Profile and Outcome of Supraclavicular Metastases in Patients with Metastatic Breast Cancer: Discordance of Receptor Status Between Primary and Metastatic Site

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Abstract. *Background: Breast cancer is a heterogenous and complex disease. A rare site of metastatic breast cancer disease is the neck. Data about supraclavicular metastases in patients with metastatic breast cancer are still lacking. Hence, our study aimed to analyze histological subtypes of supraclavicular metastases compared to the primary site. Materials and Methods: This was a retrospective hospital-based cohort study of patients with breast cancer who developed supraclavicular metastases. Diagnosis of supraclavicular metastases was confirmed by biopsy or diagnostic lymph node extirpation. Histological subtypes were analyzed and Kaplan–Meier estimates were calculated for overall survival. Results: A total of 20 patients were included in the analysis. The majority of the patients (12/20) had hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative supraclavicular metastases, disease in 3/20 patients was HR-positive/HER2-positive, HR-negative/HER2-positive in 1/20 patients and basal-like in 4/20 patients. Total discordance rates for estrogen receptor, progesterone receptor and HER2 between primary and metastatic tumors were 20.0%, 36.8% and 29.4%, respectively. The 5-year overall survival was 80%, whereas the 5-year survival after the onset of neck metastasis was 45%. Conclusion: As a rare site of metastatic breast cancer, supraclavicular metastases are associated with a worse median overall survival from their onset. The high rate of discordance of histological subtype stresses the necessity for biopsies in patients with supraclavicular metastasis.*

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Key Words: Metastatic breast cancer, neck metastasis, supraclavicular metastasis, hormone receptor.

Breast cancer is a heterogenous and complex disease (1). Breast cancer can spread to other sites of the body resulting in metastatic breast cancer (1, 2). In the course of time, approximately 20-30% of patients with early breast cancer develop distant metastases and suffer tumor-related death (3-7). A rare site of metastatic breast cancer is the neck as it accounts for 4% of patients with metastatic breast cancer (8, 9). Neck metastases can be located both in the supraclavicular area and in the upper *jugularis* level (8, 10). The receptor status is known to be an important predictive and prognostic factor and is able to switch in metastatic breast cancer (3).

Whereas lung, bone and liver metastases are usually luminal type of cancer, brain metastases are known to be of the basal type (11, 12). Data about supraclavicular metastases in patients with metastatic breast cancer are still lacking. Hence, our study aimed to analyze histological subtypes of supraclavicular metastases compared to the primary site. Of particular interest was the outcome of patients with supraclavicular metastases of breast cancer.

Materials and Methods

This was a retrospective hospital-based cohort study including unselected patients with breast cancer who developed supraclavicular metastases. Patients were treated between 2013 and 2018 at the University Hospital of Cologne. Diagnosis of supraclavicular metastasis was confirmed by biopsy or diagnostic lymph node extirpation.

The patient charts were analyzed regarding age, therapy and outcome. The histopathological reports were analyzed for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2/neu (HER2) expression of the primary tumor and the neck metastases. ER and PR expression were analyzed using the immunoreactive score (8, 13, 14). HER2 expression was analyzed according to the American Society of Clinical Oncology/College of American Pathologists guideline (8, 14). Strongly positive (3+) cases or those positive by fluorescence *in situ* hybridization were considered *HER2*-amplified tumors (8). Hormone receptor-positive was defined as ER- and/or PR-positive.

Table I. Patient characteristics.

Characteristic	N	Percentage (%)
Number of patients	20	
Age, years		
Mean (interquartile range)	56 (21-70)	
Chemotherapy		
Neoadjuvant	8	40.0
Adjuvant	12	60.0
Surgery		
BCS	13	65.0
Mastectomy	5	25.0
Unknown	2	10.0
Axillary surgery		
Sentinel node biopsy	3	15.0
Axillary lymph node dissection	15	75.0
Unknown	2	10.0
Recurrence		
Local recurrence	5	25.0
Axillary recurrence	4	20.0
Primary site		
HR-positive/HER2-negative	9	45.0
HR-positive/HER2-positive	1	5.0
HR-negative/HER2-positive	4	20.0
Basal like	3	15.0
Unknown	3	15.0
Metastatic site		
HR-positive/HER2-negative	12	60.0
HR-positive/HER2-positive	3	15.0
HR-negative/HER2-positive	1	5.0
Basal like	4	20.0
Discordance in histological subtype	9	52.9

BCS: Breast-conserving surgery, HR: hormone receptor, HER2: human epidermal growth factor receptor 2.

