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ORIGINAL ARTICLE – BREAST ONCOLOGY

Prognostic Value of Number of Removed Lymph Nodes, Number of Involved Lymph Nodes, and Lymph Node Ratio in 7502 Breast Cancer Patients Enrolled onto Trials of the Austrian Breast and Colorectal Cancer Study Group (ABCSG)

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ABSTRACT

Purpose. The number of removed axillary lymph nodes and the ratio of involved to removed lymph nodes are described as independent prognostic factors beside the absolute number of involved lymph nodes in breast cancer patients. The correlation between these factors and prognosis were investigated in trials of the Austrian Breast and Colorectal Cancer Study Group (ABCSG).

Methods. This retrospective analysis is based on the data of 7052 patients with endocrine-responsive breast cancer who were randomized in four trials of the ABCSG in the years 1990–2006 and underwent axillary lymph node dissection. The prognostic value of number of removed nodes (NRN), number of involved nodes (NIN), and ratio of involved to removed nodes (lymph node ratio, LNR) concerning recurrence-free survival and overall survival was analyzed.

Results. A total of 2718 patients had node-positive disease. No correlation was found between NRN and prognosis. Increasing NIN and LNR were significantly associated with worse recurrence-free survival and overall survival in univariate and multivariate analyses ($P < .001$). Only in the subgroup of patients with one to three positive lymph nodes and treated with mastectomy ($n = 728$) was LNR an additional prognostic factor in univariate and multivariate analyses.

Conclusions. For breast cancer patients stringently medicated in the framework of prospective adjuvant clinical trials and requiring a mandatory minimum of removed nodes, NRN does not influence prognosis, and LNR is not superior to NIN as prognostic factor. In patients with one to three positive lymph nodes and mastectomy, LNR could play a role as an additional prognostic factor.

Node status is still an important prognostic factor for patients with breast cancer.[1,2] Despite more and more evidence being available that adjuvant treatment decisions should mainly depend on the biology of the primary tumor (hormone receptor and HER-2/neu overexpression, proliferation, multigenomic profiling), positive nodes still trigger adjuvant chemotherapy in many environments, irrespective of other factors. It is well known that the number of involved nodes (NIN) is an important prognostic factor. There is a strong correlation between increasing involved

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lymph nodes and decreasing prognosis described.[3] A common division in four groups is accepted (0, 1–3, 4–9, ≥10 involved nodes), which is based on observations of many patients without adjuvant therapy. This classification has been introduced in the 2002 edition of the Union for International Cancer Control and in the guidelines of the St. Gallen Consensus Conference for primary therapy of early breast cancer since 2005.[4,5] The type of adjuvant systemic therapy and the decision for postmastectomy radiotherapy depend on the facts and the degree of node involvement in the axilla.

However, in a large series of Surveillance, Epidemiology, and End Results (SEER) data, Vinh-Hung et al. could not confirm a strong correlation between NIN and prognosis.[6] Several authors report better prognosis for patients when an adequate number of nodes was removed by axillary lymph node dissection (ALND).[7–9] All these investigations have been conducted retrospectively, and the number of required nodes for ALND is controversial.[10,11]

As recommended by Vinh-Hung et al., some authors investigated the lymph node ratio (LNR), and a prognostic value for the ratio has been suggested.[8,12,13] A higher ratio would indicate a worse prognosis.

There is, on the other hand, a suggestion that ALND ought to be waived, even in the case of a positive finding in the sentinel lymph node, according to the recently published data of Giuliano et al. for the American College of Surgeons Oncology Group Z0011 trial.[14,15] Despite several shortcomings of that trial, no differences were found between sentinel lymph node biopsy alone and ALND concerning locoregional control and prognosis. Is it responsible to forego the information about LNR in these patients?

To study the prognostic value of these factors, a large cohort of patients from four prospective clinical trials of the Austrian Breast and Colorectal Cancer Study Group (ABCSG) was investigated.

METHODS

Patients

For this analysis, the data of all node-positive patients out of 8374 patients who were randomized in four multicenter trials of the ABCSG were used.

All trials recruited patients with endocrine-responsive breast cancer. Two of the trials investigated premenopausal patients, and two were carried out in postmenopausal patients.

