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ORIGINAL ARTICLE – BREAST ONCOLOGY

A Nomogram to Predict Factors Associated with Lymph Node Metastasis in Ductal Carcinoma In Situ with Microinvasion

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ABSTRACT

Introduction. Ductal carcinoma in situ (DCIS) with foci of invasion measuring ≤ 1 mm (DCISM), represents $< 1\%$ of all invasive breast cancers. Sentinel lymph node biopsy (SLNB) has been a standard component of surgery for patients with invasive carcinoma or extensive DCIS. We hypothesize that selective performance of SLNB may be appropriate given the low incidence of sentinel node (SN) metastasis for DCISM. We investigated the clinicopathologic predictors for SN positivity in DCISM, to identify which patients might benefit from SLNB.

Methods. A retrospective review of the National Cancer Database was performed for cases from 2012 to 2015. Clinical and tumor characteristics, including SN results, were evaluated, and Pearson's Chi square tests and logistic regression were performed.

Results. Of 7803 patients with DCISM, 306 (4%) had at least one positive SN. Patients with positive SNs were younger, more often of Black race, had higher-grade histology and larger tumor size, and were more likely to have lymphovascular invasion (LVI; all $p < 0.001$). In an adjusted model, the presence of LVI was associated with the highest odds ratio (OR) for node positivity (OR 8.80, 95% confidence interval 4.56–16.96).

Conclusions. Among women with DCISM, only 4% had a positive SN. Node positivity was associated with more extensive and higher-grade DCIS, and the presence of LVI was strongly correlated with node positivity. Our data suggest that LVI is the most important factor in determining which patients with DCISM will benefit from SN biopsy.

Over 63,000 new in situ breast cancers were diagnosed in the US in 2017, representing 20–25% of all new breast cancers nationwide.[1–6] Ductal carcinoma in situ (DCIS) with microinvasion (DCISM) is a rare subset of DCIS that presents with microscopic foci of invasion measuring ≤ 1 mm in the longest diameter,[5,7–11] and comprises about 1% of all new breast cancers.[5,7,8,11–15] The term 'microinvasion' was first coined by Lagios in 1982, and was added to the American Joint Committee on Cancer (AJCC) staging classification in 1997 as a specific entity, with the designation 'T1mic'.[1,9,14,16,17] It has been suggested the prognosis is worse than pure DCIS, but better than a true T1 tumor. While among patients with pure DCIS, a 1–2% sentinel node (SN) positivity rate is typically cited and axillary staging is not routinely recommended, the upgrade rate for core biopsy-proven DCIS to invasive cancer at final pathology is at least 20%, hence a significant number of these patients may ultimately undergo axillary staging.[3,16,18–21] A positive node is a significant prognostic factor with implications for

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additional treatment planning, and therefore sentinel lymph node biopsy (SLNB) may be of importance in the decision-making process for systemic therapy in DCISM patients.

Factors associated with the likelihood of SN positivity in the DCISM population are not clearly defined. The American Society of Clinical Oncology (ASCO) guidelines for SLNB in patients with DCIS include patients with > 5 cm of disease on preoperative evaluation, with 'suspected' microinvasion, or when mastectomy is planned as removal of the breast renders subsequent SLNB technically impossible.[22,23] While SLNB in the DCISM population is recommended, there is insufficient evidence to support this indication.[22] The low incidence of this entity has made full characterization of DCISM challenging, and there is no consensus on whether DCISM should be managed as DCIS or as invasive carcinoma. Furthermore, many series were published before SLNB became the standard of care.

Our aim was to identify variables correlated with SN positivity among women with DCISM by analyzing the National Cancer Database (NCDB) and to develop a predictive model for SN involvement in patients with DCISM, allowing for an evidence-based determination of which patients would benefit from SN biopsy.

