EJGO European Journal of Gynaecological Oncology

Metastatic mammary carcinoma despite histologically negative sentinel lymph nodes: are there any indicators for estimating recurrence and metastasis rates?

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Summary

Objective: This study aimed to identify indicators for an increased frequency of recurrent or metastatic disease in women with mammary carcinoma staged negative for nodal involvement. *Materials and Methods:* 202/270 patients (age: mean 57.5, range 24-83 years) with histologically confirmed early stage mammary carcinoma negative for metastasis to the sentinel lymph nodes (SLN) were observed with respect to their clinical course for a mean period of 3.6 years following SLN extirpation. *Results:* Forty of 202 patients with negative SLN underwent chemotherapy (38/188 in the recurrence-free group *vs.* 2/14 in the group with progressive disease) and 79% of both subcollectives did not undergo chemotherapy. Seven of 188 of patients in the recurrence-free group received immunotherapy and none of the patients in the group with disease progression were treated with this modality. One hundred sixty-two of 202 patients with negative SLN underwent hormone therapy, 157/188 in the recurrence-free group and 5/14 in the group with disease progression. One hundred sixty-four of 202 patients with negative nodal status received adjuvant radiation therapy of the affected breast, 156/188 in the recurrence-free group and 8/14 in the group with disease progression. *Conclusions:* When assessing the risk profile for disease recurrence or the occurrence of metastatic disease, statistically significant differences with respect to disease progression were identified for the parameters chemo-, antibody, hormone, and radiation therapy. The preliminary observations of this study show that even those patients in an early disease stage and with negative SLNs profit from these adjuvant non-surgical therapy options.

Key words: Breast cancer; Sentinel lymph node; Recurrence and metastasis rates; Adjuvant therapy.

Introduction

Planning the therapeutic management of mammary carcinoma depends on a reliable assessment of the individual tumor's degree of malignancy. Certain prognostic factors are associated with a high probability of disease recurrence or the development of metastases.

The sentinel lymph node (SLN) concept consisting of radioactive SLN detection with consecutive SLN extirpation and histopathological examination represents the current standard of care. It is considered a safe procedure with a low false-negative detection rate and a low false-negative rate of metastases [1-4].

The objective of the present study was to determine whether, and, if yes, which indicators (patient characteristics, tumor biology, differences in therapy) could serve to predict the potential development of recurrent or metastatic disease in patients with initially negative axillary lymph nodes.

Materials and Methods

Patient collective

In accordance with the German law, pre-approval by IRB was not required for this study, which complied with the Declaration of Helsinki. Lymphoscintigraphy is a well-established and routine diagnostic procedure at the present clinic; naturally, all patients gave written informed consent prior to lymphoscintigraphy.

The analysis was based on a total of 270 consecutive patients treated according to the SLN concept who met the following inclusion criteria: histologically confirmed mammary carcinoma (pT1-2) with no clinical evidence of regional lymph node or distant metastases that was found primarily to be unifocal in configuration and of anatomically unilateral localization.

As represented schematically in Figure 1, the overall collective was broken down into two subcollectives, one with histologically positive (n = 68/270), the other with histologically negative SLN (n = 202/270). The SLN-negative patients' clinical course was comprehensively followed and documented. The mean follow-up period between patients' primary surgery and the last documented clinical follow-up examination was 3.6 years (median, 3.3 years; range 0.1-8.7 years). Inclusion criteria were a diameter of the primary tumor ≥ one mm and ≤ 50 mm, as well as a histologically unremarkable (negative) SLN extirpation. Women with inflammatory mammary carcinoma, lymphangiosis carcinomatosa, secondary carcinomas, and/or prior surgeries involving the breast or axilla, as well as patients with suspicious (at palpation or ultrasound) axillary lymph nodes were excluded from the analysis; the same applied to women who were pregnant or breast-feeding.

