Low Prognostic Nutritional Index Before Radiotherapy is a Poor Prognostic Factor for Rectum Cancer

Radyoterapi Öncesi Düşük Prognostik Nutrisyonel İndeks Rektum Kanseri için Kötü Prognostik Faktördür

Prognostic Value of PNI in Rectum Cancer

Neslihan Kurtul[1], Celalettin Eroğlu[2]
[1]Dept. of Radiation Oncology, University of Sütçü İmam, Faculty of Medicine, Kahramanmaraş,
[2]Dept. of Radiation Oncology, University of Erciyes, Faculty of Medicine, Kayseri, Turkey

The manuscript has been presented in 8th National Congress of Gastrointestinal Oncology as a poster, 08-09 April 2016, Gaziantep.

Özet

Amaç: Bu çalışmada cerrahi sonrası kemoradyoterapi uygulanan rektum kanserli hastalarda prognostik nutrisyonel indeks (PNI) değerinin sağkalım üzerine etkisi araştırıldı. Gereç ve Yöntem: Çalışmaya adjuvan kemoradyoterapi alan 65 hasta alındı. Hastalara 5040 cGy radyoterapi ve eşzamanlı 5-FUFA kemoterapisi uygulandı. Hastalar ROC analizine göre ≤46 düşük grup, 46< yüksek grup olarak 2 gruba ayrıldı. Gruplar arası sağkalım farkı log rank testi ile hesaplandı. Tek değişkenli ve çok değişkenli faktörlerin sağkalıma etkisi cox regresyon analizi kullanarak hesaplandı. Bulgular: Hastaların 22'si (%33,8) kadın 43'ü (%66,2) erkekti. NPI düşük grupta 28 (%43,1), yüksek grupta 37 (%56,9) hasta vardı. Kaplan-meier analizine göre PNI düşük grupta ortalama sağkalım 59 (%95 GA:44.95-73.08) ay iken yüksek grupta 80 (%95 GA:66.53-94.82) aydı (p=0.036). 5 yıllık sağkalım PNI düşük grupta %49, yüksek grupta %65 olarak bulundu. Tek değişkenli analizde T evre, N evre, tümör çapı ve PNI genel sağkalım üzerinde etkili idi (p<0.05). Çok değişkenli Cox regresyon analizinde T evre (p=0.014), tümör çapı (p=0.023) ve PNI (p=0.045) diğer değişkenlerden bağımsız olarak genel sağkalım üzerine etki eden prognostik faktörler olarak bulundu. Tartışma: Çalışma sonucunda radyoterapi öncesi PNI değeri rektum kanseri için kötü prognostik faktör olarak bulundu.

Anahtar Kelimeler

Prognostik Nutrisyonel İndeks; Radyoterapi; Rektum Kanseri

Abstract

Aim: The aim of this study was to examine the effect of the prognostic nutritional index (PNI) value on survival in patients with rectum cancer who received postoperative chemoradiotherapy. Material and Method: The study included 65 patients who received adjuvant chemoradiotherapy. Radiotherapy of 5040 cGy and simultaneous 5-FUFA chemotherapy was given to the patients. The patients were divided into two groups as PNI ≤46 and PNI >46 according to the ROC analysis. The differences in survival between the groups were calculated using the log rank test. The univariate and multivariate hazard ratios were calculated using the Cox proportional hazard model. Results: The patients included 22 (33.8%) females and 43 (66.2%) males. The low PNI group comprised 28 (43.1%) patients and the high PNI group, 37 (56.9%). According to the Kaplan-Meier analysis, mean survival was 59 months (95% CI; range, 44.95-73.08 months) in the low PNI group and 80 months (95% CI; range 66.53- 94.82 months) in the high PNI group. The 5-year survival rate was 49% in the low PNI group and 65% in the high PNI group. In the univariate analysis, T stage, N stage, tumor diameter, and PNI had an effect on overall survival (p<0.05). In the multivariate Cox regression analysis, T stage (p=0.014), tumor diameter (p=0.023), and PNI (p=0.045) were found to be prognostic factors affecting overall survival, independent of the other variables. Discussion: The results of the study showed that the PNI value before radiotherapy is a poor prognostic factor for rectum cancer.

