Role of Serum Uric Acid in Assessment of Rectal Cancer Metastasis

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Abstract:

Background: Colorectal cancer is the third most common non-cutaneous malignancy, and accounts for the second most frequent cause in cancer-related deaths. Early detection and diagnosis of cancer rectum and its metastasis is very helpful in treatment and prognosis ,so that accurate laboratory markers have been needed to monitoring tumor recurrence, metastasis, and prognosis. **Aim:** The aim of this study was to investigate the role of uric acid (UA) in assessing rectal cancer metastasis. **Patients and methods:** Two hundred newly diagnosed patients with cancer rectum were included in our study and divided into two groups, one with metastasis and the other without metastasis. **Results:** There were statistical significant differences regarding CA19.9, carcino-embryonic antigen (CEA), and C-reactive protein (CRP) between the 2 groups. Importantly, serum concentrations of UA in patients with lymphatic metastasis were found to be increased compared with those without metastasis (7.08±2.45 vs 4.30±1.12; P<0.0001). There were positive correlations between serum UA and CRP, CA199 and CEA (r=0.27,P=0.0001; r=0.28,P=0.0001; r=0.29,P=0.0001) in rectal cancer patients with metastasis. Multivariate analysis model revealed that CEA, CA19.9 , CRP, ESR (1st , 2nd hours) ,serum uric acid, presence of ascites, Perirectal fat plane ,Degree of tumor differentiation, and T classification, Duke's stage, total protein ,TLC and ALT level were the predictors of rectal cancer metastasis. ROC curve analysis revealed that AUC of serum UA was 0.82 , with sensitivity of 63.0 and specificity of 95.0. for prediction of metastasis in rectal cancer patients. **Conclusion:** Serum UA may be a useful marker in assessing tumor metastasis in patients with rectal cancer.

Keywords: carcino-embryonic antigen, rectal cancer, serum uric acid, tumor metastasis.

Introduction

Colorectal cancer is the third most common non-cutaneous malignancy, and accounts for the second most frequent cause in cancer-related deaths **[1].**

Adenoma is a developmental stage of rectal cancer, which is a progress from the adenoma carcinoma sequence to invasive cancer, and inflammation may play a key role in metastasis of rectal cancer [2]**.**

Oncologists have been aware that, compared with colon tumor, the diagnosis, staging and, treatment for rectal cancer have significant difference. Fortunately, local control and survival rate in colorectal cancer has been significantly improved with the improvement of operation and chemotherapy **[3, 4].**

Laboratory, the levels of carcino-embryonic antigen (CEA) have severed as an independent prognostic factor in rectal cancer patients **[5].**

Several inflammatory biomarkers are valuable and easily available for the assessment of prognosis in patients with rectal cancer such as tumor necrosis factor (TNF), interleukin (IL)-6, and C-reactive protein (CRP) **[6]**.

Moreover, CRP has been involved with recurrence and prognosis in patients with rectal cancer [7]**.** However, other laboratory markers also have been needed to monitor tumor recurrence, metastasis, and prognosis

Uric acid (UA) is the end product of purine metabolism in the body. In the past, previous study focused on the relationship between UA and gout. Recently, serum UA was found to be associated with various diseases, such as cardiovascular disease, acute ischemic stroke, and lung cancer **[8,9,10]** and increased serum UA concentrations were associated with mortality of cardiovascular disease [11].

In fact, serum UA has been regarded to be an antioxidant in the body, and presents a compensatory mechanism against inflammation **[12].**

A cross-sectional study found that elevated UA concentrations were not a risk factor of colorectal adenoma; but is a risk indicator for metabolic syndrome-related colorectal adenoma **[13].**

In spite of that, uric acid serves as a "danger signal" released from dying cells (potentially including cancer cells) and could promote anti-cancer immunity, but the acute and chronic inflammation of gout could contribute to a pro-cancer environment **[14].**

Patients and methods

Participants and materials

This longitudinal study was conducted upon 200 adult patients who were diagnosed with rectal cancer and did not received chemo or radiotherapy yet at Sohag cancer institute during the period from January 2016 to 2018.

