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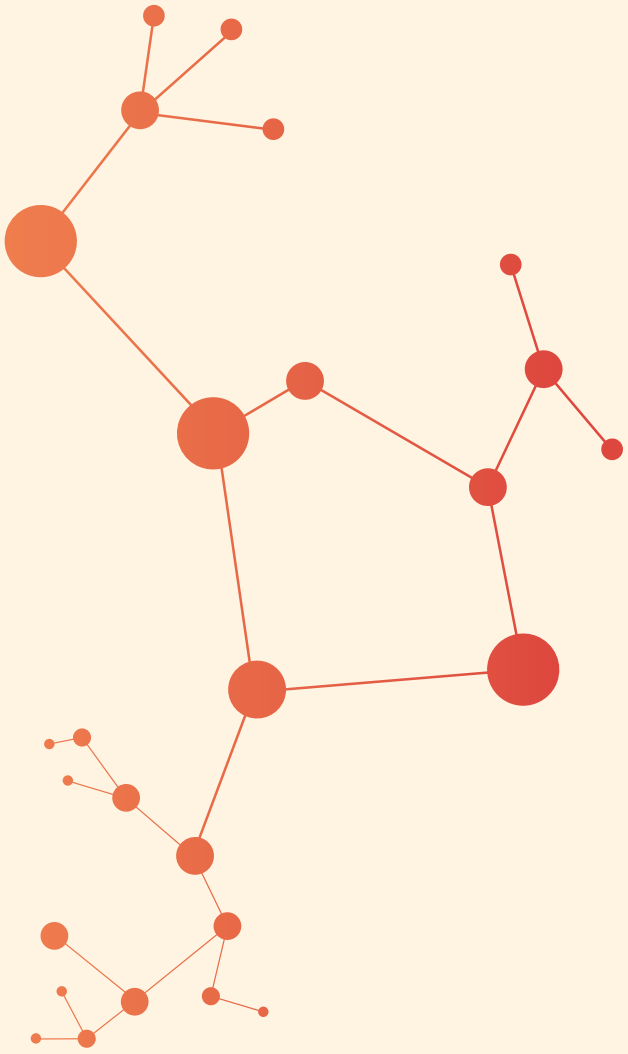

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METASTATIC BREAST CANCER

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June 2019

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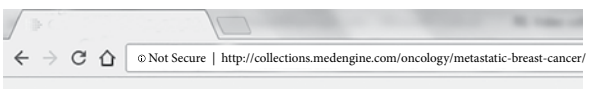

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Zhao et al. BMC Cancer (2018) 18:1290
https://doi.org/10.1186/s12885-018-5217-5

BMC Cancer

RESEARCH ARTICLE

Breast cancer primary tumor ER expression pattern predicts its expression concordance in matched synchronous lymph node metastases

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Abstract

Background: Estrogen receptor (ER) expression is important for treatment selection and prognostication of breast cancer patients. Although the metastases are the main targets of endocrine therapy, ER status is often based on the primary tumor. However, ER expression in breast cancer primary lesion may not match with its synchronous metastatic lesions in some cases. In this study, we analyzed ER expression concordance between breast cancer primary tumor and metastatic lesions.

Methods: Paraffin blocks of 100 primary breast invasive ductal carcinoma cases with axillary lymph node metastases were collected. Five tissue cores were punched out from individual primary breast cancer, and one tissue core from each lymph node metastases to assemble tissue microarrays for ER staining. Samples were then scored as 0, 1+, 2+, and 3+ according to the number and intensity of ER stained tumor cells.

Results: For cases with ER 3+ (strong expression) in all cores of primary lesions ($n = 38$), ER expression in metastatic lymph node was found in 94.7% of the patients. 91.0% of the metastatic lymph nodes were ER positive, and 84.3% of them to be 3+. Among the 46 cases of ER negative expression in all cores of primary lesions, 39 of them had all the metastatic nodes being ER negative, and ER negative nodes were seen in 95.7% of the metastases. As for 16 cases of ER inconsistent expression in primary lesions, 4 cases showed negative ER expression in all metastatic nodes, 2 cases displayed diffuse consistent ER 3+ expression, and 10 cases displayed variant ER expression.

Conclusions: The findings suggest that ER expression concordance between breast cancer primary lesion and its matched metastatic lesions could be estimated by primary tumor ER expression pattern.

Keywords: Breast cancer, Metastasis, Estrogen receptor, Concordance

Background

Estrogen receptor (ER) expression is important for treatment selection and prognostication of breast cancer patients. Although the metastases are the main targets of endocrine therapy, ER status is often based on the primary tumor. However, ER expression in breast cancer primary lesion may not match with its synchronous metastatic lesions in some cases. There are several studies reported the changes of ER expression in the metastatic tumors when compared to the primaries [1–5]. In some studies, change of ER status was regarded to be rare for metastasis [2, 4], whereas others found that metastatic tumors are different from the primary ones in ER expression [1, 3, 5].

Biological explanations for discrepant ER expression in metastases have been mentioned, including heterogeneity of the primary lesion, cancer cells early distant seeding, clonal selection, and therapy induced clonal evolution [6, 7]. Whether the extensity and intensity of

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ER positive cells in the primary lesion influence the ER status of the metastases, so far, has not been investigated.

In this study, multiple tissue cores were punched from each of 100 breast invasive ductal carcinoma primary lesion. Tissue core was also punched from every individual metastatic lymph node. The aim of the study was to analyze the agreement of ER expression among different tissue cores from the same primary lesion and each individual metastatic lymph node. The effect of ER positive cells extensity on ER expression agreement was also studied.

Methods

Patients and samples

This study was conducted with the approval of the Shaoxing Hospital Institutional Review Board. Informed consent was obtained from all the patients before surgery regarding the data and samples to be used for research. All study procedures were carried out in accordance with the ethical standards of the Helsinki Declaration. Breast invasive ductal carcinoma patients treated with mastectomy or lumpectomy, and standard level I/II axillary lymph node dissection were reviewed. Archival specimens from primary tumor and lymph node metastases were reviewed independently by two pathologists to confirm the histological diagnosis and tumor grade. Patients with both primary tumor and lymph node metastases samples were included, those received any neoadjuvant therapy were excluded. One hundred qualified patients were finally identified in the period from Jan. 2008 to Oct. 2014. Forty patients were under the age of 50 years old. The cases with high, moderate, and low differentiation were 1, 53, and 46 cases, respectively. Those with T1, T2, and T3 disease were 28, 65, and 7 cases. Sixty patients had 4 or more metastatic lymph node.

Tissue microarray (TMA) construction

A manual tissue microarrayer (TM-1, Beijing Boyikang Laboratory Instrument Limited Company, Beijing, China) was used to construct the TMAs. Five 2-mm-diameter tissue cores were punched out from the representative areas of invasive carcinoma of the donor blocks. For lymph node metastases, 2-mm-diameter tissue core was punched out from the representative area of each metastatic node. The cores were transferred into the pre-punched hole in the recipient block according to the location on the TMA map. From each TMA block, 4-μm sections were cut on a microtome (Leica RM2245, German Leica Instruments Limited Company, German) and transferred to adhesive-coated slides. One section from each tissue array block was stained with hematoxylin and eosin, and core loss or gain assessed.

ER staining and scoring

The sections were deparaffinized in xylene and hydrated through graded concentrations of ethanol to distilled water. Following the antigen retrieval, slides were incubated in 3% H_2O_2 for 10 min. After being washed, the slides were incubated overnight with primary antibody (diluted 1:400) directed against estrogen receptor alpha (clone SP1, Maixin biotechnology co., LTD, Fuzhou, China) at 4 °C. After the sections were incubated in secondary antibody, the slides were finally counterstained with hematoxylin and mounted. As positive controls we used in house positive control tissue sections as well as commercially supplied positive control sections. Known ER-positive breast cancer tissue cores were used as well. As negative controls, PBS was used instead of the primary antibody. Controls were included in each staining batch.

The ER-score was graded according to the percentage of nuclei stained tumor cells and the intensity of the staining. The proportion of positive cells was scored using a scale of 0–4, where 0 corresponded to no tumor cells were stained, 1 corresponded to < 10%, 2 corresponded to 11–50%, 3 corresponded to 51–80%, 4 corresponded to > 80% of the tumor cells were stained. The staining intensity was scored as 0, 1, 2 or 3. The TMA was evaluated independently by two pathologists (J.Z. and C.W.). In case of a discrepancy, the 2 observers simultaneously reviewed the slides under a multi-headed microscope to achieve a consensus. The immunoreactive score (IRS) is the product of a proportion score and an intensity score with a range of 0–12. The ER staining was then graded as negative expression, 0+ (IRS of 0 and 1); weak expression, 1+ (IRS of 2 and 3); moderate expression, 2+ (IRS of 4, 6 and 8); strong expression, 3+ (IRS of 9 and 12).

Results

ER expression of primary tumors and the concordance among different cores

A total of 498 cores were punched from 100 breast cancer primary lesion blocks, and tumor cells were identified in 472 cores. In 54 of 100 (54%) patients, immunostaining for ER was found in at least one core of the primary tumors. Accordingly, negative ER staining was seen in the rest 46 (46%) cases.

When all of the 472 tumor cell positive cores were analyzed, the patients were classified into three groups (Fig. 1a). One group included 38 cases, all cores obtained were found to be ER strongly expressed (3+). In another group of 46 primary lesions, all cores obtained were ER negatively stained. The third group is the rest 16 cases, a total of 80 cores were taken from the primary lesion blocks, tumor cells were found in 78 cores.

