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Prognostic Value of the Uric Acid Level and Its Effect on Survival in Stage I–III Gastric Cancer

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BACKGROUND/AIMS
Uric acid is the product of purine metabolism. In this study, we investigated the prognostic value of serum uric acid value on disease-free and overall survival (DSF and OS) in gastric cancer.

MATERIAL and METHODS
The records of 110 patients who underwent surgery for Stage I–III gastric cancer between 2012 and 2014 were retrospectively analyzed.

RESULTS
The average follow-up period was 42 months in 110 patients studied. The mean age was 63.7±11.6 years. Seventy percent of patients were male, and 43% underwent total and 57% subtotal gastrectomy. Most of gastric tumors were located in the distal stomach (56%), 24% in cardia, and 19% in corpus. While the tumor size was found to be larger than 4 cm in 60% of the patients and larger than 8 cm in 20%, according to the TNM system, 11% were Stage I , 29% Stage II, and 60% Stage III. Metastatic/excised lymph node ratio is <0.3 in 59% of patients. The mean uric acid level was 4.63±1.44. The cut-off values of uric acid were studied as 4 and 6.

CONCLUSION
When the mean distribution of the OS and DFS values according to uric acid groups was examined, there was no statistically significant difference between the groups (p>0.05). In our study, while the uric acid value was not found to be effective in DSF and OS, the stage, metastatic lymph node ratio, tumor size, and localization were found to be effective factors in OS.

Keywords: Disease-free survival, gastric cancer, overall survival, serum uric acid

INTRODUCTION

Uric acid emerges as the final enzymatic product in the breakdown of purine nucleotides and is found free in humans and great apes. The purine catabolism in humans is the shortest one among vertebrates. Urate oxidase enzyme that converts uric acid to allantoin mutates in two steps. In other mammals, the end product of purine metabolism is allantoin, and it is eliminated by urine (1, 2). As a nucleic acid turnover product, uric acid increases rapidly in the growing diseased tissues of cancer patients (3). Therefore, it might be a prognostic marker in cancer patients. To the best of our knowledge, there are no studies in the literature examining the relationship between gastric cancer and serum uric acid value (SUA) in many years (4). In this study, we investigated the prognostic value on SUA on DF and OS in gastric cancer.

MATERIALS and METHODS

The records of 110 patients who underwent curative surgery (total/subtotal gastrectomy+D2 lymph node dissection) for Stage I–III stomach cancer between 2012 and 2014 and followed-up regularly were retrospectively analyzed. Patients with Gout's disease Gout, Stage IV patients treated with palliatively or with additional organ resection, histological types other than epithelial tumors, patients treated with neoadjuvant chemotherapy, emergent cases, patients who needed blood product transfusion in the perioperative period, patients that could not complete adjuvant therapy, and patients with preoperative infection were excluded from the study, because in these cases, SUA has already increased due to its anti-inflammatory properties.

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Patients were evaluated by medical oncology and radiotherapy specialists after the operation and received the necessary adjuvant treatments. Control examinations were held once every 3 months for the first 2 years of surgery and every 6 months for the following 3 years.

Other than history and physical examination, complete blood count, biochemical assays, and tumor markers (CEA, Ca 19-9) were studied at each control. Abdominal ultrasonography, computed tomography (CT), or upper gastrointestinal (GIS) endoscopy was performed in accordance with the patients' complaints. Abdominal radiologic imaging was performed once a year in patients with no complaints or examination findings. The age, gender, blood group, type of operation, pathology, tumor size, the number of pathologic lymph and total lymph nodes, and the TNM stage were recorded. Peripheral blood samples were collected approximately 2 weeks before surgery, and SUA values were recorded.

Ethics committee approval was received for this study from the local ethics committee of Dr. Abdurrahman Yurtaslan Training and Research Hospital (AOH 2017/10/17). Written informed consent was obtained from patients who participated in this study.

Statistical Analysis

Statistical calculations were performed using the Statistical Package for the Social Sciences for Windows v 16.0 (SPSS Inc.; Chicago, IL, USA). Fisher's exact test, Pearson's chi-squared, and Mann–Whitney U analysis were used. The level of significance was set at $p<0.05$.

RESULTS

The average follow-up duration of 110 patients was 42 months, and the general characteristics are summarized in Table I. The mean age was 63.7±11.6 years. Seventy percent of the patients were male, and 43% underwent total and 57% subtotal gastrectomy. Most of gastric tumors were located in distal stomach (56%), 24% in cardia, and 19% in corpus, and 75% were reported as adenocarcinoma, 19% signed cell carcinoma, and 3% mucinous carcinoma. While the tumor size was found to be >4 cm in 60% of the patients and >8 cm in 20%, according to the TNM system, 11% were Stage I, 29% Stage II, and 60% Stage III. The mean uric acid level was found to be 4.63±1.44. The cut-off values of uric acid were studied as 4 and 6.