Rates of discordance in histological subtype between primary and metastatic sites were analyzed. In addition, localization of further metastases and further treatment were analyzed.

Statistical analysis. Patient characteristics are described using absolute numbers (percentage), mean±standard deviation (SD) or median [interquartile range (IQR)], as appropriate. Associations between two qualitative variables were tested using Fisher's exact test. Kaplan–Meier estimates for overall survival were calculated and compared by log-rank test.

Overall survival was defined as the time between diagnosis and death. Patients without an event or who were lost to follow-up were censored. All reported *p*-values are two sided and values of *p*<0.05 were considered statistically significant. As the analyses were regarded as explorative no adjustment for multiple testing was made. Statistical analyses were performed using SPSS 25 (IBM Corp., Armonk, NY, USA).

Results

A total of 20 patients were included in the analysis. Their mean age was 56 years (range=26-71 years). Among the

Table II. Localization of additional distant metastasis.

Localization	N	Percentage (%)
Liver	1	5.0
Lung	2	10.0
Bone	2	10.0
CNS	1	5.0

CNS: Central nervous system.

Table III. Further treatment after diagnosis of supraclavicular metastases from breast cancer.

Treatment	N	Percentage (%)
Surgery	8	40.0
Radiation	8	40.0
Chemotherapy	16	80.0
Electrotherapy	2	10.0
Bevacizumab treatment	8	40.0
Anti-HER2-treatment	6	30.0
Endocrine therapy	13	65.0
Other	4	20.0

HER2: Human epidermal growth factor receptor 2/neu.

study cohort, 12/20 patients underwent adjuvant therapy, and 13/20 patients underwent breast-conserving therapy at the time of primary diagnosis. Of the study cohort, 15/20 patients underwent axillary lymph node dissection. A summary of patient characteristics and treatment of primary tumor is presented in Table I.

In total, 5/20 of the patients experienced a local recurrence and 4/20 experienced an axillary recurrence. The mean time from primary diagnosis and diagnosis of supraclavicular metastasis was 7 years (range=0-21 years). The hormone receptor rates are given in Table I. Half of the patients had hormone receptor-positive primary disease.

Among the 17 patients with paired receptor status, the discordance rate of histological subtype was 52.9% (Table I). Total discordance rates for ER, PR and HER2 were 20.0% (4/20), 36.8% (7/19) and 29.4% (5/17), respectively. Additional distant metastases were detected in liver, lung, bone and central nervous system (Table II). After diagnosis of supraclavicular metastases, patients underwent further therapy as shown in Table III.

In total, 10 patients with neck metastases died (50.0%) during the follow-up period. The median overall survival after primary diagnosis was 14.0 years (Figure 1), with a 5-year overall survival rate of 80%, whereas the median survival duration after the onset of neck metastasis was 3.0 years (Figure 2), with a 5-year survival rate of 45%.

Figure 1. Overall survival after primary diagnosis.

Figure 2. Overall survival after onset of supraclavicular metastases.

Discussion

In this retrospective analysis, 20 patients with metastatic breast cancer and histologically-proven supraclavicular lymph node metastasis were reviewed.

Median survival of patients with metastatic breast cancer ranges from 2 to 3 years (15, 16). For patients with supraclavicular metastases, median overall survival of 86 months after primary diagnosis and 34 months after diagnosis of supraclavicular metastases was reported in a previously published study (8). Surprisingly, median overall survival after primary diagnosis was longer than this in the current analysis, whereas median survival after onset of supraclavicular metastases was similar at 3 years. A reason for the difference in mean overall survival might be the different pattern of oligometastatic disease of the patients analyzed. Discordance of histological subtype (ER, PR, HER2) of primary and metastatic tumors has been discussed in numerous studies since the late 1970s (17-19). Several studies showed an association between discordance of histologic subtype and worse overall survival (17, 19, 20). The current analysis confirms a high incidence of discordance of histological subtype. The change of PR in particular was observed more frequently than ER change, in accordance with several previous publications (20-23). The treatment of supraclavicular metastases seems to be a challenging medical situation in patients with metastatic breast cancer. Especially, the therapeutic effect of surgical treatment seems to be uncertain (24). Hence, a multimodal approach might be advantageous.

Conclusion

As a rare site of metastatic breast cancer, supraclavicular metastases are associated with a worse median overall survival from their onset. The high rate of discordance of histological subtype stresses the necessity for biopsies in patients with supraclavicular metastasis.

Conflicts of Interest

The Authors declare that they have no conflict of interest in regard to this study.

Ethical Approval

All procedures were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Received August 27, 2018

Revised September 11, 2018

Accepted September 12, 2018