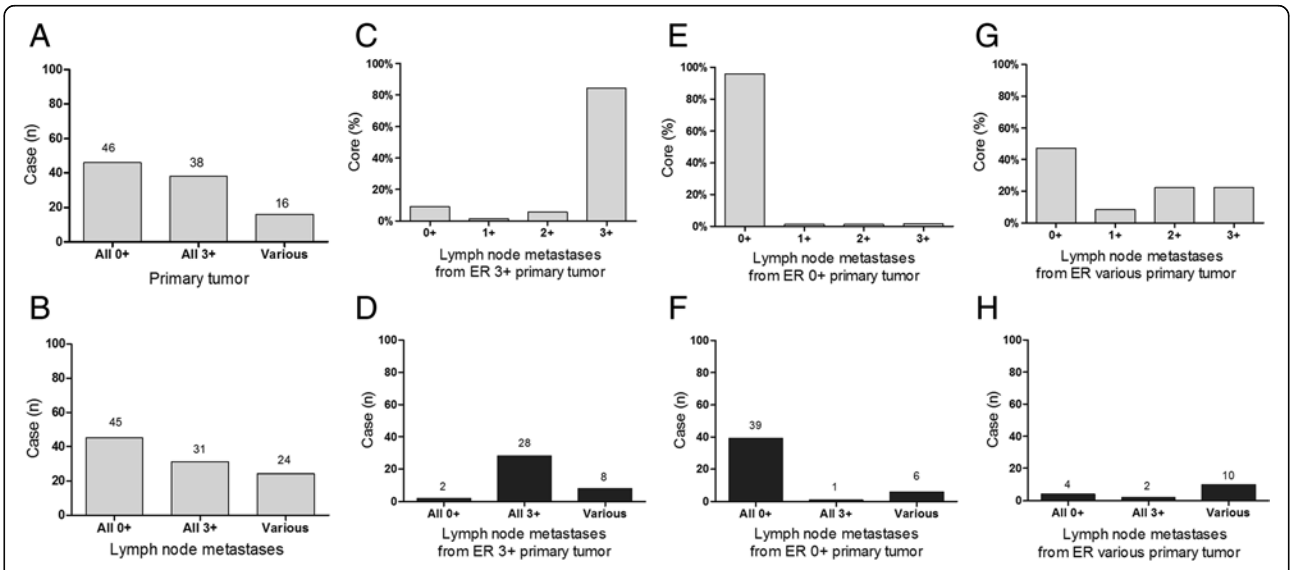

Fig. 1 ER score in primary tumor and lymph node metastases. **a**: The cases in which all cores obtained were found to be ER negatively stained (0+), strongly expressed (3+), or various ER score in primary tumor. **b**: The cases in which all cores obtained were found to be ER negatively stained (0+), strongly expressed (3+), or various ER score in lymph node metastases. **c**, **e**, and **g**: The percentage of ER expression (0+, 1+, 2+, 3+) in lymph node metastases from patients with all cores obtained to be ER strongly expressed (**c**), negatively stained (**e**), or various ER score (**g**) in primary tumor. **d**, **f**, and **h**: ER expression status in lymph node metastases from patients with all cores obtained to be ER strongly expressed (**d**), negatively stained (**f**), or various ER score (**h**) in primary tumor

Among the 78 tumor cell positive cores, the ER expression levels ranged as 3+, 2+, 1+ or 0 were found in 24 (30.8%), 30 (38.5%), 12 (15.4%), and 12 (15.4%) cores, respectively. The staining details of each core from all these 16 cases are shown in Table 1.

ER expression of lymph node metastases and the concordance among different nodes

Totally, 687 axillary lymph metastases were dissected from 100 breast cancer patients, and were punched for ER staining, tumor cells could be seen in 627 cores. In

Table 1 Cases with inconsistent cores ER expression status in primary lesions ($n = 16$)

Case ID	N of cores (3+)	N of cores (2+)	N of cores (1+)	N of cores (0+)	N of cores No tumor
1	3	1	0	1	0
2	2	1	0	1	1
3	0	3	1	1	0
4	1	2	1	1	0
5	1	3	1	0	0
6	2	3	0	0	0
7	2	2	0	1	0
8	0	3	1	0	1
9	0	3	2	0	0
10	2	1	0	2	0
11	0	2	3	0	0
12	0	3	2	0	0
13	4	1	0	0	0
14	3	1	0	1	0
15	4	1	0	0	0
16	0	0	1	4	0
Total	24	30	12	12	2

55 of 100 (55%) analyzed patients, positive ER expression was evident in at least one metastatic node core, and for the other 45 cases, all metastatic lymph nodes were scored as ER negative.

As shown in Fig. 1b, when all the 627 metastatic lymph node cores from the 100 breast cancer patients were analyzed, 31 cases were ER strongly expressed (3+) in all the node cores, while 45 cases were ER negative stained in all the cores. For the remaining 24 cases, 212 axillary lymph metastases cores were taken. The ER expression scored as 3+, 2+, 1+ or 0 were found in 60 (28.3%), 34 (16.0%), 13 (6.1%), and 105 (49.5%) cores, respectively. The staining details of each core from all these 24 cases are shown in Table 2.

Comparison of the ER status between primary tumors and lymph node metastases

In all the primary lesions samples with ER 3+ staining, 36 out of 38 (94.7%) patients had ER positive lymph node metastases. A total of 255 cores of lymph node metastases were analyzed from these 38 patients. Among them, 215 (84.3%) cores had ER expression scored 3+, 14 (5.5%) had ER expression scored 2+, and 3 (1.2%) had ER expression scored 1+. Taken together, positive ER expression (3+, 2+ or 1+) was found in 91.0% (232/255) of the lymph node metastases. Accordingly, negative ER staining was seen in 23 (9.0%) of the lymph node metastases (Fig. 1c). As shown in Fig. 1d, in 28 out of the 38 cases, all the metastatic nodes were scored as 3+ ER expression (Fig. 2). In 2 cases, all nodes were ER negatively stained. And the rest of 8 cases had uniform 3+ expression in the primary lesions, metastatic lymph nodes with 3+ ER expression were found in all cases, however lower ER expression (2+, 1+ or 0) were also seen in the nodes. Among the 83 metastatic lymph node cores obtained from these 8 cases, ER expression scored as 3+, 2+, 1+ or 0 were respectively found in 46 (55.4%), 14 (16.9%), 3 (3.6%), and 20 (24.1%) cores.

In the 46 ER negative in all the primary lesions samples group, totally 300 lymph node metastases were taken through axillary dissection, 287 (95.7%) cores had negative ER expression, 4 (1.3%) had ER expression

Table 2 Cases with inconsistant cores ER expression status in metastatic lymph nodes ($n = 24$)

Case ID	N of nodes All	N of cores (3+)	N of cores (2+)	N of cores (1+)	N of cores (0)
1	22	19	2	0	1
2	13	9	3	0	1
3	11	8	0	1	2
4	10	2	6	0	2
5	9	4	2	1	2
6	9	2	0	0	7
7	2	1	0	0	1
8	7	1	1	1	4
9	5	3	1	1	0
10	5	4	0	1	0
11	8	2	6	0	0
12	7	2	1	1	3
13	6	0	5	0	1
14	3	2	0	1	0
15	1	0	1	0	0
16	1	0	1	0	0
17	1	0	1	0	0
18	10	0	0	2	8
19	22	0	1	0	21
20	22	0	1	0	21
21	18	1	0	0	17
22	10	0	1	0	9
23	6	0	1	3	2
24	4	0	0	1	3
Total	212	60	34	13	105

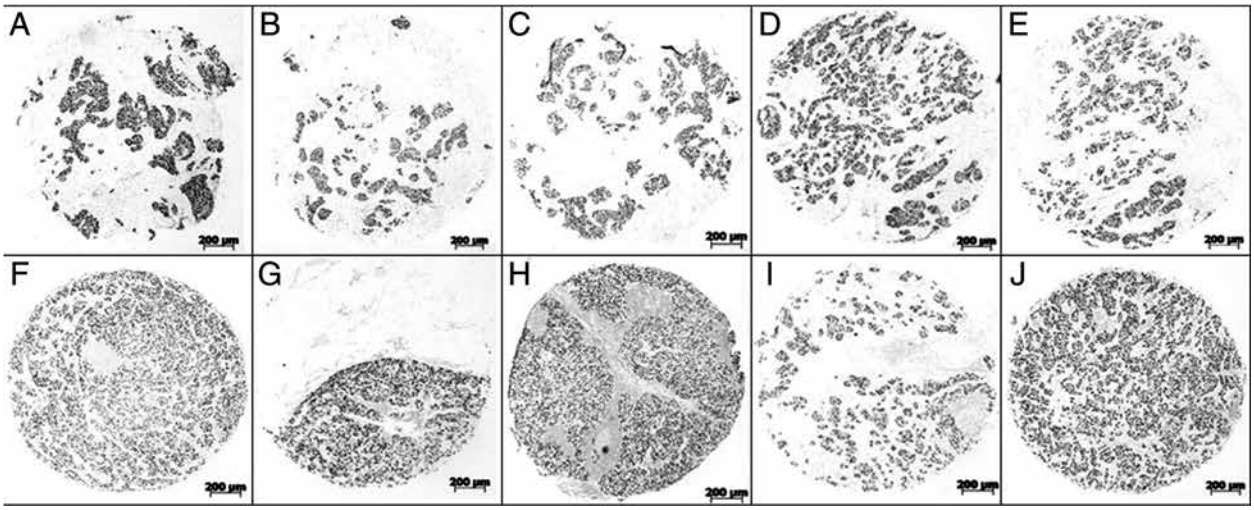

Fig. 2 Examples of concordant immunohistochemical brown stainings of breast primary tumor and corresponding metastases. These samples were from the same patient, all the primary tumor cores (**a**, **b**, **c**, **d** and **e**) were ER-stained and scored 3+, corresponding metastatic sites (**f**, **g**, **h**, **i** and **j**) were all scored as 3+ ER expression as well. This case shows concordant 3+ ER expression among different tissue cores from the same primary lesion and every individual metastatic site

scored as 1+, another 4 (1.3%) had 2+, and 5 (1.7%) had ER expression scored as 3+ (Fig. 1e). As shown in Fig. 1f, 39 out of 46 cases (84.8%) were scored as ER negative expression in all the metastatic nodes. In one case, all nodes were ER 3+. In the other 6 cases, as shown in Table 2 (case 19–24), 82 metastatic lymph nodes were dissected, 73 node cores (89.0%) were found to be ER negative, the ER positive cores ranged as 1+, 2+ or 3+ were 4 (4.9%), 4 (4.9%), and 1 (1.2%) respectively.

In the remaining 16 cases ER expression was disagreement among the cores from each primary lesion (as shown in Table 1). A total of 72 lymph node metastases were found through axillary dissection. As shown in Fig. 1 g and h, among the 16 cases, 4 of them were ER negative in all the detected 22 nodes, 12 cases were seen positive ER expression in the metastatic nodes. Within the 12 cases, 2 with all the nodes strongly expressed ER 3+, the other 10 cases had different ER expression levels, as shown in Table 2 (case 9–18). 47 metastatic nodes were found from the 10 cases, the nodes with ER expression level scored as 3+, 2+, 1+ or 0 were 13 (27.7%), 16 (34.0%), 6 (12.8%), and 12 (25.5%), respectively. Examples of variant ER expression in primary tumor and the corresponding metastatic sites are shown in Fig. 3.