Patients underwent breast-conserving therapy or modified radical mastectomy. For trials ABCSG 5 and 6, ALND in level I and II was obligatory. In trials ABCSG 8 and 12, sentinel lymph node biopsy was accepted as only axillary procedure for patients when a negative sentinel node was found and the performing surgeon had experience with at least 50 sentinel procedures by achieving a sensitivity of ≥95%. If no sentinel biopsy was performed or sentinel node showed metastasis of breast cancer, ALND for level I and II was required. Lymph nodes removed by ALND were usually assessed by routine hematoxylin and eosin staining from one section of each lymph node. A special protocol was not required.

After exclusion of the patients who underwent sentinel node biopsy only and those where less than the required number of nodes were removed, 7024 patients remained for final analysis.

When breast-conserving therapy was performed, all patients received radiotherapy in the premenopausal trials. Most postmenopausal patients received radiotherapy after breast-conserving surgery. For patients who were treated with modified radical mastectomy, radiotherapy was applied according to the local treatment guidelines; postmastectomy radiotherapy was mostly provided to patients with four or more affected nodes.

Institutional local ethics committees reviewed and approved the different protocols, and written informed consent was obtained from all patients who entered the trials.

Trial Designs

ABCSG 5 randomized 1036 premenopausal patients from 1990 to 1999. The aim of the study was a comparison between polychemotherapy of six cycles of cyclophosphamide, methotrexate, and fluorouracil, and combination antihormone therapy with goserelin and tamoxifen for 3 years followed by additional therapy with tamoxifen for 2 years. A minimum of six removed lymph nodes was required for ALND in this protocol.[16]

ABCSG 6 was a trial for 2021 postmenopausal patients who were enrolled 1990–1995. ABCSG 6 randomized patients to tamoxifen for 5 years versus a combination of aminoglutethimide and tamoxifen 2 years, followed by 3 years of tamoxifen. The minimum number of removed nodes (NRN) was six.[17]

After 5 years, 855 patients who had received complete treatment were free of recurrence and who again provided informed consent were enrolled onto an extended antihormone trial (ABCSG 6A). A total of 855 patients were rerandomized for further antihormone therapy with 3 years of anastrozole therapy or no therapy.[18]

A total of 1980 patients where follow-up was available from ABCSG trial 6 (6A) were evaluated for this investigation.

ABCSG 8 randomized 3901 postmenopausal patients (3714 eligible) postmenopausal patients in the years 1996–2004; a minimum of eight nodes was required for patients who underwent ALND ($n = 2917$). ABCSG 8 patients who underwent sentinel node biopsy only

TABLE 1 Demographics by trial

Characteristic	ABCSG 5	ABCSG 6	ABCSG 8N[a]	ABCSG 12N[a]	Total
No. of patients	1036	1980	2917	1119	7052
Median age (year)	45.3	64.6	64.0	44.0	58.9
T1	586 (56.6)	1158 (58.2)	2108 (72.3)	839 (75.0)	4658 (66.4)
T2	409 (39.5)	768 (38.8)	777 (26.6)	267 (23.9)	2221 (31.5)
T3	41 (4.0)	58 (2.9)	32 (1.1)	13 (1.2)	144 (2.0)
G1	118 (11.4)	295 (14.9)	553 (19.0)	149 (12.9)	1115 (15.8)
G2	595 (57.4)	1114 (56.3)	2223 (76.2)	708 (63.5)	4640 (65.8)
G3	289 (27.9)	434 (22.0)	0 (0.0)	267 (21.8)	964 (13.7)
GX	34 (3.3)	135 (6.8)	141 (4.8)	21 (1.8)	331 (4.7)
ER positive	928 (89.6)	1866 (94.2)	2881 (98.8)	1078 (96.9)	6753 (95.8)
PR positive	891 (86.0)	1521 (76.8)	2377 (81.5)	1119 (91.2)	5809 (82.4)
RN (mean)	14.55	13.52	15.29	16.86	14.9
RN (median)	14	13	15	16	14
Node positive	513 (49.5)	754 (38.1)	938 (32.2)	513 (45.8)	2718 (38.5)