METHODS

Data Collection and Statistical Analysis

The NCDB was queried for de-identified cases from 2012 to 2015. Inclusion criteria were patients with DCISM who underwent SN biopsy. The NCDB began recording information about both SLNB and ALND, including the number of nodes removed, in 2012.[24] Demographic, clinical, and tumor characteristics, including SN status, were collected. Tumor size refers to the extent of DCIS. Statistical analyses were completed using Pearson's Chi square tests and logistic regression, to identify clinicopathologic characteristics that correlated with SN positivity. All NCDB data are anonymous and de-identified. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Nomogram Development

Binary logistic regression models with bootstrap resampling validation were used to develop a model to estimate the probability of SN positivity. After backwards stepdown validation, predictors that remained in the model were age, race, tumor size, grade, and lymphovascular invasion (LVI). Continuous predictors were tested for linearity and were converted to categorical variables if the relationship was determined to be nonlinear. Categorical variables were collapsed over categories, with no significant differences. To maximize the sample size in the analysis, missing data were coded as unknown. Therefore, race was consolidated into four categories—Asian, White, Black and other/unknown—and the categories of well and moderately differentiated tumor grade were combined, as were poorly differentiated and undifferentiated. For multivariable analysis and nomogram scoring, the DCIS extent categories (1–7 mm or unknown, 8–15 mm, and $\geq$ 16 mm) were defined by iteratively testing different groupings to determine the optimal cut-off, because size was not linearly associated with the probability of node positivity.

Predictive accuracy was measured using the concordance index (c-index), quantifying agreement between predicted values from logistic regression and the observed probability of SN positivity. For this study, over 200 iterations of randomly selected training and test samples were run to calculate the adjusted c-index. The correlation coefficients from the final logistic model were comparatively scaled to correlate to a score of between 0 and 100 to construct the nomogram. The receiver operating characteristics (ROC) curve was used to determine cut-off values for several risk levels. The intermediate risk was selected at the point where the sum of the sensitivity and specificity was the highest; the low risk was selected at the highest sensitivity level where there were still significant differences in the predicted probabilities; and the high risk was the highest specificity level. The regression model and nomogram functions were performed using the rms package in R (version 3.4.0; http://www.R-project.org).

RESULTS

We identified 7803 patients with DCISM, of whom 306 (3.92%) had at least one positive SN and 7497 (96.04%) had negative node(s). The median age of the entire cohort was 58 years (range 20–90 years). Patients with positive SNs were younger, with a median age of 54 years compared with 58 years ($p < 0.001$), and were more often of Black race ($p < 0.001$). Patients with positive SNs were more likely to have larger extent of DCIS, with higher grade histology, and were more likely to have presence of LVI ($p < 0.001$ for all comparisons). There were no differences in estrogen receptor (ER), progesterone receptor, or HER2/neu receptor status between SN-positive and SN-negative patients. Patients with positive SNs were significantly more likely to have undergone mastectomy ($p < 0.001$). Approximately half of the patients with positive SNs went on to completion axillary lymph node dissection (ALND), while 13% of patients who had

negative SNs also had ALND. The median number of positive lymph nodes was similar between both the SN-positive and SN-negative groups (1.0 vs. 1.5) (Table 1).

In an adjusted model, several variables were associated with an increased odds ratio (OR) for nodal positivity. Black race was associated with an OR of 3.3 (95% confidence interval [CI] 1.75–6.26) for positive SNs, while poorly differentiated histology was associated with an OR of 1.36 (95% CI 1.04–1.78). Greater extent of DCIS was also associated with nodal involvement, with DCIS $\geq$ 16 mm having an OR of 3.81 (95% CI 2.57–5.65) for SN positivity. However, LVI had the greatest likelihood of nodal positivity, with an OR of 11.45 (95% CI 7.87–16.66) (Table 2). Type of surgery was non-significant in multivariable analysis, with an OR of 1.25 (95% CI 0.75–2.07; $p = 0.395$), and was therefore not included in the development of the nomogram.

The nomogram is depicted in Fig. 1. The adjusted c-index was 0.71, indicating an acceptable model for the prediction of SN positivity. Age, race, DCIS extent, grade, and LVI are all assigned point values, enabling classification of each patient into one of the categories: low (41–60 points), moderate (61–124 points), or high ($\geq$ 125 points) risk for the presence of a positive SN. The expected range of nodal positivity for each group is as follows: low (1.966–3.148%), moderate (3.151–13.405%), and high ($\geq$ 13.405%). The low-risk cut-off has a specificity of 21% and sensitivity of 93%, while the high-risk cut-off has a specificity of 98% and a sensitivity of 25%, for predicting SN involvement. The negative predictive value (NPV) was high, using all three cut-offs ($\geq$ 97%), while the positive predictive value (PPV) increased from 5% using the low-risk cut-off, to 29% using the high-risk cut-off.

