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Retrospective Long-term Results and Prognostic Factors of Treatment for Colorectal Cancer

Bahar BALTALARLI, Nese C. DEMIRKAN, Ozgur YILDIRIM, Uğur SUNGURTEKIN

Pamukkale University Faculty of Medicine, Department of Radiation Oncology, Denizli, TURKEY

ABSTRACT

To evaluate retrospectively 5-10 year overall survival rate in patients with colorectal cancer treated with or without adjuvant therapy for early stage and analyze the impact of some prognostic factors on clinical outcome we retrospectively reviewed 56 patients treated with only surgery, postoperative or preoperative 5-fluorouracil-based chemotherapy and radiotherapy. The following prognostic factors were considered at univariate analyses: age, sex, tumor location, pathological, tumoural and nodal stage, surgical procedure, pathological specimen margins and adjuvant treatment if applied. The 5 and 10 year actuarial rates for overall survival (OS) were 66 % and relapse free survival (RFS) rates were 83% and 58% respectively for all patients. Five years survival was 100%, 73% and 44% respectively for stages I, II and III ($p< 0.01$). Five years survival for N0, NI and NII disease were 81.3%, 75% and 0% respectively ($p< 0.01$). Better prognosis was observed for colon cancer compared to rectal and rectosigmoid tumors: 5 years survival rates 90%, 70% and 40% respectively ($p< 0.01$). Univariate analysis showed that nodal disease, location of tumor in a subsite of colon, pathological stage and surgical procedure had an impact on survival. Our retrospective study showed a good 5- 10 year overall survival. Factors as individual pN2, tumor location and advanced pathological stage negatively influenced survival rates. In our opinion to achive better results especially in N2 cancer and rectal and rectosigmoid tumors, especially use of appropriate chemoradiation protocols and new high art radiation technology must be considered in clinical studies in advance.

Keywords: Colorectal cancer, Prognostic factors, Radiotherapy

ÖZET

Kolorektal Kanser Tedavisinin Retrospektif Uzun Dönem Sonuçları ve Prognostik Faktörleri

Kolorektal kanserli ve postoperatif olarak adjuvan veya neoadjuvan tedavi uygulanmış veya erken klinik evrede olması nedeniyle cerrahi operasyon dışında ek tedavi uygulanmamış olan olgularda 5 ve 10 yıllık sağkalım verilerini incelemek ve olası prognostik faktörleri belirlemek amacıyla çalışma retrospektif analiz yöntemiyle planlanmıştır. Bu çalışmada Pamukkale Üniversitesi Tıp Fakültesi Radyasyon Onkolojisi Bölümüne tedavi ve izlem için başvuran ve periyodik kontrollere çağırılan 56 lokal yerleşimli kolorektal kanserli olgu dosya verileri incelenerek retrospektif yöntemle değerlendirilmiştir. Yaş, cinsiyet, tümör evresi, nodal evre, patolojik evre özellikleri, tümör yerleşimi, cerrahi yöntem, sınır tutulumu ve radyoterapi veya kemoterapi adjuvan uygulamaları gibi değişkenler yönünden sağkalımlar karşılaştırılmış ve aradaki farklar istatistiksel yönden değerlendirilmiştir. Beş ve 10 yıllık genel sağkalım oranları %66, yinelemesiz sağkalım oranları ise sırasıyla 83% ve 58%dir. Evre I, II ve III için sırasıyla sağkalım %100, %73 ve %44 olup, N0, N1 ve N2 için sırasıyla %81.3, %75 ve %0'dır. Kolon kanseri diğer rektal ve rektosigmoid yerleşimli tümörlere göre daha iyi sağkalım göstermekte olup sırasıyla 5 yıllık sağkalım %90, %70 ve %40dır ($p< 0.01$). Ortalama izlem süresi 83 ay (8-168ay) olan olgular için yapılan Kaplan Meier sağkalım analizinde log rank analizlerine göre, nodal evre, tümör yerleşimi ve patolojik evre ve cerrahi yöntemin sağkalımı etkileyen faktörler ($p< 0.001$) olduğu saptanmıştır. Kolorektal kanserli 56 olgunun retrospektif olarak değerlendirildiği bu çalışmada patolojik ve nodal evre ve tümör yerleşiminin istatistiksel anlamlılık düzeyinde sağkalıma etkili olduğu saptanmıştır. Bu çalışmada, herhangi bir kolon bölgesinde yerleşimi göz önüne alınmaksızın tüm N2 tümörlerde tedavi stratejilerinin gözden geçirilerek kemoradyoterapi seçeneklerinin uygun doz ve yoğunlukta tedaviye eklenmesi ve /veya yoğunluk ayarlı radyoterapi gibi sofistike tekniklerin kliniğe geçirilmesiyle, sağkalımı arttırmaya yönelik farklı tedavi yöntemlerinin araştırılmasını hedefleyen klinik prospektif amaçlı çalışmaların planlanması gerekliliği ortaya konmaktadır.