The study protocol was evaluated by ethical committee of Benha Faculty of Medicine and its University Hospitals and approval for the study was obtained also from Sohag cancer institute before involvement in the study. Informed consent was obtained from each patient or his/her relative.

Data collection

Studied cases were divided into two groups, group 1 with metastasis and group 2 without metastasis. All patients were subjected to history taking. ,complete clinical examinations, routine laboratory investigation [complete blood count (CBC), blood group, fasting blood sugar, total protein , ALT, AST , serum albumin ,serum total and direct bilirubin , hepatitis markers, serum creatinine ,blood Urea,(CEA), CA19.9 - C-reactive protein – ESR first and second hours], serum uric acid levels were measured at the time of diagnosis and after the 3rd month of chemotherapy . Also imaging studies (including abdomino-pelvic ultrasound, abdominal CT and barium enema), colonoscopy and histopathological records were done for the studied cases.

Statistical analysis

Data was analyzed using STATA version 12.1 (Stata Statistical Software: Release 14.2 College Station, TX: StataCorp LP.). Quantitative data was represented as mean, standard deviation, median and range. Data was analyzed using student t-test to compare means of two groups. When the data was not normally distributed Kruskal Wallis test for comparison of three or more groups and Mann-Whitney test was used to compare two groups. Wilcoxson signed rank test was used to compare uric acid level before and after chemotherapy. Qualitative data was presented as number

and percentage and compared using either Chi square test or fisher exact test. Spearman's correlation analysis was used to detect correlation between uric acid and other inflammatory and tumor markers. Roc curve analysis was used to detect best cutoff of different variables that predict metastatic rectal cancer. Sensitivity, specificity, positive predicted value and negative predictive value were also calculated. Odds ratios were obtained from logistic regression analysis. Graphs were produced by using Excel or STATA program. p value was considered significant if it was less than 0.05.

RESULTS

No statistical significant difference was detected between two groups of cancer rectum regarding sex and age. fig (1).

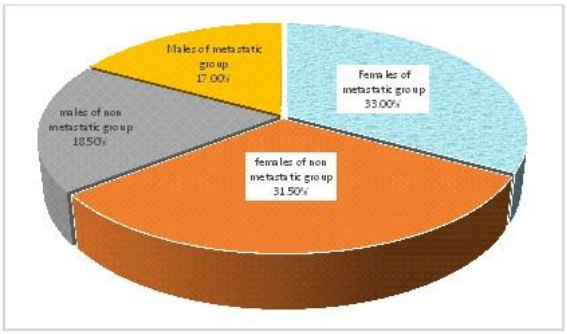


Figure (1): percentage of gender among the studied cases

There were statistical significant differences regarding CA19.9, carcino-embryonic antigen (CEA), and CRP between the 2 groups. Importantly, serum UA concentrations in patients with lymphatic metastasis (fig. 2) were found to be increased compared with patients without lymphatic metastasis (7.08±2.45 mg/dL vs 4.30±1.12 mg/dL; P<0.0001) table (1). Among the studied cases, significant positive correlations were found between serum UA levels before chemotherapy administration on one hand and CEA, CA19.9, CRP levels and number of lymph nodes affection on the other hand (r=0.27, P=0.0001; r=0.28, P=0.0001; r=0.29, P=0.0001 ;r=0.65 ,P<0.0001) table (2).

Multivariable analysis showed that CEA, CA19.9 , C-reactive protein, ESR (1st , 2nd hours) , serum uric acid, presence of ascites, perirectal fat plane , degree of tumor differentiation, and T classification, Duke's stage, total serum protein, TLC and ALT level were the predictors of rectal cancer metastasis table (3).

The present study revealed that serum UA level was significantly correlated with CRP, CEA, CA19.9 and lymphatic metastasis (P<0.0001).

