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Prospective multicenter study to validate a prediction model for surgery uptake among women with atypical breast lesions

Running head: Surgery uptake in atypical breast lesions

Key words: Atypical breast lesion, B3 lesion, breast cancer, model, biopsy, Ductal carcinoma in situ, atypical ductal hyperplasia

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Synopsis

Histologically atypical breast lesions (ABLs) identified on percutaneous biopsy lead to unnecessary surgery in 75 to 90% of women.

This is the first multicenter nationwide prospective validation of a prediction model of breast cancer that allows the avoidance of unnecessary surgery among women with any ABL including atypical ductal hyperplasia (ADH).

For the pre-specified threshold of 20% predicted probability of cancer, negative predictive value was 82% (77-87%). However, at a10% probability threshold, negative predictive value was 89% (84-94%), while 58% of the patients (and 54% in patients with ADH) could have avoided surgery with only 2 missed invasive cancers.

Abstract

Background

Diagnosis of atypical breast lesions (ABLs) leads to unnecessary surgery in 75 to 90% of women. We have previously developed a model including age, complete radiological target excision after biopsy and focus size that predicts the probability of cancer at surgery. The present study aimed to validate this model in a prospective multicenter setting.

Methods

Women with a recently diagnosed ABL on image-guided biopsy were recruited in 18 centers, before wire-guided localized excisional lumpectomy. Primary outcome was the negative predictive value (NPV) of the model.

Results

The NOMAT model could be used in 287 of the 300 patients included (195 with ADH). At surgery, 12 invasive (all grade 1), and 43 in situ carcinomas were identified (all ABL: 55/287, 19%; ADH only: 49/195, 25%). The area under the receiving operating characteristics curve of the model was 0.64 (95% CI, 0.58-0.69) for all ABL; and 0.63 for ADH only (95% CI, 0.56 to 0.70)). For the pre-specified threshold of 20% predicted probability of cancer, NPV was 82% (77-87%) for all ABL and 77% (95% CI, 71% to 83%) for patients with ADH. At a 10% threshold, NPV was 89% (84-94%) for all ABL and 85% (95% CI, 78% to 92%) for the ADH. At this threshold, 58% of the whole ABL population (and 54% of ADH patients) could have avoided surgery with only 2 missed invasive cancers.

Conclusions

The NOMAT model could be useful to avoid unnecessary surgery among women with ABL, including for patients with ADH.

Clinical Trial registration: NCT02523612

Introduction

Mammographic screening, together with better treatments, has led to improved breast cancer survival over the past 30 years (1, 2). However, the currently proposed screening strategy has received some degree of criticism, especially for its associated substantial rate of overdiagnosis and overtreatment (3). Atypical breast lesions (ABL) found on percutaneous biopsies are emblematic of this issue, as they classically lead to unnecessary surgery in 75 to 90% of women (4, 5). Furthermore, in the 10-25% of women ultimately diagnosed with cancer at surgery, the latter generally has a low propensity for progression (low-grade ductal carcinoma in situ [DCIS] or invasive carcinomas). While ongoing studies (LORD NCT02492607, LORIS ISRCTN 27544579 and COMET) have been designed to determine if a simple follow-up is safe for patients with low-grade DCIS (6-8), guidelines regarding ABL lesions remain heterogeneous. The best management of these lesions (surgery or follow-up) is still a matter of debate (9).

ABLs include the following subtypes: flat epithelial atypia (FEA), atypical ductal (ADH) or lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS). They are part of breast lesions currently referred as B3 lesions (which additionally include radial scar, papillary lesions and phyllodes tumors). ABL diagnosis depends on the pathologist's experience and has limited reproducibility, especially regarding ABL subtyping. Many ABLs have mixed components, exhibiting both ADH and ALH, as well as FEA (10). Several prediction models have been proposed to determine which lesions are associated with a high risk of upgrading to cancer at surgery, and therefore may require surgical excision (11, 12). However, most of them were focused on one or another kind of ABL. Furthermore, their performances were poorly reproducible (for example AUC 0.51 (95% confidence interval: 0.47-0.53) for Ko score in an independent validation study (13)). Based on a single-institution retrospective database, we have developed a model (NOMAT, NOMogram for ATypia) capable of predicting the presence of cancer at surgery, which was common to all ABLs (FEA, ADH, ALH or LCIS). NOMAT is based on three preoperative variables: age, complete radiological target excision after biopsy (yes/no) and focus size (≤ or > 15mm) (10). All these criteria have indeed constantly been reported as risk factors for breast cancer in numerous studies (11). NOMAT's performance was promising in the development cohort, with an area under the receiving operating characteristics (ROC) curve (AUC) of 0.72 (95 % confidence interval [CI], 0.63–0.82). For an optimal threshold of 20% of predicted probability of cancer using NOMAT, the sensitivity (Se), specificity (Sp), positive and negative predictive values (PPV and NPV) were 78%, 66%, 36%, and 90%, respectively. Our model was also externally validated by another academic team on a series of 151 patients, with an AUC of 0.65 (0.63-0.82) (14).

