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ORIGINAL ARTICLE – BREAST ONCOLOGY

Validation of the S Classification of Sentinel Lymph Node and Microanatomic Location of Sentinel Lymph Node Metastases to Predict Additional Lymph Node Involvement and Overall Survival in Breast Cancer Patients

Astrid Maria Fink, MD[1], Hannes Wondratsch, MD[2], Harald Lass, MD[3], Michael Janauer, MD[4], Paul Sevelda, MD[4], Heinrich Salzer, MD[3], Wolfgang Jurecka, MD[1], Walter Ulrich, MD[5], Andreas Chott, MD[6], and Andreas Steiner, MD[2]

[1]Department of Dermatology, Wilhelminenspital, Vienna, Austria; [2]Department of Dermatology, Krankenhaus Hietzing, Vienna, Austria; [3]Department of Obstetrics and Gynecology, Wilhelminenspital, Vienna, Austria; [4]Department of Obstetrics and Gynecology, Krankenhaus Hietzing, Vienna, Austria; [5]Department of Pathology, Krankenhaus Hietzing, Vienna, Austria; [6]Department of Pathology, Wilhelminenspital, Vienna, Austria

ABSTRACT

Background. Most patients with a positive sentinel lymph node (SN) have no further metastases in the axillary lymph nodes and may therefore not benefit from axillary lymph node dissection. In patients with melanoma, evaluation of the centripetal depth of tumor invasion in the SN, also known as the S classification of SN, and microanatomic localization of SN metastases were shown to predict non-SN involvement. This phenomenon has been less extensively studied in breast cancer. We sought to validate the S classification and microanatomic location of SN metastases in breast cancer patients with regard to their predictive value for non-SN involvement and overall survival (OS).

Methods. A total of 236 patients with positive SN followed by axillary lymph node dissection were reevaluated according to the S classification and the microanatomic location of SN (subcapsular, parenchymal, combined subcapsular and parenchymal, multifocal, extensive) metastases to predict the likelihood of non-SN metastases and OS.

Results. S classification and the microanatomic location of SN metastases were significantly correlated with non-SN status ($P < 0.001$). Especially patients with a maximum depth of invasion $\leq$0.3 mm (stage I according to the S classification) and those with SN metastases only in subcapsular location had a low probability of further non-SN metastases (7.8 and 6.1%) and a good prognosis for OS.

Conclusions. S classification and microanatomic location of SN metastases predicts the likelihood of non-SN involvement. Especially patients with subcapsular or S stage I metastases have a low probability of non-SN metastases and a good prognosis for OS.

Sentinel lymph node biopsy (SLNB) is regarded as the most accurate staging procedure for regional lymph node metastases in breast cancer. False-negative findings are few in number, and the morbidity of SLNB is less than that of axillary lymph node dissection (ALND).[1–8] Therefore, patients without tumor involvement of the SN may be spared the morbidities that result from ALND.[1,2,9,10]

However, if SN contains tumor cells, patients are advised to complete ALND to remove any residual metastatic disease within the non-SNs.[1] Most patients will have no further residual disease, implying that these patients undergo the morbidity of ALND without any benefit from additional axillary clearance.[11–14] If it would be possible to identify, with great accuracy, patients with a very low probability of non-SN involvement despite a tumor-positive SN, ALND could be reserved for those with a substantial likelihood of metastases in the non-SN.

Studies have shown that the quantity of SN metastases is highly predictive for non-SN metastases.[15–25] Although many studies have focused on the maximal diameter of the metastatic tumor deposit or the presence of extranodal

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A. M. Fink, MD
e-mail: astrid.fink@wienkav.at

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spread, a further possibility for quantification of the SN tumor burden is the evaluation of the centripetal depth of tumor cells from capsular location into the SN, also known as the S classification of SN.[16,17,19–30] This classification has been shown to predict the risk of additional positive non-SNs, especially in melanoma patients.[29–33] In a small patient sample, we were able to show that the classification can be applied for breast cancer patients.[34]

In this study, we sought to validate the accuracy of the S classification to predict non-SN status in a patient sample. We also assessed the feasibility of the S classification to determine its relationship to overall survival (OS). Additionally, the microanatomic location of SN metastases within the SN was assessed as an alternative method to predict the patients' non-SN status.[35] Special care was taken to identify patients with positive SN who were unlikely to have further positive non-SN and in whom ALND would probably be unnecessary.

