Int J Clin Exp Med 2019;12(3):2746-2752
www.ijcem.com /ISSN:1940-5901/IJCEM0085787

Original Article

Prognostic significance of preoperative serum lactate dehydrogenase in patients with resectable gastric adenocarcinoma

Halime Hanım Pençe[1], Ebubekir Gündeş[2], Aziz Serkan Senger[3], Hani Alsaadoni[4], Hüseyin Çiyiltepe[5], Selçuk Gülmez[3], Orhan Uzun[3], Ulaş Aday[6], Erdal Polat[3], Mustafa Duman[3]

[1]University of Health Sciences, Department of Biochemistry, Istanbul, Turkey; [2]Gazi Yaşargil Education and Training Hospital, Gastroenterological Surgery, Diyarbakır, Turkey; [3]Kartal Koşuyolu High Specialty and Training Hospital Gastroenterological Surgery Department, Kartal, Istanbul, Turkey; [4]University of Health Sciences, Department of Physiology, Istanbul, Turkey; [5]Fatih Sultan Mehmet Education and Training Hospital, Gastroenterological Surgery, Istanbul, Turkey; [6]Elazığ Education and Training Hospital, Gastroenterological Surgery, Elazığ, Turkey

Received September 20, 2018; Accepted November 8, 2018; Epub March 15, 2019; Published March 30, 2019

Abstract: Objective: Enzymes, such as serum lactate dehydrogenase (SLDH), have been confirmed to play an important role in tumor proliferation and prediction of prognoses in patients with various types of cancer. However, there are few studies considering SLDH's prognostic significance in gastric cancer. Methods: The present study reviewed SLDH levels and other postoperative data of 208 patients with gastric cancer that had undergone surgery from January 2010 to September 2017. Patients were classified into two groups according to SLDH levels (normal SLDH and high SLDH). The cutoff point was set according to the highest limit of normal SLDH levels. Chi-squared test was conducted to analyze relationships between SLDH and clinical features. Logistic regression analysis was also carried out to determine independent risk factors for overall survival (OS). Results: Of the patients included in the study, 160 (76.9%) were male and 48 (23.1%) were female, with a mean age was 61.36 ± 11.4 years. Results of the study showed that carcinoembryonic antigen (CEA) ($p < 0.001$), neutrophil lymphocyte ratio (NLR) (p: 0.005), maximum tumor diameter (p: 0.005), ratio of metastatic lymph nodes to excised lymph nodes (LNR) (p: 0.04), lymph node involvement (N) (p: 0.005), and depth of infiltration (T) (p: 0.001) were significantly higher in the high SLDH (HSLDH) group. Multivariate analysis conducted for OS revealed that HSLDH (> 245 U/L), maximum tumor diameter (≥ 4 cm), N (+), and T (III-IV) served as independent risk factors. Moreover, Kaplan-Meier analysis revealed that HSLDH (> 245 U/L) levels were significantly related to poor OS ($p < 001$). Conclusion: An elevation in SLDH levels suggests advanced N and T stages, as well as the existence of a large tumor mass. Furthermore, results revealed that HSLDH levels are poor independent prognostic factors for OS in resectable gastric cancer cases.

Keywords: Gastric cancer, lactate dehydrogenase, D2 lymphadenectomy

Introduction

Although prevalence of gastric cancer has declined gradually, it remains the fifth most common malignancy, worldwide, and occupies third place among all cancers in mortality rates. The main causes of death in patients with gastric cancer are recurrence and metastasis [1]. TNM classification of gastric cancer cases is very significant in the assessment of treatment modality, selection of surgical treatment, and prediction of prognosis. However, important prognostic factors, such as age, sex, location of the primary tumor, the Lauren classification, and presence of lympho-vascular invasion, are not covered by the TNM classification. Moreover, biomarkers that might aid in prognosis prediction are not covered [2].