ROC curve analysis (fig. 3); revealed that serum UA had sensitivity of 63.0 % and

specificity of 95.0 % with AUC of 0.82 in assessing metastasis in rectal cancer patients. CRP at cutoff (≥3.6) combined with uric acid at cutoff (≥6.1 mg/dL) had (≥6.1mg/dL) had AUC 0.78 with 61.5% sensitivity, 97.5 % specificity, 71.9% NPV and 96.3% PPV. On the other hand ,CEA at cutoff (≥365) when combined with Uric acid at cutoff (≥6.1mg/dL) it had AUC 0.77 with 72.0% sensitivity, 74.5 % specificity, high 73.0 % NPV and 77.8 % PPV table (4).

accuracy of 0.81, sensitivity 64.5%, specificity 92.5% , NPV 72.3% and PPV 89.7% . While the combination of CA19.9 at cutoff (≥434) with uric acid at cutoff

Lastly when ESR 2nd hours at cutoff (≥40 mm/hr) combined with Uric acid at cutoff (≥6.1mg/dL) the AUC was 0.75 with sensitivity77.5% , specificity 70.5% , NPV 78.6 % and PPV 77.8 % table (4).

Table (1) : Inflammatory, Tumor Markers and Uric Acid Levels among the Studied Groups

Variable	Metastatic group (n=100)	Non-metastatic group (n=100)	P value
CEA (ng/ml)			
Mean ± SD	718.10±415.75	389.63±341.23	<0.0001
Median (range)	658.7 (22-1478)	333 (8-1000)	
CA199(u/ml)			
Mean ± SD	1112.75±2453.42	124.70±98.81	<0.0001
Median (range)	576 (10-23602)	87.5 (5.1-434)	
C reactive protein (mg/l)			
Mean ± SD	5.55±2.88	3.13±1.49	<0.0001
Median (range)	4.4 (2.8-12)	3.0 (2.0-8.0)	
ESR 1st hours (mm/hour)			
Mean ± SD	20.78±5.52	18.65±5.28	0.006
Median (range)	20 (6-39)	20 (7-32)	
ESR 2nd hours (mm/hour)			
Mean ± SD	64.6±24.18	48.73±19.47	
Median (range)	60 (11-122)	46.5 (16-93)	<0.0001
Uric acid before CTH(mg/dl)			
Mean ± SD	7.08±2.45	4.30±1.12	
Median (range)	7.25 (2.3-11.3)	4.2 (2.46-5)	<0.0001
Uric acid after 3months of CTH(mg/dl)			
Mean ± SD	8.47±2.18	4.15±1.11	
Median (range)	8.35 (3.7-12.5)	4 (2.2-7.5)	<0.0001

*CEA (carcinembryonic antigen) *CA19, 9 (carbohydrate antigen19,9)
*ESR (erythrocyte sedimentation rare) *UA (uric acid)
*CTH (chemotherapy)

Table (2) : Correlation between Baseline (Before Chemotherapy) Serum UA Levels and Inflammatory, Tumor Markers and Number of LN Involved

Variable	Correlation coefficient (r)	P value
CEA	0.27	0.0001
CA19,9	0.28	0.0001
C reactive protein	0.29	0.0001
ESR 1st hours	0.01	0.84
ESR 2nd hours	0.21	0.003
Number of LN	0.65	<0.0001
Lymphocyte ratio	-0.03	0.63