MATERIALS AND METHODS

Study Design

Databases from two breast cancer centers were reviewed to identity all patients with histologically diagnosed breast cancer who had undergone SLNB and subsequent ALND for metastases in the SN. The pathology records were retrospectively reviewed for information on patients and tumor characteristics and SN characteristics. Slides of all patients with positive SN were reassessed according to the S classification and the microanatomic location of SN tumor burden.[29,30,35] The results were correlated with the likelihood of non-SN involvement and OS. The study was approved by the local ethics committee.

Patients

Between 1999 and 2008, prospectively collected data concerning 734 women who had undergone 737 SLNB were reviewed. None of the patients had clinical or radiographic evidence of regional or distant metastases. Patients who had received neoadjuvant therapy before SLNB were excluded. Six patients had elected to undergo bilateral SNs. In all patients, SLNB had been performed by the use of preoperative lymphoscintigraphy and a handheld gamma detection probe and with perioperative use of patent blue if necessary. All SNs were embedded in paraffin and evaluated by step sectioning and staining with hematoxylin and eosin (H&E). SNs with no metastases on H&E staining were stained by immunohistochemistry with antibodies to cytokeratin. If metastases were found in the frozen section, axillary clearance was performed in the same session. Patients with false-negative results on frozen-section diagnosis of SNs underwent axillary clearance in a second operation.

Metastases in the SN were found in 239 patients (32.4%), who were then advised to undergo ALND. Histological specimens of all positive SN were reevaluated. SN slides of three patients could not be retrieved from the archives. Finally, 236 patients with positive SN were reevaluated in our study to predict non-SN status. All patients with positive SNs underwent level I and II ALND. Seventy-seven patients (32.6%) were found to have positive non-SN after complete standard level I and II ALND.

Histological Evaluation of SN

Histological specimens of SN were reassessed by an investigator who was blinded to the patients' clinical data and the outcome of subsequent ALND. The quantity of tumor cells in the SN was reassessed according to various micromorphometric criteria. When more than one positive SN had been removed from a single lymph node basin, the most extensive and/or deepest metastatic deposit was used to categorize that basin.

SN characteristics of positive SN included the size of SN metastases according to the 6th edition of the American Joint Committee on Cancer (AJCC) staging system ($\leq$0.2 mm, >0.2 to 2 mm, and >2 mm), the number of positive SNs, and the presence of extracapsular SN metastases.[36]

The centripetal penetration depth of SN metastases into the SN, also known as S classification, was determined for each positive SN.[30] The S classification includes the maximal distance of tumor cells between the inner layer of the lymph node capsule and the tumor cells within the SN with an ocular micrometer. According to the subcapsular centripetal depth of metastatic cell invasion of the lymph node, three stages were determined on the basis of the S classification: SI, $\leq$0.3 mm; SII, 0.31 to 1 mm; and SIII, >1 mm. S0 signifies the absence of microscopically identifiable tumor cells in the SNs. This simplified version of the original S classification was used because it can be applied for various methods of SN sampling.[30] Patients with extranodal tumor extension were assigned to stage SIII. The highest S classification was used for statistical analysis.

The microanatomic location of tumor deposits within the SN according to the classification, as proposed by Dewar et al., was assessed.[35] On the basis of the anatomic location in the SN, five groups were constituted: metastases with only subcapsular involvement, only parenchymal involvement, combined subcapsular and parenchymal involvement, multifocal metastatic disease, or extensive metastases including those with extracapsular disease. When more than one positive SN had been removed from a

single lymph node basin, the most extensive metastatic deposit was used to categorize that basin.

Statistical Analysis

Data were analyzed by SPSS statistical software for Windows, version 17.0 (SPSS, Chicago, IL). Metric data such as age or survival are presented as means ± SD when normally distributed, or as medians (minimum, maximum) when skewed. Nominal and ordinal data such as the S classification are presented in percentages. Crosstabs and χ^2 tests were used to assess associations between the risk of non-SN metastasis and the S classification, Dewar classification, or the standard histological examination. An unpaired Student's *t*-test was used to compare the ages of the two groups when primary breast cancer had been diagnosed. Kaplan-Meier survival curves and log rank tests were calculated to compare SN-positive and SN-negative patients as well as patients with different S classifications. A *P* value of ≤5% was considered to indicate significance.