Keywords

Prognostic Nutritional Index; Radiotherapy; Rectum Cancer

DOI: 10.4328/JCAM.4796 Received: 02.09.2016 Accepted: 29.09.2016 Printed: 01.05.2017 J Clin Anal Med 2017;8(3): 185-9
Corresponding Author: Neslihan Kurtul, Dept. of Radiation Oncology, University of Sütçü İmam, Faculty of Medicine, Kahramanmaraş, Turkey.
GSM: +905067872841 F.: +90 3442803409 E-Mail: drneslihankurtul@gmail.com

Introduction

Colorectal cancers are the third most frequently seen cancers in both males and females [1]. Although they are the same organ, normal colon and rectum tissue are different structures embryologically, histologically, and functionally. Similarly, rectum cancers demonstrate some differences from colon cancers and have a worse prognosis [2]. The most important prognostic factors in rectum cancer are the degree of bowel wall penetration by the tumor, lymph node involvement, and the presence of distant metastasis. Tumor differentiation shows an effect on survival by increasing the risk of lymph node metastasis which is related to increased lymphovascular invasion [3]. Circumferential tumors, tumors with deep central ulceration, and fixed tumors have a worse prognosis compared to those that do not have these properties.

In the prognosis of rectum cancer, it is necessary to evaluate not only the prognostic indicators associated with the tumor but also patient-related factors. Although age, gender, and ethnicity are slightly related with survival, they can affect the choice of treatment [4].

Determination of cancer prognosis through nutritional and immunological status of the patients has been emphasized recently. PNI is a marker calculated from the serum albumin and lymphocyte count values in the peripheral blood that shows the preoperative nutritional and immunological status of the patient. It was first described by Buzby et al. to evaluate the risks of surgery to the gastrointestinal system [5]. Onedera et al. then evaluated the effect of PNI in cancer patients and a correlation was determined between low PNI and poor survival [6]. As a result of subsequent studies, it was shown to be a simple and effective method that could be used preoperatively to determine the optimum medical treatment, define the most appropriate time for surgery,and to predict cancer prognosis [7].

The PNI value has been examined before curative or palliative surgery in colorectal cancers, but the prognostic importance of the value before adjuvant radiotherapy is not known. In this study, the PNI values were examined in patients undergoing adjuvant chemoradiotherapy because of rectum cancer, which is different from colon cancer in respect to treatment and survival. To the best of our knowledge, this is the first study to evaluate the effect of PNI value before chemoradiotherapy on disease-free survival and overall survival in surgically treated rectum cancers.

Material and Method

Patients

This retrospective study included patients who underwent surgery because of rectum cancer between January 2007 and December 2011 and received adjuvant chemoradiotherapy. The clinical, pathological, and blood sample data of the patients were obtained retrospectively from the hospital records. Patients without survival data or serum albumin and lymphocyte values, those receiving radiotherapy <50Gy, those who could not receive chemotherapy, those having secondary malignancy, and those receiving neoadjuvant chemoradiotherapy were excluded from the study. After the application of the exclusion criteria, a total of 65 patients were included in the study.

TNM classification was determined according to the AJCC. All the patients were administered 5040 Gy radiotherapy and, simultaneously, two cycles 425mg/m2 fluorouracil with 20 mg/m2 folinic acid chemotherapy. After the radiotherapy, the patients were followed up at 3-month intervals for the first two years, then every six months up to five years and annually thereafter. Adjuvant chemotherapy was continued after the chemoradiotherapy. All the blood samples were taken before the chemoradiotherapy was started. The PNI value was calculated using the formula of 10 x serum albumin +0.005 x total lymphocyte count. This study was approved by the Local Ethics Committee.

Statistical analysis

For the statistical analyses of the study data, SPSS version 20.0 (IBM; SPSS Inc. Chicago, IL) software was used. Data were expressed as frequency, percentage, mean± standard deviation, and median (min-max). A value of $p<0.05$ was accepted as statistically significant.

ROC analysis was applied to determine the best predictive value of PNI for 5-year survival. The cutoff value was determined as 46 with 70% sensitivity and 57% specificity (Figure 1). The