ABCSG Austrian Breast and Colorectal Cancer Study Group, *ER* estrogen receptor, *PR* progesterone receptor, *RN* removed nodes

[a] In the ABCSG 8N and 12N trials, patients who underwent only sentinel node biopsy were excluded

($n = 797$) were excluded from this analysis. Trial 8 compared tamoxifen for 5 years with tamoxifen for 2 years followed by anastrozole for another 3 years. For the following analysis, 3718 patients were eligible.[19]

ABCSG 12 enrolled 1803 premenopausal patients during 1999–2005. For ALND, a minimum of 10 axillary lymph nodes was required ($n = 1119$). A total of 684 patients who underwent solely sentinel lymph node biopsy were excluded from this analysis. In ABCSG 12, all patients received ovarian function suppression with 3 years of goserelin but no adjuvant chemotherapy. Patients were randomized between 3 years of tamoxifen with or without acid and 3 years of anastrozole with or without zoledronic acid.[20] Trial characteristics are listed in Table 1.

Subgroup Analyses

For analysis of the prognostic value of LNR in a subgroup comparable to the population of American College of Surgery Oncology Group (ACOSOG) Z0011 trial, we selected from all trials patients with T1 or T2 tumor and one or two positive axillary lymph nodes who underwent breast-conserving therapy and adjuvant radiotherapy, and we performed additional analysis. Patients with one to three positive lymph nodes who underwent mastectomy were selectively examined for prognostic value of LNR in this subgroup.

Statistical Analysis

Covariates of the applied statistical models described below were analyzed thoroughly; categoric data [estrogen receptor (ER), progesterone receptor (PR), grading, T stage, node status] were described by frequencies and percentages. Continuous data (age, removed lymph nodes, affected lymph nodes) were described by means, standard deviations, median, and minimum and maximum, and were then plotted with histograms.

The Cox proportional hazard model was applied in a univariate and multivariate manner to model the prognostic value of removed lymph nodes. The Cox proportional hazard model was applied on time to first recurrence and survival time.

Overall survival (OS) was expressed as the number of months from the date of randomization until death. Recurrence-free survival (RFS) was defined as the interval between the day of randomization and the first evidence of recurrent breast cancer (local recurrence, contralateral carcinoma, and distant metastasis).

Univariate and multivariate models on RFS and OS were calculated examining the effect of removed lymph nodes on survival alone and in combination with age, tumor stage, ER, PR, and grading. Examining whether the affected or the ratio of affected to removed lymph nodes leads to better model fits in Cox proportional hazard modeling, the goodness of fit between the Cox models was compared by Akaike's information criterion. Univariate and multivariate Cox models on RFS, and OS with affected versus the ratio of affected and removed lymph nodes as predictors were used. In the multivariate case a saturated Cox model with additional covariates age, tumor stage, ER, PR, and grading was performed.

All patient data were processed and analyzed at the ABCSG Trial Center by SAS software (SAS Institute, Cary, NC). All statistical analyses were two sided, and significance was assigned at $P < .05$.

RESULTS

A total of 7052 patients in the four trials underwent ALND with a mean number of 14.9 (median 14) removed lymph nodes.

A total of 4334 patients (61.5%) were node negative, and 2718 patients (38.5%) had at least one positive lymph node. Only the 2718 node-positive patients were selected for final analysis after a median follow-up of 98.8 months.

The dissemination of NRN is demonstrated in Fig. 1. In univariate analysis, prognosis declines with increasing number of removed axillary lymph nodes for RFS [hazard ratio (HR) 0.6231; 95% confidence interval (CI) 0.4299–0.994; $P = .00710$] and OS (HR 0.1482; 95% CI 0.7003–0.997; $P = .00740$). In the multivariate model, the correlation between high NRN and poor prognosis lost significance for RFS (HR 0.990; $P = .1484$) and OS (HR 0.9687; $P = 1.000$) (Tables 2, 3, 4).

Distribution of NIN is presented in Fig. 2. In the univariate model, a high NIN is correlated with poor RFS (HR 1.143; 95% CI 1.124–1.161; $P < .0001$) and OS (HR 1.122; 95% CI 1.104–1.141; $P < .0001$). In the multivariate model, poor RFS (HR 1.123; $P < .0001$) and OS (HR 1.097; $P < .0001$) is associated with scores of involved nodes.

