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Research Article

The Correlation Between Systemic Inflammatory Response And Survival in Patients with Metachronous and Synchronous Liver Metastatic Colorectal Cancer

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Abstract

Objectives: Recent data suggest that a low lymphocyte count in a colorectal tumor is associated with poor prognosis. The NLR has been shown to be an effective prognostic factor for survival in colorectal and ovarian cancer. It has been suggested that the preoperative NLR may be a simple method to identify patients with a poor prognosis of colorectal cancer. The aim of this study was to evaluate the effect of the NLR on survival in patients with colorectal cancer who underwent liver metastasectomy.

Methods: The study included 76 patients who were admitted to the Medical Oncology Outpatient Clinic of Kartal Dr. Lutfi Kırdar Training and Research Hospital, who underwent liver metastasectomy and were followed up for colorectal cancer and whose clinical data and pre-metastasectomy laboratory values could be retrieved. The SPSS 17.0 software package was used in the analysis of the study. The mean, standard deviation, minimum-maximum, median, rate and frequency values were used for the descriptive statistics of the data. The distribution of the variables was assessed by the Kolmogorov Smirnov test. The independent samples t-test and Mann-Whitney U test were used for the analysis of quantitative data. The chi-square test was used for analysis of qualitative data. The Cox regression and Kaplan-Meier survival analysis were used for survival analyses. Spearman's correlation analysis was used for correlation analyses.

Results: Age had a significant effect on survival time in the univariate model ($p<0.05$). Sex, colonic localization, lymph node involvement, histological grade, metastatic status, surgical margin, diameter of metastases, number of metastases, leukocytes, neutrophils, lymphocytes, NLR, CRP, albumin and CEA parameters had no significant effect on survival in the univariate model ($p>0.05$).

Conclusion: In our study, when a survival analysis was carried out on all variables, the only variable affecting survival was age. The mean age of the metasynchronous group was 56.2±10.6 years, and the mean age of the synchronous group was 61.3±11.1 years. Despite the numerical difference, there was no statistical significance ($p=0.055$). Although the mean age of the synchronous group was numerically higher, the survival was longer. This may be due to the short follow-up time and the small sample size.

Keywords: Colorectal cancer, liver metastatis, metasynchronous, neutrophil-lymphocyte ratio

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Although advances in the treatment of metastatic colorectal cancer have improved survival in recent years, there are no simple markers that can be used to evaluate follow-up and treatment. The presence of inflammation has been used as evidence to evaluate poor prognosis in many cancer types.[1] A simple biomarker, such as the neutrophil-lymphocyte ratio (NLR), may be significant for assessing the survival of metastatic colorectal cancer.

In cases of liver metastatic colorectal cancer, survival depends on tumor stage and varies with appropriate treatment. In nonmetastatic colon cancer, curative treatment is surgery. Colorectal cancers most commonly metastasize to the liver. If the lesion is surgically resectable in liver metastatic cases, it is removed in the same session; if not, it is surgically reevaluated after chemotherapy. In specific cases, local hepatic treatments can be administered in combination with surgery. Chemotherapy options are individually selected according to the status of the patient and disease. In colon cancers, radiotherapy can only be used for palliative purposes to relieve bleeding, obstruction and pain. Although neoadjuvant radiotherapy (RT) can be used in rectal cancers, chemoradiotherapy can also be used in cases where curative surgery cannot be performed.

Numerous studies have shown that inflammation is effective in the development and prognosis of disease in cardiovascular diseases and cancers.[2] The presence of T lymphocytes in a tumor is indicative of a marked immune response to the lesion. Recent data suggest that low lymphocyte count in a colorectal tumor is associated with poor prognosis. The NLR has been shown to be an effective prognostic factor for survival in colorectal and ovarian cancer.[3, 4] It has been suggested that the preoperative NLR may be a simple method to identify patients with poor prognosis in colorectal cancer.[5]

The aim of this study was to evaluate the effect of the NLR on survival in patients with colorectal cancer who underwent liver metastasectomy.