The main objective of the present study was to evaluate NOMAT's performance among women diagnosed with ABL at breast biopsy in a multicenter prospective setting, and we explored the performance in the population restricted to patients with ADH

Patients and Methods

Patients

Women who had a recent diagnosis of ABL on image-guided biopsy for breast microcalcifications were included in this trial between July 7, 2015 and May 29, 2018, in 18 French centers. A French Ethics Committee (Comité de Protection des Personnes Ile de France) approved this study on March 11, 2015 (2015-A00045-44). The trial was registered at clinicaltrials.gov under the number NCT: NCT02523612. Women aged 18 or older were eligible for the study if diagnosed with an ABL (including flat epithelial atypia [FEA], atypical ductal [ADH] or lobular hyperplasia [ALH] and lobular carcinoma in situ [LCIS] of classic type) at percutaneous breast biopsy performed for mammographic microcalcifications. All women gave a written informed consent before study participation. Exclusion criteria were the presence of a mass lesion on ultrasound imaging; the presence of DCIS or invasive carcinoma on the biopsy specimen; a past personal history of breast cancer; a previous radiation therapy of the breast; a known germline predisposing mutation. Pregnant or breastfeeding women, patients with limitation of freedom or under guardianship, and patients unable to comply with the necessary follow-up for geographical, social or psychological reasons were also excluded. Multifocal lesions were included, and the lesion at higher risk was considered as the main lesion for characterization.

Baseline epidemiological data were collected. Locally assessed imaging features were collected as well: American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS) classification of the baseline mammographic image, visual mammographic breast density (BI-RADS), size of the target lesion before biopsy (mm), size of the biopsy needle, number of cores retrieved and completeness of the microcalcifications' removal during biopsy.

All women included in the study underwent surgical image-guided excision of the microcalcifications (lumpectomy) by their local surgeon.

Pathology

Diagnostic biopsy:

Initial diagnosis and inclusion were based on local pathological analysis to reflect real-practice conditions. There was no central review prior to inclusion.

Sections were obtained at a minimum of three levels for 11G needle biopsies and five levels for 8G needle biopsies. All slides were stained with hematoxylin–eosin-safran (HES) and analyzed by local breast pathologists according to routine practice. Epithelial atypical lesions were classified according to the World Health Organization 2012 classification as FEA, ADH, ALH, or LCIS of classic type. When several lesions were associated, the diagnosis was based on the predominant lesion but associated lesions were also documented. The number of foci with atypia and the size of the largest foci were specified for FEA and ADH. For ALH and LCIS, the percentage of lobular and ductal lesions with atypia was reported.

Surgical specimen:

On the surgical specimen, the presence of post-biopsy scar, of any residual atypical lesions, and of any malignancy either close to or at a distance from the scar was recorded. If a cancer was observed, the histological type (invasive ductal of no special type, lobular

carcinoma, invasive special type, DCIS, pleomorphic LCIS), histological grade, tumor size and margin status were specified. For invasive cancers, estrogen and progesterone receptors (ER and PR), and human epidermal growth factor receptor 2 (HER2) status were also assessed. New surgeries and subsequent treatment were reported.

The patients were classified as bearing "cancer" on the final surgical sample if either an invasive adenocarcinoma or a DCIS or pleomorphic LCIS was retrieved, whatever the extent.

Individual assessment of NOMAT model

The following variables are included in the NOMAT model: age (years), complete radiological target excision after biopsy (yes/no) and initial radiological microcalcifications focus size (≤ or > 15mm).

For each woman, the probability of cancer at surgery was predicted using the NOMAT multivariable logistic model whose parameters were slightly optimized from a previous publication (10) and locked before the start of the current NOMAT01 study : logit(P[breast cancer = 1 | age, focus size > 15, excision target] = -4.42 + 0.05*Age + 1.01*focus size > 15 -0.87*excision target).

Statistical analysis

To evaluate the performance of the NOMAT model, a sample size of 300 patients was deemed necessary. The null hypothesis was given by H0: NPV (=true negatives/(true negatives + false negatives)) = 0.80 vs. the alternative hypothesis HA: NPV > 0.80. We assumed that 50% of the patients would be classified in the low-risk group (i.e. below the pre-specified NOMAT cut-off of 20% on the scale of the predicted probability of cancer). The inclusion of 300 women would provide 84% power to reject the null hypothesis at a one-sided significance level of 5% using an empirical estimate of variance when the true NPV is equal to 0.88 under the alternative hypothesis.

