



LEVEL III LYMPH NODE DISSECTION IN BREAST CANCER.

Breast Surgery

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ABSTRACT

Axillary lymph node dissection is a crucial step in modified radical mastectomy for breast cancer, serving as a reliable method and the gold standard for assessing axillary lymph node status. It plays a vital role in prognosis evaluation and treatment planning for breast cancer patients. Anatomically, axillary lymph node dissection can be categorized into levels I, II, and III. While Level I and Level II axillary lymph node dissection are standard treatments for axillary lymph node-positive breast cancer, the inclusion of level III axillary lymph node dissection has sparked controversy. Level III axillary lymph node metastasis is a significant factor that can potentially lead to distant metastasis and recurrence, influencing the prognosis of breast cancer patients. Deciding on the necessity of level III lymph node dissection involves a review of indications, complications, and surgical procedures associated with it.

KEYWORDS

INTRODUCTION

Axillary lymph node dissection holds a crucial role in modified radical mastectomy for breast cancer. It serves as the most dependable technique and the gold standard for assessing axillary lymph node status. This procedure significantly contributes to prognosis evaluation and the formulation of treatment strategies for breast cancer patients. From an anatomical standpoint, axillary lymph nodes are categorized into three levels, demarcated by the pectoralis minor muscle. Level I axillary nodes encompass the lateral breast group, central group, and subscapular group, situated laterally to the pectoralis minor muscle. Posteriorly positioned to the deep surface of the pectoralis minor muscle lie the level II axillary lymph nodes. Meanwhile, level III axillary lymph nodes are located medially to the pectoralis minor muscle and function as the relay station for mammary gland lymphatic drainage to the supraclavicular lymph nodes or thoracic duct. Level I and II axillary lymph node dissection stands as the established clinical approach for axillary lymph node-positive breast cancer. However, the necessity of level III axillary lymph node dissection has sparked controversy.

AIM

Analysis to assess the need for level III lymph node dissection, examining indications, complications, and surgical procedures.

Indications of Level III Axillary Lymph Node Dissection

As per the NCCN Guidelines for clinical practice in breast cancer, when there is no evident disease in level II nodes, lymph node dissection should encompass the tissue beneath the axillary vein, extending from the latissimus dorsi muscle laterally to the inner edge of the pectoralis minor muscle (level I/II).² Level III dissection to the thoracic inlet is warranted solely in instances featuring apparent diseases in level I/II.

The dissection of level III lymph nodes could potentially result in postoperative paresthesia, axillary deformity, and lymphedema, among other complications. This procedure has been a subject of controversy and is considered an unconventional clinical approach. The utilization of sentinel lymph node biopsy has significantly minimized axillary trauma. The Z0011 trial has provided clear criteria for identifying breast cancer patients with positive lymph nodes who can safely avoid axillary lymph node dissection. These criteria include: ⁽¹⁾ clinical T1 or T2 stage tumors; ⁽²⁾ ≤ 2 positive sentinel lymph nodes; ⁽³⁾ undergoing breast-conserving surgery; ⁽⁴⁾ receiving postoperative whole-breast radiotherapy; and ⁽⁵⁾ undergoing systemic adjuvant therapy after surgery. Liu et al. applied the Z0011 trial criteria to Chinese patients with positive sentinel lymph nodes and identified patients with more favorable prognoses and lower risks than those in the Z0011 study. These patients could safely undergo sentinel lymph node biopsy without requiring axillary lymph node dissection. Systemic treatments like chemotherapy, endocrine therapy, and immunotherapy can eliminate residual tumor cells in the axilla, thereby reducing axillary recurrence rates. Research indicates that

20–42% of patients with positive axillary lymph nodes achieve complete pathological remission after neoadjuvant therapy (chemotherapy or immunotherapy), resulting in reduced local recurrence risks. Adjuvant chemotherapy and endocrine therapy also contribute to decreased regional recurrence risks. Nonetheless, around 20–30% of patients undergoing sentinel lymph node biopsy still need to consider axillary lymph node dissection due to positive lymph nodes. The NSABP B04 study revealed an 18.6% recurrence rate among patients with incomplete axillary lymph node dissection. For elderly patients, omitting axillary lymph node dissection does not impact disease-free survival (DFS) and overall survival (OS). Axillary lymphadenectomy has shown improved survival outcomes for patients with clinical N2–3 invasive breast cancer. While many surgeons opt for axillary lymph node dissection in cases of positive axillary lymph nodes, various factors contribute to this decision, including challenges in treating axillary recurrence, psychological implications for patients, and the complexities of maintaining rigorous follow-up.

