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Etiological findings in cases with incidental liver metastasis and factors affecting survival

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Abstract

Aim: In this study, the general characteristics of incidental liver metastasis and the factors affecting survival were investigated.

Materials and Methods: In our study, we retrospectively analyzed 216 patients with metastases in the liver at diagnosis. Patients with previously known primary malignancy and liver failure due to chronic viral hepatitis were excluded from the study.

Results: The etiological causes of metastatic liver lesions were cancer of unknown primary (CUP) 27.78%, pancreato biliary region tumors (PBRT) 19.44%, colorectal cancer (CRC) 18.98% and 12.96% gastric cancer, in order of frequency. No significant correlation was found in the concordance analysis between CT and USG in detecting metastases In the survival analysis, higher alanine aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma-glutamyl transpeptidase (GGT), cancer antigen 19-9 (CA 19-9), total bilirubin (TBIL), direct bilirubin (DBIL) levels and lower albumin levels were found to be statistically significant in patients who died compared to aliving patients ($p<0.05$). Survival is shortened and there is an inverse relationship. Good prognostic factors for overall survival: the age of 65 and below, right hepatic lobe metastasis, solitary hepatic lesion, and maximum tumor diameter is 3 cm below, and colorectal tumors. Also, there was a correlation between the presence of extrahepatic metastasis and CA-125 levels. There is a direct correlation between these increased values and the expected extrahepatic metastasis($p<0.05$).

Conclusion: Many factors are effective in predicting patient survival and prognosis in incidentally detected metastatic liver lesions. Various scoring systems can be developed with prospective, randomized controlled studies to increase their accuracy.

Introduction

The liver is a vital organ with its unique anatomy and specific physiology. It is the main metastasis site for primarily colorectal cancers (CRC), gastrointestinal system (GIS) cancers such as pancreas, stomach, esophagus, and neuroendocrine tumors (NETs) and many non-GIS tumors (such as breast cancer, melanoma, and kidney cancers). Metastatic liver tumors constitutes 20-30% of tumors [1]. In fact, 50% of patients with CRC have liver metastasis postoperatively or at the time of diagnosis [2]. Although there have been positive developments in surgery, chemotherapy and targeted agents since the last quarter-century, the prognosis in patients with liver metastases is still poor, and the average 5-year surveillance varies between 20% and 40% [3, 4]. To improve these depressing statistics, we need a better understanding of the biology of liver metastases and contributing prognostic factors.

The aim of this study was to contribute to the literature by examining the relationship between age, gender, diagnosis, metastatic tumor characteristics, pathological subtype, immunohistochemistry, imaging modalities used for diagnosis, endoscopic examinations, some laboratory parameters, general survival and presence of extrahepatic metastasis in 216 patients with incidental liver metastasis.

Materials and Methods

Determination of Patients and Data Collection

The files of 216 patients who were diagnosed with incidental tumoral masses in the liver by abdominal imaging for any reason and whose diagnosis was confirmed by liver biopsy were researched retrospectively between January 2010 and December 2019 in accordance with Declaration of Helsinki, Patient Rights Regulation of the Republic of

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Turkey Ministry of Health, and with the approval of Clinical Research Ethics Committee (Approval number: 2018 / 20-16). After obtaining informed consent from all patients and checking coagulation tests, US-guided fine needle aspiration biopsy was performed using semi-automatic liver biopsy needles through the appropriate intercostal space.

Age, gender, histopathological diagnoses, radiological imaging findings (US, CT, MRI), AST, ALT, ALP, GGT, LDH, albumin, DBIL, TBIL, iron parameters (iron, iron binding capacity, ferritin), tumor markers (AFP, CEA, PSA, CA 19-9, CA-125, CA 15-3), Hb, NLR, PLT levels, endoscopy and colonoscopy findings were retrospectively screened from the hospital computer registry database. NLR is measured by dividing the number of neutrophils by the number of lymphocytes.

Inclusion criteria

1- Being over the age of 18 at the diagnosis,

2- Histopathologically confirmed malignancy between January 2010 and December 2019, 3- Continuing follow-ups in our center.

Exclusion criteria

1- Presence of previously known primary malignancy and metastasis originating from this primary,

2- Patients diagnosed with HCC histopathologically,

3- Previous history of chronic viral hepatitis (HBV, HCV) or chronic liver disease,

4- Histopathologically the presence of benign liver tumor.

The dead or alive status of the patients was determined by questioning their identity numbers through the National Central Population Management System. The laboratory parameters at the first outpatient clinic admission were analysed. To determine the general survival, follow-up times were taken as basis from the first diagnosis. A total of 216 patients, 90 (41.6%) female and 126 (58.4%) male, were included in our study. The patients were divided into groups according to age, gender, diagnosis, histopathology and mortality. Univariate and multivariate analyzes were made to examine the correlation between survival and tumor markers (AFP, CEA, CA 19-9, CA 15-3, CA-125, PSA), hemoglobin, PLT, NLR, liver function tests (AST, ALT, GGT, ALP, LDH, albumin, TBIL, DBIL) in each group.

