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ORIGINAL ARTICLE – BREAST ONCOLOGY

Predicting Nodal Positivity in Women 70 Years of Age and Older with Hormone Receptor-Positive Breast Cancer to Aid Incorporation of a Society of Surgical Oncology Choosing Wisely Guideline into Clinical Practice

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ABSTRACT

Purpose. One of the Society of Surgical Oncology Choosing Wisely guidelines recommends avoiding routine sentinel lymph node (SLN) surgery in clinically node-negative women ≥70 years of age with hormone receptor-positive (HR+) breast cancer. We sought to assess the impact of tumor stage and grade on nodal positivity, and to develop a model to identify patients at low-risk of nodal positivity to aid adoption of the guideline.

Methods. We identified women ≥70 years of age with HR+ cN0 invasive breast cancer in the National Cancer Database (NCDB; 2010–2013) and examined the impact of tumor stage and grade on nodal positivity to identify low-risk combinations. A multivariable logistic regression model was developed to incorporate additional factors. The area under the curve (AUC) and relative risks (RR) were used to assess performance.

Results. Among 71,834 cases, the pathologic nodal positivity (pN+) rate was 15.3%. We identified low-risk criteria as grade 1, cT1mi-T1c (≤2.0 cm), or grade 2, cT1mi-T1b (≤1.0 cm), with pN+ rates of 7.8% compared with 22.3% in patients not meeting these criteria (RR 2.86, $p < 0.001$). On multivariable analysis, factors associated with pN+ status included clinical T stage, grade, and histology (each $p < 0.001$). The resulting model had AUC 0.70 and identified women with low predicted probability (<10%) of positive nodes, of whom 6.3% were pN+, versus 21.2% in those with predicted probability ≥10% (RR 3.34, $p < 0.001$).

Conclusion. The simple clinical rule (grade 1, cT1mi-T1c, or grade 2, cT1mi-T1b), as well as the predictive model, both identify women at low risk of nodal positivity where SLN surgery can be omitted.

The Society of Surgical Oncology (SSO) recently released five Choosing Wisely guidelines, one of which states "Don't routinely use sentinel lymph node (SLN) biopsy in clinically node-negative women ≥70 years of age with hormone receptor-positive (HR+) invasive breast cancer".[1] This recommendation was based on two studies showing no survival benefit from axillary lymph node dissection, although both were in the era prior to SLN surgery.[2,3]

With the release of this guideline, it is important to question whether to apply this widely to all women over 70 years of age or if there is a group at higher risk of nodal

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involvement for whom SLN surgery results could impact adjuvant treatment recommendations and potentially, patient outcome.[4] Therefore, we sought to investigate nodal positivity rates in the era of SLN surgery in this cohort using the National Cancer Database (NCDB) in order to guide evidence-based decision making when considering omission of SLN surgery. Our evaluation initially focused on the impact of tumor size and grade on nodal positivity, and we subsequently developed a multivariable predictive model for nodal positivity in women aged 70+ years with HR+ disease.

METHODS

Study Population

Women aged 70 years and older diagnosed with clinically node-negative (cN0) HR+ invasive breast cancer were identified from the NCDB for the 2010–2013 years of diagnosis. Patients were considered HR+ if they were estrogen receptor (ER) and/or progesterone receptor (PR) positive. The NCDB is a collaborative database from the American College of Surgeons and the American Cancer Society that includes hospital registry data from over 1500 Commission on Cancer (CoC)-accredited facilities. Data were collected retrospectively and de-identified. NCDB data represent over 70% of newly diagnosed cancer cases nationwide.[5] Our Institutional Review Board has deemed analysis of NCDB participant user file data as exempt from review.

Patients were identified according to the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) topography (C50.0–50.9) and histology (8000–8576, 8940–8950, 8980–8981) codes. For analysis, histologic categories included invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), and invasive mammary carcinoma (IMC), respectively. Additionally, invasive mucinous carcinoma, invasive tubular carcinoma, and invasive papillary carcinoma were considered as one category because of previously demonstrated lower risk of nodal involvement.[6,7]

Patients who did not undergo surgery, those with metastatic disease, and those coded stage cT0 were excluded, as were patients receiving neoadjuvant therapy (chemotherapy, hormone therapy, or radiation). Clinicopathologic variables analyzed included age, year of surgery, whether axillary surgery was performed, tumor stage, tumor grade, histology, ER positivity, and human epidermal growth factor receptor 2 (HER2) status. Patients were considered to have undergone axillary surgery if the number of regional lymph nodes examined was greater than zero. Prediction of pathologically positive nodal status (pN+) was restricted to the subset who underwent axillary surgery.

