomy with TME was planned after the primary tumour was regressed so that they were included in the neodjuvant CRT program.
After surgery, the following assessments were made: 12 cases (15.2%) as T0, 2 cases (2.5%) as T1, 13 cases (16.5%) as T2, 48 cases (60.8%) as T3, 4 cases (5.06%) as T4, 51 cases (64.5%) as N0, 19 cases (24%) as N1, 9 cases (11.3%) as N2, 76 cases (96.2%) as M0, and 3 cases (3.79%) as M1. Although preoperative examinations cannot provide 100% accurate staging, particularly in terms of lymph node involvement, significant changes were observed in the T and N conditions of patients after neoadjuvant CRT (Table 1). Accordingly, no T0 was detected before surgery; however, 12 patients (15.2%) were found to have T0 after n-CRT. There were 3 patients (3.79%) with T2; after treatment, 13 patients (16.5%) were found to have T2, and the percentage of patients with T3 fell from 87% to 60.8%. After the treatment, the N0 ratio increased from 37.9% to 64.5%, while the N2 ratio decreased from 26.5% to 11.3%.

Pathological evaluation

Regarding the histopathological diagnosis; adenocarcinoma, microinvasive adenocarcinoma, mucinous adenocarcinoma and signet ring cell adenocarcinoma were reported in 66 (83.54%), 8 (10.12%), 2 (2.53%) and 3 (3.79%) patients, respectively.

Concerning differentiation, during the post-operative material assessment, 3 (3.79%) patients were interpreted as poorly differentiated, 45 (56.96%) as moderately differentiated, and 19 (24.05%) as well differentiated. No tumour was detected in 12 patients (15.18%). During postoperative pathologic measurements, the average tumour diameter was 20.52 mm (range: 0–75 mm).

According to the surgeon's evaluation of the surgical resection margins during surgery, R0 resection was performed in 91% of patients. Perforation of the tumour occurred in seven patients (9%) during the perioperative or preoperative period. When the circumferential surgical margins were examined, the margin was found to be negative in 66 cases (83.54%) and positive in 13 (16.45%) cases. Table 2

The histopathological parameters of lymphatic invasion, venous invasion, neural invasion and invasion into perirectal fat tissue (mesorectum) were observed in 2 (2.53%), 3 (3.79%), 3 (3.79%), and 43 (54.43%) cases, respectively (Table 2).

Correlation with the regression of parameters was considered according to the 50% regression threshold, which is recognised generally in postoperative pathological findings. The results are shown in Table 3.

Surgical results and follow-up information of the patients are provided in Table 4. Sphincter-sparing surgery was performed in 65% of the patients, while abdominoperineal resection was performed in 35% of the patients. No early complication causing mortality was observed. The correlation between tumour regression grade and sphincter-sparing surgery was not significant (p =0.344)(Table 5).

On average, 83.54% of the patients survived during a follow-up period of 26 months. The disease-free survival rate was 72.15%. Thirteen patients (16.45%) died during follow up. Eleven deaths (13.9%) were cancer related (liver and lung metastases), and two deaths were non-cancer related. Factors affecting survival are shown in Table 6. Accordingly, the survival rate was around 90% for patients without any remaining residual tumour (pT0, pN0), while this rate decreased to 78% for patients in whom the regression was less than 50%. However, this difference was not statistically significant ($p > 0.05$). Local recurrence occurred in 12 patients. Local recurrence was observed in 12% of cases in whom regression was more than 50%, while 67.7% of the cases in which local recurrence was seen were in the group in which regression was less than 50%. The difference was notable; however, it was not statistically significant ($p > 0.05$). Remote metastasis developed in 17 patients (21.5%). Regression was greater than 50% in around 40% of cases that developed metastasis. The analysis of factors affecting local and systemic recurrence is shown in Table 7 and Table 8.

Discussion

The most important criterion in determining the prognosis of CRC is tumour stage (8) (9) . The degree of bowel wall invasion (T), presence of lymph node metastasis (N) and remote metastasis (M) are prognostic factors (8) . The survival of a patient decreases with increasing stage. (8) . Regarding the prognostic factors, emphasis has been placed on parameters such as the histological type of tumour, the differentiation grade, lymphovascular invasion, perineural invasion, the size of the desmoplastic and inflammatory reaction against tumours, lymph node metastasis, the location, age, and gender . Similarly, in our study, lymphovascular invasion appeared to be the factor affecting survival by univariate analysis; however, its significance disappeared in the multivariate analysis.

