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Value of preoperative enhanced multi−slice spiral CT scan for judging TNM staging of gastric cancer as well as its relationship with tumor marker and proliferation molecule expression

Ai−Jun Wu[1]✉, Zhen−Xian Zhang[2]

[1]*Radiology Department, the People's Hospital of Ansai County Yan'an City Shaanxi Province, Yan'an City, Shaanxi Province, 717400, China*
[2]*CT Diagnosis Department, Yan'an People's Hospital of Shaanxi Province, Yan'an City, Shaanxi Province, 716000, China*

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ABSTRACT

Objective: To study the value of preoperative enhanced multi-slice spiral CT scan for judging TNM staging of gastric cancer as well as its relationship with tumor marker and proliferation molecule expression. **Methods:** A total of 135 patients with gastric cancer who received surgical resection in our hospital between May 2012 and October 2015 were selected as the research subjects, preoperative enhanced multi-slice spiral CT scan was conducted to judge TNM staging, and serum was collected to determine the content of tumor markers; tumor tissue was collected after operation to determine the content of cytokines and pro-proliferation molecules. **Results:** CEA, CA199, CA153, CA125 and CA724 content in serum as well as TGF β 1, TGF β 2, VEGF, FGF2, PTP1B, PIK3CD, Survivin, Ezrin and YAP content in gastric cancer tissue of patients with TNM II, III and IV stage gastric cancer were significantly higher than those of patients with TNM I stage; CEA, CA199, CA153, CA125 and CA724 content in serum as well as TGF β 1, TGF β 2, VEGF, FGF_2, PTP1B, PIK3CD, Survivin, Ezrin and YAP content in gastric cancer tissue of patients with TNM III and IV stage gastric cancer were significantly higher than those of patients with TNM II stage; CEA, CA199, CA153, CA125 and CA724 content in serum as well as TGF β 1, TGF β 2, VEGF, FGF_2, PTP1B, PIK3CD, Survivin, Ezrin and YAP content in gastric cancer tissue of patients with TNM IV stage gastric cancer were significantly higher than those of patients with TNM III stage. **Conclusions:** TNM staging of gastric cancer decided by preoperative enhanced multi-slice spiral CT scan has good consistency with the content of tumor markers in serum and proliferation molecules in tumor lesion.

1. Introduction

Gastric cancer is the malignant tumor with the highest incidence in our country, and setting up effective treatment according to the condition can effectively improve the prognosis and prolong survival time of patients. Tumor TNM staging is the standard to judge gastric cancer progression, and preoperative accurate assessment of TNM staging is able to provide basis for the establishment of reasonable therapy. Multi-slice spiral CT is the imaging examination method developed in recent years, is with high resolution and can clearly show that the tumor lesion size, infiltration depth and lymph node metastasis[1,2]. At present, more and more clinical scholars have used preoperative multi-slice spiral CT examination to determine the TNM staging of tumor, but there is still no clear report about the correlation between TNM staging evaluated by multi-slice spiral CT and tumor malignancy-related molecules. In the following study, the value of preoperative enhanced multi-slice spiral CT scan for judging TNM staging of gastric cancer as well as its relationship with tumor marker and proliferation molecule expression was analyzed.

✉Corresponding author: Ai-Jun Wu, Radiology Department, the People's Hospital of Ansai County, Yan'an City, Shaanxi Province, 717400, China.
Tel: 13892101966
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2. Materials and methods

2.1. Research subjects

A total of 135 patients who were diagnosed with gastric cancer in our hospital between May 2012 and October 2015 were selected as the research subjects, and all patients received surgical treatment, were diagnosed with gastric cancer by postoperative pathological examination and received preoperative triple-phase enhanced multi-slice spiral CT scan. The included patients completed the preoperative examination and then received surgical resection, 118 cases received radical operation for gastric cancer and 17 cases received palliative surgery, including 89 male cases and 46 female cases that were (59.5±7.6) years old.