The distribution of values for LNR is shown in Fig. 3. LNR was significantly associated with reduced RFS (HR 8.036; 95% CI 6.130–10.536; $P < .0001$) and OS (HR 6.266; 95% CI 4.752–8.263; $P < .0001$) in the univariate analysis. In the multivariate model LNR was associated with decreased RFS (HR 5.835; $P < .0001$) and OS (HR 4.293; $P < .0001$).

By means of Akaike's information criterion (AIC) for comparison of prognostic value of models, the model with NIN (AIC value 9202 for RFS and 8488 for OS) was slightly better than the model with LNR as prognostic factor (AIC value 9209 for RFS and 8492 for OS).

In the subgroup of 1188 patients with T1–2 tumors and one or two positive lymph nodes who underwent breast-conserving therapy and adjuvant radiotherapy (comparable to ACOSOG Z 0011), LNR failed to prove significant correlation with disease-free survival and OS in both the univariate and multivariate model.

In the subgroup of 728 patients with one to three affected lymph nodes who underwent mastectomy, LNR correlated significantly with disease-free survival and OS in the univariate (HR 14.258; 95% CI 3.362–60.464; $P = .0003$ respective HR 4.855; 95% CI 1.177–20.024; $P = .0289$) and multivariate model (HR 7.754; $P = .0055$ respective HR 5.385; $P = .0238$). Radiotherapy including the chest wall and a supra- and infraclavicular field lost significance in the multivariate analysis (HR 1.129; $P = .5398$ respective HR 0.897; $P = .5927$).

DISCUSSION

Node status is traditionally accepted as important prognostic factor in breast cancer patients. The absence or presence of tumor involvement in lymph nodes is crucial for prognosis.[6] The presented data confirm node status as strong independent factor in the multivariate prognostic Cox regression model for all trials. In the presented series, a continual correlation of NIN and prognosis is observed. This factor remains significant after adaption for other covariates in the multivariate model.

The data of the National Surgery Adjuvant Breast and Bowel Project (NSABP) B-04 trial indicate that axillary dissection in the framework of radical surgery did not improve survival.[21] After Fisher's interpretation that breast cancer is a systemic disease from its onset, the debate has continued for decades about the goal of axillary surgery. NSABP B-04 was not powered to find a survival difference. A meta-analysis from 1999 demonstrated a survival benefit of 5.4% for ALND in breast cancer.[22]

FIG. 1 Distribution of number of removed nodes

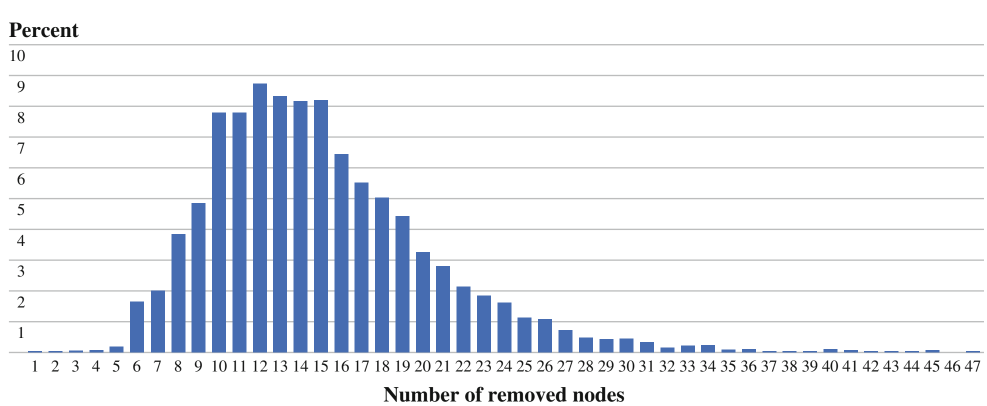


TABLE 2 Univariate and multivariate analysis of recurrence-free survival and overall survival for number of removed nodes, number of involved nodes, and lymph node ratio ($n = 2718$ node-positive patients)

