# Sentinel Lymph Node Biopsy in Patients with Breast Cancer: Comparison of Peritumoral and Periareolar Injection

## Szintigrafische Wächterlymphknotendiagnostik bei Patientinnen mit Mammakarzinom: klinische Erfahrungen nach Umstellung der Injektionstechnik von peritumoral auf periareolär

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## Abstract
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**Introduction:** Intradermal periareolar injection technique for sentinel lymph node biopsy (SLNB) may offer an advantage by including multifocal breast cancer as an additional indication. In May 2008 we changed our standard procedure from peritumoral (PT) to periareolar (PA) injection. We compared the results for corresponding periods before and after the change in procedure.

**Material and Method:** A total of 117 patients (pts.) were investigated the year after we changed our technique; a total of 152 pts were investigated in the reference period 2007. We investigated the identification rates for sentinel lymph nodes (SLN) identified scintigraphically and surgically as well as the rates of metastatic involvement (LN).

**Results:** After PT injection, scintigraphic detection of SLN failed in 5/152 pts., and in a further 10 pts. SLN was not found at surgery. In 7 of 15 pts. in whom SLN was not detected, histology demonstrated nodal involvement. Metastases were found in the SLN of 28 of 137 pts. with successful detection of SLN; no other lymph nodes were affected in 21 of these pts. (75.0 % of pts. with positive SLN detection). With PA injection at least one SLN could always be detected using scintigraphy; only 2/117 SLN could not be found intraoperatively. Metastasis was found in SLN in 34/115 pts.; in 19/34 pts., metastatic involvement was limited to the SLN with no other lymph nodes involved (55.9 % of pts. with positive detection of SLN).

**Discussion:** The detection rate for SLN was significantly higher using PA injection (98.3 % vs. 90.1 %). As axillary dissection was not done in SLN-negative patients, rates of false-negative detection cannot be determined. PA injection not only results in better detection rates, it also offers the advantage that the technique can be performed correctly regardless of tumour localisation.

## Zusammenfassung
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**Einleitung:** Die intradermale periareoläre Injektionstechnik bei der Sentinellymphknotenbiopsie (SLNB) bietet Vorteile in Bezug auf eine mögliche Ausweitung auf die Indikationsgruppe der multizentrischen Tumoren. Im Mai 2008 erfolgte eine Umstellung der Injektionsmethode von einer peritumoralen (PT) auf eine periareoläre (PA) Injektion. Die Ergebnisse nach der Umstellung wurden in entsprechenden Zeiträumen verglichen.

**Material und Methodik:** Im Jahr nach der Umstellung wurden 117 Patientinnen (Pat.) untersucht, im Vergleichsjahr 2007 152 Pat. Untersucht wurden u.a. die szintigrafische und operative Auffinderate sowie der Anteil an befallenen Lymphknoten (LN).

**Ergebnisse:** Mit der PT-Technik wurde szintigrafisch bei 5/152 Pat. kein Sentinel-LN (SLN) nachgewiesen, bei weiteren 10 Pat. konnte der SLN intraoperativ nicht gefunden werden. Sieben der insgesamt 15 Pat. ohne SLN-Nachweis zeigten einen axillären Befall. Von den 137 Pat. mit SLN-Nachweis zeigten 28 einen SLN-Befall, davon war bei 21 Pat. nur der oder die SLN befallen (75,0 % der Pat. mit positiven SLN). Mit der PA-Technik waren szintigrafisch immer SLN nachweisbar, nur 2/117 SLN wurden intraoperativ nicht gefunden. Der oder die SLN war(en) in 34/115 Fällen befallen, wobei in 19/34 Fällen nur SLN betroffen waren (55,9 % der Pat. mit positiven SLN).

**Diskussion:** Es zeigte sich mit 98,3 vs. 90,1 % eine deutlich höhere SLN-Auffinderate bei der PA-Technik. Da keine komplette axilläre Ausräumung bei SLN-negativen Patientinnen erfolgt ist, ist keine Falsch-negativ-Rate bestimmbar. Die PA-Injektionstechnik zeigt sich insgesamt bez. der Nachweisrate überlegen und bietet den Vorteil, dass die korrekte Durchführung unabhängig von der sicheren Lokalisierbarkeit des Primarius durch Palpation oder Sonografie ist.