RESULTS

A total of 737 SLNBs were performed in 731 women with breast cancer, aged on average 61.1 years (range, 22–93 years). Six patients had bilateral primary disease and underwent a bilateral SN procedure. Patient characteristics are summarized in Table 1.

A total of 236 patients (32%) had at least one positive SN and underwent complete ALND. No patient had positive bilateral SN. After complete ALND, tumor-positive non-SNs were found in 77 patients (32.6%). In the remaining 159 patients (67.4%) who had undergone complete ALND, no further metastases were found. Size of primary breast cancer was significantly associated with the result of SLNB ($P < 0.001$) and ALND ($P = 0.002$).

All specimens of positive SN were reviewed and classified according to the previously described S classification of SN. The risk of non-SN metastases was strongly correlated with centripetal tumor depth according to the S classification ($P < 0.001$). Especially patients with a centripetal tumor depth ≤0.3 mm (SI) were found to have a low risk of further metastases in the non-SNs. Table 2 shows the distribution of the SN tumor burden according to the S classification. There was no significant difference in the frequency of adjuvant therapy regarding SN metastases classified according to the S classification ($P = 0.469$).

Regarding the distribution of microanatomic location of SN metastases according to Dewar et al., the metastatic deposits were subcapsular in 49 patients (20.8%), combined subcapsular and parenchymal in 54 patients (22.9%), parenchymal in 2 patients (0.8%), multifocal in 21 patients

TABLE 1 Patient characteristics

Characteristic	Value
Tumor histology, *n* (%)	
Ductal	544 (73.8)
Lobular	102 (13.8)
Ductal and lobular	18 (2.4)
DCIS	24 (3.3)
Other	49 (6.6)
Tumor classification,[a] *n* (%)	
Tis	26 (3.5)
T1mic	12 (1.6)
T1a	41 (5.5)
T1b	138 (18.7)
T1c	338 (45.8)
T2	169 (22.9)
T3	13 (1.8)
Side of primary breast cancer, *n* (%)	
Right	350 (47.5)
Left	381 (51.7)
Bilateral	6 (0.8)
Tumor grade, *n* (%)	
I	99 (13.4)
II	412 (55.9)
III	208 (28.2)
Unknown	18 (2.4)
Estrogen receptor, *n* (%)	
Positive	620 (84.1)
Negative	116 (15.7)
Unknown	1 (0.1)
Progesterone receptor, *n* (%)	
Positive	531 (72.1)
Negative	201 (27.3)
Unknown	5 (0.6)
SNs	
Mean no. of removed SN	2.26
Range	1–10
Adjuvant therapy, *n* (%)	
Yes	584 (79.2)
No	36 (4.9)
Unknown	117 (15.9)
Positive SN, *n* (%)	236 (32)
Size of SN metastases	
≤0.2 mm	32 (13.6)
0.2–2 mm	67 (28.4)
>2 mm	137 (58.0)
Extranodal disease	62 (26.3)
Adjuvant therapy, *n* (%)	
Yes	196 (83.1)
No	4 (1.7)
Unknown	36 (15.3)

DCIS ductal carcinoma-in-situ; *SN* sentinel node

[a] Tumor classification from Singletary et al [36]

TABLE 2 Rate of additional non-SN positivity according to S classification and microanatomic location

Micromorphometric staging of SN	Additional non-SN involvement, n (%)	*P* value
S stages[a] according to Starz et al.[29,30]		<0.001
SI ($n = 51$)	4 (7.8%)	
SII ($n = 39$)	6 (20%)	
SIII ($n = 155$)	67 (43.2%)	
Microanatomic location of SN metastases according to Dewar et al. [35]		<0.001
Subcapsular ($n = 49$)	3 (6.1%)	
Combined ($n = 54$)	12 (22.2%)	
Parenchymal ($n = 2$)	0 (0%)	
Multifocal ($n = 21$)	9 (42.9%)	
Extensive ($n = 110$)	53 (48.2%)	
Standard histological classification		<0.001
≤0.2 mm ($n = 32$)	3 (9.4%)	
>0.2–2 mm ($n = 67$)	13 (19.4%)	
>2 mm ($n = 137$)	61 (44.5%)	

SN sentinel node

[a] S stages as follows: SI ≤0.3 mm; SII 0.31 to 1 mm; SIII >1 mm

(8.9%), and extensive in 110 patients (46.6%), and were statistically significantly correlated with non-SN status ($P < 0.001$). Especially patients with only subcapsular SN metastases were found to have a low risk of further metastases in the non-SNs (Table 2). There was no significant difference in the frequency of adjuvant therapy regarding SN metastases classified according to the microanatomic location of Dewar et al. ($P = 0.356$).[35]

Standard histological classification of SN also correlated significantly with non-SN status in our study ($P < 0.001$) (Table 2). The lowest frequency of non-SN metastases (9.4%) was found in patients with SN metastases of ≤0.2 mm.

