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The Benefit of Baseline Staging–Risk Assessment of Distant Breast Cancer Metastases by Tumor Stage

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Abstract. *Background: Despite recommendations of international societies, use of baseline staging in breast cancer varies considerably. We retrospectively analyzed the prevalence of metastases in each pTN stage to estimate the benefit of staging. Patients and Methods: The prevalence of metastases at primary diagnosis (M1) and in the first year after diagnosis ($M1_{12}$) was determined in 2,906 patients. Results: The prevalence of M1 was 0.95% [95% confidence interval (CI)=0.53-1.70%] in pT1pN0, 2.17% (95% CI=1.00-4.64) in pT1pN1 and 1.53% (95% CI=0.78-2.99%) in pT2pN0. The prevalence of $M1_{12}$ was 2.17% (95% CI=1.47-3.18%) in pT1pN0 and 3.25% in pathological stage IIA (upper confidence bound 5.14%). In pT2pN1 the prevalence of M1 and $M1_{12}$ was 3.49% (95% CI=1.96-6.14%) and 6.35% (95% CI=4.15-9.60%), respectively. Results for stage pT3pN0 and higher were inconclusive. Conclusion: Baseline staging can be safely abandoned in pathological stage I and IIA. Individual decisions should be made for pT2pN1. Staging is recommended in stages of pT3pN0 or higher.*

In patients with newly diagnosed breast cancer, accurate assessment of the extent of locoregional and distant tumor is considered crucial for treatment planning. In general, staging work-up includes bone scan, liver ultrasonography and chest radiography. More recently, chest computed tomography (CT), abdominal CT/ultrasound and bone scans are recommended (1, 2). Several studies demonstrated that the prevalence of detectable metastases at initial diagnosis is very low in most stages of the disease (3, 4). Hence, routine staging work-up is not recommended for all patients and is considered inappropriate for asymptomatic patients with small tumors and minimal nodal involvement. Despite available guidelines, routine use of baseline staging in breast cancer still varies considerably, with some patients still undergoing extensive staging. This situation is complicated by the fact that practical guidelines vary across leading international and national professional societies (3, 5).

The clinical practice guideline of the European Society for Medical Oncology recommends baseline radiological staging for patients with clinically positive axillary nodes, large tumors (*e.g.* ≥5 cm) or symptomatic tumors (2). According to the current guideline of the National Comprehensive Cancer Network, staging should be considered for patients with clinical stage IIIA and higher, but not for asymptomatic patients with stage I-IIB disease (1). Instead, the Breast Cancer Disease Site Group Ontario Cancer Care recommends routine bone scan in patients with pathological stage II tumors (3). Routine liver ultrasonography and chest radiography are not recommended in this group but could be considered in patients with four or more positive lymph nodes. Complete baseline staging is recommended as part of the postoperative baseline staging in those with pathological stage III tumors (3). In contrast, the German interdisciplinary S3 guideline advises against oncological staging in patients with T1N0 and T2N0 tumors only (5).

Although it is generally accepted that the yield of baseline staging increases with tumor stage, the prevalence of distant metastasis in the subgroups of each pathological tumor stage is unclear. In particular, the role of baseline staging tests in stage II breast cancer remains controversial, since the prevalence of metastases seems to vary significantly across this subgroup.

To our knowledge, this is the largest retrospective study aiming to identify subgroups of patients with asymptomatic primary breast cancer at different levels of risk for distant metastasis. The primary goal of this study was to determine the prevalence of distant metastasis for each subgroup of

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Key Words: Breast cancer, baseline staging, metastasis, tumor stage.

Table I. *Proportion of patients with metastases at initial diagnosis (M1). Numbers of patients with M0, M1 or MX are listed dependent on the pT and pN classification. The proportion of M1 and MX as well as the corresponding two-sided 95% Wilson confidence intervals (CI) are presented.*