The conversion of normal cells into cancer cells or the proliferation of cancer cells always paves the way for abnormal serum enzyme synthesis. It can do so even before the occurrence of alterations in tumor morphology, in other words,

Table 1. Clinicopathological correlations of SLDH in gastric cancer

Variable		All Cases	Normal SLDH (160) n (%)	High SLDH (48) n (%)	*p*
Age	< 60	83	62	21	0.535
	≥ 60	125	98	27	
Gender	Female	48	37	11	0.976
	Male	160	123	37	
CEA	< 5 ng/ml	172	140	32	< 0.001*
	≥ 5 ng/ml	36	20	16	
NLR	< 4	180	144	36	0.008*
	≥ 4	28	16	12	
PLR	< 160	132	104	28	0.400
	≥ 160	76	56	20	
Maximum tumor diameter (mm)	< 4 cm	76	68	8	< 0.001*
	≥ 4 cm	132	92	40	
Lymphovascular Invasion	No	72	56	16	0.831
	Yes	136	104	32	
Perineural Invasion	No	52	40	12	> 0.5
	Yes	156	120	36	
LNR	LNR: 0	56	44	12	0.04*
	0 < LNR ≤ 0,07	16	16	0	
	0,07 < LNR ≤ 0,2	60	48	12	
	LNR > 0,2	76	52	24	
N	0	60	52	8	0.005*
	1	56	48	8	
	2	48	32	16	
	3	44	28	16	
T	1	12	8	4	< 0.001*
	2	16	16	0	
	3	96	84	12	
	4	84	52	32	

(*Differences between the groups with Chi-squared test are statistically significant p < 0,05); CEA: Carcinoembryonic antigen, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, LNR: The ratio of metastatic lymph nodes to excised lymph nodes, N: Lymph node involvement T: Depth of infiltration.

before the clinically detectable stage [3]. This fact has significantly increased interest in serum enzymes.

The main paradigm originating from Warburg's study suggests that tumors with rapid proliferation, as opposed to normal cells, transform glucose in an aerobic environment into lactate, despite the small amount of ATP obtained from one molecule of glucose produced as a result of this process (4). LDH is the enzyme responsible for the reversible conversion of pyruvate produced as a result of glycolysis metabolism. LDH catalyzes the transfer of redactor equivalents from nicotinamide adenine dinucleotide (NADH) to pyruvate or from lactate to NAD+(5). It has been established that a high serum LDH level is a negative prognostic factor in many malignancies. However, there are very few studies regarding gastric cancer.

Most studies have focused on biomarkers to enhance early diagnosis and prognosis of cancer. It is of utmost importance to explore prognostic factors that may be important for survival in gastric cancer. It has a very high mortality rate and is frequently seen worldwide. The aim of the present study was, therefore, to investigate the relationship between preoperative serum lactate dehydrogenase (SLDH) lev-

Table 2. Univariate logistic regression model analysis of prognostic factors in resectable gastric cancer patients

Variable	β	Odds Ratio	95% CI	*P*-value
Age (≥ 60)	-0.265	0.767	0.440-1.338	0.350
Male sex	0.175	1.192	0.625-2.273	0.594
CEA (≥ 5)	-0.821	0.440	0.204-0.950	0.037*
NLR (≥ 4)	-0.010	0.990	0.446-2.201	0.981
PLR (≥ 160)	-0.204	0.815	0.462-1.439	0.481
SHLDH (> 245)	-1.224	0.294	0.143-0.606	0.001*
Maximum tumor diameter (≥ 4)	-1.066	0.344	0.192-0.606	0.001*
Lymphovascular Invasion (+)	-1.081	0.339	0.187-0.614	0.001*
Perineural Invasion (+)	-0.806	0.446	0.235-0.849	0.014*
LNR (> 0.07)	1.660	5.258	2.808-9.846	0.001*
N (+)	2.090	8.032	3.937-16.591	0.001*
T (III-IV)	-2.174	0.114	0.038-0.341	0.001*

(B: beta, OR; odds ratio, CI = confidence interval, *; candidate variables in the multivariate model). CEA: Carcinoembryonic antigen, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, SHLDH: Serum high lactate dehydrogenase LNR: The ratio of metastatic lymph nodes to excised lymph nodes, N: Lymph node involvement T: Depth of infiltration.

