The Breast Journal

ORIGINAL ARTICLE

Predictors of Invasion and Axillary Lymph Node Metastasis in Patients with a Core Biopsy Diagnosis of Ductal Carcinoma In Situ: An Analysis of 255 Cases

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■ **Abstract:** The diagnosis of ductal carcinoma in situ (DCIS) using core biopsy does not ensure the absence of invasion on final excision. We performed a retrospective analysis of 255 patients with DCIS who had subsequent excision. Clinical, radiologic, and pathologic findings were correlated with risk of invasion and sentinel lymph node (SLN) metastasis. Of 255 patients with DCIS, 199 had definitive surgery and 52 (26%) had invasive ductal carcinoma (IDC) on final excision. Extent of abnormal microcalcification on mammography, and presence of a radiologic/palpable mass and solid type of DCIS were significantly associated with invasion on final excision. Sentinel lymph node biopsy was performed in 131 (65.8%) patients of whom 18 (13.4%) had metastasis. Size of IDC and extent of DCIS on final pathology were significantly associated with positive SLN. Micrometastasis and isolated tumor cells comprised majority (71.4%) of the metastases in DCIS. SLN biopsy should be considered in those with high risk DCIS. ■

Key Words: Ductal carcinoma in situ, invasion, metastasis, sentinel lymph node biopsy

Ductal carcinoma in situ (DCIS) is a clonal proliferation of malignant cells confined to the ductal-lobular units without invading the periductal stroma. It accounts for approximately 20% of newly diagnosed breast cancers (1).

The core biopsy (CB) is a minimally invasive procedure for evaluating patients with abnormal breast lesions. Although fairly accurate, the diagnosis of DCIS using CB does not ensure the absence of invasion on final excision. The risk of invasion in patients with DCIS ranges from 5% to 44% in various studies (2–9).

Sentinel lymph node (SLN) mapping and biopsy are effective and accurate methods for evaluating the status of axillary lymph nodes in patients with invasive carcinoma (10). The role of SLN biopsy in patients on CB of DCIS has been the subject of much debate (3,6–9,11–13). An argument in favor of SLN biopsy is that a significant number of these patients will have invasive carcinoma on excision, and if it is not performed, an upstaging to invasive carcinoma will require additional surgery, and accurate SLN mapping could be compromised. On the other hand, for the majority of patients with a final diagnosis of DCIS, SLN biopsy may cause unnecessary risk with questionable benefits. Several studies have shown that extent/size of DCIS, comedonecrosis, and high nuclear grade are predictors of invasive carcinoma and/or SLN metastasis (2–9,11–15).

We retrospectively analyzed clinicopathologic characteristics of patients with a diagnosis of DCIS to: (a) determine the incidence of invasive carcinoma on final excision; (b) identify predictors for invasive carcinoma and SLN metastasis and (c) determine the significance of SLN metastasis in this group of patients.

MATERIALS AND METHODS

Medical records from patients with a CB diagnosis of DCIS were retrieved from the computerized laboratory information system of the University of Texas Southwestern (UTSW) Medical Center and Parkland Memorial Hospital at Dallas from January 2000 to August 2007. This study was approved by the Institutional Review Board (IRB). A total of 255 patients with a CB diagnosis of pure DCIS were retrospectively analyzed. Patients with a past history of DCIS or invasive carcinoma and those who had surgery else-

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DOI: 10.1111/j.1524-4741.2011.01069.x

where were excluded from this study. Of this group, 199 (78%) patients had definitive surgery. Patient's characteristics such as age, laterality of disease, mammographic findings including the presence of mass lesion, extent of suspicious microcalcification, and abnormal density, were recorded in each case.

All core biopsy specimens were obtained by radiologists under ultrasound or stereotactic guidance. Specimens were fixed in 10% buffered formalin and processed in a routine manner. Sections were stained with standard hematoxylin and eosin (H&E) and three deeper levels were obtained in all cases. Immunohistochemical stainings for myoepithelial markers (p63 and smooth muscle myosin) were performed if there was a suspicion of invasion. Histologic findings on all core biopsies were reviewed. These include architecture of DCIS, nuclear grade, presence of necrosis, microcalcifications, and extent of DCIS. Pathologic findings of the 199 patients who had definitive surgery were reviewed. In each case, the type of surgery, presence of invasive carcinoma, size, grade, histologic types, and sentinel lymph node status were noted. The size/extent of DCIS, pattern, grade, and presence of necrosis were also noted.