Although neoadjuvant CRT is commonly used for stage II and III rectal neoplasms today, it does not show the same effect in all patients. Indeed, tumour regression is more pronounced in patients in whom CRT is effective, and this is the most important factor in determining the likelihood of local recurrence. It is beneficial to reveal markers that identify patients that can benefit from this treatment.Such markers may facilitate the development of individual-specific treatment strategies.

In their series of 562 diseases, Das et al. found that indicators of poor response to neoadjuvant CRT include a rate of circumferential involvement of the rectal wall by the tumour of more than 60%, a CEA level of more than 2.5 ng/dl and a tumour more than 5 cm away from the anal verge (10). In fact, the purpose of using CEA in practice is to determine hepatic metastases and recurrences (11); however, in some studies, 2.5 ng/dl has been accepted as a threshold value, and 5.0 ng/dl in others. Moreover, it was emphasised that, in patients with CEA levels above these values, the prognosis was poorer, regardless of tumour stage . The decisive factors for tumour regression following neoadjuvant CRT include pre-treatment tumour size, circumferential spread of the tumour in the lumen, and its distance from the anal canal (12,13) .

Previous studies have suggested that lymph node involvement in resected specimens is the most important factor affecting long-term outcomes in patients who underwent surgery after CRT (14). This is also the most important factor that determines disease-free survival and survival with disease. The reported overall survival rate was 88% for patients without lymph node involvement and 55% for cases with lymph node involvement, whereas the reported 5-year disease-free survival rate was 85% for those without involvement, 44% for N1 patients and 35% for N2 patients. (15)

These evident differences between the lengths of survival may be associated with the biological aggressiveness of tumours of patients with positive lymph nodes despite neoadjuvant CRT. Indeed, Lim et al. reported in the same study that, in patients with persistent post-CRT lymph node positivity, primary tumour regression was less marked compared with that in N0 patients. Additionally, it was emphasised that the extent of advancement the T status of a tumour significantly increases the lymph node positivity rate. However, even in the case of T0 tumours, there is a ~9% likelihood of lymph node involvement, which explains why T status is not a good predictor of survival . (15) Similar to findings in the literature, in our study group, more than 50% regression was detected in 74% of N0 patients, while regression was detected in 21% of N1 patients. However, in terms of survival, unlike literature data, 87% of N0 patients survived, while 79% of N1 patients survived; the difference was not significant.

Another factor affecting survival is circumferential margin (CM) involvement (16) (17) . CM involvement was 16.5% in our patients, which is in line with the rates obtained at advanced colorectal surgery centres. Furthermore, in our study, 79% of patients with CM involvement during follow up survived, whereas 87% of those without involvement survived, and the difference was not statistically significant.

Another issue is that patients in whom sphincter-sparing surgery can be performed had better survival rates than those who underwent abdominoperineal resection. Tapering of the mesorectum in the section close to the pelvic floor in the distal rectum is considered a barrier to tumour spread. In addition, in the case of distal tumours, lymphatic flow occurs towards the nodes located in the pelvic wall (18). Recurrence is more common in multiple distally located rectal neoplasms, a finding that can be explained by the anatomical structure of the mesorectum and direction of lymph drainage. However, in our study, there was no significant difference in survival rates between patients who underwent abdominoperineal resection and those who underwent sphincter-sparing surgery in the follow-up period.

Radiological examinations for the purpose of staging that aim to determine the efficacy of treatment after neoadjuvant CRT have a certain margin of error. However, for assessing the effectiveness of neoadjuvant CRT, the tumour regression grade in the pathological specimen is a more realistic assessment. A statistically significant relationship was determined between regression and postoperative T and N stages, postoperative differentiation, surgical margins and invasion into perirectal fat tissue. However, although it is not appropriate to use postoperative pathological data as prognostic factors for neoadjuvant CRT, they are indicators of its effectiveness.

Several studies have reported complete regression of ~15–20% following neoadjuvant CRT (19) . In our study, this ratio was 15.18%, which is consistent with values reported in the literature. Tumour regression is known to depend on the radiation dose, combination of chemotherapy and radiotherapy, and time between preoperative treatment and surgery (20) [(21). It is expected that the regression rate will increase as factors affecting the effectiveness of the treatment are established.

The most important factors shown to affect local recurrence are the presence of tumours in the surgical margins and involvement of lymph nodes. Therefore, postoperative CRT was replaced by perioperative CRT in T3, N + patients. Indeed, in a German Oncologic Surgery study, it was reported that there was less local recurrence in those who received neoadjuvant CRT than in those who received adjuvant CRT during a follow-up period of 5 years (22). Moreover, in a Swedish, Dutch and CRO7 study, local recurrence was demonstrated to be less in those who received preoperative CRT (23).

