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Prognostic factors in metastatic breast cancer: a prospective single-centre cohort study in a Finnish University Hospital

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ABSTRACT

Objectives Although novel early breast cancer prognostic factors are being continuously discovered, only rare factors predicting survival in metastatic breast cancer have been validated. The prognostic role of early breast cancer prognostic factors in metastatic disease also remains mostly unclear.

Design and setting Prospective cohort study in a Finnish University Hospital.

Participants and outcomes 594 women with early breast cancer were originally followed. Sixty-one of these patients developed distant metastases during the follow-up, and their primary breast cancer properties, such as tumour size, nodal status, oestrogen receptor (ER) and progesterone receptor expression, grade, proliferation rate, histopathological subtype and breast cancer subtype were analysed as potential prognostic factors for metastatic disease.

Results In multivariate analysis, the presence of lymph node metastases at the time of early breast cancer surgery (HR, 2.17; 95% CI, 1.09–4.31; p=0.027) and ER status (negative vs positive, HR, 2.16; 95% CI, 1.14–4.10; p=0.018) were significant predictors of survival in metastatic disease.

Conclusions These results confirm ER status as a primary prognostic factor in metastatic breast cancer. Furthermore, it also suggests that the presence of initial lymph node metastases could serve as a prognostic factor in recurrent breast cancer.

Strengths and limitations of this study

► This study included contemporary, prospective breast cancer cohort in a University Hospital with a relatively long follow-up.
► The material did not include patients with de novo metastatic breast cancer.
► If the number of patients with metastatic breast cancer would have been larger, more detailed subgroup analyses, regarding, for example, biological subgroups possible, would have been possible.

INTRODUCTION

Breast cancer is by far the most common and deadliest cancer affecting women worldwide.[1] In contrast to considerably prolonged early breast cancer prognosis during the last decade, which is mainly due to the optimisation of adjuvant therapies, the prognosis of patients with metastatic breast cancer has hardly been prolonged, and the current median of overall survival is approximately 36 months.[2–5]

The presence of nodal involvement is the strongest predictor of outcomes for early breast cancer.[6] The clinical behaviour of metastatic breast cancer still varies greatly, and it is difficult to predict. The best validated prognostic factors in metastatic breast cancer include clinical factors, such as long relapse-free intervals, the absence of brain metastases or visceral metastases and the presence of oestrogen receptor (ER), which also serves as an essential predictive factor in metastatic settings.[7–12] De novo metastatic breast cancers also have better prognosis than recurrent breast cancer.[10 13] The possibility of using other characteristics of primary breast cancer, such as primary tumour size and axillary lymph node status as prognostic factors in metastatic breast cancer is still being discussed; however, this approach has seldom been studied in modern prospective cohorts.

Using a large prospective breast cancer cohort treated with modern treatment modalities, we aimed to determine whether primary breast cancer prognostic factors, such as tumour size, nodal status, ER and progesterone receptor (PR) expression, differentiation, proliferation rate or breast cancer subtype could also predict outcomes in recurrent metastatic breast cancer.

MATERIALS AND METHODS

The original patient material was from a prospective dataset collected in Oulu University Hospital from 2003 to 2013. The dataset
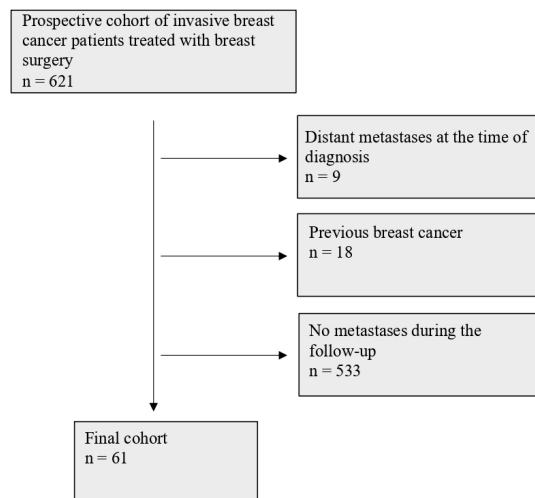
Figure 1 Flow chart of the study participants.

consisted of 594 patients with early invasive breast cancer diagnosed and treated in Oulu University Hospital, Finland. Surgery to the primary tumour was carried out according to the guidelines of the Finnish Breast Cancer Group. The dataset did not include information of the possible neoadjuvant chemotherapy, which was nevertheless very rarely administered during the study period. Patients with previous breast cancer or distant metastases at the time of diagnosis were excluded from the cohort (figure 1). During the follow-up, 61 women displayed distant metastases, and the outcomes of these patients were reported in this study.