## Introduction
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The status of the axillary lymph nodes is one of the most important prognostic factors for patients with a primary diagnosis of breast cancer. Axillary lymph node involvement is associated with a significantly higher mortality and has such a high risk of recurrence that adjuvant systemic therapy is usually indicated [1–3, 25–28]. Prior to the introduction of sentinel lymph node biopsy (SLNB), radical axillary lymphadenectomy was the standard surgical procedure for the therapy and staging of breast cancer. With the advent of more modern screening methods and as the general population has become better informed, the majority of patients now has a negative lymph node status at the time of diagnosis [4], making radical axillary lymphadenectomy an unnecessarily radical intervention with a high morbidity in these patients [5].

SLNB is a well established diagnostic procedure for the detection of tumour-draining lymph nodes. It was initially used in the therapy of other tumour types such as malignant melanoma. The diagnostic significance of SLNB is well known and has been extensively investigated [6,7]. A radioactive tracer is injected into breast tissue to show the first lymph nodes in the lymphatic flow downstream from the primary tumour. These lymph nodes are subsequently removed during surgery and histologically examined for metastasis. A negative nodal status of this first "filter station", which indicates the absence of lymphogenically metastasised tumour cells, is considered sufficient to exclude axillary metastasis, making the removal of axillary lymph nodes unnecessary in these patients. This prevents the shoulder and arm morbidity associated with axillary lymph node dissection [8–14]. Currently, the standard indication for SLNB is small, unifocal breast carcinomas with diameters of up to 2 cm (T1 tumour stage) and a clinically negative nodal status. The current consensus in Germany is that SLNB can optionally be applied to bifocal tumours or tumours with diameters of between 2 and 5 cm (T2 tumours) [15]. A further expansion of indications is currently being discussed. Other discussions have focussed on the optimal injection method for the tracer. At present, various peritumoral, periareolar and subareolar injection techniques are considered equivalent [16]. However, periareolar injection offers various advantages: the technique is easier to learn, does not require additional efforts for non-palpable tumours, and the procedure is less painful [17–19]. Cheng et al. compiled a recent review of the literature [20] which included all studies comparing injection methods in more than 100 patients.

In May 2008 the Institute for Diagnostic Radiology and Nuclear Medicine of Minden Hospital changed their previous technique of peritumoral injection to periareolar, intradermal injection. The aim of this study was to compare the results for the two methods in clinical practice. The study also focused on the identification rates for SLN using scintigraphy and at surgery.

## Material and Method
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### Patient collective

In 2007 a total of 152 patients were investigated (mean age: 61.3 years; range: 36–86 years). Between May 2008 and April 2009, a total of 117 patients were investigated (mean age: 62.1 years; range: 33–91 years). None of the patients showed axillary lymph node involvement at clinical or sonographic investigation. None of the patients had previously undergone neoadjuvant chemotherapy. Histologically, the majority of carcinomas in both groups were invasive ductal carcinomas (82.9% of patients with peritumoral injection, 72.6% of patients with periareolar injection). The rate of lobular carcinomas was significantly lower: 9.9% (peritumoral injection) and 14.5% (periareolar injection), respectively. Both groups included individual patients with ductal carcinoma in situ (2.6% of patients with peritumoral injection; 5.1% of patients with periareolar injection). The remaining patients presented with rarer tumour entities. The distribution of the different tumour stages is given in ○ Table 1. Most patients had T1 or T2 tumours. Both patient collectives included individual patients with multifocal tumours; the rate of multifocal tumours was higher in the group undergoing periareolar injection compared to the group undergoing peritumoral injection (18 of 117 pts. with periareolar injection [15%] vs. 12 of 152 pts. with peritumoral injection [8%]).

### Ethics committee

This study is a retrospective cohort study and uses anonymised data. No consent of patients was required for this retrospective analysis. No permission was sought from the local ethics committee as our regional protocol does not consider this necessary for this type of study.

