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Breast Cancer Prognostication by Pathologic Node Staging (pN-staging) System Versus Lymph Node Ratio (LNR): A Critical Review of Conflicts With Number of Nodes, Z-0011 Trial , Staging Cut-points, Neo-adjuvant Therapy, and Survival Estimation

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ABSTRACT

Background: The AJCC pN-staging system is the current risk stratification strategy for axillary nodal staging in most cancer centers. Recently, another staging system named "Lymph Node Ratio" or LNR has been developed and also postulated to have prognostic value. Precise prognostication of breast cancer by these two systems has multiple methodological dilemmas which are overlooked in the literature and still remain matters of debate.

Methods: These two issues are categorized into seven queries, including: the number of nodes considered adequate for proper axillary staging; attitude toward Z-0011 trial; impacts of neo-adjuvant therapies; the origin and evolution of stratification cutoffs; the position where patients without axillary involvement should be placed; role of diverse endpoints in survival definition, outcome analyses and prognosis prediction; and ultimately the current opinion regarding the superiority of the 2 systems. This review sought to explore these topics through analysis of 58 recently published articles found by MEDLINE search.

Results: The analysis revealed that precise prognostication by pN-staging system requires at least 10 excised-nodes, but LNR system minimally depends on the quantity of excised-nodes. Adhering to Z-0011 trial findings obstructs the provision of sufficient nodes for pN-staging. Neo-adjuvant chemotherapy alters the axillary nodal climate and therefore disrupts proper axillary staging. Cutoffs of LNR system have a more clear history of formation than the pN-staging's. Breast cancer-specific survival is the type of survival better portraying cancer-related events.

Conclusions: LNR system seems at least as accurate as pN-staging in prognostication of breast cancer patients.

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Introduction

In a heterogeneous patient population and distinctive subtypes of breast cancer (BC), "staging" is assumed to detect cancer spread and assign optimal therapy, while "prognostication" has to determine the exact course of the disease, estimate treatment success, and predict patients' survival. In

fact, staging is the classification of patients into categories based on the extent and severity of the disease at presentation and explains how the patients are at diagnosis, whereas prognostication is the outcome estimation based on the pre-experienced analysis of stage outcomes and explains how the patients will end up. As a standard global approach to cancer classification, the TNM-staging system was developed in 1987 by merging 2 former staging systems from the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC). Today, this is known as the "AJCC cancer staging system", and the 8th edition has recently been published.[1] The TNM-staging system comprises 3 elements: the T-stage represents the primary tumor size and level of invasion, the N-stage defines the level of lymph node (LN) involvement, and the M-stage describes the extent of metastases.

In BC prognostication, patients with advanced T-stages or positive metastases at presentation are considered to have an already poor prognosis; the N-stage in such patients does not provide much prognostic information. The majority of BC-patients are currently diagnosed at early stages thanks to refined screening and diagnostic modalities by modern medicine, and that is when the tumor has not yet invaded to surrounding structures or distantly metastasized.

Table 1. Ineligible patients for node-based prognostication

Category of ineligibility	Details
Advanced disease	patients with distant metastases [9, 19, 25, 27, 30, 33, 40, 41, 51, 59, 66, 78] tumor sizes more than 5cm [23] T3-T4/clinical N2-N3 (metastases in ipsilateral internal mammary or supra-clavicular LNs) [27] bilateral BC [24, 41, 58] with secondary malignancy (except for non-melanoma skin cancer or in situ cervical cancer) [10, 27, 40] inflammatory breast disease [23, 24, 60, 79] those surviving less than one month [23]
Very early-stage	in-situ BC [9, 23, 30, 33, 59, 66]
Residual disease	involved surgical margins [27] recurrence of breast cancer [60] incomplete adjuvant therapy [27] undergoing palliative therapy [25]
Neo-adjuvant therapy (controversial, see the discussions)	patients undergoing neo-adjuvant chemotherapy [2, 3, 6, 10, 19, 24, 25, 27, 28, 30, 33, 40, 58-60]
Missing data on axillary status	no evidence of LN metastasis [2, 5, 23, 27, 33, 40, 41, 51, 66] nodal involvement not confirmed by pathologic examinations [5, 9, 27, 33, 59] those undergoing sentinel LN biopsy (SLNB) alone (unclear status of non-sentinel nodes) [2, 6] LNs excised less than the adequate [5, 19, 30, 58] (see the discussions)
Miscellaneous	Male breast cancer [24, 60]

The dominant TNM-scheme in those with less advanced disease looks like "$T_{1,2}$ N_{any} $M_{0,X}$", in which the T- and M-stages do not necessarily deliver much useful prognostic information. Consequently, with the current progressed diagnostic conditions, the only evidence remaining is the N-stage to convey the severity of the disease, characterize the tumor behavior, and determine its potential for further and future progression. The capability of the N-stage in prognostication has frequently been addressed in recent literature and now, it makes the cornerstone of prognostication for early stage BCs without metastasis. Conversely, some patient populations having breast cancer are not good candidates for node-based prognostication. These cases are outlined in table 1.

