Prognosis classification of breast cancer with distant lymph node metastasis IIc or M1 category

Shu Wang (✉ SHUWANG@PKUPH.EDU.CN)

Peking University People's Hospital <https://orcid.org/0000-0002-8651-4795>

Jinbo Wu

Peking University People's Hospital

Taobo Hu

Peking University People's Hospital <https://orcid.org/0000-0001-5124-7167>

Article

Keywords: breast cancer, distant lymph nodes metastasis (DLM), IIc, M1

Posted Date: March 22nd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-295675/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: In the American Joint Commission on Cancer (AJCC) staging manual, ipsilateral supraclavicular lymph node metastases (ISLM) were defined as N3c, while contralateral supraclavicular and subclavian lymph node, contralateral internal mammary lymph node, contralateral axillary lymph node, and cervical lymph node as distant lymph nodes metastasis (DLM) were classified as M1, stage IV. Herein, we used the information recorded in the Surveillance, Epidemiology, and End Results (SEER) database to compare patients' overall survival with DLM, ISLM, and distant organ metastasis.

Methods: A total of 376 patients with ISLM, 562 patients with DLM, 5,069 patients with IIlc stage breast cancer, and 7,540 patients with distant organ metastasis from the SEER database (2004-2016) were included in the present study. R package was used to perform the Kaplan–Meier survival analysis among these four groups, and propensity score weighting (PSW) was used to minimize the differences in clinicopathological characteristics among groups

Results: After PSW, the median survival of ISLM, DLM, IIlc stage, and distant organ metastasis was 42 months, 50 months, 55 months, and 31 months, respectively. DLM achieved significantly better overall survival than distant organ metastasis ($p < 0.001$, HR=0.646, 95%CI:0.561-0.737), while there was no significant difference in long-term survival between DLM and ISLM ($p = 0.467$, HR=0.915, 95%CI:0.719-1.163) or DLM and IIlc stage ($p = 0.959$, HR=0.995, 95%CI:0.837-1.183). Surgery ($p < 0.001$, HR=0.502, 95%CI:0.375-0.674) and chemotherapy ($p = 0.007$, HR=0.701, 95%CI:0.527-0.932) could significantly improve the OS for patients with DLM. When compared with chemotherapy alone, a combination of chemotherapy, surgery, and radiotherapy could achieve better survival, with the increased median survival from 26 months to 82 months ($p < 0.001$, HR=0.366, 95%CI:0.253-0.529).

Conclusion: The prognosis of breast cancer patients with DLM was similar to ISLM and IIlc stage, but much better than that of patients with distant organ metastasis. Also, combined-modality therapy significantly improved long-term survival. Consequently, it seems more reasonable to classify DLM as IIlc category instead of M1.

Introduction

Anatomy staging of breast cancer is critical to determine prognosis and treatment choice; however, cancer staging is not an exact science. Following newly available information on etiology and various diagnosis and treatment methods, the classification and staging of cancer also tend to change.[1] In the fifth version of AJCC TNM staging, ipsilateral supraclavicular lymph node metastasis (ISLM) was defined as M1, stage IV [2]. However, related studies have confirmed that ISLM was more consistent with N3, stage III, in terms of survival prognosis and tumor biological behavior. [3, 4] Therefore, in the sixth edition of TNM, ISLM was redefined as N3c, stage IIIC [5], which changed patients' treatment decisions with ISLM in clinical practice. [6, 7] It appears that distant lymph node metastases (DLM) face the same situation. The definition of DLM in breast cancer is based on the existence of at least one of the following

conditions: contralateral internal mammary lymph node metastasis (CILM), contralateral axillary lymph node metastasis (CAM), contralateral supraclavicular, subclavian lymph node metastasis (CSLM), and cervical lymph node metastasis (CLM).[8][9] Information on DLM is lacking due to its low incidence. [10–12] As far as we know, there are no cohort studies to date on the treatment outcomes of DLM; thus, there is no consensus on how to manage these patients. DLM may have synchronous or metachronous presentation [10, 13, 14], where the former implies that DLM was found at the first visit, while the latter means that the DLM was not found at the first visit but was found during the follow-up time.

