The prognostic value of different lymph node classification systems in stage III colorectal cancer patients

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AIM: *Prognostic significance assessment of different lymph node classification systems in stage III colorectal cancer patients.*
MATERIAL AND METHODS: *A total of 85 stage III colorectal cancer patients, who had undergone surgery between January 2013 and December 2018, were divided into 3 different groups comprising of lymph node ratios (LNR) and log odds of positive lymph nodes (LODDS) as per the cutoff values of 25 and 75 percentile threshold values. They were accordingly classified as: LNR1 <0.069, LNR2 0.069-0.24, LNR3 >0.24 and LODDS1 <-0.99; -0.99≥ LODDS2 <-0.47; LODDS3 ≥-0.47. Further the LNR was assessed according to the cutoff values proposed by Berger et al. The pN statuses of all patients were also categorized as pN1 and pN2 in line with the AJCC 8th Edition. The Kaplan-Meier test and Cox regression analysis were performed to analyze the relationship among the LNR, LODDS, pN and overall survival.*
RESULTS: *While 55 patients included in the study had tumors in their colons, the localization of the tumors of 30 patients was the rectum. The means for survival time was 63.3 months +/- 3.6 [95% CI(56.2-70.4)]. When univariate analyses were conducted for the factors affecting 3 and 5-year survival of the patients, it was ascertained that there was a significant relationship only between perineural invasion (PNI) and survival. Accordingly, the 3-year survival of those with PNI was found to be 31.4% in comparison to 56% of those without PNI (p=0.025), while the figure was 5.7% for the 5-year survival of the former group and 22% for the latter (p=0.040). When the relation between the survival time of the patients and the LNR classification conducted according to the staging system developed by Berger et al. was studied, no significant relationship could be found (p>0.05). Similarly, and 0.321 respectively.*
CONCLUSION: *Although numerous studies have shown that there was a significant relationship between high LNR and increased survival, as opposed to the results of our study, the greatest obstacle before LNR's survival prediction is the absence of a consensus for standard cutoff values.*

KEY WORDS: Colorectal cancer, Lymph node classification systems, Lymph node ratio

Introduction

Colorectal cancer (CRC) has high incidence rates and is the third most common cancer both in women and men [1].

Local lymph node involvement is one of the most significant prognostic factors in CRC cases with no distant metastasis [2]. Lymph node involvement is decisive in determining who will receive adjuvant therapy within the scope of current treatment modalities for CRC cases[3]. The importance of this lies in the fact that patients who receive chemotherapy (CT) following resection have significantly lower recurrence rates than those of patients who do not, while both the overall and disease-free survival rates increase as expected. It has been demonstrated that the addition of fluorouracil (FU) to surgery led to a 17% improvement in disease-free survival and to

13% improvement in overall survival in patients with node-positive colon cancer [4]. So much so that while the 5-year disease-free survival rate in stage III CRC patients without CT was 49%, this figure goes as high as 63.6% in those who received CT [5].

Stage migration can occur dependent on various reasons like inadequate surgery or insufficient pathological analysis and patients not receiving adjuvant therapy may get the chance to have CT with the elevation in lymph node count at resection and/or those caught by pathological analyses. Identifying metastatic lymph nodes will require the patient to receive CT. Therefore the elevation in lymph node count at resection will increase the rate of accurate staging as well. Survival rates will also increase depending on the increase in odds of positive lymph node detection [6-8]. Yet, the causes of prognostic differences in patients with CRC, who happen to have the same number of resected lymph nodes, have yet to be clarified [9]. Within this context, today three different lymph node (LN) classification systems have been put forth as the status of pN in TNM staging, LNR (lymph node ratio) that represents the ratio of metastatic lymph node count to the total number of resected lymph nodes, and the log odds of positive lymph nodes (LODDS) [10]. Our aim in this study was, thus, to assess the prognostic significance of different lymph node classification systems in stage III colorectal cancer cases.