Anahtar Kelimeler: Kolorektal kanser, Prognostik faktörler, Radyoterapi

INTRODUCTION

Randomized clinical trials have demonstrated that adjuvant chemotherapy improves survival for patients with stage III colon cancer.[1-3] For patients with stage II or III rectal cancer, the combination of adjuvant chemotherapy and radiation therapy improves survival compared with surgery alone[4,5] or surgery plus radiation therapy.[6] In 1990, Consensus Conference of the National Institutes of Health strongly recommended these adjuvant therapies for patients without medical or psychosocial contraindications.[7] Furthermore widely used technologies in radiation oncology such as Intensity Modulated Radiaotherapy (IMRT) or dose painting IMRT to functionally interested areas of the tumor will help management of rectal tumors in near future as well.[8]

Prognostic factors for patients with colorectal cancer (CRC) are important for the determination of high-risk groups for recurrent disease in early stages, and for overall survival in both early stage and advanced stage. Prognosis in CRC is affected by a large number of factors. The most important of these factors are the clinical stage of presentation, surgical quality as the ability to perform curative or palliative operation, location of tumor, pathological stage and type of treatment. Moreover, many factors could influence local recurrence, disease free survival (DFS) and overall survival (OS). Many studies in Western countries and also in Turkey have been published about the prognostic factors in CRC patients.[9-11]

In this study we have evaluated the long term outcome in 56 patients with colorectal cancer who were treated between 2000 and 2007 in Pamukkale University Hospital, a tertiary care hospital in the west of Turkey. The aim of the present study was to determine 5 years and 10 years of OS with UICC stages I, II and III colorectal cancer. Particularly, we analyzed the impact of pathological and clinical factors on OS.

PATIENTS AND METHODS

We retrospectively reviewed the records of 56 patients (38 male and 18 female) with TNM stages I, II and III colorectal cancer treated between 2000 and 2007 at the Pamukkale University Hospital. Patients were treated with only surgery for early stages or preoperative/postoperative radiotherapy and 5-FU based on long term or concomittan chemotherapy for local or locally advanced disease.

Tumor site was identified by endoscopy, preoperative computerized tomography (CT) and surgical clips. Local recurrence was defined as pelvic relapse after surgery, and it was histologically or radiologically proven. The following variables were considered: age (<70 and ≥70 years), sex, tumor site, surgical procedure, pathological stage, nodal and tumoral stage, surgical margins and type of adjuvant treatment. The UICC TNM system was used for tumor stagings.

All patients were surgically treated with resection and side to side anastomosis or abdominal-perineal resection (APR). A total of 18 patients was treated with postoperative/preoperative concomitant radiotherapy with 5-FU. Radiotherapy was delivered with a total mean dose of 50 Gy (1.8-2.0 Gy/fr for five days a week) and a mean time interval of 16 weeks from surgery. A 2D radiotherapy techique was used. Target volume included surgical clips suggesting tumor bed, internal iliac nodes, obturator nodes, presacral and perirectal spaces; for T4 tumors, external iliac nodes were also included. After abdominal-perineal amputation (Miles'amputation), the perineal scar was also included in the target volume.

5-FU-based chemotherapy were administered to 46 patients. Twelve patients received postoperative chemoradiotherapy and 6 patients received preoperative concomittant chemoradiotherapy consisted of two cycles of 5-FU (endovenous bolus of 425 mg/m^2/day and 20 mg/m^2 leucoverin for four consecutive days) administered during the first and the last week of the radiotherapy treatment. Another four cycles of chemotherapy for five consecutive days were administered four weeks after the end of the radiochemotherapy treatment. The remaining patients received postoperative adjuvant 6 cycles of flurourasil based treatment. Acute and late toxicity were assessed using the Radiation Therapy Oncology Group (RTOG) scale.