Statistical analysis

In the power analysis it was calculated that at least 109 patients should be included in the study in order to detect the primary focus of incidental liver metastases at a 95 % confidence level (α: 0.05) and 80% power (β: 0.20). All statistical analyses were calculated with SPSS 17.0 program. The suitability of the variables to normal distribution was examined using the Kolmogorov-Smirnov test. Mean ± standard deviation (SD) and median (min-max) were used as descriptive statistics. Categorical variables were compared using the Chi-Square test. Bonferroni correction post-hoc analysis was conducted to determine which groups the significance of the Chi-Square test originated from. The Mann Whitney U test was used when comparing non-parametric numerical variables between two groups, and the Kruskal Wallis test was used when comparing more than two groups. Dun-Bonferroni post-hoc test was used to determine which groups the statistical significance in the Kruskal Wallis test originated from.

Spearman's correlation coefficient was performed to examine the relationship between survival time and laboratory values. $0 < |r| \leq 0.2$ very poor, $0.2 < |r| \leq 0.4$ weak, $0.4 < |r| \leq 0.6$ moderate, $0.6 < |r| \leq 0.8$ strong, $0.8 < |r| \leq 1$ as a very strong correlation was accepted. Survival tests were performed by Kaplan-Meier method. The weighted kappa statistic testing was made for agreement between CT and US. Kappa coefficient $0 \leq | \, | < 0.2$ no compatibility, $0.2 \leq |$ [199?] $| < 0.4$ weak, $0.40 \leq | \, | < 0.6$ moderate, $0.6 \leq | \, | < 0.8$ strong, $0.8 \leq | \, | < 1.00$ was evaluated as perfect level of agreement. For statistical significance $p < 0.05$ was accepted.

Results

A total of 216 patients, 90 (41.67%) female and 126 (58.33%) male, were included in the study. The mean age of the patients was 60.4 ± 37.5 and the median value was 53. 128 (59.26%) of the patients were 65 years old or younger, and 88 (40.74%) were over 65 years old. While 59 (27.3%) of the 216 cases in the study were alive, 157 (72.7%) cases had died. As the general survival parameter, the follow-up period from the diagnosis was taken as the basis. According to survival times of the patients, it was found that 5.6% survived over 5 years, 38% over 1 year, and 56.4% less than 1 year. Overall survival mean was 17.34 ± 22.52 and the median value was calculated as 8 (0.5-157) months (Table 1).

The metastatic lesions in the liver of 131 (60.65%) were bilaterally, 62 (28.7%) right lobe, and 23 (10.65%) patients were located in the left lobe. 162 (75%) of their multiple and 54 (25%) patients had a single lesion. The tumor diameter was below 3 cm in 92 (42.59%), between 3-5 cm in 39 (18.06%), and over 5 cm in 85 (39.35%) (Table 1).

The metastatic lesions were distributed according to the primary focus, the colon (14.3%), stomach(12.96%), and biliary tract (10.6%) were listed in order of frequency, while in the distribution of the groups, they were listed as CUP(27.78%), PBRT(19.44%), CRC(18.98%) and (12.96%) gastric cancer. According to histopathological subtypes; adenocarcinoma (72.7%) was the most common, followed by NET (11.6%). Among the procedures performed, 34 (25.8%) patients had a malignant lesion in the esophagus, stomach or duodenum in upper endoscopy, while 35 (29%) had a malignant lesion in the colon or rectum in colonoscopy (Table 1).

Liver metastasis was reported in all of those by CT and MRI, and in 97 (76.98%) by USG. No significant correlation was found in the concordance analysis between CT and USG in detecting metastases (Table 2).

Survival time were more significant statistically compared to under 65 years old and $\geq$ 65 years old, unilateral tumors to bilateral tumors, single tumors to multiple tumors, tumor size $<$ 3 cm to $>$ 5 cm, with and without metastases on USG, colonoscopic suspected malignant mass to

Table 1. The distributions of the features of metastatic liver tumors

Parametreler		n	%
Gender	Male	126	58.33
	Female	90	41.67
Age	65 $\leq$	128	59.26
Localization (n=216)	Bilateral	131	60.65
	Right lobe	62	28.70
	Left lobe	23	10.65
Number of tumor(n=216)	Single	54	25.00
	Multiple	162	75.00
Tumor size (n=216)	<3 cm	92	42.59
	Between 3-5 cm	39	18.06
	>5 cm	85	39.35
Diagnosis (n=216)	PBC	60	27.78
	CRC	41	18.98
	PBBT	42	19.44
	Stomach cancer	28	12.96
	Other	45	20.83
USG (n=126)	Metastasis	97	23.02
	No metastasis	29	76.98
Endoscopy (n=132)	Benign/Normal	98	74.24
	Malignant	34	25.76
Colonoscopy (n=121)	Benign/Normal	86	71.07
	Malignant	35	28.93
Isolated/Extrahepatic metastasis (n=216)	Isolated liver metastasis	128	59.26
	Coexistence of extrahepatic metastases	88	40.74
Pathology (n=216)	Adenocarcinoma	157	72.69
	NET	25	11.57
	Other	34	15.74

