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Research article

Expression and clinical significance of p75NTR in esophageal squamous cell carcinoma

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Abstract: *Objectives:* To analyze the expression and clinical significance of p75NTR in esophageal squamous cell carcinoma. *Methods:* Sixty patients with esophageal squamous cell carcinoma who underwent surgical resection in our hospital between January 2017 and January 2018 were selected as the study subjects. The content of the study was in accordance with medical ethics and approved by the medical ethics committee, and patients understood and signed an informed consent form. The clinical data of all patients were analyzed retrospectively. The positive rate of p75NTR in lymph node metastasis-positive patients, lymph node metastasis-negative patients and patients with invasion of the muscle layer was detected and statistically analyzed. *Results:* Lymph node metastasis-positive patients had a p75NTR-positive rate of 100.00% (30/30), which was significantly higher than that of lymph node metastasis-negative patients (20.00% (6/30)) ($P < 0.05$) The p75NTR-positive rate in patients with infiltration of the muscular layer was 73.33% (20/30), which was significantly higher than that of patients with infiltration of the whole layer (43.33% (13/30) ($P < 0.05$). *Conclusions:* The high expression of p75NTR in esophageal squamous cell carcinoma tissue can indicate the invasion depth of the cancerous tissue and lymph node metastasis, and the clinical introduction of the p75NTR index can be the basis for an effective prognosis prediction in patients with esophageal squamous cell carcinoma.

Keywords: esophageal squamous cell carcinoma; p75NTR; expression; clinical significance

1. Introduction

A large number of reports have shown that China is a country with a high incidence of esophageal cancer, and the incidence of esophageal cancer ranks fourth among all kinds of malignant tumors. The most common histological type is esophageal squamous cell carcinoma [1]. A typical symptom of esophageal squamous cell carcinoma is progressive dysphagia. Patients with esophageal squamous cell carcinoma have difficulty swallowing dry food at first, followed by semiliquid food, and finally, water and saliva cannot be swallowed. Patients often spit out mucus (sputum) and have hypopharyngeal saliva and esophageal secretions. The patients gradually become thin, dehydrated and weak. Persistent chest or back pain is a sign of advanced symptoms. Cancer has invaded extraesophageal tissue. When the inflammation and edema caused by the obstruction of cancerous tumors subsides temporarily or part of the cancerous tumor falls behind, the symptoms of obstruction can be temporarily alleviated, often mistaken for improvement. Horner's syndrome can occur if cancer invades the larynx to regurgitate and compress the cervical sympathetic ganglion or invades the trachea and bronchus to form esophageal, tracheal or bronchial fistula. When swallowing water or food, it can cause severe cough and respiratory infection. Relevant data show that the most critical factor affecting the survival and prognosis of esophageal squamous cell carcinogenesis patients is the invasion and metastasis of cancer cells. In esophageal squamous cell carcinoma, p75 neurotrophic factor receptor (p75ntr) is expressed in candidate CSC populations, showing high tumorigenicity and chemotherapeutic resistance [2]. Recently, it was reported that p75NTR plays an important role in the judgment of the tissue properties of esophageal squamous cell carcinoma [3].

2. Materials and method

2.1. General information

Sixty patients with esophageal squamous cell carcinoma who underwent surgical resection in our hospital between January 2017 and January 2018 were selected as the study subjects. All patients were diagnosed with selective primary carcinoma by an imaging examination, and regional lymph nodes were resected. The content of the study was in accordance with and approved by medical ethics, and all patients understood and signed an informed consent form. This research fully followed the principles of the "BMA Helsinki Convention" and was carried out with the participation and supervision of medical experts. Clinical data of all patients were retrospectively analyzed. The age of 60 patients (43 male patients, 17 female patients) ranged from 35 to 70 years, and patients 50 years old were evaluated. This study was approved by the ethics committee. Patients signed an informed consent form and enjoyed the right to all information.

