SLNB-Free Prediction of ≥pN2 Disease in Primary Breast Cancer

Research Question

Can we preoperatively predict ≥pN2 disease in patients undergoing upfront surgery for breast cancer—**without using sentinel lymph node biopsy (SLNB) data**? I.e. preoperatively identify patients with high nodal burden in patients eligible for SLNB abstention according to SOUND criteria according to ASCO guidelines (see below).

Background

Current guidelines [1] recommend omitting SLNB in selected postmenopausal patients aged ≥50 years with (SOUND criteria: Grade 1–2 tumours, tumour size ≤2 cm, hormone receptor–positive, HER2 (Human epidermal growth factor receptor 2)-negative, negative pre-operative axillary ultrasound, and undergoing breast-conserving therapy.

Since the publication of large trials (ACOSOG Z0011[2], EORTC AMAROS [3], OTOASOR trial [4], SINODAR one [5], IBCSG 23-01 [6], and SENOMAC [7]), it is now considered safe to leave behind a low nodal burden (1–2 macrometastases), provided that appropriate adjuvant treatment is administered. This implies that residual metastatic burden may be left in the axilla. The approach must be carefully weighed against the risks and side effects of axillary surgery [8].

The omission of cALND and surgical staging of the axilla leaves a clinical dilemma since ≥pN2 disease requires additional treatment considerations, most importantly the addition of CDK4/6 inhibitors (e.g., abemaciclib) in postmenopausal women and planning for radiotherapy if nodal burden is high [9-12].

Efforts have been made to provide a nomogram for the identification of high nodal burden in this patient group utilizing SLNB-data [13, 14].

Can we identify patients with ≥pN2 disease preoperatively, without relying on SLNB?

While multimodal machine learning algorithms including also data from imaging modalities may offer improved predictive accuracy for the extent of nodal involvement, simpler tools such as nomograms or risk estimation models may still serve as valuable decision-support aids. These tools can enable both patients and multidisciplinary clinical teams to develop reasonably accurate intuitions about the likelihood of ≥pN2 category disease using limited information — as proposed here, possibly also *without* information from SLNB. The suggested research aim is to develop a model based strictly on easily available ***preoperative*** available variables. Hence, for example, the prognostic marker lymphovasular invasion is omitted since it is not routinely available from core biopsy needle data.

Proposal

Develop a predictive model for ≥pN2 disease using the tabular strictly preoperative available data using a national registry extract.

Cohort considerations

For this study, only retrospective data use is feasible; the data most predate clinical introduction of SLNB-abstention (SENOMAC) in this patient population. Strictly preoperatively available predictors, as in the paper by Rejmer et al [15].

Cohort: The NKBC 2014-2023 data extract.

Ethical approval obtained from the Swedish Ethical Review Authority: 2024-02690-02

In a ≥pN2 prediction model, can we:

1) identify patients in whom ≥pN2 is very unlikely? Further risk stratification?
2) identify patients in whom risk of ≥pN2 is higher within this low-risk population. i.e. risk stratification

Statistical considerations

Cohort split by temporality: in training and test set (70/30)

Variable selection: Clinical a-priori predictors plus statistically derived least absolute shrinkage and selection operator (LASSO) logistic regression applied to all candidate predictors to select the most important. Followed by X-fold cross-validation in the training set.

Univariable logistic regression analysis to explore the unadjusted associations between each candidate predictor and the endpoint in the training set. Events-per-variable (EPV) rule ≥10.

Model selection: Model achieving the highest specificity at a sensitivity of ≥90%

The selected model will be taken to validation.

- To evaluate discriminatory ability, AUC calculated in the test set.
- Calibration assessed in the test set using calibration plots (graphical) and calibration slope/intercept (numerical).
- Clinical utility: decision curve analyses on the test set.

Kaplan-Meier curves (overall survival): 1) By nodal status. 2) High- and low risk groups bases on model. Multivariable cox regression model(s) (test for causal inference)

Endpoints

Descriptive: Prevalence of ≥pN2
Analytical: Prediction model(s) for risk stratification (≥pN2).

Clinical / Demographic Variables to a priori consider available in registry extract

Variable	
Age at diagnosis	yes
Sex	Only female
Tumour size (clinical T or mm continuous)	mm, yes
Multifocality (yes/no)	Only unifocal eligible
Screening detected	Can be included

Histology (ductal/lobular/other)	Only non-lobular eligible
Nottingham histological tumour grade	1 vs 2 (3 not eligible)
ER / PR / HER2 status (categorical)	Only ER+/HER2-
Ki-67	Can be included
Lymphovascular invasion (LVI) (yes/no)	Not preoperatively available in core needle biopsy
Size of tumour deposit in SLN (micromet ≤2 mm vs macromet >2 mm)	no SLNB data
Number of positive sentinel lymph nodes	no SLNB data
Axillary ultrasound findings (cortex thickening, absence of fatty hilum, suspicious nodes)	no imaging data
Mammograph/MRI/Other	no imaging data
Total number of sentinel nodes removed	no SLNB data

