

Hyperuricemia May Affect the Healing of Anastomosis in Dixon Surgery for Rectal Cancer: A Retrospective Study

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Research article

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Abstract

Background The impact of Hyperuricemia (HUA) on Dixon surgery is rarely reported. Anastomotic leakage (AL) is the main serious complication in Dixon surgery. We discussed the relationship between HUA and AL. Our aim was to identify these factors to provide intervention measures for clinical practice.

Methods The clinical data of 1147 patients who underwent Dixon operation for rectal cancer in the Second Affiliated Hospital of Fujian Medical University from January 2009 to December 2018 were retrospectively analyzed. Rank sum test was used for measurement data, and χ^2 test was used for counting data. In univariate analysis, significant variables ($P < 0.05$) were used for multivariate analysis, and multivariable logistic regression was used to examine their independent roles. All tests were 2-sided, $P < 0.05$ was considered statistically significant.

Results A total of 1147 patients with rectal cancer undergoing Dixon operation were included in the study, including 153 patients with HUA and 994 patients with normal uric acid (UA). The AL was 148 cases (14.9%) in UA group and 37 cases (24.2%) in HUA group. There was significant difference in AL ($P = 0.006$). The influence of HUA ($P = 0.006$), Tumor distance from the anal margin (TD) ($P = 0.024$) and preoperative chemoradiotherapy (PCT) ($P = 0.040$) on AL were significantly different. Logistic analysis showed that HUA ($P = 0.021$) and TD ($P = 0.014$) had significant effects on AL. In rectal cancer group with HUA, there were significant differences in the effects of male ($P = 0.035$), body mass index (BMI) ($P = 0.017$) and PCT ($P = 0.013$) on AL. Logistic analysis showed that there were significant differences between male ($P = 0.001$) and PCT ($P = 0.004$) on AL.

Conclusions HUA is an independent risk factor of AL in Dixon operation for rectal cancer. In patients with HUA undergoing Dixon operation, gender, BMI and PCT have significant difference on AL. Male and PCT are independent risk factors of AL.

Background

Uric acid (UA) is the final product of purine nucleoside catabolism produced by diet and endogenous nucleic acid. The elevated serum UA which is called Hyperuricemia (HUA), arising from impaired metabolism of serum UA, is common in patients with obesity, metabolic syndrome and type 2 diabetes, and is associated with diseases such as hypertension, diabetes, metabolic syndrome and chronic kidney disease [1-3]. However, the impact of HUA on surgery is rarely reported. At present, there are relatively few studies on the relationship between HUA and Dixon surgery for patients with rectal cancer. Dixon operation (anterior rectal resection) is used to resect rectal lesions with anus preservation. Anastomotic leakage (AL) is the main serious complication in Dixon operation for patients with rectal cancer, which can cause the diffusion of residual tumor cells in the cavity and immune suppression related to local inflammation, and delay the adjuvant treatment of rectal cancer after operation [4, 5]. AL increases the risk of local recurrence of rectal cancer and reduces the overall survival rate, tumor specific survival rate and disease-free survival rate of patients with rectal cancer after operation [6-8]. In addition, when AL

occurs after rectal cancer operation, peritonitis needs to be treated, and even reoperation is required, so the postoperative hospital stay will be longer and the cost of hospitalization will increase.

This paper discussed the possible impact of HUA on Dixon surgery for patients with rectal cancer through a retrospective study, and evaluate the relationship between HUA and AL of Dixon surgery for rectal cancer. Our aim was to identify these factors to provide possible predictors and interventions for clinical practice, so as to prevent the occurrence and reduce the severity of AI, thus improving the prognosis of patients.

Methods

Patients.

The electronic medical records of patients who have undergone Dixon surgery for rectal cancer in the Second Affiliated Hospital of Fujian Medical University were searched from January 2009 to December 2018. Of these patients, 143 patients underwent emergency surgery due to intestinal obstruction and 28 patients with a history of colorectal surgery were excluded. A total of 1147 consecutive patients with 185 cases of AL were included in the study. Among them, there were 37 cases of AL in 153 cases of rectal cancer patients with HUA, with 28 cases of AL in 93 cases of men. The average age of the patients was 65.23 ± 10.89 years (range, 29 to 84 years). The patients were divided into HUA group, UA group, LA group and NLA group.