Analysis No. of removed nodes (NRN)	*P*	HR (95% CI)	*P*	HR (95% CI)
Univariate analysis				
NRN	.00710	0.6231 (0.4299–0.994)	0.00740	0.1482 (0.7003–0.997)
Multivariate analysis				
NRN	.1484	0.990	.9687	1.000
Age	<.0001	0.972	<.0001	1.015
ER	.6062	1.132	.9207	0.976
PR	<.0001	0.590	<.0001	0.464
Grade	.0001	1.214	.0427	1.126
T stage	<.0001	1.868	<.0001	1.698
No. of involved nodes (NIN)				
Univariate analysis				
NIN	<.0001	1.143 (1.124–1.161)	<.0001	1.122 (1.104–1.141)
Multivariate analysis				
NIN	<.0001	1.123	<.0001	1.097
Age	<.0001	0.970	<.0001	1.016
ER	.4026	1.225	.8827	1.038
PR	<.0001	0.611	<.0001	0.677
Grade	.0087	1.166	.1236	1.097
T stage	<.0001	1.581	<.0001	1.448
Lymph node ratio (LNR)				
Univariate analysis				
LNR	<.0001	8.036 (6.130–10.536)	<.0001	6.266 (4.752–8.263)
Multivariate analysis				
LNR	<.0001	5.835	<.0001	4.293
Age	<.0001	0.971	<.0001	1.015
ER	.2787	1.3011	.7585	1.080
PR	<.0001	0.598	<.0001	0.659
Grade	.0066	1.170	.1613	1.087
T stage	<.0001	1.532	<.0001	1.427

HR hazard ratio, *CI* confidence interval, *ER* estrogen receptor, *PR* progesterone receptor

TABLE 3 Univariate and multivariate analysis of recurrence-free survival and overall survival for lymph node ratio (LNR) in patients with one or two positive lymph nodes ($n = 1188$)

Characteristic	Recurrence-free survival		Overall survival	
	P	HR (95% CI)	*P*	HR (95% CI)
Univariate analysis				
LNR	.4034	3.692 (0.172–79.026)	.1610	9.068 (0.416–197.903)
Multivariate analysis				
LNR	.2803	5.269	.1330	11.833
Age	<.0001	0.968	.0001	1.037
ER	.3052	1.694	.8558	1.115
PR	.3008	0.795	.0776	0.687
Grade	.1622	1.181	.8604	1.023
T stage	.0036	1.653	.0198	1.530

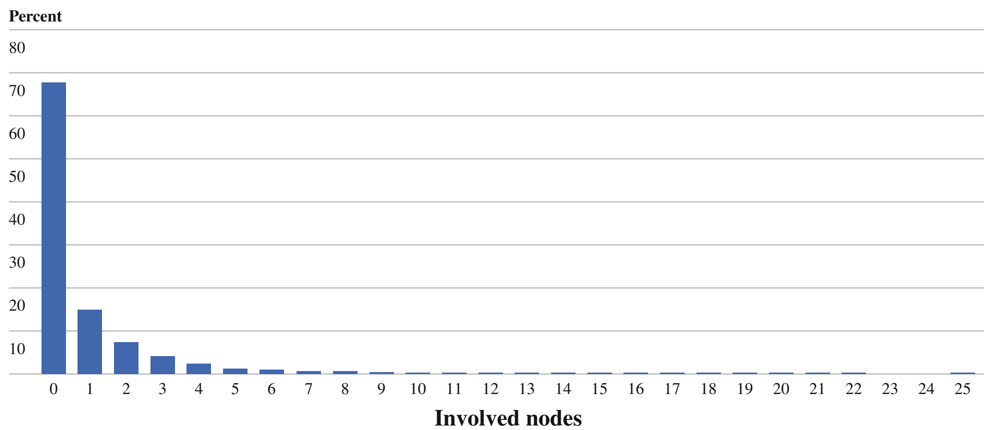
HR hazard ratio, *CI* confidence interval, *ER* estrogen receptor, *PR* progesterone receptor

TABLE 4 Univariate and multivariate analysis of recurrence-free survival and overall survival for lymph node ratio (LNR) in patients with one to three positive lymph nodes and mastectomy ($n = 728$)