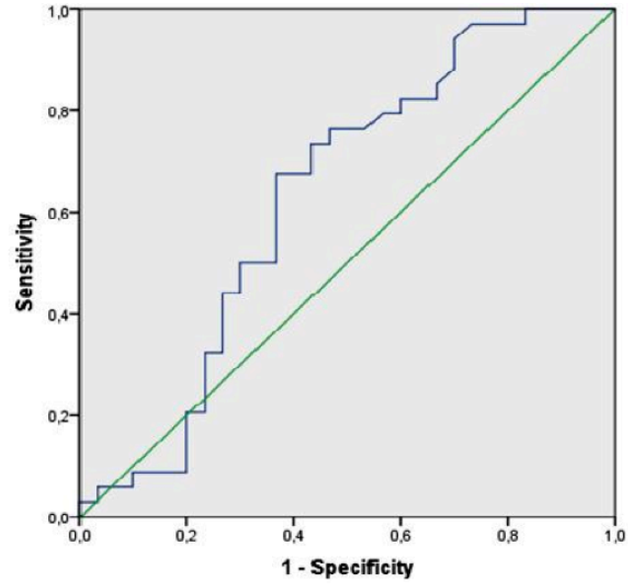

Figure 1. Receiver operating characteristic (ROC) curve analysis for the prognostic nutritional index.

area under the curve was 0.632. The patients were separated into two groups, as low PNI ≤46 and high PNI >46. The Chi-square test was used to compare the low PNI group and the high PNI group with respect to age, gender, T stage, N stage, stage, grade, perineural invasion, lymphovascular invasion, and tumor diameter.

The differences in survival between the groups were calculated with the log rank test. The survival curves were created using the Kaplan-Meier method. The univariate and multivariate hazard ratios were calculated using the Cox proportional hazard model. Significant values in the univariate Cox regression analysis were included in the multivariate analysis.

Results

The patients included 22 (33.8%) females and 43 (66.2%) males with a median age of 63 years (range, 28-81 years). The low PNI group comprised 28 (43.1%) patients and the high PNI

group, 37 (56.9%). The median follow-up period was 58 months (range, 4-112 months). The median overall survival (OS) rate was 92 months (95% CI; range, 61-122 months). The disease-free survival (DFS) rate was 90 months (95% CI; range, 55-124 months). At the end of the follow-up period, 31 (47.7%) patients had died, and 32 (49.2%) patients had developed local recurrence and/or distant metastasis.

A statistically significant relationship was determined between PNI and advanced age (p=0.04). No statistically significant relationship was determined between PNI and gender, T stage, N stage, perineural invasion, lymphovascular invasion, tumor diameter, or grade (Table 1).

Table 1. Clinical and pathological characteristics of the patients according to prognostic nutritional index groups

Variable	Low PNI grup n (%)	High PNI grup n (%)	p
	28 (43.1)	37(56.9)	
Age			0.040
≤65	11 (39.3)	24 (64.9)	
>65	17 (60.7)	13 (35.1)	
Gender			0.060
Female	6 (21.4)	16(43.2)	
Male	22(78.6)	21(56.8)	
T Status			0.394
T2	3 (10.7)	8(22.9)	
T3	21 (75.0)	24(68.6)	
T4	4(14.3)	3(8.6)	
N Status			0.785
N0	17(60.7)	20(58.8)	
N1	4(14.3)	7(20.6)	
N2	7(25.0)	7(20.6)	
Stage			0.854
I	3(10.7)	5(14.7)	
II	14(50.0)	15(44.1)	
III	11(39.3)	14(41.2)	
Perineural invasion			0.985
Absence	17(65.4)	21(65.6)	
Presence	9(34.6)	11(34.4)	
Lymphovascular invasion			0.917
Absence	20(76.9)	25(75.8)	
Presence	6(23.1)	8(24.2)	
Grade			0.196
1	5(23.8)	7(23.3)	
2	11(52.4)	21(70.0)	
3	5(23.8)	2(6.7)	
Tumor size			0.975
≤5cm	16(57.1)	21(56.8)	
>5cm	12(42.9)	16(43.7)	

In the Kaplan-Meier analysis, the T stage (p=0.019), N stage (p=0.26), grade (p=0.005), PNI (p=0.028), and tumor diameter (p=0.018) of the clinicopathological features were determined to have an effect on OS. The DFS rate was found to be affected by the T stage (p=0.021), N stage (p=0.007), stage (p=0.019), perineural invasion (p=0.011), grade (p=0.008), and tumor diameter (p=0.035).