Definition

Definition of HUA : the serum UA level of men and postmenopausal women was $> 416\mu\text{mol} / \text{L}$, and that of women was $> 339\mu\text{mol} / \text{L}$ [9].Or a history of HUA in the past. Definition of AL: AL is diagnosed by gastrointestinal radiography [10]. If there were signs of clinical leakage, such as pus or feces discharged from pelvic drainage or suspected symptoms of peritonitis, including abdominal pain, abdominal tenderness, fever, tachycardia or severe inflammatory symptoms in blood tests, the AL would be investigated. All patients were confirmed as primary rectal adenocarcinoma by colonoscopy and histopathological examination before operation.

Surgical methods.

All operations were performed by experienced and skilled colorectal surgeons in our hospital. Routine bowel preparation was performed before operation. The principle of total mesorectal excision was strictly followed in both open and laparoscopic operations. Circular stapler was used for rectal anastomosis and reconstruction. At the end of the operation, a large amount of distilled water was used to flush the abdominal cavity until it was clean. Rubber drainage tube was routinely placed beside the anastomotic stoma of rectum.

Perioperative treatment measures.

All patients were taken active preoperative preparation measures, such as correcting preoperative hypoproteinemia, anemia and water electrolyte imbalance, and were strengthened nutrition, anti-infection and other supportive treatment after surgery.

Statistical analysis.

SPSS software version 22.0 (IBM, New York) was used to analyze the data. Rank sum test was used for measurement data, and χ^2 test was used for counting data. In univariate analysis, significant variables ($P < 0.05$) were used for multivariate analysis, and multivariable logistic regression was used to examine their independent roles. All tests were 2-sided, $P < 0.05$ was considered statistically significant.

Results

Patient characteristics.

The clinical characteristics of HUA and UA group were shown in Table 1. There were 1147 consecutive patients who have undergone Dixon surgery for rectal cancer, including 153 patients with HUA and 994 patients with UA. Among them, 58 women (37.9%) and 95 men (62.1%) were in the HUA group, with an average age of 65.23 ± 10.89 years. There were 457 females (46.0%) and 537 males (54.0%) in the UA group, with an average age of 56.07 ± 12.75 years. There were no significant differences in age, gender, TNM stage and histological differentiation between HUA group and UA group, but there were significant differences in body mass index (BMI) ($P = 0.044$).

Table 1. The clinical characteristics of HUA and UA group

Characteristics	HUA(n=153)	UA(n=994)	χ^2	P
Age			1.687	0.217
>60	71(46.4%)	406(40.8%)		
≤60	82(53.6%)	588(59.2%)		
Gender			3.488	0.067
Male	95(62.1%)	537 (54.0%)		
Female	58(37.9%)	457 (46.0%)		
TNM staging			0.614	0.736
I	13(8.5%)	70(7.0%)		
II	56(36.6%)	388(39.0%)		
III	84(54.9%)	536(53.9%)		
Tumor differentiation			2.042	0.360
Well	72(47.1%)	413(41.5%)		
Moderate	32(20.9%)	208(20.9%)		
Low	49(32.0%)	373(37.5%)		
BMI			4.273	0.044 [□]
≥25kg/m ²	41(26.8%)	351(35.3%)		
<25kg/m ²	112(73.2%)	643(64.7%)		

Statistically significant at level $p < 0.05$. [□] $p < 0.05$, [▣] $p < 0.01$

HUA hyperuricemia, *UA* uric acid, *BMI* body mass index.

Effect of HUA on postoperative complications of Dixon for rectal cancer

Table 2 shows the common postoperative complications. In terms of intestinal obstruction, respiratory tract infection, deep vein thrombosis and urinary tract infection, there is no significant difference between

HUA group and UA group. There were 148 cases (14.9%) of AL in UA group and 37 cases (24.2%) in HUA group, with significant difference (P = 0.006).

