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The significance of tumor molecular marker MMP-9 combined with iconography in the staging of esophageal cancer.

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Abstract

Objective: To investigate the significance of tumor molecular marker matrix metallopeptidase 9 (MMP-9) combined with iconography in the staging of esophageal cancer.
Methods: The clinical staging of 108 esophageal careinoma patients were detected by CT image. The protein level of MMP-9 was determined by immunohistochemistry. The correlation of MMP-9 and clinical staging of esophageal careinoma was analyzed.
Results: Positive expression rate of MMP-9 was 60.19% in biopsy tissue of esophageal carcinoma, while 78.00% in patients in stage T3-T4 was higher than that in T1-T2 stage (43.10%, P<0.01). Positive expression rate of MMP-9 in lymph metastasis group (N1) was 90.91%, which was higher than that in non-lymph metastasis group (N0, 43.40%, P<0.01). Positive rate of MMP-9 was 94.12% in clinical III-IV phase, which was higher than that in stage I-II (47.30%, P<0.01). The correlation coefficient were 0.389, 0.496, 0.461 between MMP-9 protein expression and stage T, N, TNM, respectively,and presented positive correlation (P<0.05).
Conclusion: MMP-9 expression has increased in late stage tumor.

Keywords: Esophageal carcinoma, MMP-9, Iconography, Clinical staging.

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Introduction

Esophageal cancer is one of the most common human malignant tumors all over the world. About 300,000 people died of esophageal cancer each year. China has a high incidence of esophageal cancer, leading to death of about 16 million people, accounting for nearly a quarter of all cancer deaths [1]. Early clinical stage is an important factor affecting the prognosis of radiotherapy for esophageal cancer. There is no uniform staging standard of non-surgical treatment for esophageal cancer currently. How to select and formulate reasonable treatment regimen based on the stage of esophageal cancer before treatment to improve the comprehensive treatment efficacy and accurately assess the prognosis and survival, has become the hotspot and difficult problem in today's oncology research [2]. The International Union against Cancer Alliance (UICC) TNM staging criteria is only applied to access the patients after surgical resection. The vast majority of patients in the clinical treatment are already in the late stage, most of whom lose the chance of surgical treatment. In the clinical stage diagnostic of esophageal cancer, the most common diagnostic method is the chest CT scan, which is simple and safe with high security, but still having some limitations [3]. Matrix metallopeptidase 9 (MMP-9), is one member of the zinc-dependent endopeptidases, facilitating the tumor invasion and is closely correlated with tumor metastasis in various cancers, including gastric cancer, prostate cancer, and cervical cancer [4]. However, its correlation with esophageal carcinoma was reported little. With the development of molecular biology, some tumor molecular markers in tumor diagnosis, clinical staging and other aspects occupy an increasingly important position. In this study, the clinical staging of esophageal carcinoma was defined by the technique of CT imaging and the detection of MMP-9 in order to establish the clinical stage of non-surgical treatment.

Materials and Methods

General clinical data

From August 2013 to May 2016, 108 patients with esophageal carcinoma underwent thoracic CT scan before operations were included in this research. All of them were not treated with antitumor therapy before operation, including 58 males and 50 females. The median age was 62 years (ageing from 45 to 79 years old).

Clinical staging criteria of iconography

Clinical T, N stage was judged by CT image-scanning, and clinical stage was confirmed based on TNM staging criteria of UICC [5].

Determination of MMP-9 expression

The expression of MMP-9 protein in esophageal cancer tissues was detected by immunohistochemistry. Rabbit anti-human MMP-9 polyclonal antibody (Wuhan Boster Bioengineering Co., Ltd.) was diluted in 1:20 as primary antibody. Referring to Iseki K criteria's research [6], the staining intensity and the number of positive cells were considered to determine whether the protein was in positive expression.

Statistical analysis

SPSS l7.0 was used for data analysis. χ^2 test was used in counting data analysis, and Spearman rank correlation test was applied in the correlation between protein expression and clinical stage. P<0.05 indicates a statistically significant difference.

