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Relationship of preoperative gastric cancer CT enhancement ratio and perfusion parameters with serum tumor marker levels and proliferation molecule expression in tumor lesions

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ABSTRACT

Objective: To study the relationship of preoperative gastric cancer CT enhancement ratio and perfusion parameters with serum tumor marker levels and proliferation molecule expression in tumor lesions. **Methods:** A total of 68 patients with gastric cancer treated in the Second Hospital of Yulin City between May 2012 and May 2016 were chosen as observation group and sub-divided into early and middle gastric cancer group (n=41) and advanced gastric cancer group (n=27) according to the tumor stage; 50 patients diagnosed with benign gastric diseases in our hospital during the same period were selected as benign gastric lesion group. CT enhancement rate and perfusion parameters of three groups of patients were detected by CT scan, serum tumor marker levels were evacuated by enzyme-linked immunosorbent assay (ELISA), and the proliferation gene mRNA expression levels were detected by RT-PCR method. **Results:** CER, AF, BV and CL levels of advanced gastric cancer group were higher than those of early and middle gastric cancer group and benign gastric lesion group; serum CA72-4, CA19-9, CA125 and CEA contents of advanced gastric cancer group were higher than those of early and middle gastric cancer group and benign gastric lesion group; CADM1, miRNA-34a and Cystatin M mRNA expression in tissue of advanced gastric cancer group were lower than those of early and middle gastric cancer group and benign gastric lesion group while Survivin and I2PP2A mRNA expression were higher than those of early and middle gastric cancer group and benign gastric lesion group. The Pearson test showed that the CT enhancement rate and perfusion parameters in patients with gastric cancer are directly correlated with the serum tumor marker levels and the proliferation gene expression in tumor lesions. **Conclusion:** Preoperative gastric cancer CT enhancement rate and perfusion parameters are directly related to the tumor malignancy, and can be used as a reliable method for the long-term tumor diagnosis and malignancy judgment.

1. Introduction

Gastric cancer is one of the most common malignant tumor diseases, early diagnosis and tumor resection can obtain good prognosis, but the current clinical early diagnosis rate of gastric cancer is not high, and how to early screen and diagnose gastric cancer has become the focus and hotspot of current clinical research[1,2]. Gastroscope and histopathologic examination are the gold standards for diagnosis of gastric cancer, but they are invasive and time-consuming, and can't become the routine examination methods. CT perfusion imaging is the method that when contrast agent is quickly intravenously injected, CT scan is continuously conducted in the area-of-interest in order to obtain time-density curve and calculate perfusion parameters[3,4]. Current study has shown that CT perfusion parameter values are associated with the malignant degree of liver cancer, colon cancer and other malignant tumors, but there is less research in gastric cancer. In the study, CT perfusion imaging technique was applied in patients with gastric cancer in our hospital, and the correlation of CT enhancement rate and perfusion parameters with tumor malignancy was preliminarily discussed, now reported as follows:

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2. Information and methods

2.1 General information

After approved by the hospital ethics committee, 68 patients with gastric cancer treated in the Second Hospital of Yulin City between May 2012 and May 2016 were chosen as observation group and sub-divided into early and middle gastric cancer group (n=41) and advanced gastric cancer group (n=27) according to the tumor stage; 50 patients diagnosed with benign gastric diseases in our hospital during the same period were selected as benign gastric lesion group. Inclusion criteria were as follows: (1) diagnosed by clinical pathology; (2) ⩽80 years old; (3) without previous gastric surgery; (4) without operation history3 months prior to admission; (5) signing informed consent; (6) with complete clinical data, and participating in the entire study. Exclusion criteria were as follows: (1) with metastatic gastric cancer; (2) with primary malignant tumors of other organs; (3) with severe heart, liver and kidney dysfunction; (4) associated with systemic infectious diseases; (5) allergic to contrast agents.