2.2. Methods

Patients were divided into the following groups based on the lymph node metastasis classification: A lymph node metastasis-positive group (n = 30) and a lymph node metastasis-negative group (n = 30). Among them, 30 patients were lymph node metastasis-positive, and 30 patients were lymph node metastasis-negative. Patients were also divided into the following groups based on the infiltration depth: an infiltration depth of the muscular layer group (n = 30) and

an infiltration depth of the whole layer group (n = 30). Among them, 30 patients had muscle infiltration, and 30 patients had full-thickness infiltration.

HE staining was used to determine positive or negative lymph node metastasis in each group. Immunohistochemistry was used to detect the expression of the p75NTR protein in all patients. The HE staining method was performed as follows: fresh tissue samples were fixed overnight in 4% polyformaldehyde, dehydrated with a gradient concentration of sucrose solution, embedded in paraffin, and cut into 4 micron slices. Slices were floated in 40 ℃ warm water in a spreader to flatten the tissue. The tissue was placed onto slides and baked in an oven at 60 ℃. The wax was moved, and the samples were stored at room temperature. The paraffin sections were dewaxed with water. The nucleus and cytoplasm were stained with hematoxylin and eosin and then dehydrated and sealed. Finally, a microscopic examination was performed.

Immunohistochemical methods were performed as follows: The paraffin blocks were cut into 4-micron thick sections. First, the paraffin blocks were dewaxed and hydrated. Second, the antigen was repaired by the microwave method. Third, is the blocks were treated with 3% hydrogen peroxide solution and sealed. Tissue slices were incubated overnight at 4 ℃ in an antidilution solution after closure. After the first resistance treatment, the slices were washed and incubated at room temperature for 1 hour with a diluent of second resistance. DAB was used to color the slices, and then hematoxylin was used to restain the slices. The specimens were observed under a microscope.

To evaluate the quality of life of patients, the ADL score, physical function, psychological function and social function were assessed.

2.3. Observation index

The expression of p75NTR was observed as brown and yellow in immunohistochemical images. ImageJ software was used to quantify the expression of p75NTR. Pathologists read the pathology of the HE stains to determine lymph node metastasis. The positive rate of p75NTR in lymph node metastasis-positive patients, lymph node metastasis-negative patients and patients with invasion of the muscle layer was determined and statistically analyzed [4].

2.4. Statistical treatment

SPSS version 19.0 was used for data processing. Measurement data are expressed as the mean ± standard deviation (based on the t test), and count data are expressed as the % (based on the x2 test). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Lymph node metastasis

Lymph node metastasis-positive patients had a p75NTR positive rate of 100.00% (30/30), which was significantly higher than that of the lymph node metastasis-negative patients (20.00% (6/30)) ($P < 0.05$) (Figure 1and Figure 2). The results of p75NTR detection in the two groups are shown in Table 1.