In the AJCC staging system, DLM of breast cancer is classified as M1, stage IV. Nevertheless, there are controversies regarding the clinical treatment decision. Retrospective studies with a small sample size have observed that the survival prognosis of patients with DLM is more similar to patients classified as N3c or IIIC and is significantly different from the patients with distant organ metastasis, such as bone, liver, and lung.[8][9] However, whether DLM should be considered as an advanced locoregional stage or distant metastasis has not yet been answered and should be addressed by prospective trials, which are difficult to conduct since the low incidence of DLM.

The aim of this study was to use the Surveillance, Epidemiology, and End Results (SEER) database to compare the overall survival of DLM, ISLM, IIIC stage, and distant organ metastasis. Furthermore, we also aimed to analyze the impact of different treatment modalities on survival, hoping it could offer some implication to clinical practice.

Materials And Methods

Data Extraction

This study was approved by the Institutional Review Board by Chinese Center of Disease control and prevention. Data were acquired from the SEER database between January 1, 2004, and December 31, 2015, as the 6th AJCC TNM staging system was adopted by SEER in 2004. Data were extracted for all cases that were initially diagnosed as malignant primary breast cancer, while multiple primary malignant tumors were excluded. Breast cancer patients who lack information on tumor staging, therapy, or prognosis were excluded. After these steps, we excluded patients who were male and with bilateral breast cancer. The follow-up time was from breast cancer diagnosis until death or the end of the follow-up period. Finally, 376 patients with ISLM but no distant metastasis classified as N3cM0, 562 patients with DLM classified as M1-LN, 7,540 patients with distant organ metastasis classified as M1, and 5,069 patients with IIIC stage classified according to the 6th edition of AJCC were included in the study (**Figure 1**).

Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary files. The original data were downloaded from the SEER Web site server (<https://seer.cancer.gov/data/>) via the SEER*Stat software version 8.3.5 in the client-server model.[15]

Propensity score weighting (PSW)

This was a retrospective and observational study. Some significant covariates of the patients were heterogeneous and possibly affected the outcomes. Propensity score weighting (PSW) was applied to minimize the selection bias and to approximately balance the covariates among groups.[16] The propensity score for each patient was estimated by a logistic regression model in the N3cM0 group, IIc group, M1-LN group, and M1 group according to age at diagnosis, histologic type based on the ICD-O-3, tumor differentiation grade based on the ICD-O-2, T or N stage based on the Derived AJCC Stage (6th), estrogen receptor (ER) status, progesterone receptor (PR) status, Her2 status, surgery, chemotherapy and radiotherapy. The survival rate among the four groups and different treatments in M1-LN were further compared.

Statistical analysis

Overall survival (OS) was defined as the time from the date of diagnosis to the date of death due to any cause or the date at the last follow-up. The survival probability of the four groups was calculated by the Kaplan-Meier method and compared by log-rank test before and after PSW. To evaluate the impact of treatment modalities (surgery, radiotherapy, chemotherapy, comprehensive therapy) on survival, Kaplan-Meier survival analysis, and log-rank test were also used before and after PSW. The definition of surgery is presented in Supplemental **Table 1**. Baseline characteristics were compared using the χ^2 test or Fisher's exact test before and after PSW (**Table 1**, **Table S2-5**). Univariate and multivariate analyses were performed using a Cox regression proportional hazard model in the M1-LN group. The hazard ratio (HR) and corresponding 95% confidence interval (CI) were also calculated. All statistical analyses were performed in RStudio (version 1.3.1056, R Foundation for Statistical Computing, Vienna, Austria) using the packages "survival" (version 2.41–3), "nnet" (version 7.3-14), and "IPWsurvival" (version 0.5). All P values were calculated as two-sided, with $P < 0.05$ being considered as statistical significance.