Methods

Patient Selection

The study included 76 patients who were admitted to the Medical Oncology Outpatient Clinic of Kartal Dr. Lutfi Kırdar Training and Research Hospital between January 2003 and April 2013, underwent liver metastasectomy and were followed up for colorectal cancer and whose clinical data and premetastasectomy laboratory values could be reached. It was found that 8 patients underwent emergency colorectal surgery, although they had metastasis to the liver at the time of diagnosis. These patients were excluded from the study since they may reduce disease-free survival and affect the systemic inflammatory response.

The patients were divided into two groups according to the detection of metastasis in the liver. Thirty-nine patients with metasynchronous liver disease had undergone metastasectomy, and 29 patients with synchronous liver disease had undergone metastasectomy and colorectal surgery.

Statistical Analysis

The SPSS 17.0 software package was used in the analysis of the study. The mean, standard deviation, minimum-maximum, median, rate and frequency values were used for the descriptive statistics of the data. The distribution of the variables was assessed by the Kolmogorov Smirnov test. The independent samples t-test and Mann-Whitney U test were used for the analysis of the quantitative data. The chi-square test was used for analysis of the qualitative data. The Cox regression and Kaplan-Meier survival analysis were used for survival analysis. Spearman's correlation analysis was used for correlation analysis.

Results

The study included 68 patients who were admitted to the Medical Oncology Outpatient Clinic of Kartal Dr. Lutfi Kırdar Training and Research Hospital between January 2003 and April 2013, underwent liver metastatic resection and were followed up for colorectal cancer and whose clinical data and baseline laboratory values could be reached.

When the general characteristics of 68 patients were evaluated, the numbers of males and females were equal. Of the patients, 61.8% were alive. The mean follow-up time was 32.6 months. It was found that 58.9% had rectosigmoid localization. Lymph node involvement, histologic grade, and the diameter and number of metastases were evaluated with regard to progression and survival. Lymph node involvement was detected in 67.6% of the patients. When histologic grade was evaluated, it was found that 8 (11.8%) were well differentiated, 49 (72.1%) were moderately differentiated, and 11 (16.2%) were poorly differentiated. The mean metastasectomy diameter was 3 cm. The median value of metastasectomy number was 1, and the removal of 11 metastatic foci measuring less than 1 cm in one lobe in only 1 patient increased the mean (Table 1).

The laboratory parameters of the patients were evaluated. In all patient groups, the median value of WBCs was 6915/mm^3, the median value of lymphocytes was 1705/mm^3, and the median value of neutrophils was 4250/mm^3.

In 60.3% of the patients, the lymphocyte value was above 1600/mm^3. The median neutrophil to lymphocyte ratio (NLR) was 3. It was found that of the patients, 64.7% had an NLR >2.5 and 11.8% had an NLR >5.

Table 1. General Features of the Patients

	Med (Min-Max)		Mean±SD/ n-%	
Age	58	34-85	58.4±11.0	
Gender				
Female		34		50.0
Male		34		50.0
Outcome				
Alive		42		61.8
Exitus		26		38.2
Follow up period (month)	28	3-93	32.6±21.0	
Colonic Localization				
Ascending		16		23.5
Trans		6		8.8
Descending		6		8.8
Rectusigmoid		40		58.9
lymph node involvement				
-		22		32.4
+		46		67.6
Histological grade				
Good		8		11.8
Moderate		49		72.1
Poor		11		16.2
Diameter of metastasis (cm)	3	1-7	3.06±1.6	

Sixty-eight colorectal cancer patients' premetastasectomy median value of albumin was 4 g/dl, and the median value of C-reactive protein (CRP) was 14 mg/L. The median value of CEA is 5, and a CEA value above 5 is considered to be a prognostic factor. The CEA value of 48.5% of the patients was above 5.