To assess the performance of the NOMAT model, NPV, Se (=true positives/(true positives + false negatives)), Sp (=true negatives/(true negatives + false positives)), PPV (=true positives/(true positives + false positives)) were calculated for the 20% cutoff on the scale of predicted probability of cancer and were provided with 95% CIs. The discrimination of the model was assessed by an estimation of the AUC, and provided with a 95% CI. Additionally, because of its particular relevance given the recent changes in practices in women with non-ADH lesions, an unplanned subgroup analysis for patients with ADH lesions was performed. The calibration of the model was assessed using a calibration plot and complemented with a calibration intercept and slope (15). Statistical analyses were performed on SAS version 9.4 and R version 3.5.0 (using ROCR and gbm packages).

Results

Patient characteristics

Three hundred patients were included in 18 centers. Eleven patients were excluded from the analysis (Figure 1). Out of the 289 remaining patients, 2 patients had missing data for lesion size on mammography, leaving 287 patients evaluable for the assessment of the prediction model's performance.

Patients' main characteristics are reported in Table 1. Median age was 52 years (range: 32-81). ABLs at biopsy were distributed as follows: 97 ADH alone (34%), 16 ALH alone (6%), 7 classic-type LCIS (2%), 49 FEA (17%), 113 mixed lesions (39%), and 5 with undefined atypical lesions (2%). ADH was present in 195/287 patients (97 alone and 98 mixed).

Surgical findings and cancer characteristics

At the time of surgery, 174 patients (61%) had residual ABL, while 113 patients (39%) did not. The residual ABL was FEA in 99 (57%), ADH in 95 (55%), ALH in 44 (25%) and classic-type LCIS in 14 patients (8%). Among the 287 patients operated, 55 cancers were found at surgery (19%) including 41 DCIS, 2 pleiomorphic LCIS and 12 invasive carcinoma (10 of no special type, 1 tubular, and 1 lobular; all grade 1). All 12 invasive cancers were node-negative-11 stage 1 and one stage 2, with a median tumor size of 7 mm [range: 1; 25]. Ten out of 11 invasive carcinoma were ER+/PR+/HER2-, and 1 carcinoma was too small for immunohistochemistry characterization. The margins were free of disease for invasive carcinoma in 11 out of 12 patients. For DCIS or pleiomorphic LCIS, the median tumor size was 17 mm [range: 3-70]. The 43 DCIS/pleiomorphic LCIS were distributed as follows: 16 low, 23 intermediate and 3 high-grade lesions (one missing grade). For DCIS (41 patients), necrosis was observed for 8 patients (8/41, 20%) and median size of lesion was 15.5mm (Q1-Q3: 7.5–30.0 / range: 3–70).

Thirty-three patients (12%) had a secondary surgery (18 simple lumpectomy, 3 lumpectomy + sentinel lymph node dissection [SND], 1 lumpectomy + axillary lymph node dissection [ALND], 10 mastectomy + SND and 1 mastectomy + ALND). Forty-one patients (14% of the whole cohort, 75% of cancer patients) received a complementary treatment (39 radiotherapy, 1 chemotherapy, and 8 endocrine therapy).

The upgrading on surgical excision according to pathological subtype on biopsy is reported in Table 2. This rate was 25% (49/195) for patients with ADH alone or mixed with other ABL. No women with isolated FEA (n=49) at the biopsy exhibited cancer on surgical excision.

NOMAT model's performance

The AUC of the NOMAT model in the whole ABL cohort was 0.64 (95% CI, 0.58 to 0.69) (Figure 2). The AUC of the NOMAT model for patients with ADH (alone or associated, n=195) was 0.63 (95% CI, 0.56 to 0.70).

Regarding the primary outcome, using the pre-specified threshold of 20% on the predicted probability of cancer among the whole cohort (n=287), 39 patients were predicted to have cancer, with a corresponding Sensibility, Specificity, Positive Predictive Value and Negative Predictive Value of 20% (95% CI, 9% to 30%), 88% (95% CI, 84% to 92%), 28% (95% CI, 14% to 42%) and 82% (95% CI, 77% to 87%), respectively.

When applying an exploratory threshold of 10% on the predicted probability of cancer, 120 patients were predicted to have cancer (Figure 3), with a corresponding Se, Sp, PPV and NPV of 65% (95% CI, 52% to 78%), 67% (95% CI, 61% to 73%), 31% (95% CI, 23% to 39%) and 89% (95% CI, 84% to 94%), respectively. By using the model with the 10% risk threshold, 58% of the patients could have avoided surgery with only 2 missed invasive cancers but 16 missed DCIS or pleiomorphic LCIS (Figure 3A).