Table 2. The Compliance Analysis of CT and USG for Metastasis Detection

		CT			p*
		Metastasis (n)	No metastasis (n)		
USG	Metastasis (n)	95	0	0.069	0.193
	No metastasis (n)	27	2		

*Kappa test, p value.

benign ones. The median survival time of patients who died was 5.50 (0.50-92.00) months, while those who alived were 29.00 (2.00-157.00) months, and the difference was statistically significant (p <0.001). After radiological examination, 128 (59.26%) patients had isolated liver metastases and 88 (40.74%) patients had extrahepatic metastases. Bone (17.6%) and lung (16.2%) constituted one third of all metastases (Table 3).

In terms of localization, the patients with bilateral involvement most frequently died.The compared with the location of liver metastasis, 65.61% in the bilateral, 24.20% in the right sided and 10.19% in the left sided patients died. 1 and 5-year survivals of those with bilateral tumor localization are 85% and 56%, right-sided 95% and 80%, left-sided 87% and 73%, respectively. The survival time was found to be statistically significantly higher in tumors localized on the right side compared to bilateral lesions (p <0.001) (Figure 1). 21.66% of those with single metastatic liver lesions and 78.34% of those with multiple liver metastases died. The 1 and 5-year survivals of patients with a single tumor are 94% and 81%, respectively, while those with multiple tumors are 86% and 59%. Survival time was found to be significantly higher in the presence of a single lesion (p <0.01) (Figure 2).

36.94% of those with the largest metastatic liver tumor diameter below 3 cm, 19.75% of those between 3 and 5 cm and 43.31% of those above 5 cm died. 1 and 5-year survivals of those with tumor diameter below 3 cm were 90% and 74%, respectively, while those between 3 and 5 cm were 84% and 59%, those over 5 cm were 88% and 57%. A statistically significant difference was found in favor of the group below 3 cm in terms of survival compared to the group above 5 cm (p <0.01) (Figure 3).

Correlation analysis was performed between laboratory parameters and survival times. There is a positive, weak, significant relationship between survival time and albumin level. As albumin level increases, survival time increases, while albumin level decreases, survival time also decreases (r = 0.353, p <0.001). There was a negative, weak, significant relationship between the survival time and the values of AST (r = -0.219), ALP (r = -0.282], LDH (r = -0.218) and GGT (r = -0.262). There is a negative, very

Table 3. The distribution of survival times by some characteristics of patients

		Survival time (months)Median (min-max)	P value
Gender	Male	7.50 (0.50-99.00)	0.225*
	Female	10.50 (0.75-157.00)	
Age	≤65 years	12.00 (0.50-157.00)	0.005*
	>65 years	6.00 (0.50-99.00)	
Localization	Bilateral	6.00 (0.50-157.00)a.b	<0.001**
	Right lobe	15.50 (0.50-96.00)a	
	Left lobe	18.00 (0.50-94.00)b	
Number of tumor	Single	14.50 (0.50-96.00)	0.001*
	Multiple	6.75 (0.50-157.00)	
Tumor size	<3 cm	14.00 (0.50-99.00)a	0.005**
	3-5 cm	6.00 (1.00-96.00)	
	>5 cm	6.50 (1.00-157.00)a	
Diagnosis	PBC	6.75 (0.50-157.00)	0.074**
	CRC	18.00 (0.50-99.00)	
	PBBT	8.25 (1.00-57.00)	
	Stomach cancer	15.25 (1.00-96.00)	
	Other	7.00 (0.75-68.50)	
USG	Metastasis	5.50 (0.50-88.00)	0.011*
	No metastasis	12.00 (0.50-99.00)	
Endoscopy	Benign/Normal	6.00 (0.50-99.00)	0.056*
	Malignant	13.50 (1.00-96.00)	
Colonoscopy	Benign/Normal	6.25 (0.50-92.00)	0.012*
	Malignant	19.00 (1.00-99.00)	
Isolated/Extrahepatic metastasis	Isolated liver metastasis	8.50 (0.50-99.00)	0.401*
	Coexistence of extrahepatic metastases	7.00 (0.50-157.00)	
Pathology	Adenocarcinom	8.00 (0.50-157.00)	0.066**
	NET	5.00 (0.50-88.00)	
	Other	12.00 (0.75-94.00)	
Mortality	Alive	29.00 (2.00-157.00)	<0.001*
	Dead	5.50 (0.50-92.00)	

* Mann Whitney U test p value, ** Kruskal Wallis test p value. a, b show the groups from which the difference originates according to Dunn-Bonferroni post-hoc test. There is a statistically significant difference between the 2 groups with the same letter.