Patients were followed every four months for the first year, every six months from the second to the fifth year, and then once a year. Follow-up evaluation started after the completion of adjuvant treat-

ment. During the follow-up, physical examination, performance status evaluation, complete blood count, serum chemistry, tumor markers (CEA and CA 19-9 levels), chest radiography performed every four months for the first year. All these studies were repeated every six months for the subsequent 5 years. Moreover, chest-abdominal-pelvic CT scan and colonoscopy were performed annually.

Statistical Analysis: All qualitative factors were summarized as frequency and percentage and all quantitative factors as mean and standard deviation or median and range. The Kaplan-Meier method was used to analyze overall survival at 60 and 120 months of follow-up. Statistical significance between curves was evaluated using the logrank test. Univariate analysis was performed using Kaplan Meier survival analyses. Covariates were: age, gender, T and N stage, UICC staging, margin status, tumor location, surgical procedure and type of treatment. Follow-up was defined as the interval between surgery and death.

RESULTS

Median follow-up was 83 months (range 8-168), and the median age was 60 years (range 21-81). Characteristics of patients were shown in Table 1. At surgery, 40 patients (71.4%) were <70 years and 16 (28.6%) were > 70 years. A total of 52 of 56 patients (92.7%) were treated with resection and side to side anastomosis and 4 of 56 patients (%7,1) with APR. Tumors localizing in the colon intraperitoneally was most common than rectal and rectosigmoid tumors consisting of 23 (42.8%), 17 (30.3%) and 16 (28,6%) tumors respectiively. Nine patients were in stage I (16.1%), 25 (44.6%) in stage II and 22 (39.3%) in stage III according to UICC. Nodal staging were as follows, N0 was 35 (62.5%), N1 was 13 (23,2%), and N2 was 8 (16.1%). T1 stage was diagnosed in 3 (%7), T2 in 7 (12.5%), T3 in 42 (%75), T4 in 4 (7.1%) patients. Pathological macroscopic margins were free of tumor in 52 patients (92%) whereas one patient had positive specimen margins (1.7%) and information for three patients (5.1%) were not obtained from the reports. Six patients (10.7%) received preoperative radiochemotherapy, 12 (21.7%) patients postoperative radiochemotherapy, 32 (57,1%) patients had postoperative chemotherapy and 6 (10,7%) patients had no adjuvant treatment.

Table 1. Demographic, histologic and treatment characteristics of patients

Variable	Number of patients	%
Overall no	56	
Age at surgery		
<70	40	71.4
>70	16	28,6
Gender		
Male	38	67.9
Female	18	32,1
Tumor location		
Rectum	17	30.3
Rectosigmoid	16	28.6
Colon	23	42,8
Pathologic stage		
I	9	16.1
II	25	44.6
III	22	39.3
Nodal stage		
0	35	62.5
1	13	23.2
2	8	14.2
T stage		
1	3	5
2	7	12.5
3	42	0.75
4	4	7.1
Margin status		
Negative	52	92.8
Positive	1	1.7
Unknown	3	5.1
Surgery		
AR	52	92.9
APR	4	7.17,1
Adjuvant treatment		
Preoperative radiochemotherapy	6	10.7
Postoperative radiochemotherapy	12	21.7
Postoperative chemotherapy	32	57.1
No adjuvant treatment	6	10.7

Table 2. Analysis of impact of clinical charesteristics on overall (OS) and relapsefree survival (RFS)