In the present study, all three classifications correlated statistically significantly with the result of ALND. Nevertheless, the sensitivity to predict non-SN metastases was comparable between the three classifications in our study ($P = 1.0$).

At a mean follow-up of 65 months, 74 patients had died, 36 from breast cancer and 32 from other causes such as myocardial infarction, heart disease, pneumonia, major bleeding, and sepsis. The cause of death was unknown in seven patients. Mortality rates were 6.8% in the SN node-negative (2.2% due to cancer) and 16.9% in the SN node-positive group (10.2% due to cancer). Patients with positive SN had a poorer OS than those with negative SN ($P < 0.001$) in respect of cumulative OS and cancer-specific OS (Fig. 1). The ages of both groups at the diagnosis of primary breast cancer were similar ($P = 0.72$).

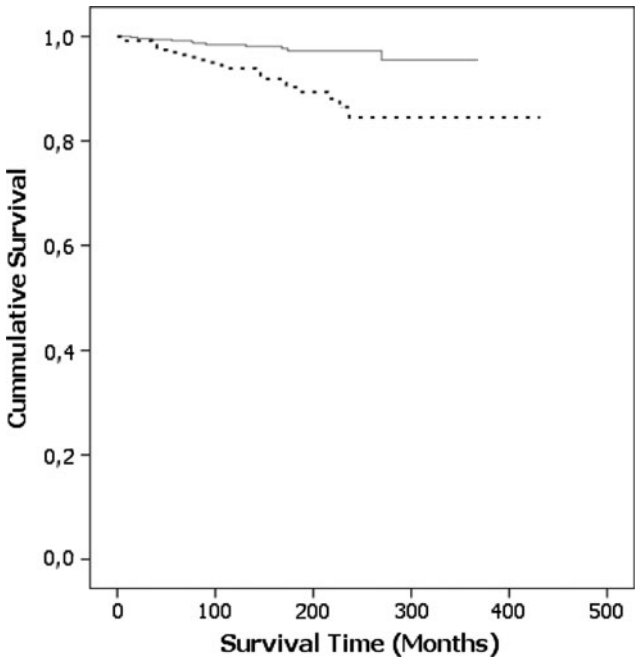

FIG. 1 Carcinoma-specific survival in patients with positive (*dotted black line*) and negative sentinel nodes (*solid gray line*) ($P < 0.001$)

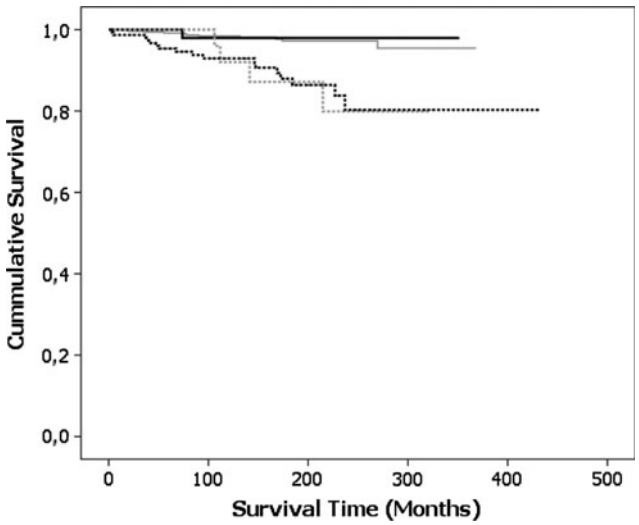

FIG. 2 Carcinoma-specific overall survival in SI-, SII-, and SIII-positive patients, and sentinel node (SN)-negative patients. SN-negative group, *black solid line*; SI, *solid gray line*; SII, *dotted gray line*; SIII, *dotted black line*