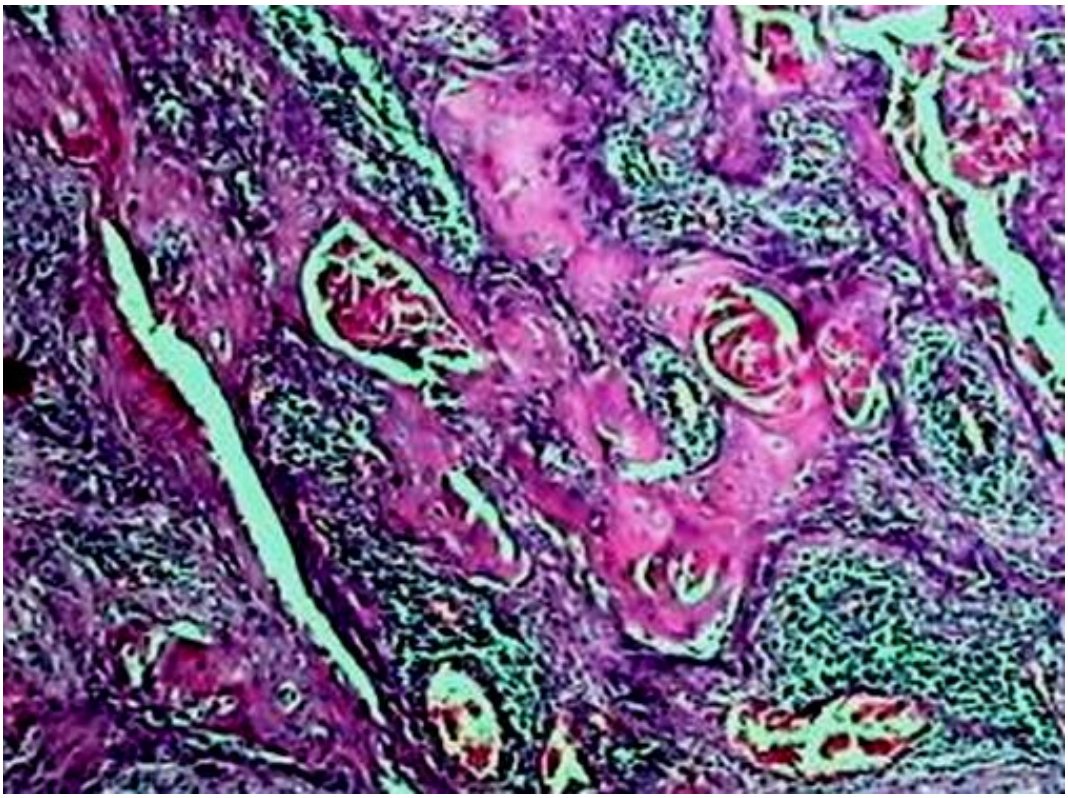

Figure 1. Lymph node metastasis-positive.

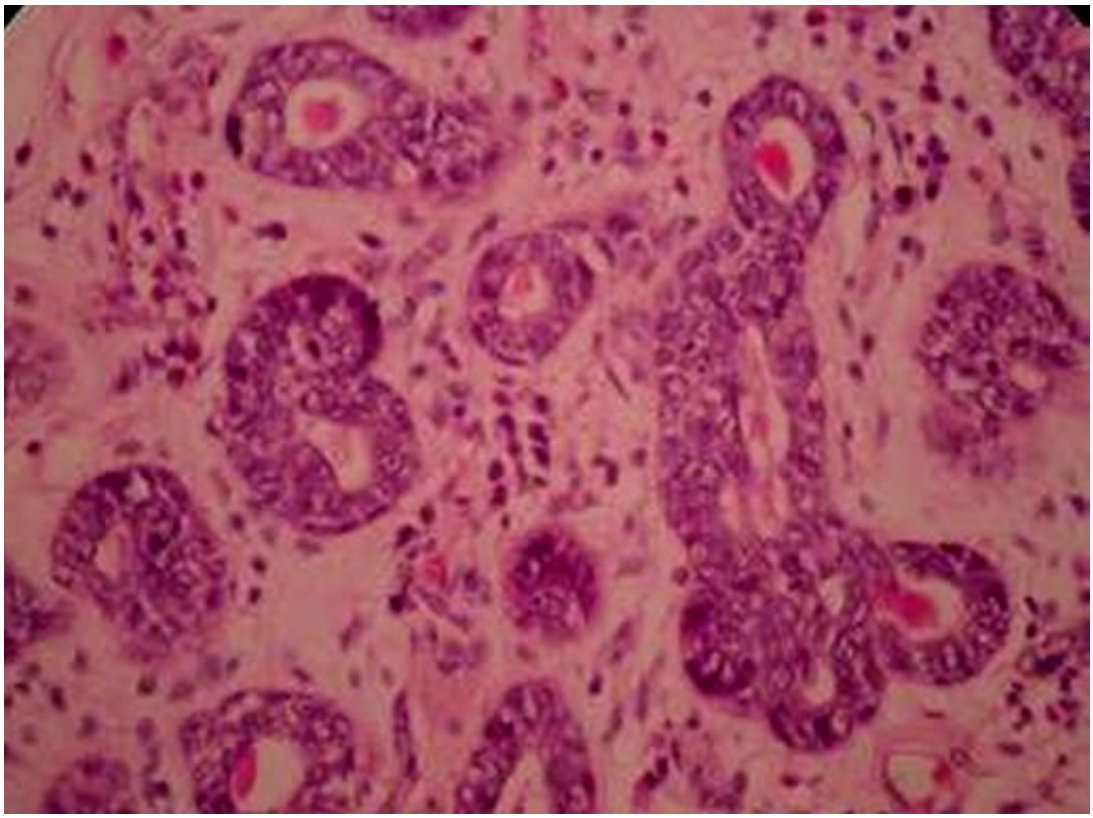

Figure 2. Lymph node metastasis-negative.