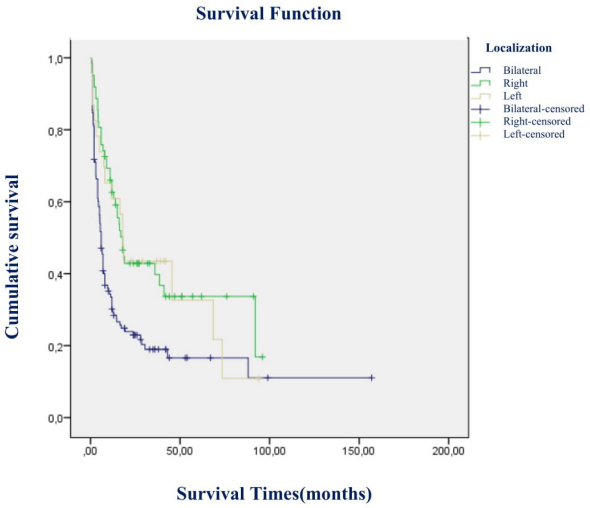

Figure 1. The inspection of survival according to tumor localization

weak, significant relationship between the values of CA19-9 (r = -0.161), TBIL (r = -0.165) and DBIL (r = -0.159) ($p < 0.05$).

ROC curve analysis was applied to determine the cut-off points of biochemistry laboratory parameters for mortality. The sensitivity and specificity rates calculated for parameters found to be significant are given in Table 4.

The median value of albumin in patients aged 65< years was 3.0 (1.4-4.0), and it was found to be statistically significantly lower ($p = 0.001$). While the median survival time of patients aged 65≥ years was 12.00 (0.50-157.00) months, it was 6.00 (0.50-99.00) months for patients aged >65 years, and this difference was statistically significant ($p < 0.01$). While 55.41% of those aged 65 ≥ years died, 44.59% of those aged 65< years. 1-year and 5-year survivals of aged 65≥ years are 89% and 69%, respectively, while it is 87% and 59% for >65 years of age. A statistically significant difference was found in favor of the group with the age of 65≥ in terms of survival ($p < 0.01$) (Figure 4).

The median value of CA-125 was 90.10 (3.4-7826.7) in patients with multiple organ metastases, which was significantly higher than those with isolated liver metastases ($p<0.05$).

Table 4. The distribution of survival times by some characteristics of patients

		Survival time (months)Median (min-max)	P value
Gender	Male	7.50 (0.50-99.00)	0.225*
	Female	10.50 (0.75-157.00)	
Age	≤65 years	12.00 (0.50-157.00)	0.005*
	>65 years	6.00 (0.50-99.00)	
Localization	Bilateral	6.00 (0.50-157.00)a.b	<0.001**
	Right lobe	15.50 (0.50-96.00)a	
	Left lobe	18.00 (0.50-94.00)b	
Number of tumor	Single	14.50 (0.50-96.00)	0.001*
	Multiple	6.75 (0.50-157.00)	
Tumor size	<3 cm	14.00 (0.50-99.00)a	0.005**
	3-5 cm	6.00 (1.00-96.00)	
	>5 cm	6.50 (1.00-157.00)a	
Diagnosis	PBC	6.75 (0.50-157.00)	0.074**
	CRC	18.00 (0.50-99.00)	
	PBBT	8.25 (1.00-57.00)	
	Stomach cancer	15.25 (1.00-96.00)	
	Other	7.00 (0.75-68.50)	
USG	Metastasis	5.50 (0.50-88.00)	0.011*
	No metastasis	12.00 (0.50-99.00)	
Endoscopy	Benign/Normal	6.00 (0.50-99.00)	0.056*
	Malignant	13.50 (1.00-96.00)	
Colonoscopy	Benign/Normal	6.25 (0.50-92.00)	0.012*
	Malignant	19.00 (1.00-99.00)	
Isolated/Extrahepatic metastasis	Isolated liver metastasis	8.50 (0.50-99.00)	0.401*
	Coexistence of extrahepatic metastases	7.00 (0.50-157.00)	
Pathology	Adenocarcinom	8.00 (0.50-157.00)	0.066**
	NET	5.00 (0.50-88.00)	
	Other	12.00 (0.75-94.00)	
Mortality	Alive	29.00 (2.00-157.00)	<0.001*
	Dead	5.50 (0.50-92.00)	

* Mann Whitney U test p value, ** Kruskal Wallis test p value. a, b show the groups from which the difference originates according to Dunn-Bonferroni post-hoc test. There is a statistically significant difference between the 2 groups with the same letter.

