의학석사 학위논문

비전이성 결장암 환자에서 예후 인자로의 혈중 요산의 중요성

Serum uric acid level as a prognostic marker in non-metastatic colon cancer

2019 년 2월

서울대학교 대학원

의학과 외과학전공

이동운

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지도교수 정 승 용

이 논문을 의학석사 학위논문으로 제출함

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논 문 초 록

Abstract

Serum uric acid level as a prognostic marker in non-metastatic colon cancer

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Objective: Uric acid may be a marker of oxidative stress, and can act as an antioxidant or a prooxidant. The role of serum uric acid (SUA) in the prognostic impact on cancer is controversial. This study aimed to evaluate whether the preoperative SUA level is associated with long-term outcomes in patients with colon cancer.

Methods: Between 2002 and 2010, 2,183 patients who underwent curative surgical resection for non-metastatic colon cancer and had available SUA value, were included. The association between the overall survival (OS) and SUA level as quintile range was analyzed according to sex, using log-rank test and Cox proportional hazard regression to identify prognostic factors.

Results: Mean SUA level was different between male and female [male (n=1,328): 5.320 ± 1.363mg/dL, female (n=855): 4.065 ± 1.180mg/dL, $p<0.001$]. In female patients, there was no difference in OS according to SUA level. In male patients, SUA levels in the lowest quintile group (≤ 4.2mg/dL) was associated with poor OS (≤4.2mg/dL = 78.9% vs 4.2-4.9mg/dL = 84.5% vs 4.9-5.6mg/dL = 86.5% vs 5.6-6.4mg/dL = 88.7% vs >6.4mg/dL = 86.3%, p=0.006). In multivariate analysis in male,

SUA level was an independently significant prognostic factor (≤ 4.2mg/dl vs 5.6-6.4mg/dl: HR = 1.828, 95% CI: 1.262-2.648, p= 0.010).

Conclusion: Our results do not support the beneficial effect of SUA on survival in colon cancer in overall, but lower SUA concentrations might be associated with poorer OS in male colon cancer patients

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keywords: colon cancer, uric acid, prognostic marker, male, overall survival

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LIST OF ABBREVIATIONS

ASA American Society of Anesthesiologists

BMI body mass index

CEA carcinoembryonic antigen

CI confidence interval

CRC colorectal cancer

CRP C-reactive protein

HR hazard ratio

LN lymph node

OS overall survival

SUA serum uric acid

Introduction

Colorectal cancer (CRC) is the third most common cancer and the third most common cause of cancer mortality in Korea (1, 2). Despite the remarkable improvement in cancer patient management including operation and adjuvant chemotherapy, about 40–50 % will still develop metastasis and die from the disease (3). It is very important to identify the patients with poor survival. Carcinoembryonic antigen (CEA) has been widely used as a prognostic biomarker for colorectal cancer (4). Several inflammatory biomarkers have been suggested as prognostic markers in CRC.

Uric acid is final oxidation products of purine nucleotide metabolism and is excreted in urine. Recent studies found serum uric acid (SUA) to be an independent predictor for cardiovascular and several metabolic disease, such as insulin resistance, obesity, hypertension, diabetes, and hyperlipidemia (5, 6). Recently, an increasing amount of attention has been paid to the relationship between SUA and survival and prognosis of malignant tumor patients. Some studies showed that hyperuricemia acts as a radical scavenger and antioxidant preventing carcinogenesis (7, 8). However, in other study, hyperuricemia contributes to tumorigenesis by promoting both transformation and tumor cell proliferation, migration, and survival (9). Recent studies reported that elevated SUA is associated with cancer risk and poor prognosis (9-11). The role of SUA in the prognostic impact of cancer is controversial.

The aim of this study was to evaluate whether the preoperative SUA level is associated with long-term outcomes in patients with colon cancer.

Material and Methods

Between 2002 and 2010, 2,466 patients were selected according to the following inclusion criteria: pathological diagnosis of colon adenocarcinoma, absence of previous treatment and distant metastases at the time of diagnosis, complete surgical resection (R0), availability of clinical information including SUA. Patients who had undergone non-curative resection (R1 or R2), died from postoperative complications, the patients with history of other malignancy were excluded. In locally advanced rectal cancer, neoadjuvant concurrent chemoradiotherapy is the standard therapy. Radiotherapy is associated with increased oxidative damage to tumor cell. A high plasma uric acid level may occur in patients undergoing radiotherapy due to increased purine metabolism by xanthine oxidase, as a consequence of tumor cell breakdown. In this study, rectal cancer (tumor within the 15 centimeter from the anal verge) was excluded due to the different treatment strategies between colon and rectal cancer

Finally, 2,183 patients were included for this study. Serum CEA levels and computed tomography (CT) scans of the abdominopelvic and chest regions were evaluated to estimate disease-extent and metastatic cancer. The SUA levels of the patients that measured at the time of diagnosis were recorded. This retrospective study was approved by the institutional ethics review board of Seoul National University Hospital.

All statistics were analyzed by SPSS statistical software (version 22.0, IBM Corp., Chicago, IL. USA). Overall survival (OS) was calculated from the day of the

surgery to the day of death by any causes or of last follow-up. Continuous variables were analyzed with the Student t-test or the Wilcoxon rank sum test. The Chi-square or the Fisher's exact tests were used to compare categorical variables. Survival was estimated using the Kaplan-Meier survival methods, and statistical significance was determined using log-rank tests. For SUA levels, patients were classified according to the quintile value. The reference group was defined as the lowest mortality incidence group in both male and female patients (5.6-6.4mg/dL in male and 4.2-5.0mg/dL in female). Hazard ratios for mortality outcomes were estimated using Cox proportional hazards regression analysis. Two-sided *P*-values were considered statistically significant if they were less than 0.05.