Table 1. The detection of p75NTR in the lymph node metastasis-negative and -positive groups.

Group	N	Positive	Negative	Detection rate
Lymph node metastasis-negative	30	6	24	20.00
Lymph node metastasis-positive	30	30	0	100.00
X^2	-	13.276	22.187	14.276
P	-	<0.05	<0.05	<0.05

3.2. Infiltration depth

The p75NTR-positive rate in patients with infiltration of the muscular layer was 73.33% (20/30), which was significantly higher than that in patient's infiltration of the whole layer (43.33% (13/30)) ($P < 0.05$) (Figure 3 and Figure 4). The results of p75NTR detection in the two groups were shown in Table 2.

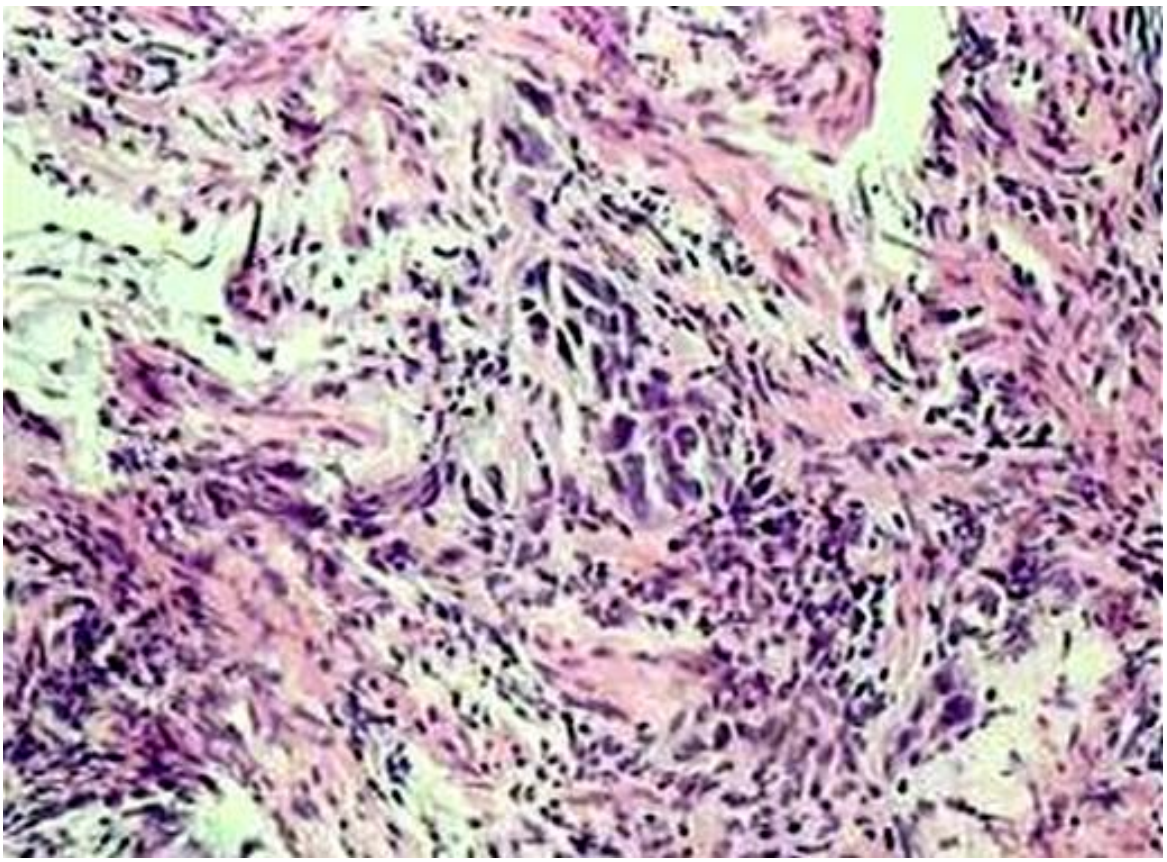

Figure 3. Depth of infiltration.