Sentinel lymph node biopsy was performed in 131/199 (65.8%) patients. The numbers of SLNs and the presence or absence of metastases were reviewed. The SLNs were entirely submitted for routine processing and detailed analysis was performed. Three serial sections at 100-micron intervals were evaluated by H&E, and cytokeratin immunostaining using AEI/AE3 and CAM5.2 antibodies was performed on those cases that were negative for routine H&E.

All SLN biopsy specimens were staged according to the sixth edition AJCC Cancer Staging Manual. Tumor deposits were characterized as macrometastasis (>2 mm, pN1), micrometastasis (>0.2 and <2 mm, pN1mi), and isolated tumor cells (<0.2 mm, pN0(i+)).

Descriptive statistical techniques were used to evaluate frequency distribution. Statistical analysis was performed using a 2-tailed Fisher exact test for categorical variables and a 2-tailed unpaired *t*-test for continuous data (Graphic Pad Prism 5.0). All p values less than 0.05 were considered statistically significant.

RESULTS

A total of 255 women had core biopsy diagnosis of DCIS, of whom, 199 had definitive surgery and 56 patients were lost to follow-up. Median age is 55, and range (32–92) years. Fifty-two (26.1%) of the 199 patients had invasive carcinoma on final excision, of whom, 41 (20.6%) were frankly invasive and 11 (5.5%) were microinvasive carcinoma. In 126 (63.3%) patients, the diagnosis of DCIS was unchanged on final pathology. No residual tumor was found in 21 of 199 patients (10.6%). The management and final pathologic diagnoses are summarized in Figure 1.

Ductal Carcinoma In Situ versus invasive carcinoma on Excision

Table 1 compares clinical/radiologic and pathologic characteristics of women with DCIS versus invasive

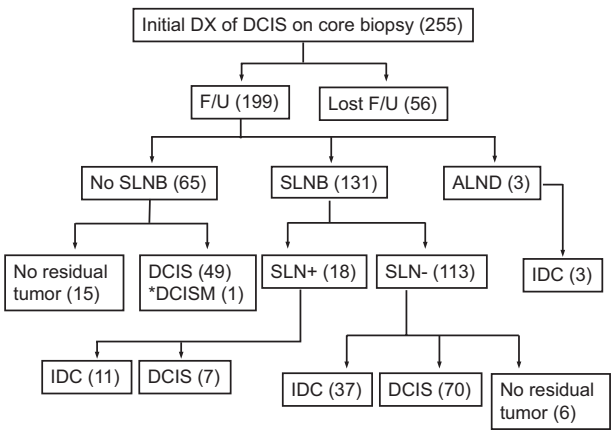

Figure 1. Management and final diagnoses of patients with DCIS using core biopsy. Numbers indicate number of patients in each category. DCISM, DCIS with microinvasion.

Table 1. Comparison of Clinical/Radiologic and Histologic Characteristics of DCIS versus Invasive Ductal Carcinoma (IDC) on Final Excision in Patients with a CB Diagnosis of DCIS

	IDC (52)	DCIS (126)	p value
Mean age (years)	54.7 ± 1.60	57.1 ± 0.934	0.170[a]
Radiologic/clinical findings			
Presence of mass lesion*	19 (36.5%)	26 (20.6%)	0.0364[b]
Size of mass lesion	3.25 ± 0.419	2.45 ± 0.349	0.147[a]
Extent of microcalcifications (cm)*	2.92 ± 0.815	72.05 ± 0.210	0.031[a]
Biopsy method*			0.013[b]
Stereotactic guided	29 (55.8%)	94 (74.6%)	
Ultrasound guided	23 (44.2%)	32 (25.4%)	
Histologic findings on core bx			
High nuclear grade	30 (57.8%)	69 (54.8%)	0.743[b]
Comedo necrosis	37 (71.5%)	83 (65.9%)	0.598[b]
Micropapillary	5 (9.6%)	12 (9.5%)	1.00[b]
Solid**	38 (73.1%)	62 (49.2%)	0.0035[b]
Cribriform	29 (55.8%)	73 (57.9%)	0.868[b]
Type of surgery**			0.0028[b]
Partial mastectomy	30 (55.8%)	101 (80.2%)	
Total mastectomy	22 (42.3%)	25 (19.8%)	

[a]unpaired *t*-test, [b]Fisher's exact test. *p < 0.05; **p < 0.005.