When the distribution of categorical variables according to the survival of cases is examined, there was a statistically significant difference between the groups in terms of the surgery type, tumor size, lymph node ratio, and disease stages ($p<0.05$).

There was no statistically significant difference between the groups in terms of other variables ($p>0.05$) (Table 2). Two different cut-off values as 2–4 and >4 and 2–6 and >6 were studied for uric acid levels. In both values, the uric acid levels had no a significant effect on OS and DFS (Table 3).

DISCUSSION

Uric acid occurs when the hypoxanthine and xanthine, which are the digestive consequence of foods and beverages containing purine nucleoside in physiological pH, enter the enzymatic reaction with xanthine oxidoreductase (5). According to the hypothesis of Ames et al. (6), the increase in the level of uric acid in the blood gives an advantage to human beings.

TABLE I. Demographic and clinical characteristics of cases

		n	%
Gender	Female	33	30
	Male	77	70
Uric acid 4	2–4	38	34.5
	>4	72	65.5
Uric acid 6	2-6	94	85.5
	>6	16	14.5
Age 50	≤50	13	11.8
	>50	97	88.2
Age 70	≤70	74	67.3
	>70	36	32.7
Surgery type	Total gastrectomy	47	42.7
	Subtotal gastrectomy	63	57.3
Pathology	Adenocarcinoma	83	75.5
	Mucinous	3	2.7
	Signet cell	21	19.1
	Diffuse	3	2.7
Localization	Cardia	26	23.6
	Corpus	21	19.1
	Antrum	61	55.5
	Whole	2	1.8
Size 4	≤4 cm	45	40.9
	>4 cm	65	59.1
Size 8	≤8 cm	88	80
	>8 cm	22	20
Ratio 0.30	≤0.30	66	60
	>0.30	44	40
Ratio 0.60-0.90	≤0.60	90	81.8
	>0.60	20	18.2
Stage	I	12	10.9
	II	32	29.1
	III	66	60
		Mean±SS	**Median (Min.–Max.)**
Age		63.71±11.69	63 (34-85)
Uric Acid		4.63±1.44	4.45 (2.1-11.2)
Tm size		5.68±3.12	5 (0.5-15)
Metastatic LN		5.98±6.87	3 (0-30)
Total LN		18.42±8.3	18 (2-40)
LN ratio		0.29±0.29	0.19 (0-0.9)
OS		23.84±17.44	22.5 (1-62)
DFS		22.47±17.67	16 (1-62)

OS: overall survival; DFS: disease free survival; LN: lenf node

TABLE 2. Distribution of categorical variables according to survival status of cases

		Exitus		Surviving			
		n	%	n	%	X^2	p
Gender	Female	19	29.2	14	31.1	0.045	0.832
	Male	46	70.8	31	68.9		
Uric acid 4	2–4	23	35.4	15	33.3	0.049	0.824
	>4	42	64.6	30	66.7		
Uric acid 6	2-6	55	84.6	39	86.7	0.090	0.764
	>6	10	15.4	6	13.3		
Age 50	≤50	5	7.7	8	17.8	2.595	0.107
	>50	60	92.3	37	82.2		
Age 70	≤70	39	60	35	77.8	3.817	0.051
	>70	26	40	10	22.2		
Surgery type	Total gastrectomy	36	55.4	11	24.4	10.402	0.001
	Subtotal gastrectomy	29	44.6	34	75.6		
Pathology	Adenocarcinoma	48	73.8	35	77.8	0.266	0.966
	Mucinous	2	3.1	1	2.2		
	Signet cell	13	20	8	17.8		
	Diffuse	2	3.1	1	2.2		
Localization	Cardia	21	32.3	5	11.1	10.947	0.007
	Corpus	14	21.5	7	15.6		
	Antrum	28	43.1	33	73.3		
	Whole	2	3.1	0	0		
Size 4	≤4 cm	18	27.7	27	60	11.482	0.001
	>4 cm	47	72.3	18	40		
Size 8	≤8 cm	47	72.3	41	91.1	5.876	0.015
	>8 cm	18	27.7	4	8.9		
Ratio 0.30	≤0.30	32	49.2	34	75.6	7.678	0.006
	>0.30	33	50.8	11	24.4		
Ratio 0.60-0.90	≤0.60	47	72.3	43	95.6	9.661	0.002
	>0.60	18	27.7	2	4.4		
Stage	I	2	3.1	10	22.2	24.140	0.001
	II	12	18.5	20	44.4		
	III	51	78.5	15	33.3		