Material and Method

A retrospective analysis was performed for the data of a total of 232 patients who had undergone colon and rectal cancer surgeries at Kartal Koşuyolu Higher Specialty Training and Research Hospital's Gastrointestinal Surgery Department between January 2013 and December 2018. Patients with negative lymph nodes and those with distant organ metastases were excluded from the study. Moreover, patients with no R0 resection, those that had had emergency surgery, those with synchronous or metachronous metastases, those receiving neoadjuvant therapy, those without histological adenocarcinoma, those with no sufficient information on lymph node involvement, and those who could not be followed up were excluded from the study as well. A total of 85 stage III colorectal cancer patients who had received curative resection were included in the study.

The variables of the study included age, sex, tumor site, differentiation degree, the number of lymph nodes analyzed, T and N (pN1-pN2) classification, lymphovascular invasion (LVI), perineural invasion (PNI), surgical modality (open vs. laparoscopic), LNR and LODDS, and overall survival. Percentile segments were utilized to identify the cutoff values for LNR and LODDS. Cutoff values were designated according to 25% and 75% percentiles. They were accordingly categorized as LNR1 <0.069, LNR2 0.069-0.24, LNR3 >0.24 and LODDS1

<-0.99; -0.99≥ LODDS2 <-0.47; LODDS 3 ≥-0.47. The cutoff values of the LNR staging system were also organized in line with the study conducted by Berger et al. [11]. The LNR was divided into 4 groups when 0.05, 0.19 and 0.39, which were the best cutoff values here, were predicated upon: LNR1 <0.05; 0.05≤ LNR2 <0.19; 0.19≤ LNR3 <0.39; 0.39≤ LNR4 ≤1.

DEFINITION OF LYMPH NODE CLASSIFICATION SYSTEMS

The TNM staging of all patients covered by the study was performed based on UICC/AJCC 8th Edition. Accordingly, category N was divided into two as pN1 (1–3 positive LNs) and pN2 (≥4 positive LNs). LNR was calculated as the ratio of the number of metastatic lymph nodes to the number of harvested lymph nodes. The following formula was used when calculating LODDS values: LODDS= log ([mLN + 0.5]/[nmLN + 0.5]). While mLN stands for the number of metastatic lymph nodes within this formula, nmLN refers to the number of non-metastatic lymph nodes.

This study was approved by the Ethics Committee of Kartal Koşuyolu Higher Specialty Training and Research Hospital (IST2019.7/44-260).

STATISTICAL METHODS

SPSS version 17.0 was used to perform the statistical analyses for the study. Histogram graphs and the Kolmogorov-Smirnov test were used for the variables' goodness-of-fit for normal distribution. Number and percentage values were used in the presentation of descriptive analyses. 2x2 tables were compared with Pearson's chi-squared and Fisher's exact tests. Spearman's correlation test was used to analyze measurable data with one another. The Kaplan-Meier test and Cox regression analysis were applied to identify the factors affecting survival. Cases where the p value was lower than 0.05 were regarded to be statistically significant.

Results

The study included 48 male (56.47%) patients along with 37 (43.53%) female patients making up a total of 85 patients. While 52 of these (61.18%) patients were below 65 years of age, 33 (38.82%) were 65 years old and older. The means for survival time was 63.3 months +/- 3.6 [95% CI(56.2-70.4)]. The tumor site was the colon in 55 (64.71%) patients, while it was the rectum in 30 (35.29%). 25 (29.41%) patients had right hemicolectomy, 25 had (29.41%) low anterior resection, and 19 (22.35%) had anterior resection (Table I)

When the factors affecting the patients' 3- and 5-year survival rates were subjected to a univariate analysis, it