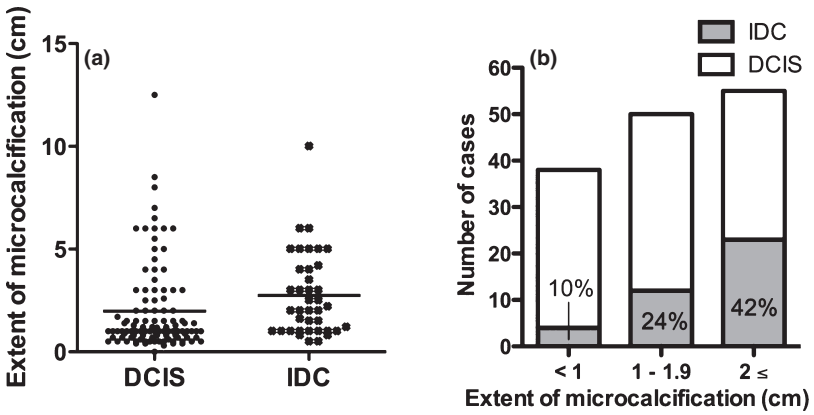

Figure 2. Extent/size of microcalcification on mammography in patients with IC versus DCIS.

carcinoma (IC) on final pathology. In 45 women with clinical or mammographic mass, 19/52 (36.5%) were upstaged to invasive ductal carcinoma (IDC) versus 26/126 (20.6%) with no visible mass. The presence of a mammographic mass was significantly associated with invasion (p = 0.0364). The extent/size of mammographic calcification was significantly high in women with invasive carcinoma (p = 0.031). Figure 2a shows distribution of size/extent of microcalcifications in patients with final diagnosis of DCIS versus IDC. In women with microcalcifications of 2 cm or larger, 42% were upstaged to invasive carcinoma (Figure 2b). In patients with microcalcification less than 1 cm, 10% were upstaged to IDC (Fig. 2b). In women with microcalcifications greater than 2.0 cm and solid-type DCIS, invasive carcinoma was present in 15/32 (47%, not shown in Table).

Comedonecrosis and grade of DCIS were not predictive of invasive carcinoma. However, solid-type DCIS was significantly higher (p = 0.0035) in women with invasive carcinoma. Although the mean tumor size was larger in women with invasive carcinoma versus DCIS, the differences did not reach statistical significance (p = 0.147).

Women with invasive carcinoma were more likely to have ultrasound-guided biopsy versus those with only DCIS (p = 0.013). Total mastectomy was performed in 42.3% of women with invasive carcinoma versus 19.8% of women with DCIS. The probability of undergoing total mastectomy was significantly higher in patients with invasive carcinoma (p = 0.0028).

Positive versus Negative SLNs

One hundred and thirty-one (65.8%) women underwent SLN biopsy. Table 2 demonstrates clinical/radiologic and pathologic features of women with positive (n = 18) versus negative SLNs (n = 113). The incidence of positive SLN in patients with a CB diagnosis of DCIS was 13.7% (18/131). Presence of mammographic mass was more frequent in the positive SLN group; however, this finding did not reach statistical significance. The extent of mammographic microcalcification was significantly higher in patients with positive SLN versus the negative (p = 0.041). There was no significant association of grade of DCIS, comedonecrosis, and pattern of DCIS with risk of SLN metastasis. Presence of invasive carcinoma, size of invasive carcinoma, and extent of DCIS on final pathology were significantly higher in the positive versus the negative SLN group. Figure 3a illustrates individual extent/size of DCIS on excision specimens in positive SLN group, negative SLN group, and no sentinel lymph node biopsy (SLNB) group. In Figure 3b, comparison is made of the extent/size of

Table 2. Comparison of Clinical/Radiologic and Pathologic Characteristics of Patients with Positive SLN versus SLN Negative Cases