Data gathering and statistical analysis

Data regarding the individual parameters were obtained from the data bank of the Munich Tumor Register; the patient records of the Clinic for Nuclear Medicine, the Clinic of Gynecology, and

Revised manuscript accepted for publication August 31, 2015

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XXXVII, n. 6, 2016
doi: 10.12892/ejgo3261.2016

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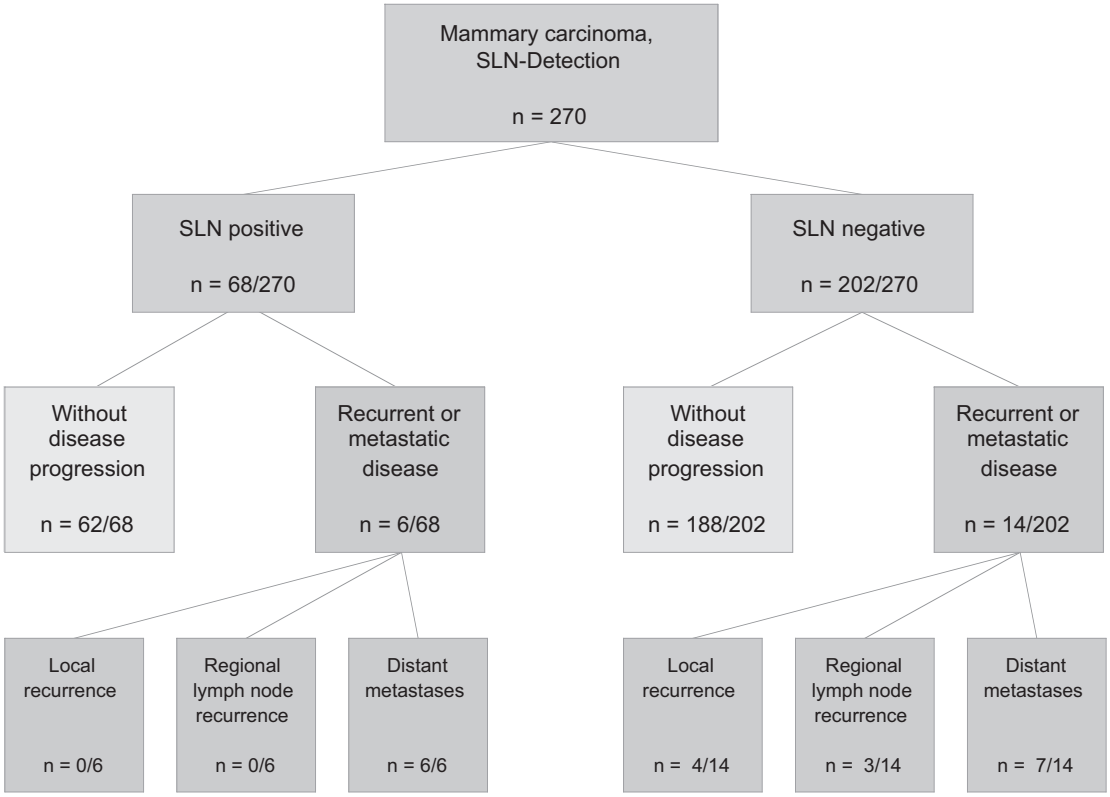

Figure 1. — Patients: overall and subcollectives.

the reports of the Institute for Pathology. Data included general patient demographics and history (e. g. age, menopausal status, body mass index), tumor-specific and histopathological data (e. g. tumor localization, diameter, histology, TNM stage, grading), receptor status (estrogen, progesterone, Her-2/neu status), therapy (surgery, chemo-, antibody, hormone, radiation therapy), and clinical course.

Patients' age at time of first diagnosis was determined (mean 57.5 years, range 24-83 years). In addition, the number of SLN excised in each case was recorded. For purposes of the statistical analysis, patients initially treated with breast-preserving therapy but later requiring mastectomy were considered as those undergoing primary mastectomy. For those undergoing adjuvant therapy, the type of therapy was recorded; if a given patient's adjuvant therapy included more than one therapy concept, this was correspondingly documented.

Following transfer of the data to an SPSS file, data were checked for plausibility with respect to the above-described parameters by comparison of the gathered data with findings from the above-mentioned databanks. The statistical analysis was performed using the Predictive Analytics Software (PASW, Version 18.0). Continuous variables were given as mean and median, standard deviation, and quartiles served to measure scatter. Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov Test. As all tested variables failed to show normal distribution ($p < 0.05$), non-parametric tests for non-normally distributed samples were used for the statistical comparisons. For the comparison of two independent, non-normally distributed samples, the authors used the Mann-Whitney U-test, while the chi-square test was used for non-categorized data. A two-sided test of significance was applied for all tests. P values < 0.05 were considered statistically significant.