Statistical Analysis

Rates of axillary surgery were estimated, and predictors of the decision to perform axillary surgery were evaluated using multivariable logistic regression. In the axillary surgery subset, clinical models predicting pN+ status were developed using a split-sample training and validation approach. For model development, a random sample of approximately two-thirds of the NCDB cohort not missing key prognostic features was used, and the remaining one-third was reserved as an independent validation set. The features of the development and validation sets derived from the axillary surgery patients were very similar (electronic supplementary Table 1).

Two approaches to model development were applied. First, we hypothesized that stratifying by clinical T stage and grade would identify subsets of patients at low risk for pN+ disease, and we thus sought to identify a simple clinical rule based on combinations of these two factors. Second, we used multivariable logistic regression to fit a clinical prediction model using a larger number of features, including patient age, clinical T stage, grade, HER2 status, and histology.

Prediction models derived in the random two-thirds model development set were then tested in the one-third validation set. Discrimination was assessed using the area under the receiver operating characteristic curve (AUC-ROC) and compared using the DeLong error method. Model calibration was assessed by comparing performance of low-risk criteria versus actual proportion with pN+ disease. Relative risk (RR) ratios with 95% confidence intervals (CIs) were used to estimate the increased risk for those not meeting versus those meeting the low-risk criteria. Matthew's correlation coefficient (MCC) was used to quantify the classification performance of binary low-risk versus higher-risk rules. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) for these rules were also estimated.

For statistical testing, we used a two-sided significance level of $p = 0.05$. Analysis was performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) and R version 3.0.2 (The R Project for Statistical Computing, Vienna, Austria).

RESULTS

Patient Population and Determinants of Axillary Surgery

The derivation of the NCDB cohort used for analysis is described in the CONSORT diagram (electronic supplementary Fig. 1), and patient demographic and clinicopathologic characteristics are presented in Table 1.

Axillary surgery was not performed in 11.7% of the NCDB cohort overall. Those who underwent axillary surgery were significantly younger (median 76 versus 83 years, $p < 0.001$), had higher T stage and higher grade, were more likely to have HER2-positive tumors, and were more likely to be treated in a community center than an academic center (electronic supplementary Table 2). Patients with ILC or IMC were more likely to undergo axillary surgery compared with IDC, while those with invasive mucinous, tubular, or papillary carcinoma were less likely.

Among the 71,834 patients who underwent axillary surgery and had pN stage documented, the rate of pN+ was 15.3% (10,979/71,834) overall. Model development and validation subsets were used in the remainder of the analysis.

Clinical T Stage and Grade Stratification Rule

Increasing tumor grade and clinical T stage were each associated with pN+ status in the model development set (Table 2). By combining these two factors, we defined a group of patients at low-risk for nodal positivity, specifically patients with grade 1, clinical T1mi-T1c (≤2.0 cm), or grade 2, clinical T1mi-T1b (≤1.0 cm) tumors, which accounted for 43.6% of patients. Within this low-risk group, the pN+ rate was 7.8% (95% CI 7.4–8.3%). Patients not in the low-risk group (which included all grade 3 tumors, cT2+ tumors, and grade 2, clinical T1c tumors) had a pN+ rate of 22.3% (95% CI 21.7–22.8%) or a relative risk of nodal positivity of 2.84 (95% CI 2.68–3.02, $p < 0.001$) [Table 2].