Results

Among the 2,183 patients, 60.8% were male (n = 1,328) and 39.2% were female (n = 855). The baseline characteristics of the study patients are presented in Table 1. The median SUA level in male patients was significantly higher than that in the female patients. The median pre-operative SUA level was 5.2 ± 0.85mg/dL in male patients and 4.0 ± 0.75mg/dL in female patients ($p<0.001$) (Figure 1.). The body mass index (BMI) was not different according to sex. The median BMI was 23.3 kg/m^2 (21.5 – 25.1) in male patients and 23.1 kg/m^2 (21.0 – 25.1) in female patients ($p= 0.802$). In male patients, the proportion of ASA score over 3 was significantly higher than that of female patients (10.4% vs. 7.5%, respectively, $p=0.022$). In female patients, the patients with preoperative CEA over 5ng/ml were more than male patients (26.5% vs. 21.5%, $p=0.014$). However, histologic grade, number of harvested lymph nodes (LNs), T stage and N stage were not different in both sexes.

The median SUA level in male patients was significantly higher than that in the female patients. Sex-specific values based on the uric acid distribution were used in this study. The characteristics of the study patients stratified by uric acid quintile are presented in Table 2 and 3, respectively. In both male and female patients, an increased SUA level was associated with increased proportion of the BMI over 25 kg/m^2. In female patients, the proportion of age over 60 tended to be higher as uric acid level increasing.

The median follow-up duration for the entire patients was 79 months (range, 1-161 months). Table 4 shows the risk factors for overall survival in male. In male patient group, univariate analysis identified age, BMI, preoperative CEA, ASA score, T and N stage and SUA as poor prognostic factors for OS. The SUA levels in the lowest quintile (≤ 4.2 mg/dL) was associated with poor OS (5 year OS: ≤4.2mg/dL = 78.9% vs 4.2-4.9mg/dL = 84.5% vs 4.9-5.6mg/dL = 86.5% vs 5.6-

6.4mg/dL = 88.7% vs >6.4mg/dL = 86.3%, p=0.006; Figure 2). In multivariate analysis, age, preoperative CEA, ASA score, T and N stage and SUA were independent significant factors for OS. The hazard ratio (HR) [95% confidence interval (CI)] for mortality comparing uric acid ≤ 4.2 mg/dL with uric acid of 5.6-6.4 mg/dL was 1.828 (1.262-2.648). In female patient group, univariates analysis identified age, preoperative CEA, ASA score, T and N stage were significant prognostic factors for OS (Table 4), but preoperative SUA was not significant prognostic factor for OS (p=0.555).

Table 5 and 6 showed the HRs (95% CI) for mortality according to SUA levels and BMI in male and female patients, respectively. In male patients, the lowest quintile of SUA levels (≤ 4.2 mg/dL) was associated with poor survival regardless of BMI [BMI <25 groups: HR (95% CI) = 1.607 (1.063-2.429), p=0.029, BMI ≥ 25 group: HR (95% CI) = 2.542 (1.103-5.859), p=0.024, respectively]. However, HRs were not statistically different by SUA levels and BMI in female patients. Figure 4 and 5 showed the adjusted HRs according to the decile range of SUA levels. In male patients, the lowest quintile group showed the poorest OS [SUA ≤3.7 group: HR (95% CI) = 3.173 (1.762-5.715), p=0.004]. In female patients, the HRs for mortality were not statistically different in all decile ranges of SUA (p=0.433).

Discussion

The purpose of the present study was to evaluate the relationship of the preoperative SUA and OS in colon cancer patients. This study demonstrated that patients with relatively lower SUA level had poor OS in male patients. However, the preoperative SUA was not associated with OS in female patients.

It is well known that SUA levels are lower in female than in male (12). The lower SUA levels of female with respect to male could be due to a higher renal excretion of urates, lower uric acid synthesis, or a different distribution of urate within body compartment (13). Hyperuricemia management is initiated and modified according to symptoms and the SUA level as a dichotomous variable in clinical practice; the upper limit of normal SUA levels often used for male is 7.0 mg/dL and for female is 6.0 mg/dL. Therefore, the sex-specific values as a quintile range were determined in this study.

The relationship between SUA and cancer was first reported by Ames *et al.*(7). Their study showed that increased SUA level was supposed to have a possible protective effect against development of cancer. In this experimental study, at physiological concentrations, uric acid reduced the oxo-heme oxidant formed by peroxide reaction with hemoglobin, protects erythrocyte ghosts against lipid peroxidation, and protects erythrocytes from peroxidative damage leading to lysis. Uric acid is an effective antioxidant like as ascorbate in these experiments. Further study by Becker et al. identified the antioxidant role of uric acid in many different organ system (8). Uric acid may serve as an oxidizable co-substrate for the enzyme cyclooxygenase. As shown for the coronary system, a major site of production of urate is the microvascular endothelium, and generally there is a net release of urate from the human myocardium in vivo. In isolated organ preparations, urate protects against reperfusion damage induced by activated granulocytes, cells known to

produce a variety of radicals and oxidants. Intriguingly, urate prevents oxidative inactivation of endothelial enzymes (cyclooxygenase, angiotensin converting enzyme) and preserves the ability of the endothelium to mediate vascular dilatation in the oxidative stress, suggesting a particular relationship between the site of urate formation and the need for a biologically potent radical scavenger and antioxidant. These studies suggested that uric acid is one of the major antioxidant in humans. The concentration is generally high in comparison to other potential non-enzymatic antioxidants, such as ascorbate, tocopherols, methionine, glutathione, etc. (14).