Discussion

In the present study, special attention was paid to the ER expression agreement among different tissue cores from the same primary lesion and their individual metastatic lymph node. The effect of ER expression pattern on ER expression concordance was studied. We found that ER expression concordance between breast cancer primary lesion and its matched synchronous lymph node metastases could be estimated by primary tumor ER expression pattern.

For patients with 3+ ER staining in all primary lesion cores, positive ER in the metastatic lymph nodes was found in about 95% of the patients. When each individual lymph node was analyzed, more than 90% of the metastatic lymph nodes were found to be ER positive in this patient group, and majority of them were 3+. For those with primary lesions being negative of ER staining in all the punched cores, although metastatic lymph node ER status gained in few cases, more than 95% of the nodes was ER negative. However, for those ER expression level varied among different punched cores from primary lesions, one quart of patients presented with ER negative lymph node metastases, one eighth with all the nodes to be strongly ER stained, about 60% with nodes expressed ER in different intensity. High concordance of ER status between the primary lesions and the paired metastatic lymph nodes could be expected in patients with uniform ER expression in all the punched cores from primary lesions, no matter it is strong ER expression or negative of ER at all. For those ER expressed in variant intensity in the primary tumor, changes of ER status in lymph node metastases were more frequent. Thus for the first time, we found that ER expression concordance between breast cancer primary lesion and its matched synchronous metastatic lesions could be estimated by primary tumor ER expression pattern.

According to our finding, diffused strong staining is the most common pattern of ER expression. Around

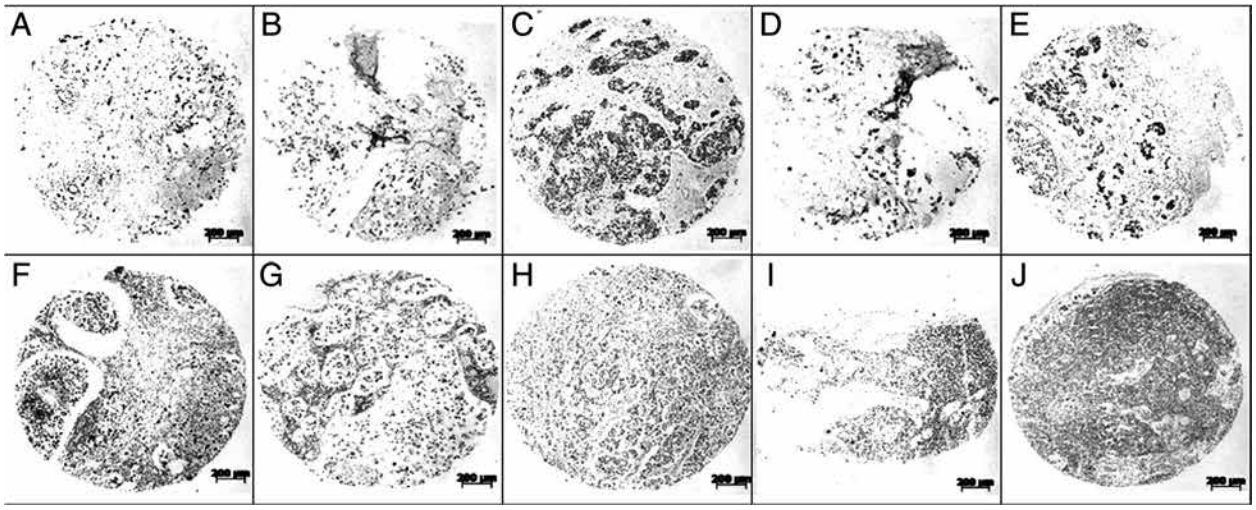

Fig. 3 Examples of various immunohistochemical stainings of breast primary tumor and corresponding metastases. These samples were from the same patient, variant ER expression was seen in the primary tumor cores (**a**, **b**, **c**, **d** and **e**), different ER expression was also found in the corresponding metastatic sites (**f**, **g**, **h**, **i** and **j**). This case shows various ER expressions among different tissue cores from the same primary lesion and every individual metastatic lymph node

80% of the ER positive breast cancer cases scored as 3+ in all the punched cores. Positive ER staining in all the cores regardless of the expression extensity (3+, 2+, and 1+), was identified in up to 10% of the cases. For the other 10% of the cases, both positive and negative ER staining was found in some of the cores from the same primary lesions. In clinical practice, it is important to keep in mind of the pattern of ER expression, as it correlated with the ER status in the metastases which matters of the response to endocrine therapy in breast cancer.

The frequency of ER expression in breast cancer has been reported to vary from 66.3% up to about 80% [8–11]. Sofi et al. reported an ER expression rate of 66.3% in 132 assessed invasive ductal carcinoma patients [8]. Thompson et al. reported ER expression rates of 79.6 and 73.7% in primary lesions and metastatic lesions, respectively [9]. In the present study, ER expression rate is lower than what previously reported. This is because, to perform our study, only those cases with lymph nodes metastases were selected. Zhu et al. and Yi et al. also reported lower ER expression rate in cases with lymph nodes metastases than those without metastases [10, 11].

The general ER expression discordance is observed in 13% of the paired samples, 7.0% of the cases gained ER expression in the matched synchronous metastatic nodes, and 6.0% lost. The frequency of ER expression discrepancy between the primary lesions and the paired metastases has been reported to vary from 2.6% up to about 22.4% [1, 3, 5]. In a review by Yeung et al., 3384 matched primary and metastatic pairs reported from 47 studies were analysed, ER expression median discordance between primary and metastatic site is 14% [12]. In respect to the general concordance, our result is consistence with the previous reports.

Conclusion

ER expression pattern of primary breast tumor could be used to predict ER expression concordance between primary lesion and its matched synchronous metastatic lesions. High concordance of ER status between the primary lesions and the paired metastatic lymph nodes could be expected in patients with uniform ER expression in all the punched cores from primary lesions, no matter it is strong ER expression or negative at all. As discordance in ER status between primary breast cancer and metastatic lesion occurred in 13.0% of cases, ER status of the metastatic site should be assessed if possible, especially in patients with variant ER expression in primary sites.

Acknowledgements

The authors would like to thank Dr. Xiao-qun Zhang from Biomedical Center, Uppsala University for editorial assistance, and thank the colleagues at the Department of Pathology for help with the immunohistochemical staining.

Funding

This work was supported in part by the Zhejiang University Research Foundation (K17–518052-002) in the design of the study and analysis, interpretation of data and in writing the manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JZ participated in the design of the study, carried out the clinical and immunohistochemical data analysis; CH and CW interpreted the histological and immunohistochemical data; WY, YG and MS contribute with the clinical data analyse and involved in drafting or revising the manuscript; YS and QW

conceived the study, interpreted the immunohistochemical data and wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
This study was conducted with the approval of the Shaoxing Hospital Institutional Review Board. Written informed consent was obtained from all participants. All study procedures were carried out in accordance with the ethical standards of the Helsinki Declaration.

Consent for publication
Not applicable.

Competing interests
All authors declared no conflict of interest.

Publisher's Note

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Received: 8 May 2018 Accepted: 13 December 2018
Published online: 27 December 2018

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Breast Cancer Research and Treatment (2019) 173:209–216
https://doi.org/10.1007/s10549-018-4968-7

EPIDEMIOLOGY

Association between prolonged metastatic free interval and recurrent metastatic breast cancer survival: findings from the SEER database

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Received: 26 July 2018 / Accepted: 12 September 2018 / Published online: 21 September 2018

Abstract

Purpose The prevalence of patients living with prolonged interval between initial breast cancer diagnosis and development of subsequent metastatic disease may be increasing with improved treatment. In order to counsel these patients as to their prognosis, we investigated the association between metastatic free interval (MFI) and subsequent survival from newly diagnosed metastatic breast cancer (MBC) in a population-level U.S. cohort.

Methods The Surveillance, Epidemiology and End Results database was used to identify patients with both an initial stage 1–3 breast cancer diagnosis and subsequent MBC diagnosis recorded from 1988 to 2014. Patients were stratified by MFI (< 5 years, 5–10 years, > 10 years). The association between MFI and metastatic breast cancer-specific mortality (MBCSM) was analyzed with Fine–Gray competing risks regression.

Results Five-year recurrent metastatic breast cancer-specific survival rate was 23%, 26%, and 35% for patients with MFI < 5, 5–10, and > 10 years, respectively. Patients with > 10 year MFI were less likely to die of breast cancer when compared with a referent group with < 5 years MFI (standard hazard ratio (SHR) 0.77 [95% CI 0.65–0.90] $P < 0.001$). There was no significant difference for patients with MFI of 5–10 years (SHR 0.92 [95% CI 0.81–1.04, P 0.191]) compared to < 5 years. Other prognostic factors like White race, lower tumor grade, and ER/PR-positive receptors were also associated with improved cancer-specific survival after diagnosis of MBC.

Conclusion Prolonged MFI greater than 10 years between initial breast cancer diagnosis and subsequent metastatic disease was found to be associated with improved recurrent MBC 5-year survival and decreased risk of breast cancer-specific mortality. This has potential implications for counseling patients as to prognosis, choice of treatment, as well as the stratification of patients considered for MBC clinical trials.

Keywords Breast neoplasms · Neoplasm metastasis · Prognosis · Disease-free survival · SEER program

Introduction

With breast cancer death rates falling on average 1.9% each year, patients are living longer after their breast cancer diagnoses [1]. Reflecting this trend, the prevalence of patients living with metastatic breast cancer in the United States has been steadily rising. Currently estimated at 154,794 in 2017, it is projected to increase by 31% from 2010 to 2020 [2]. With improved treatment and higher prevalence, it is also possible that we will observe longer intervals between initial diagnosis and subsequent metastasis. As more patients face this situation, it is important to be able to counsel them on the association between metastatic free interval and their prognosis.

Previous studies of patients treated in Japan [3], the Netherlands [4], Germany, Austria [5] France [6], and Spain [7],

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as well as patients treated at a single institution in the U.S. or enrolled in ECOG clinical trials [8, 9] have found that longer metastatic free interval (MFI) is associated with improved survival after subsequent recurrent metastatic disease diagnosis—perhaps due to differences in tumor biology, staging, size, underlying comorbidities, general health of those qualified for clinical trials, socioeconomic factors, and screening.

