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LYMPH NODE MICROMETASTASIS IN EARLY GASTRIC CANCER: A LITERATURE REVIEW

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ABSTRACT

One of the most important prognostic indicators in patients with early gastric cancer is lymph node metastasis. However, there are still a small number of early gastric cancer patients with negative lymph node metastasis who died of tumor recurrence or distant metastasis after surgery. Some scholars have proposed that lymph node micrometastasis (LNM) is the potential cause of such patients' recurrence and metastasis. Compared with macroscopic lymph node metastasis, the detection of lymph node micrometastasis is more difficult, and its clinical significance for the prognosis of gastric cancer is still controversial. The definition, identification, and importance of LNM in early gastric cancer were discussed in this review. We also summarize the research progress of gastric cancer lymph node micrometastasis.

KEYWORDS: Gastric cancer; lymph nodes metastasis; micrometastasis.

INTRODUCTION

Gastric cancer is still one of the most common types of cancer. It is the world's third greatest cause of cancer-related death, and its prevalence is rising.[1] Compared with other countries, China has more new cases of gastric cancer every year[2], and many of these patients are diagnosed with advanced metastasized gastric cancer, thus missing the best time for radical gastric cancer surgery. In gastric cancer, lymph node metastasis has always been considered the most important factor affecting the prognosis of patients.[3] On the other hand, the 5-years survival rate of patients with early mucosal and submucosal gastric cancer reached 95%~100% and 85%~95%, respectively.[4] However, some studies[5,6] found that some patients with negative lymph node metastasis using conventional histological HE staining after radical gastric cancer surgery still have postoperative gastric cancer recurrence. Therefore, previous studies proposed that the presence of lymph node micrometastasis (LNM) is the cause of this phenomenon. Because of its macroscopic difference from lymph node metastasis, the state of LNM is difficult to be diagnosed by B-ultrasound, computer tomography, positron emission tomography, and other imaging examinations.[7] Nevertheless, several studies[8,9] indicate that the status of LNM does affect the prognosis of patients with gastric cancer. Therefore, further research to study the clinical significance of LNM has a positive effect on the prevention and treatment of gastric cancer. This article reviews the most recent developments of gastric cancer treatment, focusing on LNM as an underlying cause of patients' recurrence and metastasis.

DEFINITION OF LYMPH NODE MICROMETASTASIS

In solid tumors, like the depth of invasion and distant metastasis of the primary tumor, lymph node metastasis is one of the important factors affecting the prognosis. Lymph node micrometastasis (LNM) was traditionally identified as a microscopic deposit of malignant cells with a diameter of less than 2 mm.[10] This deposit has the potential to evade immune surveillance and evolve into a macroscopic malignant tumor. Because of their unusual biological behavior and size, the Union for International Cancer Control (UICC) redefined solitary tumor cells or cell clusters measuring less than 0.2 mm in its maximum dimension as "isolated tumor cells" (ITCs). Micrometastasis is defined as tumor cell aggregates having a size >0.2 mm but ≤2 mm. Isolated tumor cells refer to single tumor cells or cell clusters <0.2 mm.[11] The goal was to accurately stage the entities and discern between their various biological behaviors. First, LNM should be considered in node staging of gastric cancer, according to the 8th TNM Classification of Malignant Tumors by the UICC.[12] Patients with LNM are assigned to the pN1(mi) stage, while those with ITCs in the lymph nodes are assigned to the pN0(i+) stage. Furthermore, if

only RT-PCR can identify micrometastasis, the N stage should be determined as pN0(mol+).[13] Second, when compared with LNM, ITCs exhibit no signs of metastatic activity, such as proliferation or circulatory system penetration. Because of the differences in outcomes, LNM is not the same as lymph node metastasis. Tumor diameters cannot surpass 3 mm due to the lack of neovascularization. Therefore, cells may be in a state of transition between proliferation and death at the same time. Breaking dormancy is thought to be aided by VEGF-C.[14] Some scholars[15,16] pointed out that micrometastasis is a dormant state without blood vessel formation. Tumor cells maintain a balance between proliferation and apoptosis. However, this state will cause tumor recurrence after a long time. This hypothesis has been further confirmed in animal models and human melanoma and breast cancer.[17,18] However, the research on biological information related to the proliferation activity of gastric cancer is extremely limited.[19,20]

DETECTION OF LYMPH NODE MICROMETASTASIS

Serial sectioning method

Serial sectioning has been used in numerous LNM detection approaches, as a result, the rate of nodal micrometastasis identification has increased significantly when compared to HE staining, which is limited since many small tumor cell clusters can be undetected.[21] Nodal micrometastasis affects about 40% of individuals who are categorized as pN0 using classic HE staining methods. With this method, the detection rate is increased as the slice intervals are narrowed. However, the method's applicability has been limited due to the drawbacks of a heavy workload and low efficiency, thus it has been supplemented with, or replaced by more sensitive techniques.

