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Original Article

Changes and predictive value of TGF-α and IGF-II in treatment of elderly rectal cancer

Yanjun Liu[1*], Xiaochen Zhang[2*], Xiaoyan Ye[3], Huihe Lv[4], Wenying Jiang[5], Jie Liu[6], Xiangdong Zhang[7]

[1]Department of Gastrointestinal Surgery, 970th Hospital of The Joint Logistics Support Force of The Chinese People's Liberation Army, Yantai, Shandong Province, China; [2]The First Department of Surgery, Tianjin Fifth Central Hospital, Tianjin City, China; Departments of [3]Hemodialysis, [7]Hepatobiliary Surgery, Laiyang Central Hospital, Yantai, Shandong Province, China; [4]Department of General Surgery, Shexian Hospital of Traditional Chinese Medicine, Handan, Hebei Province, China; [5]Department of General Surgery, The Second People's Hospital of Liaocheng, Liaocheng, Shandong Province, China; [6]Department of Gastroenterological Surgery, Cangzhou People's Hospital, Hebei Province, China. [*]Equal contributors and co-first authors.

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Abstract: Objective: This study aimed to investigate the changes and predictive value of Transforming growth factor alpha (TGF-α) and Insulin-like growth factor II (IGF-II) in the treatment of elderly patients with advanced rectal cancer. Methods: Altogether, there were 30 cases in the Lx group (rectal polyp patients), 52 cases in the Ex group (rectal cancer patients) and 35 cases in the Zc group (healthy volunteers) that were selected. The levels of TGF-α and IGF-II in serum from the Lx group, Ex group and Zc group were observed, and the levels of TGF-α and IGF-II in patients with different pathological stages, lymph node metastasis, tumor sizes were recorded, and the predictive value of TGF-α and IGF-II detection on rectal cancer was analyzed. Results: The levels of serum TGF-α and IGF-II in the Zc group were the lowest, the level in the Lx group was higher than that in the Zc group, and the levels of TGF-α and IGF-II in the Ex group were the highest (P<0.05). Compared with patients with a tumor size of less than 5 cm, TGF-α and IGF-II in patients with rectal cancer tumors greater than 5 cm increased significantly (P<0.05). The levels of TGF-α and IGF-II were the lowest in patients with highly differentiated tumors, those with moderately differentiated tumors had the second lowest and those with poorly differentiated tumors had the highest (P<0.05). TGF-α and IGF-II levels were the highest in Dukes C stage, followed by stage B and A (P<0.05). The levels of TGF-α and IGF-II in M1 patients were significantly higher than those in M0 patients (P<0.05). The area under the ROC curve of TGF-α was 0.65, the area under the ROC curve of IGF-II was 0.72, and the area under the ROC curve of combined detection was 0.87, which showed that detection of TGF-α alone and IGF-II alone can be used as a prediction index for elderly people with rectal cancer, and the combined detection of TGF-α and IGF-II has an even higher prediction and treatment value for rectal cancer. Conclusion: TGF-α and IGF-II are helpful to judge the staging, tumor size and lymph node metastasis of elderly people with rectal cancer, and both cytokines have important value in the treatment and prediction of rectal cancer.

Keywords: Rectal cancer, TGF-α, IGF-II, lymph node

Introduction

In the past ten years, the incidence rate of rectal cancer in China has gradually increased, which has a serious impact on the health of our citizens. China's incidence rate accounts for 24% of the world's total, and the mortality rate is as high as 22% [1]. At present, the clinical treatment for rectal cancer is relatively simple, it has poor prognosis with radiotherapy, chemotherapy and surgery. Through reasonable comprehensive treatment, the five-year survival rate of rectal cancer can reach more than 80% [2]. Rectal cancer is a malignant disease with high incidence of digestive system dysfunction, which is found clinically. Poor dietary habits, such as excessive protein and insufficient intake of vegetables and fruits, will lead to an increase in the incidence of rectal cancer in patients [3, 4]. According to statistics, rectal cancer patients have accounted for 60% to 70% of colorectal diseases in China, and the quality of life of patients cannot be improved. Rectal cancer lesions are mainly located at the junction of rectum and sigmoid colon. Malignant lesions occur when rectal tissue is damaged,

and there is no significant clinical feature in the early stage. Symptoms such as abdominal pain indicate that the disease has progressed [5].