	(+) SLN (18)	(-) SLN (113)	p value
Mean age (years)	55.7 ± 0.98	52.5 ± 2.69	0.230[a]
Clinical & radiologic findings			
Presence of clinical/radiologic mass lesion	7 (38.9%)	28 (24.8%)	0.252[b]
Size by radiologic/clinical estimate	3.03 ± 0.694	2.64 ± 0.32	0.599[a]
Extent of microcalcification (cm)	4.12 ± 0.83	2.59 ± 0.24	0.041[a]
Pathologic findings on core biopsy			
Presence of high nuclear grade	7 (38.9%)	67 (59.3%)	0.312[b]
Presence of comedonecrosis	12 (66.7%)	80 (70.8%)	0.783[b]
Solid	13 (72.2%)	61 (54.0%)	0.202[b]
Cribriform	11 (61.1%)	61 (54.0%)	0.619[b]
Micropapillary	1 (5.6%)	12 (10.6%)	1.00[b]
Pathologic findings on final excision			
Upstaging to IC*	11 (61.1%)	37 (32.7%)	0.033[b]
Size of IC (cm)*	2.67 ± 0.87	1.15 ± 0.21	0.016[a]
Extent/size of DCIS (cm)**	6.09 ± 0.65	3.27 ± 0.27	0.002[a]

[a]unpaired *t*-test, [b]Fisher's exact test. *p < 0.05; **p < 0.005.

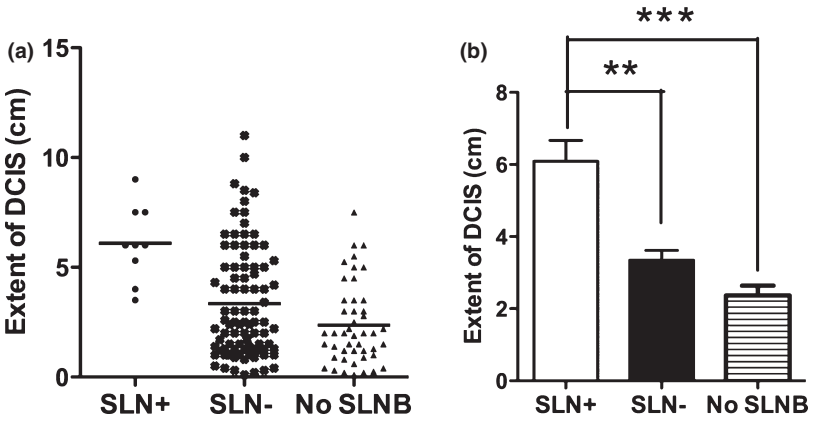

Figure 3. Extent/size of DCIS on surgical specimens in patients with positive SLN (SLN+) versus negative SLN (SLN-) and no SLN biopsy (B: **p < 0.001, ***p < 0.0001, one-way ANOVA followed by Tukey's multiple comparison post hoc test).

Table 3. Clinicopathologic Characteristics of Cases with Final Diagnoses of DCIS and Positive Sentinel Lymph Node

Surgical procedure	Size of DCIS	Histologic type & grade	SLN	ALND
Modified radical mastectomy	7.5 cm	Micropapillary, low & intermediate grade	Macrometastasis	0/9
Partial mastectomy	5.3 cm	Solid with necrosis, high grade	Micrometastasis	ND*
Modified radical mastectomy	4.0 cm	Solid with necrosis, high grade	Micrometastasis	0/17
Partial mastectomy	9.0 cm	Solid with necrosis, high grade	Micrometastasis	ND
Partial mastectomy	6.0 cm	Solid and micropapillary, high grade	Isolated tumor cells	ND
Partial mastectomy	3.5 cm	Solid and cribriform with necrosis, Intermediate grade	Isolated tumor cells	ND
Simple mastectomy	3.5 cm	Clinging and cribriform, high grade	Isolated tumor cells	ND

*ND, Not Done.

DCIS in positive SLN versus the negative group, and no SLNB group ($p = 0.0001$, $F = 10.38$, one way ANOVA followed by Turkeys multiple comparison post hoc test).