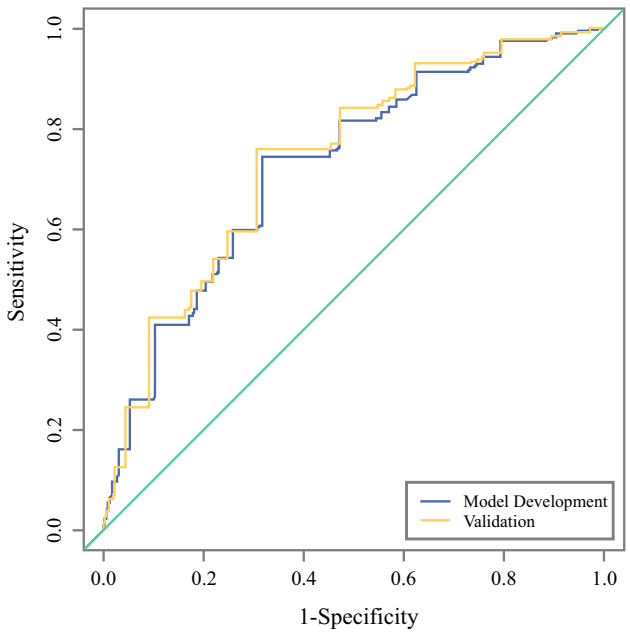

FIG. 1 Receiver operating characteristic curves for multivariable logistic regression model predicting pN+ status in model development ($N = 36{,}441$) and model validation ($N = 16{,}091$) samples. Discrimination performance was very similar in the two sets, with area under the curve estimates of 0.70 (95% CI 0.70–0.71) and 0.71 (95% CI 0.70–0.72), respectively. *CI* confidence interval

Multivariable Model Development

On univariate analysis, factors associated with an increased risk of nodal positivity were clinical T stage, grade, age, ILC or IMC, and HER2 positivity, while invasive mucinous, tubular, or papillary histology were associated with decreased risk. However, after adjustment for other factors in a multivariable model, both age and HER2 status were no longer significant ($p = 0.12$ and $p = 0.68$, respectively) and were thus not included in the final model. For HER2, the univariate odds ratio (OR) for positive versus negative was 1.28 (95% CI 1.15–1.41), but, after adjusting for other factors, the multivariable OR was attenuated to 1.02 (95% CI 0.92–1.14). Clinical T stage, grade, and histology remained significant (each $p < 0.001$) on multivariable analysis (Table 3). The resulting model had good discrimination, with AUC 0.70 (95% CI 0.70–0.71) in the model development sample (Fig. 1). The model identified 12,813 (35.2%) women with predicted probability of positive nodes <10%, of whom 812 (6.3%) had positive nodes. The remaining 64.8% had a predicted probability ≥10% and had a node positivity rate of 21.2% or a relative risk of nodal positivity of 3.34 (95% CI 3.11–3.59, $p < 0.001$). Model-predicted probabilities of pN+ status for all possible factor-level combinations are provided in electronic supplementary Table 3.

Model Validation and Comparison

Both the simple clinical (T stage/grade) rule and the multivariable logistic regression model were evaluated in the independent validation sample [$N = 16{,}091$ women, 2571 (16.0%) node-positive] (Table 4). Performance of the logistic regression model in the independent validation set was similar to that in the model development sample, with an AUC of 0.71 (95% CI 0.70–0.72) (Fig. 1). The nodal positivity rate was 5.5% for the subset with predicted probability <10%, and 21.6% when the predicted probability was ≥10% (RR 3.91, 95% CI 3.49–4.39, $p < 0.001$).

This binary classification (<10 versus ≥10% predicted probability), based on the multivariable logistic model, performed similarly in the independent validation set to the simple clinical rule, where those with grade 1, cT1mi-T1c, and grade 2, cT1mi-T1b, had pN+ rates of 7.5% compared with 22.7% pN+ (RR 3.02, 95% CI 2.76–3.30) for those not meeting these low-risk criteria. The AUC was similar ($p = 0.31$) between the two rules, but the logistic

TABLE 1 Patient demographics and clinical characteristics

	Total [$N = 82{,}555$] (%)
Age group, years	
70–74	31,859 (38.6)
75–79	23,904 (29.0)
80–84	16,011 (19.4)
85+	10,781 (13.1)
Race	
White	73,875 (89.5)
Black	5944 (7.2)
Other	2144 (2.6)
Unknown	592 (0.7)
Charlson–Deyo score	
0	63,283 (76.7)
1	15,313 (18.5)
2+	3959 (4.8)
Facility type	
Community Cancer Program	11,169 (13.5)
Comprehensive Community Cancer Program	45,305 (54.9)
Academic/Research Program	20,124 (24.4)
Integrated Network Cancer Program	5806 (7.0)
Other/unknown	151 (0.2)
Grade	
1	25,923 (31.4)
2	39,633 (48.0)
3	12,110 (14.7)
Unknown	4889 (5.9)
Histology	
IDC	57,587 (69.8)
ILC	9909 (12.0)
IMC	4533 (5.5)
Mucinous/tubular/papillary	4142 (5.0)
Other	6384 (7.7)
Clinical T stage	
cT1mi/T1a	6233 (7.6)
cT1b	17,029 (20.6)
cT1c	23,367 (28.3)
cT1, NOS	15,228 (18.4)
cT2	15,975 (19.4)
cT3/T4	1840 (2.2)
Unknown	2883 (3.5)
ER status	
Positive	81,921 (99.2)
Negative	619 (0.7)
Undetermined	15 (0.0)
PR status	
Positive	72,202 (87.5)
Negative	10,139 (12.3)
Undetermined	214 (0.3)
HER2 status	
Positive	5461 (6.6)
Negative	72,481 (87.8)
Equivocal or borderline	1794 (2.2)
Unknown/not performed	2819 (3.4)