The percentage of bilateral metastasis in the liver of the deceased (65.61%) was significantly higher than alive (47.46%) ($p < 0.05$). The percentage of the largest tumor diameter in the liver to be 3> cm in diameter in alive (57.63%) was significantly higher than those who died (36.94%) ($p < 0.05$). The percentage of liver metastasis detection by US (80.58%) in the deceased was higher than the survivors (60.87%) ($p < 0.05$). The percentage of malignant mass seen in colonoscopy in deceased patients (21.59%) was lower than alive (48.48%) ($p < 0.01$). In patients who died, NLR, AFP, CEA, CA19-9, CA15-3, CA-125, TBIL, DBIL, AST, ALT, ALP, LDH, GGT values were higher while the albumin value was lower ($p < 0.05$) (Table 5).

In patients with CUP; The CEA ($p < 0.01$), CA19-9 ($p < 0.05$) and AST ($p < 0.05$) values of the deceased were higher than the survivors.

Discussion

The annual incidence of CUPs among all cancers is approximately 10%, and their frequency is in the 6th place [4]. Although CUPs that metastasize to the liver have a poor prognosis, some subtypes diagnosed with appropriate clinical and pathological methods may have a better prognosis [5, 6]. While adenocarcinomas are the most common subtype of carcinomas (60-70%) in pathological samples of cases (with primary known/unknown liver metastases), NETs are the second most common and 10-15% of them have a better response to treatment and may have a longer survival time [3, 7]. In our study, following the literature, 72.7% of the cases had adenocarcinoma and 11.6% had NETs, and unlike the literature, no difference was observed in terms of survival times of the patients. In the literature, the male-female ratio was similar, while the male gender was a poor prognostic factor, while the median age of the patients was 60 [3, 8]. Our study was not compatible with the literature, and there was no significant difference between men and women in terms of survival time. 58.3% of the patients were male and proportionally male gender was dominant and the median age of the patients was 53.

Cancers that metastasize to the liver are frequently CRCs, lung, and breast cancers [9]. In another autopsy series, primary neoplasms that most frequently metastasize to the liver were reported as lung (25%), colon (16%), pancreas (11%), breast (10%) and stomach (6%) [10]. In our findings, the most common tumors metastasizing to the liver were CUP (27.78%), PBRT (19.44%), CRC (18.98%), gastric cancer (12.96%), but lung (6.5%) and breast (3.7%)

Table 5. Cut off points of laboratory values of patients according to mortality

	Area Under the Curve	StandardDeviation	P value	95% Confidence interval		Breakpoint	Sensitivity	Specificity
				Lower limit	Upperlimit			
NLR	0.654	0.042	0.001	0.571	0.736	4.43	43.3%	83.10%
Hb	0.474	0.043	0.564	0.390	0.559	-	-	-
PLT	0.500	0.042	0.993	0.417	0.582	-	-	-
AST	0.712	0.039	<0.001	0.635	0.788	25.5	69.4%	67.8%
ALT	0.648	0.042	0.001	0.566	0.730	27.5	56.1%	74.6%
ALP	0.733	0.042	<0.001	0.651	0.815	99.5	83.4%	55.9%
GGT	0.721	0.040	<0.001	0.643	0.800	89.0	66.2%	72.9%
T.BIL	0.645	0.042	0.001	0.563	0.727	0.52	75.0%	49.2%
D.BIL	0.649	0.041	0.001	0.570	0.729	0.33	55.1%	69.5%
Albumin	0.274	0.038	<0.001	0.199	0.349	3.35	67.9%	64.4%
LDH	0.716	0.040	<0.001	0.638	0.795	243.5	80.1%	61.0%
AFP	0.627	0.047	0.011	0.535	0.719	1.87	73.8%	53.2%
CEA	0.702	0.041	<0.001	0.622	0.783	3.75	63.5%	69.0%
CA19-9	0.696	0.038	<0.001	0.623	0.770	166.73	43.1%	93.1%
CA15-3	0.637	0.051	0.013	0.537	0.736	29.65	50.0%	82.1%
CA-125	0.711	0.050	<0.001	0.613	0.809	19.7	79.6%	60.0%
PSA	0.382	0.079	0.162	0.227	0.536	-	-	-