Analysis of Positive SLN

The total number of positive SLNs was 21 from 18 patients. Ten of 21 SLNs (48%) were macrometastasis (size >2 mm), 4 (19%,) were micrometastasis (>0.2 and <2 mm), and 7 (33%) were isolated tumor cells (<0.2 mm). The IDC group showed a higher percentage of macrometastasis 8/14 (57.1%) versus the DCIS group 2/7 (28.5%). However, this finding did not reach statistical significance, possibly due to small sample size ($p > 0.05$, Fisher's exact test). Isolated tumor cells and micrometastasis were more frequent in patients with DCIS – 5/7 (71.4%) versus the IDC group 6/14 (42.8%). Clinicopathologic characteristics of the seven patients with a final diagnosis of DCIS and positive SLN are shown in Table 3.

DISCUSSION

The rate of upstaging to invasive carcinoma on final pathology in our study with core biopsy diagnosis of DCIS is 26%; this is consistent with the overall average of 20% reported in the current literature (2–5). In a recent study by Rutstein et al., the rate of upstaging was 8% (2). The low rate of upstaging in their study was due to a high number of tissue cores obtained at the time of biopsy. In our study, the average number of tissue cores is 3–5. We did not attempt to correlate the number of cores and the rate of upstaging to invasive carcinoma.

Identifying clinical and pathologic features that can predict invasion in patients with a diagnosis of DCIS using CB is important for appropriate management, particularly the need for axillary staging by sentinel lymph node biopsy. In our study, the presence of a palpable or mammographic mass was found to be significantly associated with invasive carcinoma on final excision. Several studies have shown that the presence of a mass lesion on breast imaging was a significant predictor for invasion on final excision (16,17).

Size of the tumor by mammographic/clinical estimates did not show a significant correlation with invasive carcinoma on final excision in this study. However, the mean tumor size was 3.2 cm, which is much smaller than in previous studies (2–4,9). In the study by Dillon et al., the median tumor size did not show significant

correlation with upstaging to invasive carcinoma (4). However, tumors measuring 5.0 cm or greater were more likely to harbor invasive carcinoma. Yen et al. (3) demonstrated that mammographic size of 4.0 cm was a predictor of invasion. Similarly, in a study by Yi et al. (9), DCIS size greater than 5.0 cm was an independent predictor of invasion on final excision.

The extent of microcalcification was significantly associated with invasive carcinoma on final excision in this study. Lagios et al. (17) showed that the incidence of invasion is higher in those with microcalcifications larger than 25 mm. In a large study by Stomper et al. (18), 40% of patients with mammographic calcifications of more than 11 mm had invasive carcinoma as compared to 16% with calcifications less than 10 mm. Recently, O'Flynn et al. (19), demonstrated that the risk of invasive disease increased with increasing size of the microcalcification from 20% for size less than 11 mm to 45% for size greater than 60 mm. Dillon et al. (4) showed that calcification with other mammographic abnormalities increased the risk of finding invasive carcinoma on final excision. Contrary to the above findings, Rutstein et al. (2) found no differences in the rate of upstaging to invasive carcinoma following CB, although a patient presented with a mass lesion or microclacifications alone. Similarly, Renshaw (5) found no significant association between the presence of mass lesion or calcification and invasive carcinoma on subsequent excision.

Biopsy cores obtained by ultrasound guidance were more likely to have invasive carcinoma compared with stereotactic biopsy in our study. This is not surprising because ultrasound-guided biopsy is the preferred method of obtaining tissue in patients with mass lesions who are also more likely to harbor invasive carcinoma. Similarly, Dillon et al. (4) demonstrated that 48% of the cores obtained by ultrasound-guided biopsy had invasion on final excision versus 21% by stereotactic technique.

There are conflicting lines of evidence regarding the association of high-grade DCIS and comedonecrosis with the rate of upstaging to invasive carcinoma. Our study showed that the presence of high-grade DCIS and comedonecrosis on CB was not predictive of invasion on excision. Several studies have shown that high-grade DCIS and comedonecrosis on core biopsy were significantly associated with invasion (2,3,7,9,10). In contrast, Dillon et al. (4) found only a slightly higher rate of invasion in those with high-grade DCIS, which did not reach statistical significance; and comedonecrosis was not helpful in predicting invasion on final excision. Similarly, in a study by Goyal et al. (13), grade of DCIS and comedonecrosis did not predict invasion on final excision. In the present study, only solid-type DCIS was significantly associated with invasion, similar to the findings of Dillon et al. (4). Renshaw (5) demonstrated that DCIS with cribriform and papillary architecture were associated with increased risk of invasion, but comedonecrosis alone was not.