According to the Kaplan-Meier analysis, OS was median 54 months (95% CI; range, 26-81 months) in the low PNI group, and while the median OS could not be calculated in the high PNI group, the mean value was 81±14 months (95% CI; range 67-95 months) (p=0.028, Figure 2). The 5-year OS rate was 49% in

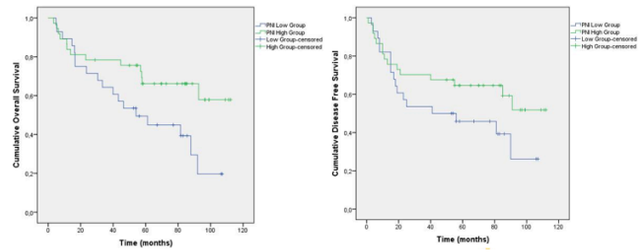

Figure 2. Median overall survival curve (p=0.028) and disease survival curve (p=0.114) according to low and high Prognostic nutritional index groups in Kaplan-Meier analysis

the low PNI group and 65% in the high PNI group. The 9-year OS rate was 20% in the low PNI group and 58% in the high PNI group. The DFS was determined as 41 months (95% CI; range, 1-101 months) in the low PNI group and the median DFS was calculated as 74±15 months (95% CI; range, 59-89 months) in the high PNI group. The 5-year DFS was found to be 45% in the low PNI group and 64% in the high PNI group. The 9-year DFS rates were 26% in the low PNI group and 52% in the high PNI group. Although the DFS was correlated with high PNI, it was not statistically significant (p=0.114).

In the univariate Cox regression analysis, T stage, N stage, tumor diameter, and PNI were found to have a statistically significant effect on overall survival (p<0.05). In the multivariate Cox regression analysis, T stage (p=0.014), tumor diameter (p=0.023), and PNI (p=0.045) were found to be prognostic factors affecting overall survival, independent of the other variables. The factors affecting OS and DFS in the Cox regression analysis are shown in Table 2 and Table 3.

Discussion

In the tumor environment, inflammation is a key element and

Table 2. Univariate and Multivariate Cox Regression Analysis According to Risk Factors for Overall Survival

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	p	HR (95% CI)	p
Age (≤65 / >65)	1.46(0.72-2.96)	0.294	-	-
Sex (Female/Male)	0.96(0.45-2.05)	0.934	-	-
T Status (T2 vs.T4)	2.11(1.04-4.28)	0.038	5.12 (1.36-19.29)	0.016
N Status (N0/N1/N2)	1.68(1.09-2.60)	0.010	2.08 (0.76-5.68)	0.151
Stage (I/II/III)	1.67(0.94-2.97)	0.076	-	-
Perineural invasion (Absence/Presence)	1.85(0.88-3.91)	0.103	-	-
Lymphovascular invasion (Absence/Presence)	1.24(0.54-2.83)	0.599	-	-
Grade (1/2/3)	1.78(0.84-3.78)	0.131	-	-
Tumor size (≤5cm/ >5cm)	2.18(1.06-4.47)	0.032	2.59(1.21-5.53)	0.014
Prognostic nutritional index (≤46 / >46)	0.45(0.22-0.93)	0.032	0.39(0.18-0.84)	0.017

Table 3. Univariate and Multivariate Cox Regression Analysis According to Risk Factors for Disease-free survival

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Age (≤65 / >65)	1.24(0.62-2.48)	0.542	-	-
Sex (Female/Male)	0.734(0.35-1.50)	0.399	-	-
T Status (T2vs.T4)	3.38(1.04-10.94)	0.042	4.77(1.19-19.10)	0.027
N Status (N0/N1/N2)	3.48(1.51-8.01)	0.003	0.786(0.25-2.38)	0.670
Stage (I/II/III)	1.91(1.07-3.40)	0.028	2.32(0.21-24.93)	0.485
Perineural invasion (Absence /Presence)	2.48(1.19-5.16)	0.014	2.94(1.36-6.36)	0.006
Lymphovascular invasion (Absence /Presence)	1.19(0.53-2.70)	0.665	-	-
Grade (1/2 /3)	1.78(0.85-3.72)	0.126	-	-
Prognostic nutritional index (Low /High)	0.57(0.28-1.15)	0.121	-	-
Tumor size (≤5cm/ >5cm)	2.08(1.03-4.20)	0.040	2.25(1.03-4.88)	0.040

plays a significant role in tumor development, metastasis, and response to treatment [8]. It is known that systemic inflammation raises the level of C-reactive protein and changes the relative proportion of white blood cells, thereby elevating the neutrophil count and decreasing the lymphocyte count [9, 10]. Lymphopenia is often observed in cancer patients at an advanced stage, and the reduced lymphocyte count is strongly associated with a poor prognosis of progression-free survival and OS in advanced cancer patients [11]. Kitayama et al. [12] found a correlation between the lymphocyte value measured in peripheral blood and better tumor response in non-metastatic rectum cancer treated with neoadjuvant chemoradiotherapy.