TABLE I - *Clinical and pathological data of the patients*

		N.	%
Age, years	<65	52	61,18%
	≥65	33	38,82%
Gender	Male	48	56,47%
	Female	37	43,53%
ASA	1	3	3,52%
	2	27	31,76%
	3	50	58,82%
	4	5	5,88%
Tumor location	Colon	55	64,71%
	Rectum	30	35,29%
Operation Type	Right hemicolectomy	25	29,41%
	Low anterior resection	25	29,41%
	Anterior resection	19	22,35%
	Abdominoperineal resection	7	8,24%
	Left hemicolectomy	6	7,06%
	Transvers hemicolectomy	3	3,53%
Grade	1	9	10,59%
	2	57	67,06%
	3	19	22,35%
T stage	1/2	7	8,24%
	3	54	63,53%
	4	24	28,24%
Number of harvested LN	Inadequate (n < 12)	12	14,11%
	Adequate (n ≥ 12)	73	85,89%
pN	pN1	55	64,70%
	pN2	30	35,30%
LVI	No	37	43,52%
	Yes	48	56,48%
PNI	No	50	58,82%
	Yes	35	41,18%
Laparoscopic vs open	Open	63	74,11%
	Laparoscopic	22	25,89%
LNR, Berger et al.	LNR1	8	9,41%
	LNR2	52	61,17%
	LNR3	21	24,71%
	LNR4	4	4,71%
LODDS	LODDS1	21	24,71%
	LODDS2	43	50,58%
	LODDS3	21	24,71%

Fig. 1: Survival curve according to LNR, Berger et al.
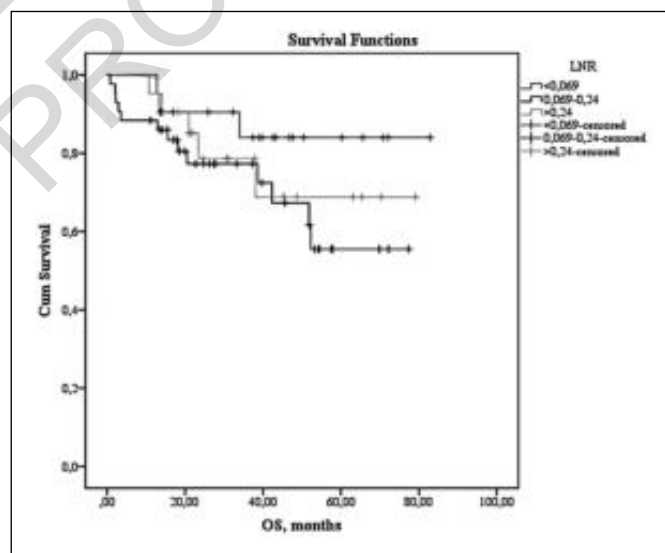
Fig. 2: Survival curve according to LNR, percentile system.

was seen that there was a significant relationship solely between PNI and both 3- and 5-year survival.

Accordingly the 3-year survival rate of those with PNI was 31.4% in comparison to the ones without PNI at 56% (p=0.025). This figure was found to be 5.7% to 22% in the 5-year survival assessment (p=0.040) (Table II).