The incidence of rectal cancer in China is far lower than that in European countries. In recent years, with the in-depth study of insulin-like growth factor (IGF), more and more factors affecting the relationship between the IGF system and colorectal cancer are known. Insulin-like growth factor receptors (IGF-IR and IGF-IIR) play an important role in the growth, anti-apoptosis and mitosis of epithelial cells, while the occurrence and development of the IGF system in colorectal cancer depends on the combined effects of circulating IGFs, IGFBP and locally synthesized IGFs, IGFBP and IGFBP proteases [6, 7]. Studies have shown that abnormal expression of IGF-I and IGF-II is related to various cancers, and colorectal cancer is one of them [8]. Transforming growth factor alpha (TGF-α) is a mitogenic polypeptide with the ability to promote cell growth and transformation, which is related to the differentiation degree and tumor stage. Over-expression of TGF-α gives cancer cells growth advantages, which is one of the common mechanisms for the occurrence of various cancers [9]. There are many studies on the expression of IGF-II and TGF-α in rectal cancer, but few reports on the change and predictive value of the combined detection of IGF-II and TGF-α in rectal cancer [10]. Therefore, through regression analysis of TGF-α and IGF-II in different cancer groups; the benign polyp group and normal patients, this study discussed the dynamic changes and predictive value of TGF-α and IGF-II in the treatment of elderly patients with advanced rectal cancer.

Methods

Research subjects and groups

Altogether, there were 52 rectal cancer patients (Ex group) diagnosed in Laiyang Central Hospital from January 2016 to December 2018 who were retrospectively analyzed. An additional 30 cases with colonic polyps (LX group), and 35 healthy volunteers (Zc group) were confirmed by pathology.

Inclusion and exclusion criteria

Inclusion criteria: patients aged 50-75 years; patients were pathologically confirmed as having rectal cancer, patients received surgical treatment; patients and their family members agreed with the study and understood the study process. Exclusion criteria: patients with other cancers and coagulase, patients who dropped out during the study period for no reason; patients without complete clinical data; patients with anti-tumor treatment history before the study.

Observation indicators

① the levels of serum TGF-α and IGF-II in the Lx group, Ex group and Zc group before treatment; ② the levels of TGF-α and IGF-II in patients with different tumor sizes before treatment; ③ the levels of TGF-α and IGF-II before treatment in patients with different tumor differentiation; ④ the levels of TGF-α and IGF-II in patients with different pathological stages before treatment; ⑤ the levels of TGF-α and IGF-II before treatment of patients with or without lymph node metastasis; ⑥ the analysis of the relationship of TGF-α and IGF-II with pathological factors. Fasting venous blood was collected from the three groups of patients, serum was collected by centrifugation, and the levels of TGF-α, IGF-II were detected by radioimmunoassay.

Staging standard

According to Dukes staging criteria, disease status was classified into grade A, B and C. Dukes A: A0: cancer was confined to the mucosa; A1: cancer was confined to submucosa; A2: cancer invaded the muscular layer of the intestinal wall and did not penetrate the serosa; B: the lesion invaded the serosa or surrounding tissues and organs, but it could be resected simultaneously; C: lymph node metastasis near the focus or distant organ metastasis was found [11]. M (distant metastasis): M0: no distant metastasis was found, M1 showed distant metastasis of the surrounding tissues and organs.

Statistical methods

The levels of serum TGF-α and IGF-II in different groups of patients were statistically analyzed by SPSS 20.0. The variables were expressed by mean ± standard deviation. The comparison among the three groups was conducted by one-way analysis of variance, the pairwise compari-

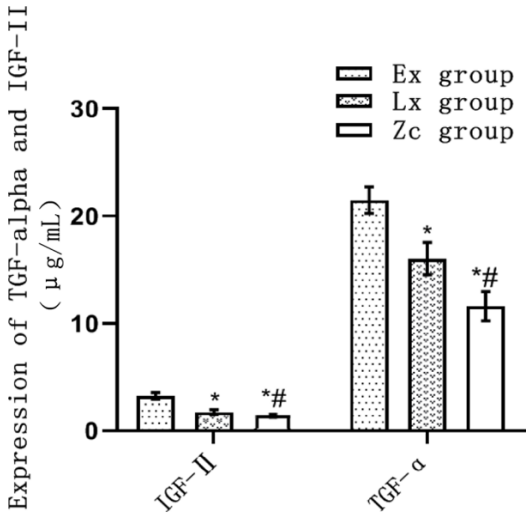

Figure 1. Levels of TGF-α and IGF-II in serum of LX group, Ex group and Zc group, *indicates compared with Ex group, P<0.05; #indicates compared with LX group, P<0.05, Lx group: rectal polyp patients; Ex group: rectal cancer patients; Zc group: healthy volunteers.