Early and middle gastric cancer group included 23 male cases and 18 female cases, they were 43-79 years old and (64.27±7.09) years old in average, and the body weight was 47-81 kg and (60.16±8.95) kg in average; advanced gastric cancer group included 15 male cases and 12 female cases, they were 45-78 years old and (64.85±8.07) years old in average, and the body weight was 46-78 kg and (63.27±8.15) kg in average; benign gastric lesion group included 26 male cases and 24 female cases, they were 41-76 years old and (61.53±8.06) years old in average, and the body weight was 48-83 kg and (69.72±8.53) kg in average. Three groups of patients were not statistically different in age, gender and weight distribution (P>0.05), and they were comparable.

2.2 CT scan parameters

Three groups of patients were fasting for solids and liquids for 6-8 h before examination and drank 1 200 mL water in one time 5 min before scanning to fill the gastric cavity. 64-slice helical CT scanner was used to scan from xiphoid to the navel, and the scanning parameters were: slice thickness 1mm, pitch 1 mm and voltage 120 kV. Routine scanning was conducted to determine the lesion scope, then body perfusion mode was used to inject 35 mL of contrast agent iopamidol (350 mgI/mL rate 5 mL/s) and 30 mL of saline through cubital vein, the images were transmitted to the workstation to obtain contrast enhancement ratio (CER) as well as the perfusion parameters: arterial flow (AF), blood volume (BV) and clearance (CL).

2.3 Serum tumor markers

2 mL of fasting peripheral venous blood was collected from three groups of patients, let stand at room temperature for 30 min and centrifuged at 4 ℃ at low speed to get supernatant, and enzyme-linked immunosorbent assay (ELISA) was used to determine the levels of tumor markers in it, including carbohydrate antigen 72-4 (CA72-4), carbohydrate antigen 19-9 (CA19-9), carbohydrate antigen 125 (CA125) and carcinoembryonic antigen (CEA).

2.4 Proliferation gene mRNA expression

Gastric lesion tissue samples were collected from three groups of patients under gastroscope, and RT-PCR method was used to determine proliferation genes CADM1, Cystatin M, miRNA-34a, Survivin and I2PP2A mRNA expression in them. The mRNA expression of benign gastric lesion group was set to 100 to calculate the mRNA expression of the other two groups accordingly.

2.5 Statistical methods

Data in the study was input in software SPSS 20.0, measurement data was in terms of mean ± standard deviation (Mean ± SD) and comparison between groups was by group t test; count data was in terms of percentage, comparison between groups was by chi-square test, correlation analysis was by Pearson test and P<0.05 indicated statistical significance in differences.

3. Results

3.1 CT scan parameters

Differences in CT scan parameters CER, AF, BV and CL levels were statistically significant among three groups of patients (P<0.05). CER, AF, BV and CL levels of early and middle gastric cancer group and advanced gastric cancer group were higher than those of benign gastric lesion group, CER, AF, BV and CL levels of advanced gastric cancer group were higher than those of early and middle gastric cancer group, and differences were statistically significant (P<0.05), shown in Table 1.

Table 1.

Comparison of CT scan parameters among three groups of patients.

Groups	n	CER	Perfusion parameters		
			AF [mL/(100 mL min)]	BV (mL/100 mL)	CL(L/s)
Advanced gastric cancer	41	0.84±0.09$^{*\#}$	121.74±15.85$^{*\#}$	20.63±2.88$^{*\#}$	5.71±0.68$^{*\#}$
Early and middle gastric cancer	27	0.71±0.08*	108.62±11.14*	19.17±2.09*	4.28±0.59*
Benign gastric lesion	50	0.57±0.06	95.37±9.09	18.94±1.76	3.72±0.41

Note: compared with benign gastric lesion group, $^{*}P$<0.05; compared with early and middle gastric cancer group, $^{\#}P$<0.05.

3.2 Serum tumor markers

Differences in serum tumor markers CA72-4, CA19-9, CA125 and CEA contents were statistically significant among three groups of patients (P<0.05). Serum CA72-4, CA19-9, CA125 and CEA contents of early and middle gastric cancer group and advanced gastric cancer group were higher than those of benign gastric lesion group, serum CA72-4, CA19-9, CA125 and CEA contents of advanced gastric cancer group were higher than those of early and middle gastric cancer group, and differences were statistically significant (P<0.05), shown in Table 2.

