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Research Progress on Lymph Node Metastasis in Breast Cancer

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Abstract: ***Breast cancer remains the most common malignant tumor in women, with its prognosis closely linked to lymph node metastasis. This review summarizes the current research progress on lymph node metastasis in breast cancer, focusing on imaging diagnosis, sentinel lymph node biopsy (SNB), prognostic factors, and molecular subtypes. Breast cancer is the most common malignant tumor in women. According to the 2018 Statistical Report of the American Cancer Society, there were over 260,000 new cases of breast cancer in 2018, with more than 40,000 deaths attributed to the disease; its overall incidence accounted for 30% of all newly diagnosed tumors in women, showing an upward trend [1]. Reports indicate that the incidence of breast cancer among women in China is comparable to international levels and continues to rise, with approximately 270,000 new cases annually [2]. Since 1990, mortality rates from breast cancer have been declining due to advancements in treatment and early detection methods [3]. It is well established that the prognosis of breast cancer is closely associated with lymph node metastasis [4]. Therefore, evaluating lymph node metastasis and its clinical characteristics holds significant importance for predicting disease prognosis. This article reviews current clinical research progress on breast cancer lymph node metastasis.***

1. Imaging Examination for Lymph Node Metastasis

Imaging examinations are widely utilized in clinical diagnosis and treatment due to their non-invasive nature. Imaging studies are frequently referenced for diagnosing lymph node metastasis in breast cancer. Common imaging modalities include ultrasonography, magnetic resonance imaging (MRI), and positron emission tomography/computed tomography (PET/CT). Ultrasonography, owing to its simplicity, cost-effectiveness, and non-invasiveness, remains the most prevalent method for evaluating lymph nodes. Abnormal cortical thickness, presence of non-gate cortical blood flow, and round hypoechoic areas with absent lymph nodes constitute the most critical diagnostic markers for lymph node metastasis [5]. However, nearly all experimental studies indicate that color Doppler ultrasound exhibits high specificity but low sensitivity for detecting metastatic lymph nodes [6]. In recent years, advancements in ultrasound-guided puncture techniques have enriched the diagnostic approaches for metastatic lymph nodes; nonetheless, color Doppler ultrasound remains subject to further refinement. PET/CT demonstrates low sensitivity for diagnosing lymph node metastasis due to its limited spatial resolution and lack of standardized criteria [7], and its high radiation exposure limits clinical application in this context. MRI has emerged as one of the most critical diagnostic modalities for breast cancer. Its superior soft tissue resolution and radiation-free nature have led to increasing adoption in breast cancer diagnosis [8]. Studies indicate that metastatic lymph nodes exhibit longer short diameters compared to reactive lymph nodes, with the sensitivity and specificity for diagnosing metastatic lymph nodes based on the absence of lymph nodes being 60% and 100%, respectively [9]. Compared to ultrasound MRI, which can visualize bilateral axillary structures, contrast-enhanced imaging improves the detection rate of metastatic lymph nodes—particularly those differing in number, morphology, or size from contralateral lymph nodes—and also enhances the identification of lymph nodes that are difficult to palpate during clinical examinations. Early detection is associated with reduced incidence and mortality rates of breast cancer [10]. Although imaging examinations may be less critical for evaluating lymph node metastasis, they play a significant role in the early detection and prognosis of breast cancer.

2. Sentinel Lymph Node Biopsy

Due to the limited accuracy of imaging examinations in detecting lymph node metastasis, the current definitive diagnosis of lymph node metastasis in breast cancer primarily relies on surgical biopsy or fine-needle aspiration biopsy (FNAB). However, FNAB is only feasible for lymph nodes that exhibit significant enlargement or evident imaging abnormalities. Therefore, surgical biopsy remains the most critical diagnostic modality for breast cancer lymph node metastasis. The concept of sentinel lymph node biopsy (SNB) was first reported by Morton et al. in the early 1990s [11] in the context of cutaneous melanoma, and was subsequently extended to breast cancer patients [12]. Today, SNB has become the standard procedure for axillary staging in early-stage breast cancer [13]. As a minimally invasive technique, SNB enables accurate assessment of axillary lymph node metastasis and reduces complications associated with axillary lymph node dissection [14]. In 1992, Morton and colleagues pioneered the use of blue dye for SNB [11], followed by Krag et al.'s introduction of radioactive isotopes for SNB in 1993 [15]. To enhance SNB accuracy, the combination of blue dye and radioactive isotope techniques recommended by Moffit Cancer Center [16] has been widely adopted, with additional studies confirming its advantages. SNB is widely regarded as a viable alternative to axillary lymph node dissection (ALND) for clinically evaluating axillary treatment in patients with negative lymph node metastasis, owing to its comparable disease-free survival (DFS), overall survival (OS), and local regional recurrence (LRR) rates [17]. Although reports indicate that radiation exposure from the use of radioactive isotopes in sentinel lymph node biopsy is limited and safe for pregnant surgeons and patients [18], concerns about the hazards of radiation exposure remain an obstacle to the adoption of combined approaches. Moreover, many hospitals in developing countries, including China, currently lack the capability or

accreditation to operate nuclear medicine equipment. Consequently, single-dye tracing remains the predominant method for sentinel lymph node biopsy domestically. This poses challenges for clinical practice, necessitating cautious handling of sentinel lymph node biopsies. In particular, whether the number of required sentinel lymph nodes for biopsy should be increased remains a question under consideration among many clinicians.