### Radiopharmaceuticals

$^{99m}$Tc-labelled colloids with particle sizes of between 20 and 100 nm (mainly NANOCIS, obtained from CIS bio GmbH, IBA Group, Berlin, Germany) were used for injection. Suitably sized particles quickly pass from the interstitial space to the lymph

**Table 1** Distribution of tumour stages in the patient collectives with peritumoral and periareolar injection. The difference in the distribution of tumour stages was not statistically significant (p = 0.29).

| Tumour stage | Peritumoral injection | | Periareolar injection | |
| --- | --- | --- | --- | --- |
| | Number of patients | Relative frequency (%) | Number of patients | Relative frequency (%) |
| Ductal carcinoma in situ | 4 | 2,6 | 6 | 5,1 |
| pT1a | 7 | 4,6 | 3 | 2,6 |
| pT1b | 18 | 11,8 | 9 | 7,7 |
| pT1c | 59 | 38,8 | 44 | 37,6 |
| pT2 | 62 | 40,8 | 48 | 41,0 |
| pT3 | 1 | 0,66 | 3 | 2,6 |
| pT4a | 0 | 0 | 4 | 3,6 |
| pT4b | 1 | 0,66 | 0 | 0 |
| Total | 152 | | 117 | |

capillaries [21]. Phagocytosis of the particles occurs in the intermediary lymph nodes by the reticuloendothelial system of the lymph nodes, which together with mechanical retention of the tracer, is responsible for the concentration of tracer in the first intermediary lymph node(s).

### Injection methods

In 2007 peritumoral injection was used for detection. After palpation, sonographic visualisation of the tumour and disinfection of the skin, fan-shaped peritumoral injection was done at two opposing injection sites together with subdermal injection above the tumour area, where necessary.

After May 2008 the injection method consisted of intradermal, periareolar injection of $^{99m}$Tc nano colloids. Four injections of approx. 0.2 ml of the radiopharmaceutical were done at the transition area of the areola to the normal cutis in the 3, 6, 9 and 12 o'clock positions.

The dosage of the radiopharmaceutical depends on whether intraoperative identification is planned for the same day or for the following day. Approx. 50 MBq is administered if surgery is planned on the same day, and dosages between 150 and 200 MBq are administered if surgery is planned for the following day.

### Scintigraphy

Static images of the chest were obtained 60 to 180 minutes post injection with and without lead coverage of the injection sites. Imaging was done using a dual-head gamma camera. Mapping of the body contours for anatomical orientation was either done with a Co-57 flood source phantom or by tracing the contours of the body with a tracer-filled syringe. Static images were obtained ventrally and laterally with a matrix of $128 \times 128$. The lymph node(s) showing the highest tracer intensity were considered the sentinel lymph nodes, although assessment was done based purely on visual impressions. The sentinel lymph nodes were subsequently tagged with the patient placed in the position for surgery. Tagging was done using a radioactive point source with camera monitoring of the source where the tracer had accumulated. The sites were then marked ventrally using a water-resistant pen so they could be found during surgery.

### Intraoperative detection

Surgery was done in our hospital by one of three experienced surgeons; the same surgeons performed all operations in both periods of data acquisition. All surgeons were experienced in the use of the injection techniques prior to the start of data acquisition as SLN detection in breast cancer patients has been carried out in our hospital since 2003. A gamma probe with a collimator was used for SLN detection intraoperatively to reduce interference from scattered radiation. Alternatively, we used the C-Trak System (Care Wise, Morgan Hill, CA, USA) and the Gamma Finder (World of Medicine AG, Ludwigsstadt, Germany). Using a transcutaneous approach we searched for maximum activity signal in the axilla at the level of the ventral marking. A small skin incision was done and further dissection was then performed with little loss of blood and minimal trauma with repeated use of the gamma probe. Finally the lymph nodes which had accumulated the radionuclide were removed and examined ex vivo for the presence of nuclide accumulation. If several lymph nodes in close proximity to one another showed nuclide accumulation, the nodes were removed by en bloc resection. After the resection of lymph nodes, the site was examined for any remaining activity

and was palpated by the surgeon. If less than 20% of tracer activity in the SLN was still present after SLN resection, this measured amount was considered negligible and no further lymph node dissection was done. If the measured value was higher, additional nodes were removed and considered as SLN.

Obtained specimens were examined intraoperatively; histopathological investigation of frozen sections done by the Institute for Pathology, Cytology & Molecular Pathology of Minden Clinics. In the mean time the primary tumour was resected using either mastectomy or breast conserving surgery. If metastasis was found in a SLN, additional lymph nodes on the affected side were removed. The resected SLN were removed and examined histopathologically. If metastasis was found in an SLN, resection of axillary lymph nodes was done in a second procedure.

