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Clinical significance of internal mammary lymph node metastasis for breast cancer: Analysis of 337 breast cancer patients

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ABSTRACT

Purpose: Internal mammary nodes (IMNs) is a major pathway of lymphatic drainage for breast cancer, apart from axillary lymph node (ALN). However, owing to lack of a feasible and safe biopsy method, management of IMNs is still controversial in breast surgery.

Methods: From 2005 to 2009, a total of 337 consecutive breast cancer women patients were recruited. All patients underwent IMNs biopsy through intercostal space or endoscopic lymphatic chain resection. The ER, PR and HER-2 status were retested according to the current ASCO/CAP guidelines. We analyzed the relationship between clinical pathological parameters and IMNs metastasis and investigated the high risk factors and prognostic values of IMNs metastasis in breast cancer.

Results: Among 337 patients, 314 patients underwent intercostal space IMNs biopsy and 23 patients underwent endoscopic lymphatic chain resection. A total of 63 (18.69%) patients were pathologically diagnosed with IMNs metastasis. Among them, 28 (44.44%) patients changed the pathological lymph node staging, and 15 cases (23.81%) changed the postoperative comprehensive treatment program and accepted extended postoperative radiotherapy. Multivariate analysis showed that compared with no ALN involvement, the risk of IMNs metastasis was significantly increased in patients with 1–3 ALN involvement (OR = 42.097, 95% CI = 5.225–339.178; $P = 0.0004$) and ≥4 ALN involvement (OR = 82.429, 95%CI = 10.134–670.496; $P < 0.0001$). The risk of IMNs metastasis in HER-2 positive patients was significantly higher than that in negative patients (OR = 5.452, 95% CI = 2.353–12.634; $P < 0.0001$). However, we did not find IMNs involvement was an independent indicator for both overall survival and disease-free survival.

Conclusions: Our clinical practice and data indicated that IMNs biopsy through intercostal space and endoscopic lymphatic chain resection are effective and minimally invasive methods to detect the IMNs status, which may be helpful for accurate tumor staging, risk assessment and option of chemotherapy or radiotherapy to improve the patients' survival.

1. Background

Regional lymph node management is an important part of breast cancer surgery. The internal mammary nodes (IMN) drain about 25% of all lymphatics of the breast [1,2]. Although current evidence suggests that the IMN chain is a major pathway of lymphatic drainage, with 18%–33% of patients with operable breast cancer having metastases to the IMN, the management of IMN in breast cancer is still controversial [3–6].

The IMN chain is located behind the intercostal muscles and costal cartilages and lies close to the internal mammary vein and artery [7]. In the 1950s it became customary to remove these nodes during radical mastectomy [8]. Initial studies showed that about one-third of breast cancer patients had IMN involvement [9–11] and that patients with IMN metastasis had worse outcome. It was suggested that metastases to axillary lymph nodes (ALN) or the IMN had the same prognostic relevance for breast cancer patients [12–19]. However, randomized trials [20–24] later showed that overall survival (OS) and disease-free survival (DFS) in breast

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cancer patients were comparable with extensive radical mastectomy and with radical mastectomy, while the quality of life of patients was worse and surgical complications more with the former surgery. As a result, extensive radical mastectomy was gradually abandoned.

IMN sampling can be useful for nodal staging and can help guide therapy [25–35]. For example, addition of local radiotherapy to the treatment regimen has been shown to benefit patients with IMN metastases [36,37]. Therefore, surgical sampling remains crucial for management of breast cancer [38,39]. However, there is no safe method for biopsy of IMN, and the management of IMN remains a problem in breast cancer surgery.

The purpose of this study was to identify the risk factors associated with metastasis to the IMN, and to determine the relationship between IMN metastasis and prognosis.

2. Patients and methods

2.1. Patient selection

A total of 337 consecutive breast cancer women patients treated at the Southwest Hospital, Third Military Medical University, Chongqing, China, during 2005–2009 were included in this retrospective study. Patients with newly diagnosed, histopathologically confirmed breast cancer were eligible for inclusion, with no restrictions of age or pathological types. The exclusion criteria were pregnancy, presence of distant metastasis, unwillingness to undergo biopsy/surgical procedures, congestive heart failure, ischemic heart disease, other malignancies, severe hepatic or renal dysfunction, and altered mental status.

This study was approved by the Clinic Ethics Review Committee of Southwest Hospital, Third Military Medical University. Written informed consent was obtained from all participants.