Positive SLN was noted in 13.7% of our patients who underwent SLN biopsy. Our rate is comparable to previous studies (7,9,11–15). Extent of abnormal microcalcification was significantly associated with positive SLN. This finding was also a predictor of invasion in our study. The extent of microcalcification on mammography is reflective of the extent of DCIS on pathologic evaluation, and patients with extensive DCIS were significantly associated with positive SLN in our study. Therefore, this may serve as a useful parameter for the decision to perform SLN biopsy in patients with a biopsy diagnosis of DCIS. Several authors have demonstrated that size of DCIS was a predictor of positive SLN (3,9,15,20).

In patients with SLN metastasis, 67% had invasive carcinoma on final excision. Macrometastasis comprised 48% (10/21) of the positive SLN and these were detected by routine H&E. Micrometastasis and isolated tumor cells (ITCs) were noted in 52% (11/21); these were detected only by detailed histologic evaluation and cytokeratin immunohistochemistry.

The increased detection of micrometastases and ITCs in patients that were otherwise negative by conventional H&E has been the subject of extensive debate (21–24). Some investigators have demonstrated a significantly poor prognosis and increased risk of distant metastasis associated with small volume metastasis in patients with IC (22,23). Others have demonstrated no effect on the prognosis and questioned the clinical relevance of ITCs in patients with invasive carcinoma (22,23). Recently, Mittendorf et al. (25) showed that ITCs are true metastasis that may have prognostic significance, particularly, in those with lobular histology. Some authors believe that ITCs may be due to iatrogenic displacement of tumor cells brought about by manipulation of the tumor during surgical procedures (24,26).

The implications of SLN metastasis in patients with DCIS have not been well defined and there are no specific guidelines regarding axillary staging in this

group of patients. Yen et al. (3) noted that 3% of the 99 patients with pure DCIS on final pathology had positive SLN, and all were micrometastasis. All three patients received systemic chemotherapy and one had complete axillary clearance. Yi et al. (9) showed that 1.9% of patients with a final diagnosis of DCIS or microinvasion had positive SLN by routine H&E and immunohistochemical analysis. In our study, the incidence of positive SLN in patients with a final diagnosis of DCIS was 9%. A majority (71%) were micrometastasis and ITCs. Our findings are similar to those in the study by Klauber-DeMore et al. (11), in which 12% of patients with high-risk DCIS had positive SLN and 78% were micrometastasis detected by immunohistochemistry only.

The failure to detect invasion in patients with lymph node metastasis is most likely due to sampling error. Small foci of invasion may go undetected in spite of extensive pathologic evaluation, and high-risk DCIS are more likely to harbor small foci of invasive carcinoma that may go undetected even with thorough sampling. According to Moore et al., SLN biopsy in high-risk DCIS is a means of identifying those who may have unrecognized invasive disease and therefore, at risk for distant disease (15). It has been shown that 1–2% of women with DCIS who develop distant metastasis may represent a subset of patient with positive SLN (15). Therefore, positive SLN in patients with high-risk DCIS may serve as a marker for invasion if it cannot be demonstrated on the breast specimen. In the setting of DCIS, the passive transport of tumor cells to lymph nodes, brought about by previous surgical procedures such as core biopsy, fine needle aspiration, and breast manipulation, is also a remote possibility (26,27). However, an argument against this theory is that passive displacement of tumor cells in SLNs of patient with prior breast manipulation is not as frequent as the procedure itself.

The management of patients with micrometastasis of SLN in patients with DCIS is not yet known. In the study by Yen et al. (3), micrometastasis did not have impact on survival in their patients. They concluded that axillary dissection or systemic chemotherapy is unlikely to improve survival in this group of patients. Given the low probability of metastasis to other non-sentinel lymph nodes, none of our patients with micrometastasis or ITCs underwent axillary dissection or systemic chemotherapy. However, long-term follow-up is required to determine if the metastasis is associated with adverse outcome.

In conclusion, SLN biopsy is not indicated in all patients with a CB diagnosis of DCIS. However, it should be considered in those who are at risk of invasion; this includes women with radiologic/palpable mass and extensive DCIS. In patients with high-risk DCIS, the presence of metastasis in SLN may be indicative of the presence of occult invasion.

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