Our study expands upon the previous literature by exploring a previously unstudied cohort of patients in the United States using a large population-based registry, which allows for the analysis of greater numbers of patients and the analysis of prolonged MFI greater than 10 years. We analyzed the Surveillance, Epidemiology and End Results (SEER) database to examine our hypothesis that an especially prolonged interval between initial stage 1–3 breast cancer and subsequent metastatic diagnosis would be associated with improved survival.

Methods

Data source and cohort selection

We performed a retrospective cohort study using the NCI-sponsored SEER database [10]. Capturing 97% of incident cancers through 18 tumor registries, the SEER Program collects and publishes cancer incidence, survival, and treatment data for 28% of the US population [11].

As shown in Fig. 1, we started with a national cohort of 1,465,100 breast cancer cases (primary site = C500-C506, C508-C509) diagnosed between 1973 and 2014. Of these, we included only the 52,917 cases of metastatic breast cancer diagnosed between 1988 and 2014 (AJCC 6th M = M1). Then we excluded 44,374 cases recorded as the first sequential diagnosis of cancer (sequence < = 1: de novo metastatic cases), leaving 8543. Furthermore, we excluded 5782 cases without a previous stage 1–3 breast cancer diagnosis recorded in SEER, leaving 2761. Of these, 488 cases were excluded because of discordant dates of diagnosis (date of metastatic disease was recorded prior to date of first primary), leaving 2313. Our final cohort included 2308 cases with known survival times.

Construction of variables

The primary independent variable of interest in this study was metastatic free interval (MFI)—the time between initial breast cancer diagnosis and subsequent recurrent metastatic cancer diagnosis, categorized as < 5 years, 5–10 years, > 10 years.

Using characteristics recorded at the time of metastatic diagnosis, we categorized: race as White, Black, or other; marital status as married, unmarried, or other; grade as well differentiated (1), moderately differentiated (2), or poorly differentiated or anaplastic (3 and 4); histologic type as ductal, lobular, or other; ER and PR status as positive, negative, borderline/unknown (which includes all cases prior to 1990, as this variable was not recorded prior to then); tumor laterality as left, right, unknown; year of metastatic diagnosis as pre-2000 or post-2000. We included age at metastatic diagnosis as a continuous variable. We were not able to include information on site of metastasis or HER2 status because this information was not recorded in SEER prior to 2010 [12].

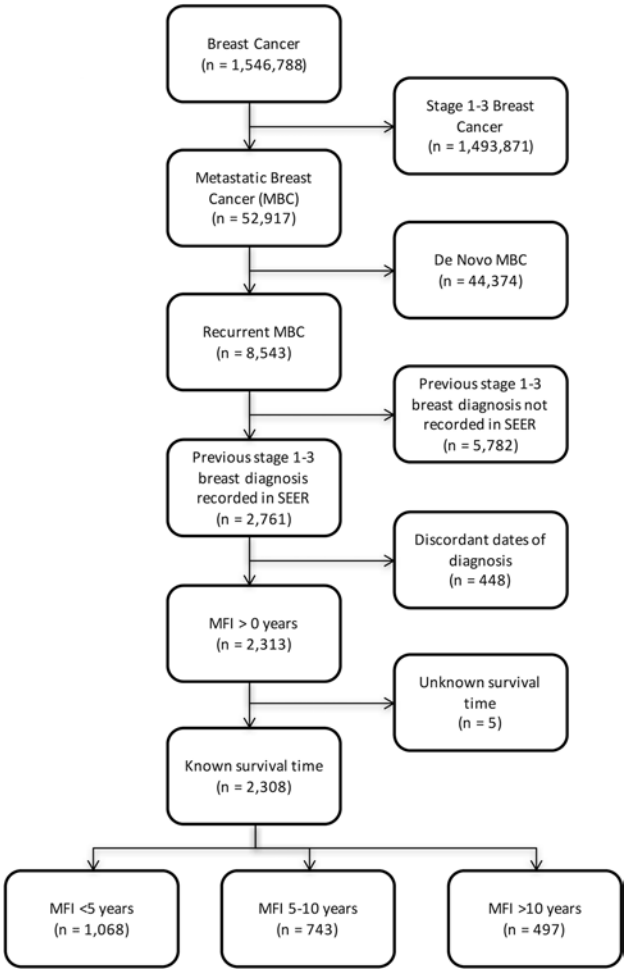

Fig. 1 Selection criteria

Statistical analysis

We compared baseline patient characteristics across MFI categories with the chi-squared test or Fisher's exact test (categorical) or Kruskal–Wallis test (continuous). Unadjusted survival analysis was first performed by the log-rank test, and unadjusted overall survival estimates were generated by the Kaplan–Meier method.

We performed stepwise multivariable Fine and Gray competing risks regression analysis to determine metastatic breast cancer-specific mortality (MBCSM) as a function of categories of MFI, taking into account the competing risk of non-breast cancer death [13]. These categories of MFI (< 5 years, 5–10 years, and > 10 years) were defined prior to competing risks regression after reviewing the distribution of MFI within our sample. In the preliminary multivariate model, we selected all co-variables with $P < 0.10$ from univariate Fine–Gray competing risks analysis. We subsequently excluded all co-variables with $P > 0.10$ in the preliminary multivariate model. The final multivariable model was adjusted for the demographics of race, grade, ER status, PR status, and year of metastatic diagnosis. We also generated a cumulative incidence plot from the Fine–Gray analysis.

After determining favorable prognostic factors from competing risks regression, we also compared a subset of patients with those prognostic factors against a subset without the favorable prognostic factors using unadjusted overall survival estimates generated by the Kaplan–Meier method.

We determined statistical significance with 2-sided P values and a threshold of 0.05, performing all statistical analyses using STATA 13.0.

Results

Baseline patient characteristics

We identified 2308 patients whose prior stage 1–3 breast cancer diagnosis and subsequent metastatic disease were both recorded in SEER. There were 1068 patients with MFI < 5 years, 743 with MFI of 5–10 years, and 497 patients with MFI > 10 years. As shown in Table 1, age at metastatic diagnosis, grade, ER status, PR status, and year of metastatic diagnosis were statistically different when compared across the three MFI categories (< 5 years, 5–10 years, > 10 years).

Of note, patients were older with increasing MFI (median age 59 vs. 62 vs. 66 years, $P < 0.001$). With respect to race, as MFI increased, higher percentages of White (72.57% vs. 76.46%) or other race (7.40% vs. 8.85%) patients were found, while a lower percentage of Black patients (20.04% vs. 14.69%) was found ($P = 0.056$). Patients with longer MFI had the highest percentage of low-grade tumors (7.44%), while those with shorter MFI had the highest percentage of high-grade tumors (40.36%) ($P = 0.002$). Patients with longer MFI had the highest rate of ER- and PR-positive status (68.81%, 55.13%), while those with shorter MFI had a higher rate of ER- and PR-negative status (27.25%, 38.58%) (both $P < 0.001$).

Median follow-up, median overall survival, and 5-year breast cancer-specific survival

The median follow-up after metastatic recurrence using all patients was 15 months (IQR 5–30 months) for those with MFI < 5 years, 19 months (IQR 6–40 months) for those with MFI 5–10 years, and 17 months (IQR 6–37 months) for those with MFI > 10 years.

The median overall survival after recurrent metastatic breast cancer diagnosis was 25 months (range 1–221 months, Fig. 2). Median overall survival for patients with MFI < 5 years was 20 months, while for patients with MFI > 10 years it was 35 months. Five-year recurrent metastatic breast cancer-specific survival rate was 23%, 26%, and 35% for patients with MFI < 5, 5–10, and > 10 years, respectively. Breast cancer was the cause of death for the majority of patients (58%, Table 2). Interestingly, Table 2 also shows a lower percentage of patients with MFI > 10 years died of breast cancer compared to those with MFI 5–10 years and MFI < 5 years (45% vs. 56% and 65%).

Association between MFI and metastatic breast cancer-specific mortality (MBCSM)

Taking into account non-cancer death, cumulative incidence estimates (Fig. 3) of metastatic breast cancer-specific mortality (MBCSM) after a subsequent metastatic diagnosis were significantly higher among patients with shorter MFI (< 5 years) than for those with longer MFI (> 10 years), ($P < 0.001$).

On multivariable Fine–Gray competing risks regression (Table 3), as MFI increased, risk of MBCSM decreased: patients with 5–10 year or > 10 year MFI had a reduced risk of MBCSM compared with a referent group of patients with < 5 years MFI [standard hazard ratio (SHR) 0.92, 95% CI 0.81–1.04; and SHR 0.77, 95% CI 0.65–0.90; $P = 0.191$ and < 0.001, respectively].

