Clinical significance of the neutrophil-to-lymphocyte ratio in oligometastatic breast cancer

Yuka Inoue1 · Makoto Fujishima2 · Makiko Ono3 · Jun Masuda4 · Yukinori Ozaki4 · Tetsuyo Maeda1 · Natsue Uehiro1 · Yoko Takahashi1 · Takayuki Kobayashi4 · Takehiko Sakai1 · Tomo Osako5 · Takayuki Ueno1 · Shinji Ohno6

Received: 7 July 2022 / Accepted: 22 August 2022 / Published online: 24 September 2022 © The Author(s) 2022

Abstract

Purpose This study investigated the clinical impact of pretreatment neutrophil-to-lymphocyte ratio (NLR) on survival in patients with oligometastatic breast cancer.

Patients and methods We collected data from 397 patients who underwent primary breast surgery from 2004 to 2015 and developed recurrence during the follow-up. We reviewed the images and clinical information and defined OMD according to the European Society for Medical Oncology advanced breast cancer guidelines. The NLR was calculated using pretreatment data of primary breast cancer. The cutoff value of the NLR was determined by receiver operating characteristic curve with Youden Index.

Results Among 397 patients, 131 had OMD at recurrence. The low-NLR group included patients of significantly older age at primary cancer than those in the high-NLR group. A low NLR indicated a better overall survival ($p = 0.023$) after adjusting for relevant factors, including estrogen receptor status, surgical resection of metastatic disease, metastatic organ number, disease-free interval, and liver metastasis than did the high-NLR group. We developed prognostic models for OMD using six independent prognostic factors, including the NLR. The number of factors was associated with overall survival; patients with all six favorable factors showed a good overall survival of 90.9% at 8 years and those with four or more factors showed 70.4%.

Conclusions The NLR was an independent prognostic factor for overall survival in OMD. The number of favorable prognostic factors was associated with overall survival. A prognostic model, including the NLR, will help identify patients with a favorable prognosis.

Keywords Oligometastatic breast cancer · Neutrophil-to-lymphocyte ratio · NLR · Oligometastatic disease · Breast cancer

Introduction

Because metastatic breast cancer (MBC) is an incurable disease, systemic therapy for palliation is the standard of care for affected patients [1, 2]. Approximately 30%–40% of patients with MBC will develop widespread metastases [3–5]. Although the advancement of systemic therapy for MBC has led to improved overall survival (OS), the median OS ranges widely from 8 months to 4 years [6–8]. However, in clinical practice, some patients achieve the status of no evident disease or long-term survival with controlled MBC.

Hellman and Weichselbaum first proposed the concept of oligometastatic disease (OMD) as a distinct cancer state between locally confined and systemically metastatic disease in 1995 [9]. Although patients with OMD are considered as potentially curable [6], there are no clear diagnostic criteria or treatment guidelines for OMD, and it is unclear who will benefit from treatment of curative intent. The European Society for Medical Oncology (ESMO) advanced breast cancer (ABC) guidelines define OMD as low volume metastatic disease with a limited number and size of metastatic lesions (up to five lesions and not necessarily in the same organ) [10]. Conversely, German experts define it as a limited number of metastases in one body organ [11].

Recent reports have shown that the neutrophil-to-lymphocyte ratio (NLR) correlates with survival in patients with cancer, including breast cancer [12, 13]. Although inflammatory cells and mediators in the tumor microenvironment play an important role in cancer progression, which may be reflected by systemic immune status [14],
the clinical significance of NLR in oligometastatic breast cancer requires elucidation. This study investigated the clinical impact of pretreatment NLR on the survival of patients with oligometastatic breast cancer to help identify patients who will benefit from treatment of curative intent.

Patients and methods

We analyzed the data from 397 patients who underwent primary breast surgery from 2004 to 2015 and developed recurrence in sites other than central nervous system during follow-up in our institution. Their (neo)adjuvant therapy was administered based on the guidelines of the Japanese Breast Cancer Society [15]. We reviewed the images and clinical information and defined OMD according to the ESMO ABC guidelines [10]. The NLR was defined as the absolute blood neutrophil count divided by the absolute lymphocyte count in the peripheral blood and was calculated using pretreatment data of the patients at the time of primary breast cancer. The cutoff value of the NLR was determined by receiver operating characteristics curve analysis using the Youden index. OS was defined as the period from the day of diagnosis of breast cancer recurrence until the day of death from any cause. JMP software, version 8.0.0 (SAS Institute, Cary, NC), was used for all statistical analyses. The results are expressed as the mean ± standard deviation or number. Group differences in continuous variables were assessed by the Mann–Whitney test. Group differences in categorical variables were assessed by the chi-squared test. Survival curves were plotted by the Kaplan–Meier method and compared by the log-rank test. Survival data were evaluated using a multivariate Cox proportional hazards model. Differences were considered significant at two-sided p < 0.05. A prognostic model for OMD was developed using favorable prognostic factors on multivariate analysis. Harrell’s C-index was used to evaluate the prognostic strength of models [16].