The pathologic N-stage by the AJCC system (to wit the pN-stage) is based on the absolute number of involved axillary LNs dissected. If none of theexcised nodes are involved by the cancer, the stage is pN0, if 1 to 3 nodes are involved the stage is pN1, 4 to 9 is pN2, and ≥10 is pN3. A more advanced stage in this system indicates a more advanced disease, and thus, a worse prognosis might be expected. But recently, the prognostic value of pN-staging system has been put into question by a novel system named "Lymph Node Ratio" (LNR). The advent of LNR has added a new entry in the oncologic lexicon as it has been widely postulated to have prognostic value for many types of cancers.[2-4] LNR, rather than depending on the absolute number of involved nodes, is in the form of a mathematical fraction, showing the decimal proportion of axillary nodal involvement. In this fraction, the absolute number of involved nodes is the numerator,

and the total number of dissected nodes is the denominator.It can be envisioned that the LNR concept arose in response to the need for adaptation to the unintentional variability of excised LNs for cancer staging, as it regards the excised LNs and their rate of involvement as a sample from the axilla, representing the whole axillary nodal climate. The most common classification scheme by the LNR system places the patients into 3 categories. The grouping is based on 2 cut-points in the LNR quantity, which are 0.20 and 0.65. Accordingly, the patients having $0<LNR\leq0.20$ are categorized to be of low-risk, those with $0.20<LNR\leq0.65$ as intermediate-risk, and those with $LNR>0.65$ as high-risk.[5]

Both the AJCC and LNR conceptual frameworks have established capacities for prognostication. The hierarchical approach to node-based staging and prognostication virtually comprise 3 steps: the axillary surgery and nodal excision, the staging strategies based on the number of nodes retrieved, and the prognostication process. Multiple dilemmas are encountered while utilizing the 2 systems, which require careful attention since these areas, may effectively alter the precision of prognostication. In the first step (i.e. axillary workup), the most challenging issue is the number of LNs needed for an appropriate staging of the axilla; this refers to the extent of axillary dissection. But, before the nodal excision, there is the neo-adjuvant chemotherapy having the potential to change both the total number and positivity of axillary LNs; this also might invoke staging conflicts. Meanwhile, the findings of Z-0011 trial obligate to minimize axillary manipulations to merely excision of the sentinels; by adhering to these findings, no axillary staging is practically permitted. In the second step, there is the diversity of systems' strategies in patient stratification into risk categories that makes comparatively heterogeneous groups; a system providing a more holistic approach towards the inclusion of various subsets of patients logically would be favored in comparison. The third step is the prognostication process, which is an outcome estimation based on pre-experienced analyses. For survival analyses, we have various start- and end-points (events), defining different types of survival; each of these points in time describe the disease outcomes in their point of view that are not necessarily the same. Added to many other questions, these topics concern with how these a systems measure the stage and prognosis, and if they do the same task, why their outcomes of analysis sometimes widely conflict? There is a necessity for discussion on the strengths and weaknesses of the 2 systems and the obstacles in the precision of their prognostication, which may determine the superior system. We have tried to address these topics in this narrative review (Figure 1).

Methods

Search strategy and selection criteria

Multiple procedural approaches, methodological metrics, and therapeutic modalities may impact precise prognostications based on axillary nodal staging, and these are often overlooked in the literature. We had 7 queries in mind, knowing the answers of which could elucidate unknown aspects of node-based prognostications and provide greater accuracy in predicting patients' survival. The queries were:

1. The number of excised-LNs considered adequate for appropriate axillary staging;
2. Attitude against Z-0011 trial findings regarding the extent of axillary dissection;
3. Complexities in staging made by neo-adjuvant chemotherapy;
4. The origin and evolution of stratification cutoffs by the 2 systems;
5. The LNR risk group corresponding to pN0 in pN-staging system;
6. Start- and end-points best evaluating patients with breast cancer survival;
7. And finally, benefits, limitations, and comparative value of both staging systems in prognostication.

To address these issues, we searched MEDLINE for English-language sources, using the following keywords: breast cancer, lymph node ratio or LNR, pN-staging, pathological node staging, overall survival or OS, disease-free survival or DFS, survival, and prognosis. To get the most recent data, sources published in 2000 or later (until early March 2017) were selected. Among the retrieved articles, we searched bibliographies for relevant papers, evaluating either of the 2 systems individually or comparing the 2 staging systems in the areas of interest of the queries. We had a finally 58 papers that met our criteria for covering the 7 issues described above. Opinions expressed under each topic may also reflect our personal viewpoints.

Results and Discussion

How many LNs should be excised for accurate staging of the axilla?

Both the LNR and pN-staging systems inherently depend on the quantity of excised axillary LNs, and therefore, some degrees of axillary LN dissection (ALND) are required. The question raised here is that how extensive the ALND must be performed and how many LNs should it minimally provide for a proper axillary staging? The literature, unfortunately, fails to define a precise minimum level or adequacy goal for nodal excision that suffices the staging requirements, while there are a variety of recommendations for this, such as 3, 4, 6, 11, 12, 13, 14, 15, and 16.[3,5-19] Even full clearance of the axilla has been suggested.[8,20] With these, it is quite apparent that there is no consensus about the target