The impact of axillary therapy on survival remains a subject of controversy. For a majority of breast cancer patients, undergoing level III axillary lymph node dissection can be considered excessive treatment. Kodama et al. conducted a comparison between T1/2/3 and N0/1a/1b (International Union of Cancer Staging 1987) breast cancer patients who underwent either level III or level I axillary lymph node clearance. Their findings indicated that the 10-year overall survival rates were 87.8% and 89.6% ($P = 0.552$), while the 10-year disease-free survival rates were 74.1% and 76.6%, respectively ($P = 0.7$). As the survival rate did not improve with level III axillary lymph node clearance in T1/2/3 and N0/1a/1b patients, its recommendation was not supported. In another study, Tominaga et al. compared overall survival outcomes between patients with stage II breast cancer who underwent level III versus level II axillary lymph node clearance. Their research revealed 10-year overall survival rates of 86.6% and 85.7% ($P = 0.931$), along with 10-year disease-free survival rates of 73.3% and 77.8%, respectively, for patients undergoing level II or level III axillary lymph node dissection ($P = 0.666$). As a result, they suggested that additional level III axillary lymph node clearance might not offer any benefits. It's worth noting that these two studies did not specifically focus on patients with positive lymph nodes. In Kodama and Tominaga's studies, the lymph node metastasis rates were 32.1% and 32.7%, respectively. In Kodama's study, the rate of level III axillary lymph node invasion was only 7.4%. Consequently, level III axillary lymph node dissection could potentially remove a higher proportion of positive lymph nodes in patients with lymph node-positive breast cancer.

Even though level III cleaning doesn't contribute to improved survival,²⁰ metastasis in level III axillary lymph nodes remains a significant factor triggering distant recurrence.²¹ It serves as a vital parameter for assessing breast cancer patients' prognosis. Once tumor cells infiltrate axillary lymph nodes, they can disseminate through the lymphatic system, often extending to the neck and chest cavity.

Performing level III axillary lymph node cleaning can enhance the comprehensiveness of axillary lymph node dissection in cases of preoperative positive axillary lymph nodes. Additionally, it holds important implications for guiding postoperative treatment and enhancing prognosis. Notably, level III axillary lymph node invasion doesn't stand as an independent prognostic factor. Although level III axillary lymph node dissection contributes to more precise classification according to the American Joint Committee on Cancer Staging, it doesn't result in a significant survival advantage.²¹ While standard practice entails level I+II axillary lymph node dissection, level III cleaning is a less common approach. Level III axillary lymph node dissection is performed selectively, mainly in patients with extensive axillary lymph node invasion and/or evident level II/III axillary lymph node involvement.²¹ This scenario predominantly arises in cases of locally advanced breast cancer at clinical stages T3-4 and N1-2.22 Although level III axillary lymph node invasion doesn't independently predict regional recurrence, it might serve as an indicator for distant metastasis-free survival. Undertaking level III axillary lymph node dissection during modified radical mastectomy can mitigate the risk of distant metastasis.

Initial clinical investigations into the extent of lymph node metastasis among patients with positive axillary lymph nodes in breast cancer indicated that 20–58% of cases with axillary lymph node metastasis were localized within level I. Meanwhile, 20–29% and 16–32% of patients displayed metastasis confined to levels I+II and levels I+III, respectively. Around 20% of individuals received a diagnosis of pathological level III metastasis.^{23,24} The highest rate of level III metastasis was documented in Khafagy's study, where among 59 patients with positive axillary lymph nodes, 31 (52.5%) exhibited level III axillary lymph node metastasis. In a separate investigation conducted by Tao et al., out of 87 patients with positive axillary lymph nodes, 18 (20.7%) were identified with level III axillary lymph node metastasis.²⁶ Yildirim's research reported a level III axillary lymph node metastasis rate ranging from 15% to 31%.²¹ Another study, focusing on T0-2 axillary lymph node-positive breast cancer patients who underwent neoadjuvant chemotherapy, revealed that only 0.9% of patients displayed level III axillary lymph node invasion.²⁷