Immunohistochemical staining method

Conventional histopathological examinations are almost helpless for the detection of lymph node micrometastasis. With the popularization of molecular techniques, immunohistochemical staining is often used for the detection of lymph node micrometastasis. Among them, epithelial cell markers such as cytokeratin are the most important. The biggest advantage of immunohistochemical staining is that it can distinguish cells in lymph nodes from the morphology, and simultaneously detect lymph node metastases that are not found using HE staining. Jeuck *et al.*[8] used immunohistochemical staining to detect the lymph nodes of 95 patients with gastric cancer whose staging was pN0 confirmed by traditional histological examination, and 14 of them were detected to have lymph node micrometastasis. Although immunohistochemical staining has many advantages for detecting LNM, there are some problems in the application of this technique. Mantel *et al.*[22] research showed that at least five (5) lymph node areas should be evaluated using immunohistochemical staining to detect LNM in patients with colorectal cancer. With this method, immunohistochemical staining require more time and effort. However, Yu JW *et al.*[23] established a rapid immunohistochemical staining procedure that can diagnose LNM within 30 minutes, and they have applied this technique to detect the LNM status of gastrointestinal cancer during surgery. Nonetheless, this method has not been widely accepted.

RT-PCR technology

The most significant benefit of reverse transcription polymerase chain reaction (RT-PCR) is its sensitivity, which allows 1 tumor cell in 1×10^7 cells to be detected.[24] In recent years, with the development of molecular biotechnology, RT-PCR has also been used for the detection of LNM. The use of RT-PCR boosted the rate of LNM detection to a level that was higher than that reached with IHC.[25] Cytokeratin (CK) and carcinoembryonic antigen (CEA) are usually used as target markers for the detection of LNM.[25,26] Although RT-PCR technology has high sensitivity for detecting a small number of occult cancer cells in lymph nodes, some reports determined that RT-PCR application on LNM detection is still problematic for two (2) reasons. First, due to contamination or pseudogene interference, RT-PCR detection of lymph node micrometastasis may have false positive results.[27] Secondly, because of the heterogeneous expression of target markers, there is a possibility of false negative results.[28] Horibe *et al.*[29] developed a rapid method to detect lymph node micrometastasis, which uses a reverse transcription cycle-mediated isothermal amplification (RT-LAMP) reaction. This technique can issue the result within one hour, making it possible to use RT-PCR to detect LNM during surgery.

THE CLINICAL SIGNIFICANCE OF LYMPH NODE MICROMETASTASIS (LNM) IN GASTRIC CANCER

Research on the safety of early gastric cancer surgery

In recent years, taking accounts on the quality of life of patients after minimal invasive surgery has been more and more widely used. Some scholars have begun to study the clinical efficacy of sentinel lymph node navigation surgery for gastric cancer patients without lymph node metastasis (stage cN0) before surgery.[30] The sentinel lymph node biopsy technology is a milestone in the field of breast surgery. Its application enables breast cancer patients with negative axillary lymph nodes to avoid axillary lymph node dissection, further reduces the scope of surgery, and reduces the trauma caused by surgery. For a long time, the clinical application of sentinel lymph node biopsy was limited to a few tumors such as breast cancer and melanoma. However, a recent prospective multicenter study is optimistic about the feasibility of sentinel lymph node biopsy for gastric cancer surgery.[31] A major controversy relative to the application of sentinel lymph node biopsy for early gastric cancer is the decision to perform gastrectomy lymph node dissection after the sentinel lymph node biopsy suggests micrometastasis is too

aggressive.[32] In breast cancer, this condition has been confirmed by clinical trials that no further surgical treatment is required.[33,34] Meanwhile, Jo *et al.*[35] selected 90 patients with early gastric cancer (postoperative pathological staging pT1N1) who underwent D1+β and more lymph node dissection and gastrectomy at the National Cancer Center of Korea between March 2001 and December 2005. Follow-up and immunohistochemical methods were used to detect LNM. At the same time, terminal deoxynucleotidyl transferase-mediated dUTP notch end labeling assay was used to detect the proliferation and apoptosis of tumor cells in lymph nodes. The results showed that compared with other tumors, LNM in patients with early gastric cancer had higher proliferative activity and apoptosis activity. At the same time, micrometastasis was also detected in the N2 station lymph nodes of some patients. Therefore, they concluded that if early gastric cancer is used in sentinel lymph nodes, micrometastasis is detected during the biopsy, especially at station N2; hence, the necessity to use D1+β or even more regional lymph node dissection.