Table 1. Levels of TGF-α and IGF-II in different tumor sizes ($\bar{x}$±s)

Group	n	IGF-II (μg/mL)	TGF-α (μg/mL)
≥5 cm	22	2.54±1.11	21.35±7.12
<5 cm	30	2.03±0.82	18.67±5.71
t		12.25	13.53
P		<0.001	<0.001

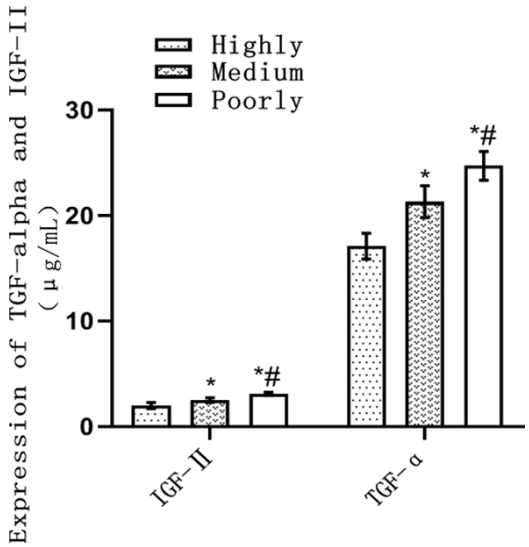

Figure 2. Levels of TGF-α and IGF-II in patients with different tumor differentiation, *indicates compared with highly differentiated patients, P<0.05; #indicates compared with moderately differentiated tumor patients, P<0.05.

son was conducted by LSD t or bonferonni test. The difference was significant with P<0.05.

Results

General data

The general data showed that among 52 rectal cancer patients, 22 cases had tumors that were more than 5 cm, and 30 cases had tumors that were less than 5 cm. According to Dukes stage, 14 cases were in stage A, 26 cases were in stage B, and 12 cases were in stage C; 12 patients were in M0, and 40 patients were in M1. Patients were divided into groups with 16 cases of high differentiation, 26 cases of medium differentiation, and 10 cases of low differentiation according to the degree of tumor differentiation. There was no significant difference in clinical data comparison among the Lx group, Ex group and Zc group (P>0.05).

Levels of TGF-α and IGF-II in serum of Lx group, Ex group and Zc group

The levels of serum TGF-α and IGF-II in the Zc group were the lowest. The levels of TGF-α and IGF-II in the Ex group were the highest. Compared with Zc group, the levels of TGF-α and IGF-II in Ex group increased (P<0.05). See **Figure 1**.

Levels of TGF-α and IGF-II in different tumor sizes

Compared to patients with tumor size less than 5 cm, TGF-α and IGF-II in patients with rectal cancer tumors greater than 5 cm increased significantly (P<0.05). See **Table 1**.

Levels of TGF-α and IGF-II in patients with different tumor differentiation

The levels of TGF-α and IGF-II in patients with highly differentiated tumors were the lowest, while the levels of TGF-α and IGF-II in moderately differentiated tumor patients were higher than those in the highly differentiated group, and the levels of TGF-α and IGF-II in poorly differentiated tumor patients were the highest (P<0.05). See **Figure 2**.