In patients with sentinel lymph node metastasis, additional axillary lymph node dissection is typically required [19]. However, studies indicate that 20%–60% of breast cancer patients with sentinel lymph node metastasis do not develop further axillary lymph node metastasis [20]. For these patients, axillary lymph node dissection offers no clinical benefit and may lead to complications such as postoperative lymphedema, restricted shoulder joint mobility, and axillary numbness. The ACOSOG Z0011 trial demonstrated that patients with T1–T2 invasive breast cancer and only 1 or 2 sentinel lymph node metastases achieved comparable survival rates with breast-conserving surgery and systemic therapy versus axillary lymph node dissection (10-year OS rates of 80.2% vs. 78.2%) [21]. Consequently, the American Society of Clinical Oncology (ASCO) guidelines recommend against axillary lymph node dissection for breast-conserving surgery with whole-breast radiotherapy in patients with only 1–2 sentinel lymph node metastases [22]. The 2017 St. Gallen Consensus advocates for surgical downgrading and upgrading adjuvant systemic therapy for early-stage breast cancer [23]. A small domestic study suggested that ≥3 positive sentinel lymph node metastases, sentinel lymph node macrophage infiltration, and lymphovascular invasion are associated with non-NSLN metastasis. When only 0 or 1 risk factors are present, alternative systemic adjuvant therapy may be considered, but further evaluation is warranted; however, axillary lymph node dissection should be considered if two or, particularly, three risk factors are present [24].

3. Impact of Lymph Node Metastasis Rate on Prognosis

Currently, the most widely used breast cancer staging guideline is the American Joint Committee on Cancer (AJCC) [25], although its TNM classification system remains flawed. The AJCC staging system requires examination of 15 lymph nodes and classification based on their anatomical location [26]. However, due to factors such as the inability to resect all 15 lymph nodes, incomplete staging may occur. Recent studies have demonstrated that the lymph node metastasis rate is superior to the sensitivity and accuracy of the AJCC TNM staging system's 7th edition guidelines in assessing prognosis for gastric cancer [27]. Similarly, research has shown that the lymph node metastasis rate for colon cancer is more accurate than the AJCC staging system, even after thorough lymph node dissection [28]. Previous oncological studies indicate that the lymph node metastasis rate (the ratio of metastasis-positive lymph nodes to the total number of examined lymph nodes) serves as a negative prognostic indicator for cancer survival [29]. Although multiple factors may interfere with the utility of lymph node metastasis rate as a prognostic tool for breast cancer—including tumor size, disease stage, or the use of adjuvant therapies that may affect lymph node assessment [30]—a study involving over 7,000 breast cancer patients demonstrated its usefulness in evaluating prognosis for patients with 1–3 lymph node metastases [31]. Recommendations have been made to incorporate the lymph node metastasis rate into breast cancer staging protocols [32].

4. Impact of Lymphatic Infiltration on Prognosis

The lymph node metastasis process of breast tumor cells typically involves invasion of lymphatic vessels to reach the cortex, deposition in subcapsular lymph sinuses, passage through the paracortical region, and eventual entry into the lymphatic portal [33]. Tumor cells can not only detach from the primary tumor site and invade pre-existing lymphatic vessels within the tissue to cause metastasis but also induce lymphangiogenesis. In recent years, with the discovery of lymphatic endothelial cell markers such as LYVE-1, VEGER-3, podoplanin, Prox-1, and D2-40, research on lymphangiogenesis and lymphatic invasion in tumor tissues has garnered significant attention [34]. For lymphatic infiltration, the internationally recognized method for assessing lymphatic vascular invasion is D2-40 immunostaining [35]. Compared to traditional 苏 HE staining, monoclonal antibody D2-40 immunostaining significantly enhances the accuracy and specificity in detecting lymphatic invasion, thereby providing more reliable insights into tumor lymph node metastasis [36]. However, the temporal relationship between lymphatic infiltration and lymph node metastasis remains controversial and requires further investigation through multicenter, large-sample studies.

5. Relationship Between Lymph Node Metastasis and Molecular Typing

As is well known, breast cancer is a heterogeneous disease classified based on ER, PR, HER-2, and Ki-67 markers. ER and PR are intracellular steroid hormone receptors that have garnered widespread attention since 1986. Measurable ER and PR are detected in approximately 50–86% of breast cancer patients [37]. Her2 gene amplification is another critical prognostic and predictive factor for breast cancer. Approximately 20% of breast cancer patients exhibit Her2/neu gene amplification, leading to glycoprotein overexpression. This oncogene is associated with tumor invasiveness and chemotherapy resistance [38].

The prognosis of breast cancer is closely associated with molecular subtypes [39]. These molecular subtypes include Luminal A (ER-positive, high PR expression, HER-2-negative, and low Ki-67 expression), Luminal B (ER-positive, HER-2-negative, and high Ki-67 expression; PR-negative or low PR expression; or ER, PR, and HER-2 are all positive), HER-2-positive (HER-2-positive, ER and PR-negative), and triple-negative (ER, PR, and HER-2-negative) [40]. The prevailing consensus holds that lymph node metastasis is correlated with molecular subtype, with Luminal A serving as the baseline; patients with Luminal B exhibit an increased risk of axillary metastasis, whereas triple-negative breast cancer, despite its poorer prognosis, shows no elevated risk of axillary lymph node metastasis [41].

6. Summary

Lymph node metastasis in breast cancer has consistently been a focal point of clinical research. The mechanisms underlying breast cancer lymph node metastasis are well understood, and analyzing the relationship between lymph node metastasis and ER, PR, and Her-2 expression holds significant implications for predicting disease prognosis and guiding subsequent treatment strategies. Additionally, current breast cancer therapies emphasize minimally invasive surgical approaches and more comprehensive multimodal treatments [23]. Consequently, further research is warranted regarding the clinical value of axillary lymph node dissection following sentinel lymph node metastasis. Concurrently, studies investigating the correlation between lymphatic invasion and lymph node metastasis rates with prognosis are highly valuable.

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