Characteristic	Recurrence-free survival		Overall survival	
	P	HR (95% CI)	*P*	HR (95% CI)
Univariate analysis				
LNR	.0003	14.258 (3.362–60.464)	.0289	4.855 (1.177–20.024)
Multivariate analysis				
LNR	.0055	7.754	.0238	5.385
Age	<.0001	0.958	.2216	1.009
ER	.4312	1.495	.4353	0.737
PR	.0439	0.663	.0147	0.640
Grade	.0330	1.342	.2272	1.138
T stage	.5398	1.129	.1221	1.227

HR hazard ratio, *CI* confidence interval, *ER* estrogen receptor, *PR* progesterone receptor

FIG. 2 Distribution of number of involved nodes



From this point of view, ALND is more than a staging procedure. Survival is an additional aim, one apart from locoregional control. Therefore, it is obvious to claim the resection of a sufficient number of axillary lymph nodes.

Early experience concerning this issue was gained in three reports from the Danish Breast Cancer Cooperative Group from 1985 to 1992.[7,23,24] In the last of those reports, Axelsson et al. investigated a number of 13,851 patients and found a significantly better prognosis when at least 10 axillary lymph nodes were dissected.[7] Krag and Single analyzed 72,102 patients and found a risk reduction for OS of 5% for dissection of every additional five resected nodes in node-negative patients in node-positive patients.[25] To our knowledge, only three reports indicate that the NRN did not influence survival.[26–28]

Finally, in only one small series of 290 node-negative breast cancer patients did Camp et al. find a worse 5-year survival in patients who had 20 or more axillary nodes resected compared to patients with fewer resected nodes (HR 1.37–9.52, $P = .01$).[29]

Correlation of poor prognosis and small NRN can be interpreted by understaging.[7,9] In the presented series, understaging is of less importance because in all patients, a minimum of six lymph nodes were removed, and all patients received adjuvant therapy despite node status.

On the other hand, increasing NIN was correlated with poor prognosis in univariate analysis, even though NIN lost significance in the multivariate model. This effect could be explained by the surgeon's intraoperative decision to enlarge the extent of axillary clearance in case of suspicious widespread node involvement or proven positive sentinel node.

In the past decade, several authors have highlighted the additional importance of LNR. The need of 10 or more negative nodes for improvement of prognosis was first noticed by an analysis of the Danish Breast Cancer Cooperative Group in 1992.[7] In a more recent evaluation of nine randomized trials of the International Breast Cancer Study Group for patients with one to three involved nodes, the lowest locoregional failure was also achieved by removal of additional 10 uninvolved nodes.[13]

Others formed a model with more variables to estimate the number of required uninvolved nodes. Iyer et al. found T classification, number of examined nodes, and number of observed positive nodes determining accuracy of the extent of axillar node positivity.[30] Vinh-Hung et al. showed in 16,978 node-positive patients a 5-year survival increase from 50% to 91% by removal of zero to 30 uninvolved nodes.[6]

Other models calculate LNR in percentages. The cutoff values for significant differences in prognosis lie between 10% and 40% of involved nodes.[12,27,31,32]

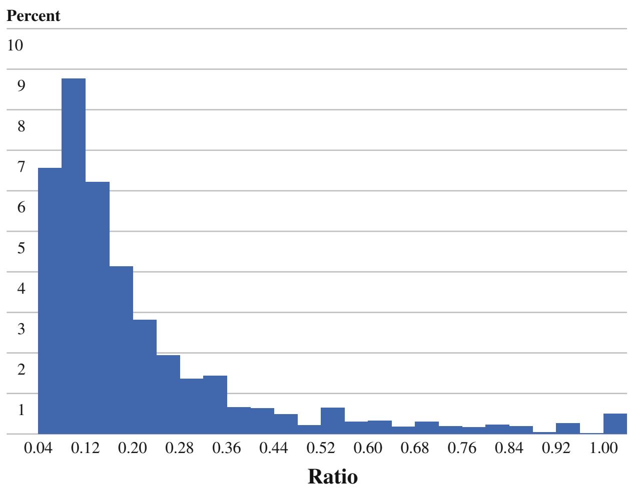


FIG. 3 Distribution of lymph node ratio (only node-positive patients)