Association between other variables and breast cancer-specific mortality after diagnosis of metastatic breast cancer

In multivariate analysis, Black patients had a higher risk of MBCSM (SHR 1.24, 95% CI 1.08–1.44, $P = 0.004$) compared with a referent group of White patients after a diagnosis of metastatic breast cancer. Patients with higher tumor grade (Grade 2 vs. Grade 1 SHR 1.27, 95% CI 0.99–1.63, $P = 0.062$; and Grade 3,4 vs. Grade 1 SHR 1.60, 95% CI 1.25–2.05, $P < 0.001$), ER-negative status (vs. ER-positive status SHR 1.40, 95% CI 1.17–1.67, $P < 0.001$), and PR-negative status (vs. PR-positive status SHR 1.25, 95% CI 1.07–1.46, $P = 0.006$) also had a higher risk of MBCSM. Finally, patients with a metastatic diagnosis post-2000 had a

Table 1 Patient demographics

Characteristic	MFI < 5 years	MFI 5–10 years	MFI > 10 years	*P*
Number of patients	1068	743	497	
Median age (IQR), years	59 (49–71)	62 (53–74)	66 (59–76)	< 0.001*
Marital status				
Married	510 (47.75%)	334 (44.95%)	229 (46.08%)	0.316
Unmarried	506 (47.38%)	356 (47.91%)	237 (47.69%)	
Unknown	52 (4.87%)	53 (7.13%)	31 (6.24%)	
Race				
White	775 (72.57%)	568 (76.45%)	380 (76.46%)	0.056
Black	214 (20.04%)	119 (16.02%)	73 (14.69%)	
Other	79 (7.40%)	56 (7.54%)	44 (8.85%)	
Grade				
1	62 (5.81%)	52 (7.00%)	37 (7.44%)	0.002
2	281 (26.31%)	230 (30.96%)	153 (30.78%)	
3 and 4	431 (40.36%)	403 (35.98%)	329 (37.47%)	
N/A	294 (27.53%)	228 (30.69%)	152 (30.58%)	
Histologic type				
Ductal	686 (64.23%)	481 (64.74%)	331 (66.60%)	0.331
Lobular	123 (11.52%)	101 (13.59%)	51 (10.26%)	
Other	259 (24.25%)	161 (21.67%)	115 (23.14%)	
ER status				
Positive	531 (49.72%)	489 (65.81%)	342 (68.81%)	< 0.001
Negative	291 (27.25%)	141 (18.98%)	94 (18.91%)	
Borderline/unknown/not 1990 + Breast	246 (23.03%)	113 (15.21%)	61 (12.27%)	
PR status				
Positive	393 (36.8%)	359 (48.32%)	274 (55.13%)	< 0.001
Negative	412 (38.58%)	255 (34.32%)	156 (31.39%)	
Borderline/unknown/not 1990 + Breast	263 (24.63%)	383 (25.62%)	287 (17.31%)	
Tumor laterality				
Right-sided	491 (45.97%)	345 (46.43%)	223 (44.87%)	0.090
Left-sided	512 (47.94%)	334 (44.95%)	226 (45.47%)	
Unknown	65 (6.09%)	64 (8.61%)	48 (9.66%)	
Year of metastatic diagnosis				
Pre-2000	169 (15.82%)	42 (5.65%)	< 10 (< 2%)	< 0.001
Post-2000	899 (84.18%)	701 (94.35%)	> 490 (> 98%)	

Year of metastatic diagnosis reported as < 10 to protect patient confidentiality

*Kruskal–Wallis

lower risk of MBCSM when compared to those with a metastatic diagnosis pre-2000 (SHR 0.77, 95% CI 0.65–0.92, $P = 0.004$).

Subset analysis: prognostic factors

The median overall survival of patients after recurrent breast cancer metastasis with favorable prognostic factors (longer MFI, ER/PR positive, lower grade, White race) was 40 months compared to a median survival of 8 months for those with less favorable prognostic factors (shorter MFI, ER/PR negative, higher grade, Black race).

Discussion

Metastatic free interval of greater than 10 years was significantly associated with improved recurrent metastatic breast cancer 5-year survival and decreased breast cancer-specific mortality. Our study is unique in that it was based on US population-level data and accounted for prolonged metastatic free interval of 10 years and beyond as opposed to a 2- or 5-year MFI cut-off more commonly used in previous studies [3–9]. As expected, we also confirmed clinical and demographic variables associated with survival. Thus, our analysis is consistent with previous studies and adds further insights for patients who develop metastatic disease.

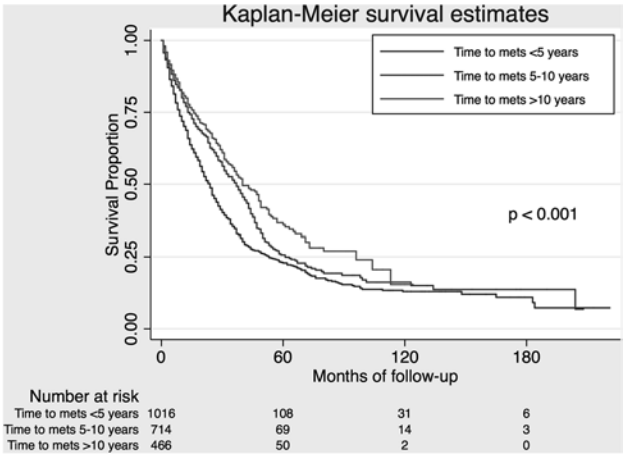

Fig. 2 Overall survival

Although we cannot definitively explain why longer MFI is associated with improved survival, we found that multiple positive prognostic factors are associated with a longer time to metastasis (lower grade of tumor and ER/PR-positive status), consistent with other studies [3–9]. Therefore, it is likely that long MFI is a prognostic marker because it indicates more indolent disease even after diagnosis of metastatic disease. Thus, for patients who are faced with the devastating news that they have metastatic breast cancer, a longer MFI may indicate that their disease may progress more slowly than others with metastatic disease.

This also has implications for stratification of patients in clinical trials. Studies of a cohort that is enriched with patients with long MFI may be biased towards longer survival. These findings could also influence treatment strategies; for example, patients with longer MFI could be candidates for initial treatment with single-agent endocrine therapy (i.e., an aromatase inhibitor (AI)) rather than combination therapy with an AI and CDK4/6 inhibitor, thereby reserving the more toxic combination for the second line following progression.

Regarding race, it has been found previously that Black patients are more likely to be diagnosed with ER−/PR− disease, which has a worse prognosis [14–19]. Other factors, such as delayed diagnosis and delayed treatment of Black patients may also contribute to the observed trends [20]. This may explain the higher percentage of Black patients with shorter observed MFI. The initial breast cancer might be diagnosed at a higher stage with further progression, leading to a higher risk of MBCSM upon a subsequent metastatic diagnosis.

Regarding year of metastatic diagnosis, the decreased risk of MBCSM in patients with metastatic diagnosis post-2000 may be associated with the improvement in therapeutic agents [21].

Our study has several limitations. SEER does not actively follow patients other than to determine vital status [12]. Thus, recurrent metastasis is often not recorded in SEER unless a patient receives treatment for the recurrent disease. This results in under-reporting of metastatic recurrence because older patients often decline or do not receive treatment [22]. It is unclear whether under-ascertainment of metastatic disease would create a systematic bias that would impact the conclusions of our study. The fact that we confirm many elements of prior analyses gives us confidence as to the validity of our findings. Another limitation of our study is that we could not include site of recurrent metastasis or HER2 status, which have been found to be significant prognostic factor in previous studies [5, 6, 23, 24]. Furthermore, we did not include initial tumor information in our model. Rather, we focused on the clinical factors of the disease at time of metastasis so that patients can be

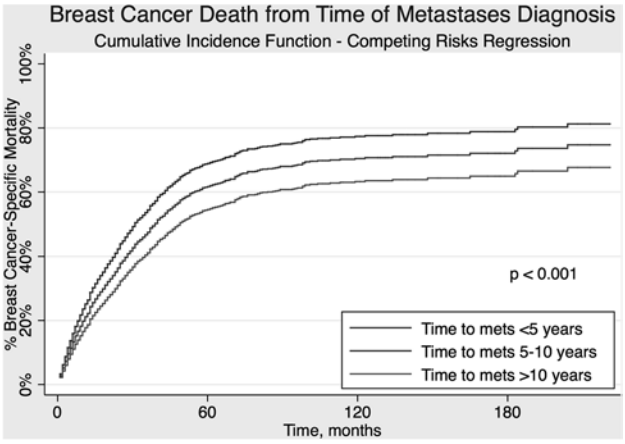

Fig. 3 Competing risks regression—cumulative incidence of breast cancer death, taking into account the competing risk of non-breast cancer death

Table 2 Causes of death

Cause of death	Overall	MFI < 5 years	MFI 5–10 years	MFI > 10 years
Alive	722 (31.28%)	230 (21.54%)	272 (36.61%)	220 (44.27%)
Breast cancer death	1338 (57.97%)	699 (65.45%)	414 (55.72%)	225 (45.27%)
Other cancer death	111 (4.81%)	70 (6.55%)	20 (2.69%)	21 (4.23%)
Heart disease	44 (1.91%)	20 (1.87%)	14 (1.88%)	10 (2.01%)
Other non-cancer death	93 (4.03%)	49 (4.59%)	23 (3.1%)	21 (4.23%)

Table 3 Multivariable Fine and Gray competing risks regression for breast cancer-specific mortality among patients with subsequent metastatic breast cancer

Characteristic	Univariate analysis		Multivariate analysis	
	SHR (95% CI)	*P*	SHR (95% CI)	*P*
Metastatic free interval				
<5 years	1.0 (ref)		1.0 (ref)	
5–10 years	0.82 (0.73–0.93)	< 0.001	0.92 (0.81–1.04)	0.191
>10 years	0.65 (0.56–0.76)	< 0.001	0.77 (0.65–0.90)	< 0.001
Age (per year increase)	1.00 (0.99–1.00)	0.172	*	
Marital status				
Married	1.0 (ref)		*	
Not married	1.10 (0.99–1.23)	0.087	*	
Unknown	1.17 (0.93–1.47)	0.179	*	
Race				
White	1.0 (ref)		1.0 (ref)	
Black	1.30 (1.13–1.49)	< 0.001	1.24 (1.08–1.44)	0.003
Other	1.05 (0.85–1.30)	0.629	1.11 (0.90–1.38)	0.332
Grade				
1	1.0 (ref)		1.0 (ref)	
2	1.34 (1.04–1.71)	0.022	1.27 (0.99–1.63)	0.062
3 and 4	2.00 (1.57–2.55)	< 0.001	1.60 (1.25–2.05)	< 0.001
N/A	1.47 (1.15–1.89)	0.002	1.24 (0.96–1.59)	0.099
Histologic type				
Ductal	1.0 (ref)		*	
Lobular	0.94 (0.80–1.09)	0.404	*	
Other	0.99 (0.86–1.13)	0.874	*	
ER status				
Positive	1.0 (ref)		1.0 (ref)	
Negative	1.90 (1.66–2.18)	< 0.001	1.40 (1.17–1.67)	< 0.001
Borderline/unknown/not 1990 + Breast	1.59 (1.37–1.84)	< 0.001	1.75 (1.18–2.61)	0.005
PR status				
Positive	1.0 (ref)		1.0 (ref)	
Negative	1.67 (1.48–1.89)	< 0.001	1.25 (1.07–1.46)	0.006
Borderline/unknown/not 1990 + Breast	1.58 (1.36–1.83)	< 0.001	0.90 (0.61–1.33)	0.613
Tumor laterality				
Right-sided	1.0 (ref)		*	
Left-sided	1.01 (0.90–1.12)	0.916	*	
Unknown	0.77 (0.61–0.97)	0.026	*	
Year of metastatic diagnosis				
Pre-2000	1.0 (ref)		1.0 (ref)	
Post-2000	0.67 (0.57–0.79)	< 0.001	0.77 (0.65–0.92)	0.004

*Not included in multivariate model

informed of prognosis even when not much is known about their prior tumor—whether they cannot recall or the records are lost over time.