2.2. Surgical procedure

2.2.1. Intercostal space IMN biopsy

The details of the procedure have been reported previously. Briefly, a retractor was used to expose the intercostal space, and the thoracic transverse fascia was incised. The internal thoracic vessels were identified by careful dissection. The internal mammary lymph nodes, which are usually located close to the internal thoracic vessels, were readily identified anterior, lateral, or medial to the vessels. If the lymph nodes were not found in the intercostal space, the costal cartilage was sought and the two costal cartilages above and below the intercostal space were resected. Care was taken to avoid injury to the perforating branches of the internal mammary artery to the intercostal space. After biopsy of the nodes, fine silk suture was used to close the separated pectoralis major muscle.

2.2.2. Endoscopic lymphatic chain resection

The details of the procedure have been reported previously. Briefly, trocars were introduced into thoracic cavity through three <15 mm incisions placed at the third, fifth, and seventh intercostal spaces along the midaxillary line. A 10-mm rigid 30° thoracoscope was used to visualize the thoracic cavity and identify and expose the internal thoracic vessels and the IMN chain. Using an ultrasonically activated scalpel, the distal parts of the internal thoracic vessels were sectioned between two vascular clips, and all collateral branches issuing from the internal thoracic vessels were transected. This allowed complete dissection of the IMN chain from the first to the sixth rib. The resected specimen was removed through the 10-mm thoracoscope Because the IMN chain lies close to the parietal pleura, special care was taken to avoid injury to the pleura during intercostal space IMN biopsy or endoscopic lymphatic chain resection. Small pleural tears were either left alone or sutured with nonabsorbable material.

2.3. Pathologic and immunohistochemical analysis

All breast tumor and lymph node specimens were sent for pathologic evaluation to the Institute of Pathology and Southwest Cancer Center, Southwest Hospital, Third Military Medical University, Chongqing, China. Immunostaining for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) protein was re-performed on consecutive tissue sections before the current data analysis, considering the changes in the criteria for diagnosis of ER, PR, and HER-2 positivity as well as technological advances since the time of the operations. The tumor was regarded as positive for ER and PR if $\geq$ 1% of the cells showed nuclear staining. HER-2 positivity was defined as intense and complete membrane staining in >10% of the tumor cells or HER-2 gene amplification by fluorescence in situ hybridization assay.

2.4. Postoperative treatment and follow up

Postoperative radiotherapy and adjuvant treatments were applied according to the NCCN Clinical Practice Guidelines in Oncology. All patients were followed up in the outpatient department at 3 monthly intervals. Median follow-up duration was 56 months (range, 13–107 months).

2.5. Statistical analysis

Differences in clinical and pathological characteristics between IMN positive and IMN negative groups were evaluated by the chi-square test or *t*-test. The endpoints of prognosis were OS (defined as the time from surgery until the date of death due to any cause) and DFS (defined as the time from surgery to the date of local relapse or distant metastasis). OS and DFS were analyzed by the Kaplan–Meier method, and the log-rank test was used to assess differences between groups.

Multivariate analysis to identify the factors independently associated with prognosis was performed using the Cox proportional hazards model. The variables entered into the model were age (as a continuous variable); side of tumor (right, left); site of tumor (upper inner quadrant, lower inner quadrant, upper outer quadrant, lower outer quadrant, and central); T stage (<2 cm, $\geq$2 cm); number of involved ALN (0, 1–3, $\geq$4); type of IMN operation (dissection, biopsy); pathological type (invasive ductal carcinoma, others); ER status (ER+, ER−); PR status (PR+, PR−); HER2 status (HER-2+, HER-2−); and IMN status (IMN+, IMN−). The odds ratio (OR) and hazard ratio (HR) and the corresponding 95% confidence intervals (CI) were calculated.

GraphPad Prism, version 6.0 (GraphPad Software Inc., La Jolla, CA, USA) was used for drawing the Kaplan–Meier curves and for the log-rank test. All other analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA). All tests were two-sided. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Overview of IMN metastasis in the study cohort

The mean age of the 337 patients was 46.17 ± 9.68 years (range, 23–79 years). The tumor was located on the left side in 189 patients and on the right side in 148 patients. Of the 337 patients, 314 underwent intercostal space IMN biopsy (Fig. 1), with the mean number of IMN removed being 1.89 ± 1.39. The remaining 23 patients underwent endoscopic lymphatic chain resection (Fig. 2),