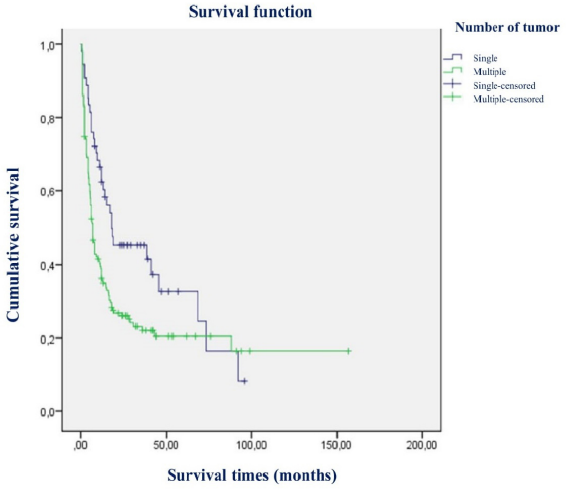

Figure 2. The inspection of survival according to tumor number

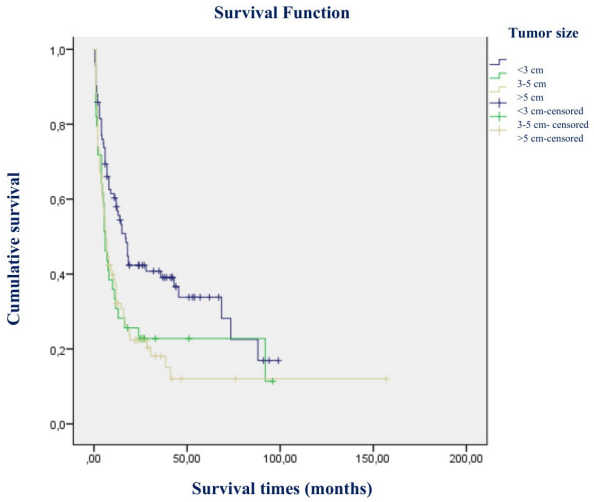

Figure 3. The inspection of survival according to tumor size

cancers were less common. The survival of patients with liver metastases of unknown origin at the time of diagnosis ranges from 11 weeks to 11 months [6], and in our study, the median survival was calculated as 8 months under the literature. While the sensitivity of conventional (non-contrasted) US was low (50-75%) [11], the sensitivity and specificity of conventional US in detecting liver metastases in our clinic was 77.8% and it was compatible with the literature.

Low tumor volume in the liver, small or single lesions, localization of lesions in a single lobe provided the best result for liver metastasis surgery, and thus, it has been reported to have positive effects on survival [12]. In our study, it was found that there was a significant relationship between the following features of the metastatic tumor in the liver and longer survival: 3> cm in diameter, single lesion, and right lobe localization.

In the literature, the rate of metastasis to the right lobe has been reported as 60-70%, and around 30-40% in the left lobe [13]. In our case, 60.6% was located bilaterally, 28.7% in the right lobe, and 10.6% in the left lobe. Consistent with the literature, although the right lobe is dominant, we think that the reason why it is proportionally different is that bilateral lesions were not included in the study in previous studies. Tumors located in the right lobe tend to cause multiple metastases due to the blood supply and size of the right lobe, so it is expected to be more aggressive. Contrary to popular belief, a significant relationship was found between being localized in the right lobe and longer survival. We think that this is due to higher rates of metastasis of CRCs and non-small cell NETs with high

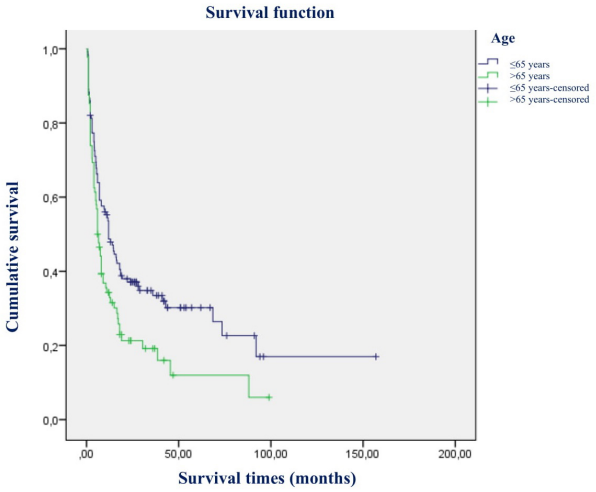

Figure 4. The inspection of survival according to age

expected survival [13, 14] to the right lobe, and also to the low number of tumors that metastasize to the left lobe [12].

In a retrospective study on iron deficiency anemia, malignancy was found in approximately 1.9% in gastroscopy and 9.3% in colonoscopy [15]. In our case, malignancy was detected in 27.7% in gastroscopy and 26.08% in colonoscopy in patients with Hb <13gr/dl, and it was higher than stated. The effect of low Hb on mortality was significant in patients with CRC, but not in patients with gastric cancer.

Studies on liver metastases in the literature mostly focused on those secondary to CRC, and prognostic factors were generally given on patients with CRC [16–18]. In a review, the presence of extrahepatic metastasis (outside the lung), CEA level higher than 10 ng / mL, right-sided colon cancer, and ≥6 metastatic lesions in the liver were stated as prognostic factors in patients with CRC with metastatic liver [19]. In our study, right-sided liver metastatic tumors, single liver metastases, and liver metastases with less than 3 cm diameter, malignant mass at colonoscopy, CEA <3.75 ng / mL were evaluated as good prognostic factors in our study (Table 3).

Patients with malignant masses on colonoscopy have early symptoms due to the mass effect, so they are likely to be diagnosed early. And, those masses are diagnosed almost always with CRCs. Resection is possible in CRCs even if they are metastatic at the time of diagnosis [20). Minimally invasive procedures for metastasis and metastasis surgery are also possible in patients with CRC with liver metastasis [20]. Long survival is expected in CRCs due to all these reasons. For these reasons, we attribute the evaluation of malignant mass detected by colonoscopy as a good prognostic factor.