Variable	Overall survival			Relapse free survival		
	5 years (%)	10 Years	p	5 years (%)	10 Years	p
Age at surgery						
<70	66,1	62,9	NS (0,4)	73,9	64,8	NS (0,3)
>70	78,7	78,7		91,7	45,8	
Gender						
Male	66,5	62.8	NS (0,4)	78,2	58,9	NS (0,7)
Female	74,7	74,7		74,7	65	
Tumor location						
Rectum	70,1	–	<0,05 (0,002)	801	–	
Rectosigmoid	40,1	32,1		64,8	43,2	(0,09)
Pathologic stage						
I	100		<0,05	1001		
II	78.4	73.2	(0.009)	85	72.7	(0.006)
III	44,1	44.1		51,8	0,00	
Nodal stage						
N0	81,3	77.6	<0,05	89	70	<0,05
N1	75	75	(0.00)	83	41	(0.00)
N2	0	0		0	0	
T stage						
1	100					
2	85.7	85.7	NS	85.7	85.7	(0.069)
3	70.2	64.3	(0.3)	74.7	55.7	
4	66.7	0	50	0.00		
Margin status						
Negative	68.5	65.8	NS	75.1	56.6	NS
Positive			(0.8)			
Unknown	66.7	0		50	0.00	
Surgery						
AR	74.5	71.8	0.00	80.4	63.2	0.00
APR	0	0		0	0	
Adjuvant treatment						
Preoperative radiochemotherapy	66.7	–	NS	80	–	NS
Postoperative radiochemotherapy	63.5	63.5	(0.5)	70	70	(0.5)
Postoperative chemotherapy	66.2	62.1		74.2	51.2	
No adjuvant treatment	100			100	100	

Thirthynine patients were alive and 17 patients (4 female,13 male) were dead at the time of analyses.

Thirteen patients recurred and 3 had second primers one as brain tumour, the second as stomach and the other as colon tumour. Ten patients died because of disease progression, one patient had a second primary brain tumour and one of them had cardiovascular death. Two of the six patients who were treated with preoperative chemoradiotherapy had died and the 5 years survival was 66.7%, twelve patients were treated with postoperative combination chemoradiotherapy and three of the patients had died

Table 3. Distribution of pathological nodal staging (pN) relating tumor localization on survival

Pathological Nodal stage	Tumor localization	Number of patients	Event (death)	5 years survival (%)	p
N0	Colon	15	1	92.9	0.03
	Rectum	10	1	90	
	Rectosigmoid	10	5	58.3	
NI	Colon	7	0		0.04
	Rectum	5	2	60	
	rectosigmoid	1	1	0	
N2	Colon	1	1	0	NS (0.1)
	Rectum	2	2	0	
	rectosigmoid	5	4	0	

with 69.3% 5 years survival. 32 patients were treated postoperatively with long course of 5 Fu based chemotherapy regimens, 11 of the patients had died with a 5 years survival of 66.2%. The 9 patients whith early stage disease who did not have any adjuvant treatment had 100% survival.

The individual evaluation of pT, pN and UICC cancer staging characteristics showed that the pN2, stage III and surgical procedure had statistically significant impacts on overall survival ($p< 0.05$). All statistical analyses were performed using SPSS® software 16.0 (SPSS Inc,)

The 5-year univariate analysis showed that age ≥70 years, sex, tumoral stage, margin status, and adjuvant treatment strategies did not have a statistically significant impact on OS (Table 2).

While the N2 variable, pathological stage and surgical procedure were statistically significant factors for RFS ($p< 0.05$), the other factors were not ($p> 0.05$).

High rectum and rectosigmoid junction tumors and low rectal tumour location demonstrated worse prognosis than other locations such as colon location ($p< 0.05$). Distribution of pathological nodal staging (pN) related with tumor localization on survival was demonstated in Table 3. Colon tumors did not have better prognosis than rectal and rectosigmoid tumors regarding with nodal stage ($p> 0.05$). While, rectal and rectosigmoidal tumors had similar survivals for stage I and II, stage III tumors had poorer prognosis than stage III colon cancer (Table 4).

Table 4. Distribution of pathological staging (pTN)relating tumor localization an survival

Pathological stage	Tumor localization	Number of patients	Event	5 years survival (%)	10 years survival (%)	p
Stage I	Colon	3	0	100	100	
	Rectum	6	0	100	100	
Stage 2	Colon	12	1	90	90	NS (0.2)
	Rectum	4	1	75	-	
	Rectosigmoid	9	4	66.2	53.3	
Stage 3	Colon	8	1	85.7	85.7	0.01
	Rectum	7	4	42	-	
	Rectosigmoid	7	6	0	0	

