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Is Here any Benefit to Perform Extensive Nodal Dissection in Primary or Recurrent Forms of Breast Cancer with Supraclavicular Lymph Node Involvement?

*Laurent P, Duhoux FP, Schmitz S, Fellah L, Galant C and Berliere M**

Breast Clinic, King Albert II Cancer Institute, Cliniques Universitaires Saint-Luc, Belgium

Abstract

Background: Breast oncologic surgery and especially nodal surgery has become more minimally invasive. However some aggressive breast cancers exhibit at their primary or recurrent presentation extensive nodal invasion at the axillary, retropectoralis, supraclavicular and sometimes cervical levels. Surgical treatment of these tumors is not standardized.

Material and Methods: Between April 2013 and April 2018, 12 primary breast cancer patients (group I) and 5 recurrent breast cancer patients (group II) were included in a monocentric, prospective non-randomized study approved by our local ethics committee. All the patients had cytologically or histologically proven supraclavicular lymph node invasion. Six of the 12 primary tumors were triple negative and the 6 others were HER2 positive tumors. In group II, 2 were triple negative, 2 HER2 positive and one Hormone Receptor (HR) positive. All patients underwent PET/CT and breast MRI at baseline. Visceral metastases were absent in all cases. In the group of primary tumors, all the patients received neoadjuvant chemotherapy plus anti HER2 agents for HER2 positive tumors. In the group of recurrent diseases, neoadjuvant chemotherapy plus anti HER2 agents in case of HER2 positive disease was administered in 4 patients and surgery was performed first for the HR positive tumor. Radiotherapy was administered to all patients with primary tumors and cervical radiotherapy to 3 of the 5 patients with recurrent tumors.

The following parameters were assessed: disease free survival, overall survival and adverse effects of surgery.

Results: The median follow-up period was respectively 44 months (12-60) in group I and 42 months (12-59) in group II.

In group I, 10 of the 12 included patients are still alive (although one developed signs of recurrence-a bone lesion). One patient died of metastatic evolution one year after the diagnosis and the second died of pneumonitis 3 years after the diagnosis. In group II, 3 patients are still alive with no signs of recurrence and 2 died of metastatic evolution, respectively 24 and 28 months after recurrence. Concerning side effects, no persistent chronic pain, or motor deficits are noted. Lymphedema is present in 4 of the 13 patients still alive.

Discussion: Patients with nodal metastases outside the axilla seem to benefit from extensive surgery integrated in a multidisciplinary therapeutic approach. Some studies have demonstrated survival benefits for patients undergoing surgical resection of these nodes.

Conclusion: In breast tumors (especially HER2 positive and triple negative tumors) presenting with extensive supraclavicular nodal invasion and no visceral metastases, surgical excision can be integrated in the multidisciplinary approach for patients responding to neoadjuvant treatments. Patients need to be followed for a long time to confirm survival benefits.

Keywords: Breast Cancer; Lymph Node; Tumors

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Correspondence:
Martine Berliere, Breast Clinic, King Albert II Cancer Institute, Cliniques Universitaires Saint-Luc, Belgium, E-mail: martine.berliere@uclouvain.be

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Introduction

Breast cancer is the most common cancer in women and is the second cause of cancer-related death. Distant metastases are described in 5% to 7% of women with breast cancer at the time of presentation. The most frequent sites of metastatic lesions are bone, lung or liver. Despite the high prevalence of breast cancer, lymph nodes in the neck are relatively rare but occur in

about 7% of metastatic breast cancer [1]. Since the sixth edition of the AJCC (American Joint Committee on Cancer-Tumor Node Metastasis) staging system for breast cancer, metastases located in the supraclavicular fossa have been considered as locoregional lesions (N3c). Lymph node metastases located above the supraclavicular region are not mentioned but should be considered as distant metastases [2].

Only a limited number of essentially retrospective studies have focused on the prognosis, tumor characteristics and treatment modalities of breast cancer patients with synchronous or metachronous supraclavicular lymph nodes metastases [3-7].

Material and Methods

Between April 2013 and April 2018, 12 primary breast cancer patients (group I) and 5 recurrent breast cancer patients (group II) were included in a monocentric prospective non randomized study approved by our local ethics committee. All the patients had cytologically or histologically proven supraclavicular lymph node invasion. Six of the 12 primary tumors were triple negative and the 6 others were HER2 positive tumors. In group II, 2 were triple negative, 2 HER2 positive and one tumor was Hormone Receptors (HR) positive. Initial assessment comprised medical history, physical examination, mammography, ultrasonography, breast magnetic resonance imaging, Positron Emission Tomography-CT (PET/CT), biopsy of the breast, and fine needle aspiration or biopsy of suspicious lymph nodes. Visceral metastases were absent in all cases. The same modalities were used for recurrent patients, except for breast biopsy.

In the group of primary tumors, all the patients received neoadjuvant chemotherapy plus anti HER2 agents for HER2 positive tumors. In the group of recurrent diseases, neoadjuvant chemotherapy was administered in 4 patients, and 2 of them also received anti-HER2 agents, while surgery was first performed for the HR positive tumor. Neoadjuvant chemotherapy for triple negative tumors consisted of anthracycline-based regimens followed by taxane-based regimens. For HER2 positive tumors, trastuzumab was added to taxane-based regimens, with the recent addition of a second HER2-blocking agent, pertuzumab. For recurrent diseases, taxane-based regimens were used to avoid the cumulative cardiac toxicity of anthracyclines. In group I, surgery consisted of either mastectomy or breast-conservative surgery, according to institutional guidelines [8]. Extensive nodal dissection was performed with the collaboration of a head and neck surgeon. In group II, no recurrent disease was observed in the breasts, and extensive nodal dissection was performed. Radiotherapy was administered in all primary tumors and targeted to the breast or chest wall and ipsilateral apex and supraclavicular fossa compartment, and cervical radiotherapy was administered in 3 of the 5 recurrent tumors.