IDC invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *IMC* invasive mammary carcinoma, *NOS* not otherwise specified, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

regression-derived rule showed higher sensitivity (88 versus 79%, $p < 0.001$), while the simple clinical rule showed higher specificity (49 versus 39%, $p < 0.001$). Both rules had a high NPV, at 94 and 92%. Additional performance metrics are provided in Table 4.

DISCUSSION

In breast cancer patients aged 70+ years with HR+ invasive breast cancer, tumor stage, grade, and histology are highly correlated with risk of nodal positivity. By combining tumor stage and grade, we defined a low-risk group (grade 1, T1mi-T1c, or grade 2, T1mi-T1b tumors) that had a lymph node positivity rate of approximately 8% overall (range 4–11%) and a higher risk group (patients not meeting the low-risk criteria) with a rate >20% overall (range 12–50%). These simple clinical criteria of grade 1, T1mi-T1c, or grade 2, T1mi-T1b can easily be applied in practice to select patients who have a low likelihood of nodal positivity, and are thus ideal for adopting the SSO Choosing Wisely guideline of avoiding SLN surgery. Incorporating these simple clinical criteria alone would avoid SLN surgery in approximately 44% of women aged 70+ years with cN0 HR+ breast cancer, reserving SLN surgery for the remainder of patients who are at a threefold higher risk of nodal positivity and may thus benefit from surgical staging of the axilla to guide adjuvant treatment recommendations, including indication for nodal radiation and length of adjuvant hormonal therapy, both of which may influence clinical outcome and, potentially, survival.[4,8–10]

Additionally, we have developed a comprehensive multivariable model that performs well to predict rates of nodal positivity in this patient population. Interestingly, HER2 status was not associated with nodal positivity in multivariable analysis. The model provides predicted probabilities of pN+ status on a continuum for all possible combinations of the features of cT stage, grade, and histology. When reduced to a binary classification of low-risk

TABLE 2 Rates of pN+ disease in women aged ≥70 years with HR+ cN0 invasive disease, stratified by clinical T stage and grade in the model development sample [$N = 36{,}441$]

	N	*N* (%) pN+	*p* value
Overall	36,441	5818 (16.0)	–
Clinical T stage			<0.001
cT1mi/T1a	3435	207 (6.0)	
cT1b	9683	731 (7.5)	
cT1c	13,323	1982 (14.9)	
cT2	9055	2485 (27.4)	
T3/T4	945	413 (43.7)	
Grade			<0.001
1	11,616	1199 (10.3)	
2	18,641	3203 (17.2)	
3	6184	1416 (22.9)	
Combined grade and clinical T stage			<0.001
Grade 1, cT1mi/T1a	1602	63 (3.9)	
Grade 1, cT1b	4105	244 (5.9)	
Grade 1, cT1c	4021	455 (11.3)	
Grade 1, cT2	1704	379 (22.2)	
Grade 1, cT3/T4	184	58 (31.5)	
Grade 2, cT1mi/T1a	1495	105 (7.0)	
Grade 2, cT1b	4682	378 (8.1)	
Grade 2, cT1c	7134	1136 (15.9)	
Grade 2, cT2	4842	1364 (28.2)	
Grade 2, cT3/T4	488	220 (45.1)	
Grade 3, cT1mi/T1a	338	39 (11.5)	
Grade 3, cT1b	896	109 (12.2)	
Grade 3, cT1c	2168	391 (18.0)	
Grade 3, cT2	2509	742 (29.6)	
Grade 3, cT3/T4	273	135 (49.5)	
Low-risk rule			<0.001
Grade 1, T1mi-T1c, or Grade 2, T1mi-T1b	15,905	1245 (7.8)	
Grade 3, T2+, or Grade 2, T1c	20,536	4573 (22.3)	