In our study, regression of 12 of 13 patients in whom the surgical margin was found to be positive was in the group with ≤50% regression. Lymph node assessment is an important prognostic factor in CRC (24). An

inverse relationship was found between prognosis and the number of positive lymph nodes. Regardless of the presence of metastasis, the total number of lymph nodes is an independent risk factor (24). A minimum of 12 lymph nodes is necessary to determine the stage during the assessment of colorectal surgery material (25). The average number of lymph nodes found in our study was 9.39, which is close to the optimum value. Another important fact to note is that the number of lymph nodes retrieved from a specimen depends not only on the surgeon but also the experience and rigor of the pathologist who examines that specimen.

The survival rate decreases, and the metastasis rate increases, in the presence of vascular and neural invasion (26) . Venous invasion is also associated with local invasion of rectal carcinoma (27). In our study, two cases had lymphovascular invasion, and perineural invasion was observed in three cases. Although lymphovascular invasion appears to have a significant effect on survival in univariate analysis, this was absent in multivariate analysis.

In a Swedish study, short-term 25-Gy RT was reported to have a positive effect on local control as well as survival (28). In this study, the 5-year survival rate was 58% in patients who underwent surgery after RT and 48% in those who only had surgery. However, a significant difference in this study was that TME, a recognised technique today, was not practised routinely.

Unlike the Swedish study, in a Danish study, no significant difference in 5-year survival was found between a patient group who received TME routinely after CRT and one that received TME directly without CRT (29) . In our study, the local recurrence rate was approximately 15% on an average follow-up period of 2.2 years, slightly higher than reported previously. When the first dataset in our series is considered, a remote metastasis rate of ~21% during an average follow up of 2.2 years indicates that neoadjuvant CRT will not exert a positive effect on survival.

Similarly, in a Polish study, TME was performed 7 days after short-term CRT in one patient group and 4 weeks later after short-term CRT in another group. It was discovered that time allowed before surgery after CRT had no significant effect and that a significant difference occurred in patients in whom downstaging was achieved. The most important factor affecting survival was the rate of tumour downsizing/downstaging after CRT. Pach et al. reported that the 5-year survival was 90% in patients responding to CRT, compared to ~60% for patients who failed to respond to treatment (30) . In line with the Polish study, Stipa et al. demonstrated that in patients for whom full regression was achieved with CRT the 5-year survival rate was significantly different from that of patients failing to respond to CRT (96% versus 54%) (31). Moreover, CRT did not increase the likelihood of sphincter-sparing surgery (30) . In our study, no significant difference was found in recurrence or survival between patients with complete or >50% regression.

Another issue considered to affect local recurrence and survival is the time between completion of CRT and surgery. In their randomised study, Patch et al. reported no significant difference in survival between patients who underwent TME 1 week and 4 weeks after 25-Gy RT. They associated this with some patients not responding to RT and the tumour advancing farther during the longer period. However, they concluded that a longer waiting period after CRT results in greater tumour shrinkage and that the surgical procedure becomes easier. In this regard, Wolthuis et al., compared 356 patients who waited for less or more than 7 weeks after CRT; the complete tumour regression rate and 5-year survival rate increased significantly with prolonged waiting periods, without a negative impact on oncologic outcomes (32). In our study, although there was no standard waiting period due to a busy surgery schedule, patients underwent surgery within 4 to 8 weeks on average.

Since this study was retrospective, there were some difficulties in obtaining the data of the patients. In particular, it was not possible to

have access to all of the reports of imaging tests carried out by outside centres. Additionally, endoscopic biopsy blocks and preparations of patients who were diagnosed outside of our hospital were unavailable, so these patients were excluded from the study. Neoadjuvant treatment has been applied only in our hospital since 2007, so the number of patients who met the inclusion criteria was limited. Another limitation of this study was the short follow-up period. Although most of the recurrences and metastases occurred within the first 2 years, it would be more appropriate to evaluate our practice with 5-year follow-up results. Some of the parameters that were not statistically significant may become significant if the number of patients and length of the follow-up period were increased.

In summary, hyperfractionated RT sterilises the margins of the mesorectum and prevents the development of tumour cell remnants, thus reducing the likelihood of local recurrence and preventing tumour cells from metastasising to remote organs. The ideal surgical technique after neoadjuvant CRT is TME. The important question is the optimum time for surgery after CRT. In our study, the number of cases was limited, and the follow-up period was short. Therefore, it would be appropriate to await the 5-year outcome and perform a reassessment.

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