Results

Baseline characteristics of the patients

The clinical and pathological features of the primary tumors and the treatments of these cohorts are summarized in **Table 1** and **Table S2-5**. The average age of diagnosis for patients with M1-LN was 59.1 (range 25-95) years old. Out of 562 patients with M1-LN, 39.0%, 13.2%, 39.5% were with T1-2, T3 and T4, respectively, 8.4%, 37.7%, 11.9%, and 38.1% were with N0, N1, N2 and N3, respectively, while 72.8% had ductal carcinoma. Also, the majority of M1-LN patients (54.3%) had poorly grade based on the ICD-O-2. 57.5% of the patients received surgery, including 31.1% who received radical surgery and 26.0% who received local surgery. Radiation and chemotherapy were performed in 36.5% and 70.8% of the patients, respectively.

Survival analysis

For the survival analyses, patients' numbers in each background factor were adjusted by weighting propensity score. After the adjustment, the clinical and pathological factors no longer differed among cohorts (**Table 1, Table S2-5**). Kaplan–Meier survival curves and people's number at risk at different follow-up times were performed before and after PSW (**Figure 2A & B**).

Before PSW, the median OS for patients in N3cM0, IIlc, M1-LN, M1 were 64 months, 98 months, 45 months, and 26 months, respectively; M1-LN had worse OS than N3cM0 ($p=0.008$, $HR=1.284$, $95\%CI:1.067-1.543$) and IIlc ($p<0.001$, $HR=1.72$, $95\%CI:1.524-1.941$), but much better OS than M1 patients ($p<0.001$, $HR=0.551$, $95\%CI:0.491-0.619$).

After PSW, the median OS for patients in N3cM0, IIlc, M1-LN, M1 were 42 months, 55 months, 50 months, and 31 months, respectively. The adjusted survival curves showed that M1-LN had a similar OS compared to N3cM0 ($p=0.467$, $HR=0.915$, $95\%CI:0.719-1.163$) and IIlc ($p=0.959$, $HR=0.995$, $95\%CI:0.837-1.183$), and had significantly better OS than M1 ($p<0.001$, $HR=0.646$, $95\%CI:0.561-0.737$).

In order to evaluate the impact of treatment strategies on OS, Kaplan –Meier survival curves were performed before and after PSW in the M1-LN group according to whether chemotherapy, radiotherapy, or surgery was done. Patients in the M1-LN group achieved significant survival benefit if they underwent either surgery ($p<0.001$) or chemotherapy ($p<0.05$) before and after PSW (**Figure 3A&B, E&F**), while radiotherapy led to some survival benefits ($p<0.001$, $HR=0.467$, $95\%CI:0.361-0.604$) before PSM, but not after PSW ($p=0.117$, $HR=0.74$, $95\%CI:0.527-1.038$, **Figure 3C&D**). When compared with chemotherapy alone, comprehensive therapy (surgery, chemotherapy, and radiotherapy) led to better survival before and after PSW ($p<0.001$, **Figure 3G&H**), with the median survival increasing from 26 months to 82 months.

Prognostic factors

Univariate and multivariate analysis was performed (**Table 2**). Under multivariate analysis by Cox regression model, surgery and chemotherapy resulted as independent favorable factors as well as PR positive and HER2 positive. In contrast, lobular carcinoma, T4, and poor grade resulted as independent risk factors for prognosis.

Discussion

In the AJCC staging system, ISLM is defined as N3, while contralateral supraclavicular and subclavian lymph node, contralateral internal mammary lymph node, contralateral axillary lymph node metastasis (CAM), and cervical lymph node metastasis (CLM) are defined as DLM and classified as M1, stage IV. There are limited data and a number of controversies on DLM staging and clinical treatment decisions. Our study used the information recorded in the SEER database to address these issues.