2.2. Multi-slice spiral CT scan

Siemens SOMATOM Emotion16 CT machine was used for inspection, patients received intramuscular injection of anisodamine 20 mg before inspection, then accepted CT scan with the range from 2-3 cm above diaphragm to umbilical level, and received injection of iohexol 80-100 mL with flow rate of 3.0 mL/s by cubital vein after the scope of enhanced scan was determined, the trigger threshold was set to 100 Hu, arterial phase, portal venous phase and equilibrium phase were started, scanning slice thickness was 5.0 mm, slice distance was 5.0 mm, collimation width was 16 mm 0.6 mm and matrix was 512×512, and TNM staging was judged after reconstruction: (1) T staging: those confined to the mucosa and submucosa were at T1, those infiltrating muscular layer or serous layer were at T2, those breaking through serous layer but not involving the surrounding tissues were at T3 and those breaking through the serous layer and invading surrounding tissues were at T4; (2) N staging: those without lymph node metastasis were at N0, those with lymph node metastasis within 3cm from the lesions were at N1 and those with lymph node metastasis more than 3 cm from the lesions were at N2; (3) M staging: those without distant metastasis were at M0 and those with distant metastasis were at M1. TNM staging was comprehensively judged according to the T staging, N staging and M staging.

2.3. Detection of tumor marker content in serum

A total of 5 mL of peripheral venous blood was collected from patients with gastric cancer after admission and centrifuged at 3 000 r/min to separate serum, and electrochemical luminescence kit was used to detect carcinoembryonic antigen (CEA), carbohydrate antigen CA199, CA153, CA125 and CA724 content.

2.4. Detection of proliferation molecule expression in tumor lesion

After surgical resection, tumor lesion was collected from patients with gastric cancer and divided into two, one was added in protein lysis buffer to extract protein samples, and enzyme-linked immunosorbent assay kit was used to detect transforming growth factor β 1 (TGF β 1), TGF β 2, vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF_2) content; the other was added in Trizol lysis buffer to extract the RNA, and fluorescent quantitative PCR kit was used to detect *PTP1B, PIK3CD, Survivin* and *Ezrin* mRNA levels.

2.5. Statistical methods

SPSS20.0 software was used to input and analyze data, measurement data analysis between two groups was performed by *t* test and $P<0.05$ indicated statistical significant differences.

3. Results

3.1. Tumor marker content in serum of patients with different TNM stages of gastric cancer

CEA, CA199, CA153, CA125 and CA724 content in serum of patients with TNM II, III and IV stage gastric cancer were significantly higher than those of patients with TNM I stage; CEA, CA199, CA153, CA125 and CA724 content in serum of patients with TNM III and IV stage gastric cancer were significantly higher than those of patients with TNM II stage; CEA, CA199, CA153, CA125 and CA724 content in serum of patients with TNM IV stage gastric cancer were significantly higher than those of patients with TNM III stage ($P<0.05$) (Table 1).

3.2. Cytokine content in gastric cancer tissues with different TNM stages

TGF β 1, TGF β 2, VEGF and FGF_2 content in gastric cancer tissues with TNM II, III and IV stage were significantly higher than those in tissues with TNM I stage; TGF β 1, TGF β 2, VEGF and FGF_2 content in gastric cancer tissues with TNM III and IV stage were significantly higher than those in tissues with TNM II stage; TGF β 1, TGF β 2, VEGF and FGF_2 content in gastric cancer tissues with TNM IV stage were significantly higher than those in tissues with TNM III stage ($P<0.05$) (Table 2).