Multiple studies have explored the relationship between axillary lymph node metastasis and clinical-pathological factors. Toma et al. reported a connection between nuclear grade 3 and level III axillary lymph node invasion.²⁸ Ung et al. discovered correlations with axillary lymph node palpability, pathological tumor size, and lymph vessel invasion.²⁹ Veronesi et al. conducted a study involving 539 breast cancer patients, revealing level III axillary lymph node invasion in 16.9% of T1 breast cancer cases.²⁴ This investigation also indicated a potential link between level II or III axillary lymph node invasion and the number of metastatic nodes. In instances where patients had only one level I axillary lymph node metastasis, 8% also exhibited higher-level axillary lymph node metastasis. Similarly, among patients with two level I axillary lymph node metastases, 25.3% displayed higher-level axillary lymph node metastasis. The rate escalated to a remarkable 65.8% for patients with four or more level I axillary lymph node metastases. Yildirim's findings suggested that important pathological factors, including level III axillary lymph node involvement, tumor size, lymph node and vascular invasion, and the number of positive axillary lymph nodes, were indicative of distant metastasis.²¹ In a single-factor analysis, Yildirim observed associations between tumor size, lymph node and vascular invasion, extracapsular involvement, premenopausal status, and level III axillary lymph node metastasis. A multiple-factor analysis indicated that only the number of positive lymph nodes correlated with level III axillary lymph node positivity, though this couldn't be confirmed before surgery. Yildirim's study identified a threshold of 7 positive nodes for level III involvement. Dillon proposed that level III clearance might have a selective but definite role in lymph node-positive breast carcinoma patients.¹² Utilizing pathological features of primary tumors can aid in assessing the risk of level III axillary lymph node invasion. For patients with axillary lymph node-positive breast cancer, predictive factors of level III infiltration included tumor size (OR = 1.36, 95% CI: 1.2–1.5, $P < 0.001$), invasive lobular carcinoma (OR = 3.6, 95% CI: 1.9–6.95, $P < 0.001$), extracapsular involvement (OR = 0.27, 95% CI: 0.18–0.4, $P < 0.001$), and lymph node vascular infiltration (OR = 0.58, 95% CI: 0.35–1, $P = 0.04$). For tumors exceeding 3 cm in diameter, the risk of level III metastasis was notably elevated at 34%. In patients with invasive lobular carcinoma and positive lymph nodes, the rate of level III axillary lymph node positivity reached 41%. Predictive factors for

level III invasion in sentinel lymph node-positive patients encompassed invasive lobular carcinoma (OR = 4.1, 95% CI: 1–16.8, $P = 0.049$), lymph node extracapsular involvement (OR = 0.18, 95% CI: 0.06–0.57, $P = 0.003$), and at least one positive sentinel lymph node (OR = 4.9, 95% CI: 1.5–16.1, $P = 0.009$). Fan's research indicated that factors like tumor size, lymph node biopsy techniques, and primary tumor response to neoadjuvant chemotherapy through ultrasound could anticipate the risk of level III axillary lymph node involvement.²⁷ Notably, the rate of pathological complete response in axillary lymph nodes after neoadjuvant chemotherapy was considerably higher in the primary tumor effective group compared to the ineffective group (36.5% [73/200] vs. 19.1% [17/89], $P = 0.003$). Effective neoadjuvant chemotherapy seemed to decrease the level III positivity rate. Independent predictors of axillary lymph node positivity included node positivity verified through ultrasound-guided needle biopsy, large tumor size, and primary tumor nonresponse to neoadjuvant chemotherapy. The level III axillary lymph node-positive rate stood at a mere 4.9% for patients devoid of risk factors, while those with three risk factors ($T > 2$ cm, axillary lymph node positivity confirmed by fine needle biopsy, and noneffective neoadjuvant chemotherapy) displayed a level III invasion rate as high as 23.7%. Patients presenting two or more risk factors should be considered for level III clearance, as their level III involvement rate reached at least 20%. Wang et al. recommended considering level III axillary lymph node dissection for tumors at stage T3 or above with negative estrogen receptor (ER) expression confirmed by preoperative breast tumor needle biopsy. Additionally, it was suggested in cases where intraoperative detection indicated axillary lymph node metastasis suspected to be at level I–II or accompanied by extra lymph node tissue infiltration.³⁰ Risk factors for axillary lymph node metastasis included the number of axillary lymph node metastases at levels I–II, external node involvement, and negative ER expression. Stratified analysis indicated that level III axillary lymph node metastasis was more likely if tumors above T3 were laterally positioned ($P = 0.035$). With negative ER expression, the likelihood of level III lymph node metastasis increased with tumor stage progression.