An additional limitation is that our cohort included only 212 patients with a metastatic diagnosis before the year 2000 compared with 2096 after the year 2000. Thus, our length of follow-up for patients with MFI > 10 years was limited past 5 years. One explanation is that SEER included fewer registries before 2000, thus capturing fewer patients [25]. However, that our patients were skewed to more recent years improves the contemporary nature of our findings. Finally, we emphasize the importance of distinguishing clinical significance from statistical significance, as clinicians and patients must discern whether these statistically significant findings are clinically meaningful. We acknowledge that treatment strategies may not change based on these differences at this time.

Conclusion

In conclusion, patients with a new diagnosis of metastatic breast cancer with very prolonged MFI (> 10 years) have higher breast cancer-specific 5-year survival compared to those with shorter MFI. These patients have more favorable prognostic factors as well. These findings can be used to counsel patients and inform interpretation of clinical trials.

Author contributions Enoch Chang: Conceptualization, data curation, formal statistical analysis and interpretation of data, funding acquisition, investigation, methodology, software, validation, visualization, writing—original draft, and writing—review and editing. Sarah S. Mougalian: Analysis and interpretation of data, writing—review and editing. Kerin B. Adelson: Analysis and interpretation of data, writing—review and editing. Melissa R. Young: Analysis and interpretation of data, writing—review and editing. James B. Yu: Conceptualization, data curation, formal statistical analysis and interpretation of data, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing—original draft, and writing—review and editing.

Funding Enoch Chang was supported by the NIDDK of the NIH under Award Number T35DK104689. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Compliance with ethical standards

Conflict of interest Sarah S. Mougalian MD: Consulting role with Eisai. Stocks: Gilead, Coronado Biosciences, Roche. Research funding from Genentech, Pfizer; Kerin B. Adelson MD: Immediate family member is employed with Lyra Health; Consulting role with Wellpoint; Travel, Accommodations, Expenses from Genentech; Honoraria from Genentech; James B. Yu MD, MHS: Consulting role with Augmenix. Research funding from twenty-first Century Oncology.

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Chinese Journal of Integrative Medicine
Available online at link.springer.com/journal/11655
Journal homepage: www.cjim.cn/zxyjhen/zxyjhen/ch/index.aspx
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Original Article

Sublingual Nodules: Diagnostic Markers of Metastatic Breast Cancer*

YANG Xue[1,2], ZHU Cui-hong[3], CAO Rui[1], HAO Jian[1], and WU Xiong-zhi[1]

ABSTRACT **Objective**: To evaluate the diagnostic significance of sublingual nodules for metastasis of patients with breast cancer and further to explore the mechanisms of sublingual nodules. **Methods**: The image data of 117 in-patients with breast cancer in stage Ⅰ–Ⅳ in Tianjin Medical University Cancer Institute and Hospital from December 2009 to September 2011 were assessed retrospectively. All photos of patients' tongue were recorded by the digital camera of uniform type within 1 month after serological examination and regular re-examined by computed tomography (CT), magnetic resonance imaging and positron emission tomography CT. The presence of sublingual nodules was the positive standard. Chi square test and two-independent-sample test were used to determine the diagnostic value between the status of sublingual nodules and Clinico-pathological characteristics. The optimal cut-off of uric acid (UA) level to diagnose sublingual nodules was determined by receiver operating curve (ROC) analysis. **Results**: Breast cancer patients with sublingual nodules had a higher risk of recurrence and/or metastasis than patients without it (P<0.001). Sublingual nodules was significantly correlated with increased serum UA level (P=0.001). The optimal cut-off value of UA level to diagnose sublingual nodules was 290 μmol/L. Furthermore, the elevated serum UA level (≥290 μmol/L) was significantly related to breast cancer recurrence and/or metastasis (P<0.001). **Conclusions**: Sublingual nodules were potential diagnostic markers for metastatic breast cancer. The formation of sublingual nodules was associated with elevated level of serum UA.

KEYWORDS breast cancer, sublingual nodule, metastasis, recurrence, serum uric acid, Chinese medicine, diagnosis

Breast cancer was the most common cancer in women and ranks as the second cause of death for females in the world. In 2011, approximate 39,520 women died of breast cancer in United States.[1] About 30% of patients with early-stage tumors will occur distant metastases after primary treatment.[2] Although combined therapy decreased mortality rates, recurrence or distant metastasis of breast cancer (MBC) patients remains a leading cause of death.[3] The average overall survival time of MBC is about 3 years.[4] Thus, early diagnosis for MBC could obtain timely treatment, which favors a better prognosis.

Imaging diagnosis methods, such as contrast enhanced computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography CT (PET-CT), are routinely used in surveillance of MBC, which have high accuracy in the detection of existing metastases. However, it is difficult to make an early prediction of metastases or recurrent of breast cancer due to lack of typical symptoms or signs.[5-8] Serological examination including tumor markers is used for the monitoring of metastatic disease during treatment, though its accuracy is not high.[9,10] To reduce metastases-related mortality, the development of new methods for early prediction of MBC is very meaningful.

Tongue diagnosis is an important diagnostic method in Chinese medicine (CM), and tongue appearance is an outer manifestation of the status of human body, which reflects the characteristics of pathogenic factors and condition of the internal organs.[11,12] Sublingual nodules are important features

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DOI: https://doi.org/10.1007/s11655-018-2837-1

of tongue, which are the pathological products that result from phlegm and dampness stagnated in the back of the tongue. The presence of sublingual nodules is a sign of stagnation of phlegm. According to the CM theory, stagnation of phlegm, poison and blood stasis are the principal pathological factors of tumors including breast cancer. Stagnation and invasion of phlegm elsewhere is the pivotal pathogenesis of recurrence and metastasis of breast cancer.[13] Therefore, we assumed that sublingual nodules may be a predicted marker for recurrence and/or metastasis in breast cancer patients.

Blood uric acid (UA) is an end product from purine derivatives in human metabolism. Various diseases such as excess adiposity, diabetes, cardiovascular disease go along with elevated levels of UA, because of metabolic disorders.[14,15] Elevated UA level under normal range has been shown to increase risk of metabolic syndrome.[15,16] The metabolic syndrome was a risk factor for the development and progression of breast cancer.[17] Thus, UA may be an important bridge between the formation of sublingual nodules and recurrence and/or metastatic breast cancer.

The purpose of this study is to evaluate the diagnostic significance of sublingual nodules for recurrence and/or metastasis of patients with breast cancer and further to explore the relationship between sublingual nodules and UA level.

METHODS

Ethics

This study was approved by the local ethics committee of Tianjin Medical University Cancer Institute and Hospital (No. bc2015002). The procedures were performed according to the approved guidelines and Helsinki Declaration. Informed consents were obtained from all participants involved in this study.

Inclusion and Exclusion Criteria

Major inclusion criteria were as follows: female; aged 18 years or older; pathological testing for all patients to diagnose breast cancer. Major exclusion criteria were as follows: concurrent cancer; pregnant or breastfeeding women; severe mental disorder; incomplete medical records; patients who did not undergo regular re-examination.

Patients

Totally, 117 patients with breast cancer in stage Ⅰ–Ⅳ, according to American Joint Committee on Cancer (AJCC) stage standard for breast cancer (Version 2010),[18] admitted in Tianjin Medical University Cancer Institute and Hospital from December 2009 to September 2011 were included in this study, among which there were 55 patients confirmed with recurrence and/or metastasis. Contrast enhanced CT, MRI, PET-CT or biopsy were performed to confirm their local recurrence or distant metastasis. Patients were informed that the detail information of face have not been collected on photos.

Investigation Indices

All photos of patients' tongue were taken within 1 month after regular re-examined by CT, MRI, PET-CT and biopsy. The presence of sublingual nodules was regarded as positive results (Figure 1). Immunohistochemical testing for all patients was performed to confirm the expressions of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (Her-2). All antibodies of ER (ab3575), PR (ab63605), and Her-2 (ab16901) were obtained from Abcam (USA). Pathological testing for all patients was performed to confirm tumor node metastasis (TNM) classification. Serological examinations, including UA, total cholesterol (TC), triglyceride (TG), carbohydrate antigen 153 (CA153) and carcinoembryonic antigen (CEA), were detected within 1 month before or after the photos taken.

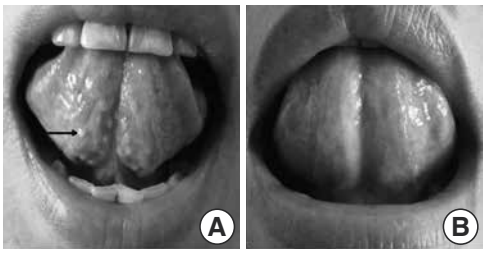

Figure 1. Status of Sublingual Nodules

Notes: A: Positive of sublingual nodules: several nodules on the sublingual mucosa. B: Negative of sublingual nodules: the smooth sublingual mucosa.

Statistical Analysis

Screening test for the status of sublingual nodules, χ^2 test for paired data and Kappa test were used to determine the diagnostic value for recurrence and/or metastasis in breast cancer patients. Kolmogorov-Smirnov test was used to determine the distribution of UA, TC, TG, CA153 and CEA. Data with the skewed distribution were presented as median (quartile interval). The association between the status of sublingual nodules and Clinico-pathological

character was evaluated by Chi square test and two-independent-sample test. The optimal cut-off of UA level to diagnose sublingual nodules was determined by receiver operating curve (ROC) analysis. Statistical analysis was performed by SPSS 16.0 software (Chicago, USA). A *P*-value<0.05 was considered statistical significance.

RESULTS

Characteristics of Patients

The age of patients ranged from 32 to 79 years with a median age of 51 years. Median survival was 70.0 months (range, 36–165 months). Fifty-five (47.0%) patients had suffered a relapse and 29 (24.8%) patients had died by their most recent follow-up visit.