### Statistical analysis

Fisher's exact test was used to determine the distribution of tumour stages between the groups and the differences in detection rates. Unpaired t-test was used to determine whether the numbers of detected sentinel lymph nodes differed significantly between groups. A p-value $< 0.05$ was considered significant. The subgroup of multifocal tumours was too small for statistical analysis. Stat View 5.0 (SAS Institute Inc., Cary, NC, USA) and R 2.15.0 (The R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis.

## Results
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### Scintigraphic detection of sentinel lymph nodes

No sentinel lymph node (SLN) was found in 5 women who had peritumoral injection (3.3%, ○ Table 2). One SLN was found in 60 women (39.5%), two SLN were found in 44 women (28.9%) and more than two SLN were found in the remaining women (28%). Three patients additionally showed parasternal lymphatic flow. In the group with periareolar injection one SLN was found in the majority of cases (75/117 patients, 64.1%). Two sentinel lymph nodes were found in 33 women (28.2%), more than two sentinel lymph nodes were only found in 9 patients (7.7%). The mean number of SLN detected scintigraphically after peritumoral injection was significantly higher than after periareolar injection ($1.9 \pm 1.1$ vs. $1.4 \pm 0.7$ SLN, $p < 0.001$).

### Intraoperative detection of sentinel lymph nodes and total number of successful SLN biopsies

No SLN were found intraoperatively after peritumoral injection in 10 patients despite scintigraphic SLN detection. SLN biopsy was successful in 90.1% of patients (○ Table 2). The remaining 15 patients underwent axillary lymph node dissection. After

**Table 2**  Detection rates for SLN biopsy (scintigraphically, intaoperatively, total number).

| Type of injection | Scintigraphic SLN detection | Intraoperative SLN detection | Patients with successful SLN biopsy |
|---|---|---|---|
| Peritumoral | 147/152 96.7% | 137/147 93.2% | 137/152 90.1% |
| Periareolar | 117/117 100% | 115/117 98.3% | 115/117 98.3% |
| p-value | 0.071 (n. s.) | 0.072 (n. s.) | 0.0094 |

n. s. = not significant

periareolar injection, intraoperative detection failed only in 2 patients, resulting in successful SLN biopsy in 98.3% of cases. The difference in the number of successful sentinel lymph node biopsies was significant (p = 0.0094).

In both groups, a mean of 1.9 lymph nodes were considered sentinel lymph nodes intraoperatively and resected (peritumoral group 1.9 ± 1.1; periareolar group 1.9 ± 1.3).

### Metastatic involvement of sentinel lymph nodes

In the patient collective with peritumoral injection, 28 of 137 patients (20.4%) had metastasis in one or more sentinel lymph nodes. In 21 of these 28 patients (75.0%) subsequent systematic lymphadenectomy showed no metastatic involvement in any other lymph nodes. In the collective with periareolar injection the rate of involvement was 29.6% (35/115 patients), a slightly higher percentage but not statistically significant (p = 0.11). In this collective again metastases were limited to the SLN in the majority of patients (19/34 patients, 55.9%).

### Patients with negative SLN biopsy after peritumoral injection

As mentioned above, SLN biopsy was negative in 15/152 patients after peritumoral injection. Eleven of these patients had tumour stage pT2, the others had tumour stage T1. Primary tumours were located in all quadrants, but the majority were in the upper quadrants (in the upper external quadrant in 5 patients and in the upper internal quadrant in 5 patients). Systematic lymphadenectomy in this collective showed lymph node involvement in a high number of cases (7/15 patients, 46.7%). The difference in the rate of involvement of the axillary lymph nodes was borderline significant compared to the total collective with peritumoral injection (p = 0.046).

### Patients with multifocal tumours

12 of 152 patients (7.9%) in the group with peritumoral injection had multifocal tumours. The number was higher in the patient collective with periareolar injection (18 of 117 patients, 15.4%). After peritumoral injection SLN biopsy was negative in 2 of 12 patients (16.7%). The rate of successful SLN detection was therefore lower than in the total collective with peritumoral injection (83.3 vs. 90.1%). In the group with periareolar injection SLN biopsy was negative in one of 18 patients with multifocal tumours (successful SLN detection in 94.4% of patients with multifocal tumours compared to 98.3% of the total collective with periareolar injection). No statistical comparison was done due to the limited number of patients with multifocal tumours.