When the relation between the survival times of the patients with the LNR classification done according to Berger et al.'s staging system method was scrutinized, no significant relationship could be ascertained (p>0.05). In the same vein, no significant relationship could be established between the number of metastatic LNs (pN) and survival and between the LODDS staging system and survival. Further, no significant relationship could be found in the effect of 3 groups on survival that we had
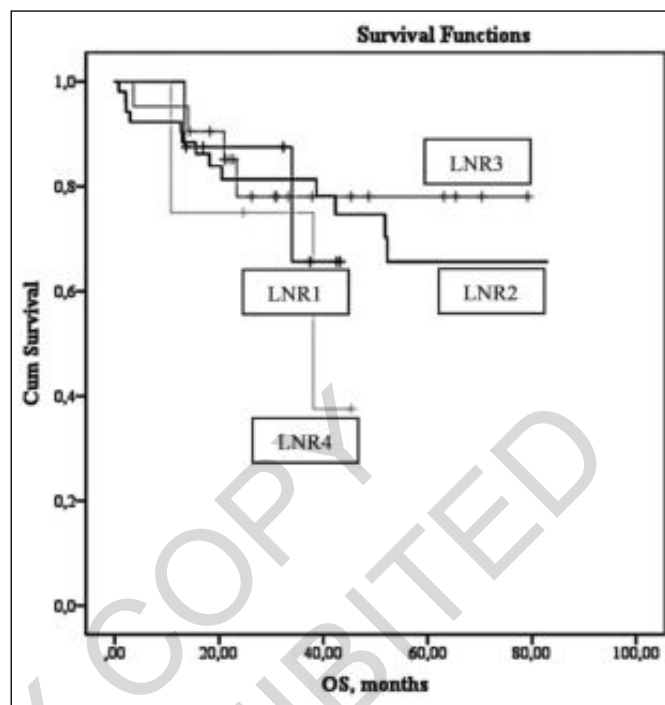
formed by classifying the LNR values of all patients included in our study according to 25 and 75 percentile threshold values (Table III, Figs. 1-4).

The impact of variables on survival subjected to a univariate analysis was also put to multivariate Cox regression analysis but no significant relationship could be established (Table IV).

No significant correlation could be found when the factors affecting overall survival were analyzed (Table V).

Table II - *Univariate 3- and 5-year survival analysis results of 85 stage III-CRC patients.*

|		3 year survival N.	(%)	3 year survival p	5 year survival N.	(%)	5 year survival p
Age, years	≤65	26	50,0%	0,339	9	17,3%	0.517
	>65	13	39,4%		4	12,1%	
Sex	Male	23	47,9%	0,668	9	18,8%	0.313
	Female	16	43,2%		4	10,8%	
ASA	1	1	33,3%	0,179	1	33,3%	0.641
	2	14	51,8%		4	14,8%	
	3	24	48,0%		8	16,0%	
	4	0	0,0%		0	0,0%	
Tumor location	Colon	26	47,3%	0,728	9	16,4%	0.711
	Rectum	13	43,3%		4	13,3%	
Grade	G1	4	44,4%	0,646	2	22,2%	0.544
	G2	28	49,1%		7	12,3%	
	G3	7	36,8%		4	21,1%	
T stage	T1/T2	5	44,4%	0,080	1	14,3%	0.079
	T3	20	37,0%		5	9,3%	
	T4	14	58,3%		7	29,2%	
Number of harvested LN	Inadequate (n < 12)	7	58,3%	0,350	4	33,3%	0.061
	Adequate (n ≥ 12)	32	43,8%		9	12,3%	
pN	pN1	29	52,7%	0,086	9	16,4%	0.711
	pN2	10	33,3%		4	13,3%	
LVI	No	15	40,5%	0,386	4	10,8%	0.313
	Yes	24	50,0%		9	18,8%	
PNI	No	28	56,0%	0,025	11	22,0%	0.040
	Yes	11	31,4%		2	5,7%	
Surgical approach	Open	27	42,9%	0,344	10	15,9%	0.802
	Laparoscopic	12	54,5%		3	13,6%	
LNR. Berger et al.	LNR1	3	37,5%	0,503	0	0,0%	0.465
	LNR2	27	51,9%		9	17,3%	
	LNR3	7	33,3%		4	19,0%	
	LNR4	2	50,0%		0	0,0%	
LODDS	LODDS1	14	66,7%	0,081	4	19,0%	0.637
	LODDS2	16	37,2%		5	11,6%	
	LODDS3	9	42,9%		4	19,0%	