Figure 2 shows cancer-specific OS for patients with SI, SII, and SIII disease compared to SN-negative patients. Patients with SI disease had a similar cumulative and cancer-specific OS as SN-negative patients ($P = 0.6$ and 0.8). With regard to the microanatomic location of SN metastases, patients with only subcapsular SN according to

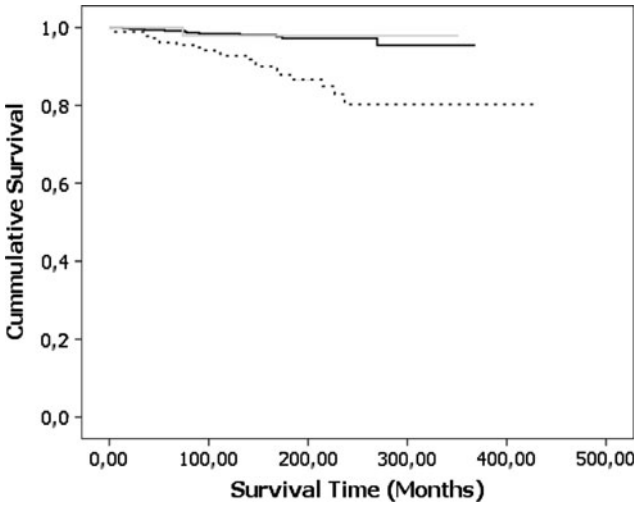

FIG. 3 Carcinoma-specific overall survival according to the microanatomic location of sentinel node (SN) deposits and SN-negative patients. SN-negative group, *solid black line*; subcapsular located metastases, *solid gray line*; nonsubcapsular located metastases, *dotted black line*

Dewar et al. had no significantly different cumulative OS ($P = 0.9$) or cumulative cancer-specific OS ($P = 0.8$) (Fig. 3) compared to those with tumor free SNs.

DISCUSSION

Most breast cancer patients with positive SNs have no additional non-SN involvement.[11–14] The SN tumor burden in particular has been shown to be correlated with non-SN status in the literature.[15–25] Congruent with the information reported in the published literature, 67.4% of patients in the present study had no further non-SN disease after ALND.

Although many studies have focused on the maximal diameter of the metastatic tumor deposit or the presence of extranodal spread, Starz et al. proposed a different classification by measuring the centripetal depth of metastases within the SN to predict non-SN status.[29,30] Another method to evaluate tumor burden is to assess microanatomic location, as previously described by Dewar et al.[35] Both methods of tumor quantification were initially introduced to predict non-SN status in melanoma patients but can also be used in breast cancer patients.[34] Our study was undertaken to validate the S classification and microanatomic location of SN tumor burden to predict non-SN status in breast cancer patients and its impact on OS. We tried to identify a subgroup of patients with SN metastases, but with a very low probability of non-SN involvement.

We found that S classification was a statistically significant predictor of non-SN status and patient outcome. Especially patients with SI disease had a very low risk of further metastases in the non-SN and an excellent OS comparable to those of patients with negative SN. Our results confirm those of several previous studies reporting the predictive value of non-SN involvement and the prognostic impact of the S classification in melanoma patients.[29–33,37,38] The value of the S classification has been scarcely investigated in breast cancer.[34] In our previous study, S stages of positive SN were highly predictive of the likelihood of further non-SNs in a small series of breast cancer patients, with very low risk (zero in our previous study) for SI patients having further metastases in non-SN. In the present study, we were able to validate our previous observation to the effect that S classification predicts non-SN status, although the likelihood of further non-SN metastases in SI patients was 7.8%, which is higher than that registered in our previous study. This may have been due to the larger patient sample of the present investigation. The risk of further non-SN metastases in SI patients was low and within the range of the previously reported false-negative rates for SLNB in multicenter trials (between 7.2 and 12.9%).[1–7,39,40] We suggest that S classification may serve as an additional tool to predict ALND and OS in breast cancer patients. S classification of SN is a reproducible and easy method to determine the quantity of tumor burden within the SN and is associated with excellent interobserver agreement.[38] One limitation of the S classification is that SN with extracapsular spread has not been classified by Starz et al.[29,30] Because extracapsular spread is associated with a high risk of further non-SN and a poorer outcome, we assigned such findings to the SIII category.[17,18]