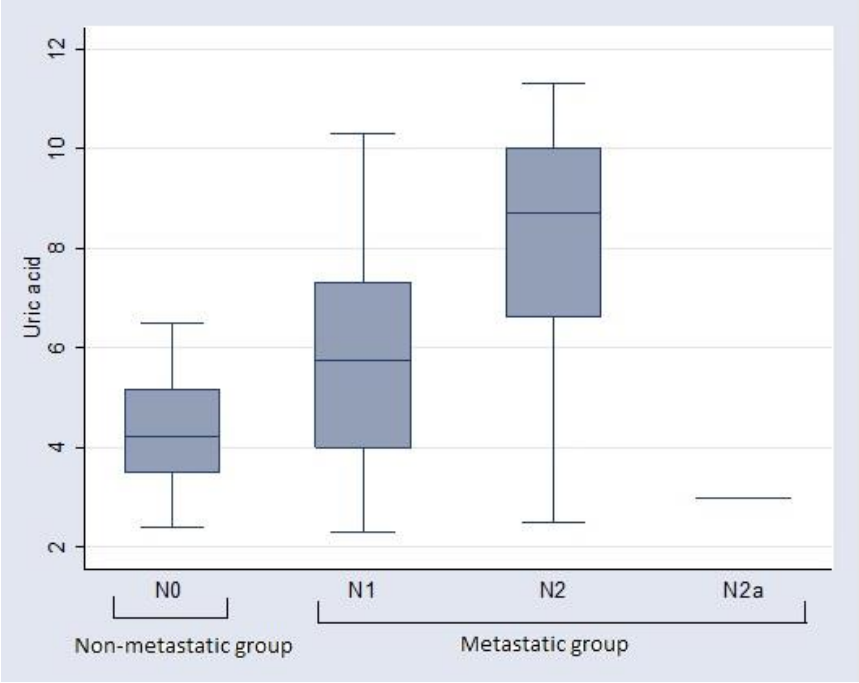


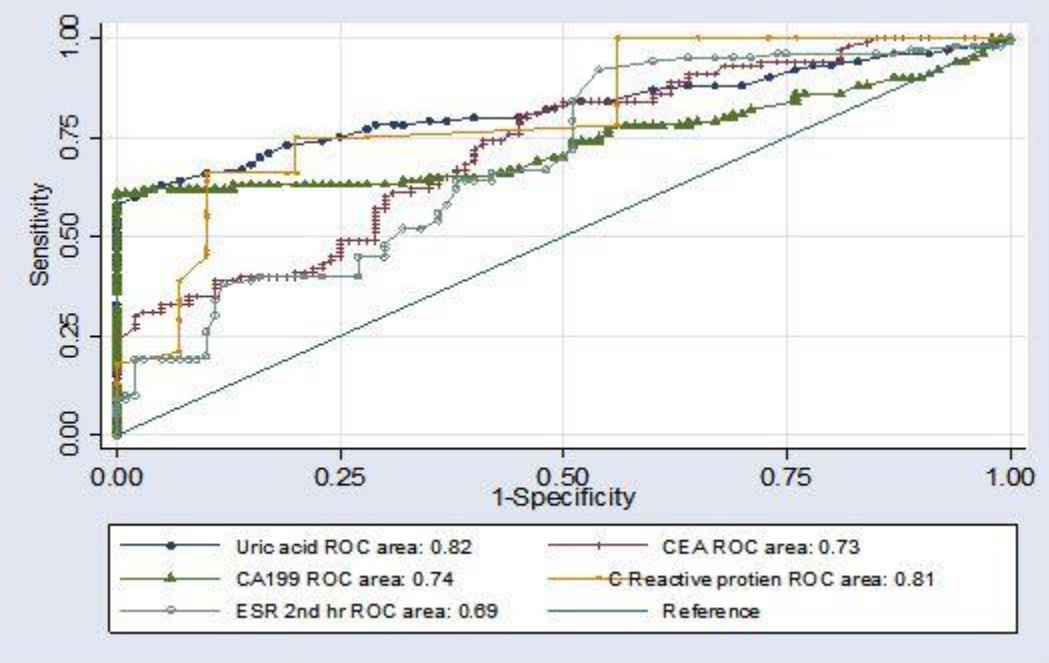
fig. 2: serum UA concentrations in patients with lymphatic metastasis compared with patients without lymphatic metastasis

Table (3) : Multiple Logistic Regression Analysis for Predictors of Metastatsis in Rectal Cancer

