Nodal Positive Breast Cancer and Its Regional Lymph Node Involvement

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Abstract

Purpose: In breast cancer, the lymph node status is of prognostic importance. This study shows the distribution of lymph nodes metastases of node-positive breast cancer patients. Risk factors for lymph node metastases are described.

Methods: 2095 patients with primary breast cancer were analyzed. Analysis included descriptive and statistical analysis.

Results: The nodal stage was positive in 39.4% of all patients and negative in 60.6%. If the nodal stage was positive, only 1 lymph node was involved in 36% of the patients; more than 1 lymph node was involved in 64% of the patients. With an increasing number of lymph node metastases in level I, the probability of an involvement in level III also increases (F 437.845, $p = .000$). Other indicators are evidence of hemangiosis (F 247.728, $p = .000$) or lymphangiosis (F 167.368, $P = .000$). Despite <10 affected lymph nodes, 3.4% of the patients had nodal stage N3 due to level III involvement.

Conclusion: Even with only a small number of lymph node metastases in level I higher lymphatic stations are often affected. The data cannot lead to a decision regarding an operation or radiation indication, but they can better substantiate the risk for certain therapy decisions.

Introduction

In breast cancer, the lymph node status, together with the tumor biology, is of prognostic importance and a decisive factor in therapy planning (1). Data from axillary radiation therapy studies with a benefit of local control, mortality and overall survival suggest that affected lymph nodes, surgically not removed or not irradiated represent a risk of metastasis (2). To our best of knowledge it is not known yet how often the individual lymph node level I, II, III and interpectoral are affected in a positive nodal status. These data were presented in the present study. An attempt was made to determine risk factors for the affection of higher lymph node stations using discriminant analysis.

Materials And Methods

Patients:

We analyzed all cases of breast cancer at the St. Josefs Hospital Offenburg who underwent conventional axillary dissection from 1997 to 2010 with 2095 patients. The lymph nodes of axillary levels I to III and interpectoral were removed and examined separately histopathologically. The results were recorded in our MaDos documentation system.

Data management and statistics:

All data of the tumor documentation system MaDos were exported in Microsoft Excel 2010. These data were then transferred to WinSTAT (version 2012.1) and SPSS (version 21) for further statistical analysis. The analysis included descriptive analysis (median, standard deviation, ranges) and statistical analysis (Chi², discriminant analysis)

Ethics:

This study was performed in line with the principles of the Declaration of Helsinki. The approval for the project was given by the ethics committee of the University of Freiburg (application number 72/20). Informed consent was obtained from all participants.

Results

In our patient collective of 2095 patients with conventional axillary dissection, the nodal status was node-negative (N -) in 1270 (61%) and node-positive (N +) in 825 patients (39%).

1. Frequency of surgery for N + in level I, II, III and interpectoral

In order to analyze the correct lymph node distribution, it was necessary to know the operation frequency of the specific nodal stations. In patients with affected lymph nodes, the lymphadenectomy was performed in level I in 100%, in level II in 99%, in level III in 95% and in interpectoral in 71% of all patients.

2. Number of removed and affected lymph nodes related to the surgery in the corresponding level with N +

Table 1 shows that with positive nodal stage, level I was affected in 98.7%. Skip metastases were found in 11 patients, meaning other stations than level I of the lymphatic drainage were affected. Level II was affected in 29%, level III in 18.5% and interpectoral in 9.6%. If the nodal stage was positive, a mean of a total of 26.5 lymph nodes were removed (range: 3 - 77), including 16.5 lymph nodes in level I, 6.4 lymph nodes in level II, 2.7 lymph nodes in level III and 1.3 in interpectoral. The mean was 5.6 lymph node metastases (range: 1 - 51).

Table 1
Number of removed and affected lymph nodes related to the surgery in the corresponding level with N +

	level I	level II	level III	interpectoral	total number
surgery	825	816	785	582	825
N+	814	237	145	56	
%	98.7	29.0	18.5	9.6	
removed LN, mean	16.5	6.4	2.7	1.3	26.5
SD	5.6	3.6	2	1.4	8.9
min - max	3 - 49	0 - 23	0 - 18	0 - 9	3 - 77
affected LN, mean	4	1,1	0,4	0,2	5.6
SD	4.6	2.4	1.2	0.6	7.6
min - max	0 - 30	0 - 19	0 - 12	0 - 7	1 - 51
SD: standard deviation, LN: lymph nodes					

3. Number of affected lymph nodes in 825 cases of nodal positive patients

Table 2 shows that of a total of 825 patients with positive node status, 295 patients (35.8%) had only one lymph node metastasis and 530 patients (64.2%) had more than one. 60.9% of the patients had 1 to 3 lymph node metastases and in 21.9% 4 to 9 lymph nodes were affected. 17.2% had more than 9 lymph node metastases. The mean was 5.6 lymph node metastases.