Dewar et al. proposed a different classification that was based on the microanatomic location of metastases within the SN in melanoma patients.[35] In conformity with the observation in melanoma patients by Dewar et al., in our study, microanatomic location of SN was statistically significantly predictive of further non-SN status involvement in our breast cancer patients and revealed a low probability of non-SN involvement for those with SN metastases confined to a subcapsular site. We observed additional non-SN positivity in 6.1%, a frequency that is similar to previously reported false-negative rates of SLNB.[1–7,39,40] Furthermore, OS in patients with subcapsular metastases was comparable to that in SN-negative patients. Therefore, the microanatomic classification of Dewar et al. seems to be a promising prognostic tool for SN-positive patients. Given these results, we suggest that assessment of the microanatomic location of SN metastases could serve as an additional useful tool to predict ALND and prognosis in breast cancer patients. To our knowledge, there is only one series of patients in whom the microanatomic location of SN was assessed in respect of the non-SN status.[41] Van Deurzen et al. showed a positive correlation between microanatomic location and non-SN status, although the

microanatomic location of SN metastases was not exactly consistent with that proposed by Dewar et al., especially because of the absence of the "multifocal" category in the study by Van Deurzen et al., which is defined as multiple discrete deposits in the SN.[41] In the latter study, the frequency of non-SN involvement in patients with only subcapsular involvement was higher than that registered in our study.

In our study, S classification and microanatomic location of SN metastases statistically significantly correlated with non-SN status. The sensitivity was comparable to the standard histological examination based on the size of SN metastases. Therefore, the additional value of S classification or microanatomic location of SN metastases compared to standard histological classification remains questionable.

There are some recently published results from prospective randomized trials regarding SLNB surgery in breast cancer patients that should be addressed. The NSABP B-32 trial recently demonstrated that SN-negative patients definitively do not benefit from further ALND.[42] The impact of immunohistochemistry (IHC)-detected SN metastases have been investigated in the ACOSOG Z0010 trial of the American College of Surgeon Oncology Group. Recently published data of the ACOSOG Z0010 trial showed that SN metastases only detected by IHC have no marked effect on OS. Patients with metastases only detectable with IHC have the same OS as H&E-negative patients.[43] In our study, 27 patients (11.3%) had SN metastases only detected by IHC with an OS comparable with SN negative patients in our study ($P = 0.245$). The ACOSOG Z0011 was designed to investigate whether ALND was beneficial in patients with positive SLNB. Although the study was closed because of poor accrual, no clinical benefit could be proved for ALND regarding disease-free survival and OS.[44] Tumor deposits in the SN of $\leq$0.2 mm and micrometastases (defined as metastases >0.2 to $\leq$2.0 mm), have been considered separate categories in the current 6th edition of the AJCC staging system.[36,45] In our study, carcinoma-specific survival in SN metastases of $\leq$0.2 mm was comparable to SN-negative patients ($P = 0.578$), whereas patients with micrometastases had a statistically significant worse OS ($P = 0.001$) compared to SN-negative patients.

The study is limited by its retrospective design. However, the latter was the most efficient means of verifying different microanatomic classifications of SNs in a large sample of breast cancer patients. Although patients with SI disease or only subcapsular SN involvement had excellent survival, comparable to that of SN-negative patients, the mean follow-up period of 65 months was probably too short to draw conclusions about long-term survival. Furthermore, we did not evaluate disease-free survival and were therefore unable to draw any conclusions about recurrent disease. Patients with a minimal SN tumor burden may experience recurrent disease earlier than SN-negative patients. If this is true, then patients with SI or subcapsular metastases in the SN should not be treated as node-negative patients, because it seems to represent a biologically more aggressive type of disease with a substantially shorter period until recurrence. To our knowledge, this is the first study investigating both classifications in a large sample of breast cancer patients.

In conclusion, we were able to validate the S classification of SN and microanatomic location of tumor deposits in SN as a method to predict non-SN status in breast cancer patients. Although no subgroup was entirely devoid of the risk of further non-SN, patients with a centripetal tumor depth of $\leq$0.3 mm (SI) or patients with only subcapsular metastases had a very low risk of further non-SN status and a similar OS to SN-negative patients. Further large-scale prospective trials will be needed to confirm these results and possibly spare patients the morbidity of ALND with a positive SN.

DISCLOSURE The authors declare no conflict of interest.

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