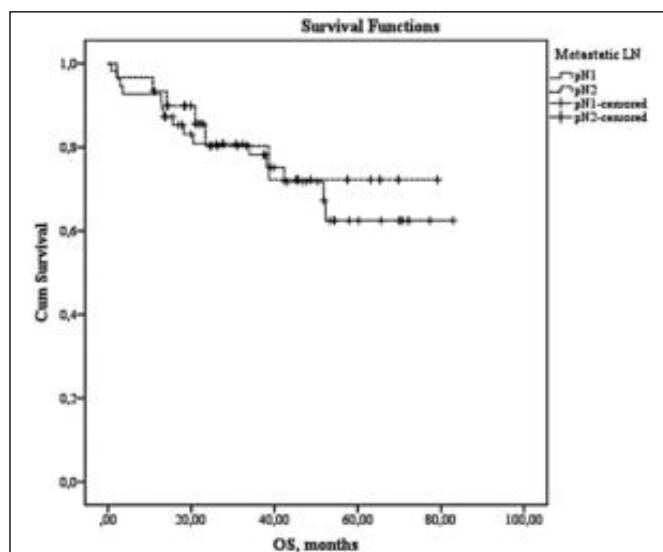Chi-squared test
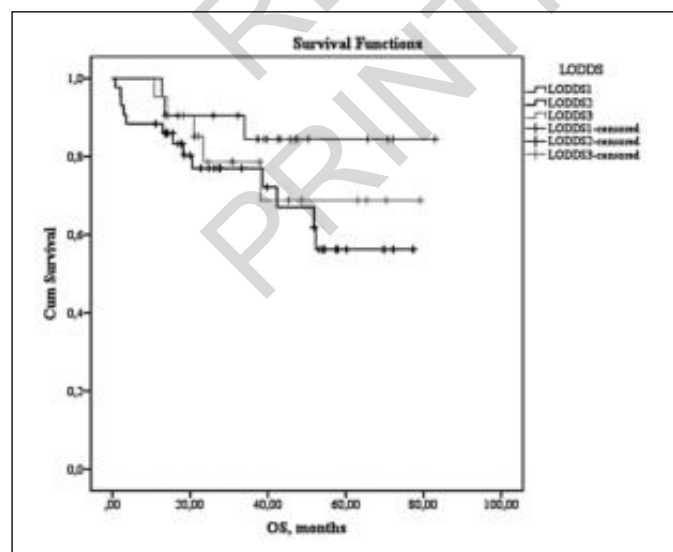
Fig. 3: Survival curve according to LODDS.

Fig. 4: Survival curve according to pN.

TABLE III - *The Kaplan-Meier test results revealing the relationship between overall survival and variables.*

	Variables	Estimate	Std. Error	95% Confidence Interval	p
LNR, Berger et al.	LNR1	37,455	3,660	30,282-44,628	0,622
	LNR2	63,773	4,500	54,953-72,594	
	LNR3	65,410	6,180	53,296-77,523	
	LNR4	33,954	6,968	20,297-47,611	
	Overall	63,347	3,617	56,257-70,438	
LNR, percentile system	LNR1	73,115	5,232	62,860-83,370	0,321
	LNR2	55,275	4,907	45,657-64,893	
	LNR3	62,017	6,575	49,129-74,905	
	Overall	63,347	3,617	56,257-70,438	
LODDS	LODDS1	73,326	5,133	63,266-83,386	0,313
	LODDS2	55,360	4,910	45,737-64,984	
	LODDS3	62,017	6,575	49,129-74,905	
	Overall	63,347	3,617	56,257-70,438	
pN	pN1	62,180	4,453	53,452-70,909	0,662
	pN2	63,343	5,700	52,170-74,515	
	Overall	63,347	3,617	56,257-70,438	

The Kaplan-Meier Test

TABLE IV - *Cox regression analysis results on the impact of 3 different lymph node staging systems on overall survival.*

		p	HR	95% CI
pN	pN1	0,393	1	-
	pN2	0,465	1,592	0,519-4,881
LODDS	LODDS1	0,915	1	-
	LODDS2	0,773	0,697	0,060-8,042
	LODDS3	0,864	1,109	0,340-3,610
LNR, percentile system	LNR1	0,279	1	-
	LNR2	0,244	0,381	0,054-5,131
	LNR3	0,902	1,076	0,334-3,469