Table 2
Number of affected lymph nodes in 825 cases of nodal positive patients

	frequency at N +	
Number of affected lymph nodes	n	%
1 LN	295	35.8
2 LN	117	14.2
3 LN	90	10.9
4 LN	51	6.2
5 LN	47	5.7
6 LN	24	2.9
7 LN	15	1.8
8 LN	29	3.5
9 LN	15	1.8
≥ 10 LN	142	17.2
1 - 3 LN	502	60.9
4 - 9 LN	181	21.9
total number	825	100
LN: lymph nodes, N+: nodal positive, n: number of patients		

4. Frequency of axillary involvement with 0, 1, 2, 3 or more affected lymph nodes in level I.

If there were no lymph node metastases in level I but an involvement of higher lymph nodes, the distribution of lymph node metastases in a total of 825 patients with positive node status shows that level I was not affected in 11 patients (1.33%). Lymph node metastases were found in level II in 3 patients, in level III in 4 patients and in interpectoral in 4 patients.

Table 3 shows the distribution of lymph node metastasis in patients with 1, 2, 3 or more lymph node metastases in level I. Of 312 patients with 1 affected lymph node in level I, a total of 27 of the patients (8.7%) had lymph node involvement in higher lymphatic stations. In 6 patients, several lymph node stations were affected. In relation to the frequency of surgery in the higher lymphatic stations, this corresponds to a value of 5.8% for level II, 3,0% for level III and 2.7% for interpectoral. Of 120 patients with

2 affected lymph nodes in level I, a total of 21 (17.5%) of the patients had lymph node involvement in higher lymphatic stations. Several lymph node stations were affected in 1 patient. In relation to the frequency of surgery in the higher lymphatic stations, this corresponds to a value of 10.8% for level II, 3.4% for level III and 5.4% for interpectoral.

Table 3
Frequency of axillary involvement with 0, 1, 2, 3 or more affected lymph nodes in level I.

Affected node stations	1 lymph node metastasis in Level I			2 lymph node metastases in Level I			3 lymph node metastases in Level I			≥4 lymph node metastases in level I		
	LA	n	%	LA	n	%	LA	n	%	LA	n	%
level I	312	312	100	120	120	100	92	92	100	290	290	100
level II, III or ip		27	8.7		21	17.5		22	23.9		199	68.6
level II	308	18	5.8	120	13	10.8	90	17	18.9	287	186	64.8
level III	300	9	3.0	117	4	3.4	86	8	9.3	271	120	44.3
ip	221	6	2.7	92	5	5.4	64	5	7.8	196	36	18.4
LA: lymphadenectomy; n: number of patients with lymph node metastases; %: percentage of affected lymph node station in relation to the frequency of surgery; ip: interpectoral												

Of 92 patients with 3 affected lymph nodes in level I, a total of 22 (23.9%) of the patients had lymph node involvement in higher lymphatic stations. In 8 patients, several lymph node stations were affected. In relation to the frequency of surgery in the higher lymphatic stations, this corresponds to a value of 18.9% for level II, 9.3% for level III and 7.8% for interpectoral.

Of 290 patients with ≥4 affected lymph nodes in level I, 199 (68.6%) of the patients had lymph node involvement in higher lymphatic stations. In 143 patients, several lymph node stations were affected. In relation to the frequency of surgery in the higher lymphatic stations, this corresponds to a value of 64.8% for level II, 44.3% for level III and 18.4% for the interpectoral.

(A detailed table with more information is available upon request.)

5. Number of affected lymph nodes and nodal status

Table 4 shows that of a total of 683 patients with lymph node involvement of <10 lymph nodes, who could not be assigned to stage N3 due to the number of affected lymph nodes, 28 of these patients (4.1%) had stage N3.

Table 4
Number of affected lymph nodes and nodal status

Number of total affected lymph nodes	Number of patients	N1	N2	N3	
n	n	n	n	n	%
1	295	291	0	4	1.4
2	117	116	0	1	0.9
3	90	84	0	6	6.7
4 - 9	181	0	164	17	9.4
total number	683	491	164	28	4.1
≥10	142	0	0	142	100
N: nodal status N1 – 3					

6. Influencing variables for lymph node metastases in level III

6.1 Chi-square contingency test

Table 5 shows that in the univariate chi-square analysis according to Pearson (uncorrected), age, BMI and molecular biological factors (hormone receptor status, Her2 status) were not found to be significant for an association with lymph node metastases in level III. The proliferation markers (Ki67 / MIB) or invasion markers (uPA / PAI-1) were also not significant. In contrast, the tumor stage (T1-T4), tumor size, grading, lymphangiosis, hemangiosis and the number of affected lymph nodes in level I (≤ 3 / > 3) were found to be highly significant. The location in the inner or central quadrant was also significant for lymph node metastases in level III.