Table 3. Multiple logistic regression model analysis of prognostic related factors in resectable gastric cancer

Variable	β	OR	95% CI	*P*-value
SHLDH (> 245)	1.105	3.018	1.244-7.223	0.015*
CEA (≥ 5)	0.151	1.163	0.486-2.784	0.734
Maximum tumor diameter (≥ 4)	-0.701	0.498	0.248-0.995	0.048*
Lymphovascular Invasion (+)	-0.151	0.860	0.390-1.897	0.709
Perineural Invasion (+)	-0.678	0.508	0.230-1.122	0.394
LNR (> 0.07)	0.531	1.701	0.708-4.088	0.235
N (+)	1.298	3.662	1.336-10.040	0.012*
T (III-IV)	1.448	4.257	1.112-16.289	0.034*

(β: beta, OR; odds ratio, CI = confidence interval, *; independent risk factor for overall survival); SHLDH: Serum high lactate dehydrogenase, CEA: Carcinoembryonic antigen, LNR: The ratio of metastatic lymph nodes to excised lymph nodes, N: Lymph node involvement T: Depth of infiltration.

els and prognosis of the disease in patients diagnosed with gastric cancer.

Methods

Ethical declaration

Written informed consent was obtained from all patients before the procedure. Kartal Koşuyolu Higher Training and Research Hospital's Advisory Board for Clinical Trials ratified the study. The study was conducted in accordance with ethical principles put forward by the World Health Organization's Declaration of Helsinki.

Study plan

Cases of patients diagnosed with gastric cancer at Kartal Koşuyolu Higher Training and Research Hospital's Gastroenterology Surgery Clinic in Istanbul, Turkey, from January 2010 to September 2017, were studied retrospectively.

Study population

Conditions of all patients diagnosed with gastric adenocarcinoma were confirmed by gastroscopic biopsies. Thoracoabdominal computed tomography (CT) was performed on all patients for preoperative staging. Inadequate file data, patients with R2 resections, metastatic patients, patients that had neoadjuvant therapy, mortality cases within the first 30 days of the postoperative period, and patients with comorbid conditions that might have been responsible for elevation in LDH levels (hepatic disease and/or excessive alcohol abuse, hemolysis, nephrotic syndrome, etc.) were excluded from the study.

A total of 380 patients with gastric cancer were followed up and treated at the clinic within the specified time period. Of these, 208 patients meeting the inclusion criteria, having undergone a total or subtotal gastrectomy and D2 lymph node dissection, were included in the study.

Measurement and grouping of LDH

LDH measurement for preoperatively drawn blood samples was conducted locally utilizing the Roche Cobas 8000 analyzer (Roche Diagnostics, Mannheim, Germany). While the normal range of SLDH was 120-245 U/L, results were in the same range, according to the same analyzer from 2010 to 2017. SLDH levels were classified into two groups with ≤ 245 signifying