Pylori-preserving gastrectomy is a type of function-preserving subtotal gastrectomy. Usually, patients undergoing this kind of surgery are required to determine the tumor stage as cT1cN0 before surgery, and the tumor is located in the body of the stomach and the distance between the tumor border and the pylorus is at least> 4 cm. Compared with traditional distal gastrectomy, this procedure has the advantages of preventing delayed gastric emptying and reducing postprandial symptoms. This procedure has been used in many hospitals in Japan and South Korea.[36,37] However, in order to preserve the nerves and supply vessels that innervate the pylorus, pyloric preserving gastrectomy is not complete for lymph node anatomy in the 5th and 6th groups. This has always been a safety issue in the implementation of pyloric sparing gastrectomy. Studies have shown that pyloric sparing gastrectomy for early gastric cancer may be safe, because the metastasis rates of the 5th and 6th groups of lymph nodes for tumors more than 5 cm from the pylorus are 0~0.9% and 0~1.8%, respectively.[38] On the other hand, Kim *et al.*[38] performed micrometastasis detection on the lymph nodes of groups 5 and 6 of 196 patients with gastric cancer (the tumor is more than 5 cm from the pylorus) who underwent traditional gastric cancer radical surgery. The result was that there was no micrometastasis in lymph node group 5 of all the patients under study and only one (1) patient (0.77%) had been detected with micrometastasis in the sixth lymph node, proving the oncological safety of pylorus sparing gastrectomy.

The prognosis of patients with gastric cancer

For a long time, lymph node metastasis has been acknowledged as an important factor affecting the prognosis of gastric cancer patients. However, the influence of LNM on the prognosis of gastric cancer remains divisive. Jeuck *et al.*[8] used immunohistochemical methods to detect the lymph nodes of 95 patients with gastric cancer who were determined to be negative for lymph node metastasis by traditional histological examinations. As a result, 16 patients were found to have micrometastasis in the lymph nodes where they further performed survival analysis. Result showed that lymph node micrometastasis is a risk factor for gastric cancer recurrence, but not a risk factor that affects the survival of patients. On the other hand, Ru *et al.*[9] used CK19 and CD44v6 immunohistochemical staining methods to detect a total of 349 lymph nodes in 45 patients with cardia adenocarcinoma. As a result, 15 patients tested positive for CK19 and 12 patients CD44v6 was detected positive, statistical analysis showed that the recurrence rate of these patients was significantly higher than that of patients with negative lymph node metastasis. In addition, they also had a lower 2-year survival rate. The study of Lee *et al.*[29] also reached a similar conclusion. Li *et al.*[39] searched the relevant literature describing gastric cancer micrometastasis from 1966 to 2013, and then performed a statistical analysis on the 18 documents that met the requirements. The results showed that compared with the negative lymph node micrometastasis, the lymph node micrometastasis was positive. Of patients have a worse 5-year survival rate (HR=2.81, 95% CI=1.96~4.02). For patients with postoperative pathological staging of pT1-2N0, this difference is more significant (HR=3.52, 95% CI =1.88~6.62). Although these studies are contradictory, the view that lymph node micrometastasis increases the risk of gastric cancer recurrence is consistent.

CONCLUSIONS

Almost all of the recent lymph node metastatic studies have been retrospective. Studies on the processes of LNM proliferation are scarce. Although the concept of micrometastasis is proposed in the tumor staging system formulated by UICC and AJCC, the current tumor staging system or guidelines do not include micrometastasis in pathological staging. With the popularization of immunohistochemical staining methods, some institutions have adopted micrometastasis as part of pathological diagnosis, but this approach has not been widely used. However, many studies have confirmed that lymph node micrometastasis does affect the prognosis of gastric cancer patients. Therefore, further studies on LNM on gastric cancer is needed to correlate related clinical findings for better credibility. Further, there is a need to adopt a more reasonable staging system to guide gastric cancer patients. Lastly, the prognosis of a patient greatly depends in the treatment and recurrence assessment risk upon diagnosis.

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