Table 2. Effect of HUA on postoperative complications of Dixon for rectal cancer

Postoperative complication	HUA(n=153)	UA(n=994)	χ^2	P
AL			8.466	0.006 ^{□□}
Yes	37(24.2%)	148(14.9%)		
No	116(75.8%)	846(85.1%)		
Ileus			2.460	0.128
Yes	27(17.6%)	129(13.0%)		
No	126(82.4%)	865 (87.0%)		
Respiratory infection			2.752	0.101
Yes	32(20.9%)	155(15.6%)		
No	121(79.1%)	839(84.4%)		
Deep venous thrombosis			1.591	0.232
Yes	8(5.2%)	31(3.1%)		
No	145(94.8%)	963(96.9%)		
Urinary tract infection			0.477	0.489
Yes	29(19.0%)	166(16.7%)		
No	124(81.0%)	828(83.3%)		

Statistically significant at level $p < 0.05$. ^{□□} $p < 0.01$

HUA hyperuricemia, UA uric acid, AL anastomotic leakage.

Role of HUA on AL in Dixon operation for rectal cancer

In Table 3, the relationship between HUA and AL of Dixon operation for rectal cancer was further discussed. It was found that age, gender, TNM stage, histological differentiation, BMI, surgical method and protective stoma had no significant effect on AL, while HUA (P = 0.006), Tumor distance from the anal margin (TD) (P = 0.024), PCT (P = 0.040) had significant differences on AL. In Table 4, logistic

regression analysis showed that HUA (P = 0.021, OR 1.823, 95% CI, 1.079-2.519) and TD (P = 0.014, OR 0.669, 95% CI, 0.463-0.917) had significant difference on AL, while PCT (P = 0.060, OR 1.687, 95% CI, 0.981-2.630) had no significant difference.

Table 3. Role of HUA on AL in Dixon operation for rectal cancer

Characteristics	AL(n=185)	NAL(n=962)	χ^2	P
Age			0.438	0.516
>60	81(43.8%)	396(41.2%)		
≤60	104(56.2%)	566(58.8%)		
Gender			0.527	0.517
Male	109(58.9%)	539(56.0%)		
Female	76(41.1%)	423(44.0%)		
HUA			8.466	0.006 ^{□□}
Yes	37(20.0%)	116(12.1%)		
No	148(80.0%)	846(87.9%)		
TNM staging			0.981	0.612
I	15(8.1%)	68(7.1%)		
II	76(41.1%)	368(38.2%)		
III	94(50.8%)	526(54.7%)		
Tumor differentiation			2.635	0.268
Well	87(47.0%)	398(41.4%)		
Moderate	32(17.3%)	208(21.6%)		
Low	66(35.7%)	356(37.0%)		
TD			5.523	0.024 [□]
<7cm	63(34.1%)	247(25.7%)		
≥7cm	122(65.9%)	715(74.3%)		
BMI			2.438	0.128
≥25kg/m ²	54(29.2%)	338(35.1%)		
<25kg/m ²	131(70.8%)	624(64.9%)		
PCT			4.834	0.040 [□]
Yes	26(14.1%)	85(8.8%)		
No	159(85.9%)	877(91.2%)		
Laparoscopic surgery			1.525	0.240

Yes	128(69.2%)	708(73.6%)		
No	57(30.8%)	254(26.4%)		
Preventive ostomy surgery			0.178	0.675
Yes	68(36.8%)	338(35.1%)		
No	117(63.2%)	624(64.9%)		

Statistically significant at level $p < 0.05$. □ $p < 0.05$, ▣ $p < 0.01$

HUA hyperuricemia, *UA* uric acid, *AL* anastomotic leakage, *NAL* non anastomotic leakage, *TD* tumor distance from the anal margin, *BMI* body mass index, *PCT* preoperative chemoradiotherapy.

Table 4. Logistic regression analysis for the relationship between HUA and AL of Dixon surgery for rectal cancer.

Characteristics	OR	95%CI	P
HUA	1.823	1.079-2.519	0.021 [□]
TD	0.669	0.463-0.917	0.014 [□]
PCT	1.687	0.981-2.630	0.060

Logistic regression. □ $p < 0.05$

HUA hyperuricemia, *TD* tumor distance from the anal margin, *PCT* preoperative chemoradiotherapy.