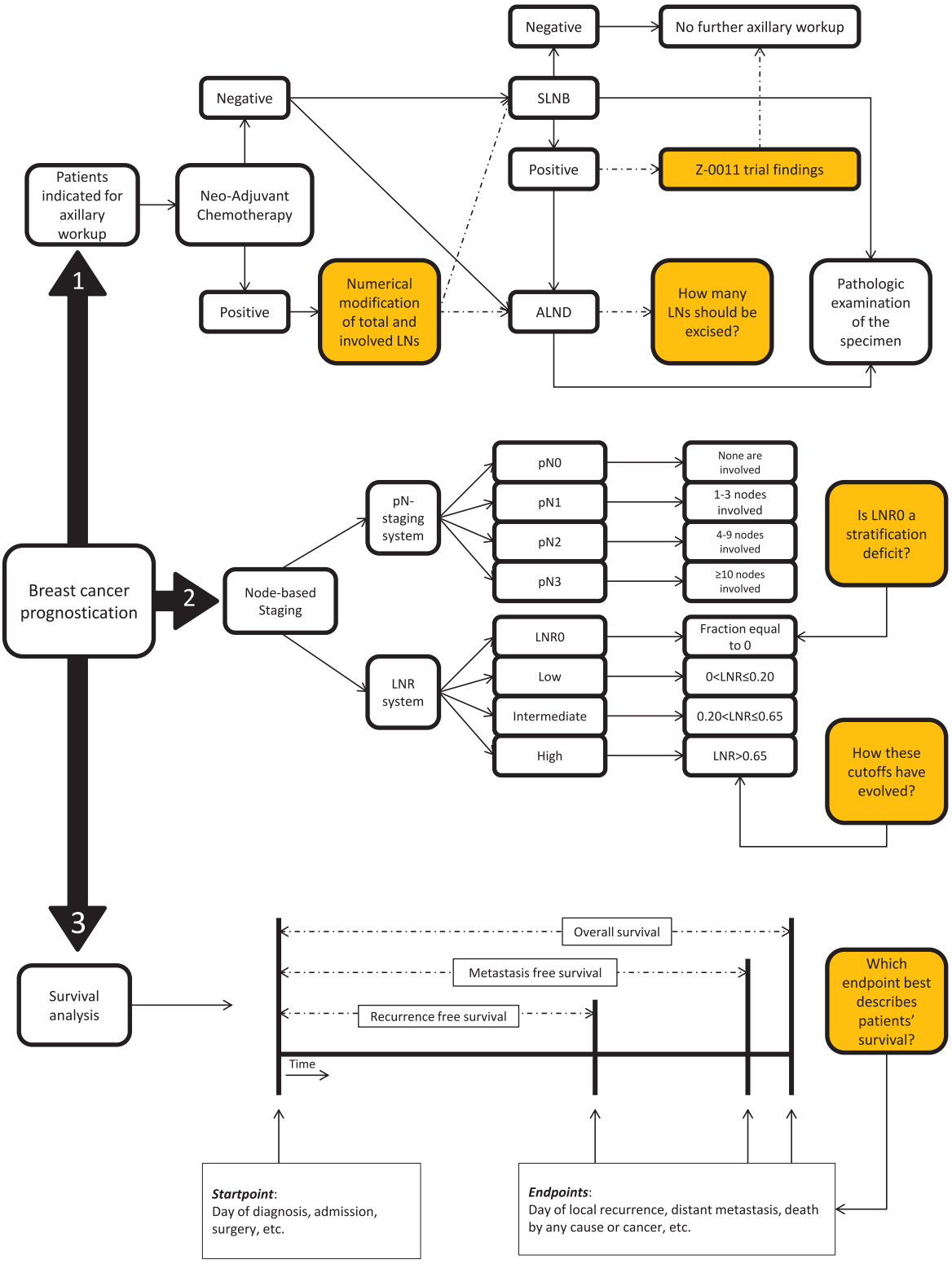

Figure 1. Hierarchical steps of node-based staging and prognostication and areas where dilemmas appear: this process has 3 steps, including axillary surgery, node-based staging, and prognostication. In step 1, with or without NAC, patients undergo axillary sampling; but, in those undergoing NAC, the number and positivity of axillary nodes might be altered. In patients indicated for SLNB, no further axillary workup would be performed if the results are negative, but if positive, ALND is the standard approach, while findings of Z-0011 trial prohibits ALND and subsequently the staging (for those having up to 2 positive sentinels). In those undergoing ALND (directly or after SLNB), the extent of dissection is a matter of query. Step 2 is based on the pathologic results of axillary sample; the dilemmas of categorization schemes by the 2 systems are reflected here. Step 3 describes how different end-points make different survival results.
SLNB: Sentinel Lymph Node Biopsy; ALND: Axillary Lymph Node Dissection; LNR: Lymph Node Ratio; pN-stage: Pathologic Node Stage.

number of nodes needed to be excised for axillary staging.

Prior to discussing the adequacy level for ALND, a distinction must be made between the "total number of nodes excised" and the "number of involved nodes excised"; because the first one is the crude product of ALND and contains a mixture of involved and uninvolved LNs, while the second is the basis for pN-staging system with thresholds described in the introduction. For a proper pN-staging, the minimal extent of ALND must logically provide as much LNs that fulfill the requirements of the highest pN-stage. Consider this example: a patient with 9 examined nodes that all are involved by the cancer (the whole specimen contents) would be staged as pN2, while we have no clue about the involvement of the 10th node if it was excised. If the 10th excised node was involved, the patient would be staged as pN3, and with 9 of 9 involvement rate, the probability of 10th node involvement seems quite high. The uncertainty about the 10th node may raise the doubt that we might have understaged the axilla (pN2 vs. pN3). As a matter of fact, to report the highest pN-stage for a patient (i.e., pN3), the examined axillary specimen must include at least 10 involved nodes, meaning that the total number of nodes excised should exceed the quantity of 10. The minimum of 10 is the minimum logical quantity for excision and pathologic examination so that if all were involved, the patient, then, would be staged as pN3. This fact also applies to the lower pN-stages as you may never stage a patient as pN2 unless you have excised ≥4 nodes. On the other hand, as a more extensive ALND significantly increases the chance to find more involved nodes[3, 21, 22] and we have no maximum level defined for the extent of ALND, the ALND may theoretically be continued until 10 involved nodes are found, since any number beyond 10 will still be regarded as pN3. However, this idea is not approved by many surgeons due to possible morbidities. The minimum of 10 is the threshold approved by many studies.[3,6,7,11,15,23-35] The NSABP B-04 study acknowledges that this minimum increases the reliability of reported axillary LN status;[11, 36, 37] also, the precision of prognostication has been found by Axelsson *et al.* to significantly improve when at least 10 axillary LNs are dissected.[38]