	Inclusion criteria	**Exclusion criteria**
	Need for outcome measure pN2 - SLNB+ followed by cALND - SLNB benign findings, final pN-status is considered N0 Only feasible in patients in whom omission of SLNB is under consideration.	Only SLNB is **not** an exclusion criterium
SOUND criteria, ASCO guidelines	- ≤2 cm breast cancer - negative finding on preoperative ALN ultrasound - Postmenopausal and ≥50 years - Unifocal invasive ductal carcinoma - Nottingham grades 1-2 - Hormone receptor–positive, HER2-negative - adjuvant endocrine therapy - Undergoing upfront breast-conservation surgery - whole-breast RT in patients <65 years of age	

REFERENCES

1. Park KU, Somerfield MR, Anne N, Brackstone M, Conlin AK, Couto HL, Dengel LT, Eisen A, Harvey BE, Hawley J *et al*: **Sentinel Lymph Node Biopsy in Early-Stage Breast Cancer: ASCO Guideline Update**. *Journal of Clinical Oncology* 2025, **43**(14):1720-1741.
2. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, Ollila DW, Hansen NM, Whitworth PW, Blumencranz PW *et al*: **Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial**. *JAMA* 2017, **318**(10):918-926.
3. Bartels SAL, Donker M, Poncet C, Sauve N, Straver ME, van de Velde CJH, Mansel RE, Blanken C, Orzalesi L, Klinkenbijl JHG *et al*: **Radiotherapy or Surgery of the Axilla After a Positive Sentinel Node in Breast Cancer: 10-Year Results of the Randomized Controlled EORTC 10981-22023 AMAROS Trial**. *J Clin Oncol* 2023, **41**(12):2159-2165.
4. Savolt A, Peley G, Polgar C, Udvarhelyi N, Rubovszky G, Kovacs E, Gyorffy B, Kasler M, Matrai Z: **Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla - Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial**. *Eur J Surg Oncol* 2017, **43**(4):672-679.
5. Tinterri C, Gentile D, Gatzemeier W, Sagona A, Barbieri E, Testori A, Errico V, Bottini A, Marrazzo E, Dani C *et al*: **Preservation of Axillary Lymph Nodes Compared with Complete Dissection in T1-2 Breast Cancer Patients Presenting One or Two Metastatic Sentinel Lymph Nodes: The SINODAR-ONE Multicenter Randomized Clinical Trial**. *Ann Surg Oncol* 2022, **29**(9):5732-5744.
6. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, Baratella P, Chifu C, Sargenti M, Intra M *et al*: **Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial**. *Lancet Oncol* 2013, **14**(4):297-305.
7. de Boniface J, Filtenborg Tvedskov T, Ryden L, Szulkin R, Reimer T, Kuhn T, Kontos M, Gentilini OD, Olofsson Bagge R, Sund M *et al*: **Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases**. *N Engl J Med* 2024, **390**(13):1163-1175.
8. de Boniface J, Appelgren M, Szulkin R, Alkner S, Andersson Y, Bergkvist L, Frisell J, Gentilini OD, Kontos M, Kuhn T *et al*: **Completion axillary lymph node dissection for the identification of pN2-3 status as an indication for adjuvant CDK4/6 inhibitor treatment: a post-hoc analysis of the randomised, phase 3 SENOMAC trial**. *Lancet Oncol* 2024, **25**(9):1222-1230.
9. Rastogi P, O'Shaughnessy J, Martin M, Boyle F, Cortes J, Rugo HS, Goetz MP, Hamilton EP, Huang CS, Senkus E *et al*: **Adjuvant Abemaciclib Plus Endocrine Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative, High-Risk Early Breast Cancer: Results From a Preplanned monarchE Overall Survival Interim Analysis, Including 5-Year Efficacy Outcomes**. *J Clin Oncol* 2024, **42**(9):987-993.
10. Cardoso F, van't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S, Pierga JY, Brain E, Causeret S, DeLorenzi M *et al*: **70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer**. *N Engl J Med* 2016, **375**(8):717-729.
11. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, Zackrisson S, Senkus E, clinicalguidelines@esmo.org EGCEa: **Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-updagger**. *Ann Oncol* 2019, **30**(8):1194-1220.
12. Johnston SRD, Harbeck N, Hegg R, Toi M, Martin M, Shao ZM, Zhang QY, Rodriguez JLM, Campone M, Hamilton E *et al*: **Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2−, Node-Positive, High-Risk, Early Breast Cancer (monarchE)**. *Journal of Clinical Oncology* 2020, **38**(34):3987-3998.
13. Skarping I, Bendahl PO, Szulkin R, Alkner S, Andersson Y, Bergkvist L, Christiansen P, Filtenborg Tvedskov T, Frisell J, Gentilini OD *et al*: **Prediction of High Nodal Burden in Patients With Sentinel Node-Positive Luminal ERBB2-Negative Breast Cancer**. *JAMA Surg* 2024, **159**(12):1393-1403.
14. Wanis KN, Dong W, Shen Y, Meric-Bernstam F, Adesoye T, Kuerer HM, Caudle AS, Tamirisa N, DeSnyder SM, Sun SX *et al*: **Predicting pathologic >/=N2 disease in women with breast cancer**. *NPJ Breast Cancer* 2025, **11**(1):46.
15. Rejmer C, Dihge L, Bendahl PO, Fornvik D, Dustler M, Ryden L: **Preoperative prediction of nodal status using clinical data and artificial intelligence derived mammogram features enabling abstention of sentinel lymph node biopsy in breast cancer**. *Front Oncol* 2024, **14**:1394448.