Cox regression analysis
HR: hazard ratio, CI: confidence interval

TABLE V - *Correlation table of the factors affecting overall survival.*

	OS, months	
	r	p
Age	0.021	0.852
ASA	−0.139	0.205
Grade	−0.078	0.480
T stage	0.106	0.334
pN	−0.135	0.219
LNR (percentile system)	−0.133	0.226
LODDS	−0.136	0.215

Spearman's Correlation test

Discussion

Today adjuvant therapy is the gold standard for stage III colorectal cancer. The most important factor taken into account in this decision is lymph node involvement [12]. The results - it is seen that while this figure is 54-66% in pN1 it drops to 28-37% in pN2 [22,23]. We studied the impact of metastatic LNs on survival within the scope of our study but could not establish any significant relationship between the two (p=0.662). Moreover, we analyzed the impact of 12 and more lymph nodes, and less than 12 LN yield on 5-year overall survival but could not find any significant relationship either (p=0.061).

Yet the number of resected lymph nodes does not affect the current AJCC N stage [24]. The concept of LNR has been proposed to remedy this problem. The first study on this subject was conducted on gastric cancer cases and the reported findings suggested that it could bear prognostic significance [25]. The first study on the subject in CRC, however, was the one by Berger et al. published in 2005 [11]. Some of the subsequent studies reported that LNR was superior to N stage in node positive CRC [26] although some others argued that N stage was superior to LNR in predicting survival, albeit rare [27]. Another controversy is the absence of consensus on a worldwide recognized standard cutoff value for LNR in predicting prognosis. For instance, Rosenberg et al. [28] divided LNR into 5 sub-groups according to their cutoff values as 0, 0.17, 0.41 and 0.69, while Wang et al. [29] divided it into 4 by selecting the cutoff values at 7-25-50% and Berger et al. [11] also divided it into 4 groups:

LNR1 <0.05; 0.05 ≤ LNR2 <0.19; 0.19 ≤ LNR3 <0.39; and 0.39 ≤ LNR4 ≤1. In the study by Wang et al., the authors found that patients with high LNR rates from whom more than 12 LNs were resected had worse prognoses than those with less than 12 LNs resected. The authors also pointed out that the increase in the number of resected lymph nodes signified a benefit for survival in patients with low LNR[30]. Berger et al., on the other hand, stated that LNR had no prognostic value whatsoever in cases with less than 10 resected LNs [11]. We divided LNR into 3 sub-groups within the scope of our study according to 25 and 75 percentiles as LNR1<0.069, LNR 2 0.069-0.24 and LNR 3 >0.24. We further performed statistical analyses for overall survival according to the study by Berger et al. Neither analysis revealed a correlation between overall survival and LNR.

LODDS has recently been acknowledged as a novel prognostic indicator on which Wang et al. conducted a study covering 24,477 stage III colon cancer patients registered in the Surveillance Epidemiology and End Results (SEER) database arguing that LODDS was a better prognostic factor than pN and LNR [31]. While a couple of studies supported the same findings [32-34], there is also another study that found LNR better fitting in comparison to the other two[35]. Arslan et al. concluded that LODDS yielded more valuable data than LNR in patients with node negative colon cancer independent of the number of harvested LNs [36]. As per the cutoff values used for LODDS, the results of studies rather vary in the same way as LNR. For instance, in Pei et al.'s study covering 56,747 CRC patients reached through the SEER database, the authors assessed the cutoff values for LODDS in two different classifications in comparison to that of Persiani et al. [32] and Wang et al. [31]. The authors deduced that LODDS was not superior to other staging systems when the impact of categorical cutoff values on staging systems was predicated upon although LODDS presented a better staging system. We were not able to establish a significant relationship between LODDS and survival.