When examining the nuclear grade of DCIS or pleiomorphic LCIS according to this 10% cut-off of predicted probability of cancer, no high-grade would have been missed and 61% (14/23) of intermediate-grade DCIS would have been identified as high-risk.

For the ADH population (ADH alone or associated with other ABL) (n=195), when applying the pre-specified threshold of 20% on the predicted probability of cancer, 29 patients were predicted to have cancer, with a corresponding Sensibility, Specificity, Positive Predictive Value and Negative Predictive Value of 22% (95% CI, 11% to 34%), 88% (95% CI, 82% to 93%), 38% (95% CI, 20% to 56%) and 77% (95% CI, 71% to 83%), respectively. When applying an exploratory threshold of 10% on the predicted probability of cancer among this ADH population, 90 patients were predicted to have cancer, with a corresponding Sensibility, Specificity, Positive Predictive Value and Negative Predictive Value of 67% (95% CI, 54% to 80%), 61% (95% CI, 53% to 69%), 37% (95% CI, 27% to 47%) and 85% (95% CI, 78% to 92%), respectively. By using the model with the exploratory 10% risk threshold, 105/195 (54%) patients could have avoided surgery with only 2 missed invasive cancers but 14 missed DCIS or pleiomorphic LCIS (Figure 3B).

Regarding the calibration of the NOMAT model, small risks of cancer were moderately overestimated, whereas large risks of cancer were severely underestimated (calibration slope equal to 0.49 [95% CI, 0.19 to 0.80], with an intercept equal to 0.65 [95% CI, 0.33 to 0.96]) (Figure 4).

Discussion

This study is the first prospective multicentric validation of a model to predict the probability of cancer for women with ABL on biopsy. The NOMAT model performed modestly well in this multicentric prospective validation cohort. The trial reached its primary objective: at a pre-specified threshold of 20% predicted probability of cancer, the NPV of NOMAT was beyond 80%, precisely 82% (95% CI, 77% to 87%). The model's discrimination in this validation series appeared lower compared to the initial study results (AUC 0.64 vs. 0.72), which is often observed in validation studies. The performance of the model similar in the analysis restricted to patients with ADH (alone or associated, AUC equal to 0.63). When applying an exploratory cut-off of 10%, the NPV was estimated to be 89% (95% CI, 84% to 94%), which appeared more relevant. Indeed, this threshold would lead to avoid 58% of surgeries (and 54% in patients with ADH) with only 2 missed invasive cancers and 16 missed DCIS or pleiomorphic LCIS (none being high-grade).

Several international studies currently question the management of low-grade DCIS and propose an alternative of follow-up for those lesions (LORD NCT02492607, LORIS ISRCTN 27544579 and COMET (6-8)). In this respect, a model allowing the avoidance of surgery for ABL should primarily identify the risk for invasive cancer and high-grade DCIS. This is what we obtain with NOMAT, based on current results, which appears as a useful decisional tool for clinicians face to ABL on biopsy.

International recommendations have been published regarding each type of benign breast lesion or B3 lesions. Minimally invasive management of B3 lesions (except ADH) with vacuum-assisted biopsy (VAB) was considered an appropriate alternative to first-line open surgical excision in most cases, but with more frequent follow-up, especially for ALH (9). If decision for surgery is based essentially on pathology analysis, a key question is how to be sure of the type of B3 lesion. In the literature review by Mooney et al. (11), 23% of ADH cases [0-62%], 9% of ALH cases [0-67%], and 18% of LCIS cases [0-60%] were upgraded on average at surgery (16-20). Indeed, the trend over the last several years is to not excise ALH and classic LCIS identified on core biopsy when there are concordant imaging findings. This recommendation is now in the NCCN and international guidelines (9, 21). In those guidelines, the major unresolved and clinically relevant question is which women with ADH on core biopsy can be spared excision.

However, the pathological reproducibility is lower for ABL as compared to cancer. Elmore et al. studied diagnostic concordance among pathologists interpreting breast biopsy specimens (22): for invasive carcinoma cases, 96% (95% CI, 94%-97%) were concordant, and 4% (95% CI, 3%-6%) underinterpreted; among DCIS cases, 84% (95% CI, 82%-86%) were concordant, 3% (95% CI, 2%-4%) overinterpreted, and 13% (95% CI, 12%-15%) underinterpreted; while among ABL cases, 48% (95% CI, 44%-52%) were concordant, 17% (95% CI, 15%-21%) overinterpreted, and 35% (95% CI, 31%-39%) underinterpreted. Moreover, lesions are often mixed (in our study, nearly 40% of patients). These elements may explain why it is difficult to rely solely on the pathological report of the biopsy to decide between surgery or follow-up. Our model does not integrate B3 subtyping, therefore saving a mandatory central review of the lesions.