Results

Table 1 presents the statistically analyzed parameters, together with the respective statistical test method and the calculated level of statistical significance for patients with negative nodal status who within the observation period experienced disease progression (recurrent or metastatic disease; n = 14/202) *vs.* those who did not experience relapse (n = 188/202).

Table 2 provides an overview of the adjuvant therapies undergone by women in the overall collective (positive and negative nodal status; n = 270). Patients underwent one or more of the following therapies, which are given in descending order of frequency: percutaneous radiation, hormone therapy, chemotherapy, and immunotherapy. This order also corresponds with the frequency of the application of the respective methods in the subcollectives with negative and positive nodal status. Many patients were treated with more than one adjuvant therapy modality.

The age distribution in the two subcollectives was quite homogeneous and the respective means and medians lay

Table 1. — *Statistical comparisons of patient, tumor, and therapeutic parameters in SLN-negative patients without (n = 188/202) and with (n = 14/202) recurrent or metastatic disease.*

		Histological features of the primary tumors	without progression n		with progression n		p-value	
Age (yrs.)		Mean	**58.7**		**58.5**		0.774	not significant
		Median	**59.9**		**59.0**			
		Standard deviation	**10.986**		**16.290**			
Menopausal Status		pre-menopausal	**46**	24%	**6**	43%	0.202	not significant
		post-menopausal	**142**	76%	**8**	57%		
Body-Mass Index (kg/m^2)		Mean	**25.6**		**25.9**		0.883	not significant
		Median	**25.0**		**25.0**			
		Standard deviation	**5.048**		**5.683**			
		Range	**15 - 47**		**19 - 39**			
Number of excised Sentinel Lymph Nodes		n ≤ 3	**162**	86%	**10**	71%	0.283	not significant
		4 ≥ n ≤ 9	**25**	13%	**4**	29%		
		n ≥ 10	**1**	1%	**0**			
Tumor	**Localization**	centrally	**3**	2%	**0**		0.522	not significant
		upper inner quadrant	**31**	16%	**1**	7%		
		lower inner quadrant	**20**	11%	**1**	7%		
		upper outer quadrant	**103**	55%	**11**	79%		
		lower outer quadrant	**25**	13%	**1**	7%		
		Mamilla / Areola	**6**	3%	**0**			
	Diameter (mm)	Mean	**17.5**		**19.1**		0.496	not significant
		Median	**17.0**		**20.5**			
		Standard deviation	**8.501**		**10.575**			
	Histology	ductal	**135**	72%	**13**	93%	0.431	not significant
		lobular	**24**	13%	**0**			
		in situ	**22**	11%	**0**			
		others	**7**	4%	**1**	7%		
	pT-Stage	pT1a	**10**	5%	**1**	7%	0.172	not significant
		pT1b	**30**	16%	**1**	7%		
		pT1c	**76**	41%	**4**	29%		
		pT2	**61**	32%	**7**	50%		
		pT1 mic	**1**	1%	**1**	7%		
		pT in situ	**10**	5%	**0**			
	Grading	G1	**31**	17%	**0**		0.107	not significant
		G2	**104**	55%	**7**	50%		
		G3	**53**	28%	**7**	50%		
Receptor-Status	**Estrogen, Progesterone**	Estrogen	**23**	12%	**2**	14%		not significant
		Progesterone	**11**	6%	**2**	14%		
		Estrogen + Progesterone	**129**	69%	**6**	43%		
		negative	**23**	12%	**4**	29%		
		unknown	**2**	1%				
	HER2/neu	no expression	**161**	85%	**12**	86%	0.878	not significant
		overexpression	**5**	3%	**0**			
		intense overexpression	**20**	11%	**2**	14%		
		unknown	**2**	1%	**0**			
Therapy	**Surgical technique**	Breast-preserving	**153**	81%	**13**	93%	0.472	not significant
		Mastectomy	**35**	19%	**1**	7%		
	Chemotherapy	performed	**38**	20%	**2**	14%	0.04	significant
		contraindicated	**1**	1%	**1**	7%		
		not performed / refused by patient	**149**	79%	**11**	79%		
	Antibody therapy (Immunotherapy)	performed	**7**	4%	**0**		0.043	significant
		not performed / refused by patient	**181**	96%	**14**	100%		
	Hormone therapy (endocrine therapy)	performed	**157**	84%	**5**	36%	0.0001	significant
		not performed / refused by patient	**31**	16%	**9**	64%		
	Radiation therapy	performed	**156**	83%	**8**	57%	0.019	significant
		not performed / refused by patient	**32**	17%	**6**	43%		