Results

The MMP-9 expression in esophageal carcinoma tissues

The positive rate of MMP-9 in esophageal cancer tissues was 60.19% (65/108).

Staging results of esophageal cancer

According to CT images, there were 9, 49, 44 and 6 cases for T1, T2, T3 and T4 phase in 108 cases of patients with esophageal cancer respectively; N0, N1 stage were 53 and 55 cases; UICC International TNM staging I, II, III, IV were 10, 64, 31 and 3 cases.

MMP-9 expression in different clinical stages

In this study, cases in T1, T4 stage and I, IV stage were rare, so the T1 stage was combined with T2 stage, T3 with T4, I with II, III with IV, the correlation between the MMP-9 expression and T, N and TNM staging was analyzed. The results showed the expression of MMP-9 was correlated with the T, N staging. The positive rate of MMP-9 in stage T1~T2 was 43.10%, and the positive rate in stage T3~T4 was 78.00%. The difference was statistically significant (χ^2=12.158, P<0.01). The positive expression rate of MMP-9 in patients without lymph node metastasis (N0) was 43.40% and 90.91% in patients with lymph node metastasis (N1), with statistically significant difference (χ^2=20.322, P<0.01).The expression of MM-P was correlated with TNM staging. The positive expression rate of MMP-9 in stage I to II was 47.30%, and the positive rate in stage III to IV was 94.12%. The difference was statistically significant (χ^2=16.251, P<0.01). The results are shown in Table 1. The results showed a positive correlation (Table 1). The expression of MMP-9 was positively correlated with T, N and TNM staging, and the correlation coefficient r was 0.389, 0.496, and 0.461 respectively (P <0.05) (Table 2).

Table 1. *MMP-9 expression in different clinical stages.*

Clinical Stages	Cases	MMP-9 expression		χ^2	P
		Positive (cases)	Positive (%)	rate	
T staging					
T1-T2	58	25	43.10%	12.158	<0.01
T3-T4	50	39	78.00%		
N Staging					
N0	53	23	43.40%	20.322	<0.01
N1	55	50	90.91%		
TNM					
I-II	74	35	47.30%	16.251	<0.01
II-IV	34	32	94.12%		

Table 2. *The correlation between TNM stage and MMP-9.*

Stage	r value	P value
T	0.389	P<0.05
N	0.496	P<0.05
TNM	0.461	P<0.05

Discussion

Esophageal cancer is an esophageal cancer with high incidence. Its staging is of great significance in improving the clinical efficacy and prognosis of esophageal cancer. With the understanding of the clinical treatment of esophageal cancer in depth, its clinical stage become the tumor hot once again [2]. However, there is no unified staging standard for non-surgical treatment of esophageal cancer. Some scholars have proposedstaging criteria based on CT imaging for the prognosis of esophageal cancer with a good reference value. But the staging criteria are more complex. Clinical application is not convenient. With the development of molecular biology and immunology, tumor molecular markers play an increasingly important role in tumor diagnosis, prognosis, evaluation of drug efficacy, etc. The application of molecular markers in clinical staging is gradually increasing [7,8]. But there is still a lack of system combined esophageal cancer imaging staging with tumor molecular markers staging.

Matrix metalloproteinases (MMPs), also known as matrix factors, are a group of zinc-related metalloproteases that can be divided into collagenases, matrix-degrading enzymes and gelatinases. MMP-9, a member of gelatinasesfamily, is a type of gelatin enzyme to degradetype IV collagen, which is the main component of the basement membrane [9]. Extracellularmatrix (ECM) is composed of basal membrane and interstitial substance, which plays a role as a "wall" in tumor infiltration and metastasis. It is necessary to destroy ECM during the process of tumor metastasis. MMP-9 can degrade and destroy extracellular matrix and basement membrane to make the tumor cells through the defect of the basement membrane infiltrating to the surrounding normal