While several prediction models aiming to avoid surgery have been proposed previously, most concerned specific subtypes and none has been prospectively validated so far. Several models have included the number of ADH foci (4, 11, 23-25). However, in our multicentric study, although we collected this factor prospectively, it was missing in 48 out of 195 lesions with ADH (alone or mixed with other lesions), illustrating the limitation for daily

use without expert analysis. Two machine learning models have been developed recently. A random forest model was developed within a single-institution series of 1006 patients, with as most important predictors, age and histology (26). This model has not been validated yet. Harrington et al. developed and evaluated six machine learning models on a small patient series of 124 women. They reported that patient's age at time of the biopsy together with lesion size were the most important predictors of upgrade, as in our model (27). Our model can be used as a tool to inform women regarding their probability of cancer within a biopsied microcalcification spot and help decision-making between surgical or follow-up strategies. Such decisions undoubtedly need to be adapted to each patient's anxiety level, tolerance to uncertainty and adherence to follow-up. Patients' preference with adapted evaluation of risks shall guide the final decisions.

Some weaknesses can be acknowledged for this study. All patients were operated and this study did not intend to evaluate the long-term risk of cancer in the presence or absence of surgery. It provides the scientific community with a validated, short-term, surgical-decision model. No central pathological review of the slides was implemented, but our objective was to develop a daily practice tool, and expert review is not always available for these frequent ABLs. Very few patients had an MRI whereas, for some authors, this imaging could add valuable information in the investigation of breast lesions (28, 29). With an exploratory threshold of 10% in our validation study, surgery would have been avoided in 58% of women with only 2 missed invasive cancer and 16 missed DCIS or pleiomorphic LCIS (but not high-grade). Thus, the use of NOMAT safely allows avoidance of surgery at a preferred threshold of 10% probability. This threshold needs to be confirmed in future studies. Prospective follow-up data of women who were spared surgery shall be gathered to confirm the long-term safety of such an approach. Finally, the model's discrimination and calibration could be improved. Indeed, a secondary aim of the NOMAT01 study is to use biomarkers to further improve the performances of the model. Imperfect calibration may be linked to the differences of case mix between the development cohort and the present one. Regarding the three predictors of the NOMAT01 model the current study included slightly younger patients; of note however is that the distribution of ABL subtypes was rather different.

Also some patients had multiple lesions, and the decision to pursue the "highest risk" lesion can be arguable. Most of the time this "highest risk" lesion was ADH and, in the literature, to decide on patient management, the existence of ADH usually determines the choice for surgery (9, 21).

In conclusion, we conducted the first multicentric prospective validation of a model that predicts the probability of breast cancer at surgery among women with ABL. The model performed modestly well in this multicentric prospective validation cohort and may need some recalibration. The use of a model such as NOMAT allows the safe avoidance of surgery at the exploratory threshold of 10% probability of cancer. The NOMAT model can help inform women and guide decisions between surgical excision or follow-up and can be applied to all ABLs identified on microcalcifications.

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Table 1: Description of patients' characteristics at inclusion (n=287)

Age at inclusion	N	287	
	Median (Min ; Max)	52 (32 ; 81)	
Family history of breast cancer (first and second degree)	N	284	
	No	166	58.5%
	Yes	118	41.5%
Personal history of breast biopsy	N	286	
	No	238	83.2%
	Yes	48	16.8%
Personal history of atypical lesion	N	282	
	No	266	94.3%
	Yes	16	5.7%
	Ipsilateral	10	62.5%
	Contralateral	6	37.5%
Menopausal	N	283	
	No	139	49.1%
	Yes	144	50.9%
Hormone Replacement Therapy	N	144	
	No	103	71.5%
	Yes	41	28.5%

Table 2: Upgrading on surgical excision according to pathological subtype on biopsy (n=287)

All patients	Cancer on surgical excision (= DCIS, pleiomorphic LCIS, IC) (n=55) n (%)	No cancer on surgical excision (n=232) n (%)
ADH alone (n=97)	27 (27.8)	70 (72.2)
ALH alone (n=16)	1 (6.25)	15 (93.75)
LCIS alone (n=7)	1 (14.3)	6 (85.7)
FEA (n=49)	0 (0.0)	49 (100.0)
Mixed lesions (n=113)	23 (20.4)	90 (79.6)
Undefined atypical lesions (n=5)	3 (60.0)	2 (40.0)
Subgroup		
ADH alone and mixed (n=195)	49 (25.1)	146 (74.9)