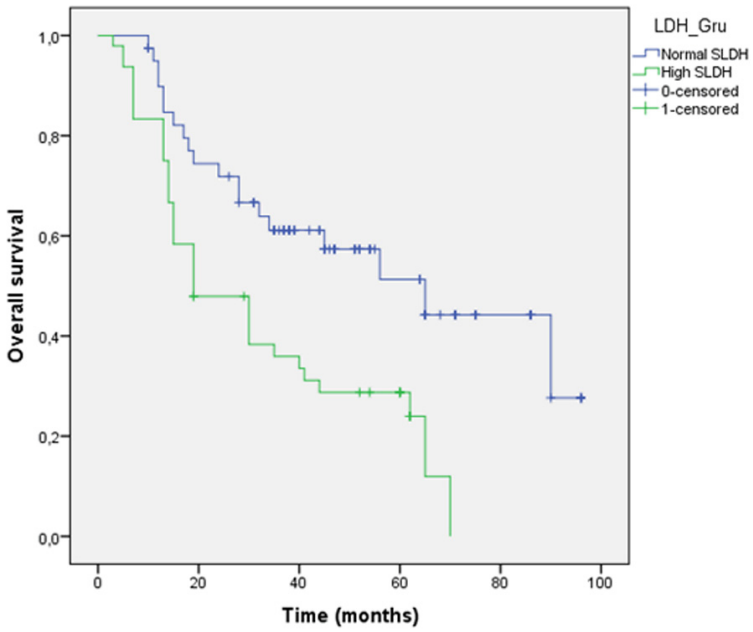

Figure 1. Kaplan-Meier analysis shows that patients with high SLDH have significantly poorer overall survival than those with normal SLDH ($p < 0.001$).

normal SLDH (NSLDH) and > 245 signifying high SLDH (HSLDH).

Data

Age, sex, history of comorbidity, carcinogenic embryonic antigen (CEA), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and SLDH data of patients covered by the study were preoperatively recorded. From pathology reports, maximum tumor diameter (mm), invasion depth (T), number of excised lymph nodes and number of detected metastatic lymph nodes (N), and the presence of lymphovascular and perineural invasion were also recorded. Pathological staging of tumors was conducted according to the 7th edition of the TNM staging system published by the American Joint Committee on Cancer (AJCC) [6].

Primary endpoint of the study

The study explored the correlation between preoperative SLDH levels and the prognostic value in patients with gastric cancer.

Statistical analysis

Data collected within the scope of the study were analyzed using IBM SPSS Statistics version 21 for Windows software (IBM, Armonk, NY, USA). Mean, minimum, maximum, and standard deviation (SD) figures were computed for the data collected from patients covered by the study. The Kolmogorov-Smirnov test was utilized to check data distribution. Categorical groups were compared by the Chi-squared test, with p-values < 0.05 set as the cutoff for statistical significance. The first step in the formation of a multivariate logistic regression model for relevant factors in mortality cases related to gastric cancer was univariate logistic regression analysis of each variable. This was conducted to ascertain prospective variables that were likely to be included in the model. In cases where the results of the Wald test statistics were lower than the level of error that was set as the probability value ($p < 0.25$), relevant variables were included in the multivariate model. Odds ratios (OR) and confidence intervals (95% CI) of the results were computed, with the significance set at $p < 0.05$. The Kaplan-Meier method was used to estimate survival rates between the SLDH groups, while comparisons were conducted by the log-rank test. Significance was set at $p < 0.05$.

Results

Patients and tumor characteristics

Ultimately, 160 (76.9%) male patients and 48 (23.1%) female patients were included in the study. The mean age of patients was 61.36 ± 11.4 years. The median size of tumors per the largest diameter was 50 mm (0.8-15.0 cm). Elevated SLDH levels (above the upper limit of the normal value range of the test [> 245 U/L]) were seen in 23.07% (48 of 208) of the patients with resectable gastric cancer. CEA (p <0.001), NLR (p: 0.008), maximum tumor diameter (p < 0.001), LNR (p: 0.04), N stage (p: 0.005), and T stage ($p < 0.001$) were found to be significantly higher in the HSLDH group than the NSLDH group. **Table 1** presents the clinicopathological characteristics and SLDH correlations in patients with gastric cancer.

Independent prognostic factors in resectable gastric cancer

LDH and clinicopathological characteristics were explored to define risk factors that affected postoperative OS. Results of the significance test of the coefficients of variables included in each univariate model are shown in **Table 2**, revealing that CEA (≥ 5), HSLDH (> 245 U/L), maximum tumor diameter (≥ 4 cm), lymphovascular invasion, perineural invasion, LNR (> 0.07), N (+), and T (III-IV) had a statistically significant relationship with the dependent variable. These variables were determined as prospective ones for the multivariate model.