Irrespective of the goal to excise a specific number of nodes, it is not always feasible for the surgeons to resect the precise number of nodes, as the nodes might be non-palpable or indistinguishable from the surrounding adipose tissue. What a surgeon does through ALND is the excision of axillary fat-pad, while the exact number of nodes is later revealed by the pathologic examination of the specimen. Variables influencing the final number of examined nodes include the extent of ALND, the method of analysis used by the pathologist, and the actual physiologic number of nodes individually existing from the patient.[39, 40] These conditions practically diminish the surgeons' capacity to predetermine the number of nodes needed to be excised. On the other hand, surgeons' clinical concept and personal intent also may contrast regarding the extent of ALND; as some have doubts and fears about adverse aftermaths following an extensive ALND like lymphedema and injuries to local neurovasculature[7,8] or do not believe that an extensive ALND might improve patients' survival.[2] Conversely, some others deem an extensive ALND not only clears involved LNs, but also removes potential routes of metastasis by the excision of uninvolved LNs, and thereby may improve survival.[41] Testifying to that, Krag *et al.* demonstrated that even when all regional LNs are pathologically negative, the number of nodes removed is associated with survival.[42] Vinh-hung *et al.* similarly reported that removal of uninvolved nodes increases the 5-year survival.[43]

Three issues worth emphasizing here about the pN-staging system: firstly, achieving a minimum of 10 nodes is not actually under the full control of the surgeon as s/he only resects the axillary fat-pad. Secondly, after 10 involved nodes are identified, any number of involved nodes beyond that is still regarded as stage pN3. And thirdly, the extent of ALND is associated with morbidities. These 3 issues may have had active roles in the conceptualization of the LNR system. The LNR as a fraction is not confined by the number of excised LNs as it works with proportions and still can be calculated with as few LNs provided through sentinel LN biopsy (SLNB).[7,44-47] The LNR system also makes difference between the patients with over 10 involved nodes based on the proportion made with the total number of excised LNs. Moreover, the less extensive ALND needed for LNR staging may lower the risk of morbidities. With these, the LNR system seems theoretically so versatile and capable to overcome these obstacles, and this makes it more clinically appealing than the pN-staging system.

Attitude against the Z-0011 trial: the debate on the extent of axillary surgery

Adhering to the standards, surgeons often perform ALND if axillary involvement is revealed by SLNB. [21] In 2010, 2011, and newly in 2016, the American College of Surgeons Oncology Group (ACOSOG) published the results of Z-0011 trial, which has prospectively assessed the patients with sentinel node metastasis.[48-50] These patients were randomized to undergo ALND after SLNB vs. SLNB alone without specific axillary treatment, and then, they were evaluated for loco-regional recurrence. The results of this study surprisingly showed that after a median follow-up of 9.25 years, the 2 groups were not significantly different regarding loco-regional recurrence and prognosis.[48] Despite the confirmed repetition of the results through the

follow-up reports, the idea seems to have multiple flaws that may conflict with the current staging systems:

1. Generalizability: as defined by the trial, eligible patients for exemption from ALND must be over 18 years, have clinical T1 T2 N0 disease (be clinically node-negative) , and in whom the involvement of up to 2 sentinels is detected by hematoxylin and eosin staining (not by immunohistochemistry). A positive sentinel was regarded to LNs including any of the 3 pathologic forms of macro-metastasis (pN1, 2 or 3), micro-metastasis ($pN1_{(mi)}$), or isolated tumor cells ($pN0_{(i+)}$), and no distinction was made between them since at the time that trial was initiated, the 5th edition of AJCC cancer staging manual was in effect which considered all the 3 forms as positive nodes.[50] They also must have undergone "whole" breast irradiation after "partial" mastectomy (breast conserving therapy) with adjuvant systemic chemotherapy by choice.[11, 21, 35, 39] These specifications point out that the Z-0011 trial cannot be extended to the patients undergoing mastectomy or lumpectomy without radiotherapy, those not receiving whole-breast tangential field radiotherapy or undergoing accelerated partial breast irradiation or taking third field (nodal) irradiation, those with more than 2 sentinel nodes involved, patients with multi-centric disease, patients receiving neo-adjuvant therapy, or having matted nodes, and those the involvement of sentinels is detected by immunohistochemistry.[11, 35, 51]

2. Prohibiting the axillary staging: by limiting the axillary workup to mere excision of the sentinels, no axillary staging is actually permitted by the Z-0011 trial. As mentioned before, the AJCC pN-staging requires at least 10 nodes to be excised for a proper axillary staging, but according to Z-0011 trial, whether or not the sentinel is involved, no further axillary dissection must be performed (note that if more than 2 sentinels were involved, the ALND must be performed). The omission of ALND obstructs the realistic prospection of the axillary disease burden. Even Z-0011 trial itself acknowledges that 27.3% of non-sentinel nodes in the ALND-group harbored metastases;[21, 50] this is in a group of patients who have been clinically negative for axillary involvement, and as clear it is, the clinical presentation may widely differ from the factual dimensions of axillary involvement.

3. Loco-regional control: without clearing the axilla from cancer, the chance remains for the residual axillary disease to spread, while the findings of the Z-0011 trial do not necessitate loco-regional control. It should be noted that ALND not only provides prognostic information, but also optimizes regional control and remains a strongly recommended surgical procedure for clinically node-positive patients or for patients with bulky disease.[3, 19] As a rule, any study population is a sample, and as the trial included macro-metastases too, the results of the Z-0011 trial on 891 cases may not be repeated by other studies (contrary to IBCSG 23-01study that only included micro-metastases as limited sentinel LN involvement – see below).

4. Limiting the LNR value: The information provided by the LNR can identify the subpopulations of patients requiring adjuvant radiotherapy or prognosticate the patients without altering the current treatment guidelines or undergoing extensive ALND.[2, 11, 21, 35] These are useful applications of LNR that we may lose if ALND is not performed. LNR calculation requires the quantification of both positive and total numbers of excised LNs, which is provided through ALND, and the ALND again is not permitted following Z-0011 trial findings. However, the LNR can be calculated, using few LNs provided by SLNB (sentinels LNR or SLNR), and this has been reported to independently predict the involvement of non-sentinels.[7, 11] But theoretically, the involvement probability of the sentinels is surely beyond the non-sentinels, which lifts the numerator of the SLNR fraction and does not necessarily indicate the factual balance of involved and uninvolved nodes. Having this in mind, the "up to 2 positive sentinels" among the unpredictable few numbers of dyed LNs may decline the precision of calculated SLNR.