Following studies reported about the relationship of hyperuricemia with cancer patients outcomes. Dziaman *et al.* reported that among plasma antioxidants, only higher uric acid levels were associated with longer survival among colon cancer patients (15). In this study, they analyzed the association between OS and the parameters of oxidative stress and oxidatively damaged DNA in 89 colon cancer patients (45 males and 44 females). The parameter included the i) the status of antioxidant vitamins and uric acid; ii) 8-oxodGuo/8-oxoGua levels in cellular DNA and in urine; iii) expression of genes which products participate in removal of oxidatively damaged DNA, namely OGG1, APE1, MTH1, ANPG and PARP-1. Patients were followed 100 months after surgery or until death. In this study, among plasma antioxidants, only uric acid level coincided with longer survival. Patients with high uric acid plasma level (values higher than 277.8 mM) lived longer than those with low uric acid level (5 year-OS 66% vs. 40%, respectively; p=0.006). And when analyzing the levels of plasma uric acid in combination with leukocyte 8-oxodGuo or urinary 8-oxoGua, it was found that patients with low 8-oxodGuo in leukocyte and high plasma uric acid (above 277.8 mM) had much better survival than in patients with high leukocyte 8-oxodGuo and low plasma uric acid (5 year OS=89% vs. 55%; p<0.007). Taghizadeh *et al*. reported epidemiological study about

the association SUA levels and mortality due to three common types of cancer (lung, colorectal, and prostate) among males using the Vlagtwedde–Vlaardingen cohort. In total, 1,823 males had data available on SUA and analyzed SUA levels as tertiles (<5 mg/dL, 5–5.8 mg/dL, >5.8 mg/dL). In this study, SUA levels higher than 5.8 mg/dL were significantly associated with a lower risk of mortality from any cancer including colorectal cancer [HR (95% CI) : 0.68 (0.48–0.97)] (16).

However, others have reported that high levels of SUA were associated with a higher risk of mortality from cancer. Several epidemiological studies reported about relationship between uric acid and risk of cancer mortality (9, 10). Although uric acid can act as a systemic antioxidant in vivo, its pro-inflammatory properties have been suggested to play an important role in the pathogenesis of cancer. Strasak *et al.* prospectively examined the relation of SUA to risk of cancer events and mortality in a large cohort of 83,683 apparently healthy male Austrian adults across a wide age range (10). In Cox proportional hazards models in this study, adjusted for age, BMI, blood glucose, smoking status, occupational status, and year of examination, high SUA levels were positively related to risk of total cancer mortality (p for trend < 0.001), showing a clear dose–response relationship; the HR (95% CI) for the highest versus lowest quintile of SUA was 1.41 (1.22–1.62). In cancer site-specific analyses, high SUA levels were independently related to mortality from malignant neoplasms of digestive organs (p = 0.03). In this study, there were 680 deaths due to malignant neoplasms of digestive organ during 13.6 years. The proportions of colon cancer in malignant neoplasms of digestive organ were not demonstrated. They have reported that high levels of SUA were associated with a higher risk of mortality from cancer among males after adjustment for established risk factors.

Elevated SUA levels have also been positively associated with high circulating levels of the inflammatory mediators which may increase the risk of some cancer,

and associated with a poorer clinical prognosis and unfavorable outcomes in some cancers (17, 18). Yan *et al.* reported the meta-analysis about the relationship between high SUA and cancer incidence and mortality (18). When stratifying analysis by specific sites of cancer, significant relationship between high SUA levels and the risk of lymphoid and hematopoietic system cancers was observed, but relationship between other specific sites of cancer was not clear. A recent retrospective study which analyzed 475 newly diagnosis rectal cancer patients, demonstrated that SUA, CEA, and C-reactive protein (CRP) was increased in rectal cancer patients with metastasis compared with those without metastasis (19). In this study, SUA concentrations were positively correlated with CRP in patients with rectal cancer (correlation coefficient= 0.305, p=0.002). In this study, SUA, CEA, and CRP was increased in rectal cancer patients with metastasis compared with those without metastasis, and higher SUA levels were associated with metastatic rectal cancer patients in multiple logistic regression analysis.