Levels of TGF-α and IGF-II in patients with different Dukes stages

Compared with Dukes stage A patients, the levels of serum TGF-α and IGF-II in Dukes stage

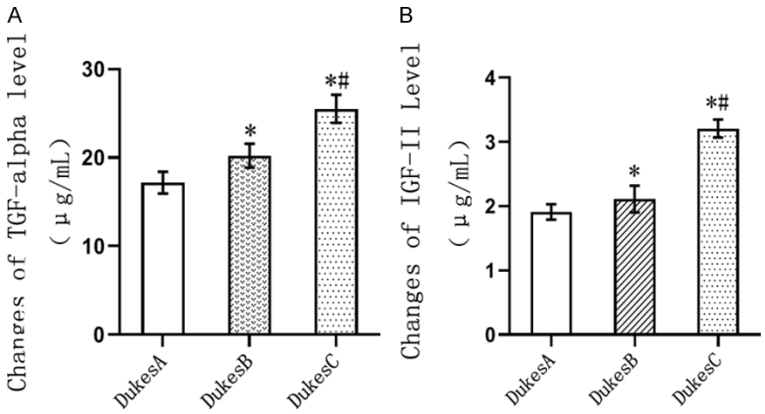

Figure 3. Levels of TGF-α and IGF-II in patients with different Dukes stages. A: Levels of TGF-α in patients with different Dukes stages; B: Levels of IGF-II in patients with different Dukes stages; *indicates compared with Dukes stage A patients, P<0.05; #indicates compared with Dukes stage B patients, P<0.05.

nificantly, with the highest levels of TGF-α and IGF-II in stage C, the second in stage B and the lowest in stage A (P<0.05). See **Figure 3**.

Levels of TGF-α and IGF-II in patients with lymph node metastasis

The levels of TGF-α and IGF-II in M1 patients were significantly higher than those in M0 patients (P<0.05). See **Table 2**.

Predictive value analysis of TGF-α and IGF-II detection for rectal cancer

Table 2. Levels of TGF-α and IGF-II in patients with lymph node metastasis ($\bar{x}\pm s$)

Group	N	IGF-II (μg/mL)	TGF-α (μg/mL)
M0	12	1.74±0.54	111.26±15.57
M1	40	3.11±1.69	132.24±20.41
t		20.08	10.96
P		<0.001	<0.001

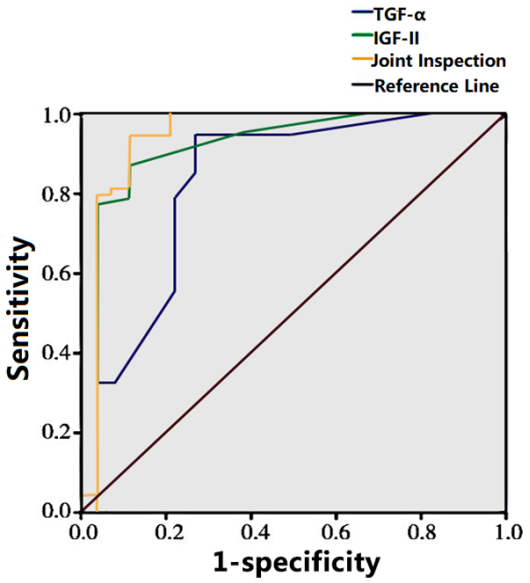

Figure 4. Predictive value analysis of TGF-α and IGF-II detection for rectal cancer (ROC curve).

B patients increased. Compared with Dukes stage B patients, the levels of serum TGF-α and IGF-II in Dukes stage C patients increased sig-

The test variables were analyzed from serum levels of TGF-α and IGF-II, and their sensitivity and specificity prediction were carried out. It showed that TGF-α and IGF-II can be used as predictive indicators for elderly patients with rectal cancer. Combined detection of TGF-α and IGF-II had higher predictive and therapeutic value for rectal cancer screening. The area under the TGF-α ROC curve was 0.65, the area under the IGF-II ROC curve was 0.72, and the area under the combined detection ROC curve was 0.87. See **Figure 4**.

Discussion

Rectal cancer is a malignant disease with high incidence rate, stemming from digestive system tumors. Rectal cancer greatly interferes with the quality of life of patients, and it has a serious impact on their physical and mental health. A large number of studies reported that TGF-α and IGF-II participate in the proliferation and differentiation of cancer cells, and that they play a key role in the occurrence and development of various tumors [12, 13]. IGF-II exists in human tissues and blood. Abnormal expression of IGF-II is found in cancers such as lung cancer and liver cancer. Abnormal expression of IGF-II is an inducing factor for poor prognosis, and its dysregulation promotes cancer cell proliferation [14].