Table 5
Influencing variables for lymph node metastases in level III

Category	Lymph node metastasis in Level III	p	Chi ²
Age		ns	
< 53Jahre	6.8% (30/440)		
53 bis 62 Jahre	5.9% (23/390)		
63 bis 71 Jahre	8.4% (36/430)		
> 71 Jahre	7.6% (30/395)		
BMI		ns	
≤ 25	5.4% (31/576)		
> 25 ≤ 30	6.0% (33/552)		
30 bis 34,9	9.3% (25/268)		
≥ 35	7.9% (8/101)		
inside quadrant *		0.036	4.382
no	8.2% (85/1034)		
yes	5.5% (34/621)		
central quadrant ***		0.001	10.675
no	6.6% (102/1540)		
yes	14.8% (17/115)		
tumor stage ***		< 0.001	61.551
T1	4.4% (46/1047)		
T2	9.7% (50/513)		
T3	21.7% (13/47)		
T4	21.7% (10/46)		
tumor size ***		< 0.001	32.316
≤ 10mm	2% (5/252)		
11 ≤ 20mm	5.8% (33/570)		

* = $p \leq 0.05$; ** = $p \leq 0.01$; *** = $p \leq 0.001$; ns = not significant

Category	Lymph node metastasis in Level III	p	Chi ²
21 ≤ 35mm	9.7% (35/361)		
> 35mm	16.9% (20/118)		
Grading ***		< 0.001	17.269
G1	2.9% (3/102)		
G2	5.8% (62/1069)		
G3	11.2% (54/484)		
Lymphangiosis ***		< 0.001	111.938
no	2.0% (12/612)		
yes	23.4% (67/286)		
Hemangiosis ***		< 0.001	132.990
no	4.4% (34/768)		
yes	41.9% (31/74)		
Number of affected lymph nodes in level I ***		< 0.001	515.974
0 - 3	1.3% (19/1421)		
> 3	42.7% (100/234)		
hormone receptor		ns	
ER and PR negative	7.7% (14/181)		
ER or PR positive	7.1% (105/1474)		
Her2		ns	
negative	7.2% (106/1472)		
positive	7.1% (12/183)		
uPA		ns	
negative	8.9% (65/729)		
positive	6.8% (841/599)		

* = p ≤ 0.05; ** = p ≤ 0.01; *** = p ≤ 0.001; ns = not significant

Category	Lymph node metastasis in Level III	p	Chi ²
PAI-1		ns	
negative	8.2% (57/698)		
positive	7.8% (50/639)		
proliferation (Ki67/MIB)		ns	
not increased ($< 30/50$)	6.9% (73/1064)		
increased ($\geq 30/50$)	7.8% (46/591)		
* = $p \leq 0.05$; ** = $p \leq 0.01$; *** = $p \leq 0.001$; ns = not significant			

6.2 Discriminant analysis

A step-by-step discriminant analysis was performed with the significant variables from the chi-square contingency test. The group differences were found to be significant in the discriminant analysis (Wilks-Lambda .587, $\text{Chi}^2 = 380.489$, $p = .000$). The most important prognostic factors were the number of positive lymph nodes in level I ($\leq 3 / > 3$) ($F = 437.845$, $p = .000$), hemangiosis ($F = 247.728$, $p = .000$) and lymphangiosis ($F = 167.368$, $p = .000$).

The classification results show that 91.9% (730/794) of the originally grouped cases were correctly classified. In particular, the negative predictive value was at 85.3% (677/794). However, the positive predictive value was 6.7% (53/794).

7. Axillary relapse

Table 6 shows the number of axillary relapses as first event, either alone or in combination with a local relapse. It is also shown how often a distant metastasis occurs later.