DISCUSSION

The optimal management strategy for axillary staging in patients with DCISM is unclear. We identified factors associated with SN positivity in a large national database and built a predictive model to address this issue. We found only a small percentage of patients who underwent axillary staging had positive SNs (4%). Younger age, greater extent of DCIS, Black race, high-grade histology, and LVI were all significant predictors. Many of these features have previously been noted to be both predictors of SN involvement with DCIS or DCISM, and predictors of microinvasion in patients with pure DCIS on core biopsy. Overall, these variables are suggestive of more aggressive biology.[4,5,16,21,24–27]

Multiple studies have identified features that demonstrate a more aggressive biology in DCISM compared with pure DCIS, including tumors > 5 cm, high-grade histology, comedo necrosis, microcalcifications, and the presence of SN metastases.[5,12,13,16,21,25,28–30] DCISM patients tend to have a greater extent of disease than pure DCIS and are more commonly diagnosed with a palpable mass.[10,28] An association between negative-hormone receptor (HR) status, microinvasive disease, and positive SNs has also been reported, which has led some authors to suggest that ER-negative patients may benefit more from SLNB than ER-positive patients.[1,13,24,31,32] In a single-institution review of 174 cases of DCISM, Orzalesi and colleagues found no correlation between DCISM and HR-subtype,[33] and, in our cohort, HR status was not found to be significantly associated with nodal positivity among DCISM patients. LVI was the strongest predictor of SN positivity in our study, which is corroborated by several previous publications.[33] Matsen and colleagues also found that LVI was a predictor of a positive SLN, with an OR of 10.83, while Ko et al. found LVI and ER positivity were predictive factors.[33–35] DCISM is defined pathologically by the presence of one or more invasive disease foci measuring $\leq$ 1 mm. The classification system does not distinguish cases in which there are multiple foci of microinvasion.[16] It is possible that more aggressive tumors may have multiple foci of microinvasion at the time of diagnosis, and this may contribute to locoregional spread. Only a few authors have noted an association of SN positivity with multifocal microinvasion.[13,31]

Various series have found DCISM to have axillary node positivity rates ranging from 0 to 20%.[1,5,11,13,15,16,29,36–38] A recent meta-analysis of 968 patients by Gojon et al. reported a 3.2% rate of SLN macrometastasis among patients with DCISM, and a 5.6% overall rate of LN positivity, which supports our findings.[37] Magnoni and colleagues report an overall 12.1% rate of axillary nodal involvement, with rates of macrometastasis of 1.9%.[15] In terms of outcomes, Pu et al. reported a 5-year survival rate of over 99% in their cohort, while Matsen et al. reported a 96% 5-year recurrence-free survival rate.[5,35] Larger tumor size was associated with poorer overall disease-free survival and breast cancer-specific survival.[5] These authors concluded that given the low rates of nodal positivity, rates of distant metastasis < 2%, and overall excellent prognosis, routine SLNB for DCISM is not warranted and the decision for SLNB should be individualized.[37] In their recent review of DCISM compared with DCIS, Kim et al. concluded that although patients with DCISM should undergo axillary staging, like invasive carcinomas, they have outcomes similar to pure DCIS and should be treated and followed-up as DCIS patients.[13] However, two long-term studies demonstrated that breast cancer-specific outcomes are worse among DCISM patients. Sopik et al. found that at 20 years of follow-up, DCISM had double the breast cancer-specific mortality compared with DCIS

TABLE 1 Association of clinicopathologic variables and lymph node positivity in patients with DCISM who underwent sentinel lymph node biopsy