The former rationale for axillary clearance was that it could eliminate micro-metastases and isolated tumor cells harbored in axillary LNs, and therefore, it could provide therapeutic benefits.[2, 3, 52] The Z-0011 trial itself contradicts the concept that ALND gives better loco-regional control or improves survival. Congruently, the recent International Breast Cancer Study Group (IBCSG) 23-01 study on patients with micro-metastases in sentinels showed no statistical difference in disease-free survival of patients, who underwent ALND versus those who did not.[53] Additionally, the data from NSABP B-04 trial also indicate that axillary dissection in the framework of radical surgery does not improve survival (however, it was not powered to detect differences of 5% or less).[37] By now, it can be regarded as evidential that survival and prognosis would not necessarily be altered by the excision of involved sentinels instead of extensive ALND, and therefore, we had better preserve the advantages of ALND for the many patients, who do not meet the Z-0011 trial application criteria.

Challenging complexities of staging after neo-adjuvant chemotherapy

Added to the many therapeutic benefits of neo-adjuvant chemotherapy (NAC), it has been mainly used to downsize large tumors for the ease of resection, and this has decreased the rate of mastectomies as breast conservation becomes feasible for more patients. [32, 54] NAC may influence

staging in several areas:

1. Concerning the primary tumor (pT-stage), pathologic examination of patients receiving NAC has revealed multiple foci of scattered residual tumor cells interspersed with fibrotic cells. In these patients, a precise pT-staging necessitates the removal of larger margins or a wider local excision. [55,56]

2. The NAC has the potential to decline the "total number of axillary Lns," and the post-NAC ALND may provide fewer numbers of excised LNs. If this number declines to quantities fewer than 10, the axillary pN-staging might not be reliable.[24,32,57]

3. The administration of NAC also has the potential to change the axillary histological environment by decreasing the "number of involved nodes." The axilla subsequently might be understaged; a phenomenon referred to as "stage migration".[2,3,6,10,19,24,25,27,28,30,33,40,58-60]

4. Based on the new post-NAC stage, the adequacy of the treatments delivered to these patients is a matter of query.[2,4,24,32,39,41,57,60,61]

5. By fluctuating numbers of total and involved nodes, the LNR might hypothetically transit towards either of the two extremes, since it is not predictable to what degrees the numerator and the denominator of LNR may change, thus, the resultant LNR might not be that reliable.

No doubt that NAC may widely disrupt both the LNR and pN-staging systems, therefore, most of the authors prefer to stage the axilla prior to the commencement of any treatments, and consider the NAC an exclusion criterion for node-based staging.[2, 3, 6, 10, 19, 24, 25, 27, 28, 30, 33, 40, 58-60] But, contrary to this, emerging trends strongly suggest that NAC can be administered prior to axillary workups. In support of this, Pilewskie *et al.* recently postulated that if 3 or more post-NAC sentinels are excised, the results of SLNB remain accurate, and thereby, nodal positivity is reliable.[62] Studies analyzing LNR value after NAC or comparing prognostic value of LNR vs. pN-staging systems in post-NAC patients are so few; some concluded that the LNR system takes precedence over the pN-staging system by its added adaptive staging compatibilities,[32, 57, 63] while Saxena *et al.* believe both LNR and pN-staging systems remain significant prognostic factors in post-NAC patients.[32]

Cutoff points: origins and evolution

In spite of its widespread acceptance, clues are so scarce regarding how pN-staging cutoffs have been developed. It seems that they were rather empirically discovered than being mathematically calculated. LNR with its growing interest, on the other hand, has an apparent history of formation. LNR, as a continuous variable, inherently lacks any categories within it; therefore, group stratification based on patients' LNR requires some thresholds to be defined in the quantity of LNR. While no clear consensus has yet been reached for the optimal LNR cutoffs,[7, 11, 22, 58] many authors have categorized the patients based on a two-group strategy, using a single cutoff point. This cutoff has approximately been proposed to lie somewhere between 0.10 and 0.40 and, more precisely, found to be 0.20 or 0.25.[7, 22, 26, 35, 58, 61, 64, 65] Stratifications to more than 2 groups (normally 3 groups by 2 cutoffs) have more frequently been suggested, where the lower threshold in these studies is congruent with the cutoff defined by two-group classification scheme. The thresholds more commonly used here are 0.10 and 0.30[22], 0.10 and 0.50[16,17,40,61], 0.18 and 0.64[30], 0.20 and 0.60[66], 0.20 and 0.65[2,4,5,9,11,12,14,19,21,29,32,34,51,59,60,67,68], 0.25 and 0.50[61], 0.30 and 0.80[40] and 0.40 and 0.80.[25] Knowing the processes by which these cutoffs have been established, may help better comprehend the LNR stratification rationale. These cutoffs are based on:

1. The median LNR; the patients above and below the median were put into separate groups;[15]

2. Similarity of patient numbers in each group;[17, 22]

3. Equal percentile segmentation; such as quartile grouping (e.g. <25%, 25-49%, 50-74%, 75-100%);[24,28]

4. Unequal percentile segmentation with no clear causality (e.g. 0.1 and 0.5 or 0.2 and 0.6)[27] or addressed to previously published analyses;[11,16,67]

5. The magnitude of log-rank test χ^2 for pair-wise comparisons;[4, 22] the log-rank test is used to evaluate survival groups defined by Kaplan-Meier curves. While significant, a higher χ^2 means a better discrimination of subdivided groups.