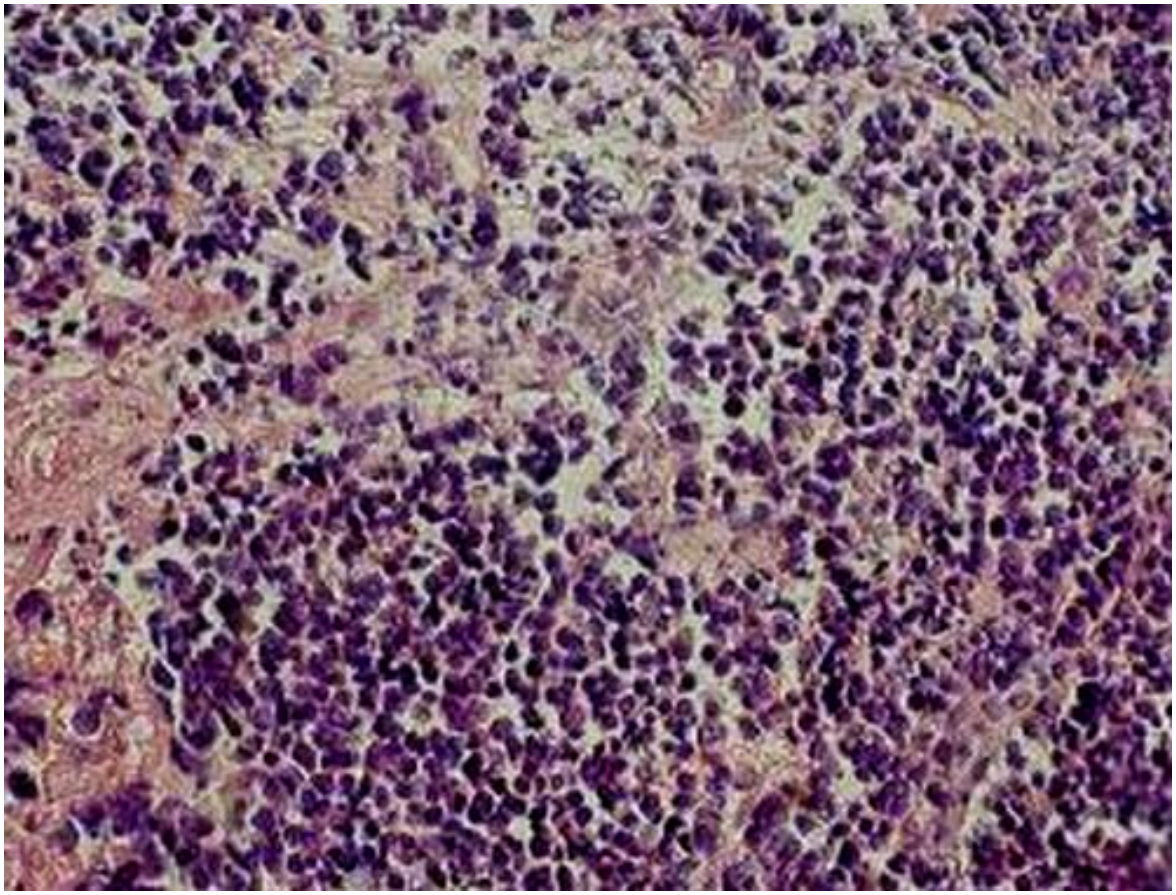

Figure 4. Deep muscular layer.

Table 2. Comparison of p75NTR detection in patients with infiltration of the muscular layer and the whole layer.