Variable	Sentinel node-positive (n = 306)	Sentinel node-negative (n = 7497)	p value
Median age, years (range)	54 (20–86)	58 (22–90)	< 0.001
Race/ethnicity			< 0.001
White	204 (67.11)	5651 (75.72)	
Black	68 (22.37)	881 (11.8)	
Asian	13 (4.28)	487 (6.53)	
Hispanic	18 (5.92)	381 (5.11)	
Other	1 (0.33)	63 (0.84)	
Year of diagnosis			0.787
2012	69 (22.55)	1757 (23.44)	
2013	72 (23.53)	1870 (24.94)	
2014	79 (25.82)	1951 (26.02)	
2015	86 (28.10)	1919 (25.60)	
Facility type			0.133
Community	17 (6.32)	573 (8.03)	
Comprehensive community	98 (36.43)	2961 (41.48)	
Academic	124 (46.10)	2804 (39.28)	
Integrated network	30 (11.15)	801 (11.22)	
Insurance			< 0.001
None	8 (2.64)	96 (1.29)	
Private	199 (65.68)	4726 (63.59)	
Medicaid	31 (10.23)	398 (5.36)	
Medicare	61 (20.13)	2127 (28.62)	
Other	4 (1.32)	85 (1.14)	
Surgery type			< 0.001
Breast conservation	82 (26.80)	3961 (52.83)	
Mastectomy	224 (73.20)	3536 (47.17)	
Axillary node dissection			< 0.001
Yes	158 (51.63)	985 (13.14)	
No	148 (48.37)	6512 (86.86)	
Number of patients with any positive node	302 (98.7)	54 (0.7)	< 0.001
Lymphovascular invasion	59 (24.69)	116 (1.94)	< 0.001
Extent of DCIS (tumor size), mm [mean (range)]	14.99 (1–100)	4.03 (1–120)	< 0.001
Grade			< 0.001
I (well-differentiated)	27 (13.30)	960 (21.75)	
II (moderately differentiated)	75 (36.95)	1896 (42.96)	
III (poorly differentiated)	98 (48.28)	1504 (34.08)	
IV (undifferentiated)	3 (1.48)	53 (1.2)	
Estrogen receptor			0.485
Positive	205 (67.88)	5083 (69.76)	
Negative	97 (32.12)	2203 (30.24)	
Progesterone receptor			0.960
Positive	168 (56.19)	3994 (56.33)	
Negative	131 (43.81)	3096 (43.67)	
HER2/neu receptor			0.976
Positive	90 (37.34)	1713 (37.44)	
Negative	151 (62.66)	2862 (62.56)	

Data are expressed as n(%) unless otherwise specified

DCIS ductal carcinoma in situ, *DCISM* microinvasive DCIS

TABLE 2 Multivariable analysis of clinicopathologic factors associated with node positivity among patients with DCISM who underwent sentinel lymph node biopsy

Variable	Node-positive (n = 306) (%)	Node-negative (n = 7497) (%)	Multivariable p value	OR (95% CI)	Nomogram score
Median age, years (range)	54 (45–63)	58 (50–66)	< 0.001	0.98 (0.97–0.99)	0.78 × each year under 90
Race/ethnicity					
Asian	13 (4)	489 (6)	Reference	Reference	0
White	219 (72)	5988 (80)	0.094	1.66 (0.92–3.02)	21
Other/unknown	6 (2)	131 (2)	0.209	1.92 (0.69–5.29)	27
Black	68 (22)	889 (12)	< 0.001	3.31 (1.75–6.26)	49
Grade					
Well to moderately differentiated or unknown	205 (67)	5940 (79)	Reference	Reference	0
Poorly differentiated and undifferentiated	101 (33)	1557 (21)	0.024	1.36 (1.04–1.78)	13
Lymphovascular invasion					
Absent	180 (59)	5871 (78)	Reference	Reference	0
Unknown	67 (22)	1510 (20)	0.013	1.44 (1.08–1.93)	15
Present	59 (19)	116 (2)	< 0.001	11.45	(7.87–16.66)
100					
Tumor size					
1–7 mm or unknown	246 (80)	7181 (96)	Reference	Reference	0
8–15 mm	12 (4)	124 (2)	0.003	2.66 (1.41–5.01)	40
16 mm or larger	48 (16)	192 (2)	< 0.001	3.81 (2.57–5.65)	55

DCISM microinvasive ductal carcinoma in situ, *OR* odds ratio, *CI* confidence interval

(3.8% vs. 6.9%), and similar mortality as those with small invasive cancers.[32] Similarly, Wang et al. found a 20-year cancer-specific mortality rate of 4% in DCIS and 9.65% in DCISM, suggesting that greater attention to nodal disease burden and adjuvant therapy may be of importance in this population.[39]