3.3. Pro-proliferation molecule expression in gastric cancer tissues with different TNM stages

PTP1B, PIK3CD, Survivin, Ezrin and *YAP* mRNA content in gastric cancer tissues with TNM II, III and IV stage were significantly

higher than those in tissues with TNM I stage; *PTP1B, PIK3CD, Survivin, Ezrin* and *YAP* mRNA content in gastric cancer tissues with TNM III and IV stage were significantly higher than those in tissues with TNM II stage; *PTP1B, PIK3CD, Survivin, Ezrin* and *YAP* mRNA content in gastric cancer tissues with TNM IV stage were significantly higher than those in tissues with TNM III stage (P<0.05) (Table 3).

4. Discussion

TNM staging of gastric cancer can reflect the progression of tumor, and accurate judgment of TNM can provide reference for the evaluation of lesion resectability as well as disease prognosis and outcome. Enhanced multi-slice spiral CT scan is the high-resolution CT scan method developed in recent years, and it can clearly show the tumor lesion and surrounding tissue infiltration, which provides the basis for the judgment of the TNM staging[3]. In order to make clear the correlation between the TNM staging judged by enhanced multi-slice spiral CT scan and malignant tumor progression, serum levels of tumor markers were compared among patients with different TNM stages of gastric cancer in the study. Tumor markers are a type of active substances synthesized and secreted by cancer cells or produced after the body responds to cancer cells, and they are directly related to the degree of tumor load[4,5]. CEA, CA199, CA153, CA125 and CA724 are the common clinical tumor markers for gastric cancer, and the increase of their serum content is consistent with the growth of tumor tissue[6-8]. In the study, analysis of the serum content of above tumor markers showed that the higher the TNM staging of gastric cancer, the higher the CEA, CA199, CA153, CA125 and CA724 content in serum. This means that the TNM staging of gastric cancer decided by preoperative enhanced multi-slice spiral CT scan has good consistency with the increase of serum tumor marker content and can reflect the degree of load in gastric cancer.

In the development of gastric cancer, a variety of cytokines in local lesions are involved in the regulation of cell growth, extracellular matrix remodeling, angiogenesis and other processes, and then promote the growth of gastric cancer tissue. TGF β 1 and TGF β 2 are the important members of the TGF β family, and can promote the cellular epithelial mesenchymal transition as well as epithelial phenotype transition to mesenchymal phenotype, which make cells obtain stronger movement function and infiltrate towards the surrounding tissue[9,10]; VEGF is a cytokine that can promote endothelial cell proliferation, and lymphatic endothelial cells and vascular endothelial cells can proliferate under the stimulation of VEGF and then form new lymph vessels and blood vessels, which provide favorable conditions for the hematogenous metastasis and lymphatic metastasis of cancer cells[11,12]; FGF_2 itself has a certain effect on promoting lymphangiogenesis, and can also induce and promote local cells to secrete VEGF and indirectly play a role in promoting angiogenesis and lymphangiogenesis[13]. In the study, the analysis of the content of these cytokines in gastric cancer tissues with different TNM stages showed that the higher the TNM staging of gastric cancer, the higher the TGF β 1, TGF β 2, VEGF and FGF_2 content in lesion tissues. This means that the TNM staging of gastric

Table 1

Comparison of tumor marker content in serum among patients with different TNM stages of gastric cancer.

Groups	Case No.	CEA (ng/mL)	CA199 (U/mL)	CA153 (U/mL)	CA125 (U/mL)	CA724 (U/mL)
TNM I stage	26	30.35±5.42	63.35±9.34	29.45±3.65	38.65±5.51	13.25±2.13
TNM II stage	42	44.23±6.75◇	81.54±9.76◇	40.23±5.67◇	55.32±6.86◇	17.86±2.51◇
TNM III stage	38	58.92±7.46◇◆	97.86±10.34◇◆	56.15±7.83◇◆	66.13±9.55◇◆	23.14±3.29◇◆
TNM IV stage	29	79.15±8.94◇◆△	135.75±19.36◇◆△	83.34±9.53◇◆△	92.32±10.35◇◆△	32.36±4.41◇◆△

◇: compared with TNM I stage, P<0.05; ◆: compared with TNM II stage, P<0.05; △: compared with TNM III stage, P<0.05.