Tumor stage	M0, n	M1, n	MX, n	Sum, n	M1 and MX	95% CI
pT1pN0	1142	3	8	1153	0.95%	0.53-1.70%
pT1pN1a	271	6	0	277	2.17%	1.00-4.64%
pT1pN2a	55	3	0	58	5.17%	1.77-14.14%
pT1pN3a	37	8	4	49	24.49%	14.60-38.09%
pT1pN3c	0	2	0	2	100.00%	34.24-100.00%
pT2pN0	515	5	3	523	1.53%	0.78-2.99%
pT2pN1a	304	10	1	315	3.49%	1.96-6.14%
pT2pN2a	151	9	3	163	7.36%	4.26-12.43%
pT2pN3a	107	8	0	115	6.96%	3.57-13.13%
pT3pN0	29	0	1	30	3.33%	0.59-16.67%
pT3N1a	25	0	0	25	0.00%	0.00-13.32%
pT3pN2a	31	2	1	34	8.82%	3.05-22.96%
pT3pN3a	43	7	1	51	15.69%	8.17-28.01%
pT4pN0	29	2	0	31	6.45%	1.79-20.72%
pT4pN1a	21	3	0	24	12.50%	4.34-31.00%
pT4pN2a	17	2	1	20	15.00%	5.24-36.04%
pT4pN3a	26	8	1	35	25.71%	14.16-42.07%
pT4pN3b	0	1	0	1	100.00%	20.65-100.00%

Table II. *Proportion of metastases at 12 months' follow-up ($M1_{12}$). Three categories of metastasis are distinguished: no distant metastasis (M0), distant metastasis ($M1_{12}$) and M status unknown/indeterminate (MX). Numbers of patients with M0, $M1_{12}$ or MX are listed dependent on the pT and pN classification. The proportion of $M1_{12}$ and MX as well as the corresponding two-sided 95% Wilson confidence intervals (CI) are presented.*

	M0, n	$M1_{12}$, n	MX, n	Sum, n	$M1_{12}$ and MX	95% CI
pT1pN0	1128	19	6	1153	2.17%	1.47-3.18%
pT1pN1a	267	10	0	277	3.61%	1.97-6.52%
pT1pN2a	55	3	0	58	5.17%	1.77-14.14%
pT1pN3a	37	11	1	49	24.49%	14.60-38.09%
pT1pN3c	0	2	0	2	100.00%	34.24-100.00%
pT2pN0	506	15	2	523	3.25%	2.04-5.14%
pT2pN1a	295	20	0	315	6.35%	4.15-9.60%
pT2pN2a	140	22	1	163	14.11%	9.59-20.28%
pT2pN3a	96	19	0	115	16.52%	10.84-24.37%
pT3pN0	27	2	1	30	10.00%	3.46-25.62%
pT3N1a	24	1	0	25	4.00%	0.71-19.54%
pT3pN2a	29	4	1	34	14.71%	6.45-30.13%
pT3pN3a	36	14	1	51	29.41%	18.71-43.00%
pT4pN0	29	2	0	31	6.45%	1.79-20.72%
pT4pN1a	20	4	0	24	16.67%	6.68-35.85%
pT4pN2a	14	4	1	20	25.00%	11.19-46.87%
pT4pN3a	19	15	1	35	45.71%	30.47-61.81%
pT4pN3b	0	1	0	1	100.00%	20.65-100.00

pathological tumor stage. In addition, a multivariate analysis was performed to evaluate the prognostic value of tumor stage to other clinically important covariables.

Patients and Methods

This retrospective study included 2906 asymptomatic patients with newly diagnosed breast cancer who were referred to the Hannover Medical School between 1992-2009. Since the early 1980s, the Cancer Registry, Hannover Medical School, has recorded all patients with breast cancer who were referred to the Department of Obstetrics and Gynecology. Patient and tumor characteristics were documented based upon the medical records. Follow-up data were obtained by retrieving subsequent patient contact documented in the medical information system of the Hannover Medical School. The system includes information from practitioners and appropriate registration offices.

In this study, only patients with known pathological T and N status were included. Staging was allocated according to the sixth edition of the TNM staging system of the American Joint Committee on Cancer (6). All patients who received neoadjuvant therapy were excluded from this study. The majority of the patients underwent baseline staging including bone scan, liver ultrasonography and chest radiography. More recently, chest and abdominal computed tomographic scans were preferentially used. Missing or incomplete data (*i.e.* MX, missing HER2/neu and hormone receptor status, grading) are mainly due to the retrospective nature of the analysis.