Results

Among 397 cases with recurrent breast cancer, 131 cases (33%) had OMD. The median follow-up from recurrence was 59 months (range 6–151 months). The cutoff value of the NLR was 2.52 by the Youden index using data from patients with OMD, and 93 patients (71%) were classified in the low-NLR group. The absolute counts of neutrophil and lymphocyte were plotted on a graph (Supplementary Fig. 1). Table 1 shows the background characteristics of patients at primary breast cancer according to the NLR groups. The low-NLR group included patients of significantly older age at primary breast cancer than those in the high-NLR group (p = 0.0026). There were no significant differences in clinical stage or subtype between the two groups. More patients received endocrine therapy as adjuvant therapy in the high-NLR group than in the low-NLR group (p = 0.0447).

Table 2 shows the clinical characteristics of patients at recurrence and the treatment for OMD by the NLR groups. The low-NLR group included patients of significantly older age at recurrence than those in the high-NLR group (p = 0.0037). There were no significant differences in disease-free interval (DFI), number of metastatic organs, number of metastatic lesions, presence/absence of distant metastasis, or site of metastasis between the two groups. Moreover, there were no significant differences in the 1st-line therapy for OMD after recurrence between the two groups (Table 2).

Figure 1A shows the OS of patients with OMD by the NLR groups. Those in the low NLR had better OS (p = 0.023) after adjusting for estrogen receptor (ER) status, age at recurrence, (neo)adjuvant chemotherapy, surgical resection of metastatic disease, metastatic organ number, DFI, and liver metastasis (Table 3). In addition, no (neo)adjuvant chemotherapy (p = 0.0044), surgical resection (p = 0.0416), single metastatic organ (p = 0.05), DFI > 2 years (p = 0.007), and no liver metastasis (p = 0.02) were independent favorable prognostic factors (Table 3). In the whole population of patients with recurrent breast cancer, the NLR was prognostic (p = 0.0052) while it was not in patients with recurrent breast cancer without OMD (p = 0.134) (Supplementary Fig. 2A and B). Thus, the prognostic significance of NLR was more prominent for patients with OMD than for those without.

To select patients with favorable prognosis likely to benefit from treatment of curative intent, prognosis was compared according to the number of favorable prognostic factors, including no (neo)adjuvant chemotherapy, surgical resection, single metastatic organ, DFI > 2 years, no liver metastasis, and low NLR. The number of prognostic factors was associated with OS (p < 0.001) (Fig. 1B). The OS at 8 years was calculated based on the number of included factors (Table 4). Patients with all six of the favorable factors showed an excellent 8-year OS of 90.9% (p = 0.001; hazard ratio [HR] = 9.14), while patients with five or more factors showed an OS of 75.6% (p = 0.0025) and those with four or more factors showed an OS of 70.4% (p < 0.001) (Supplementary Fig. 3). The concordance of each model was evaluated using Harrell’s C-index, with a C-index of 0.737 for the model with NLR, which was higher than for the model without NLR (a C-index of 0.72). For the prediction of 5-year OS, we constructed a nomogram using these predictive factors (Fig. 2).
Discussion

This study showed that a low NLR was an independent favorable prognostic factor for breast OMD. Although the association between the NLR and prognosis in breast cancer has been reported in multiple studies [12, 13], to the best of our knowledge, this is the first report to show the prognostic significance of the NLR in OMD. A recent systematic review of breast OMD demonstrated that comparing to those without, patients with solitary metastasis, > 24-month interval between primary tumor and OMD, no or limited involved axillary lymph nodes at primary diagnosis, and hormone-receptor positivity were associated with better prognosis [17]. However, the NLR was not considered in that study. Our study results may enable clinicians to better predict the prognosis of patients with OMD by considering the NLR in the prognostic model.