Multivariate analysis of the factors related to prognosis was conducted. Logistic regression analysis identified HSLDH (p = 0.015, OR 3,018, 95% CI 1.244-7.223), maximum tumor diameter (≥ 4 cm) (p = 0.048, OR = 0.498, 95% CI 0.248-0.995), N (+) (p = 0.012, OR 3,662, 95% CI 1.336-10.040), and T (III-IV) (p = 0.034, OR 4.257, 95% CI 1.12-16.289) as independent risk factors (**Table 3**). Other variables that were found to be significant by univariate analysis, however, were not found to be significant, according to results of multivariate analysis.

To further analyze the prognostic significance of SLDH in patients with resectable gastric cancer, the Kaplan-Meier method was utilized to analyze survival rates of patients according to their SLDH profiles. Mortality was seen in 111 (53.4%) patients within the study period. The mean survival period was found to be 58.6 ± 3.04 months in the NSLDH group, while it was 32.3 ± 3.56 months in the HSLDH group, with no significant differences indicated between the two (log-rank; p: 0.001) (**Figure 1**).

Discussion

The present study investigated the relationship between SLDH levels and prognoses of patients with resectable gastric cancer. Results revealed that HSLDH levels were significantly related to short OS. Moreover, results indicated an association with advanced N and T stages, with a positive correlation to large tumor masses.

The fact that cancer cells might show atypical metabolic characteristics was first understood as a result of the pioneering studies conducted by Warburg in the first half of the 20th century [7, 8]. Normal cells break glycose down into pyruvate in the presence of oxygen by way of glycolysis, completely oxidizing most of the formed pyruvate inside the mitochondria by oxidative phosphorylation, transforming it into CO_2. Under anaerobic conditions, however, normal cells do not direct glycolytic pyruvate to mitochondrial oxidation. Instead, they are mostly reduced to lactate [9]. The main paradigm, based on Warburg's studies, indicates that rapidly proliferating tumors, as opposed to normal cells, transform glucose into lactate in an aerobic environment, although the amount of ATP obtained by one molecule of glucose produced as a result of this process is very small. This apparently irrational phenomenon is called the *Warburg effect* or *aerobic glycolysis* [7, 9]. It is indeed the Warburg effect that plays a key role among most of the metabolic pathways found in tumor cells [10]. These apparently damaging behaviors of cancer cells are advantageous for survival, as they render proliferating cells indifferent to temporary or permanent hypoxic conditions. They also contribute to the production of nucleosides and amino acids thanks to the elevated uptake of glucose in cancer tissues, providing a very rapid path for energy production [10, 11]. Furthermore, within this process, lactate is not only a waste product but, on the contrary, acts as an agent that enhances tumor invasion by developing cell migration, new vascular webbing, escape from the immune system, and radioactive resistance [11, 12].

One of the most important glycolytic targets, which catalyzes the reversible conversion of pyruvate to lactate simultaneously with the oxidation of cofactor NAD to NAD+, is the LDH enzyme. Human isoform LDH-A or LDH5 is composed of four A sub-units (LDH-A4) and is expressed mostly in hepatic and muscular tissues. Previous studies have demonstrated that over-regulated LDH-A plays an important role in cell proliferation in invasive glycolytic cancers and enables the survival of the tumors, even in environments with low oxygen concentration [11]. These factors led the present study to investigate the relationship between LDH levels and prognoses of patients with resectable gastric cancer.

The prognostic significance of SLDH has been shown in various types of cancer, notably in cases of hematological malignity. SLDH is a

predictor of poor survival in diffuse large B-cell lymphoma and is one of the five risk factors listed by the International Prognostic Index [13].

Recent clinical studies have shown that elevated SLDH is an independent predictor of OS in esophageal [14], breast [15], colorectal [16, 17], pancreatic [18], nephritic [19], skin [20], and nasopharyngeal tumors [21].