A previous study of Stage III CRC patients showed better OS and DFS in patients with high lymphocyte levels that had infiltrated the tumor micro-environment compared to patients with low levels [13]. A correlation was also shown in nasopharynx cancer patients between low percentage of lymphocyte and poor survival [14]. In addition to albumin being a good marker showing the nutritional status of the patient, it has recently been used as a marker of inflammatory response. Heys et al. [15] first determined a relationship between hypoalbuminemia and increased risk of mortality in a study of 431 patients with localized colorectal cancer. Current studies of colorectal cancer patients have shown a linear relationship between serum albumin level and postoperative morbidity and mortality [16]. On the basis of these studies, it can be said that there is a close correlation between low albumin and lymphocyte values and poor cancer survival. Therefore, to predict the prognosis of patients, scoring scales have been developed that include the albumin and lymphocyte values such as the Glasgow Prognostic Score, the neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, lymphocyte-monocyte ratio, and PNI.

PNI is a simple, cost-effective, and well-validated tool that is calculated from the serum albumin and total lymphocyte count to show the immuno-nutritional status of patients. It was first used by Onedera et al. [6] to determine the nutritional status of patients who had undergone surgery for gastrointestinal cancer. Although a cutoff value of 45 for PNI is accepted as malnutrition, some authors have defined a cutoff value of 40 based on the study of Onedera et al. and others have used different cutoff values of 44.7, 48, and 44.6. In the current study, the cutoff value was defined as 46 using ROC curve analysis as in the study by Jiang et al. [17].

In a study of 219 CRC patients, Nozoe et. al. [18] showed an increase in depth of tumor invasion and, accordingly, an increased tumor stage with low PNI. Although there was a relationship between low PNI and advanced age, which was close to statistical significance (p=0.06), no relationship was determined between gender, lymph node metastasis, lymphatic permeation, venous invasion, and PNI, which is consistent with the findings of the current study. When the survival analysis was examined, tumor stage, PNI, and venous invasion had an effect on survival, independent of other factors.

Mohri et al. [19] determined that low PNI was a poor prognostic factor for postoperative complications and OS, especially in Stage II-III CRC. However, this correlation was not seen at Stage IV. As Stage IV disease was not included in the current study, the conclusion was reached of a correlation between low PNI and poor OS in locally advanced disease. Furthermore, in the Mohri et al. study, low PNI was more often seen in patients aged over 65 years, with large tumor size, and a higher TNM stage. In the current study, low PNI was also seen more often in patients over 65 years of age, but there was no correlation with tumor size and stage. These results are supported by a large cohort study that showed that rates of low PNI increased at an advanced age and, in contrast to Stage IV, reduced survival at Stages II-III [20].

In the current study, no relationship was found between tumor diameter, T stage, and N stage in the postoperative pathology evaluation; this is thought to be due to the absence of a tumor. However, low PNI was still correlated with poor OS. This result can be explained by the relationship of the low PNI in the preoperative period with the tumor-systemic immune/inflammatory response, as it has been suggested that a larger volume of tumor cells leads to higher production of proinflammatory cytokines, which in turn suppresses the hepatic production of albumin [16, 21].

The PNI in the postoperative period can have a negative effect on OS through different routes such as impaired nutrition, nutritional or inflammatory changes that can develop after surgery, or patient tolerance to adjuvant treatments. Previous studies have shown that malnutrition has weakened the immune system, lowered the response to chemotherapy, and consequently has caused poor survival [22, 23]. In addition to these factors, albumin itself may increase the efficacy of associated chemotherapeutic drugs [24]. Therefore, the PNI value must initially be calculated before CRT, and nutritional support must be considered for patients with low albumin and PNI levels.

In conclusion, in contrast to studies where the PNI value was examined preoperatively in patients with colorectal cancer, the PNI value before radiotherapy in patients undergoing postoperative adjuvant chemoradiotherapy because of rectum cancer was found to be a poor prognostic factor. However, as this was the first study and was retrospective, further prospective studies with a high number of patients are needed to better clarify this subject.