Some studies have suggested that local treatment for metastatic lesions, such as surgery and radiotherapy, improves the survival of patients with OMD [18]. The SABR-COMET trial, a phase 2 randomized trial, demonstrated that stereotactic ablative radiotherapy improved the prognosis of patients with OMD from different primary cancers, including breast cancer [19]. The SABR-COMET-3 trial, a phase 3 trial of the same concept, including breast cancer patients with OMD, is currently underway [20]. Some studies have examined outcomes after surgical resection of lung, liver, and brain metastases and suggested good long-term disease control and survival for selected patients [21–24]. There are also some case–control studies suggesting a survival benefit from surgical resection of metastatic lesions in patients with breast OMD [25–30]. However, these studies are retrospective, limited by number of patients, and conducted in

| Table 1 | The background characteristics of patients with primary breast cancer according to NLR group |
|---------|---------------------------------------------|
|         | High-NLR | Low-NLR | P value |
| Age at primary breast cancer (median, range) | 47 (29–73) | 55 (27–86) | 0.0026 |
| NLR  |
| Neutrophil-to-lymphocyte ratio, ER estrogen receptor, PR progesterone receptor, HER2 human epidermal growth factor receptor type2. Statistically significant P values are shown in bold. |
| Stage |
| 0     | 0 (0) | 3 (3) | 0.40 |
| I     | 6 (16) | 18 (19) |
| II    | 18 (47) | 49 (53) |
| III   | 14 (37) | 23 (25) |
| ER    |
| –     | 6 (16) | 31 (33) | 0.054 |
| +     | 32 (84) | 62 (67) |
| PR    |
| –     | 18 (47) | 50 (54) | 0.56 |
| +     | 20 (53) | 43 (46) |
| HER2  |
| –     | 31 (82) | 72 (77) | 0.65 |
| +     | 7 (18) | 23 (21) |
| Subtype |
| HR+HER2− | 28 (74) | 55 (59) | 0.16 |
| HR+HER2+ | 5 (13) | 8 (9) |
| HR−HER2+ | 2 (5) | 12 (13) |
| HR−HER2− | 3 (8) | 18 (19) |
| Adjuvant endocrine therapy |
| No | 8 (21) | 37 (40) | 0.0447 |
| Yes | 30 (79) | 56 (60) |
| (Neo)adjuvant chemotherapy |
| No | 7 (18) | 24 (26) | 0.50 |
| Yes | 31 (82) | 69 (74) |
| (Neo)adjuvant anti-HER2 therapy |
| No | 35 (92) | 78 (84) | 0.27 |
| Yes | 3 (8) | 15 (16) |
| (%) | (%) | (%) |
highly selective cohorts; thus, a selection bias cannot be avoided. Indeed, the Korean case–control study showed better survival in patients with surgical resection of pulmonary metastases than in patients without surgery, but in the multivariate analysis, surgical resection did not remain an independent prognostic factor [26]. Therefore, it is unclear whether surgery itself contributes to the improved prognosis of patients with OMD. However, these studies do not exclude the possibility that surgical resection of metastatic lesions may provide some survival benefit in highly selected patients with favorable prognosis. A refined prognostic model that can select these patients with favorable prognosis would help to indicate those who would benefit from intensive treatment of curative intent, including surgery. Our results suggest that the addition of the NLR to conventional prognostic factors would be useful in such a prognostic model.

Most studies that examined prognostic factors in OMD focused on tumor-related factors, such as the number of metastatic lesions, metastatic organs, and tumor subtypes. However, it is now clear that host-related factors also affect patient prognosis. In this study, we showed that the NLR at primary diagnosis indicated the survival in patients with