Table 2

Comparison of cytokine content among gastric cancer tissues with different TNM stages (ng/mg total protein).

Groups	Case No.	TGF β 1	TGF β 2	VEGF	FGF_2
TNM I stage	26	5.38±0.77	3.65±0.51	10.35±1.42	2.32±0.35
TNM II stage	42	8.14±0.94◇	5.73±0.77◇	15.64±1.87◇	3.88±0.54◇
TNM III stage	38	11.34±1.45◇◆	7.69±0.84◇◆	22.36±3.26◇◆	5.19±0.73◇◆
TNM IV stage	29	14.54±2.14◇◆△	9.14±1.16◇◆△	31.43±4.38◇◆△	6.72±0.92◇◆△

◇: compared with TNM I stage, P<0.05; ◆: compared with TNM II stage, P<0.05; △: compared with TNM III stage, P<0.05.

Table 3

Comparison of pro-proliferation molecule expression among gastric cancer tissues with different TNM stages (/ β *-actin*).

Groups	Case No.	*PTP1B*	*PIK3CD*	*Survivin*	*Ezrin*	*YAP*
TNM I stage	26	1.05±0.14	1.08±0.13	1.03±0.11	0.94±0.12	0.98±0.09
TNM II stage	42	1.68±0.22◇	1.62±0.19◇	1.57±0.17◇	1.77±0.20◇	1.52±0.18◇
TNM III stage	38	2.17±0.29◇◆	2.24±0.27◇◆	1.93±0.23◇◆	2.35±0.31◇◆	1.97±0.24◇◆
TNM IV stage	29	2.94±0.43◇◆△	3.17±0.39◇◆△	2.78±0.35◇◆△	3.31±0.44◇◆△	2.54±0.32◇◆△

◇: compared with TNM I stage, P<0.05; ◆: compared with TNM II stage, P<0.05; △: compared with TNM III stage, P<0.05.

cancer decided by preoperative enhanced multi-slice spiral CT scan has good consistency with the increase of pro-growth cytokine content in lesion tissues and can reflect the invasive growth of cancer cells as well as lymphangiogenesis and angiogenesis.

A large number of new blood vessels in gastric cancer lesions not only provide a direct pathway for the hematogenous metastasis of cancer cells, but also provide the nutrients for the proliferation of cells in lesions and are conducive to cell proliferation. PTP1B, PIK3CD, Survivin, Ezrin and YAP are the pro-proliferation molecules that have regulatory effect on gastric cancer cell proliferation. Both PTP1B and PIK3CD can promote downstream molecule phosphorylation to induce cell proliferation, and *in vitro* studies have confirmed that excessively expressing PTP1B and PIK3CD can promote gastric cancer cell proliferation activity[14,15]; Survivin belongs to anti-apoptosis protein family, and it can not only inhibit the cascade mediated by Caspase-3 and Caspase-7 to block apoptosis, but can also inhibit the cell cycle arrest effect mediated by p21 to promote cell proliferation[16,17]; Ezrin is a kind of cytoskeleton cross linker protein that can activate the expression of YAP in the Hippo pathway to promote cell proliferation[18]. In the study, the analysis of the content of above pro-proliferation molecules in gastric cancer tissues with different TNM stages showed that the higher the TNM staging of gastric cancer, the higher the *PTP1B, PIK3CD, Survivin, Ezrin* and *YAP* mRNA content in lesion tissues. This means that the TNM staging of gastric cancer decided by preoperative enhanced multi-slice spiral CT scan has good consistency with the increase of pro-proliferation molecule content in lesion tissues and can reflect the proliferation activity of cancer cells.

To sum up, TNM staging of gastric cancer decided by preoperative enhanced multi-slice spiral CT scan has good consistency with the content of tumor markers in serum and proliferation molecules in tumor lesion.

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