Abbreviations: ADH=atypical ductal hyperplasia – ALH=atypical lobular hyperplasia – LCIS=lobular carcinoma in situ – FEA=flat epithelial atypia

Figure 1: Flowchart of the NOMAT01 study

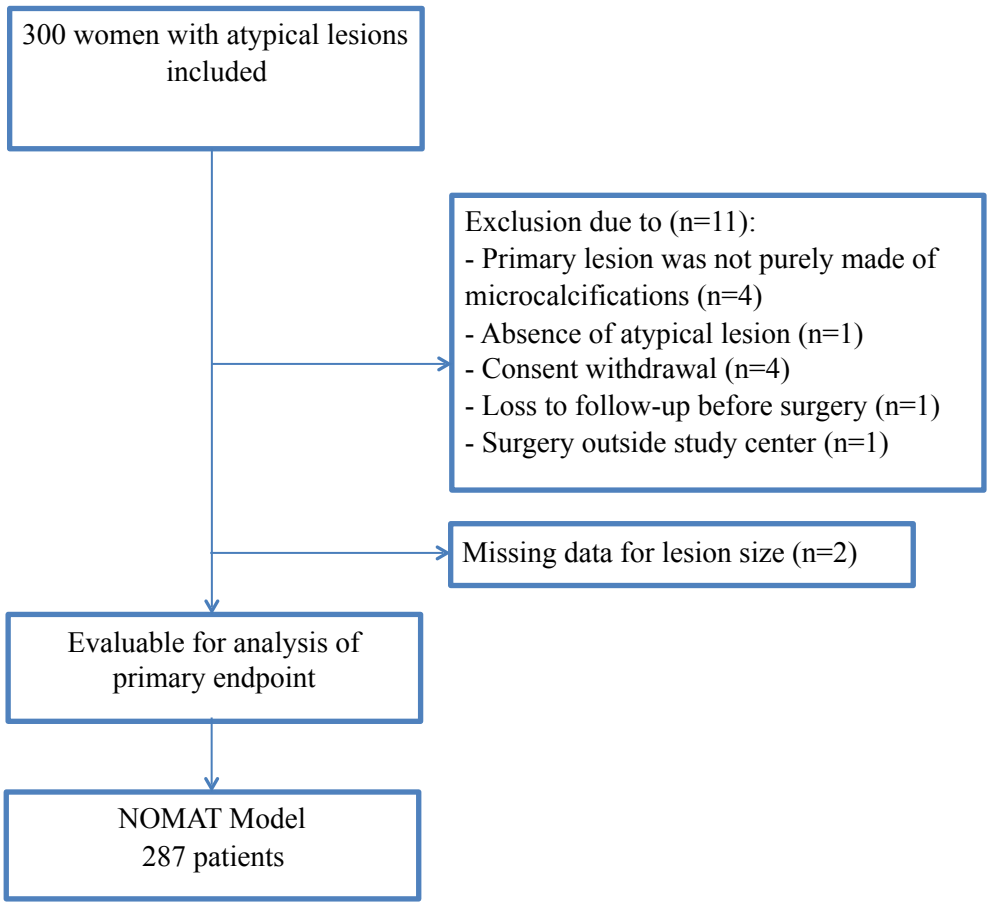


Figure 2: ROC curve of the NOMAT model

The Area Under the Receiving Operating Characteristics Curve (AUC) of the NOMAT model in the whole cohort (n=287) was 0.64 (95% CI, 0.58 to 0.69).