### Discussion
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The change of injection technique used for sentinel lymph node biopsy in patients with breast cancer was performed in May 2008 in our clinic primarily for practical reasons. One advantage of the periareolar injection technique with regard to small tumours is that the tumour does not have to be palpable or visualised sonographically. Another advantage is that the injection technique remains the same even for multifocal tumours, an important aspect in view of the fact that the numbers of patients with multifocal tumours presenting to our hospital have increased over time. This retrospective analysis aims to investigate whether the change in injection technique has had a negative im-

pact on detection rates and whether the detection rates in our hospital correspond to those reported in the literature.

In our hospital the change of injection method from peritumoral to periareolar injection resulted in a significant improvement in the detection rate for SLN. This is in accordance with the results of the largest multi-centre study on this topic, the FRANSENODE study [18]. The detection rates with a rate of 90.1% for peritumoral injection and of 98.3% for periareolar injection are within the ranges reported in recent studies. In an overview article published in 2011 the reported detection rates ranged from 78 to 99.1% for peritumoral injection and between 92.7 and 100% for periareolar injection [20].

In the group of patients with peritumoral injection it was noticeable that negative SLN biopsy was associated in a large number of cases with axillary lymph node involvement. Out of a total of 15 patients with negative SLN biopsy, 7 (47%) had axillary involvement. This effect was not found in the patients with periareolar injection. In a retrospective analysis published in 2003, Brenot-Rossi et al. also showed that the percentage of patients with axillary lymph node involvement was significantly higher in the group of patients with negative SLN biopsy [22]. It was suggested that the negative SLN biopsy might indicate a blockade of lymph vessels by tumour cells. While insufficient amounts of the tracer pass into the axilla after peritumoral injection, other lymphatic flow paths are available with periareolar injection, so that higher SLN detection rates are possible even with lymph node involvement. However, our patient numbers were not sufficient to allow a more precise analysis. The primary tumours of the patients with negative SLN biopsy were not located in the upper external quadrant in the majority of cases. A masking of axillary lymph nodes by the diffusion of the radiocolloid into tissue, as postulated in other studies for tumours in unfavourable locations in the upper external quadrant [17–19], does not appear to have played any role in our collective.

In both groups the numbers of patients with multifocal tumours were too small for statistical analysis and thus it was not possible to make any definitive statement regarding patients with multifocal tumours. In a retrospective analysis published in 2008, Holl et al. reported a reduced detection rate after peritumoral injection in patients with multifocal tumours [23]. This trend also appears to be detectable in our study; however the numbers of patients are too low for statistical analysis.

It was not possible to determine a false-negative rate in our collectives as no systematic lymphadenectomy was done in patients with negative sentinel lymph node status. Moreover, the follow-up period is still to short to assess the rate of axillary recurrence. The high rate of patients with only SLN involvement may be an indirect indication that the correct lymph node was identified as the sentinel lymph node with both methods. In a recent meta-analysis of studies published between 1993 and 2011 there was no significant difference in the rates of false-negative results after peritumoral and periareolar injection [24].

One of the limitations of the present study is that it is a retrospective data analysis. The patient collectives did not differ significantly with regard to tumour stages; however the study was neither randomised nor were patients assigned according to tumour stage. As this was a retrospective study it was not possible to determine all potential factors which might have influenced successful sentinel detection. Thus, the body mass index (BMI) was not available for all patients, and could therefore not be included in the analysis. As intraoperative detection was done in both groups by the same surgeons, all of whom had several years ex-

perience of SLN biopsy prior to the start of data acquisition, a learning curve which would result in a higher detection rate for the periareolar injection group is unlikely but cannot be completely excluded.

## Conclusion
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Peritumoral and periareolar injection for sentinel lymph node biopsy in patients with breast cancer are currently still considered equivalent. Periareolar injection offers practical advantages: the method is easier to learn, additional imaging of non-palpable lesions is not required, and the intradermal injection technique is less painful. In our collective, periareolar injection additionally proved to result in better SLN detection rates compared to peritumoral injection. Even if our data do not permit determination of the rate of false-negative results, the high number of patients with metastasis in only the SLN indicates that sentinel lymph nodes can be identified correctly with both injection methods.

## Conflict of Interest
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None.

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