close together. This applies even to the age ranges for the youngest and oldest patients at the time of first diagnosis. The majority of patients in both subcollectives were post-menopausal. It is noteworthy that a comparatively higher percentage of women who developed recurrent disease had been pre-menopausal at the time of first diagnosis (43% *vs.* 25% in the subcollective of women not developing recurrent or metastatic disease). The mean and median BMI lay close together for both groups. Minimum BMI in the recurrence-free patients was 15 kg/m², compared with 19

Table 2. — *Absolute frequency of adjuvant therapy methods in the overall collective (n = 270) and relative frequency in the SLN negative and SLN positive subcollectives; the sum (n > 270) results from the combined therapies conducted in many patients.*

	n	SLN		
Radiation therapy	232/270	negative	164/202	81%
		positive	68/68	100%
Hormone therapy (endocrine Therapy)	215/270	negative	162/202	80%
		positive	53/68	78%
Chemotherapy	91/270	negative	40/202	20%
		positive	51/68	75%
Antibody therapy (Immunotherapy)	16/270	negative	7/202	3%
		positive	9/68	13%

kg/m² in the group that did experience disease progression. There was a larger spread with respect to maximum BMI, with 47 kg/m² in the recurrence-free group compared to 39 kg/m² in the group experiencing disease progression. A majority of patients in both subcollectives underwent excision of one to three SLN (86% in the recurrence-free group *vs.* 71% in the group with disease progression). Removal of four to nine SLN was much less frequent, occurring in 13% of recurrence-free patients and 29% of patients who did experience disease progression. In only one case (a patient in the recurrence-free subcollective) were ten or more SLN removed. The most frequent tumor localization in both groups was the upper outer quadrant (recurrence-free: 55% and disease progression: 79%). Localization of the tumor in the central glandular body was very rare, occurring in only 2% of the recurrence-free subgroup. Mean and median tumor diameters were slightly higher in the subgroup with disease progression compared with the recurrence-free subgroup. Invasive ductal mammary carcinoma was by far the most frequent type of malignancy. Less frequent tumor types, including mucinous, gelatinous, medullary, papillary, and tubular carcinomas, were documented. While the pT1c stage predominated in the recurrence-free group (40%), followed by the pT2 stage (32%), pT2 represented the more frequent stage in the subcollective of patients with disease progression (50%). There were differences between the comparison groups with respect to the percent distribution of tumor grading. In the recurrence-free subgroup, under consideration of all differentiation groups, an overwhelming majority corresponded to G2 (55%), while, for the subcollective with progressive disease, there was an even distribution to the lower differentiation grades corresponding to G2 and G3, at 50% each. In the subcollective with disease progression, 14% each showed either estrogen or progesterone dependence, while 43% showed a combination of estrogen and progesterone dependent growth and 29% exhibited a negative hormone-receptor status. Over 85% of patients in both subcollectives exhibited no expression of the Her-2/neu gene. Hyperexpression was observed in 13% of patients in the recurrence-free group compared with 14% of patients in the subgroup with disease progression. Breast-preserving surgery was performed in 81% of patients in the recurrence-free group compared with 93% in the group with disease progression. In the recurrence-free group, 19% underwent mastectomy compared with 7% in the group with disease progression.

A total of 40/202 patients with negative nodal status underwent chemotherapy (38/188 (20%) in the recurrence-free group *vs.* 2/14 (14%) in the group with progressive disease). The overwhelming majorities of both subcollectives did not undergo chemotherapy (79% each for the subcollectives with and without recurrent disease); there was a statistically significant difference between both subcollectives ($p = 0.040$). 7/188 (4%) of patients in the recurrence-free group received immunotherapy; none of the patients in the group with disease progression were treated with this modality; there was a statistically significant difference between both subcollectives ($p = 0.043$). A total of 162/202 patients with negative nodal status underwent hormone therapy, 157/188 (84%) in the recurrence-free group and 5/14 (36%) in the group with disease progression; there was a statistically highly significant difference between both subcollectives ($p = 0.0001$). A total of 164/202 patients with negative nodal status received adjuvant radiation therapy of the affected breast, 156/188 (83%) in the recurrence-free group, and 8/14 (57%) in the group with disease progression; there was a statistically significant difference between both subcollectives ($p = 0.019$).