Risk factors of AL in Dixon operation for rectal cancer patients with HUA

In Table 5, the risk factors of AL in patients with HUA undergoing Dixon operation were further analyzed. It was found that age, TNM stage, histological differentiation, TD, surgical method and protective stoma had no significant influence on AL, while gender ($P = 0.035$), BMI ($P = 0.017$) and PCT ($P = 0.013$) had significant differences. In Table 6, further logistic regression analysis showed that gender ($P = 0.001$, OR 0.410, 95% CI, 0.058-0.460), PCT ($P = 0.004$, OR 0.386, 95% CI, 0.093-0.642) had significant difference on AL, while BMI ($P = 0.066$, OR 2.949, 95% CI, 0.939-7.034) had no significant difference.

Table 5. Risk factors of AL in Dixon operation for rectal cancer patients with HUA.

Characteristics	AL(n=37)	NAL(n=116)	χ^2	P
Age			0.209	0.706
>60	15(40.5%)	52(44.8%)		
≤60	22(59.5%)	64(55.2%)		
Gender			4.540	0.035 [□]
Male	28(75.7%)	65(56.0%)		
Female	9(24.3%)	51(44.0%)		
BMI			6.682	0.017 [□]
≥25kg/m ²	13(35.1%)	18(15.5%)		
<25kg/m ²	24(64.9%)	98(84.5%)		
TNM staging			1.249	0.535
□	2(5.4%)	11(9.5%)		
□	16(43.2%)	40(34.5%)		
□	19(51.4%)	65(56.0%)		
Tumor differentiation			0.791	0.673
Well	14(37.8%)	52(44.8%)		
Moderate	11 (29.7%)	27(23.3%)		
Low	12(32.4%)	37(31.9%)		
TD			0.067	0.839
<7cm	12(32.4%)	35(30.1%)		
≥7cm	25(67.6%)	81(69.8%)		
PCT			6.204	0.013 [□]
Yes	23(62.2%)	45(38.8%)		
No	14(37.8%)	71(61.2%)		
Laparoscopic surgery			0.819	0.434
Yes	26(70.3%)	72(62.1%)		
No	11(29.7%)	44(37.9%)		
Preventive ostomy surgery			0.938	0.415

Yes	9(24.3%)	38(32.8%)
No	28(75.7%)	78(67.2%)

Statistically significant at level $p < 0.05$. [□] $p < 0.05$

HUA hyperuricemia, *UA* uric acid, *AL* anastomotic leakage, *NAL* non anastomotic leakage, *TD* tumor distance from the anal margin, *BMI* body mass index, *PCT* preoperative chemoradiotherapy.

Table 6. Logistic regression analysis for the relationship between risk factors of Dixon surgery and rectal cancer patients with HUA.

Characteristics	OR	95%CI	P
Gender	0.410	0.058-0.460	0.001 ^{□□}
BMI	2.949	0.939-7.034	0.066
PCT	0.386	0.093-0.642	0.004 ^{□□}

Logistic regression. ^{□□} $p < 0.01$

BMI body mass index, *PCT* preoperative chemoradiotherapy.

Discussion

In our study, we found that in patients with rectal cancer undergone Dixon surgery, TD and PCT showed a significant relationship with AL, which was consistent with previous studies [11–13]. At the same time, we also found that HUA was significantly related to AL. Further logistic regression analysis showed that not only TD, but also HUA were also Independent risk factors for AL. It indicated that HUA may be a risk factor for AL.

HUA is an early-onset metabolic disorder that occurs earlier than hypertriglyceridemia, diabetes and hypertension [14]. We speculated that HUA may affect the healing of anastomotic stoma after Dixon operation for rectal cancer. The possible reasons may be as follows: The first, HUA is associated with inflammation. HUA shows association with increased inflammatory capacity of various tissues and immune cell [15]. Soluble UA promote inflammatory response through the effects of oxidative stress, pro-inflammatory signals, autophagy and intracellular immune metabolic sensors, such as the increase of white blood cells, C-reactive protein level and the number of circulating cytokines involved in the natural immune response [16]. The second, HUA is relevant to microvascular disease. As UA has relevance to pro-inflammatory and immune effects, it can damage the microvessels in the intracellular environment and promote the rise of blood pressure [17, 18]. Because of microvascular lesions, the blood supply of rectal

anastomosis is poor, which affects the anti-infection ability and healing effect of rectal cancer anastomosis.