tissue. The cancer cells escaped from the primary lesion and survived in the cycle, and then adhered to theendothelial cells for transferring target organ for endothelial barrier evasion and degradation of the extracellular matrix, finally growed in the new environment [10]. MMP-9 is overexpressed in a variety of malignancies, including colon, breast, esophageal and gastric carcinoma, and is recognized as an important link in tumor invasion and metastasis [10,11]. Ohashi et al. [12] determined MMP-9 expression in specimens of esophageal squamous cell carcinoma after surgery and found its expression was significantly increasedin cancer tissue, and was significantly correlated tothe depth of tumor invasion, indicating that MMP-9 played a role in invasion and metastasis of esophageal cancer, which may be an important index to reflect the biological behavior and invasion of esophageal carcinoma. It suggests that MMP-9 positive index should be combined with T and N staging of CT image to be the reference standard of esophageal cancer clinical staging.

The positive expression rate of MMP-9 in esophageal cancer tissues was 60.19%, and the expression of MMP-9 in T3~T4 stage, lymph node metastasis N1 stage and clinical III-IV stage was significantly higher than that in corresponding T1~2, N0 and clinical I~II stage. MMP-9 plays an important role in the development of microenvironment for tumor growth, invasion and metastasis. In the later stages of tumor, MMP-9 expression was higher. In this study, we further analyzed the correlation of MMP-9 expression with T stage, N stage, TNM stage, the results demonstrated the expression was positively correlated with the clinical stage of esophageal cancer. T-staging, N staging and TNM staging later, the MMP- 9 protein expression higher. In summary, MMP-9 expression has increased in late stage tumor. It may play an important role in occurrence, development, invasion and metastasis of esophageal cancer. The timely and effective detection of MMP-9 in esophageal cancer tissue are in clinical significance of determination of the degree of invasion of esophageal cancer, lymph node metastasis and prognosis.

Reference

1. Yang X. Epidemiology, Endoscopy and Pathological Features of Esophageal Cancer and Barrett 's esophagus. Southern Medical University 2015.
2. Wang J, Zhuang H, Zhuang H. Advance of clinical staging of esophagus cancer. China Rehab Clin Oncol 2012; 1: 90-92.
3. Shu X, Yang B, Cheng K. Clinical Value of Spiral CT in the Surgical Treatment of esophagus cancer. Anhui Med J 2013; 34: 781-783.
4. Chen S, Liu W, Wang K, Fan Y, Chen J, Ma J, Wang X, He D, Zeng J, Li L. Tetrandrine inhibits migration and invasion of human renal cell carcinoma by regulating Akt/NF-κB/ MMP-9 signaling. PLoS One 2017; 12: e0173725.
5. Talsma K, van Hagen P, Grotenhuis BA, Steyerberg EW, Tilanus HW, van Lanschot JJ, Wijnhoven BP. Comparison of the 6th and 7th Editions of the UICC-AJCC TNM Classification for Esophageal Cancer. Ann Surg Oncol 2012; 19: 2142-2148.
6. Iseki K, Tatsuta M, Uehara H. Inhibition of angiogenesis as a mechanism for inhibition by 1alpha-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 of colon carcinogenesis induced by azoxymethane in Wistar rats. Int J Cancer 1999; 81: 730-733.
7. Yan F, Duan L, Li X. Clinical significance of detection of tumor markers in patients with different stages of lung cancer. Modern J Integrated Traditional Chinese Western Med 2011; 20: 1873-1874.
8. Fei B. Expression of Autophagy Gene Beclin - 1 in Gastric Carcinoma of Different Clinical Stages and Its Clinical Significance. Jilin university 2016.
9. Chen Z, Yao P. MMPs and their correlation with tumor progression. Everybody Health ten-day 2015.
10. De L, Guo L. MMP-9 and Its Relationship with Malignant Tumor. Inner Mongolia Med J 2014; 46: 696-698.
11. Xiao M, Liang Q. MMP-9 in the regulation of malignant tumor expression mechanism. Yanbian Medical College 2015.
12. Ohashi K, Nemoto T, Nakamura K, Nemori R. Increased expression of matrix metalloproteinase 7 and 9 and membrane type 1-matrix metalloproteinase in esophageal squamous cell carcinomas. Cancer 2000; 88: 2201-2209.

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