Discussion

Objective of the present study was to determine whether any patient-, tumor- or therapy-specific indicators could be identified in patients diagnosed and treated using the SLN concept that would predict the increased progression (local recurrence, locoregional lymph node recurrence, distant metastases) of the primary malignancy in patients with mammary carcinoma, but negative SLN status.

A variety of independent prognostic factors have been discussed in the literature as potentially predictive of the individual disease course [5-10]. These include the localization and diameter of the tumor, the tumor histology, its staging and grading, the histological hormone receptor status, and patient characteristics, such as age and weight. The Nottingham Prognosis Index (NPI) has been established as a means of estimating the individual prognosis, taking into consideration factors such as lymph node involvement, tumor size, and grading. The value of the NPI with respect to nodally negative stages of mammary carcinoma, however, has remained controversial in the literature [8, 11]. While, on the one hand, the NPI has been described in stud-

ies of the impact of different parameters (divergent histological assessment of grading, different surgical techniques, differences in the learning curve regarding SLN detection) as a stable prognostic factor for adjuvant therapy modalities in patients with positive lymph node status, the index has been critically reviewed with respect to a negative lymph node status and shown to be not significant [8, 11]. Thus, the NPI was considered unsuitable for the question addressed in the current study of patients with negative nodal status and was not determined. In addition, several studies have found that the patient's age at the time of first diagnosis is correlated with the disease course. For example, patients aged 35-49 years have a good prognosis in comparison with the age group above 75 years. On the other hand, mammary carcinoma in patients below the age of 35 years has a poor prognosis [12].

In the present study of patients with negative SLN status, the authors observed no statistically significant differences between the comparison groups (subcollectives that were either recurrence-free or showed disease progression) in terms of patient- or tumor-specific characteristics or surgical technique used. There was no significant difference with respect to either age, menopausal status or BMI between the groups, with and without disease progression, although it has been postulated in the literature that high BMI might be associated with a poorer prognosis [7]. There was a tendential, though not statistically significant shift towards higher tumor stages in the subgroup of patients with disease progression: while stage pT1c predominated among recurrence-free patients, pT2 was more common in the progression group. Furthermore, none of the other statistically analyzed tumor-specific parameters (localization, diameter, histology or grading) could be shown to a significant indicator of disease progression, although reports in the literature have seen tumor diameter as a prognostic parameter [13, 14], which might be due to the rather small population of malignant progression in cases of negative SLN.

The International St. Gallen Consensus Conference established risk groups for mammary carcinoma patients according to which the probability of axillary lymph node involvement increases in relation to increasing tumor size and influences both recurrence-free survival and overall survival. Patients without lymph node involvement but a tumor size > two cm were placed in a moderate risk group [13, 15]. Other authors found that tumor size exerts a large impact on the five-year survival rate: the five-year survival rate was 93% in patients with pT1 tumors, compared with only 55% in patients with pT2 tumors [12]. Data from the present own patient collective failed to support this correlation in a statistically significant way for SLN-negative patients. This applies also to the number of SLN removed ($n \leq 3, 4 - 9, \geq 10$) and also to the surgical technique (breast-preserving surgery *vs.* mastectomy). With respect to tumor histology, the present statistical analysis agreed with findings of a recently published investigation that reached the conclusion that the histological tumor type should not be considered as the importance prognostic parameter regarding the risk of progression [10]; there was no statistically significant correlation in this regard during the observation period.

It is known that estrogen and progesterone induce cell growth by binding to hormone receptors on the cell. The hormones exert a growth stimulating effect on both healthy breast tissue and on malignant cells. Reports in the literature have discussed a direct correlation between survival and hormone receptor status [16]. Thus, the estrogen and progesterone receptor status could be considered a prognostic (assessing the probability of progression) and/or predictive (with respect to the targeted choice of therapeutic modality) parameter. Both a positive estrogen receptor status and a positive test for progesterone receptors exert a favorable effect on the prognosis as these correlate with a more robust response to hormones. This is especially true when both types of hormone receptors are identified. By contrast, a negative hormone receptor status is associated with a poorer prognosis. Here, one might ask whether this is to be ascribed to the predictive value, since hormone receptor positive mammary carcinomas respond well to endocrine therapy. No positive correlation could be found for the SLN negative patients in the present study. On the other hand, it is possible that the fortunately quite low percentage of patients experiencing progression of their malignant disease may have served to conceal a more unequivocal statistical correlation.