| Table 2 | The clinical characteristics at recurrence and the treatment for OMD according to NLR groups |
|---------|---------------------------------|---------------------------------|----------------|
|         | High-NLR n=38                   | Low-NLR n=93                    | P value       |
| Age at recurrence(median, range) | 49 (30–78)                      | 57 (31–86)                      | **0.0037**    |
| DFI(month, median, range)       | 30 (6–97)                       | 30 (2–98)                       | 0.60          |
| Number of metastatic organs     |                                |                                |               |
| 1                                 | 36 (95)                         | 83 (89)                         | 0.57          |
| 2                                 | 2 (5)                           | 9 (10)                          |               |
| 3                                 | 0 (0)                           | 1 (1)                           |               |
| Number of metastatic lesions     |                                |                                |               |
| 1                                 | 20 (53)                         | 57 (62)                         | 0.73          |
| 2                                 | 7 (18)                          | 16 (17)                         |               |
| 3                                 | 7 (18)                          | 13 (14)                         |               |
| 4                                 | 3 (8)                           | 3 (3)                           |               |
| 5                                 | 1 (3)                           | 3 (3)                           |               |
| Distant metastasis               |                                |                                | 1.00          |
| Yes                               | 25 (66)                         | 62 (67)                         |               |
| No                                | 13 (34)                         | 31 (33)                         |               |
| Site of metastasis               |                                |                                |               |
| Local                             | 4 (11)                          | 13 (14)                         | 0.77          |
| Region LN                         | 11 (29)                         | 23 (25)                         | 0.66          |
| Bone                              | 12 (32)                         | 27 (29)                         | 0.83          |
| Liver                             | 7 (18)                          | 16 (17)                         | 1.00          |
| Lung/pleura                       | 5 (13)                          | 19 (20)                         | 0.46          |
| Distant LN                        | 1 (3)                           | 6 (6)                           | 0.67          |
| Surgery for OMD                   |                                |                                |               |
| No                                | 29 (76)                         | 63 (71)                         | 0.66          |
| Yes                               | 9 (24)                          | 26 (29)                         |               |
| RT for OMD                        |                                |                                |               |
| No                                | 32 (84)                         | 75 (81)                         | 0.80          |
| Yes                               | 6 (16)                          | 18 (19)                         |               |
| 1st line                          |                                |                                |               |
| Chemotherapy                      | 11 (30)                         | 44 (47)                         | 0.079         |
| Endocrine therapy                | 24 (65)                         | 45 (48)                         | 0.11          |
| Anti-HER2 therapy*               | 5 (13)                          | 18 (19)                         | 0.61          |

* A breakdown of the anti-HER2 therapy is shown in supplementary Table 1.
breast OMD, probably because it may reflect the host anti-cancer immune status.

Limitations

One of the major limitations in this study was its small number of patients, which resulted partly from it being a single institutional study. Therefore, the survival analysis of this population needs to be interpreted with caution. We are planning a multicenter study with a larger population to confirm the results of this study. Another limitation is that the NLR at the time of recurrence could not be calculated because white blood cell fractions were not measured in all patients at recurrence. However, our result suggested that the NLR at primary cancer impacted survival even after recurrence, indicating the importance of the primary immune status throughout the disease course. The difference in the proportion of patients given adjuvant endocrine therapy between the two groups is another limitation (Table 1). Because female hormones have been reported to affect T-cell proliferation and neutrophil counts [31, 32], adjuvant endocrine therapy may have affected the systemic immune status. To reduce such a bias, we included ER status, which was associated with administration of adjuvant endocrine therapy, in the multivariate analysis,
which showed that the NLR was prognostic independent of ER status (Table 3).

**Conclusion**

The NLR was an independent prognostic factor for OS in OMD. The number of favorable prognostic factors was associated with survival. We developed a new prognostic model for OMD using the NLR, which will help to decide treatment strategy for patients with OMD.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s10549-022-06726-w.

**Author contributions** YI, MF, and MO conceived and designed the study. YI and MF carried out the analysis. SO advised on the study design. TO contributed to the pathological assessment. JM, YO, TM, NU, YT, TK, and TS contributed to data acquisition. All authors contributed to the interpretation of the findings. TU drafted the initial manuscript, and all authors contributed to the revisions of the manuscript. The authors read and approved the final manuscript.

**Data availability** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Declarations**

**Conflict of interest** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Ethical approval** This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the institutional Ethics Committee.

**Consent for publication** All authors agree to publish this article.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