In studies conducted on breast cancer patients with liver metastases, it has been reported that albumin and TBIL levels are useful in predicting survival [21, 22]. GGT, ALT, AST, ALP, LDH, and CA 15-3 levels were also found to be significantly higher in patients with liver metastasis compared to those without [21]. In a study comparing patients with and without liver metastases in patients with CRCs, GGT, ALT, AST, LDH, and CEA levels were found to be significantly higher in those with liver metastasis [17]. In the same study, it was stated that LDH can also be used to predict the expected life span in patients with CRC with liver metastasis [17]. In a study in which patients with HCC and metastatic liver were evaluated, when AST> 80 IU / L, ALT> 80 IU / L and albumin <3.0 g / dL were taken as the cut-off point, higher values had a negative effect on survival, while PLT values were not statistically significant on survival [23]. In our study, it was found that there was a positive correlation between survival time and mortality and albumin in liver metastases independent of diagnosis, and a negative significant correlation between levels of AST, ALP, LDH, GGT, CA 19-9, TBIL, and DBIL. However, while ALT levels had no significant effect on survival time, their effect on mortality was significant. Similar to the literature, there was no significant relationship between PLT values and survival and mortality. Again, the median value of albumin in patients over 65 years of age was 3.0 (1.4-4.0), and it was found to be statistically significantly lower than younger patients. Albumin is a suitable marker showing the synthesis function of the liver and is associated with malnutrition and low systemic inflammatory response [23]. Therefore, we concluded that the poor prognosis of patients over 65 years of age is closely related to low albumin levels. NLR has recently been used as a systemic inflammation marker. Inflammation plays an important role in the proliferation of tumoral cells, angiogenesis, and metastatic processes, and NLR values have prognostic importance in cancer patients [24]. In a retrospective study conducted with 83 patients with metastatic CRC, the cut-off points were taken as 1.94 for NLR and 100 ng / mL for CEA, and the combination of NLR-CEA was shown to have a strong prognostic value in predicting both disease-free and overall survival [25]. In our study, cut-off points were found as 4.43 ng / mL for NLR and 3.75 ng / mL for CEA in the ROC analysis we performed on all patients with liver metastases. While CEA and NLR levels had an effect on mortality, their effect on survival was not significant. It was observed that AFP, CA15-3, CA-125, ALT levels had a significant effect on mortality, but not on survival.

In a retrospective study involving 430 lung cancer patients by Yihan et al., CA-125 and CA 19-9 levels were found to be closely related to age, adenocarcinoma subtype, bone, and pleural metastasis [26]. Even in adenocarcinoma, CA-125 has more prognostic importance than CA 19-9 and is also predictive in detecting brain metastases [26]. Even if the preoperative AFP concentration is ≤200 ng / mL, CA-125 levels above 30 U / mL are indicative of poor prognosis [27]. In our study, CA-125 levels were significantly higher in patients with extrahepatic metastasis compared to those with isolated liver metastasis, and this is consistent with the literature. Therefore, in our opinion, CA-125 can be a good marker in predicting the presence of extrahepatic metastasis. However, in our study, unlike the studies mentioned above, the effect of CA 19-9 levels on survival time was found to be significantly higher in adenocarcinomas, in contrast to CA-125. In a study conducted with 75 pancreatic cancer patients, a significant relationship was found

Table 6. The distribution of survival times by some characteristics of patients

		Survival time (months)Median (min-max)	P value
Gender	Male	7.50 (0.50-99.00)	0.225*
	Female	10.50 (0.75-157.00)	
Age	≤65 years	12.00 (0.50-157.00)	0.005*
	> 65 years	6.00 (0.50-99.00)	
Localization	Bilateral	6.00 (0.50-157.00)a.b	< 0.001**
	Right lobe	15.50 (0.50-96.00)a	
	Left lobe	18.00 (0.50-94.00)b	
Number of tumor	Single	14.50 (0.50-96.00)	0.001*
	Multiple	6.75 (0.50-157.00)	
Tumor size	< 3 cm	14.00 (0.50-99.00)a	0.005**
	3-5 cm	6.00 (1.00-96.00)	
	> 5 cm	6.50 (1.00-157.00)a	
Diagnosis	PBC	6.75 (0.50-157.00)	0.074**
	CRC	18.00 (0.50-99.00)	
	PBBT	8.25 (1.00-57.00)	
	Stomach cancer	15.25 (1.00-96.00)	
	Other	7.00 (0.75-68.50)	
USG	Metastasis	5.50 (0.50-88.00)	0.011*
	No metastasis	12.00 (0.50-99.00)	
Endoscopy	Benign/Normal	6.00 (0.50-99.00)	0.056*
	Malignant	13.50 (1.00-96.00)	
Colonoscopy	Benign/Normal	6.25 (0.50-92.00)	0.012*
	Malignant	19.00 (1.00-99.00)	
Isolated/Extrahepatic metastasis	Isolated liver metastasis	8.50 (0.50-99.00)	0.401*
	Coexistence of extrahepatic metastases	7.00 (0.50-157.00)	
Pathology	Adenocarcinom	8.00 (0.50-157.00)	0.066**
	NET	5.00 (0.50-88.00)	
	Other	12.00 (0.75-94.00)	
Mortality	Alive	29.00 (2.00-157.00)	< 0.001*
	Dead	5.50 (0.50-92.00)	