The use of adjuvant systemic therapy among DCISM patients is varied. Lyons et al. found that 57% of patients with any positive SNs received adjuvant chemotherapy, which increased to 100% among those specifically with macrometastases.[14] Their study reviewed patients treated from 1996 to 2004, before the use of genomic profiling and targeted therapy. Pu et al. found that treatment with adjuvant chemotherapy did not impact disease-free survival.[5] With the release of the TAILORx trial, most patients with early-stage, HR-positive, node-negative invasive disease will now forgo chemotherapy.[40] Furthermore, recent work by Wang et al. has also suggested that low OncotypeDX scores are also prognostic among patients with T1-2N1 disease. In the future, many of these patients will also avoid chemotherapy [41–43] and the potential influence of a positive SLNB on DCISM treatment planning is likely to be very small.[14,40]

One unusual finding of our review was that 13% of patients with a negative SLNB underwent ALND, and several were found to have positive nodes. The reasons for this are unclear as these may have been patients with a negative SN but a positive non-sentinel or clinically suspicious node, leading to performance of an ALND. However, this is not a unique finding among studies utilizing the NCDB. In their study of axillary surgery among the DCIS population using the NCDB, Miller et al. found that 11% of patients undergoing mastectomy were treated with an ALND. The authors postulate that these may have been patients in which there was a high preoperative possibility or clinical suspicion of invasive disease, and the

