A retrospective study of different local treatments in breast cancer patients with synchronous ipsilateral supraclavicular lymph node metastasis

ABSTRACT

Aim: To evaluate the local treatment outcome and efficacy of supraclavicular lymph node dissection and radical radiotherapy for breast cancer patients with synchronous ipsilateral supraclavicular lymph node metastasis (ISLM).

Materials and Methods: A total of 29 patients with ISLM in the absence of distant metastases were retrospectively analyzed. All patients received radical or modified radical mastectomy and systemic therapy. Thirteen patients received supraclavicular lymph node dissection surgery and the other patients were treated with radical radiotherapy.

Results: At the median follow-up of 47 months, 23 patients had developed distant metastases. The 3-year distant metastasis-free survival (DMFS) rates were 46.2% for the supraclavicular lymph node dissection group and 31.3% for the radical radiotherapy group. The 5-year overall survival rates were 46.2% for the supraclavicular lymph node dissection group and 37.5% for the radical radiotherapy group.

Conclusion: Breast cancer with ISLM should be considered as a locoregional disease. Besides systemic therapy, local therapy may be helpful in enhancing local control and correspondingly reducing distant metastasis. In some individual patients, supraclavicular lymph node dissection might get a good prognosis.

KEY WORDS: Breast cancer, metastasis, supraclavicular lymph node

INTRODUCTION

Breast cancer is the most common malignancy affecting women and the second leading cause of cancer death in the US and in some big cities in China.[1] The ipsilateral supraclavicular lymph node metastasis (ISLM) in breast cancer patients is a difficult problem to manage. The incidence of breast cancer patients presenting with ISLM without distant spread at the time of diagnosis is low (1-4.3%).[2,3] Historically, the position of the patients with ISLM has changed more often in the classification system. Previously it was considered as an inevitable signal of micrometastasis due to poor prognosis and was thus classified as M1 disease in 1988. However, supraclavicular metastasis was again categorized as N3 in the current sixth version of Union for International Cancer Control (UICC)/AJCC staging system in 2003,[4] based on the finding that aggressive treatment of patients with ISLM resulted in an outcome comparable to that in patients with locally advanced breast cancer without distant metastasis.[5] So, it seems reasonable to consider breast cancer with ISLM without signs of distant metastatic disease as a locoregional disease. Thereby, it might be a potentially curable disease. Selective patients with ISLM should be treated with a curative intent rather than palliative intent.

Patients with ISLM should be offered a combined modality approach, including systemic therapy, surgery, and radiotherapy. Furthermore, local treatment, usually including axillary and supraclavicular lymph node, either by surgical clearance or by radical radiotherapy, can prevent the tumor cells from drainage, might be play a more important role. However, the role of surgical removal of the supraclavicular nodes is uncertain compared with radical radiotherapy. To our knowledge, the available literature comparing these two local treatments of ISLM is scarce. All the related reports up to date have mixed them up. Therefore, in addition to investigating the role of surgical removal of the supraclavicular nodes in Chinese patients, we also try to reveal the potential difference between these two treatments, hoping to bring more insight into clinical practice.
MATERIALS AND METHODS

Patients
The study population comprised primary breast cancer patients in Tianjin Medical University Cancer Institute and Hospital between January 2005 and October 2005. Twenty-nine patients had pathologic proof of isolated ipsilateral supraclavicular lymph node metastases. All the patients were synchronous ISLM, who has no evidence of distant metastasis within 3 months, defined as ISLM at the primary diagnosis of breast cancer. A systemic survey included serum tumor markers, chest X-ray, bone scan, and ultrasound scan of the liver and neck for all patients.

All the patients were females with Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1. Detailed characteristics are listed in Table 1.

Treatment
All patients in this study received radical or modified radical mastectomy. Lymph node dissection of levels I, II, and III was performed. All patients received chemotherapy with a regimen containing anthracycline and taxane after the identification of ISLM. After chemotherapy, the patients received comprehensive external beam radiotherapy (RT) to the chest wall and the regional lymphatics as a component of their treatment. The dosage was 45-50 Gv in 20-25 fractions over 5 weeks. The patients with hormone receptor positive received further hormonal therapy.

Thirteen patients (supraclavicular lymph node dissection group) received more radical surgery (supraclavicular level IV and V lymph node dissection). In patients who received neck dissection, the average number of removed lymph nodes was 10 and the average number of positive nodes was 4.

In the other patients (radical radiotherapy group) who did not undergo supraclavicular lymph node dissection surgery, initial RT was followed by an additional 10-20 Gy boost to supraclavicular regions.

Statistical analysis
Distant metastasis-free survival (DMFS) was defined as the time from the identification with histologically or cytologically proven ISLM until that of distant metastasis either alone or combined with locoregional recurrences. The overall survival (OS) was defined as the time of the identification of supraclavicular lymph node metastasis (SLNM) until death, whether or not death was related to breast cancer. DMFS and OS rates were computed according to the Kaplan–Meier method, and the survival curves were compared by using the log-rank test. The Cox regression model provided multivariate analysis of prognostic factors for OS.

RESULTS

Patient and disease characteristics are summarized in Table 1. The median patient age at diagnosis was 47 years (range 28-69 years). All characteristics were statistically similar between the two groups (P > 0.05). The axillary lymph nodes were involved in all the patients. Of the patients with ISLM, vascular or lymphatic invasion was involved in 28 patients. The histological tumor type, defined according to the World Health Organization’s classification system, was infiltrating ductal carcinoma in 26 patients and infiltrating lobular carcinoma in 3 patients. Clinical staging indicated that 13 (44.8%) and 16 (55.2%) patients exhibited Stage T1 to T2 and Stage T3 to T4 disease, respectively. Hormone receptor positive tumors were identified in 19 (65.5%) patients. A total of 10 patients (34.5%) were positive for the HER2 receptor, when assessed by immunohistochemistry or fluorescence in situ hybridization (FISH).