6. Receiver operating characteristic (ROC) curves;[26, 69] the ROC curve is a graphical plot, showing the performance of a binary classifier system by varying discrimination thresholds. A threshold best discriminating the patients regarding prognosis is selected as a cutoff point.

7. Bootstrapping procedure;[5, 27] in simple terms, this procedure is literally "stratification by trial", in which cutoff points are proposed from a very close point to the beginning of LNR (i.e., 0.00) to the highest level of LNR (i.e., 1.00) at very short intervals (e.g., 0.05). At any iteration of the procedure (sampling with replacement), the resulting groups are evaluated for their difference in prognosis by submission to Cox regression analysis. Accordingly, LNR levels, which make groups with the strongest significant difference in their prognosis, are used as cutoff points.

The bootstrapping procedure employed by Vinh-Hung *et al.* in 2009 defining 2 thresholds (0.20 and 0.65) has most been referenced and used as cutoff points[5] because it uses a reasonable mathematical method, which - compared with the other methods - is more stable, reliable, and capable in discriminating the patients in terms of prognosis. In the work of Vinh-Hung *et al.*, three risk groups were defined based on 2 thresholds in the LNR: the low-risk

on 2 thresholds in the LNR: the low-risk group (LNR≤0.20), the intermediate-risk group (0.20<LNR≤0.65), and the high-risk group (LNR>0.65).[5] Although the method of Vinh-hung *et al.* is the most credited in the literature, a meta-analysis by Lui *et al.* in 2013 showed that a variety of available proposed thresholds in the literature could be used (except for 0.80).[39]

The dilemma of LNR0: should this be included?

The pN-staging system uses absolute integers for classification of node-positive patients, but it gives distinctive credits to the positivity versus negativity of the LNs; therefore, this system allocates a distinct "pN0" group for the inclusion of node-negative cases. But, for LNR, the story is different. Curiously, the majority of studies utilizing LNR staging system have included only node-positive cases[2,5,9,11,12,14,17,19,29,31,34,51,59-61,67,68] and the quantity of LNR by them is regarded as a positive decimal value (0<LNR≤1). In this system, there is no room for node-negatives, despite the fact that mathematically the numerator of a fraction is allowed to take the value of zero, and then, the overall value of the fraction would be equal to zero. So, theoretically the LNR system must include an "LNR0" group, since it is clinically quite probable for patients undergoing ALND that none of their excised nodes turn out to be positive. Why the LNR0 group is widely overlooked may be because of the lack of its role clarity, or the wrong assumption considering the node-negative cases who had undergone ALND are equal to those not even getting the indication of ALND. This point conversely has been clearly noted by the pN-staging system. However, among the studied papers for this review, only few have accredited the inclusion of an LNR0 group in the LNR system to place node-negatives in.[4,11,15,21,32] The LNR0 is a separate risk category standing lower than the "low-risk group" in the common LNR scheme. In systems with a lower cutoff point not excluding node-negative cases (e.g. LNR<0.2 as the lower cutoff), LNR0 patients may erroneously be placed in the low-risk group that creates confusion while performing subgroup analysis. Integrating the LNR0 group into the LNR system makes it utterly comprehensive and provides a holistic approach when confronting patient populations with different N-stages, and ultimately makes it more comparable with the pN-staging system.

Statistically, comparisons need a baseline so that the groups of patient population can be compared with. As in "case-control studies," patients are compared with the control group regarding the "characteristic of interest". It seems reasonable that patient groups having the characteristic of axillary involvement be compared with patients without that characteristic. In "Cox-regression analysis", patients are stratified based on "hazard ratios", which describes the proportionality of hazards of (at least) 2 groups, of which one is considered as baseline. In this type of analysis, the group containing more cases within it, is referred to as the baseline group to increase the statistical power and more accurate discrimination of group differences. Likewise, for this type of analysis, the selection of pN0 or LNR0 as baseline groups may better demonstrate the probable stepwise increase in hazard ratios of the ordinal risk groups (i.e. pN1, 2, 3 and LNR low, intermediate and high). In "Kaplan-Meier survival estimates," groups are evaluated based on their survival functions, where a significant log-rank test conveys a statistical difference between at least 2 of the subgroups. In Kaplan-Meier analysis, the overall P values representing the significance of log-rank test do not necessarily mean that all the subgroups are significantly distinct regarding survival or prognosis (with only 2 groups being statistically different, the P value of the log-rank test will be significant). Thus, if node-positive subgroups of LNR or pN-staging systems did not statistically differ regarding the prognosis by Kaplan-Meier analysis, by the inclusion of pN0 or LNR0, the significance of log-rank test might be expected (this significant difference may occur between the pN0 -or LNR0- group and any of other higher stages). For the purpose of both statistical needs and comprehensiveness of LNR, it seems rational to include node-negative cases as the LNR0 group in LNR risk stratification system.

What end-points are most appropriate for breast cancer survival analyses?

In survival analyses (like Kaplan-Meier and Cox-regression), 2 points in time should be defined that are the start-point and the end-point; the survival is the time interval between these 2 points. In any way, the patients are stratified into subgroups (pN-staging or LNR systems), these points should clearly be defined. There are no major conflicts among the authors about the start-point, as the date of diagnosis[2,4,6,11,16,24,27,67,70], the date of surgery or tumor-excision,[10,27,40] or the date of randomization into treatment groups[35] are typically used.

However, authors use different definitions of survival based on the "end-points." This can cause multiple different survivals (Figure 1). Whenever the end-points are met, they are marked as "events" in data sheets, and when there is no event for a patient, she will be "censored" at the last registered follow-up she is known to be alive. Consistent utilization of possible definitions for survival is important, while a special attention must be paid to the "cause of death". Three types of survival are often studied:

1. Overall Survival (OS): in this type of survival, "death from any cause" is considered as the end-point.[3,4,11,24,32,33,70] No matter what happens between the start- and end-points, the interval is considered the

patient's survival.