Understanding the risk factors and predictive factors for level III axillary lymph node metastasis can provide valuable guidance for devising an appropriate treatment strategy by the surgeon and/or tumor radiotherapist.

Complications of Level III Axillary Lymph Node Dissection

Studies suggest that the dissection of level I–III axillary lymph nodes has not been shown to enhance the long-term effectiveness of breast cancer surgery,^{13,31} it can amplify complications like lymphedema of the affected limb, paresthesia, pain, limited shoulder joint mobility, effusion, and other issues,³² potentially resulting from excessive treatment. Nevertheless, substantial complications arising from axillary lymph node dissection have been rare in the literature, and serious concerns such as axillary vein/artery thrombosis or injury and axillary motor nerve damage have been infrequently reported. Although level III axillary lymph node dissection might extend the duration and entail greater blood loss compared to level I dissection, it doesn't impact clinical outcomes. No significant discrepancies were observed between the two groups in follow-up symptoms such as upper limb pain, pectoralis major atrophy, upper limb motor function, and social function.¹⁹ In patients with similar-stage breast cancer who underwent standard axillary lymph node dissection, there was no escalation in the incidence of malformation linked to supplementary lymph node dissection. The occurrence of postoperative upper extremity lymphedema ranges from 6% to 30%,²⁵ contingent on the criteria adopted to define lymphedema and the adequacy of follow-up. Currently, the prevailing belief is that the risk of lymphedema is minimal if the adventitia of the axillary vein remains unharmed. Thus, surgeons should exercise caution to preserve the integrity of the outer membrane surrounding the axillary vein when maneuvering the brachial plexus fat above the axillary vein for lymph node dissection.³³

Surgical Options for Level III Axillary Lymph Node Dissection

Two commonly utilized approaches for exposing the subclavian area during level III dissection are recognized. One method involves retracting the pectoralis major and minor muscles, while the other involves splitting the pectoralis major muscle, known as the Kodama method. Building upon these foundations, a series of studies has introduced several enhanced techniques. Muscolino et al. put forth a practical approach to access level III axillary lymph nodes by splitting the pectoralis major muscle and immobilizing the pectoralis minor

muscle.³⁴ Although this technique offers a confined exposure space, it has garnered endorsement from other clinicians.³⁵ This method proves beneficial in revealing the axillary apex and streamlining the dissection of upper axillary vein lymph nodes (supraclavicular lymph nodes) that may be involved in locally advanced breast cancer cases. Moreover, for the preservation of muscles, prepectoral lymph node dissection is advocated. Alfredo et al. discovered that subpectoral dissection often results in the retention of lymph nodes at the axillary apex.²² In cases where preservation of the pectoralis major and minor muscles is imperative during level I–III lymph node dissection in breast cancer patients, a recommended approach is to subpectoral level III lymph nodes through the posterior space of the pectoralis major muscle. Hadjiminis et al. introduced a secure method for effectively cleaning level III axillary lymph nodes.³⁶ This involves a transverse incision that splits the pectoralis major muscle on its center point where the axillary vein traverses the first rib. Positioned 5 cm laterally and 1 cm superior to the suprasternal notch, this technique allows lateral retraction of the pectoralis minor and dissection of the neurovascular bundle to the pectoralis major, followed by retraction using a silicone sling. Particularly advantageous for mastectomy patients, this muscle splitting incision can be executed without necessitating a separate skin incision. The method proves especially advantageous for patients with level III recurrence as it enables direct access to level III without traversing previously operated levels I and II, thereby minimizing the risk of nerve or vessel injury during dissection.

CONCLUSION

Underestimating the count of positive lymph nodes can result in inaccurate evaluations of distant metastasis risk, thereby jeopardizing local and regional control and negatively impacting subsequent treatment outcomes.²⁵ Analyzing the risk factors and predictive factors for level III lymph node invasion is crucial for informing treatment strategy choices. Considering level III axillary lymph node dissection based on risk factors is a logical approach, yet its impact on survival rates warrants further study.

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