Distant metastases occurred in 9 (69.2%) patients of supraclavicular lymph node dissection group and in 14 (87.5%) patients of radical radiotherapy group after median follow-up time of 43 (range 8-83) months and 27 (range 5-53) months.
respectively. The 3-year DMFS rates were 46.2% for the supraclavicular lymph node dissection group and 31.3% for the radical radiotherapy group (\(P = 0.107\)) [Figure 1].

During the follow-up period, nine patients died and the 5-year OS rate of the supraclavicular lymph node dissection group was 46.2%. On the other hand, the 5-year OS rate of the radical radiotherapy group was 37.5%. There was no statistically significant difference between the OS curve of the two groups (\(P = 0.492\)) [Figure 2].

Prognostic factors of the patients with ISLM were evaluated and two factors were identified as significant indicators of poor prognosis. Multivariate analysis suggested that the grade status (\(P = 0.026\)) and hormone receptor (\(P = 0.011\)) were independent predictors for those patients.

**DISCUSSION**

In 2001, Brito et al. published their study on 70 patients with isolated ipsilateral supraclavicular metastases in breast cancer patients who underwent multimodality treatment.[7] It appeared that patients with ISLM had better outcomes than patients with distant metastatic disease. Hence, the 2003 revision of the UICC/AJCC breast cancer TNM staging system has appropriately reclassified patients presenting with ISLM from M1 to a new category, IIIC.[5] Nevertheless, we should keep in mind that patients presenting with ISLM are at high risk for harboring distant metastatic disease, even when clinically detectable metastases are not evident. The applied multimodality treatment consisting of chemotherapy, surgery, and radiotherapy should be further investigated.

Clinical staging is generally used for the purpose of decision making of treatment allocation. This is important because it was believed by some people that once supraclavicular lymph node metastasis occurs, it is no longer curable. TNM staging system has reclassified the ISLM from M1 to IIIC. The regional therapy for ISLM should be considered important. However, there are no specific guidelines for the treatment of patients with ISLM and surgical resection of the supraclavicular regions is not routinely performed as part of mastectomy.

The role of local surgical treatment of supraclavicular metastases is not yet clear. Sometimes local surgical treatment may be considered when radiotherapy cannot be offered to a patient in an attempt to maximize locoregional control. Nevertheless, some authors advocated a surgical therapy with curative intent for patients with tumor spread confined to the ipsilateral supraclavicular nodes. In a study that described the course of patients with supraclavicular recurrence after primary disease, it was shown that surgical removal of the supraclavicular nodes was a prognostic factor for OS.[8] Tezuka et al. found that local surgical treatment of supraclavicular metastases could lead to a good prognosis.[9] So, they thought that excision of the recurrent supraclavicular lymph nodes should be considered after careful examination in some individual cases.

For the first time, the prognosis of surgical resection of the supraclavicular region is compared with that of radical radiotherapy in the present study. No significant difference was found between the two groups with respect to the important clinical features including age, menstrual status, primary tumor size, histologic grade, hormonal receptors, C-erbB2 over-expression, and so on.

It has been considered that patients of breast cancer with ISLM have a poor prognosis. Clinical studies carried out reported 5-year survival rates in patients with ISLM to range from 5 to 34%.[10-13] In 2001, Brito et al. reported that the 5-year OS of patients with ISLM was 41% after multimodality treatment. Similar outcomes have been seen in other reports since then.[14,15] The 5-year OS rates were reported to be 33.6-38%. In this study,
the 3-year DMFS rate for ISLM patients was 37.9%, which means more than half of the women would develop distant metastases in 3 years. In our study, the 5-year OS rate was 41.4%, which was very close to Brito et al.’s report. Furthermore, we compared the prognosis of a different local therapy. The 3-year DMFS rates were 46.2% for the supraclavicular lymph node dissection group and 31.3% for the radical radiotherapy group. There was no statistically significant difference between the two groups. We also compared the OS of the two groups. The 5-year OS rate of the supraclavicular lymph node dissection group was 46.2% and that of the radical radiotherapy group was 37.5%. The clinical outcome of the dissection group was not significantly superior to that of the radical radiotherapy group. According to the results of this study and others, the temporary tumor control of ISLM is not the main problem. The major issue remains the development of metastases at distant sites. Therefore, it should be borne in mind that even though ISLM is a locoregional disease, it might be a precursor of widespread disseminated disease.

Although the prognosis of the two groups seems comparable, some differences were found. Among the supraclavicular lymph node dissection group patients, there were three patients who had survived more than 5 years without any recurrence. But we could not find any patient with 5-year DMFS in the other group. It suggests that supraclavicular lymph node dissection should be considered in some individual cases.

In this study, the high histological grade levels and hormone receptor negative tumors were shown to be associated with poor prognosis of ISLM patients. However, one thing must be pointed out. This finding merely implies that disease extent is reflected by the parameters. In that sense, data presented here indicate that more valuable indicator of OS among ISLM patients should be further investigated.

In conclusion, breast cancer with ISLM should be considered as a locoregional disease. Patients with ISLM should be offered a combined modality approach, including systemic therapy, surgery, and radiotherapy. Although there are no specific guidelines for the treatment of patients with ISLM, local therapy may be more helpful in enhancing local control and correspondingly reducing distant metastasis. In some individual patients, supraclavicular lymph node dissection might get a good prognosis. Therefore, highly individualized comprehensive multimodality treatment is the optimal choice up to now that provides patients a chance of being cured.

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