Recently, Cho *et al.* reported that low uric acid level was also significantly associated with increased risk of all-type of cancer mortality in male and non-significant increase in cancer mortality among female (20). This cohort study included all male and female, 18 years of age or older who participated in a screening health examination between 2002 and 2012. In male with uric acid <3.5 mg/dL showed increased risk cancer mortality. Low SUA level was significantly associated with increased risk of cancer mortality in men after adjusting for glomerular filtration rate. The corresponding HRs (95% CI) for cancer mortality in male with uric acid <3.5 mg/dL compared in male with uric acid of 6.5-7.4 mg/dL were 1.62 (1.07-2.44). In female group, the lowest UA group (<2.5 mg/dl) was associated with increased risk of cancer mortality [HRs (95% CI) =1.58 (0.76-3.29)], but the difference was not statistically significant. Our study showed similar patterns that lowest SUA (<4.2

mg/dL) in male patients were associated with poorer survival. And in female patients SUA level do not affect the overall survival. This result may suggest the different metabolic capacity of uric acid according to sex (12), but the mechanism underlying the different risk of cancer mortality related to uric acid level has not been fully understood. Some studies suggested that patients with lower SUA level may reflect the general condition of patients such as malnutrition (21). However, in our studies, the male patients with BMI over 25 in lowest quintiles (<4.2 mg/dl) have higher HRs comparing BMI under 25 [HR (95% CI): 2.542 (1.103 – 5.859) vs.1.607 (1.063 – 2.429)]. Malnutrition could not explain poor OS in patients with lower SUA in this study.

Our results suggest that SUA reflect not only the nutritional state but also reactive oxygen production. The patients with hypouricemia are hypothesized to potentiate cancer cell proliferation due to decreased antioxidant potential and reactive oxygen species production.

Similar to other retrospective studies, our study has several limitations. First, we did not collect the data about dietary factors and drug histories such as urate-lowering medications. Second, information on alcohol intakes, physical activity and medical history such as kidney function were not fully analyzed. There were possibilities of selection bias, because our data is from single institution's database.

Conclusion

In conclusion, our results do not support the beneficial effect of SUA on survival in colon cancer in overall, but lower SUA concentrations might be associated with poor long-term outcomes in male colon cancer patients

Table 1. Baseline characteristics in total study population

	Total	Male n =1,328	Female n=855	P value
Age		62.96 ± 10.91	62.27 ±11.93	0.173
≤60	773 (35.4%)	444 (33.4%)	329 (38.5%)	0.016
>60	1,410 (64.6%)	884 (66.6%)	526 (61.5%)	
Uric acid (mg/dL)		5.32 ± 1.36	4.06 ± 1.18	0.001
BMI (kg/m^2)		12.63 ± 6.44	23.55 ± 6.02	0.802
< 25	1,606 (73.6%)	978 (73.6%)	628 (73.5%)	0.920
≥ 25	577 (26.4%)	350 (26.4%)	227 (26.5%)	
ASA				0.022
1+2	1,981 (90.7%)	1,190 (89.6%)	791 (92.5%)	
≥ 3	202 (9.3%)	138 (10.4%)	64 (7.5%)	
Preoperative CEA (ng/ml)		6.05 ± 0.64	6.98 ±1.08	0.431
≤ 5	1,674 (76.7%)	1,042 (78.5%)	632 (73.9%)	0.014
> 5	509 (23.3%)	286 (21.5%)	223 (26.1%)	
Histologic grade				0.070
Low	1,950 (89.3%)	1,199 (90.3%)	751 (87.8%)	
High	233 (10.7%)	129 (9.7%)	104 (12.2%)	
Harvest LNs		19.27 ± 11.29	20.79 ± 35.42	0.145
< 12	539 (24.7%)	330 (24.8%)	209 (24.4%)	0.830
≥ 12	1,644 (75.3%)	998 (75.2%)	646 (75.6%)	
T stage				
1	246 (11.3%)	159 (12.0%)	87 (10.2%)	0.249
2	256 (11.7%)	157 (11.8%)	99 (11.6%)	
3	1,513 (69.3%)	920 (69.3%)	593 (69.4%)	
4	168 (7.7%)	92 (6.9%)	76 (8.9%)	
N stage				
0	1,295 (59.3%)	804 (60.5%)	491 (57.4%)	0.342

1	606 (27.8%)	356 (26.8%)	250 (29.2%)
2	282 (12.9%)	168 (12.7%)	114 (39.2%)

BMI : body mass index, ASA :American Society of Anesthesiologists, CEA : carcinoembryonic antigen, LN : lymph node

Table 2. Male patients characteristics according to quintiles of serum uric acid level

Covariates	Uric acid levels quintiles (mg/dL)					
	≤ 4.2 n=267	4.2 - 4.9 n=269	4.9 – 5.6 n=288	5.6 – 6.4 n=262	6.4 < n=242	p
Age						0.050
≤60	79 (29.6)	77 (28.6)	111 (38.5)	97 (37.0)	80 (33.1)	
>60	188 (70.4)	192 (71.4)	117 (61.5)	165 (63.0)	162 (66.9)	
BMI (kg/m^2)						0.001
< 25	217 (81.3)	204 (78.8)	217 (75.3)	187 (71.4)	153 (63.2)	
≥ 25	50 (18.7)	65 (24.2)	71 (24.7)	75 (28.6)	89 (36.8)	
ASA						0.110
1+2	236 (88.4)	238 (88.5)	269 (93.4)	237 (90.5)	210 (86.8)	
≥ 3	31 (11.6)	31 (11.5)	19 (6.6)	25 (9.5)	32 (13.2)	
Preoperative CEA (ng/ml)						0.440
≤ 5	206 (77.2)	202 (75.1)	232 (80.6)	212 (80.9)	190 (78.5)	
> 5	61 (22.8)	67 (24.9)	56 (19.4)	50 (19.1)	52 (21.5)	
Histologic grade						0.444
Low	247 (92.5)	239 (88.8)	255 (88.5)	236 (90.1)	222 (91.7)	
High	20 (7.5)	30 (11.2)	33 (11.5)	26 (9.9)	20 (8.3)	
Harvest LNs						0.052
< 12	55 (20.6)	60 (22.3)	78 (27.1)	62 (23.7)	75 (31.0)	
≥ 12	212 (79.4)	209 (77.7)	210 (72.9)	200 (76.3)	167 (69.0)	
T stage						0.434
1	25 (9.4)	36 (13.4)	38 (13.2)	27 (10.3)	33 (13.6)	
2	30 (11.2)	31 (11.5)	42 (14.6)	33 (12.6)	21 (8.7)	
3	189 (70.8)	183 (68.0)	189 (65.6)	182 (69.5)	177 (73.1)	
4	23 (8.6)	19 (7.1)	19 (6.6)	20 (7.6)	11 (4.5)	
N stage						0.612
0	169 (63.3)	155 (57.6)	179 (57.3)	150 (57.3)	151 (62.4)	
1	62 (23.2)	74 (27.5)	77 (29.4)	77 (29.4)	66 (27.3)	
2	36 (13.5)	40 (14.9)	32 (11.1)	35(13.4)	25 (10.3)	