The available literature is quite exiguous, and it mainly consists of small retrospective series and a few case reports. CAM is the most studied DLM. From 1995–2020, three relatively larger sample-sized studies reported on a total of 154 patients with CAM [8, 17]. In one of these studies, 47 patients with CAM were

suspected of having N3 disease, showing better response than at other sites of distant dissemination, when subjected to surgical and systemic treatments with curative intent [8]; while the other two studies draw a contrary conclusion from 28 and 23 patients, respectively that CAM was most likely to be stage IV. [10, 17] KROG 18 – 02 study that included 78 patients indicated that patients with breast cancer who had ipsilateral CLM without other distant metastasis might benefit from locoregional treatment of the ipsilateral breast and systemic therapies, just as those with N3c disease.[9] It remains unclear whether DLM should be considered an advanced locoregional stage or distant metastasis. Accordingly, prospective trials should address this issue, which is very difficult to conduct due to the low incidence of DLM. To the best of our knowledge, our study is the largest sample-sized study conducted to investigate the survival outcomes of patients with DLM.

In our study, we found no significant difference in long-term survival between DLM, N3c, and IIc stage. Surgery and chemotherapy could significantly improve the OS for patients with DLM, where the multivariate analysis also showed that surgery and chemotherapy were independent favorable prognostic factors. Compared with chemotherapy alone, a combination of chemotherapy, surgery, and radiotherapy could achieve better survival. Accordingly, it is reasonable to reconsider DLM as a loco-regional disease and adopt a curative approach.

DLM is more common in patients with previous surgery or radiotherapy, resulting in disrupted primary lymphatic drainage. Repeated sentinel node biopsy in patients with locally recurrent breast cancer showed about 30% aberrant regional lymphatic drainage, including CAM.[18, 19] The possible explanations for DLM of aberrant regional lymphatic drainage also support DLM as advanced stage III disease but do not provide support for hematogenous spread (stage IV).

DLM can happen synchronously and metachronously. In a retrospective study conducted at Mayo Clinic, most patients (18/23, 78.3%) had a metachronous CAM presentation, whereas 5 (21.7%) developed CAM synchronous with the primary breast tumor [17]. Synchronous CAM seemed to have more aggressive primary tumor features: 4/5 (80%) had inflammatory breast cancer, a high-grade disease requiring neoadjuvant chemotherapy, clinical findings of a large tumor (11–20 cm), and N2–N3 axillary disease. A literature review showed that among 84 patients with isolated CAM (65% metachronous and 35% synchronous), patients who developed synchronous CAM typically had LABC or inflammatory breast cancer at the time of initial diagnosis [20]. Our results were similar with previous studies, as all the patients in our study had synchronous DLM, of which 39.5% were T4 and 38.1% were N3, thus implying that disease burden in the breast and in the ipsilateral axilla led to the diversion of lymphatic flow to DLM.

Interestingly, Chkheidze's study reported that in most synchronous CAM cases (6/7), CAM was incidentally detected at the time by contralateral SLN at the time of contralateral prophylactic mastectomy.[20] A large cohort study from Milan showed that contralateral or bilateral lymph drainage could be seen in T1-2 N0 early breast cancer patients, where the incidence rate was quite low, less than 1%.[21] It is possible that DLM is not that rare, especially in patients with higher T and N stage. In our

study, the incidence of DLM in IIIC patients was at least 4.1%, and the incidence in N3c patients was at least 22.3% (data wasn't showed). Furthermore, we were curious about the starting point of metachronous DLM. In addition to local recurrence and aberrant drainage, it was important to learn whether it could result from undetected synchronous DLM. If so, lymphoscintigraphy may be necessary at the initial evaluation. Although it is not cost-effective from an SLNB perspective, it may be necessary for axillary staging of locally advanced patients such as inflammatory breast cancer or N3. Advanced imaging methods, such as PET-CT, could be used as an optional choice.

There are some limitations to the present study. Due to the characteristics of the SEER database, we were unable to distinguish the specific lymph node location of DLM. Also, the treatment details were not available. The extent of the radiation fields is unknown, and it is unclear whether the radiation included the distant lymph node. Regarding the analysis of molecular traits, our findings were limited by the incompleteness of the molecular subtyping and the information on HER2 status. Our study was a retrospective analysis, and despite the fact that PSW was performed, it was difficult to completely eliminate the bias. Therefore, reported results need to be further verified by future randomized control trials.