pN+ pathologic node-positive, *HR+* hormone receptor-positive

(defined as <10%) versus higher risk (≥10%), the logistic probability-based classification performance was similar to that of the simple clinical (T stage and grade) rule. By accurately selecting those patients who may not need SLN surgery through use of either model, a substantial number (35–44%) of women aged 70+ years with cN0 HR+ breast cancer would benefit from lower morbidity, along with significant cost savings in this era of increasing healthcare expenditures, which is in accordance with the goal of the Choosing Wisely campaign. Omitting SLN surgery in only those meeting our low-risk criteria, but continuing SLN surgery for others, would allow for detection of pN+ disease in the majority, where present (sensitivity 79–88%), and yet is a less nihilistic approach than omitting SLN surgery in all women aged 70+ years with HR+ breast cancer. Several nomograms for clinical prediction are available online and are frequently used. The current nomogram was developed based on data from 36,441 women over 70 years of age with HR+ disease, compared with the currently available online calculators that have a broader range of patients included and a significantly smaller sample of women over 70 years of age.

There is limited information on breast cancer outcomes in the elderly population, even though rates of breast cancer in women over 70 years of age have been increasing over the last 30 years.[11] Although it is frequently assumed that older women have less aggressive breast cancers, multiple recent studies have shown this is not necessarily the case.[11–15] Furthermore, evidence suggests that older women had higher disease-specific mortality and risk of relapse, even when controlled for both tumor and treatment variables.[15] Additional retrospective studies have confirmed these results of higher mastectomy rates, lower rates of adjuvant treatment, shorter disease-free survival, and poorer overall survival for older women.[11,13,14] Taken together, these studies suggest there are already disparities in both treatment and outcomes for older women, and raise the question of whether eliminating surgical axillary

TABLE 3 Final multivariable logistic regression model predicting pN+ status in the model development sample [$N = 36,441$]

Variable	pN+		Univariate		Multivariate	
	Yes [$N = 5818$] (%)	No [$N = 30,623$] (%)	OR (95% CI)	p-value	OR (95% CI)	p-value
Clinical T stage						
cT1mi/T1a	207 (6.0)	3228 (94.0)	1.0 reference		1.0 reference	
cT1b	731 (7.5)	8952 (92.5)	1.27 (1.09–1.49)	0.003	1.24 (1.06–1.46)	0.008
cT1c	1982 (14.9)	11,341 (85.1)	2.73 (2.35–3.16)	<0.001	2.53 (2.18–2.94)	<0.001
cT2	2485 (27.4)	6570 (72.6)	5.90 (5.09–6.84)	<0.001	5.27 (4.53–6.12)	<0.001
T3/T4	413 (43.7)	532 (56.3)	12.11 (10.01–14.65)	<0.001	10.99 (9.04–13.35)	<0.001
Grade						
1	1199 (10.3)	10,417 (89.7)	1.0 reference		1.0 reference	
2	3203 (17.2)	15,438 (82.8)	1.80 (1.68–1.93)	<0.001	1.34 (1.24–1.44)	<0.001
3	1416 (22.9)	4768 (77.1)	2.58 (2.37–2.81)	<0.001	1.56 (1.43–1.71)	<0.001
Histology						
IDC	3935 (15.7)	21,203 (84.3)	1.0 reference		1.0 reference	
ILC	969 (21.3)	3579 (78.7)	1.46 (1.35–1.58)	<0.001	1.18 (1.09–1.28)	<0.001
IMC	503 (22.8)	1706 (77.2)	1.59 (1.43–1.76)	<0.001	1.42 (1.28–1.59)	<0.001
Mucinous, Tubular, Papillary	67 (3.9)	1652 (96.1)	0.22 (0.17–0.28)	<0.001	0.22 (0.17–0.28)	<0.001
Other	344 (12.2)	2483 (87.8)	0.75 (0.66–0.84)	<0.001	0.67 (0.59–0.76)	<0.001

IDC invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *IMC* invasive mammary, *pN+* pathologic node-positive, *OR* odds ratio, *CI* confidence interval

staging may lead to even further undertreatment of this population, suggesting a more selective approach to omission of SLN surgery should be considered.