Variable	Odds ratio (95% confidence interval)	P value
Grade	3.803(2.023-7.151)	0.000
Degree of differentiation	2.958(1.936-4.519)	0.000
Perirectal fat plane	2.01(1.42-2.86)	0.000
Total protein	0.296 (0.159-0.550)	0.000
Uric acid	2.06 (1.49-2.83)	<0.0001
C reactive protein	1.82 (1.37-2.43)	<0.0001
Ascites	4.5(1.90-10.89)	0.001
CA19,9	1.004 (1.001-1.007)	0.001
CEA	1.002 (1.001-1.003)	0.005
ESR 1st hours	1.076(1.020- 1.136)	0.007
Duke's stage	1.812(1.61- 2.058)	0.008
T classification	1.512(1.11- 2.058)	0.009
ALT	1.027(1.004-1.050)	0.019
ESR 2nd hours	1.03 (1.01-1.06)	0.02
TLC	0.879 (0.788 - 0.980)	0.021
Neutrophil	0.979(0.956-1.002)	0.075
M classification	0.77 (0.5720- 1.036)	0.085
Size of mass by CT	1.118 (0.833-1.501)	0.454
Blood group	0 .961(0.866-1.066)	0.459
MCHC	1.047(0.88- 1.243)	0.595

Table (4) :combination between inflammatory, tumor markers and uric acid for predicting metastatic rectal cancer

Diagnostic accuracy %	NPP %	PPV %	Specificity%	Sensitivity %	Best cut off point	P value	AUC	Combination
73.2	73.0	77.8	74.5	72	≥365	<0.0001	0.77	**CEA and UA**
79.7	71.9	96.3	97.5	61.5	≥434	<0.0001	0.78	**CA199 and UA**
78.5	72.3	89.7	92.5	64.5	≥3.6	<0.0001	0.81	**C reactive protein and UA**
74.0	78.6	77.8	70.5	77.5	≥40	<0.0001	0.75	**ESR 2nd hours and UA**



Discussion

Several inflammatory biomarkers are valuable and easily available for the assessment of prognosis in patients with rectal cancer however, other laboratory markers also have been needed to monitor tumor recurrence, metastasis, and prognosis[6,7].

In this study, we found that there were high statistical significant differences between patients with metastatic and non-metastatic cancer rectum regarding CEA,CA19.9 ,ESR 2nd hour , (UA) before and 3months after chemotherapy and statistical significant difference between them regarding ESR 1st hour, These results were in agreement with the study done by Ahmet Ozan Cetin et al., [15] and Cheng Yuan et al., [16] who found that serum UA, CEA, CA19.9 and CRP was increased in rectal cancer patients with metastasis compared with those without metastasis. Also these results were in agreement with that done by Ruo-Han Tseng et al., [17] & Hentrich et al .,[18] and F.Selcukbiricik et al ., [19] who found that patients with metastatic colorectal cancer who had received bevacizumab therapy showing significant increases of serum uric acid as a part of tumor lysis syndrome .

In the current study, statistically significant positive correlations were

detected between serum UA levels before chemotherapy administration on one hand and CEA,CA19.9, CRP and number of lymph nodes affection on other hand. These results were in agreement with the study done by Ahmet Ozan Cetin et al ., [15] and Cheng Yuan et al., [16] who found that serum UA, CEA, CA19.9 and CRP was increased in rectal cancer patients with metastasis compared with those without metastasis and observed that serum UA concentrations were positively correlated with CRP and CEA level in rectal cancer patients with metastasis. This may be due to the presence of more severe inflammatory response that may contribute to increased serum UA concentration in rectal cancer patients with metastasis.

The present work found non-significant correlation between serum uric acid levels before chemotherapy administration and ESR 1st hours and neutrophil / lymphocyte ratio ,these results were in disagreement with **Ahmet Ozan Cetin et al., [15] and Mehmet Artaç et al .,[20]** who reported that preoperative N/L ratio was a prognostic factor in CRC . But, this was in disagreement with the study of **Walsh et al [21]** who concluded that preoperative N/L ratio greater than 5 was correlated with overall and cancer-specific survival in univariate analysis. Again it disagreed with the study of **Mehmet Artaç1 et al., [20]** who studied 90 patients with CRC, aimed to investigate prognostic impact of neutrophil/lymphocyte ratio, platelet count, CRP, and serum albumin levels in metastatic Colorectal Cancer patients treated with FOLFIRI-Bevacizumab and found that 47% of patients with N/L ratio >2.5 showed progressive disease versus 43 % in patients with N/L ratio <2.5 (p value= 0.025).This difference may be due to difference in number of patients of both studies and due to different effect of chemotherapy on neutrophils.