2. Disease Free Survival (DFS): in which "disease-related events" or again "death from any cause" make the end-points.[2, 6, 10, 11, 27, 40] A variety of survivals derive from DFS, such as event-free survival,[70] recurrence-free survival,[22, 35] local recurrence-free survival,[71] metastasis-free survival,[15] or distant metastasis-free survival.[65] Some of the exact end-points defined for DFS are any recurrence (local, regional, or distant), contra-lateral invasive breast cancer or ductal carcinoma in situ, or a second primary cancer.[6,22,40]

3. Cancer-specific Survival (CSS)[41] or breast cancer-specific survival (BCSS):[16,67] survivals of this type also define the end-points as cancer-related events, such as recurrence and metastasis, but place an emphasis on"deaths from breast cancer".[70]

The information which is crucial for patients with breast cancer is the accurate prediction of recurrence and mortality of "breast cancer",[22] not "deaths from any cause" or "disease non-specific deaths". Accordingly, the OS and DFS derived survivals necessarily cannot determine the patient's survival solely based on her breast cancer, since multiple factors other than breast cancer itself may alter the outcomes. Analysis results may widely differ based on the end-points selected, and each presents a unique portrayal of survival functions in their own viewpoints. Although not explicitly stated in the literature, but it is a logical implication that BCSS best suits for BC survival analyses. However, there are limitations using BCSS since the data on cause of death or recurrence are not always at reach, and if it was, it could improve the precision. On the other hand, the current knowledge on the prognostic value of LNR and pN-staging systems has mostly come from analyses using OS- and DFS-derived endpoints.[32,33]

LNR or pN-staging: which is superior in prognostication?

An optimal analogy between the LNR and pN-staging systems is when their prognosticative performances are assessed on a single patient population. Two of the most credited methods for survival analysis are Kaplan-Meier (KM) survival estimates (curves) and Cox proportional hazard ratios. The KM analysis evaluates the survival functions of the subgroups (of pN-staging or LNR systems), and its results contain a log-rank test χ^2 value, a P value, a survival table, and a graphical plot by choice. The log-rank test calculates the χ^2, which shows survival differentiation between the subgroups, and P value represents the significance of the difference.[72] In the graph, the survival functions of the subgroups are plotted as curves on 2 perpendicular axes, while the X-axis of the plot shows serial times and the Y-axis defines the probability of surviving at a given time on the curve. When KM results of the 2 systems are statistically compared, the superiority of a system might be revealed by a significant P value, or if both P values were significant, the superiority of a system might be revealed by the magnitude of χ^2 value. When the graphs are compared, the system more efficiently stratifying the patients would ideally have distinct curves with no crosses and a balanced distance between the curves (distances are approximately equal); a wider distance between the curves indicates better subgroup discrimination by that classifier system, while a narrower distance means those subgroups have similar survivals. Overlaps of the curves mean those curves have the same survival function at that interval, while crosses are points in time where survival functions of one or both of the curves change discordantly in regard of the other (the steepness of the curves change directions). Among the references of this review, better survival differentiation and much better balance between the curves have been reported by the LNR system (Figure 2, Graphs A, B, and C).[2,5,9,11,19,21]

The Cox-regression method also follows similar principles; however, it uses proportional hazard ratios instead of survival functions and provides visually similar curves to the KM method, but somehow upside-down (at time 0, the survival rate is 1, while the hazard ratio is 0). The curves of this analysis show the increased rate of having an event proportionate to the baseline group (usually the one with the lowest risk) (Figure 2, Graph D). The curves of Cox proportionate hazard ratios normally do not cross, and if so, the proportionality of the hazards might be questioned. The added advantage of this method is the feasibility of inclusion of several predictor covariates into the regression so that to see if one can independently predict the event occurrence. In Cox analysis, when the LNR and pN-staging systems were included in the regression as covariates, the pN-staging system has repeatedly been reported to lose its significance as an independent predictor of survival.[5,6,9,11,19,21,28,35,57,61,65,66,71]

Comparisons have been made concerning the prognosticative efficacy of the 2 systems among certain subgroups of patients, like women in younger ages and those undergoing breast conservation,[13] certain subtypes of tumors like her2/neu-enriched,[60] triple-negative,[2] and luminal-A tumors;[6] again, the LNR system was proved by them to be a better survival predictor than the pN-staging system (despite the need to incorporate these biologic factors has been recognized by the 8th edition of AJCC cancer staging manual).[1] More interestingly, the LNR system has been capable of stratifying separate risk groups with different survivals within the pN-staging system subgroups.[9, 27] This means even if the LNR system does not get the chance to surrogate the pN-staging system, by its integration