Competing interests

The authors declare that they have no competing interests.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65(1):5-29.
2. Li M, Li J, Zhao A, Gu J. Colorectal cancer or colon and rectal cancer? Oncology 2008;73(1-2):52-7.
3. Brodsky JT, Richard GK, Cohen AM, Minsky BD. Variables correlated with the risk of lymph node metastasis in early rectal cancer. Cancer 1992;69(2):322-6.
4. Halperin EC, Brady LW, Wazer DE, Perez CA. Perez & Brady's principles and practice of radiation oncology: Lippincott Williams & Wilkins; 2013.
5. Buzby GP, Mullen JL, Matthews DC, Hobbs CL, Rosato EF. Prognostic nutritional index in gastrointestinal surgery. The American Journal of Surgery 1980;139(1):160-7.
6. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. Nihon Geka Gakkai Zasshi 1984;85(9):1001-5.
7. Sun K, Chen S, Xu J, Li G, He Y. The prognostic significance of the prognostic nutritional index in cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol 2014;140(9):1537-49.
8. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454(7203):436-44.
9. Epstein FH, Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. New England Journal of Medicine 1999;340(6):448-54.
10. Song A, Eo W, Lee S. Comparison of selected inflammation-based prognostic markers in relapsed or refractory metastatic colorectal cancer patients. World J Gastroenterol 2015;21(43):12410.
11. Ray-Coquard I, Cropet C, Van Glabbeke M, Sebban C, Le Cesne A, Judson I, et al. Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas. Cancer Research 2009;69(13):5383-91.
12. Kitayama J, Yasuda K, Kawai K, Sunami E, Nagawa H. Circulating lymphocyte number has a positive association with tumor response in neoadjuvant chemoradiotherapy for advanced rectal cancer. Radiation Oncology 2010;5(1):1.
13. Huh JW, Lee JH, Kim HR. Prognostic significance of tumor-infiltrating lymphocytes for patients with colorectal cancer. Archives of Surgery 2012;147(4):366-72.
14. He JR, Shen GP, Ren ZF, Qin H, Cui C, Zhang Y, et al. Pretreatment levels of peripheral neutrophils and lymphocytes as independent prognostic factors in patients with nasopharyngeal carcinoma. Head & Neck 2012;34(12):1769-76.
15. Heys S, Walker L, Deehan D, Eremin O. Serum albumin: a prognostic indicator in patients with colorectal cancer. J R Coll Surg Edinb 1998;43(3):163-8.
16. Chiang J, Chang C, Jiang S, Yeh C, You J, Hsieh P, et al. Pre□operative serum albumin level substantially predicts post□operative morbidity and mortality among patients with colorectal cancer who undergo elective colectomy. Eur J Cancer Care (Engl). 2015. doi: 10.1111/ecc.12403.
17. Jiang N, Deng J-Y, Ding X-W, Ke B, Liu N, Zhang R-P, et al. Prognostic nutritional index predicts postoperative complications and long-term outcomes of gastric cancer. World journal of gastroenterology: WJG 2014;20(30):10537.
18. Nozoe T, Kohno M, Iguchi T, Mori E, Maeda T, Matsukuma A, et al. The prognostic nutritional index can be a prognostic indicator in colorectal carcinoma. Surgery Today 2012;42(6):532-5.
19. Mohri Y, Inoue Y, Tanaka K, Hiro J, Uchida K, Kusunoki M. Prognostic nutritional index predicts postoperative outcome in colorectal cancer. World Journal of Surgery 2013;37(11):2688-92.
20. Jian-hui C, Iskandar EA, Cai S-i, Chen C-q, Wu H, Xu J-b, et al. Significance of Onodera's prognostic nutritional index in patients with colorectal cancer: a large cohort study in a single Chinese institution. Tumor Biology 2015:1-7.
21. Cengiz O, Kocer B, Sürmeli S, Santicky M-J, Soran A. Are pretreatment serum albumin and cholesterol levels prognostic tools in patients with colorectal carcinoma? Medical Science Monitor Basic Research 2006;12(6):240-7.
22. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior tochemotherapy in cancer patients. The American Journal of Medicine 1980;69(4):491-7.
23. Ross P, Ashley S, Norton A, Priest K, Waters J, Eisen T, et al. Do patients with weight loss have a worse outcome when undergoing chemotherapy for lung cancers? British Journal of Cancer 2004;90(10):1905-11.
24. Sugibayashi K, Morimoto Y, Nadai T, Kato Y, Hasegawa A, Arita T. Drug-carrier property of albumin microspheres in chemotherapy. II. Preparation and tissue distribution in mice of microsphere-entrapped 5-fluorouracil. Chemical and Pharmaceutical Bulletin 1979;27(1):204-9.

How to cite this article:
Kurtul N, Eroğlu C. Low Prognostic Nutritional Index Before Radiotherapy is a Poor Prognostic Factor for Rectum Cancer. J Clin Anal Med 2017;8(3): 185-9.