Patients and tumor characteristics are listed in Table 1 and 2.

The following parameters were assessed: Disease Free Survival (DFS), Overall Survival (OS) and adverse effects of surgery.

Results

The median follow-up period was respectively 44 months (12-60) in group I and 42 months (12-59) in group II.

In group I, 10 of the 12 included patients are still alive (although one developed signs of recurrence - a bone lesion). One patient died of metastatic evolution one year after the diagnosis and the second died of pneumonitis 3 years after the diagnosis. The DFS and OS were respectively 75% and 83.3%. In group II, 3 patients are still alive with no signs of recurrence and 2 have died of metastatic evolution, respectively 24 and 28 months after recurrence. The DFS and OS are at 60%.

Table 1: Synchronous supraclavicular nodes (n=12 patients).

Mean age	45 years (34-68)
Mean duration of follow-up	44 months (12-60)
Histologic subtype	
- Infiltrating ductal carcinoma	10
- Infiltrating lobular carcinoma	2
Grade	
- II	1
- III	11
HR status	
- Positive	1
- Negative	11
HER2 status	
- Positive	6
- Negative	6
Neoadjuvant chemotherapy	
- Yes	12
- No	0
Extensive surgery	
- Yes	12
- No	0
Radiotherapy	12
Anti-HER2 agents	6
Endocrine therapy	
- Yes	1
- No	11

Concerning side effects, no persistent chronic pain, or motor deficits are noted. Lymphedema is present in 5 of the 13 patients still alive (3/12 in group I (25%) and 2/5 in group II (40%)).

Discussion

In the literature, only few studies have evaluated breast cancer patients with synchronous metastatic supraclavicular lymph nodes [1,3,4,6,8]. Before 2002, breast cancer patients who were in this clinical context were considered as incurable because of the metastatic status. The study performed by Brito [4] and the MD Anderson Cancer Center demonstrated that a multidisciplinary strategy applied to this group of patients could improve overall and disease free survival and recommended modifying the classification of these patients and changing the therapeutic approach.

The sixth edition of the American Joint Committee on Cancer-Tumor Node Metastasis (AJC-TNM) staging system reclassified ISCLN (Ipsilateral Supraclavicular Lymph node metastasis) from M1 to N3C [2]. This update illustrates the improved survival of patients who presented with involved cervical nodes and the fact that for recurrent diseases, cervical nodes can mean isolated recurrence and not systemic disease.

Table 2: Recurrent disease (n=5 patients).

Mean age	49 years (38-74)
Mean duration of follow-up	42 months (11-59)
Histologic subtype	
- Infiltrating ductal carcinoma	4
- Infiltrating lobular carcinoma	1
Grade	
- II	4
- III	1
HR status	
- Positive	1
- Negative	4
HER2 status	
- Positive	2
- Negative	3
Neoadjuvant chemotherapy	
- Yes	4
- No	1
Radiotherapy	
- Yes	4
- No	1
Anti-HER2 agents	
- Yes	2
- No	3
Endocrine therapy	
- Yes	1
- No	4

During the last decade, important progress has been made in the systemic treatment of aggressive subtypes of breast cancer [8-9]. The neoadjuvant approach [9], consisting of neoadjuvant chemotherapy alone for triple negative breast cancers and neoadjuvant chemotherapy associated with HER2 blocking agents for HER2 positive disease, allows for the identification of patients with a good clinical response to systemic therapies. A more aggressive multidisciplinary approach can be offered to these selected patients with locally advanced breast cancer, in an attempt to cure them. In this context, only few studies have focused on the role of neck dissection [3-5]. The study of Brito and the study of Chen [3-5] have demonstrated a significant improvement in 5 and 10-year survival without distant metastases for patients who had neck dissections of level I and part of III and V. Our small study observed good results after nodal dissection performed by a head and neck surgeon.

We need to insist on the fact that our study has important biases: this is a small, unicentric and non-randomized study but nevertheless, preliminary results of this multidisciplinary approach are encouraging.

The same progress has been observed for oligometastatic patients: in this group of patients, surgery can be proposed after primary response to neoadjuvant therapies and only if surgery is able to resect the entirety of the lesions, which is the case for cervical nodes.

Concerning side effects and morbidity of the surgical approach, in our series we did not observe any persistent chronic pain or motor deficits. However, lymphedema of the ipsilateral arm was noted in 25% of patients of group I and 40% of patients of group II, but this second group is a too small to draw any conclusions.

These results did not differ from the results observed in the literature after extensive nodal dissection [10].

Conclusion

In breast tumors (especially HER2 positive and triple negative tumors) presenting with extensive supraclavicular nodal invasion and no visceral metastases, surgical excision can be integrated in the multidisciplinary approach for patients responding to neoadjuvant treatments. Patients need to be followed for a long time to confirm survival benefits. In the near future, prospective randomized trials need to be conducted to confirm these interesting results.

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