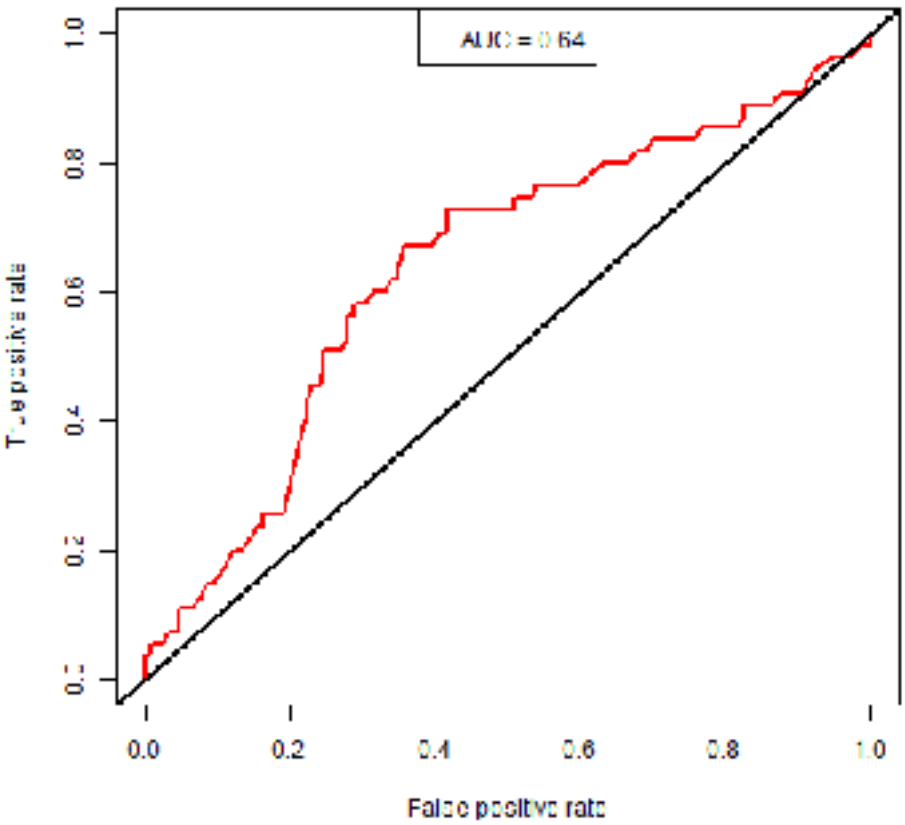


Figure 3: Predicted probability of breast cancer for the whole cohort (n=287, Figure 3A) and for patients with ADH (alone or associated, n=195, Figure 3B)

The patients were classified as bearing "cancer" on the final surgical sample if either an invasive adenocarcinoma or a DCIS or pleomorphic LCIS was retrieved, whatever the extent.