There are few studies in the literature considering SLDH levels of patients with gastric cancer, however. In a 2013 study by Kostakis et al., conducted with 140 patients with colorectal cancer and 40 patients with gastric cancer [22], the authors found that SLDH levels of patients with colorectal cancer were elevated in T4, N2, and/or M1 cancer cases. They did not find any significant clinicopathological relationship in patients with gastric cancer, suggesting that this was related to the limited number of patients with gastric cancer covered by their study. Three hundred sixty-five patients with gastric cancer were included in a study conducted by Zhao et al. in 2014 [23]. Results of this study revealed that pathological T stage, metastasis, pTNM stage, and recurrence were statistically higher in the group with high SLDH. A total of 619 patients with gastric and gastroesophageal junction tumors were covered in a study conducted by Wang et al. in 2016 [24]. The authors concluded that high preoperative SLDH levels were independently related to poor OS and disease-free survival (DFS), notably in male patients.

There were some significant limitations to the present study. The fact that it was a retrospective observational study, conducted with a limited number of patients, resulted in limitations in the study's design. Moreover, analysis was limited to a select sub-group that had T1-T4, any N, and M0 patients. This was done to investigate whether the determinant had a prognostic significance for resectable patients. Further studies should be conducted to comprehend the prognostic value of the same parameters in systemic diseases in relation to chemotherapeutic regimes. Future multi-centered, well-designed, and prospective studies can provide more accurate evidence.

However, results of the present study suggest that preoperative SLDH levels can be employed as a prognostic factor. Moreover, results also suggest that treatment plans should consider not only the TNM stage but also serum enzymes related to prognosis. The complete mechanisms and functions of SLDH in gastric cancer remain unclarified. This simple prognostic assessment can be utilized to screen patients for personalized therapy in the future.

Disclosure of conflict of interest

None.

Address correspondence to: Ebubekir Gündeş, Gazi Yaşargil Education and Training Hospital, Gastroenterological Surgery, Diyarbakır, Turkey. Tel: +90 [505] 8606740; E-mail: ebubekir82@hotmail.com

References

[1] Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11. Lyon, France: International Agency for Research on Cancer. 2013. Available at: http://globocan.iarc.fr.

[2] Catalano V, Labianca R, Beretta GD, Gatta G, de Braud F, Van Cutsem E. Gastric cancer. Crit Rev Oncol Hematol 2009; 71: 127-164.

[3] Ferreira LMR, Hebrant A, Dumont JE. Metabolic reprogramming of the tumor. Oncogene 2012; 31: 3999-4011.

[4] Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science 2009; 324: 1029-1033.

[5] Hirschhaeuser F, Sattler UG, Mueller-Klieser W. Lactate: a metabolic key player in cancer. Cancer Res 2011; 71: 6921-6925.

[6] Edge SB, Compton CC. The American joint committee on cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010; 17: 1471-1474.

[7] Cantor JR, Sabatini DM. Cancer cell metabolism: one hallmark, many faces. Cancer Discov 2012; 2: 881-898.

[8] Willem HK, Patricia LB, Chi VD. Otto Warburg's contributions to current concepts of cancer metabolism. Nat Rev Cancer 2011; 11: 325-337.

[9] Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science 2009; 324: 1029-1033.

[10] Granchi C, Fancelli D, Minutolo F. An update on therapeutic opportunities offered by cancer glycolytic metabolism. Bioorg Med Chem Lett 2014; 24: 4915-4925.

[11] Salamon S, Podbregar E, Kubatka P, Büsselberg D, Caprnda M, Opatrilova R, Valentova V, Adamek M, Kruzliak P, Podbregar M. Glucose metabolism in cancer and ischemia: possible therapeutic consequences of the warburg effect. Nutr Cancer 2017; 69: 177-183.