There was no significant difference between the metasynchronous and synchronous groups in terms of the age and sex distribution of the patients (p>0.05). The mean follow-up time of the patients was 30.9 months in the metasynchronous group and 35.0 months in the synchronous group. There was no significant difference, but the numerical difference was 4.1 months.

There was no significant difference between the metasynchronous and synchronous groups in terms of the distribution of colonic localization and the number of metastases (p>0.05). The lymph node involvement of the metasynchronous group was significantly higher and the histological grade was significantly better than those of the synchronous group (p<0.05). The metastasis diameter was significantly higher in the metasynchronous group than that in the synchronous group (p<0.05) (Table 2).

There was no significant difference between the metasynchronous and synchronous groups in terms of the NLR value, NLR >2.5 and NLR >5 (p>0.05). The mean NLR values were above 2.5 in both groups. There was no difference between the metasynchronous and synchronous groups in terms of leukocytes and neutrophils (p>0.05). The CRP value and CEA level were significantly lower in the metasynchronous group than those in the synchronous group (p<0.05). There was no significant difference between the metasynchronous and synchronous groups in terms of a CEA of >5 (p>0.05), and the CEA level was above 5 in both groups (Table 3).

The survival time was 51.69 months in the metasynchronous group and 61.73 months in the synchronous group,

Table 2. Comparative evaluation of the metachronous and synchronous liver metastatic colorectal cancer groups

	Metastesectomy State				
	Metachronous		Synchronous		
	Mean±SD/n-%	Med (Min-Max)	Mean±SD/n-%	Med (Min-Max)	P
Colonic Localization					
Asc.	9 23.1		7 24.1		0.575
Trans.	3 7.7		3 10.3		
Desc.	2 5.1		4 13.8		
Rectos.	25 64.1		15 51.7		
lymph node involvement					
+	17 43.6		5 17.2		0.022
-	22 56.4		24 82.8		
Histological grade					
Good	8 20.5		0 0.0		0.023
Moderate	24 61.5		25 86.2		
Poor	7 17.9		4 13.8		
Diameter of metastasis (cm)	3.6±1.5	4 1-7	2.2±1.2	2 1 - 6	0.000
Number of Metastasis	1.6±1.6	1 0-11	1.3±0.5	1 1 - 3	0.454

Table 3. The comparision of the laboratuary parameters between metachronous and synchronous liver metastatic colorectal cancer groups

	Metastesectomy State								
	Metachronous				Synchronous				
	Mean±SD/n-%		Med (Min-Mak)		Mean±SD/n-%		Med (Min-Mak)		p
WBC	7517±2867		6710	3580-14500	7458±2135		7150	4890-11690	0.926
NEU	4761±2420		4090	1230-11000	4918±1655		4680	2690-8700	0.765
Lymp	1864±733		1760	650-4170	1690±684		1680	720-4300	0.323
Lymp									
≤1600	16	41.0			11	37.9			0.796
1600<	23	59.0			18	62.1			
NLO	2.9±2.1		3	1-13	3.3±1.7		3	1-10	0.487
NLO									
≤2,5	15	38.5	9	31.0					0.526
2,5<	24	61.5	20	69.0					
NLO									
≤5	35	89.7			25	86.2			0.654
5<	4	10.3			4	13.8			
CRP	28±52		7	1-189	41±56		20	0-207	0.015
Albumin	4±1		4	2-5	4±1		4	2-5	0.891
CEA	14.2±20.8		4	1-88	88.6±213.8		14	1-951	**0.024**
CEA									
≤5	23	59.0			12	41.4			0.151
5<	16	41.0			17	58.6			

and there was no difference between the two groups (p>0.05) . There was a difference between the two groups after the 30th month, but it was not statistically significant.

The 1-year survival rate of the synchronous group was 97%, the 3-year survival rate was 61%, and the 5-year survival rate was 58%, while the 1-year survival rate of the metasynchronous group was 89%, the 3-year survival rate was 75%, and the 5-year survival rate was 72%.