3.3 Proliferation gene mRNA expression

Differences in proliferation genes CADM1, Cystatin M, miRNA-34a, Survivin and I2PP2A mRNA expression in lesion tissue were statistically significant among three groups of patients (P<0.05). CADM1, miRNA-34a and Cystatin M mRNA expression in tissue of early and middle gastric cancer group and advanced gastric cancer group were lower than those of benign gastric lesion group while Survivin and I2PP2A mRNA expression were higher than those of benign gastric lesion group; CADM1, miRNA-34a and Cystatin M mRNA expression in tissue of advanced gastric cancer group were lower than those of early and middle gastric cancer group while Survivin and I2PP2A mRNA expression were higher than those of early and middle gastric cancer group, and differences were statistically significant (P<0.05), shown in Table 3.

3.4 Correlation analysis

Correlation analysis between CT scan parameters and disease severity in patients with gastric cancer was as follows: Pearson test showed that the CT scan parameters CER, AF, BV and CL levels in patients with gastric cancer were positively correlated with the serum tumor markers CA72-4, CA19-9, CA125 and CEA levels; they were negatively correlated with proliferation genes CADM1, miRNA-34a and Cystatin M mRNA expression, and positively correlated with Survivin and I2PP2A mRNA expression (P<0.05).

4. Discussion

CT perfusion imaging technology has been widely used in the screening and metastasis judgment of liver cancer, renal cancer, colorectal cancer and other malignant tumors in recent years, and compared with gastroscopy, it has the advantages such as simple operation and less pain, so it is popular with clinical physicians and patients[5,6]. At present, there is not much research on the application of CT perfusion imaging in gastric cancer, the correlation between CT perfusion parameters and gastric cancer grade is also uncertain, and it is used as the main research objective and specifically elaborated in the study. Contrast enhancement rate (CER), arterial flow (AF), blood volume (BV) and clearance (CL) are the main parameters of CT perfusion imaging, and their levels can directly reflect the status of tumor angiogenesis[7]. Tumor tissue is mainly from the capillary network-abundant glandular tissue, and long contrast agent stay in the blood vessels causes the elevated CER levels; AF and BV are the most reliable parameters to evaluate tumor vessels, and along with the vigorous tumor angiogenesis, their levels also rise; CL can reflect the vascular structural integrity, new tumor vessels are less mature and with incomplete structure and high permeability, so the CL level rises[8]. It was found in the study that compared with benign gastric lesion group, patients with gastric cancer were with higher levels of CT perfusion imaging CER, AF, BV and CL; compared with patients with early and middle gastric cancer, patients with advanced gastric cancer were with even higher CER, AF, BV and CL levels, indicating that there are abnormal levels of CT perfusion imaging parameters in patients with gastric cancer, the abnormal degree is related to the condition of gastric cancer, but the specific correlation remains to be further studied.

Serum tumor marker levels and proliferation gene expression in lesion tissue are the clinical recognized reliable indexes to determine the tumor stage. Carbohydrate antigen 72-4 (CA72-4), carbohydrate antigen 19-9 (CA19-9), carbohydrate antigen 125 (CA125) and carcinoembryonic antigen (CEA) are the broad-spectrum tumor markers and they are abnormally expressed in a variety of malignant tumors[9,10]. CEA level is little in blood circulation of normal adults, and its content increase is closely related to the number of proliferated cancer cells. Both CA19-9 and CA125 belong to carbohydrate tumor markers, and their levels increase in the malignant gastrointestinal tract tumor. The study of CHENG Peng[11] shows that CEA, CA19-9 and CA125 mediate the process of gastric cancer cell falling from the primary lesions and adhering to adjacent tissue. CA72-4 is the marker of the gastrointestinal tract and ovarian tumors, it does not exist in benign tumor or normal human tissue, and it has a very high diagnostic value for the occurrence of malignant

Table 2.

Comparison of serum tumor marker contents among three groups of patients (g/mL).

Groups	n	CA72-4	CA19-9	CA125	CEA
Advanced gastric cancer	41	21.74±2.85$^{*\#}$	45.69±5.12$^{*\#}$	25.73±3.41$^{*\#}$	17.84±2.73$^{*\#}$
Early and middle gastric cancer	27	12.68±1.74*	22.75±2.95*	13.72±1.88*	8.29±0.91*
Benign gastric lesion	50	1.98±0.23	8.93±0.91	8.63±0.97	1.73±0.19

Note: compared with benign gastric lesion group, $^{*}P$<0.05; compared with early and middle gastric cancer group, $^{\#}P$<0.05.