The prevalence of metastases at initial diagnosis (M1) in the first 12 months of follow-up after primary diagnosis ($M1_{12}$) was determined. All cases of MX were classified as M1. The analysis of $M1_{12}$ was performed to include patients with subclinical metastases and false-negative results at initial diagnosis. The prevalence was determined for each pathological tumor stage. This retrospective study was approved by the Institutional Review Board (approval number 1130-2011) of the Hannover Medical School and conducted according to all current ethical guidelines.

Statistical analysis. The prevalence of metastases (M1 and $M1_{12}$) and the corresponding two-sided 95% Wilson confidence interval (CI) were calculated for each subgroup of pathological tumor stage. A multivariate model investigating the association between the occurrence of metastasis and possible risk factors was created. For patients among whom the risk of metastasis was less than 5%, abandoning routine staging seemed appropriate. Thus, the variable staging abandoned was dichotomized to pT1pN0, pT1pN1a with pT2pN0 *versus* all other stages in the analysis of M1, and to pT1pN0 *versus* all other stages in the analysis of $M1_{12}$. The relevance of the staging abandoned to the occurrence of metastasis was evaluated with logistic regression models. Firstly, a univariate logistic regression model was computed for the tumor stage and for each candidate risk factor separately. In order to adjust the prognostic value of pathological tumor stage for further factors, multivariate logistic regression models were computed including the tumor stage and all factors with a *p*-value of 0.2 or less in the univariate analyses. In order to achieve a small and meaningful model, the number of factors was reduced in a backward selection, where factors remained in the model if the *p*-value was 0.15 or less. The model was checked for multicolinearity among the variables by

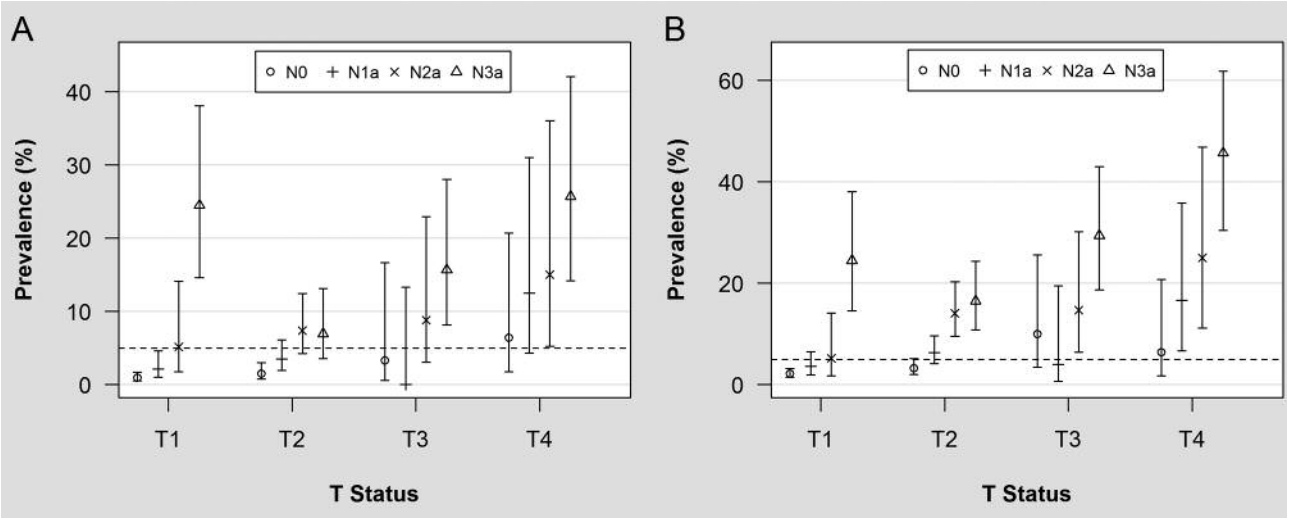

Figure 1. *The prevalence of metastases and corresponding confidence intervals are shown for each pathological tumor stage. Metastatic prevalence at initial diagnosis (M1) (A) and at 12 months of follow-up ($M1_{12}$) (B). The upper boundary of the 95% confidence interval for M1 was less than 5% for the tumor stages pT1pN0, pT1pN1 and pT2pN0. For $M1_{12}$, it was less than 5% for patients with pT1pN0 only.*

computing the tolerance for each variable regressed on all others in the model. Multicolinearity may exist if the tolerance is less than 0.4. The results are presented listing absolute and relative frequencies, the odds ratios and their corresponding two-sided 95% CIs and the two-sided *p*-value. In 24 out of 2906 patients (0.8%) the M status was unknown (MX). In the primary analysis, MX was replaced by M1. For statistical analyses, we used SAS®, Version, 9.2 and R, Version 2.15.1; SAS Institute Inc., Cary, NC, USA.