Tumours were classed into five intrinsic subtypes according to the European Society for Medical Oncology (ESMO) clinical practice guidelines on breast cancer.[14] Luminal A-like carcinomas expressed ER and PR, showed Ki-67 expression in <15% of the cells, and did not overexpress human epidermal growth factor receptor 2 (HER2). Luminal B-like (HER2-negative) carcinomas were ER-positive and HER2-negative. In addition, they showed either Ki-67 expression in ≥15% of cells, or they were PR-negative. Luminal B-like (HER2-positive) tumours expressed ER and overexpressed HER2. Triple-negative breast carcinomas (TNBCs) were defined as tumours with no ER, PR and HER2 expression. HER2-positive (non-luminal) cases overexpressed HER2 without ER or PR positivity. The distribution between subtypes in the cohort is described in detail in table 1.

The histopathology was evaluated according to current WHO classification and stage was assessed using tumour, node, metastases (TNM) classification. The expressions of ER, PR and Ki-67 were studied using immunohistochemistry as previously described.[15] HER2 expression was studied using immunohistochemistry and chromogenic in situ hybridisation (CISH) to confirm positive results. A positive result of six or more gene copies in CISH was considered HER2-positive.[16]

Table 1 Primary tumour characteristics

	n (%)
Tumour size	
T1	20 (32.8)
T2	33 (54.1)
T3	7 (11.5)
T4	1 (1.6)
Nodal status	
N0	16 (26.2)
N1	22 (36.1)
N2	15 (24.6)
N3	8 (13.1)
Histopathology	
Ductal	47 (77.0)
Lobular	11 (18.0)
Other	3 (4.9)
Histopathological grade	
Grade 1	0 (0)
Grade 2	25 (41.0)
Grade 3	34 (55.7)
Unknown	2 (3.3)
ER expression	
Negative (0%)	14 (23.0)
Weak (1%–9%)	2 (3.3)
Moderate (10%–59%)	6 (9.8)
High (>59%)	39 (63.9)
PR expression	
Negative (0%)	22 (36.1)
Weak (1%–9%)	5 (8.2)
Moderate (10%–59%)	5 (8.2)
High (>59%)	29 (47.5)
HER2 status	
HER2-negative	52 (85.2)
HER2-positive (CISH)	9 (14.8)
Ki-67 expression	
Negative (<5%)	2 (3.3)
Weak (5%–14%)	15 (24.6)
Moderate (15%–30%)	20 (32.8)
High (>30%)	24 (39.3)
Focality	
Unifocal	50 (82.1)
Multifocal	11 (18.0)
Subtype	
Luminal A-like	13 (21.3)
Luminal B-like (HER2-negative)	29 (47.5)
Luminal B-like (HER2-positive)	5 (8.2)
HER2-positive, non-luminal	3 (4.9)

Continued

Table 1 Continued

	n (%)
Triple-negative	10 (16.4)
Unknown	1 (1.6)
The first site of the distant metastasis	
Bone only	17 (27.9)
Lung only	9 (14.8)
Liver only	5 (8.2)
Other	6 (9.6)
Multiple sites	24 (39.3)

CISH, chromogenic in situ hybridisation; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

Statistical analyses

Statistical analysis was performed using IBM SPSS Statistics software, V.25.0.0.0 for Mac (IBM Corporation). Survival was analysed with Kaplan-Meier curves and the log-rank tests. Correction for multiple comparisons was not made. Survival in metastatic disease was calculated from the date when metastasis was first observed in imaging to the time of death. Multivariate analysis was conducted using Cox multivariate regression analysis. P values <0.05 were considered significant.

Patient and public involvement

Patients or public were not involved in the design, conduct, reporting or dissemination of this study.