In our study, gender had no significant effect on AL in Dixon operation for rectal cancer, but it had a significant effect on AL in patients with HUA. It indicated that male was an independent risk factor for AL. The influence of gender on AL in Dixon operation for rectal cancer with HUA may be multifactorial. The overall prevalence of HUA in men is significantly higher than that in women [19]. middle-aged men tend to have more unhealthy lifestyle risk factors, such as more drinking and less physical exercise. Moreover, due to the increase of insulin resistance and central obesity, UA may be increased [20–23]. Androgen can also cause HUA by inhibiting UA excretion [24]. All these factors may lead to HUA which may result in AL.

Some studies have found that BMI is a risk factor, even an independent risk factor, for AL in resection for colorectal cancer [25–27]. However, the other studies also have shown that BMI is not related to the possibility of AL in rectal cancer surgery [28]. In our study, BMI was a risk factor for AL only in Dixon patients with HUA, but it was no significant difference through multivariate logistic regression analysis. Studies have shown that obesity is closely related to HUA, especially in postmenopausal women [29]. Obesity is considered to be the main cause of a large number of chronic diseases, and is also an established risk factor for the development of HUA. It is related to the excessive production and poor excretion of serum UA, which leads to the damage of UA metabolism [30]. At the same time, adipose tissue can also increase the secretion of UA in obese people, which may lead to excessive production of UA and increase the occurrence of AL [31].

Our study found that PCT was significantly associated with AL in Dixon operation and Dixon operation with HUA. Previous studies have demonstrated that PCT usually increases AL and perineal wound infection and the healing time of anastomotic stoma is longer [32, 33]. This may be due to the damage of immune system of anti-infection and anti-tumor immunity [34]. In addition, PCT usually causes anastomotic inflammation and edema, resulting in relative anastomotic ischemia, local inflammation and tissue fibrosis, which is not conducive to anastomotic healing and increase the risk of AL [35, 36]. However, some studies have suggested that PCT does not increase the risk of AL in rectal cancer resection [37]. In this study, we found that PCT was only an independent risk factor for AL in Dixon operation for patients with HUA. It may be that the patients with HUA are often at risk for a variety of other diseases, including hypertension, acute and chronic kidney disease, obesity, metabolic syndrome, fatty liver and diabetes, which increase the incidence of AL in Dixon surgery for rectal cancer with HUA [38, 39].

Our research has some limitations. The study was conducted in a single hospital, which may have selection bias and lack of representativeness. The bias of surgical experience of doctors in different surgical groups and the relatively small number of patients with HUA in this study may affect us to explore the statistical significance of other important factors, such as intraoperative blood loss, operation time and other important factors. In spite of these limitations, our findings may have important clinical significance.

Conclusions

In summary, our findings indicate that HUA is an independent risk factor for AL in Dixon operation for rectal cancer. In patients with HUA undergoing Dixon operation, gender, BMI and PCT have significant difference on AL. Male and PCT are independent risk factors for AL.

Abbreviations

HUA Hyperuricemia

AL Anastomotic leakage

UA Uric acid

TD Tumor distance from the anal margin

PCT Preoperative chemoradiotherapy

BMI Body mass index

Declarations

Acknowledgements

None

Author contributions

XC Z. and JB S designed the study; XC Z. conducted main literature search and wrote the first draft of the paper. XC Z. and JB S were responsible for statistical analyses. Both authors read and approved the final manuscript. Both authors contributed equally to this work and should be considered co-first authors.

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Availability of data and materials

Correspondence and requests for materials should be addressed to X.C.Z on reasonable request.

Ethics approval and consent to participate

The present study was conducted in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all participants included in the study. The Ethics

Committee of the Second Affiliated Hospital of Fujian Medical University gave the ethics approval for this retrospective study.

Consent for publication

Not applicable.

Conflict of interest

The authors declare that they have no conflict of interest.

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