Amplification of the Her-2/neu gene and the associated hyperexpression are associated with a more unfavorable prognosis and, according to reports in the literature, can be identified in about a third of all cases of mammary carcinoma. The findings of the present study with respect to Her-2/neu status correlate well with a comprehensive study of Chinese women which found that Her-2/neu expression represents an important prognostic factor for patients with positive, but not negative, nodal status [17].

In comparison with the patient and tumor specific characteristics, and the surgical technique employed in each respective case, a comparison of the recurrence-free subcollective and the group of patients experiencing disease progression did return statistically significant differences for all of the non-surgical adjuvant therapy modalities. For example, a tendentially smaller percentage of patients with disease progression had undergone adjuvant chemotherapy than did patients not experiencing disease recurrence. This could indicate a diagnostic gap in the detection and/or histopathological examination of the SLN. Because of their small size, micrometastases may potentially escape detection at the histopathological examination [18, 19]. The significance of micrometastases for the prognosis and for the development of recurrent disease remains controversial in the literature [6, 14, 20, 21]. Patients with

isolated tumor cells are considered equivalent to patients with negative nodal status in the current guidelines of the American Joint Committee.

Similarly, the presence of "skip" metastases, which occur in up to 4% of cases of mammary carcinoma and which, because of their irregular pattern of metastasis formation along the draining lymphatic structures, are not always reliably detected with the SLN concept, represent a problem is this regard [11, 22]. This could have the result that systemic disease might not be adequately recognized. On the other hand, patients with occult metastases would profit from adjuvant therapy.

False-negative SLN extirpation and the resulting deferral of radical axillary dissection is statistically rare and thus clinically acceptable, although it is known that this represents a risk of axillary micrometastases that could lead to regional lymph node recurrence [4, 22-24]. In the present collective, however, none of the women with the histological classification of micrometastasis formation (pNmic) developed locoregional lymph node recurrence.

Breast-preserving therapy was an indication for postoperative radiotherapy in all patients treated with this technique. The target volume dose of 50 Gy was administered in five fractioned doses of 1.8-2.0 Gy per week. There was a statistically significant difference between the subcollectives with and without progressive disease with respect to adjuvant radiation. Percutaneous radiation of the affected breast and thorax wall following surgery was administered in 83% of recurrence-free mammary carcinoma patients compared with only 57% in the group developing recurrent disease. Similar results were documented for the patients receiving endocrine therapy, there being a highly significant difference between the two subcollectives. Here, 84% of recurrence-free patients underwent adjuvant hormonal therapy compared to only 36% of those ultimately experiencing disease progression. There was also a statistically significant correlation with respect to disease progression *vs.* maintained remission in patients treated with immunotherapy (antibody therapy). This adjuvant therapy form, however, was only infrequently used in the present patient collective: none of the women in the group with disease progression and only 4% of those not experiencing recurrent disease underwent this therapy.

The development and clinical establishment of modern diagnostic modalities on the molecular-genetic level have promoted targeted therapeutic decision-making in the treatment of women with mammary carcinoma [5]. This is especially true for the specific application of adjuvant therapy options. Against this background, the preliminary observations of the present study support the conclusion that the targeted application of the above-mentioned non-surgical adjuvant therapeutic modalities may, despite a negative SLN extirpation status, and given certain pre-requisites (e. g. adequate receptor status), lead to a statistically less frequent progression of patient's malignant disease. A plausible explanation for this observation could be that systemic adjuvant therapy and/or local radiation minimizes the risk of occult metastasis formation secondary to micrometastases or so-called "isolated tumor cells", resulting in a lower rate of recurrent or metastatic disease.

Conclusions

The prognosis of SLN negative patients with mammary carcinoma is impacted decisively by their utilization of adjuvant therapy options. The present findings underline that patients might benefit from non-surgical adjuvant therapy options even in the early stages of mammary carcinoma despite negative SLN findings.

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