RESULTS

Sixty-one patients of the originally 594 women ultimately developed distant metastases during the follow-up. Of these, 50 patients died of breast cancer during the follow-up. The median disease-free interval was 39.0 months in the patients who had distant metastases. The median follow-up time starting from the early breast cancer diagnosis was 72.0 months in patients who later developed metastases.

The median follow-up of the patients during their metastatic breast cancer was 18.0 months (mean 30.2 months). The Kaplan-Meier estimate for median survival of the patients with metastatic breast cancer was 77.0 months in those with luminal A-like breast cancers, 29.0 months in those with luminal B-like (HER2-negative) disease and 11.0, 26.0 and 12.0 months in those with HER2-positive, non-luminal, luminal B-like (HER2-positive) and TNBC subtype, respectively.

Patients with metastatic local lymph nodes at the time of definitive surgery displayed poorer survival outcomes for metastatic disease (p=0.031) (figure 2). The Kaplan-Meier estimate for median survival in metastatic disease in lymph node-negative patients was 33.0 months, and in lymph node-positive patients, it was 19.0 months. Only N0 versus N1–3 classification was significant. No prognostic

differences between the patients with N1, N2 or N3 disease subtypes (p=0.78) were detected.

Of the more traditional prognostic factors related to metastatic disease, ER positivity of the primary tumour (p=0.011), Ki-67 expression ranging from 0% to 14% (vs over 14%) in primary tumours (p=0.032) and grades I–II (vs grade III) primary tumours (p=0.012) were associated with better survival in metastatic disease in univariate analysis. Breast cancer subtype (determined from the initial surgical samples) also predicted survival with metastatic breast cancer (p=0.0078), Also, the patients with luminal A-like breast cancer had significantly prolonged survival, when compared with all other subtypes (p=0.017). Primary tumour size, PR or HER2 expression, the site of the first metastasis in bone versus elsewhere, disease-free interval (≤24 months vs >24 months) or age at disease onset were not associated with metastatic disease survival.

When assessed separately by different biological subtypes, initial lymph node metastases predicted worse prognosis only in the patients with the luminal A subtype in univariate analysis (p=0.019), but the small sample size of each subgroup limited the reliability of this analysis (data not shown).

In multivariate analysis, the presence of lymph node metastases at the time of initial diagnosis predicted poorer survival overall (HR, 2.17; 95% CI, 1.09–4.31; p=0.027) when tumour size (T1 vs T2–4) (HR, 1.33; 95% CI, 0.71–2.47; p=0.37) and ER status (negative vs positive) (HR, 2.16; 95% CI, 1.14–4.10; p=0.018) were included in the analysis. The proportional hazards assumption was met in the analysis. Breast cancer subtype, Ki-67 expression or grade did not remain significant prognostic factors after multivariate analysis.

DISCUSSION

As the main observation, we report in this prospectively collected and contemporary cohort from a Finnish University Hospital that the presence of local lymph node metastasis at the time of early breast cancer surgery predicted short survival in subsequent metastatic breast cancer. Our results also supported previous results of ER negativity in primary breast cancer as an adverse prognostic factor for disease recurrence.