Only a few of the above-mentioned analyses compared the different parameters concerning the axillary nodes. In the multivariate model, Iyer et al. described NIN and NRN as a predictor for prognosis.[30] Other studies showed only LNR as significant for prognosis, whereas NIN lost significance.[12,27,28,33]

From our point of view, it is difficult to put together correlating factors into one multivariate model.[34–36] Figure 4 demonstrates graphically the strong correlation between the different factors of NRN, NIN, and LNR in the actual data in a 3D scatterplot. As shown, NIN and LNR remain a strong prognostic factor for RFS and OS even in the multivariate analysis (Fig. 5). By means of Akaike's information criteria to compare the prognostic value of models, including NIN is slightly better than models including LNR.

The validity of the actual results is limited by the kind of retrospective analysis from four different clinical trials. Potential bias could be caused by excluding patients who had only undergone sentinel lymph node biopsy. These patients mostly come from the group with a better prognosis. On the other hand, the crucial questions of this analysis regard only the node-positive patients, and all of them underwent ALND. Only a negligible bias can be assumed by the different adjuvant therapies used in the analyzed trials. In all trials, tamoxifen (in combination with goserelin for premenopausal women) was part of one therapy arm. Except for the group of patients that received additional zoledronic acid in ABCSG 12, the patients in the experimental arm of adjuvant therapy in the other trials did not experience improved prognosis.[20]

The debate about the extent of axillary surgery, particularly for node-positive patients, has continued since the publication of the results of the ACOSOG Z0011 trial by Giuliano et al.[14,15] In this protocol, patients with T1 or T2

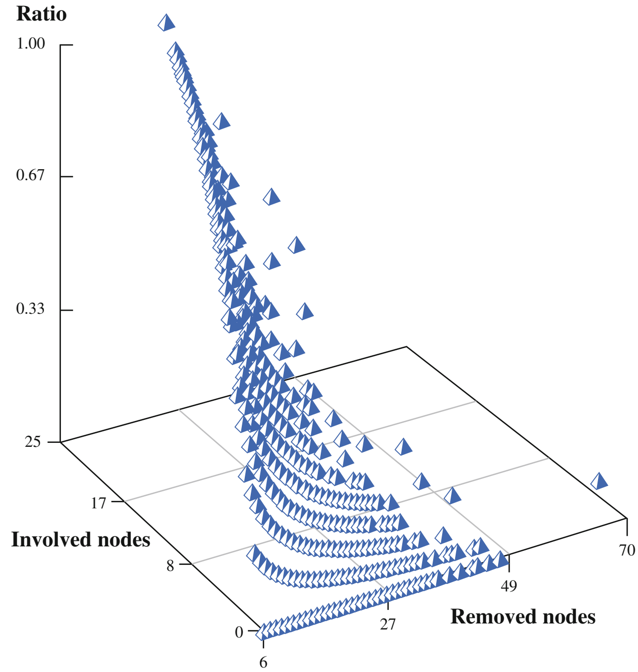


FIG. 4 3D-scattered plot of correlation between number of removed nodes, number of involved nodes, and lymph node ratio

tumors and negative clinical node status and one or two positive sentinel lymph nodes were randomized to completing ALND or no further axillary surgery. All patients in this trial received breast-conserving therapy with radiotherapy of tangential fields. Adjuvant therapy was delivered to 97% of patients, and 58% of all patients received adjuvant chemotherapy. After a median follow-up of 6.3 years, no difference was observed for locoregional control and prognosis between the two treatment groups. Despite several shortcoming precluding the general applicability of this trial, the fact that no difference was observed for locoregional control and prognosis between the two treatment groups has gained exaggerated attention in many environments.[37]

To investigate the value of the ACOSOG Z0011 data, an analysis of a comparable subgroup of the presented data of 1188 patients with T1–2 tumors, and one or two positive lymph nodes treated with breast-conserving therapy and radiotherapy failed to show the prognostic value of LNR. Considering the fact that in our actual data a minimum of six lymph nodes were removed, these results could at least be interpreted as contradictory to the ACOSOG Z0011 conclusions for this selected subgroup.