Table 6
Axillary relapse

Axillary relapse	Nodal stage N0		Nodal stage N+		Total number	
	n =1270		n = 825		n = 2095	
	n	%	n	%	n	%
Axillary relapse only first event	3	0.24	4	0.49	7	0.33
Axillary relapse AND local breast relapse first event	2	0.16	1	0.12	3	0.14
Axillary relapse total	5	0.39	5	0.61	10	0.47
Axillary relapse AND later distant metastasis	2	0.16	2	0.24	4	0.19

Discussion

Determining the lymph node status is a diagnostic measure. It is of prognostic importance and is used for therapy planning (1). In addition, axillary lymphadenectomy also served to reduce the tumor burden. The benefit of axillary radiation therapy shows that unremoved, untreated metastases can have consequences for local control and disease-free survival (2). This suggests that any affected lymph nodes that were left were successfully treated by radiation therapy. This assumption is confirmed by the available data with the detection of lymph node metastases in higher lymphatic stations even with a low metastatic lymph node load in level I. As shown in the case of only 1, 2 or 3 affected lymph nodes in level I, level III was affected in 3.0%, 3.4% and 9.3% of the patients and the interpectoral in 2.7%, 5.4% and 7.8%. In the case of 1-3 affected lymph nodes in level I, the proportions of affected lymph nodes in level III (21/503) and in interpectoral (16/377) were both 4.2%. In the case of more than 3 affected lymph nodes in level I the proportion was 44.3% in level III and 18.4% in interpectoral. These data are similar to the results of Joshi, S. et al. (3). Their results showed a proportion of 9.4% positive lymph nodes in level III if 1-3 lymph nodes in level I and II were affected and a proportion of 53.2% in the case of 4 affected lymph nodes. In our overall results, level III was affected in 18.5% and interpectoral in 9.6% if there was a positive nodal status. Joshi et al. showed this proportion to be 27.3% and 4.7%, respectively (3). Other study groups were also able to demonstrate a level III infestation between 15% and 59% (4) (5) (6).

Altogether, in the case of only 1 affected lymph node in level I, lymph nodes metastases were detectable in the subsequent lymph node stations level II, III and interpectoral in 8% of the patients. In the case of 2 affected lymph nodes in level I, the proportion was 15% and in the case of 3 affected lymph nodes in level I, the proportion was 20%. In the case of unaffected lymph nodes in level I, 11 of 825 patients (1.3% [based on operation frequency 1.5%]) had a positive nodal stage in level II, III or interpectoral

(interpectoral). It would therefore be a false negative nodal stage. Whether a false negative rate of 1.5% justifies a conventional axillary lymphadenectomy is currently decided in the negative based on the data from the sentinel lymphadenectomy (7) (8) (9).

683 of the 825 patients with lymph node metastases had <10 affected lymph nodes, which corresponds to the nodal stage N1 or N2. The surgery of level III resulted in a change of stage from stage N2 to stage N3 in 4.1% (28 /683) of these patients due to lymph node metastases in level III (chapter 5).

A total of 170 of the 825 patients with lymph node metastases had nodal stage N3, 142 (83.5%) patients with more than 9 affected lymph nodes and 28 (16.5%) patients with <10 affected lymph nodes, which is prognostic and also possibly with therapeutic consequences.

Indicators of level III lymph node involvement in the chi-square test were tumor stage, tumor size, grading, lymphangiosis, hemangiosis and the number of affected lymph nodes in level I (≤ 3 / > 3).

The location in the inner or central quadrant was also significant for lymph node metastases in level III. This corresponds to the numbers of other published data (3). The discriminant analysis showed the number of positive lymph nodes in level I (≤ 3 / > 3), hemangiosis and lymphangiosis as the most important prognostic factors for lymph node metastases in level III. Exclusion of lymph node metastases in level III can be assumed at 85.3% in the absence of these factors. However, the positive predictive value in this study was 6.7%. Even if some studies showed better local control with effects on overall survival (10) (16), NSABP B-04, as the first randomized study, was not able to show a survival benefit from conventional axillary dissection (11). However, these described factors should be viewed as a particular risk for lymph node metastases and should possibly be included when considering the radiation treatment plan. Also, it should be noted, that breast cancer metastases are also known to be radio-resistant (12); and resistance rates of 8-15% must be expected (13).

Conclusions

This study showed that even with only a small number of lymph node metastases in level I, the higher lymphatic stations are often affected too. If the node status is positive, more than 1 lymph node is involved in 64%. The data cannot lead to a decision regarding an operation or radiation indication, but it can better substantiate the risk for certain therapy decisions.

A further improvement in the imaging of the localization of lymph node metastases and examinations for the prediction of a possible radio resistance would be desirable.

Declarations

Data Availability

The datasets generated during and analysed during the current study are not publicly available due to all data are listed in our own tumor documentation system MaDos but are available from the corresponding author on reasonable request..

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Author Contributions

HM: Study concepts, Study design, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review

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Competing Interests Statement

The authors declare no competing interests.

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