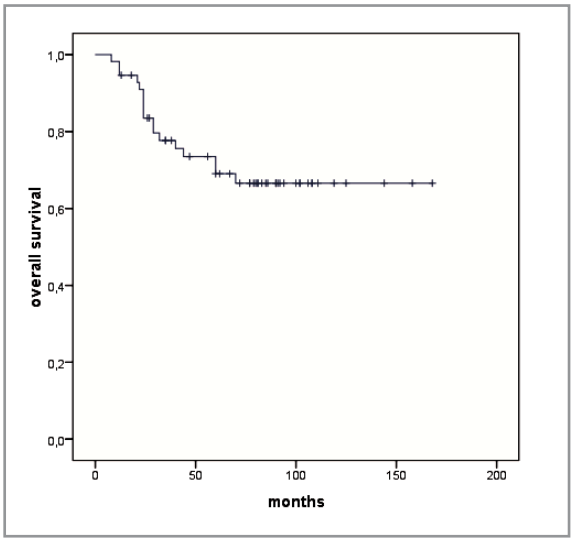

Figure 1. Kaplan meier curve of overall survival of 56 patients

Kaplan Meier survival curve for the whole group of patients was shown in Figure 1.

Kaplan Meier survival curve for the group of patients regarding pathological, nodal stage, treatment methods and tumor localization were shown in Figure 2.

DISCUSSION

The historical combined randomized postoperative 5-FU-based chemoradiation trials demonstrated an improvement in LC ranging from 83% to 92% with a mean survival rate of 60% for rectal cancer.[12-14] Higher survival rates were also reported for colon cancer patients receiving postoperative chemotherapy.[15] Though with all limitations of a retrospective analysis, with a long period of collection and differences in technologies, radiotherapy and surgery procedures and treatment policies we confirmed the importance of some factors that explain the heterogeneity within stages II and III and location of tumor regarding with prognosis. Regarding with survival, 5-year stage-specific survivals of colorectal cancer patients were 100% for stage I, 78.4% for stage II and 44.1% for stage III. Investigators from Thailend had reported 5-year stage-specific survivals of 100% for stage I, 68% for stage II, 44% for stage III, and 2% for stage IV colorectal cancer patients.[16] From Korea 5-year stage-specific survivals of 89% for Dukes' stage A, 75% for Dukes' stage B, 49% for Dukes' stage C, and 12% for Dukes' stage D was reported for colorectal cancer patients.[17]

Colon cancer patients had a tendency to live longer than rectal cancer patients. In colon cancer, 5-year stage-specific survivals of patients in the present study were 100% for stage I and 90% for stage II, and 85.7% for stage III patients. When compared with a study from the United States Surveillance, Epidemiology, and End Results (SEER) data, the 5-year stage-specific survivals of colon cancer in American's study were 93% for stage I, 82% for stage II, 59% for stage III.[15] This present study had 5-year stage-specific survivals of colon cancer approximately similar to American study. However, 5-year survival rates of colon cancer patients receiving 5-FU based adjuvant chemotherapy (66%) reported by the Intergroup 0089 study was somewhat lower.[18]

In rectal cancer, 5-year survival rates as 100% for stage I, 75% for stage II and 42% for stage III were observed. Yalman et all reported 67.6% for stage II and 41.4% for stage III five years overall survival in 290 patients with rectal carcinoma.[19] The results were comparable with the 5-years overall survival rates of rectal cancer treated with adjuvant treatment, ranging from 37% to 79%.[20]

The results of other studies on prognostic factors for colon and rectal cancer treated with resection only and adjuvant treatment showed that age, sex, stage, histological grade, direct spread of tumor, venous invasion, and rectal location were prognostic factors for colorectal cancer.[10,11] The results of previous studies except age and sex were similar to the present study as both were not found to be prognostic factors in the presented study.

Our data confirmed the following evaluations: factors such as pN2, III pathological stage and tumor localization and type of surgical procedure influenced OS.

As regards tumor stage, Gunderson et al. demonstrated a negative influence of T and N factors because a locally advanced tumor (T3-T4, N plus) had a worse prognostic evolution than others with a single factor alone (T3N0 or T1-2 N1). Therefore, sta-