Results

The prevalence of metastases (M1) at initial staging was 3.5% irrespective of tumor stage. The prevalence of metastases ($M1_{12}$) was 6.3%. For tumor stages pT1pN0, pT1pN1 and pT2pN0, M1 was less than 5%. $M1_{12}$ was less than 5% for tumor stage pT1pN0. The prevalences and corresponding CIs are shown for each pathological tumor stage in Tables I and II and Figure 1.

In the majority of patients, only one organ site was involved. Multiple organ sites were involved in 8 out of 79 patients (M1) and 25 out of 169 patients ($M1_{12}$). Bone metastases were most frequently detected, followed by liver metastases and pulmonary/pleural metastases. The median follow-up was 71 months.

Patients with node-positive breast cancer had a significantly higher risk of distant metastasis than did node-negative patients in the multivariate analysis at M1, (data not shown) and after 12 months' follow-up ($M1_{12}$) (Tables III and IV). In the backward selected model at 12 months' follow-up, the risk of distant metastasis increased with the number of positive axillary lymph nodes (Table IV).

Increasing tumor size was associated with a higher risk of metastasis if patients had a nodal status of pN0, pN1 or pN2. However, in the analysis of M1, distant metastases were relatively more common in those with small tumors <pT1c and pN3 (three out of seven patients) than in those with larger node-positive tumors ≥pT2 and pN3 (26 out of 202 patients). This finding is consistent with the analysis of $M1_{12}$ (Tables I and II).

No difference between positive and negative hormone receptor status was found in the analysis of M1. However, patients lacking hormone receptor status had a higher risk of metastases. In the analysis of $M1_{12}$, patients with positive hormone receptor status had a smaller risk of metastases than those with hormone receptor-negative tumors. Patients with no reported hormone receptor status had a higher risk of metastasis than those with a negative hormone receptor status (Table IV). A trend for reduced risk in those with highly differentiated tumor and an increased risk in those with poorly differentiated cancer was observed (Table IV). In the multivariate analysis of M_{12}, the factor 'staging abandoned' was not included in the model after backward variable selection because this factor is highly associated with the size of the tumor and the nodal status.

Discussion

Although it is generally accepted that the likelihood of metastasis is extremely low in asymptomatic early breast cancer, routine use of baseline staging still varies considerably (7). Risk assessment of each tumor stage will

Table III. *Baseline patient and disease characteristics at 12 months' follow-up ($M1_{12}$). The frequencies of dichotomous and categorical variables with more than two outcomes after 12 months are presented. Three categories of outcome status of metastasis are distinguished: no distant metastasis (M0), distant metastasis ($M1_{12}$) and M status unknown/indeterminate (MX). In the primary analysis, patients with MX were treated as $M1_{12}$.*