**References**

1. Senkus E et al (2015) Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 26(Suppl 5):v8-30
2. Kwapisz D (2019) Oligometastatic breast cancer. Breast Cancer 26(2):138–146
3. Reyes DK, Pienta KJ (2015) The biology and treatment of oligometastatic cancer. Oncotarget 6(11):8491–8524
4. Camacho LH et al (2007) Pilot study of regional, hepatic intra-arterial paclitaxel in patients with breast carcinoma metastatic to the liver. Cancer 109(11):2190–2196
5. O’Shaughnessy J et al (2002) Superior survival with capecitabine plus docetaxel combination therapy in
anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 20(12):2812–2823
6. Pagani O et al (2010) International guidelines for management of metastatic breast cancer: can metastatic breast cancer be cured? J Natl Cancer Inst 102(7):456–463
7. Hortobagyi GN (2002) Can we cure limited metastatic breast cancer? J Clin Oncol 20(3):620–623
8. Guarnieri V, Conte PF (2004) The curability of breast cancer and the treatment of advanced disease. Eur J Nucl Med Mol Imaging 31(Suppl 1):S149–S161
9. Hellman S, Weichselbaum RR (1995) Oligometastases. J Clin Oncol 13(1):8–10
10. Cardoso F et al (2018) 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4) dagger. Ann Oncol 29(8):1634–1657
11. Thomssen C et al (2016) ABC3 consensus: assessment by a German Group of Experts. Breast Care (Basel) 11(1):61–70
12. Ethier JL et al (2017) Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: a systematic review and meta-analysis. Breast Cancer Res 19(1):2
13. Templeton AJ, et al (2014) Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst 106(6):dju124
14. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144(5):646–674
15. Shimoi T, et al (2020) The Japanese Breast Cancer Society Clinical Practice Guidelines for systemic treatment of breast cancer, 2018 edition. Breast Cancer 27(3):322–331
16. Harrell FE Jr et al (1982) Evaluating the yield of medical tests. JAMA 247(18):2543–2546
17. van Ommen-Nijhof A et al (2020) Prognostic factors in patients with oligometastatic breast cancer—a systematic review. Cancer Treat Rev 91:102114
18. Ueno T (2022) Surgical management of metastatic breast cancer: a mini review. Front Oncol 12:910544
19. Palma DA et al (2019) Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet 393(10185):2051–2058
20. Olson R et al (2020) Stereotactic ablative radiotherapy for the comprehensive treatment of 1–3 oligometastatic tumors (SABR-COMET-3): study protocol for a randomized phase III trial. BMC Cancer 20(1):380
21. Pastoreno U et al (1997) Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg 113(1):37–49
22. Fong Y et al (1997) Liver resection for colorectal metastases. J Clin Oncol 15(3):938–946
23. Kent CL, McDuff SGR, Salama JK (2021) Oligometastatic breast cancer: where are we now and where are we headed?—A narrative review. Ann Palliat Med 10(5):5954–5968
24. Friedel G et al (2002) Results of lung metastasectomy from breast cancer: prognostic criteria on the basis of 467 cases of the International Registry of Lung Metastases. Eur J Cardiothorac Surg 22(3):335–344
25. Staren ED et al (1992) Pulmonary resection for metastatic breast cancer. Arch Surg 127(11):1282–1284
26. Yhim HY et al (2010) Prognostic factors for recurrent breast cancer patients with an isolated, limited number of lung metastases and implications for pulmonary metastasectomy. Cancer 116(12):2890–2901
27. Mariani P et al (2013) Liver metastases from breast cancer: Surgical resection or not? A case-matched control study in highly selected patients. Eur J Surg Oncol 39(12):1377–1383
28. Sadot E et al (2016) Hepatic resection or ablation for isolated breast cancer liver metastasis: a case-control study with comparison to medically treated patients. Ann Surg 264(1):147–154
29. Abbas H et al (2017) Breast cancer liver metastases in a UK tertiary centre: outcomes following referral to tumour board meeting. Int J Surg 44:152–159
30. Ruiz A et al (2018) Surgical resection versus systemic therapy for breast cancer liver metastases: results of a European case matched comparison. Eur J Cancer 95:1–10
31. Habib P et al (2018) Estrogen serum concentration affects blood immune cell composition and polarization in human females under controlled ovarian stimulation. J Steroid Biochem Mol Biol 178:340–347
32. Porter VR et al (2001) Immune effects of hormone replacement therapy in post-menopausal women. Exp Gerontol 36(2):311–326

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Yuka Inoue1 · Makoto Fujishima2 · Makiko Ono3 · Jun Masuda4 · Yukinori Ozaki4 · Tetsuya Maeda1 · Natsume Uehiro1 · Yoko Takahashi1 · Takayuki Kobayashi4 · Takehiko Sakai1 · Tomo Osako2 · Takayuki Ueno1 · Shinji Ohno6

Yuka Inoue
yuka.inoue@jfcr.or.jp

Makoto Fujishima
fujishima@kuma-h.or.jp

Makiko Ono
makiko.ono@jfcr.or.jp

Jun Masuda
jun.masuda@jfcr.or.jp

Yukinori Ozaki
yukinori.ozaki@jfcr.or.jp

Tetsuya Maeda
tetsuyomaeda@jfcr.or.jp

Natsume Uehiro
natsume.uehiro@jfcr.or.jp

Yoko Takahashi
yo.takahashi@jfcr.or.jp

Takayuki Kobayashi
yukinori.ozaki@jfcr.or.jp

Takehiko Sakai	
takehiko.sakai@jfcr.or.jp

Tomo Osako
tomo.osako@jfcr.or.jp

Shinji Ohno
shinji.ohno@jfcr.or.jp