The most established prognostic factors of better outcome in metastatic breast cancer include ER positivity, long disease-free interval (usually defined as at least 2 years), low number of metastatic sites and bone-only localisation of metastases.[7–13 17–19] HER2 appears to no longer represent a prognostic factor in the era of targeted treatments, and prognostic factors also slightly differ between HER2-positive and HER2-negative patients.[20 21] Emerging metastatic breast cancer prognostic factors include circulating tumour cells, gene expression panels, circulating tumour markers and miRNAs; however, they have not yet been sufficiently validated.[22–25] Whereas ER status, a lengthy disease-free interval and metastatic load are established and obvious prognostic factors for metastatic
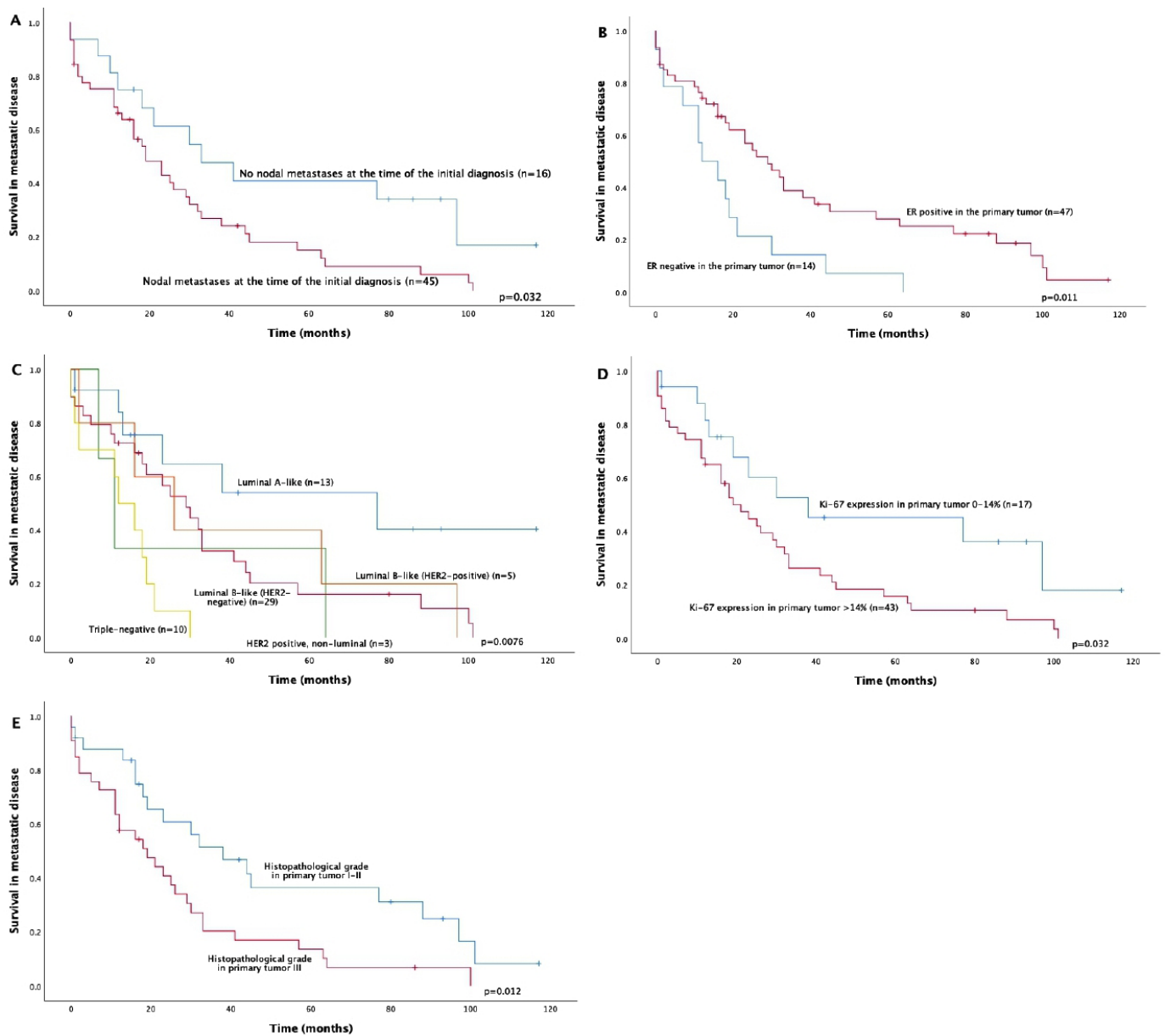
Figure 2 Associations between primary tumour properties and survival in metastatic breast cancer. In multivariate analysis, only ER expression and initial nodal status remained as significant factors. ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2.

breast cancer, the presence of lymph node metastases at the time of initial diagnosis has not been widely studied in metastatic breast cancer, although it is the strongest prognostic factor in early breast cancer. In the current study, we concentrated solely on primary breast cancer characteristics, and we did not assess other characteristics, such as disease-free interval, metastasis load or metastasis location as prognostic factors.

Some previous studies with mostly retrospective cohort settings and outdated treatment modalities have reported the initial nodal status as a prognostic factor in metastatic breast cancer, whereas others have not found such an association.[7 9 26 27] In the pioneer work of Clark *et al*, nodal involvement at time of initial diagnosis was associated with shorter survival.[12] Another retrospective

single-institute study also concluded that lymph node involvement at primary diagnosis predicted unfavourable outcomes in metastatic breast cancer, although the first patients were enrolled in the study cohort in the 1960s.[28] In line with these studies, a Spanish retrospective registry study suggested that the initial lymph node status should be part of the prognostic index in recurrent metastatic breast cancer.[29] In addition to considerable change in the oncological treatments of breast cancer during the last decades, also surgical techniques, especially axillary procedures have developed considerably. The current results from the prospective data with modern treatments thus support and confirm earlier results.