Variable	Sample size (N=2906), n (%)	M0 (N=2722), n (%)	$M1_{12}$ (N=169), n (%)	MX (N=15), n (%)
Staging abandoned				
No	1753 (60.32%)	1594 (90.93%)	150 (8.56%)	9 (0.51%)
Yes	1153 (39.68%)	1128 (97.83%)	19 (1.65%)	6 (0.52%)
Age				
<60 Years	1706 (58.71%)	1603 (93.96%)	93 (5.45%)	10 (0.59%)
≥60 Years	1200 (41.29%)	1119 (93.25%)	76 (6.33%)	5 (0.42%)
Hormone receptors				
Negative	663 (22.81%)	601 (90.68%)	58 (8.75%)	4 (0.60%)
Positive	2137 (73.54%)	2029 (94.95%)	101 (4.73%)	7 (0.33%)
Missing	106 (3.65%)	92 (86.79%)	10 (9.43%)	4 (3.77%)
HER2				
Negative	674 (23.19%)	636 (94.36%)	34 (5.04%)	4 (0.59%)
Positive	150 (5.16%)	141 (94.00%)	7 (4.67%)	2 (1.33%)
Missing	2082 (71.64%)	1945 (93.42%)	128 (6.15%)	9 (0.43%)
Grade				
1	192 (6.61%)	190 (98.96%)	2 (1.04%)	0 (0.00%)
2	1387 (47.73%)	1321 (95.24%)	59 (4.25%)	7 (0.50%)
3	1027 (35.34%)	928 (90.36%)	94 (9.15%)	5 (0.49%)
4	8 (0.28%)	5 (62.50%)	2 (25.00%)	1 (12.50%)
Missing	292 (10.05%)	278 (95.21%)	12 (4.11%)	2 (0.68%)
Size of tumor				
pT1a, pT1b, pT1mi	429 (14.76%)	420 (97.90%)	5 (1.17%)	4 (0.93%)
pT1, pT1c	1110 (38.20%)	1067 (96.13%)	40 (3.60%)	3 (0.27%)
pT2, pT2a, pT2b	1116 (38.40%)	1037 (92.92%)	76 (6.81%)	3 (0.27%)
pT3	140 (4.82%)	116 (82.86%)	21 (15.00%)	3 (2.14%)
All stages of pT4	111 (3.82%)	82 (73.87%)	27 (24.32%)	2 (1.80%)
Nodal status				
pN0	1737 (59.77%)	1690 (97.29%)	38 (2.19%)	9 (0.52%)
pN1a	641 (22.06%)	606 (94.54%)	35 (5.46%)	0 (0.00%)
pN2a	275 (9.46%)	238 (86.55%)	34 (12.36%)	3 (1.09%)
pN3a	253 (8.71%)	188 (74.31%)	62 (24.51%)	3 (1.19%)
Year of diagnosis				
1992-1997	915 (31.49%)	864 (94.43%)	45 (4.92%)	6 (0.66%)
1998-2003	1154 (39.71%)	1067 (92.46%)	83 (7.19%)	4 (0.35%)
2004-2009	837 (28.80%)	791 (94.50%)	41 (4.90%)	5 (0.60%)

help identify those patients who will derive the most benefit from baseline staging.

In our study, the overall prevalence, frequency and location of metastases are in agreement with previous studies (3, 8, 9, 10, 16). Our results suggest that the risk of missing metastases in pathological stage I and stage IIA breast cancer is extremely low. In the analysis of $M1_{12}$, the prevalence of metastases in pathological stage I breast cancer was slightly higher than in the M1 analysis. For pathological stage IIA breast cancer the upper confidence bound was 5.14%, but the prevalence still remained low.

A major concern of baseline screening in early breast cancer is the high rate of false-positive or indeterminate findings (4, 8). Overdiagnosis of metastasis is potentially harmful because it can lead to considerable psychological distress and potentially wrong treatment decisions. Indeterminate findings can cause anxiety and generate costly additional investigations. The false-positive rate of bone scans varies between 6% and 22% (4, 9, 12). Routine liver ultrasound has a false-positive rate of 6-7% (4, 9). The limited value of chest x-ray in asymptomatic patients with breast cancer and other tumor entities has been shown in numerous studies (13-16). The false-positive rate of chest x-ray in asymptomatic patients varies between 3-23% (3, 4, 9).

The diagnostic accuracy of CT scans is supposedly higher than that of more traditional imaging modalities. Hence, leading international societies endorse the use of chest CT, abdominal ultrasound or abdominal CT scan for baseline

Table IV. *Multivariate primary analysis at 12 months' follow-up ($M1_{12}$).*

Model $M1_{12}$ after backward variable selection (n=2,906)		
Variable	Odds ratio (95% CI)	*p*-Value
Hormone receptors (ref: negative)		0.0005
Positive	0.646 (0.451-0.926)	0.0174
Missing	2.035 (1.031-4.020)	0.0407
Grade (ref: 2)		0.0712
1	0.338 (0.080-1.417)	0.1378
3	1.334 (0.936-1.902)	0.1105
4	4.104 (0.785-21.450)	0.0942
Missing	0.839 (0.447-1.576)	0.5859
Tumor size (ref: pT1a,pT1b,pT1mi)		<0.0001
pT1, pT1c	1.423 (0.677-2.988)	0.3519
pT2, pT2a, pT2b	1.688 (0.813-3.505)	0.1600
pT3	2.428 (1.038-5.681)	0.0408
All stages of pT4	5.488 (2.362-12.751)	<0.0001
Nodal status (ref: N0)		<0.0001
N1a	1.822 (1.150-2.887)	0.0107
N2a	4.042 (2.492-6.555)	<0.0001
N3a	7.560 (4.814-11.873)	<0.0001