* Mann Whitney U test p value, ** Kruskal Wallis test p value. a, b show the groups from which the difference originates according to Dunn-Bonferroni post-hoc test. There is a statistically significant difference between the 2 groups with the same letter.

between the doubling time of CA19-9 and CEA with prognosis [28], whereas in another study conducted with CRC patients, CA 19-9 was reported to have no prognostic significance [17]. In CUPs, tumor markers (CEA, CA 19-9, CA 15-3, CA 125, beta-HCG) were elevated in more than 40% of patients, except for AFP, depending on the histological pattern, number of metastases, and localization. The level of tumor markers also had a predictive effect on chemotherapy response and survival[29]. Contrary to the literature, the effect of CEA levels in CUPs and CA 19-9 levels in CRCs on mortality was significant. In conclusion, although tumor marker changes according to histological pattern, location and number of metastases, it may have prognostic importance.

In the literature, preoperative serum CEA elevation has been reported in 16-58% of gastric cancer cases, while in some, the elevation of AFP in both serum and tissue has been reported [30]. AFP expressing stomach cancers; rapid proliferation, low apoptosis, and rich vascularization abilities; causes poor prognosis and reduced survival [16]. In our study, while AFP levels did not have a significant contribution to mortality in patients with gastric cancer. When we included all cancers with liver metastases, the effect of AFP on mortality was significant, but not on survival time. The effect of CEA, TBIL, AST, ALP, GGT levels on mortality was found significant in patients with gastric cancer, but like AFP not on survival time.

Although there is no consensus in the guidelines, PSA is considered to be <2.5-3 ng / mL in young men and 4 ng / mL as the cut-off value above the age of 50 [31]. In our study, the PSA median value was 1.38 ng / mL (0.16-14.03) in male patients over 65 years of age, which was statistically significantly higher than in young patients. Prostate cancers usually metastasize to other organs before they metastasize to the liver, and a total of 9 prostate cancer cases with isolated liver metastases have been reported in the literature [32]. Our only patient with prostate cancer had extrahepatic metastases like the literature.

Conclusions

The presence of metastases in the liver is the most important determinant of survival. In our study, a significant relationship was found between albumin, AST, ALP, LDH, GGT, CA 19-9, TBIL, DBIL levels with overall survival. At the same time, a significant correlation was found between levels of albumin, AFP, CEA, CA19-9, CA15-3, CA-125, TBIL, DBIL, AST, ALT, ALP, LDH, GGT and mortality.It was shown that age 65 years and younger, right

lobe liver metastasis, solitary hepatic lesion, maximum tumor diameter less than 3 cm and primary CRC diagnosis are good prognostic factors for overall survival. In addition, a correlation was observed between the presence of extrahepatic metastasis and CA-125 levels.

Conflict of Interest

All authors declare that there is no conflict of interest between them.

Abbreviations

ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, ALP: Alkaline Phosphatase, CT: Computed Tomography, CA: Carbohydrate Antigen, CEA: Carcinoembryonic Antigen, CK7: Cytokeratin 7, CK20: Cytokeratin 20, D.BIL: Direct Bilirubin, GGT: Gamma Glutamyl Transferase, GIS: Gastrointestinal System, GIST: Gastrointestinal Stromal Tumor, Hb: Hemoglobin, HBV: Hepatitis B Virus, HCC: Hepatocellular Carcinoma, HCV: Hepatitis C Virus, ICAM: Intracellular Adhesion Molecule, FNAB: Fine Needle Aspiration Biopsy, SCLC: Small Cell Lung Carcinoma, NSCLC: Non-Small Cell Lung Carcinoma, CRC: Colorectal Cancer, LDH: Lactate Dehydrogenase, MRI: Magnetic Resonance Imaging, NCAM: Neural Cell Adhesion Molecule, NET: Neuroendocrine Tumors, NLR: Neutrophil Lymphocyte Ratio, PBRT: Pancreato Biliary Region Tumors, CUP: Cancer of Unknown Primary, PLT: Platelet, PSA: Prostate Specific Antigen, RCC: Renal Cell Carcinoma, RES: Reticuloendothelial System, SCC: Squamous Cell Carcinoma, TACE:Transarterial Chemoembolization, TARE: Transarterial Radioembolization, T.BIL: Total Bilirubin, USG: Ultrasonographic Imaging.

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