Conclusion

The prognosis of breast cancer patients with DLM was similar to those at ISLM and IIIC stage, but much better than in those with distant organ metastasis. Combined-modality therapy in accordance with the curable principle of locally advanced breast significantly improved long-term survival. Accordingly, it seems more reasonable to classify DLM as IIIC category instead of M1.

Declarations

Authors' contributions: Jinbo Wu and Taobo Hu participated in the study design and coordination and participated in the data analysis and written the draft. Shu Wang conceived the idea and design the study. All authors approved the final manuscript.

Fundings: This study was sponsored by Minister of Science and Technology of People's Republic of China (2016YFC0901302).

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

References

1. Fleming, I. and J. Yarbro, *AJCC cancer staging manual. 1st edn. American Joint Committee on Cancer* 1977.
2. Fleming, I., et al., *AJCC cancer staging manual. 5th edn. American Joint Committee on Cancer.* 1997, Lippincott-Raven, Philadelphia.

3. Brito, R.A., et al., *Long-term results of combined-modality therapy for locally advanced breast cancer with ipsilateral supraclavicular metastases: The University of Texas M.D. Anderson Cancer Center experience*. J Clin Oncol, 2001. **19**(3): p. 628–33.
4. Liu, X.H., L. Zhang, and B. Chen, *A meta-analysis of the prognosis in patients with breast cancer with ipsilateral supraclavicular lymph node metastasis versus patients with stage IIIb/c or IV breast cancer*. Chronic Dis Transl Med, 2015. **1**(4): p. 236–242.
5. Greene, F.L., et al., *AJCC cancer staging handbook: TNM classification of malignant tumors*. 2002: Springer Science & Business Media.
6. Chen, Q.T., et al., *Surgery of the Primary Tumor Offers Survival Benefits of Breast Cancer with Synchronous Ipsilateral Supraclavicular Lymph Node Metastasis*. World J Surg, 2020. **44**(4): p. 1163–1172.
7. Jung, J., et al., *Treatment Outcome of Breast Cancer with Pathologically Proven Synchronous Ipsilateral Supraclavicular Lymph Node Metastases*. J Breast Cancer, 2015. **18**(2): p. 167–172.
8. Magnoni, F., et al., *Contralateral Axillary Lymph Node Metastases from Breast Carcinoma: Is it Time to Review TNM Cancer Staging?* Annals of Surgical Oncology, 2020.
9. Kim, J.S., et al., *Cervical Lymph Node Involvement above the Supraclavicular Fossa in Breast Cancer: Comparison with Stage IIIC (KROG 18 – 02)*. J Breast Cancer, 2020. **23**(2): p. 194–204.
10. Wang, W., et al., *Management of contralateral axillary lymph node metastasis from breast cancer: a clinical dilemma*. Tumori, 2014. **100**(6): p. 600–4.
11. Daoud, J., et al., *Contralateral axillary nodal metastases of breast cancer*. Bulletin du Cancer, 1998. **85**(8): p. 713–5.
12. Pedersen, A.N., et al., *Supraclavicular recurrence after early breast cancer: a curable condition?* Breast Cancer Res Treat, 2011. **125**(3): p. 815–22.
13. Bisase, B. and C. Kerawala, *Survey of UK practice for management of breast cancer metastases to the neck*. Ann R Coll Surg Engl, 2012. **94**(7): p. 484–9.
14. Gingerich, J., et al., *Contralateral axillary lymph node metastasis in second primary Breast cancer: Case report and review of the literature*. Int J Surg Case Rep, 2017. **40**: p. 47–49.
15. *Surveillance, Epidemiology and End Results Program. About the SEER Program 2019*: <https://seer.cancer.gov/about>.
16. Cole, S.R. and M.A. Hernan, *Adjusted survival curves with inverse probability weights*. Comput Methods Programs Biomed, 2004. **75**(1): p. 45–9.
17. Guru, S.D., et al., *Contralateral Axillary Metastases in Breast Cancer: Stage IV Disease or a Locoregional Event?* American Surgeon, 2019. **85**(12): p. 1391–1396.
18. Maaskant-Braat, A.J., et al., *Repeat sentinel node biopsy in patients with locally recurrent breast cancer: a systematic review and meta-analysis of the literature*. Breast Cancer Res Treat, 2013. **138**(1): p. 13–20.