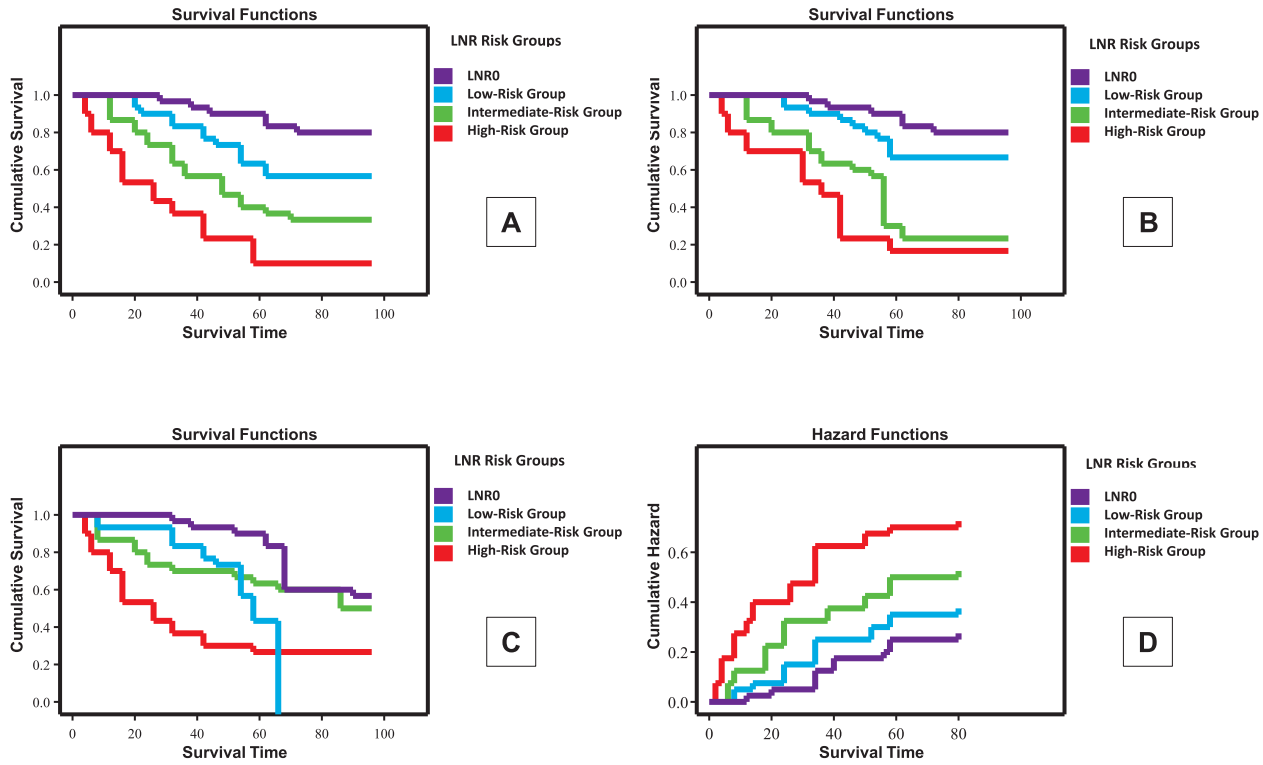

Figure 2. Visual and graphical differences of survival and hazard curves by Kaplan-Meier and Cox-regression analyses; **Graph A** represents an optimal discrimination of patient-groups by a classifier system, including 4 categories (e.g. the LNR system). The curves are well-balanced as the distances between the curves are approximately the same. There are no crosses or overlaps in this graph and the group with lowest risk stays at top of the others until the endpoint, while the survival functions of higher risk groups respectively start to step down earlier in the time. **Graph B** shows the same information as graph A, but the curves are not balanced since the distances between the curves are not equal and change through the time. **Graph C** indicates the presentation of a flawed classifier system. The curves not only are not balanced, but also the blue curve crosses both the green and red curves and hits to the bottom somewhere around the 60 point; this means the last patient of this group has experienced an event at that time. The higher steepness of the blue curve shows more trends to experience events across the time; perhaps this curve must be defined as the highest risk-group in that classifier system not the second. The overlap by the green and violet curves means their group members had the same survivals at that time interval. **Graph D** depicts hazard ratios of four-group classifier system. Despite the distances are not equal, they follow a stepwise increase; this represents stepwise increase of hazards compared to the baseline group. Groups with better survivals (lower hazards) stay lower in this graph. The curves from survival functions start from the highest point on cumulative survival axis, while the hazard curves start from the 0 point on the cumulative hazard axis since at time 0, the survival rate is 1, while the hazard ratio is 0.

into the pN-staging system, it may improve the staging and prognostication.[21] Moreover, by its more accurate determination of the extent of axillary LN involvement without extensive axillary dissection, LNR can identify patients requiring adjuvant radiotherapy.[2, 35, 73] When the number of excised LNs is so few that the pN-staging system cannot go further than the pN1-stage (excision limited to the sentinels), the LNR system, thereupon, can predict the involvement of non-sentinels.[2,21]

Ultimately, among the reference papers comparing the 2 staging systems, only few have concluded that pN-staging system may more accurately prognosticate BC patients than the LNR system, or support that the 2 systems have equal prognostication values,[3,6,16,19,27,33,66] while the majority of authors acknowledge that LNR system outperforms the pN-staging systems in many investigated domains[2-7,10,16,19,22,24,26-28,30-34,39-41,58,59,61,65,66,68,71,74-77] and provides a tailored approach to address the diversity of patient populations.

The precise and realistic prognostication by pN-staging system requires at least 10 LNs in the pathologic specimen, while LNR system minimally depends on the quantity of LNs and maintains its prognostic value with various numbers of excised LNs. Adhering to the findings of Z-0011 trial obstructs the provision of sufficient LNs for a proper pN-staging, but with those few LNs, LNR can still be calculated. Neo-adjuvant therapies may reduce both the total and positive axillary LNs to inadequate levels of pN-staging; however, the accuracy of staging by LNR system in post-neo-adjuvant patients has been supported by some articles. There is ambiguity in the literature about how the pN-staging cutoffs have evolved, whereas common LNR cutoffs have been calculated through a reasonable mathematical method. Among different types of

survival, BCSS better portrays cancer-related event. The integration of LNR0 into the LNR system makes it comprehensive and comparable to the pN-staging system. With the evidence compiled in this review, LNR is potentially competent to surrogate the pN-staging system and become the standard of classification for early-stage breast cancer.

Authors' contribution

AS conceived the project, raised the queries, provided topic scenarios as well as categorization schemes, drew the diagrams, and wrote the drafts and the final manuscript. SZ and NM did the initial literature search; the results were reviewed by SZ, AE, NM, and AS. AK organized and managed the team, supervised the work, and did the scientific edits. DNK edited and critically revised the content and approved the final work. All authors have approved the final article.

Conflict of interest

The authors declare that they have no conflicts of interest.

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