BMI : body mass index, ASA :American Society of Anesthesiologists, CEA : carcinoembryonic antigen, LN : lymph node

Table 3. Female patients characteristics according to quintiles of serum uric acid level

Covariates	Uric acid levels quintiles (mg/dL)					
	≤ 3.1 n=182	3.1 - 3.7 n=172	3.7 – 4.2 n=180	4.2 – 5.0 n=166	5.0 < n=155	p
Age						<0.001
≤60	74 (40.7)	89 (51.7)	66 (36.7)	59 (35.5)	41 (26.5)	
>60	108 (59.3)	83 (48.3)	114 (63.3)	107 (64.5)	114 (73.5)	
BMI (kg/m^2)						0.003
< 25	150 (82.4)	131 (76.2)	133 (73.9)	111 (66.9)	103 (66.5)	
≥ 25	32 (17.6)	41 (23.8)	47 (26.1)	55 (33.1)	52 (33.5)	
ASA						0.026
1+2	175 (96.2)	163 (94.8)	160 (88.9)	155 (93.4)	138 (89.0)	
≥ 3	7 (3.8)	9 (5.2)	20 (11.1)	11 (6.6)	17 (11.0)	
Preoperative CEA (ng/ml)						0.219
≤ 5	134 (73.6)	126 (73.3)	130 (72.2)	134 (80.7)	108 (69.7)	
> 5	48 (26.4)	46 (26.7)	50 (27.8)	32 (19.3)	47 (30.3)	
Histologic grade						0.119
Low	165 (90.7)	152 (88.4)	148 (82.2)	149 (89.8)	137 (88.4)	
High	17 (9.3)	20 (11.6)	32 (17.8)	17 (10.2)	18 (11.6)	
Harvest LNs						0.309
< 12	42 (23.1)	45 (26.2)	39 (21.7)	36 (21.7)	47 (30.3)	
≥ 12	140 (76.9)	127 (73.8)	141 (78.3)	130 (78.3)	108 (69.7)	
T stage						0.324
1	11 (6.0)	13 (7.6)	22 (12.2)	22 (13.3)	19 (12.3)	
2	17 (9.3)	17 (9.9)	23 (12.8)	18 (10.8)	24 (15.5)	
3	138 (75.8)	125 (72.7)	119 (66.1)	113 (68.1)	98 (63.2)	
4	16 (8.8)	17 (9.9)	16 (8.9)	13 (7.8)	14 (9.0)	
N stage						0.671
0	99 (54.4)	101 (58.7)	95 (52.8)	100 (60.2)	96 (61.9)	
1	60 (33.0)	46 (26.7)	56 (31.1)	47 (28.3)	41 (26.5)	
2	23 (12.6)	25 (14.5)	29 (16.1)	19 (11.4)	18 (11.6)	

BMI : body mass index, ASA : American Society of Anesthesiologists, CEA : carcinoembryonic antigen, LN : lymph node

Table 4. The risk factors for overall survival in male patients

Covariates	Univariate analysis		Multivariate analysis		
	5YR-OS	p	HR	95% CI	p
Age		<0.001			<0.001
≤60	89.3%		1		
>60	82.5%		2.273	1.681 – 3.074	
BMI (kg/m^2)		0.07			0.022
< 25	83.6%		1		
≥ 25	88.7%		0.706	0.524 – 0.950	
ASA		<0.001			0.001
1+2	95.0%		1		
≥ 3	71.7%		1.841	1.355 – 2.503	
Preoperative CEA (ng/ml)		<0.001			0.003
≤ 5	87.1%				
> 5	77.0%		1.490	1.146 – 1.938	
Histologic grade		0.584			
Low	85.2%				
High	82.8%				
Harvest LNs		0.812			
< 12	85.7%				
≥ 12	84.7%				
T stage		<0.001			<0.001
1	93.6%		1		
2	90.9%		1.082	0.584 – 2.005	
3	84.7%		1.279	0.789 – 2.075	
4	62.9%		3.309	1.877 – 5.833	
N stage		<0.001			
0	89.5%		1		
1	81.8%		1.530	1.152 – 2.031	
2	69.8%		3.005	2.204 – 4.096	
Uric acid (mg/dL)		0.006			0.010
≤ 4.2	78.9%		1.828	1.262 – 2.648	
4.2 - 4.9	84.5%		1.128	0.756 – 1.684	
4.9 – 5.6	86.5%		1.390	0.943– 2.049	
5.6 – 6.4	88.7%		ref		
6.4 <	86.3%		1.179	0.775 – 1.794	