Group	N	Positive	Negative	Detection rate
Depth of infiltration	30	13	17	43.33
Deep muscular layer	30	20	10	73.33
X^2	-	5.287	6.391	8.226
P	-	<0.05	<0.05	<0.05

3.3. Comparison of quality of life in patients before and after treatment

In this study, the ADL, body function, psychological function and social function scores were significantly higher in the lymph node metastasis-negative group than in the lymph node metastasis-positive group ($P < 0.05$) (Table 3).

Table 3. Quality of life assessment results in the two groups of patients (x + s points).

Group	ADL	Somatic function	Mental function	Social function
Lymph node metastasis-negative (n = 30)	16.2 ± 3.7	59.6 ± 7.5	65.8 ± 9.2	57.2 ± 6.5
Lymph node metastasis-positive (n = 30)	11.6 ± 3.2	53.2 ± 7.1	56.7 ± 8.4	51.1 ± 6.0
t	16.32	15.78	15.55	12.31
P	<0.05	<0.05	<0.05	<0.01

4. Discussion

Esophageal cancer is a common malignant tumor with high invasiveness and lethality. Its mortality rate is the fourth highest of malignant tumors in China [5]. Approximately 70% to 80% of patients are in an advanced stage at diagnosis, and the 5-year survival rate is only 20%. Therefore, the comprehensive treatment of esophageal cancer has received increasing attention. Preoperative radiotherapy and chemotherapy have become hot research topics in clinical research on locally advanced esophageal cancer [6,7]. More than 90% of the pathological types of esophageal cancer in China are squamous cell carcinomas, which are more sensitive to radiotherapy and chemotherapy [8]. The purpose of preoperative radiotherapy and chemotherapy is first to reduce the size of the tumor, reduce the staging of esophageal cancer, and then improve the radical resection rate and the integrity of surgical resection [9]. Second, the rate of lymph node metastasis decreases, the incidence of perioperative complications does not increase, the survival rate is improved, and the incidence of residual cancer is reduced. Domestic and foreign research reports have shown that [10,11] the new adjuvant chemotherapy DF regimen (cisplatin + 5-fluorouracil) plus surgery can improve the 3-year survival rate of patients, which coincides with our research conclusions. Wu Longqiu et al [12]. reported that at present, the main research direction of radiotherapy for locally advanced esophageal cancer is to optimize 3D-CRT/IMRT radiotherapy technology, to search for individualized radiotherapy schemes, and to improve the sensitivity of radiotherapy combined with chemotherapeutic drugs [13].

In recent years, a large number of studies have shown that p75NTR can be used as an important basis for predicting lymphocyte metastasis in esophageal squamous cell carcinoma. Through the formation of the extramedullary niche, stem cells can migrate to the outside of the blood vessel or bone marrow, and further colonization and differentiation reactions can be carried out to participate in the process of the tissue remodeling reaction. Furthermore, it can actively evaluate the depth of invasion of esophageal squamous cell carcinoma patients [14,15]. p75NTR is a structural neurotrophic factor receptor that acts as a death receptor. At present, functional studies of p75NTR have mainly focused on the central nervous system. As one of the potential tumor inhibitors, it has been reported that p75NTR can effectively inhibit the growth and value-added response of prostate cancer, and some data suggest that p75NTR can be used as a survival receptor to promote the brain metastasis of melanoma cells [16]. These contradictory results suggest that p75NTR may play

different roles in different environments and tumors. According to the observation data reported in this study, p75NTR has a close, positive correlation with lymph node metastasis and the depth of invasion in esophageal squamous cell carcinoma and can be used as an important basis for clinical diagnosis and prognosis prediction [17,18].

5. Conclusion

The data in this study showed that the high expression of p75NTR in esophageal squamous cell carcinoma could indicate the depth of invasion and lymph node metastasis in esophageal squamous cell carcinoma. The detection of p75NTR in clinical practice could be used as an effective prognostic basis for esophageal squamous cell carcinoma patients. However, the sensitivity and specificity of p75NTR expression in the diagnosis of esophageal squamous cell carcinoma need further study. This will be the next phase of our research plan for good clinical promotion.

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Conflict of interest

The authors declare that they have no conflict of interest.

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