Figure 3A

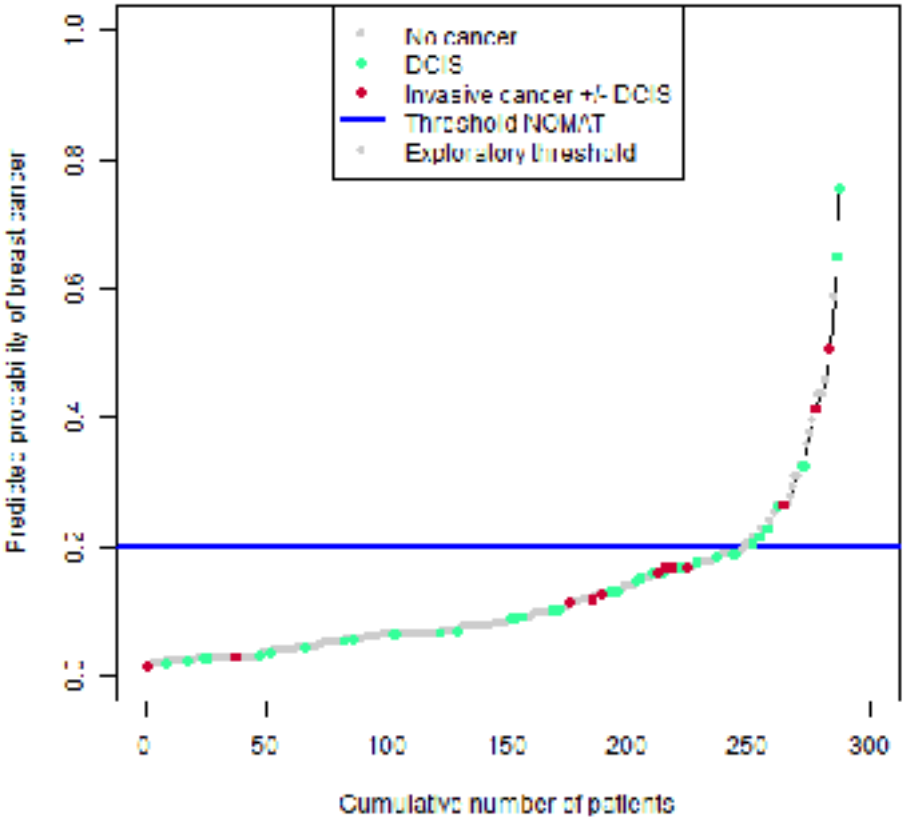


Figure 3B

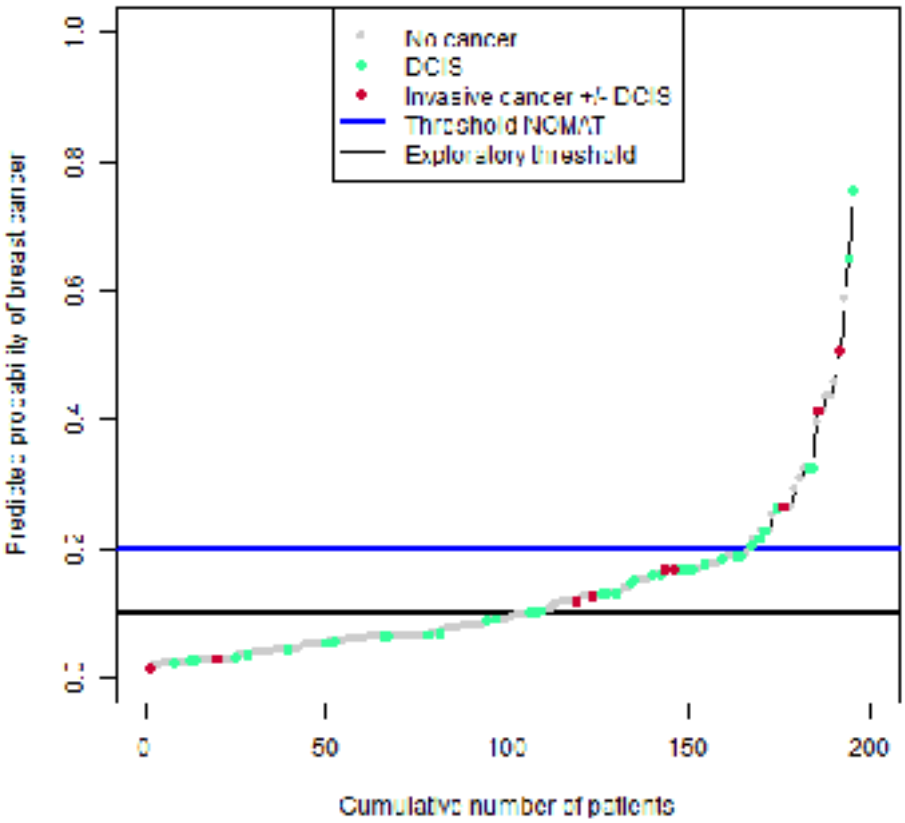
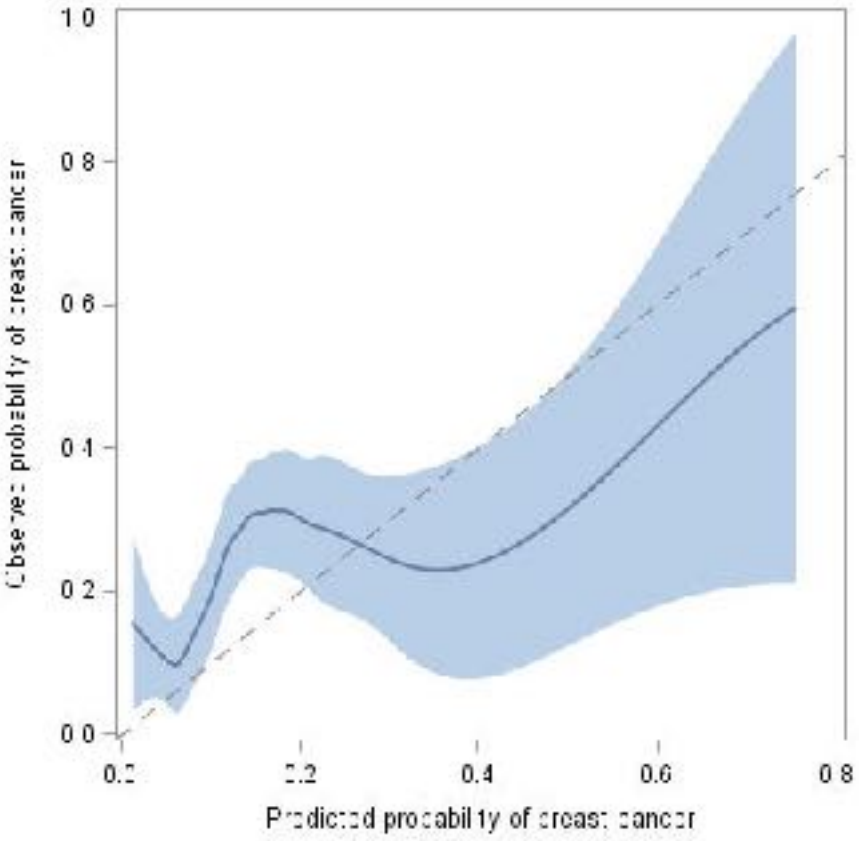

No cancer
DCIS
Invasive cancer +/- DCIS
Threshold NOMAT
Exploratory threshold
Predicted probability of breast cancer
0.0
0.2
0.4
0.6
0.8
1.0
0
50
100
150
200
Cumulative number of patients

Figure 4: Calibration plot of the NOMAT model (n=287)

Blue line corresponds to a LOESS fit (with 95% confidence bounds), the dotted line to the theoretical perfect calibration.