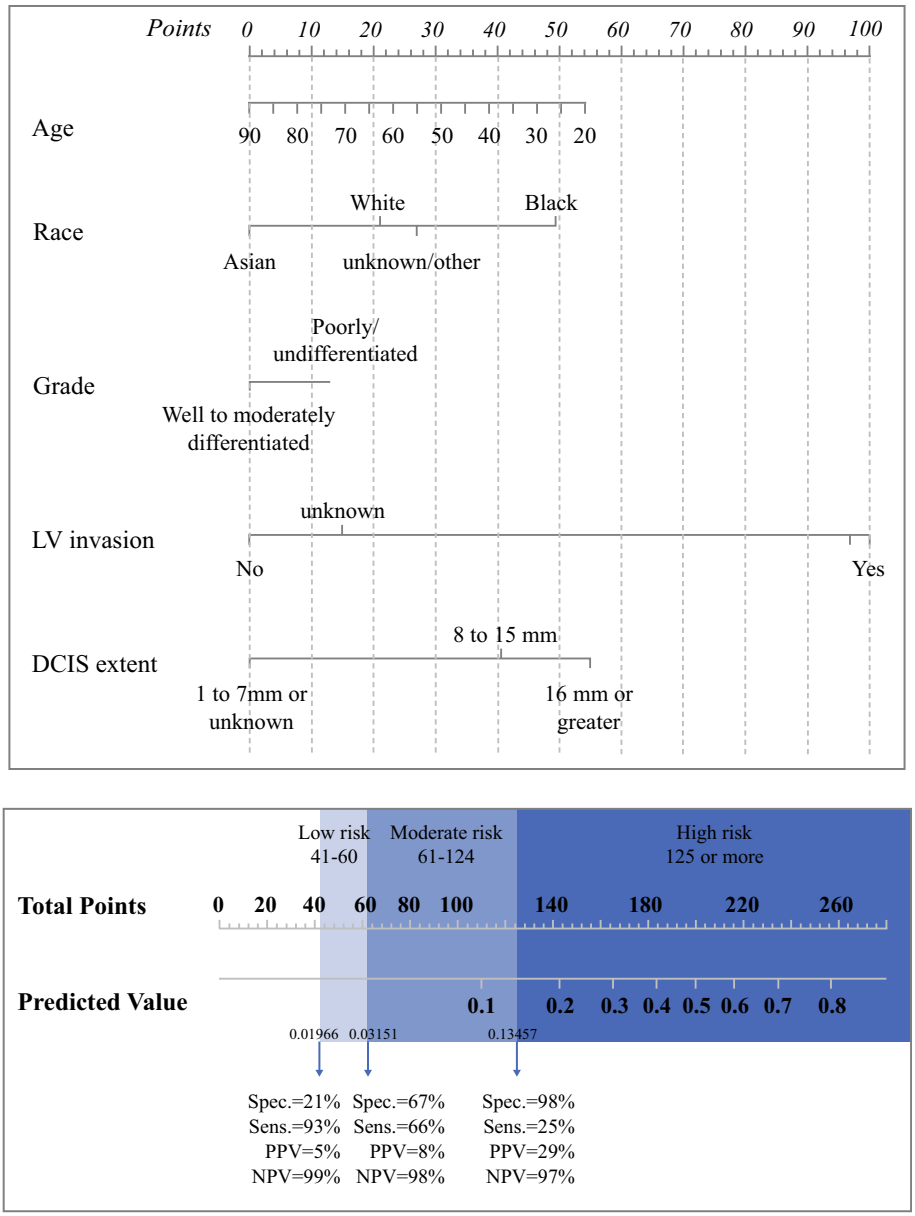

FIG. 1 Nomogram for the prediction of positive sentinel lymph node biopsy in patients with DCISM. *DCIS* ductal carcinoma in situ, *DCISM* microinvasive DCIS, *LV* lymphovascular, *Spec.* specificity, *Sens.* sensitivity, *PPV* positive predictive value, *NPV* negative predictive value

surgeon exercised judgment in deciding a concurrent ALND.[24] Positive SNs were also associated with mastectomy in our study. Mastectomy is more often performed for very large-volume DCISs, which are more likely to have microscopic invasion and the potential for positive SNs. Interestingly, in our dataset, although, as expected, a very small number of SN-negative patients were found to have other positive lymph nodes (0.7%), these patients had a significantly higher median number of positive nodes and range of positive nodes when compared with SN-positive patients. With the data available in the NCDB, it is difficult to comment on these cases further.

The first model to assist in the prediction of SN metastases was introduced in 2007 and became a part of routine clinical practice.[44] In this study, we propose a nomogram to predict which patients with DCISM would benefit from SN biopsy. Application of our model to a theoretical sample of 1000 patients is demonstrated in Table 3. Using estimates from our data, 39 patients are expected to have positive SNs. Based on the low risk cut-off, 800 patients would have SLNB, including 36 of the predicted positive patients. Three predicted positive patients would be missed, and 197 patients would be spared unnecessary surgery. With the moderate cut-off, 339 patients would have SLNB, including 26 of the 39 predicted positive patients. At the high-risk cut-off, 33 patients are selected for SLNB and 10 are predicted positive, but 29 of the predicted positive patients would be missed.

TABLE 3 Nomogram application to a theoretical sample of 1000 patients

	Total	Low risk		Moderate risk		High risk	
		No SLNB	SLNB	No SLNB	SLNB	No SLNB	SLNB
SN+	39	3	36	13	26	29	10
SN−	961	197	764	648	313	938	23
Total	1000	200	800	661	339	967	33

SN sentinel node, *SLNB* sentinel lymph node biopsy, *DCISM* microinvasive ductal carcinoma in situ

Utilizing this model, a significant proportion of patients can be spared an unnecessary procedure, while capturing most patients who are likely to have positive SNs.

The strengths of our study include the use of a large cohort from a modern comprehensive national database and the development of a predictive model that can be used to assist in surgical decision making. This represents the largest dataset to date to address this question, and may allow selected patients to avoid axillary staging. This retrospective study has inherent weaknesses, among which is the inability to address the impact of multifocal microinvasion on SN positivity. In addition, the nomogram will require further validation in an independent sample.

CONCLUSIONS

SLNB should not be mandatory among DCISM patients, but should be applied selectively to patients at the highest risk for the presence of invasive disease, including those with LVI and high-grade histology. Utilizing the statistical power of the NCDB database, we have provided a nomogram for use in patients with DCISM to predict the risk of SN involvement, thereby facilitating individualized decision making and selective SLNB surgery.

Table 1 demonstrates the univariable analysis for clinicopathologic variables and sentinel node positivity among patients with DCISM who underwent sentinel node biopsy

Table 2 demonstrates significant findings from multivariable analysis of the clinicopathologic factors that were found to be significant on univariable analysis. These were added to the nomogram model. The scores allotted to each variable in the nomogram are demonstrated in the right-hand column

Table 3 illustrates how the proposed low-, moderate- and high-risk cut-offs would apply in a theoretical population of 1000 DCISM patients when consideration is being given to the performance of a sentinel node biopsy

Figure 1 illustrates the predictive model for sentinel node positivity in patients with DCISM with the low-, moderate- and high-risk cut-offs and their associated sensitivity, specificity, PPV and NPV. The nomogram scores generated in multivariable analysis (Table 2) are applied here to categorize patients as low, moderate, or high risk for nodal involvement and inform the choice to perform or omit a sentinel lymph node biopsy

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