Perineural invasion is the most important path of cancer spread and has a significant impact on CRC prognosis. Further it is closely related to histopathological features that indicate tumor aggression [37]. The results of our study revealed that those with positive PNI had significantly worse 3-year (31.4% vs. 56.0%, p=0.025) and 5-year (5.7% vs. 22%, p=0.040) survival rates in comparison to those with negative PNI. Our results were similar to those of other studies [38,39]. Shirouzu et al. reported that rectal cancer patients with PNI of stage III lesions had a significantly lower 8-year survival rate (26.7%, p < 0.001) [40].

This study has certain limitations. First of all, the study had a retrospective design. As many factors that might affect survival were excluded and only stage III CRC patients were included, the number of patients was relatively low. Further, disease-free survival could not be covered due to difficulties in reaching related data.

Conclusion

A classification that would ascertain prognosis and adjuvant CT candidates in a more certain manner still proves to be a controversy despite numerous studies, and the search for a better prediction for this issue is ongoing. Although numerous studies have shown that there was a significant relationship between high LNR and increased survival, as opposed to our study, the greatest obstacle before LNR's survival prediction is the absence of a consensus for standard cutoff values. We believe that this issue needs to be investigated with larger population series and should be supported by further studies.

Riassunto

Con analisi retrospettiva un totale di85 pazienti con carcinoma del colon-retto in stadio III, sottoposti a intervento chirurgico tra gennaio 2013 e dicembre 2018, sono stati divisi in 3 diversi gruppi comprendenti rapporti linfonodali (LNR) e log delle probabilità di linfonodi positivi (LODDS) come per i valori di cutoff dei valori soglia del 25 e 75 percentile. Sono stati pertanto classificati come: LNR1 <0,069, LNR2 0,069-0,24, LNR3> 0,24 e LODDS1 <-0,99; -0,99≥ LODDS2 <-0.47; LODDS3 ≥-0,47. Inoltre l'LNR è stato valutato in base ai valori di cutoff proposti da Berger et al. Gli stati pN di tutti i pazienti sono stati anche classificati come pN1 e pN2 in linea con l'ottava edizione AJCC. Il test Kaplan-Meier e l'analisi di regressione di Cox sono stati eseguiti per analizzare la relazione tra LNR, LODDS, pN e sopravvivenza globale.

In 55 pazienti inclusi nello studio il tumore era a sede colica, ed in 30 la neoplasia era rettale. La sopravvivenza media erano di 63,3 mesi +/- 3,6 [IC 95% (56,2-70,4)]. Quando sono state condotte analisi univariate per i fattori che influenzano la sopravvivenza a 3 e 5 anni dei pazienti, è stato accertato che esisteva una relazione significativa solo tra invasione perineurale (PNI) e sopravvivenza.

Di conseguenza, la sopravvivenza a 3 anni di quelli con PNI è risultata essere del 31,4% rispetto al 56% di quelli senza PNI (p = 0,025), mentre il dato era del 5,7% per la sopravvivenza a 5 anni del precedente gruppo e 22 % per quest'ultimo (p = 0,040). Quando è stata studiata la relazione tra il tempo di sopravvivenza dei pazienti e la classificazione LNR condotta secondo il sistema di stadiazione sviluppato da Berger et al., non è stata trovata alcuna relazione significativa (p> 0,05). Allo stesso modo, non vi era alcuna relazione significativa tra pN, LODDS e il loro sistema di stadiazione LNR e sopravvivenza. I valori di p di queste categorie erano rispettivamente 0,662, 0,313 e 0,321.

CONCLUSIONE: Sebbene numerosi studi abbiano dimostrato l'esistenza di una relazione significativa tra LNR elevato e aumento della sopravvivenza, al contrario dei risultati del nostro studio, il maggiore ostacolo prima della previsione di sopravvivenza di LNR è l'assenza di un consenso per i valori di cutoff standard.

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