Age had a significant effect on survival time in the univariate model (p<0.05). Sex, colonic localization, lymph node involvement, histological grade, metastatic status, surgical margin, diameter of metastasis, number of metastases, leukocytes, neutrophils, lymphocytes, NLR, CRP, albumin and CEA parameters had no significant effect on survival in the univariate model (p>0.05).

Discussion

Approximately 50-60% of patients diagnosed with colorectal cancer develop liver metastases, and 80-90% of these are not eligible for resection.[6–9] The contribution of resection to survival has been reported to be 40-51% for three years and 25-38% for five years.[10, 11] In colorectal cancer, liver metastasis is commonly metasynchronous, while synchronous liver disease is seen in approximately 20-34% of cases.[12–14] In autopsy studies, it has been found that more than half of patients with colorectal cancer have liver metastasis, and it has been reported to be the most common cause of death.[15]

In our study, of the patients with colorectal cancer who underwent liver metastasectomy, 43% (29 patients) had synchronous liver disease, while 57% (39 patients) had metasynchronous liver disease. The patients with synchronous liver metastasis underwent elective simultaneous colorectal surgery and metastasectomy, and the patients with metasynchronous liver metastasis underwent elective metastasectomy.

In 2006, Manfredi et al.[16] evaluated the survival times of metasynchronous and synchronous liver diseases in 13,463 patients with liver metastatic colorectal cancer who underwent hepatic resection. It was found that the 1-year survival was 34.8% and that the 5-year survival was 3.3% in synchronous liver metastatic disease, while the 1-year survival was 37.6% and the 5-year survival was 6.1% in metasynchronous liver metastatic disease. In the 2010 study by Mekenkamp et al.,[17] the clinical characteristics of 550 patients with liver metastasis who were not eligible for resection were evaluated. When metasynchronous liver disease (270 patients) and synchronous liver disease (280 patients) were compared, the predicted survival times were 18.5 months and 17.6 months, respectively, and there was no significant difference

(p=0.24). The presence of cured patients after metastasectomy increases the 5-year disease-free survival to 20%.[18–20]

In our study, the 1-year survival was 89% and the 5-year survival was 72% in synchronous liver metastatic disease after metastasectomy. The 1-year survival was 97% and the 5-year survival was 58% in patients with metasynchronous liver metastasis. In synchronous liver disease, the 1-year survival was relatively worse, while the 5-year survival was better. The survival time was 51.7 months in metasynchronous liver disease, while the survival time was 61.7 months in synchronous liver disease. The survival difference between the two groups was not significant. (p=0.435) The expected survival time in both groups was longer compared to other studies in the literature.

In colorectal cancer, the presence of extrahepatic metastasis, more than three metastatic foci or a disease-free survival time shorter than 12 months are associated with poor prognosis.[21–23] In our study, the disease-free survival after colorectal surgery was 9.8 months in the metasynchronous group. This may be one of the factors explaining the lower 5-year survival in the metasynchronous group.

In a 2006 retrospective study by Tsai et al.[24] including 155 patients, it was found that multiple segment involvement (p=0.008) and bilateral lobe involvement (p=0.016) were significantly higher in synchronous liver disease than those in metasynchronous liver disease. In another 2010 study, it was revealed that the diameter and number of metastases were associated with surviva.[25]

In our study, the number of patients with lymph node involvement in metasynchronous liver disease was significantly higher compared to synchronous liver disease. (p=0.022) The number of metastases was not found to be associated with survival, while the diameter of metastases was greater in the metasynchronous group. (p=0.000) These two factors are other factors that affect survival.