OS: overall survival, HR: hazard ratio, CI: confidence interval, BMI : body mass index, ASA :American Society of Anesthesiologists, CEA : carcinoembryonic antigen, LN : lymph node

Table 5. The risk factors for overall survival in female patients

Covariates	Univariate analysis		Multivariate analysis		
	5YR-OS	p	HR	95% CI	p
Age		<0.001			<0.001
≤60	92.4%		1		
>60	82.2%		2.325	1.615 – 3.349	
BMI (kg/m^2)		0.265			
< 25	83.7%				
≥ 25	88.8%				
ASA		0.011			0.001
1+2	86.2%		1		
≥ 3	71.9%		2.088	1.344 – 3.243	
Preoperative CEA (ng/ml)		<0.001			0.002
≤ 5	88.5%				
> 5	75.5%		1.649	1.193 – 2.279	
Histologic grade		0.113			
Low	85.6%				
High	81.7%				
Harvest LNs		0.765			<0.001
< 12	85.1%				
≥ 12	84.7%		1.540	1.257 – 1.887	
T stage		<0.001			0.001
1	98.9%		1		
2	92.9%		2.668	0.742 – 9.587	
3	83.8%		3.792	1.194 – 12.041	
4	69.7%		6.198	1.823 – 21.074	
N stage		<0.001			<0.001
0	90.3%		1		
1	83.9%		1.823	1.260 – 2.638	
2	65.5%		3.734	2.493 – 5.593	
Uric acid (mg/dL)		0.555			
≤ 3.1	83.4%				
3.1 - 3.7	82.2%				
3.7 – 4.2	86.0%				
4.2 – 5.0	90.9%				
5.0 <	83.0%				

OS: overall survival, HR: hazard ratio, CI: confidence interval, BMI : body mass index, ASA :American Society of Anesthesiologists, CEA : carcinoembryonic antigen, LN : lymph node

Table 6. Hazard ratios (95% confidence interval) of mortality according to uric acid level in BMI subgroups among male patients

Covariates	Uric acid levels quintiles (mg/dL)				
	≤ 4.2 n=267	4.2 - 4.9 n=269	4.9 – 5.6 n=288	5.6 – 6.4 n=262	6.4 < n=242
BMI, kg/m^2					
< 25	1.607 (1.063- 2.429)	1.084 (0.692- 1.699)	1.247 (0.805- 1.933)	Ref	1.219 (0.757- 1.963)
≥ 25	2.542 (1.103- 5.859)	1.170 (0.482- 2.843)	1.633 (0.714- 3.736)	Ref	0.828 (0.344- 1.993)

Table 7. Hazard ratios (95% confidence interval) of mortality according to uric acid level in BMI subgroups among female patients

Covariates	Uric acid levels quintiles (mg/dL)				
	≤ 3.1 n=182	3.1 - 3.7 n=172	3.7 – 4.2 n=180	4.2 – 5.0 n=166	5.0 < n=155
BMI, kg/m^2					
< 25	1.232 (0.683- 2.222)	1.324 (0.716- 2.447)	1.068 (0.582- 1.960)	Ref	0.956 (0.500- 1.825)
≥ 25	1.968 (0.611- 6.335)	2.322 (0.751- 7.180)	0.853 (0.239- 3.050)	Ref	2.179 (0.793- 5.986)

Figure 1. Serum uric acid according to sex

Figure 2. 5 year overall survival according to interquatile range in male patients