CI: Confidence interval. Hormone receptor status, nodal status and the size of tumor were of prognostic value in the multivariate primary analysis of $M1_{12}$.

testing (2, 14). In a recent study, the value of preoperative CT in detecting lung and liver metastases was investigated (17). Distant metastases were found in 0.2% of those with stage I breast cancer, while 13.4% (60 out of 448) of the patients had false-positive lesions. None of the 838 patients with stage II breast cancer had lung or liver metastases, while 14.4% (121 out of 838) of the patients had a false-positive finding. In stage III breast cancer, 6% (25 out of 417) of the findings were true positives and 14.2% (59 out of 417) were false positives (17). In another recent study, the false-positive rate for the total population was 8.5% on CT scan and 7.7%, 9.0% and 8.7% in stages I, II and III, respectively (11).

Due to the retrospective nature of our study, we were not able to accurately determine the false-negative and false-positive rate of each imaging modality. However, our results indicate that baseline staging in pathological stage I and stage IIA breast cancer would pick up only very few metastases but generate a significant number of false-positive or indeterminate findings. In our study, the prevalence of metastases in pT2pN1 (stage IIB) was 3.49% (95% CI=1.96-6.14%) in the analysis of M1 and 6.35% (95% CI=4.15-9.60%) in the analysis of $M1_{12}$. Given a false-positive rate of 9-14% in stage II breast cancer, the risk of overdiagnosing metastasis is higher than the chance of detecting true metastatic disease (11, 17, 18). For pT2pN1, the benefit of baseline staging must be carefully weighed against the potential disadvantages. Missing metastases is clearly an unfortunate event, but the risk of undertreatment is highly unlikely. In contrast to this, false-positive findings do carry the risk of undertreatment. Patients with assumed metastatic disease will only receive palliative, instead of curative treatment.

The prevalence of metastases (M1) in pT3pN0 (stage IIB) tumors was 3.3% (95% CI=0.59-16.67%) and 10% (95% CI=3.46-25.62%) in the analysis of $M1_{12}$, respectively. The accurate prevalence of metastases remains indeterminate for this subgroup and the remaining higher tumor stages due to the small numbers of patients and the large variability seen in the CIs.

The multivariate analysis points to the importance of tumor biology, suggesting that node-positive, hormone receptor-negative, large breast carcinomas are associated with an increased risk of distant metastasis. It is of interest to note that small tumors (<pT1c pN3) with extensive axillary lymph node involvement tended to have a markedly increased risk of distant metastasis. Previous studies have shown that breast cancer subtypes are associated with unique patterns of metastatic spread with notable differences in survival (19). However, a limitation of our study is the variability of methods used to determine the hormone receptor status. During the era of this cohort, the methods, thresholds for positivity and interpretation criteria have changed significantly. In addition the HER2/neu status was unknown in the majority of our patients.

In conclusion, our results support current guidelines according to which baseline staging can be safely abandoned in asymptomatic patients with pathological stage I and IIA breast cancer. The lowest risk of distant metastasis was observed in hormone receptor-positive, G1/G2, pT1pN0 breast cancer. The risk of distant metastasis is somewhat higher for pT2pN1 (stage IIB) breast cancer. However, with the considerable risk of false or indeterminate findings in mind, it is appropriate to abandon routine baseline staging for this subgroup. Baseline staging should remain part of clinical work-up in pT3pN0 (stage IIB) cancer and higher stages.

Ethical Standards

This retrospective study was approved by the Institutional Review Board of the Hannover Medical School and conducted according to all current ethical guidelines. The experiments/methods used comply with the current laws of Germany.

Conflicts of Interest

The Authors declare that they have no conflict of interest.

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