Multiple logistic regression analysis of this study revealed that CEA, CA19.9 , C-reactive protein, ESR (1st , 2nd hours) , serum uric acid, presence of ascites, perirectal fat plane , degree of tumor differentiation, T classification , Duke's stage, total protein ,TLC and ALT level were the predictors of rectal cancer metastasis . These results were in agreement with the study of **Ahmet Ozan Cetin et al [15]** who studied 150 patients with stage II and III colorectal adenocarcinoma and found that increased serum uric acid level was significantly positively correlated with

stage IIA and stage IIIB (r=0.598, p=0.029), N3 disease, (r=0.618, p=0.024), grade III tumor (r=0.631, p=0.029), presence of weight loss (r=0.539, p=0.037), presence of lymphovascular invasion (r=0.621, p=0.031), recurrence with other organ metastases (r=0.648, p=0.018), baseline platelet counts (r=0.496, p=0.042), baseline CEA levels (r=0.509, p=0.036), baseline CA19.9 levels (r=0.645, p=0.028), and a shorter disease-free survival rates (r=0.651, p=0.018),which is considered as a the predictors of rectal cancer stage II and III (stages of cancer rectum with metastasis).

This study shows that statistical significant positive correlation was detected between metastatic rectal cancer on one hand and serum uric acid and C-reactive protein level on other hand (Odds ratio 2.06-1.82 and p value <0.0001and <0.0001 respectively) , also significant positive correlations were between CEA, CA199 and ESR 2nd hours levels and rectal cancer metastasis (Odds ratio 1.002 -1.004and1.03 and p value 0.0 respectively). These results coincided with study done by **Cheng Yuan et al [16]** who found that elevated serum levels of UA were significant prognostic marker for lymphatic metastasis in patients with rectal cancer, independently of CRP, CEA, and tumor diameter (odds ratio [OR] 1.035, 95% confidence interval [CI] 1.013–1.057, P= 0.002). Another study conducted by **Ahmet Ozan Cetin et al [15]** revealed that increased serum uric acid level was positively correlated with stage IIA and stage IIIB (r=0.598, p=0.029), N3 disease, (r=0.618, p=0.024), grade III tumor (r=0.631, p=0.029), presence of weight loss (r=0.539, p=0.037), presence of lymphovascular invasion (r=0.621, p=0.031), recurrence with liver metastases (r=0.648, p=0.018), baseline platelet counts (r=0.496, p=0.042), baseline CEA levels (r=0.509, p=0.036), baseline CA19-9 levels (r=0.645, p=0.028), and a shorter disease-free survival rates (r=0.651, p= ROC curve analysis revealed that serum UA had sensitivity of 63.0 % and specificity of 95.0 % with AUC of 0.82 in assessing metastasis in rectal cancer patients 0.018).

Yuan et al. [16] reported that serum UA had sensitivity of 0.864 and specificity of 0.739 in assessing metastatic rectal cancer patients, results that .

In the current study, there are, however, several limitations. First, a relatively small sample size in this study is a major limitation. Moreover, some confounders associated with UA, such as diet, exercise,

were not included as variables in multiple regression analysis, and more clinical parameters for the severity of the disease were needed to explain the relationship between serum UA and metastasis status in multiple regression analysis. Despite these limitations, our results suggest that serum UA may be a useful marker in assessing tumor metastasis in patients with rectal cancer.

Ethical review:

The study was approved by the Ethics Committee of Benha Faculaty of Medicine and its University Hospitals and approval for the study was obtained also from Sohag cancer institute before involvement in the study, informed consent was obtained from each patients or his/her relative.

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