The diagnosis of nodal positivity may impact adjuvant treatment recommendations that can in turn impact long-term recurrence or even survival. Both radiation therapy decisions (including the omission of radiation after breast-conserving surgery [BCS] in endocrine-sensitive tumors, whether to include regional nodal irradiation after BCS, and whether or not to administer post-mastectomy radiotherapy) and decisions for extended length of aromatase inhibitor therapy are largely determined by nodal status.[8–10,16,17] Extension of anti-hormonal therapy to 10 years has a substantial impact in reducing late distant recurrence, particularly for women with node-positive disease, which would be unknown if surgical staging is omitted altogether.[8]

Despite the frequent misconception that older women only have less aggressive, hormonally responsive tumors, there are still a significant proportion of these women at risk for pathologic nodal disease. Indeed, when axillary surgical staging is completely omitted in women $\geq$70 years of age with early-stage breast cancer, there is an increased rate of regional recurrence.[18] Meta-analysis of two randomized controlled trials including 692 patients found a relative risk of axillary recurrence of 0.24 when comparing axillary staging with no axillary staging. However in these trials, the majority of patients had ALND as opposed to SLN surgery. There were no significant differences in in-breast recurrence, distant recurrence, or overall or breast cancer-specific mortality.

Similar findings regarding the importance of tumor size have been reported by the Austrian group who reported a nodal positivity rate of 32% in 1425 women aged 70 years or older with endocrine responsive disease, and also found that tumor size was important for patient selection, recommending that axillary staging could be omitted in pT1a-b tumors.[19]

There are some limitations to our study, including its retrospective nature and the inherent errors in national database projects relying on available data without the ability to resolve inconsistencies or missingness. Another limitation involves coding of axillary surgery in NCDB. We defined axillary surgery performed as >0 nodes removed and examined by a pathologist. The alternative variable that codes whether or not regional lymph node surgery was performed has the disadvantage of including fine-needle aspiration only in the yes category. The limitation of our approach was that the number of lymph nodes examined has a prefilled value of zero, which would not allow us to differentiate zero nodes examined from missing data, possibly giving a slight overestimate of the proportion of patients with no axillary surgery. Another limitation is the lack of Ki-67 data, which may be another useful parameter in differentiating luminal A from luminal B tumors that might impact the rates of nodal positivity, but this information is unavailable from the NCDB.

TABLE 4 Model performance metrics evaluated in the independent validation sample [$N = 16{,}091$]

Model			
Logistic predicted probability (continuous)			
AUC (95% CI)			0.71 (0.71–0.72)
	Mean	*N*	*N* (%) pN+
Predicted probability			
<10%	0.06 (0.02)	5620	310 (5.5)
10–19%	0.15 (0.03)	6194	947 (15.3)
20–29%	0.26 (0.03)	2427	683 (28.1)
30–39%	0.32 (0.02)	1645	536 (32.6)
≥40%	0.48 (0.03)	205	95 (46.3)
			Estimate (95% CI)
Dichotomized logistic regression predicted probability (≥10% vs. <10%)			
Percentage of patients classified low-risk			34.9% (34.2–35.7%)
AUC			0.64 (0.63–0.64)
MCC			0.21 (0.20–0.22)
Sensitivity			88% (87–89%)
Specificity			39% (38–40%)
NPV			94% (94–95%)
PPV			22% (21–22%)
Percentage pN+ in the low-risk group			5.5% (4.9–6.2%)
Percentage pN+ in the higher-risk group			21.6% (20.8–22.4%)
Relative risk of pN+ disease			3.91 (3.49–4.39)
Simple rule based on cT stage and grade (low risk = grade 1, cT1mi-cT1c, or grade 2, cT1mi-cT1b)			
Percentage of patients classified low-risk			44.4% (43.6–45.2%)
AUC			0.64 (0.63–0.65)
MCC			0.21 (0.19–0.22)
Sensitivity			79% (77–81%)
Specificity			49% (48–50%)
NPV			92% (92–93%)
PPV			23% (22–24%)
Percentage pN+ in the low-risk group			7.5% (6.9–8.2%)
Percentage pN+ in the higher-risk group			22.7% (21.9–23.6%)
Relative risk of pN+ disease			3.02 (2.76–3.30)

AUC area under curve, *MCC* Matthew's correlation coefficient, *NPV* negative predictive value, *PPV* positive predictive value, *pN+* pathologic node-positive, *CI* confidence interval, *AUC* area under the curve

CONCLUSIONS

We have developed a simple clinical rule that can be easily remembered and adopted in practice, along with a more granular clinical risk prediction model providing an estimated probability of pN+ status (ranging from 1 to 57%). Both the simple clinical rule and the multivariable model allow us to individualize the care of women aged 70+ years based on more tumor factors than HR status alone, and can guide surgical decision making, with the potential to increase adoption of the SSO Choosing Wisely guideline.

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and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

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