19. Port, E.R., et al., *Reoperative sentinel lymph node biopsy: a new frontier in the management of ipsilateral breast tumor recurrence*. Ann Surg Oncol, 2007. **14**(8): p. 2209–14.
20. Chkheidze, R., et al., *Isolated Contralateral Axillary Lymph Node Involvement in Breast Cancer Represents a Locally Advanced Disease Not Distant Metastases*. Clin Breast Cancer, 2018. **18**(4): p. 298–304.
21. Trifiro, G., L. Ravasi, and G. Paganelli, *Contralateral or bilateral lymph drainage revealed by breast lymphoscintigraphy*. Eur J Nucl Med Mol Imaging, 2008. **35**(2): p. 225–9.

Tables

Due to technical limitations, the tables are only available as a download in the supplemental files section.

Figures

Figure 1. Patients enrollment for breast cancer with ipsilateral supraclavicular lymph node metastasis (N3cM0), IIIC staging (IIIC), distant lymph node metastasis (M1-LN), and distant organ metastasis (M1).

Figure 1

Patients enrollment for breast cancer with ipsilateral supraclavicular lymph node metastasis (N3cM0), IIIC staging (IIIC), distant lymph node metastasis (M1-LN), and distant organ metastasis (M1).

Figure 2. Kaplan–Meier analysis for overall survival (OS) of N3cM0, IIIC, M1-LN and M1 groups. (A) Unadjusted OS. (B) Propensity score weighting (PSW) to adjusted OS.

1

Figure 2

Kaplan–Meier analysis for overall survival (OS) of N3cM0, IIIC, M1-LN and M1 groups. (A) Unadjusted OS. (B) Propensity score weighting (PSW) to adjusted OS.

Figure 3. Kaplan–Meier analysis for overall survival (OS) of patients who underwent different treatment measures in M1-LN. (A) Unadjusted OS of patients with and without chemotherapy. (B) Propensity score weighting (PSW) to adjusted OS of patients with and without chemotherapy. (C) Unadjusted OS of patients with and without radiotherapy. (D) Propensity score weighting (PSW) to adjusted OS of patients with and without radiotherapy. (E) Unadjusted OS of patients with and without surgery. (F) Propensity score weighting (PSW) to adjusted OS of patients with and without surgery. (G) Unadjusted OS of patients who underwent comprehensive therapy (surgery, chemotherapy and radiotherapy) and those who received chemotherapy only. (H) Propensity score weighting (PSW) to adjusted OS of patients who underwent comprehensive therapy (surgery, chemotherapy and radiotherapy) and those who received chemotherapy only.

Figure 3

Kaplan–Meier analysis for overall survival (OS) of patients who underwent different treatment measures in M1-LN. (A) Unadjusted OS of patients with and without chemotherapy. (B) Propensity score weighting (PSW) to adjusted OS of patients with and without chemotherapy. (C) Unadjusted OS of patients with and without radiotherapy. (D) Propensity score weighting (PSW) to adjusted OS of patients with and without radiotherapy. (E) Unadjusted OS of patients with and without surgery. (F) Propensity score weighting

(PSW) to adjusted OS of patients with and without surgery. (G) Unadjusted OS of patients who underwent comprehensive therapy (surgery, chemotherapy and radiotherapy) and those who received chemotherapy only. (H) Propensity score weighting (PSW) to adjusted OS of patients who underwent comprehensive therapy (surgery, chemotherapy and radiotherapy) and those who received chemotherapy only.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplement.docx](#)
- [Tables.pdf](#)