Table 3.

Comparison of proliferation gene mRNA expression in lesion tissue among three groups of patients.

Groups	n	CADM1	Cystatin M	miRNA-34a	Survivin	I2PP2A
Advanced gastric cancer	41	35.72±4.09$^{*\#}$	29.56±3.74$^{*\#}$	37.04±4.52$^{*\#}$	218.64±27.95$^{*\#}$	192.51±23.46$^{*\#}$
Early and middle gastric cancer	27	67.88±7.12*	64.09±7.11*	69.35±7.42*	153.27±18.94*	141.07±18.63*
Benign gastric lesion	50	100.00±9.73	100.00±11.64	100.00±9.84	100.00±9.38	100.00±10.17

Note: compared with benign gastric lesion group, $^{*}P$<0.05; compared with early and middle gastric cancer group, $^{\#}P$<0.05.

tumors. The study of ZHANG Jin-feng[12] confirms that there is high expression of CA72-4 in patients with gastric cancer. In the study, the levels of above tumor markers were detected, and it was found that serum CA72-4, CA19-9, CA125 and CEA contents are generally high in patients with gastric cancer, and CA72-4, CA19-9, CA125 and CEA levels are higher in patients with advanced gastric cancer, confirming that the serum tumor markers are the effective auxiliary means for gastric cancer diagnosis and disease judgment.

The basis of sustained malignant tumor progression is infinite proliferation of tumor cells, and the abnormal expression of related proliferation genes becomes the key to the occurrence and development of the tumors[13,14]. Many studies have confirmed that CADM1 plays the role of the tumor suppressor in different tissues, and CADM1 expression deletion is closely related to the tumor progression and metastasis. Cystatin M belongs to the cysteine protease inhibitor family, and is involved in cell survival, proliferation, differentiation, metastasis and various other processes[15,16]. The study of ZHAO Ya-min[17] shows that Cystatin M can inhibit gastric cancer cell migration ability. miRNA-34a is regulated by the p53 directly, and it has been confirmed that it can inhibit the malignant degree of colorectal cancer, pancreatic cancer and lung cancer. Survivin is a member of the anti-apoptotic protein family, it is only expressed in tumor and embryonic tissue, and highly expressed Survivin can block cell apoptosis and escape the tumor cell identification and removal by the body's immune system[18,19]. Studies have shown that I2PP2A expression in uterus, rectum and other tumor tissues is 2 times and even more of that in normal tissue. The study of ZHANG Rong[20] shows that after I2PP2A gene silence, gastric cancer cell proliferation and migration ability decline. In the study, the above gene mRNA expression levels in gastric lesion tissue were detected, and it was found that compared with benign lesion group, patients with gastric cancer were with lower CADM1, miRNA-34a and Cystatin M mRNA expression, and higher Survivin and I2PP2A mRNA expression in tissue; compared with early and middle gastric cancer group, advanced gastric cancer group were with even lower CADM1, miRNA-34a and Cystatin M mRNA expression, and higher Survivin and I2PP2A mRNA expression. The above results show that the there is abnormal expression of proliferation genes in patients with gastric cancer, and the specific expression levels are directly related to tumor malignancy.

In order to define the judgment value of CT perfusion imaging parameters for malignant degree of gastric cancer, Pearson test was used for analysis in the study, and it was found that CT scan parameters CER, AF, BV and CL levels in patients with gastric cancer were positively correlated with tumor markers CA72-4, CA19-9, CA125 and CEA levels; they were negatively correlated with proliferation genes CADM1, miRNA-34a and Cystatin M mRNA expression, and positively correlated with Survivin and I2PP2A mRNA expression. Thus it is concluded that preoperative gastric cancer CT enhancement rate and perfusion parameters are directly correlated with the tumor malignancy, can be used as the reliable means for long-term tumor diagnosis and malignant degree judgment, and are worthy of popularization and application in clinical practice in the future.

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