The results of ACOSOG Z0011 have lead to new recommendations of the St. Gallen Consensus panel for primary therapy of early breast cancer in 2011 for axillary surgery.[38] It is no longer recommended that complete axillary dissection be performed in patients when isolated tumor cells or micrometastases up to 2 mm are detected in

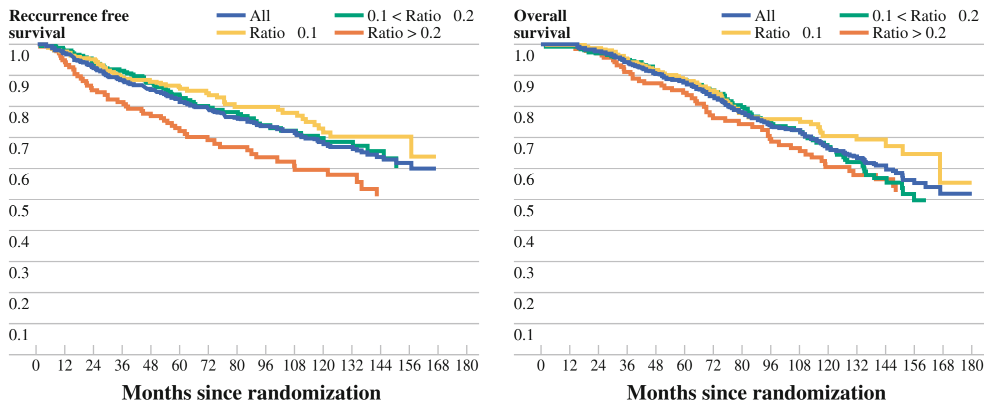


FIG. 5 Comparison of Kaplan–Meier curves for different lymph node ratio values for recurrence-free survival and overall survival of the subgroup with mastectomy and 1–3 involved lymph nodes

the sentinel node, regardless of type of breast surgery. The panel accepted the option of omitting axillary dissection for macrometastases in the context of lumpectomy and radiotherapy for patients with clinically node-negative disease and one or two positive sentinel lymph nodes as reported from ACOSOG trial Z0011. The panel, however, was very clear that this practice, which is based on a specific clinical trial setting, should not be extended more generally, such as to patients undergoing mastectomy, those who will not receive whole-breast tangential field radiotherapy, those with involvement of more than two sentinel nodes, and patients receiving neoadjuvant therapy.

The second relevant subgroup analysis was conducted for 728 patients with one to three positive lymph nodes and treated with mastectomy. Whereas postmastectomy radiotherapy is clearly indicated for patients with more than four affected lymph nodes, the need for postmastectomy radiotherapy is controversial in patients with one to three involved lymph nodes.[38–41] Solely retrospective series with small numbers of patients could prove radiotherapy is beneficial in this situation.[42,43] The largest series was published by Overgaard of the Danish Breast Cancer Group; a substantial prognostic effect was observed for postmastectomy radiotherapy for 1152 patients who had at least eight resected axillary lymph nodes.[44] It remains unresolved whether this effect would be maintained if the patients had received adequate systemic therapy.

Furthermore, it is uncertain which patients with one to three positive nodes would most benefit from postmastectomy radiotherapy. In the presented subgroup analysis, LNR is an excellent prognostic factor.

Radiotherapy failed to improve the prognostic outcome in the multivariate analysis in this subgroup. Considering that only 133 patients (18%) of this subgroup received radiotherapy, this subgroup analysis is probably not powerful enough to answer this question.

In any case, LNR could play a role in the selection of patients who could benefit from postmastectomy radiotherapy when one to three lymph nodes are affected. Truong et al. observed similar results in a cohort of 542 patients and found that LNR higher than a cutoff level of 25% is correlated with worse prognosis.[45] The hypothesis that radiotherapy could balance prognosis in this subgroup must be confirmed in a prospective trial.

In summary, little additional information is gained by the examination of the number of removed lymph nodes and LNR in addition to the NIN in breast cancer patients with moderate recurrence risk who obtain adequate systemic adjuvant therapy in the framework of a clinical trial. Only the subgroup with one to three positive lymph nodes and mastectomy could benefit from identifying the LNR as decision guidance for use of adjuvant radiotherapy.

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