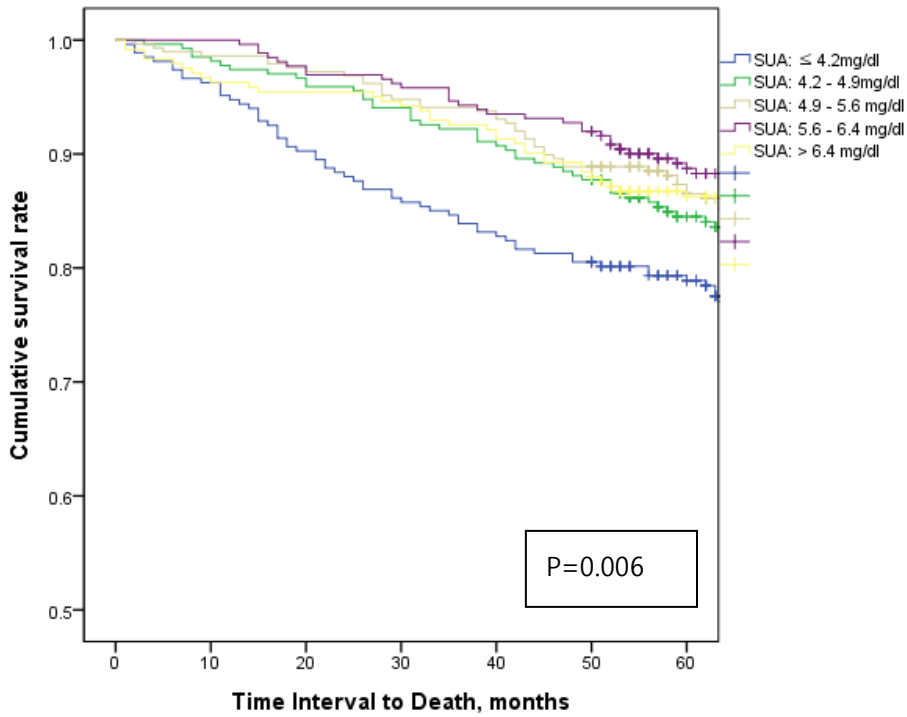


Figure 3. 5 year overall survival according to quintile range in female patients

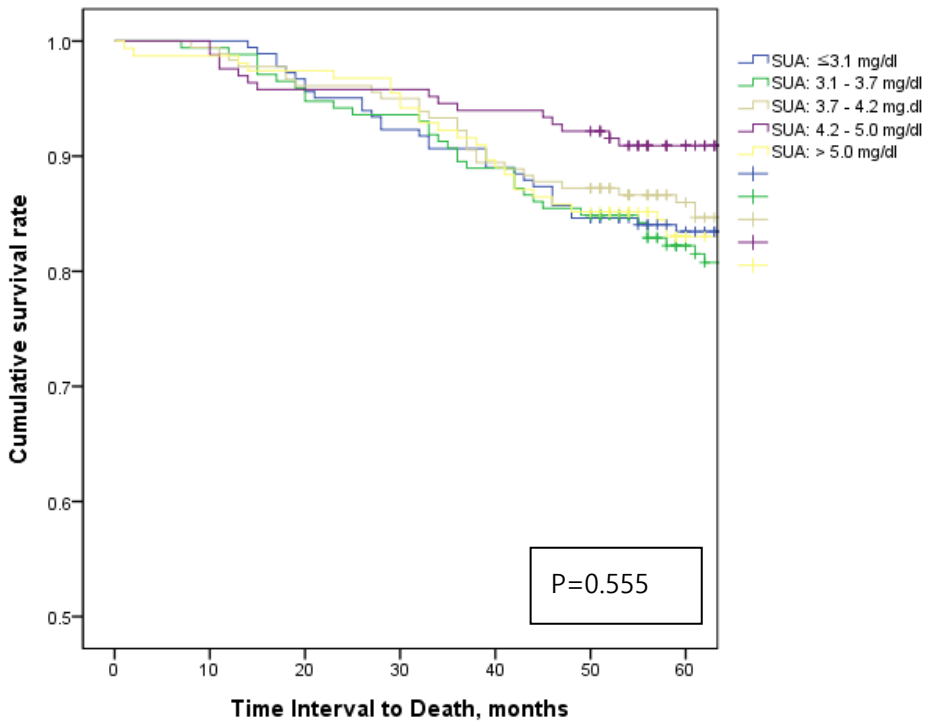


Figure 4. Adjusted HRs according to decile range in male patients

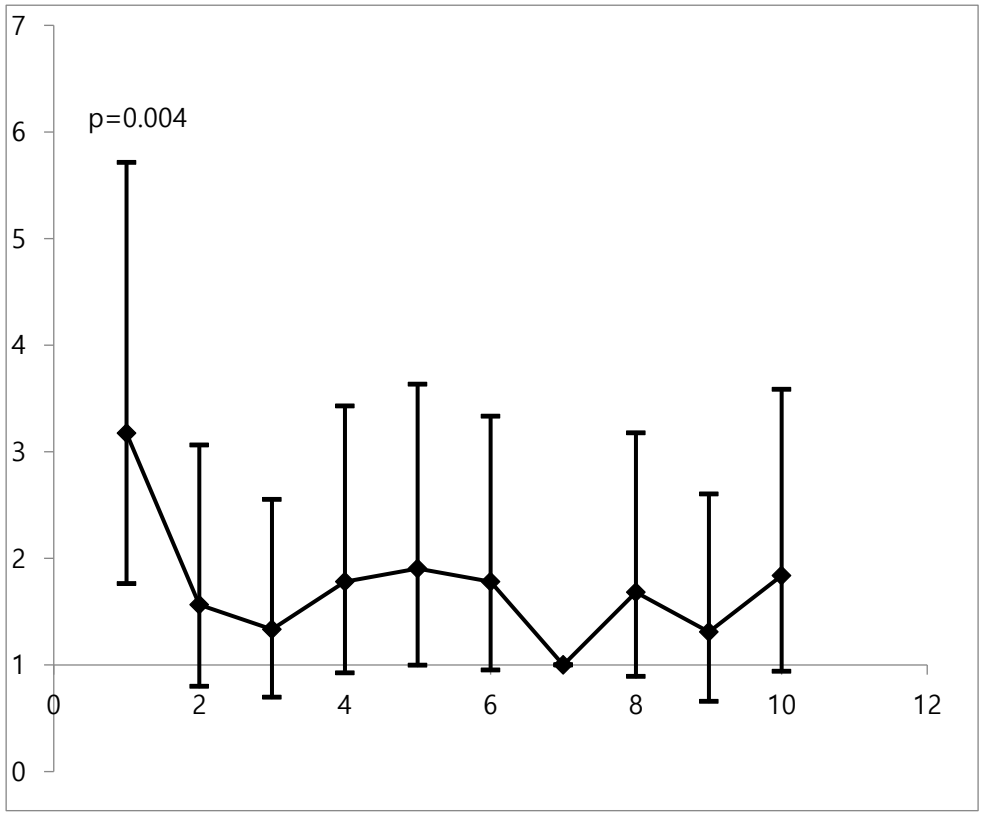
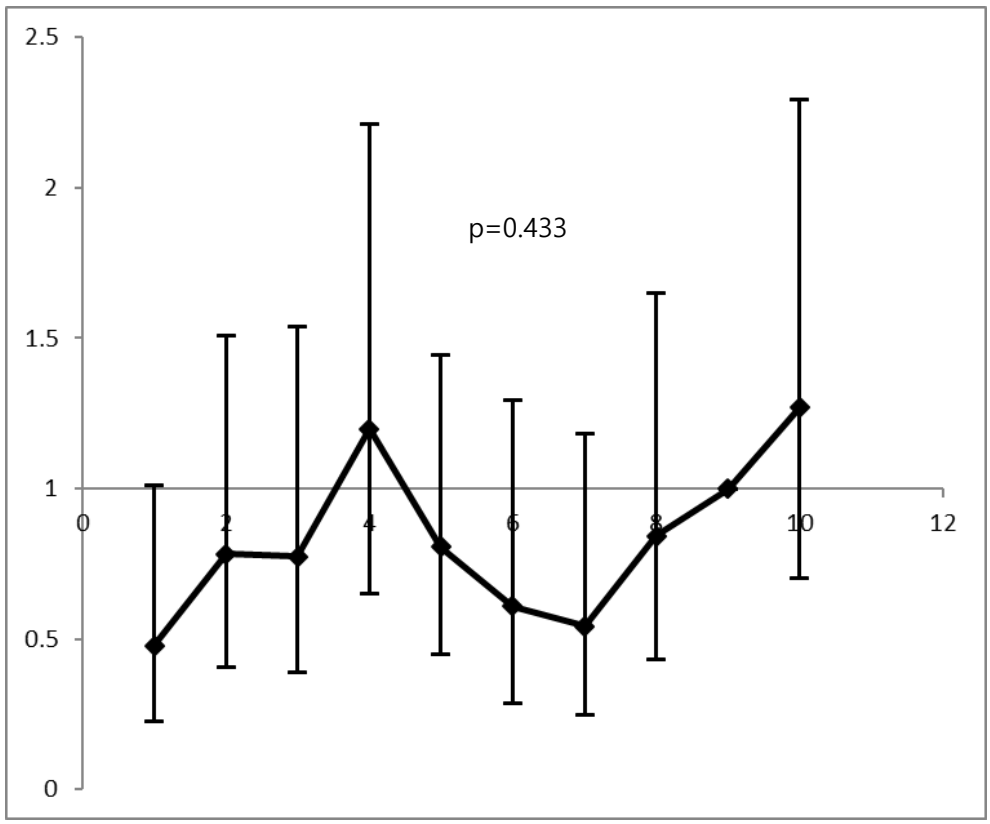