The neutrophil to lymphocyte ratio (NLR) has been shown to be an indicator of inflammation in many studies. In the 2010 study by Chau et al.,[26] the correlation between NLR >5 and survival was evaluated in 349 patients with stage 4 colorectal cancer. An ECOG performance score of ≥1 (p=0.002), NLR >5 (p=0.01), hypoalbuminemia (p=0.03), and single-agent chemotherapy (p=0.0001) were found to be increased risk factors for progression. In the study by Lee et al. on 1061 patients with cervical cancer, it was found that patients with an NLR >1.9 were younger and had a lower stage. In patients with cervical cancer, the pretreatment NLR was evaluated as a poor independent prognostic factor.[27]

In a 2012 study, NLO >2.5 examined before breast cancer adjuvant chemotherapy and disease-specific survival were compared. Four hundred forty-two patients with breast cancer were followed up between 2000 and 2010. The patients were classified according to age, histology (ductal, lobular, others), histologic grade, T stage, N stage, receptor status and molecular subtype. No correlation could be established between NLR >2.5 and disease-specific survival. However, there was a significant correlation with Luminal A, a molecular subtype (p=0.009).[28]

In our study, 64.7% of 68 patients had an NLR >2.5, and the mean NLR value was 3.1±2.0. NLR >2.5 at the time of diagnosis may be an indicator of metasynchronous and synchronous liver metastasis. It was detected in 61.5% of the metasynchronous group and 69.0% of the synchronous group, but the difference between the groups was not significant (p=0.526). The mean value of the NLR was 2.9±2.1 in the metasynchronous group and 3.3±1.7 in the synchronous group. Although not statistically significant, there was a numerical difference between them. The mean NLR was above 2.5 in both groups. The reason for it not being statistically significant may be an insufficient number of patients.

In our study, the levels of CEA (carioembryonic antigen) and CRP (C-reactive protein) were significantly higher in the synchronous group than those in the metasynchronous group. (p>0.05-p=0.015) In a study of 243 patients with metastatic colorectal cancer, the correlation between the CEA level, NLR, platelet-to-lymphocyte ratio (PLR) and prognosis was evaluated. The CEA level (p<0.0001) and NLR (p=0.028) were shown to be independent predictors.[29] In the 2013 study by Nishikawa et al.,[30] it was revealed that the CRP value examined before surgical resection in patients with hepatocellular cancer was predictive for recurrence. In our study, the detection of significantly higher CEA and CRP in the synchronous group may be considered to support the numerically high NLR in the synchronous group. In a study where the sample size is larger and the follow-up times are longer, different results can be obtained between the NLR and survival.

In our study, when a survival analysis was carried out on all variables, the only variable affecting survival was age. The mean age of the metasynchronous group was 56.2±10.6 years, and the mean age of the synchronous group was 61.3±11.1 years. Despite the numerical difference, there was no statistical significance (p=0.055).

Although the mean age of the synchronous group was numerically higher, the survival was longer. This may be due to the short follow-up time and the small sample size.

Conclusion

In patients with synchronous and metasynchronous liver metastatic colorectal cancer, the presence of NLO >2.5 in 61% and 69% of the patients before metastasectomy may

be cautionary in terms of liver metastasis for patients with colorectal cancer.

The mean value of the NLR was 2.9±2.1 in the metasynchronous group and 3.3±1.7 in the synchronous group. Although not statistically significant, there was a numerical difference between them. The reason for it not being statistically significant may be the small sample size.

There was no correlation between NLR >2.5 and the survival of synchronous and metasynchronous liver metastatic colorectal cancer. The numerically higher NLR and statistically significantly higher CRP values in the synchronous liver disease group can be evaluated as an indicator of the presence of systemic inflammation of synchronous liver metastatic colorectal cancer.

The inability to establish a correlation between systemic inflammation and survival can be attributed to three main causes. These are the short survival times in the metasynchronous group as opposed to the general group, the small sample size, and the short follow-up time. Further studies with larger sample sizes are needed to evaluate the markers of systemic inflammation.

Disclosures

Ethics Committee Approval: The study was approved by the Dr. L.Kırdar Kartal Training and Research Hospital Ethic Committee in March 2015.

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Conflict of Interest: None declared.

Authorship Contributions: Concept – M.A.; Design – M.A.; Supervision – G.P.; Materials – G.P.; Data collection &/or processing – E.A.P.; Analysis and/or interpretation – A.E.; Writing – E.A.P.

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