TABLE 3. Mean distribution of OS and DFS values according to uric acid groups

	Uric Acid	Mean ± SS	Median (Min.-Max.)	Z	p
OS	2-4	24.76±14.69	24.5 (2-45)	-	0.513
	>4	23.35±18.81	20.5 (1-62)	0.655	
DFS	2-4	22.34±15.44	17 (2-45)	-	0.617
	>4	22.54±18.85	16 (1-62)	0.500	
OS	2-6	24.51±17.28	24.5 (1-62)	-	0.535
	>6	19.88±18.47	12 (1-45)	0.620	
DFS	2-6	22.95±17.61	19 (1-62)	-	0.671
	>6	19.69±18.38	11.5 (1-45)	0.424	

OS: overall survival; DFS: disease-free survival

As shown in the in vitro experiments, uric acid has antioxidant properties by eliminating singlet oxygen, peroxyl radicals, and hydroxyl radicals.

This reaction of uric acid with oxidants can cause cell damage by leading to the formation of other radicals, and this creates a paradox whether it is oxidant or antioxidant. Elevated uric acid levels can cause hypertension, obesity, type 2 diabetes, dyslipidemia, renal damage, and cancer (6, 7). In the study by Kolonel et al. (3) solely on male subjects, while the uric acid level was found to be unrelated to stomach, colon, rectum, lung, bladder, and hematopoietic system cancers, high SUA levels were associated with prostate cancer. As a nucleic acid turnover product, uric acid increases rapidly in the growing diseased tissues of cancer patients, and this may lead to hyperuricemia. SUA with an antioxidant property rich in blood is a free radical scavenger that cleans metal ions (8, 9). Uric acid activates proinflammatory cytokines such as extracellular signal-regulated kinase, mitogen-activated protein kinases, cyclooxygenase-2, and platelet-derived growth factor. It was shown *in vivo* studies in rats that increased uric acid levels are associated with vascular injury, which has been shown to cause renal damage and hypertension (10-12). As uric acid may cause hyperuricemia in cancer patients, it may also increase secretion from the kidneys due to damage to the tubules or tumor-related factors and may lead to hypouricemia (3). Increased SUA also lead to cardiovascular, respiratory, and renal diseases and metabolic syndromes (13, 14). Increased SUA values strengthen the inflammatory response and show both oxidant and antioxidant properties and trigger many diseases, from gout to cancer. It is claimed in cancer that it is effective in increased cell turnover and tumor lysis syndrome (15-17). While low SUA levels damage neurons, high levels provide neuroprotection by contributing to inflammation. Because of its antioxidant effects, SUA has been claimed to protect against cancer. However, studies on cancer and cancer-related mortality are showing contradictory results. While Kuo et al. (18) claim that low SUA levels are associated with cancer-related mortality, Strasak et al. (19) showed that a high SUA level is an independent risk factor for total cancer mortality (15). The relationship between cancer and SUA is complex. In their most recent meta-analysis, Dovell et al. (20) emphasized that the increase in SUA values is related to cancer. In a study of 16,000 Swedish patients with gout, it has been observed that an increased uric acid level increases the incidence of oral cavity, pharynx, colon, liver, bile duct, pancreas, lung, skin (melanoma, nonmelanoma), endometrium, and renal cancers (21). Cetin et al. (22) suggested that high SUA levels in Stage IIIA and IIIB colorectal cancer patients may lead to early metastasis. Although Taghizadeh et al. (23) suggest that high SUA levels lead to low cancer mortality, other studies have shown that increased SUA is an independent risk factor for mortality (19, 24, 25).

In this study, we investigated the prognostic value of SUA on DFS and OS in Stage I–III gastric cancer. In our study, both hyperuricemic and hyporuricemic SUA values were not found to be a prognostic factor in Stage I–III stomach cancer. Its impact on both DFS and OS is not statistically significant. There have not been specific studies in the literature for the relation between gastric cancer and SUA in many years, since 1946. In this

sense, to the best of our knowledge, our work is the first in the literature, and extensive prospective randomized studies are required to explore this issue further.

Ethics Committee Approval: Ethics committee approval was received for this study from the local ethics committee of Dr.Abdurrahman Yurtaslan Training and Research Hospital (AOH 2017/10/17).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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