Diagnostic Value of Sublingual Nodules Status for MBC

Patients with sublingual nodules had a higher risk of recurrence and/or metastasis than those without it (Table 1, *P*<0.001). No significant differences were observed in baseline characteristics between patients with sublingual nodules and patients without it (*P*>0.05, Table 2). There was no significant difference in diagnosis of recurrence and/or metastasis between the status of sublingual nodules and the traditional diagnostic criteria (*P*=0.845). Kappa was 0.553 (*P*<0.001). The sensitivity, specificity, positive predictive value and negative predictive value were 74.5%, 80.6%, 77.4% and 78.1%, respectively.

Table 1. Relationship between the Status of Sublingual Nodules and Recurrence and/or Metastasis of Breast Cancer (Case)

Recurrence and/or metastasis	Sublingual nodule		χ^2	*P*
	Positive	Negative		
Yes	41	14	35.827	<0.001
No	12	50		

Diagnostic Value of Serological Examination for Status of Sublingual Nodules

No significant difference was found in TC, TG, CA153 and CEA levels between patients with and without sublingual nodules. Interestingly, UA level was higher in patients with sublingual nodules than patients without it in this study (Table 3, *P*=0.001). We calculated an optimal cut-off level for UA as 290 μmol/L (normal range 150–400 μmol/L) to diagnose sublingual nodules by ROC analysis (Figure 2, Table 4). In addition, there was no significant difference for the numbers of

Table 2. Baseline Characteristics of Patients with/without Breast Cancer (Case)

Clinicopathological parameter	Sublingual nodule		Positive rate (%)	χ^2	*P*
	Positive	Negative			
Primary tumor (T)					
T1	17	26	39.5		
T2	30	33	47.6	1.096	0.578
T3/T4	6	5	54.5		
Lymph node (N)					
N0	20	30	40.0		
N1	23	20	53.5	1.977	0.577
N2	5	6	45.5		
N3	5	8	38.5		
TNM stage					
Ⅰ	11	18	37.9		
Ⅱ	27	30	47.4	0.853	0.653
Ⅲ/Ⅳ	15	16	48.4		
Histotype					
Invasive ductal breast carcinoma	44	42	51.2		
Other invasive breast cancer	8	18	30.8	4.885	0.087
Noninvasive carcinoma (intraductal carcinoma and lobular carcinoma)	1	4	20.0		
ER					
Positive	25	32	43.9	0.093	0.760
Negative	28	32	46.7		
PR					
Positive	18	30	37.5	1.998	0.158
Negative	35	34	50.7		
Her-2					
Positive	27	33	45.0	0.004	0.947
Negative	26	31	45.6		

Notes: ER: estrogen receptor, PR: progesterone receptor, Her-2: human epithelial growth factor receptor-2; TNM: tumor node metastasis

Table 3. Serological Examination of Patients with Breast Cancer [Median (Quartile Interval)]

Sublingual nodule	Blood UA (μmol/L)	TC (mmol/L)	TG (mmol/L)	CA153 (U/mL)	CEA (μg/L)
Positive	277.85 (77.30)	5.26 (1.47)	1.20 (1.10)	14.19 (14.39)	2.32 (2.14)
Negative	236.14 (48.15)	5.28 (1.95)	1.38 (1.35)	12.00 (11.01)	2.18 (2.20)
P	0.001	0.957	0.702	0.242	0.218

Notes: UA: uric acid; TC: total cholesterol; TG: triglyceride; CA153: carbohydrate antigen 153; CEA: carcinoembryonic antigen

sublingual nodules in patients with different UA levels, 7.5±2.5 in low-UA group (<290 μmol/L) and 8.0±4.6 in high-UA group (≥290 μmol/L, *P*=0.585). The elevated UA level (≥290 μmol/L) were significantly correlated with recurrence and/or metastatic of patients with breast cancer (χ^2=17.628, *P*<0.001, Table 4).

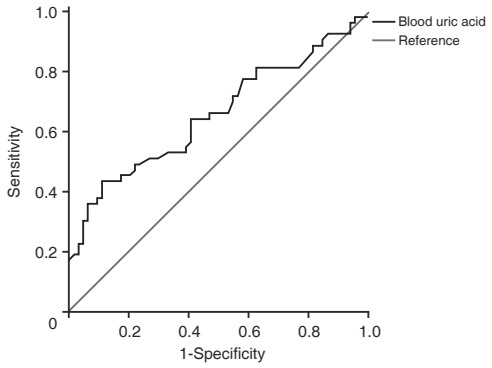

Figure 2. Receiver Operating Curve of Sublingual Nodules and Blood Uric Acid Levels

Table 4. Relationship between Blood UA, Sublingual Nodules, and Recurrence and/or Metastasis of Breast Cancer (Case)

Variable		Blood UA (μmol/L)		χ^2	*P*
		<290	≥290		
Sublingual nodule	Positive	30	23	16.020	<0.001
	Negative	57	7		
Recurrence and/or metastasis	Yes	31	24	17.628	<0.001
	No	56	6		

Note: UA: uric acid

DISCUSSION

Recent years, the relationships between tongue diagnosis and diseases, including cancer[19-21] and appendicitis[22] have been explored. For example, our previous study found that the nodule and eminence on frenulum labii superioris was potential diagnostic markers for metastatic colorectal cancer.[21] And purple-bluish tongue was significantly correlated with increased platelet and associated with recurrence of epithelial ovarian cancer.[23]

Dramatically, our data demonstrated that breast cancer patients with sublingual nodules had a higher risk of recurrence and/or metastasis. There was no significant difference in diagnosis of recurrence or/and metastasis between the status of sublingual nodules and the traditional diagnostic criteria. The Kappa test proved a good consistency. Hence, our results indicated that the sublingual nodules could predict recurrence and/or metastasis of breast cancer.

Study showed that the levels of TG and TC were higher in phlegm turbidity syndrome.[24] Furthermore, serum UA level was found to be a risk factor of metabolic syndrome.[16] In our study, there was no significant difference observed in TC, TG, CA153 and CEA levels between patients with sublingual nodules and patients without it. However, the level of serum UA was significantly associated with the status of sublingual nodules. The optimal cut-off value of UA to diagnose the sublingual nodules was 290 μmol/L.

The correlativity between serum UA level and prognosis of patients with cancer has been widely investigated. Boffetta, et al[25] demonstrated that patients with gout had more incidence of cancer and proposed hyperuricemia may be an early manifestation of the carcinogenic process. The UA level at time of diagnosis as an independent prognostic factor in patients with pancreatic cancer was found by Stotz, et al firstly.[14] The optimal cut-off value of UA for pancreatic cancer prognostic prediction is 5.1 mg/dL (normal range 3.4–7.0 mg/dL), which is basically consistent with our study (≥290 μmol/L). In this study, the UA level was significantly correlated with recurrence and/or metastatic breast cancer. UA is a pro-inflammatory factor that stimulates human mononuclear cells to produce interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α.[26] In addition, infusion of UA into mice also leads to a marked increase in circulating TNF-α levels.[27] It is well known that inflammation itself and these inflammatory factors such as TNF-α and IL-6 are all significantly related to tumor progression.[28,29] Therefore, these studies indicate that UA is an indirect pro-tumor factor, and whether there are direct effects needs further investigation. Although the mechanism how UA affects recurrence and/or metastasis of breast cancer is unclear and deserves further research, our results indicated that breast cancer patients should regularly monitor UA levels to predict recurrence or metastasis risks. Besides, low purine diets for gout patients may be also beneficial to patient with breast cancer to prevent recurrence or metastasis.

One major limitation of this study is that the sample size is relatively small, and the study is retrospective. A large number of multicenter prospective randomized trials should be undertaken

comparing the relationship between sublingual nodules and recurrence and/or metastasis of breast cancer.

In conclusion, sublingual nodules are potential diagnostic markers for MBC. The formation of sublingual nodules was associated with elevated level of serum UA. Sublingual nodules together with high level of UA may be used as simple and direct indicators to monitor recurrence and/or metastasis of breast cancer.

Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Yang X analyzed data and wrote this manuscript. Zhu CH collected and analyzed the patient data. Cao R and Hao J helped to collect the patient data and modify the final manuscript. Wu XZ designed the study and approved the final manuscript.

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(Accepted August 30, 2016; First Online April 17, 2018)
Edited by YU Ming-zhu

Indian Journal of Surgical Oncology (September 2018) 9(3):336–339
https://doi.org/10.1007/s13193-018-0724-z

CASE REPORT

Stridor as the First Presentation of Metastatic Breast Cancer that Was Managed with Chemotherapy: a Case Report

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Received: 12 June 2017 / Accepted: 11 January 2018 / Published online: 25 January 2018

Abstract
Supraclavicular nodal metastases of breast cancer are rare and occur in about 8% of newly diagnosed cases. It is rarely discussed in the literature that breast cancer was metastasizing to higher levels of the cervical nodes. We report a case of metastatic breast cancer to the deep cervical lymph nodes that caused stridor due to compression of the recurrent laryngeal nerve which was diagnosed by indirect laryngoscopy. After full investigations, urgent chemotherapy was started and it showed a dramatic response with disappearance of the lymph node after two cycles with resolution of the stridor. This report also highlights the association of other metastatic sites with this higher level of neck nodal metastases of breast cancer.

Keywords Breast cancer · Metastatic · Stridor · Computed tomography

Introduction

It is known that patients with supraclavicular nodal metastases due to breast cancer are of intermediate risk categorization between stage IIIB and stage IV (staged as IIIC) [1]. Response to treatment of such patients was shown to be better than other systemic metastatic cases [2]. Since survival outcome of breast cancer with isolated supraclavicular nodal metastases was shown to be superior to other metastatic sites, the target of therapy in those patients was with a radical intent [1]. It is rarely mentioned in the literature that there are nodal metastases to the neck groups higher than the supraclavicular one [3]. We present a rare case which was admitted to our outpatient surgical clinic by a stridor that was associated with left breast palpable lump. After detailed investigations, it was found to be a metastatic breast cancer with malignant neck nodal metastases compressing the recurrent laryngeal nerve.

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Case Presentation

A 61-year-old lady came to the surgical oncology clinic complaining of left breast lump that was associated with stridor with a recent darkness of the skin coloration all over the body.

History Taking

She was diabetic, on insulin 7 years ago, and hypertensive. The condition started 4 months earlier by observation of the left breast lump. Later, she noticed a difficulty of breathing at rest with a sense of impending suffocation without altered deglutition.