In our study, any metastasis found in local lymph nodes at the time of definitive surgery was associated with dismal

metastatic cancer survival outcomes. The Kaplan-Meier estimate for median survival was prolonged from 19 to 33 months in patients without lymph node metastases at the time of initial diagnosis. Although lymph node metastases in general are associated with other factors of poor prognosis, our study suggested that this result was independent of tumour size and ER expression. Node positivity may reflect not only higher metastatic potential of breast cancer, but it can possibly decipher impaired immunological microenvironments.[30] Interestingly, a recent paper by Ullah *et al* using evolutionary genomic analyses of primary tumours and metastatic lesions suggested that ipsilateral axillary lymph node status in primary breast cancer was very useful for predicting the tumourigenic capability of the primary tumour; however, it did not drive metastasis per se.[31] Several other papers have suggested that metastatic lymph nodes did not eventually metastasise.[32 33] However, it was also recently shown that the removal of metastatic axillary lymph nodes resulted in the disappearance of circulating tumour DNA, and discussion on these issues continues.[34]

It has to be emphasised that all our patients had recurrent breast cancer, and our material did not include samples from patients with de novo metastatic breast cancer. Whereas this makes the material more uniform, the results may not be suitable for generalising to de novo metastatic breast cancers, which have a different natural course from recurrent breast cancers.[10 13] Nevertheless, the prognostic value of ER status has also been previously demonstrated in recurrent breast cancer, and the initial lymph node status obviously cannot be evaluated in de novo metastatic cancers.[8 9 18] As an other limitation, we were unable to address the results separately in subgroups, for example, according to biological subtypes, due to relatively low number of patients with metastatic breast cancer. On the other hand, our study was based on a prospective cohort from a university clinic, and the patients were treated with up-to-date surgical and oncological treatment modalities.

Our results confirmed that ER negativity in primary tumour was associated with short survival for metastatic disease. This obviously is not only due to the more aggressive nature of the cancer but also because of the lack of ER-targeted treatments. Compelling evidence has demonstrated ER negativity in the primary tumour as an adverse prognostic factor in various previous studies.[8 9 12 13 18] ER status frequently changes in metastatic breast cancer, and the negative conversion of ER status is also a predictor of poor prognosis.[35] Most previous studies have divided metastatic breast cancers only to three subgroups: ER/PR-positive, HER2-positive and TNBC. We used the widely recognised ESMO guidelines for subtyping our cases. Although the number of patients in each subgroup was rather limited, the patients with slowly proliferating, ER-responsive luminal A-like breast cancers still had significantly prolonged survival in metastatic breast cancer compared with other subtypes. TNBC has the worst outcome of all subtypes in

metastatic breast cancer, a finding which was mirrored in our study.[36]

Predicting the course of metastatic breast cancer is of primary importance in clinical practice; however, its status as a highly heterogenous disease at both the intrapatient and interpatient levels makes metastatic breast cancer very unpredictable.[31 37] Current metastatic breast cancer guidelines recommend starting treatment with chemotherapy or even with a combination chemotherapy instead of hormonal treatments in patients with visceral crisis or rapidly progressing ER-positive, HER2-negative breast cancer.[2 38] If novel adverse prognostic factors of metastatic breast cancer, such as initial nodal status, could be confirmed, these patients should receive more aggressive first-line metastatic breast cancer therapy.

In conclusion, our results strengthen the role of primary tumour ER negativity as an adverse prognostic factor in patients with recurrent breast cancer; however, they also suggest that initial lymph node status may be a prognostic factor for metastatic disease course. Future studies should also evaluate the prognostic power of isolated tumour cells, micrometastases and the absolute number of metastatic lymph nodes, which were not addressed in our material. More research is also clearly needed to clarify whether axillary lymph node metastases are able to seed metastatic cells or whether they are purely an indicator of aggressive disease.

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