TGF-α belongs to the epidermal growth factor (EGF) family and plays a biological role when combined with EGF receptor. It can activate

proto-oncogenes and transcription factors, promote signal transmission at the cell membrane, participate in proliferation and differentiation of cancer cells, and promote tumor invasion and metastasis. It plays an important role in the occurrence and development of tumors [8].

Some studies have confirmed that IGF-II can inhibit tumors in the initial stage of tumor formation. After the growth of a tumor, IGF-II has a reverse effect, promoting the increase of blood vessels and cancer cells, and thus the immune function is disordered or lost [15]. IGF-II receptors consist of IGF-1R and IGF-2R. IGF-1R is an isomeric tetramer with tyrosine kinase activity formed by the cleavage of a precursor protein. It is necessary for cell growth and has the function of promoting cell division and proliferation. IGF-2R mainly participates in the transportation of lysosomal enzymes in cells, and has tumor inhibition effects. Loss of IGF-2R expression or dysfunction may lead to an increase in IGF-2 concentration in local tissues. IGF-2 binding to IGF-1R activates the growth signal pathway in cells, thus promoting cell proliferation and differentiation [9]. The decrease of IGF-2R expression not only increases the growth rate of cultured cells *in vitro*, but also increases the growth rate of xenotransplantation of tumors *in vivo*, so the expression of IGF-II is closely related to the occurrence and development of tumors [16].

This study found that the levels of serum TGF-α and IGF-II were the lowest in normal group, the second lowest in the rectal polyp group, and the highest in rectal cancer group. The levels of TGF-α and IGF-II in patients with rectal cancer tumors greater than 5 cm were higher than those in patients with rectal cancer tumors of less than 5 cm. TGF-α and IGF-II were the highest in Dukes C stage, second highest in B stage, and the lowest in A stage. Dukes staging standards can be used for grading treatment of rectal cancer tissue according to TGF-α level, Gleason score, clinical staging and lymph node metastasis. Other treatment methods such as chemotherapy can be used as soon as possible to improve the patient's condition and prolong the patient's survival time [17]. Some studies have confirmed that the expression of TGF-α in patients with rectal cancer categories C1 and B2 was significantly higher than TGF-α in patients with rectal cancer categories A and B1, and the negative regulation of TGF-α in disease progression is one of the reasons that promotes tumor growth [18].

This study found that the levels of TGF-α and IGF-II were the highest in patients with lymph node metastasis, and lowest in patients with high differentiation; the second highest in patients with medium differentiation tumor, and the highest in patients with low differentiation. Detection of TGF-α and IGF-II alone can be used as predictive indicators for rectal cancer in the elderly. Combined detection of TGF-α and IGF-II has high predictive and therapeutic value for rectal cancer. TGF-α belongs to the epidermal growth factors, which can activate proto-oncogenes and transcription factors, promote cell membrane signaling, participate in cancer cell proliferation and differentiation, and promote tumor infiltration and metastasis. It has been reported that IGF-II and TGF-α increase most clearly when digestive tract tumors occur. IGF-II is a single-chain polypeptide with a similar structure to insulin [19]. It can combine with the IGF-II receptor, inhibit apoptosis of tumor cells by inhibiting intracellular signal transduction, and promote the process of cell mitosis. It also has a positive effect on proliferation and differentiation of tumor cells [20, 21]. Therefore, combined detection of TGF-α and IGF-II is of great value for the prediction and treatment of rectal cancer.

To sum up, the expression levels of TGF-α and IGF-II play an important role in the development of rectal cancer. Over-expression of TGF-α and IGF-II may be an important reason for the aggravation of rectal cancer patients. There are still some certain deficiencies in the research process. Due to the limitation of time, no large amount of sample data has been collected. More methods should be used for research in future experiments. TGF-α and IGF-II are helpful to judge the staging, tumor size and lymph node metastasis of elderly patients with rectal cancer and have important value in the treatment and prediction of rectal cancer.

Disclosure of conflict of interest

None.

Address correspondence to: Xiangdong Zhang, Department of Hepatobiliary Surgery, Laiyang Central Hospital, No.111 Changshan Road, Yantai

265200, Shandong Province, China. Tel: +86-0535-7232223; Fax: +86-0535-7232223; E-mail: zhangxiangdong07h8@163.com

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