Figure 5. Adjusted HRs according to decile range in female patients



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요약(국문초록)

목적: 혈중 요산은 산화 스트레스의 중요한 표지자의 역할을 할 수 있다. 하지만 혈중 요산은 체내에서 항산화물질 (antioxidant)로 작용할 수도 있지만, 산화촉진제 (prooxidant)의 역할을 할 수도 있다. 암환자에서 혈중 요산이 장기 생존에 대해 어떤 역할을 하는지에 대해서는 아직 불분명하다. 이에 결장암 환자에서 수술 전 혈중 요산이 예후에 영향을 미치는지 알아보고자 한다.

방법: 2002년부터 2010년까지 비전이성 결장암 환자로 근치적 수술을 시행받고 혈중 요산수치가 측정되었던 환자 2,183명을 연구 대상으로 하였다. 각 환자의 임상병리 정보와 생존 자료를 후향적으로 조사하였다. 성별에 따른 혈중 요산 수치에 대라 오분위 수를 기준으로 환자를 분류하였고 로그순위 검정과 Cox 회귀 분석을 통해 혈중 요산 수치와 전체 생존율과의 연관성을 분석 하였다.

결과: 남성 (n=1,328)과 여성 (n=855)의 혈중 요산 수치의 중앙값은 통계적으로 유의하게 차이가 있었다 [남성 (n=1,328): 5.320 ± 1.363mg/dL, 여성 (n=855): 4.065 ± 1.180mg/dL, $p<0.001$]. 각 혈중 요산 수치의 오분위수에 따라 남성과 여성에서 각각 전체 생존율을 분석하였을 때, 여성의 경우 통계적으로 유의한 차이가 없었으나 남성의 경우 가장 낮은 오분위수 그룹 (≤4.2 mg/dL)에서 5년 전체 생존률이 통계적으로 유의하게 낮았다 (5년 전체 생존률: ≤4.2mg/dL = 78.9% vs 4.2-4.9mg/dL = 84.5% vs 4.9-5.6mg/dL = 86.5% vs 5.6-6.4mg/dL = 88.7% vs >6.4mg/dL = 86.3%, P값 = 0.006). 남성에 대한 다변량 분석에서 혈중 요산 수치는 독립적으로 유의한 예후인자였다 (≤4.2mg/dl vs 5.6-6.4mg/dl: 위험비 = 1.828, 95%

신뢰구간 = 1.262-2.648, P값= 0.010).

결론: 결장암에서 혈중 요산은 항산화제로써 예후에 도움을 주는 역할은 보이지 않으며, 남성 환자의 경우 낮은 요산 수치가 예후에 나쁜 영향을 줄 수 있다.

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주요어 : 대장암, 예후 인자, 혈중 요산, 전체 생존율, 남성

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