[12] Draoui N, Schicke O, Fernandes A, Drozak X, Nahra F, Dumont A, Douxfils J, Hermans E, Dogné JM, Corbau R, Marchand A, Chaltin P, Sonveaux P, Feron O, Riant O. Synthesis and pharmacological evaluation of carboxycoumarins as a new antitumor treatment targeting lactate transport in cancer cells. Bioorg Med Chem 2013; 21: 7107-7117.

[13] Zhou Z, Sehn LH, Rademaker AW, Gordon LI, Lacasce AS, Crosby-Thompson A, Vanderplas A, Zelenetz AD, Abel GA, Rodriguez MA, Nademanee A, Kaminski MS, Czuczman MS, Millenson M, Niland J, Gascoyne RD, Connors JM, Friedberg JW, Winter JN. An enhanced international prognostic index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood 2014; 123: 837-842.

[14] Polee MB, Hop WC, Kok TC, Eskens FA, van der Burg ME, Splinter TA, Siersema PD, Tilanus HW, Stoter G, van der Gaast A. Prognostic factors for survival in patients with advanced oesophageal cancer treated with cisplatin-based combination chemotherapy. Br J Cancer 2003: 89: 2045-2050.

[15] Brown JE, Cook RJ, Lipton A, Coleman RE. Serum lactate dehydrogenase is prognostic for survival in patients with bone metastases from breast cancer: a retrospective analysis in bisphosphonate-treated patients. Clin Cancer Res 2012; 18: 6348-6355.

[16] Koukourakis MI, Giatromanolaki A, Harsis AL, Sivridis E. Comparison of metabolic pathways between cancer cells and stromal cells in colorectal carcinomas: a metabolic survival role for tumor associated stroma. Cancer Res 2006; 66: 632-637.

[17] Koukourakis MI, Giatromanolaki A, Simopoulos C, Polychronidis A, Sivridis E. Lactate dehydrogenase 5 (LDH5) relates to up-regulated hypoxia indicible factor pathway and metastasis in colorectal cancer. Clin Exp Matastasis 2005; 22: 25-30.

[18] Tas F, Aykan F, Alici S, Kaytan E, Aydiner A, Topuz E. Prognostic factors in pancreatic carcinoma: serum LDH levels predict survival in metastatic disease. Am J Clin Oncol 2001; 24: 547-550.

[19] Armstrong AJ, George DJ, Halabi S. Serum lactate dehydrogenase predicts for overall survival benefit in patients with metastatic renal cell carcinoma treated with inhibition of mammalian target of rapamycin. J Clin Oncol 2012; 30: 3402-3407.

[20] Weide B, Elsässer M, Büttner P, Pflugfelder A, Leiter U, Eigentler TK, Bauer J, Witte M, Meier F, Garbe C. Serum markers lactate dehydrogenase and S100B predict independently disease outcome in melanoma patients with distant metastasis. Br J Cancer 2012; 107: 422-428.

[21] Jin Y, Ye X, Shao L, Lin BC, He CX, Zhang BB, Zhang YP. Serum lactic dehydrogenase strongly predicts survival in metastatic nasopharyngeal carcinoma treated with palliative chemotherapy. Eur J Cancer 2013; 49: 1619-1626.

[22] Kostakis ID, Vaiopoulos AG, Philippou A, Papavassiliou AG, Koutsilieris M, Kouraklis G. Preoperative serum lactate dehydrogenase levels in colorectal and gastric cancer: a hospital-based case-control study. Biomark Med 2013; 7: 131-7.

[23] Zhao Z, Han F, Yang S, Hua L, Wu J, Zhan W. The clinicopathologic importance of serum lactic dehydrogenase in patients with gastric cancer. Dis Markers 2014; 2014: 140913.

[24] Wang ZX, Yang LP, Qiu MZ, Wang ZQ, Zhou YX, Wang F, Zhang DS, Wang FH, Li YH, Xu RH. Prognostic value of preoperative serum lactate dehydrogenase levels for resectable gastric cancer and prognostic nomograms. Oncotarget 2016; 28; 7: 39945-39956.