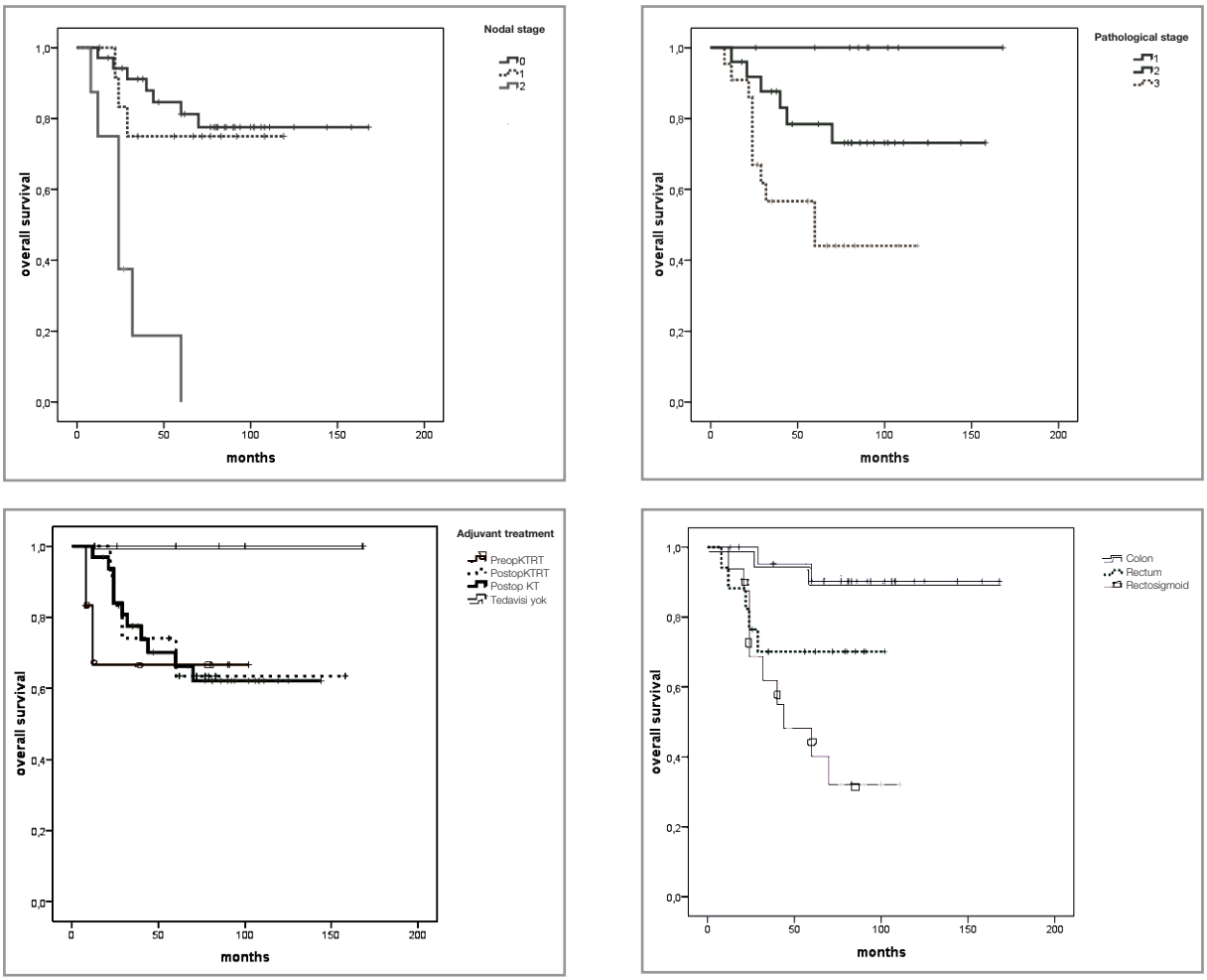

Figure 2. Kaplan Meier survival curves for the group of patients regarding pathological , nodal stage, treatment method and tumor localization

ges II (T3-4 N0) and IIIA (T1-2 N1) had a better prognosis than stages IIIB (T3N1) and IIIC (T3-4 N2).[20] Greene et al. analyzed data entered in a National Cancer Data Base for 5.987 stage III patients with rectal cancer between 1991 and 1993.[21] In stage IIIA patients 60% 5-year survival, IIIB patients 41%, and IIIC patients 29% were observed, with significant differences in all stages. In this analyses pathological stage I, II and III had 100%, 75% and 44% 5 years survival for rectal patients.