On clinical examination, there was a suspicious left breast lump with an ipsilateral malignant-looking axillary lymph node. The breast skin was edematous with thickening that was provisionally categorized as inflammatory type of breast cancer. Indirect laryngoscopic assessment showed a narrowed

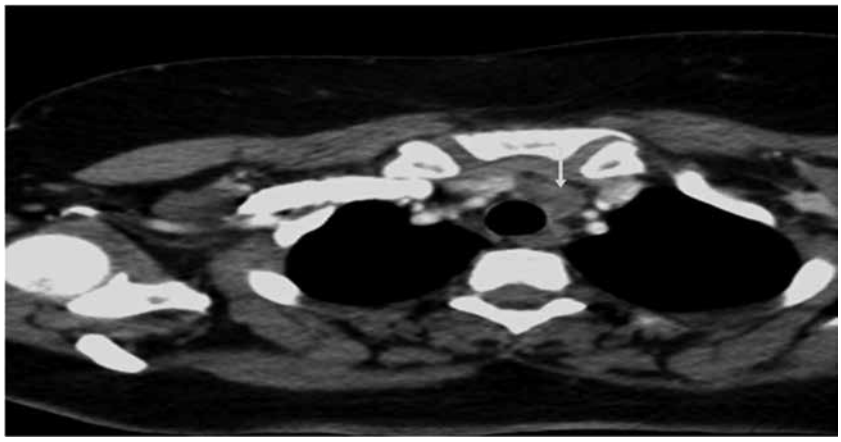

Fig. 1 CT scan of the neck and chest at the level of branches of the aortic arch. There is evidence of malignant lymphadenopathy (arrow) just inner to the left common carotid artery that is compressing the left recurrent laryngeal nerve

glottic opening at rest with an urgent need for tracheostomy. Bilateral sonomammographic evaluation revealed a multicenteric left breast carcinoma (largest mass was with a maximal diameter of 8.5 cm) with diffuse breast and skin edema (T4d), a suspicious right breast mass of 7 mm size with a fine microcalcifications, and bilateral malignant-looking axillary lymph nodes (multiple in the left and one in the right were suspicious). Then, bone scan and pan CT (multi-detector computed tomography "MDCT") of skull base, neck, chest, abdomen, and pelvis was decided.

Pan CT Technique

This scanning was performed using Brilliance 64 (Philips Healthcare, Best, Netherlands). It was done with 3 mm slice thickness. The post-contrast study was performed using 120 ml of low osmolar non-ionic contrast medium (ioversol; Optiray 350) at a flow rate of 5 ml/s. All images were transferred to the workstation [Extended Brilliance Workspace V3.5.0.2254 (EBW)] for post processing. The images were viewed on soft tissue and bone setting.

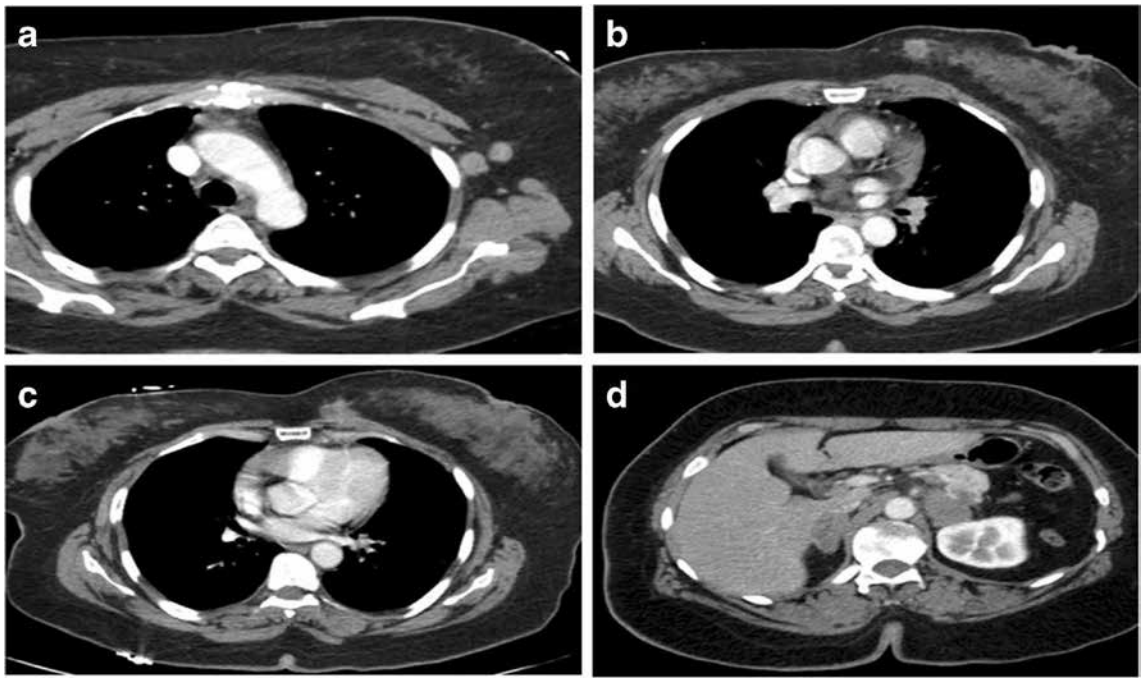

Fig. 2 **a** At the level of the axilla, there is a malignant left axillary lymphadenopathy. **b**, **c** At the level of the breast, there are two malignant left breast masses. A deeper one invades the pectoralis major muscle. **d** At the level of the upper abdomen, there are bilateral suprarenal metastases

Table 1 Biologic markers of the case

ER: strong positive staining in more than > 67% of neoplastic cells (score 8/8)
PR: negative staining of neoplastic cells (score 0)
Her-2 neu: moderate complete membranous activity in > 10% of tumor cells (score +2)
Ki 67: positive staining in 50% of neoplastic cells

Imaging Findings

It showed a small metastatic osteolytic bony lesion in the mid-thoracic vertebrae, a malignant lymphadenopathy just inner to the origin of the left carotid artery that is compressing the left recurrent laryngeal nerve (Fig. 1), two breast masses with malignant characters (Fig. 2b, c) that are associated with a malignant left axillary lymphadenopathy (Fig. 2a), bilateral suprarenal metastases (Fig. 2c), and two left cerebral parietal lobe metastases (leptomeningeal in location) with the largest one measuring 2 cm.

Tissue Diagnosis

A core needle biopsy was taken from the left breast mass and it revealed an invasive ductal carcinoma. Table 1 shows details of its biologic markers.

The Response to an Urgent Chemotherapy Protocol

Immediately, the patient started AC protocol every 3 weeks (Adriamycin 60 mg/m^2 cyclophosphamide 600 mg/m^2 BSA). The first cycle achieved a good clinical response, stridor was relieved, and she was able to recline. Further clinical improvement regarding respiratory symptoms was achieved after the second cycle. Radiologic reevaluation was ordered after the second cycle which confirmed a satisfactory laryngeal inlet (Fig. 3a) and complete response of the neck lymphadenopathy (Fig. 3b). As regards brain metastases, the patient was referred to the radiation oncology and neurosurgical teams for proper decision as regards the further management.

Discussion

Supraclavicular nodal metastases are rare with breast cancer and these occur in about 8% of newly diagnosed cases [4, 5]. It is rarely discussed in the literature that breast cancer was metastasizing to higher levels of the neck nodes than the supraclavicular group (4). In a study by Sesterhenn and his coworkers [3], nodal metastases to the neck were 66.7% in region V (8/12 cases), area IV 58.3% (7/12 cases), 50% in area III (6/12 cases), and 8.3% in area II (1/12 cases) with no recorded metastases in region I or VI. In his study, five patients out of 12 (41.7%) developed other distant metastases after the initial detection and management of neck node metastases within a 6-month interval [3]. We show a very rare presentation of neck nodal metastases that compressed the recurrent laryngeal nerve causing stridor. The management of this stridor was simply carried out with chemotherapy as first aid. The second observation that we noticed is the close association with a diffuse metastatic process when the nodal secondaries are in a higher level than the supraclavicular group. Most of the recent literatures categorized isolated cervical nodal metastases to the supraclavicular group to be a locally advanced disease rather than a distant metastatic one [6]. Some advocated surgical management as an initial line of treatment for neck node metastases with a modest 5-year survival approaching 30% [4, 7]. Some advised combined

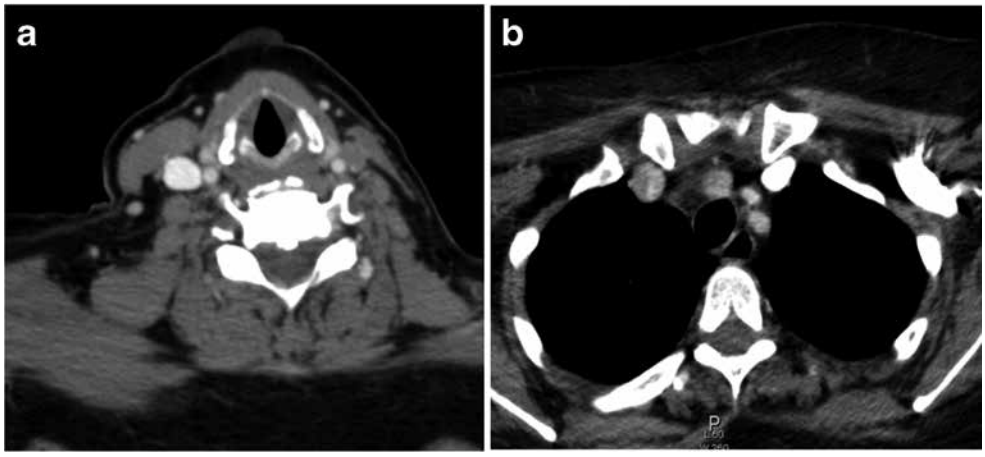

Fig. 3 Follow-up after 40 days. CT scan of the neck and upper chest. **a** At the level of the vocal cord, there is normal laryngeal inlet. **b** At the level of branches of the aortic arch, there is a complete disappearance of the previous malignant lymphadenopathy just inner to the left common carotid artery

chemotherapy and a radical dose of radiotherapy [8]. Nevertheless, we must be aware that the presence of these higher metastatic levels is usually a mirror of systemic spread with a high possibility of other coincident metastatic process.

Conclusions

Although metastases of breast cancer to higher levels of cervical lymph nodes are very rare, it is reported by this study to compress the recurrent laryngeal nerve causing stridor that was managed successfully with chemotherapy.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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