Another Turkish data collected from 14 different hospitals in Turkey in a large cohort of 502 patients showed that N2 stage (4 or more lymph node metastasis) had the poorest survival with 36,1%, whereas N1 with 40.6% and N0 with 66.2%.[22] In this present analyses the patients with pathological NO had 81.3 and N1 had 75% and N2 had 0% survival, with similarity for NO and N1 but worse outcome for N2 patients.

N2 stage seemed to be the worst prognotic factor which was demonstrated in similar studies and in the present study this also could be due to the smaller number of patients.

Regarding with tumor localization, while rectal and rectosigmoidal tumors had similar survival for stage I and II, for stage III tumors poor prognosis compared to stage III colon cancer was observed (Table 4). Colon tumors had also better prognosis compared to rectal and rectosigmoid tumors regarding with pathological stage ($p< 0.01$). Nevertheless, N2 status was not affected by tumor localization since this is strongly the most prognostic indicator, all the colorectal tumors had poorest survival in this stage (5 years survival 0%).

Long term radiotherapy and chemoradiation schemes are aimed at tumor downstaging. Evidence has been gathered from large randomized trials (Total Mesorectal Excision trial [TME], Swedish Rectal Cancer Trial, and Cancer Research UK [CR07]) with a total number of 4.427 patients, showing that for primarily resectable rectal cancer, short-term preoperative radiotherapy (5 Gy daily for 5 days) resulted in local recurrence rates lower than 5%, especially in combination with TME surgery.[23,24,25] For locally advanced tumors, long-term radiotherapy (approximately 50 Gy) in combination with neoadjuvant chemotherapy is the treatment of choice.[26,27] The combination of the above-mentioned differences in therapy results in improved prognosis of patients with rectal cancer, especially with respect to local recurrence.

Regarding the tumor location, Benzoni et al. examined clinical outcome in patients enrolled in a neoadjuvant chemoradiation therapy followed by surgery protocol for rectal cancer, distinguishing between intraperitoneal and extraperitoneal cancer.[28] The DFS and OS were poor for extraperitoneal than for intraperitoneal rectal cancer. Data from Genovesi et all confirmed these evaluations in the multivariate analysis, with a negative influence of extraperitoneal tumor location on DFS and CSS.[29] In this present study the carsinomas presenting at the lower rectum also had 40% 5 years survival which is comparable to the other studies as well. Pathological studies of the Circumferential Resection magrin (CRM) at the level of the anorectal junction and anal canal sphincter show higher rates of CRM involvement due to dissection along the thinning mesorectum on to the anal sphincter.[30] So it's clear that for distal rectal cancers, abdominoperianal amputation has poorer local control and overall survival. The worst overall survival regarding the four patients who had abdominoperianal amputation might be due to small number of patients and locally advanced stage.

In this present study, although most of the tumors located in rectosigmoid were T3 and /or node positive, the neoadjuvant treatment strategies hads not been employed adequately for N2 rectosigmoid and intraperitoneal tumor sites according to the faculties treatment policies. As a result, the survival had been effected poorly for this localization of tumors. This could be explained also by either an incomplete lymphatic resection or inappropriate application of chemoradiation protocols.

One well recognized late effect of radiation therapy is an increased risk of second primary malignancy. In our study a second primary cancer devolped in three patients affecting the colon, brain and stomach. The NSABP R02 trial reported second primary malignancy in 5.9 % of the patients with an increased risk of colon and prostate cancer. In Krook's study this rate was 5.8% affecting brain, breast, colon, endometrium, kidney, larynx, lip, lung and pancreas.[6] As the study had a long duration of follow up, our data did not demonstrate such a high risk of second malignancies which also might be related with the small number of patients cohort .

All these data support the concept of heterogenity between colorectal cancers and the need to identify reliable markers to detect unfavorable patient who could be cured with the appropriate therapy regimens regarding these issues. Between all rewiewed prognostics, nodal positivity seems to be the worst which in turn must change our habits in applying treatment policies, especially in using type of preoperative or postoperative chemoradiotherapy regimens for colon and rectosigmoidal tumors as in rectal carsinomas.

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Correspondence

Dr. Bahar BALTALARLI

Pamukkale Üniversitesi Tıp Fakültesi

Radyasyon Onkolojisi Anabilim Dalı

Kınıklı

DENİZLİ / TURKEY

Tel: (+90.258) 444 07 28

Fax: (+90.258) 213 10 34

e-mail: baharbaltalarli@yahoo.co.uk