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# Invasive lobular cancer: lymph node involvement

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# Conflict of interest

- Honoraria from Medicinske Tidskrifter (lecturing)
  
- Funding
  - Swedish Research Council
  - Swedish Cancer Society
  - The Erling Persson Family Foundation
  - Sjöbergstiftelsen
  - Governmental funding for clinical research (Alf)

# Why is invasive lobular cancer so fascinating for a surgeon?



CASE REPORT

Taylor & Francis  
healthsciences

## Small Bowel Obstruction Caused by Intestinal Metastases from Undiagnosed Breast Cancer: Report of Two Cases

Lisa Rydén<sup>1</sup>, Gunilla Chebil<sup>2</sup> and Per-Ebbe Jönsson<sup>1</sup>

From the <sup>1</sup>Departments of Surgery, and <sup>2</sup>Pathology, Helsingborgs Lasarett, Helsingborg, Sweden

Eur J Surg 2002; 168: 648–650



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# Invasive lobular cancer

- Risk factors for lymph node involvement
- Invasive lobular cancer and sentinel node biopsy
- Invasive lobular cancer and nodal status (low burden vs high burden)
- Invasive lobular cancer and putative consequence of de-escalating axillary surgery

**"LESS IS MORE"**

**1900**

**1950**

**2000**

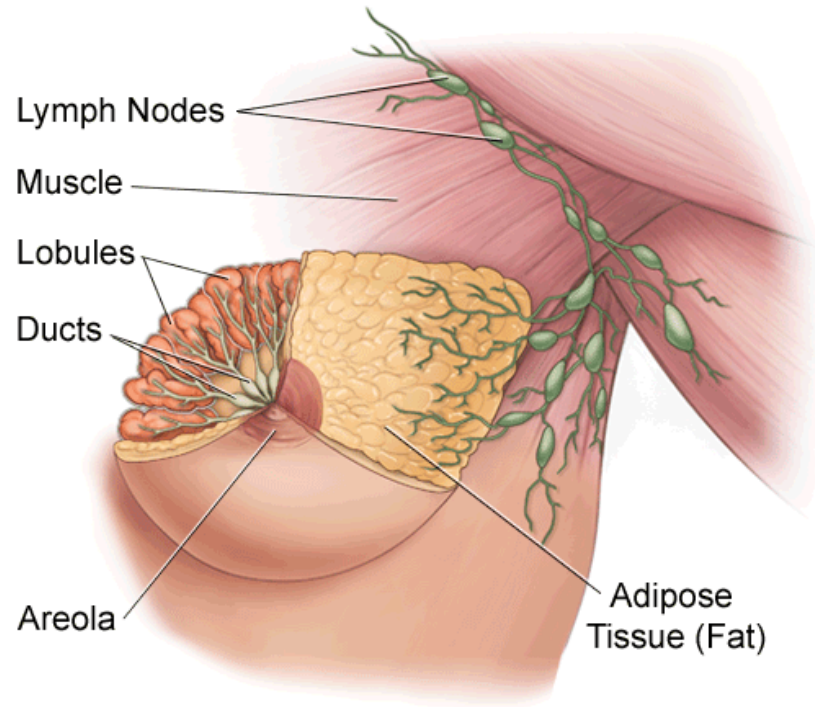
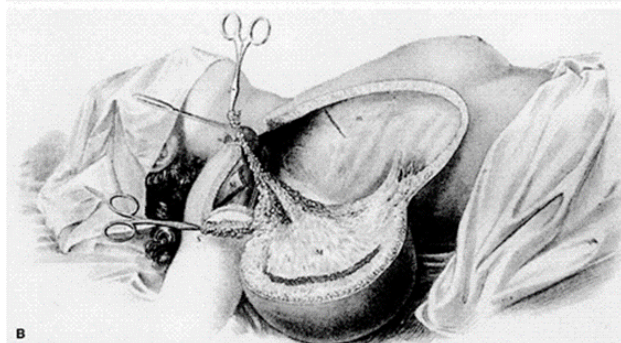
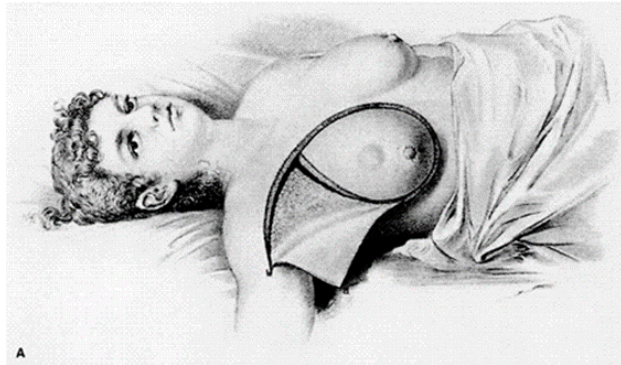
Radical mastectomy

Modified radical mastectomy

Breast-conserving surgery

Breast reconstruction

**Front View of Breast**



Sentinel node biopsy

No axillary dissection

No axillary staging



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# Development of axillary surgery

ALND as staging method

Sentinel node biopsy for all cN0

ALND only for pN1

Sentinel node biopsy only for pN1-2+

Abstaining sentinel node biopsy for selected patients

**ASCO**® AMERICAN SOCIETY OF CLINICAL ONCOLOGY

- **75-80% of breast cancer patients are node negative at diagnosis**
- **Nodal status is a riskstratifying factor for adjuvant therapy in a minor proportion of patients**



# Lymphatic spread – chronology or biology?

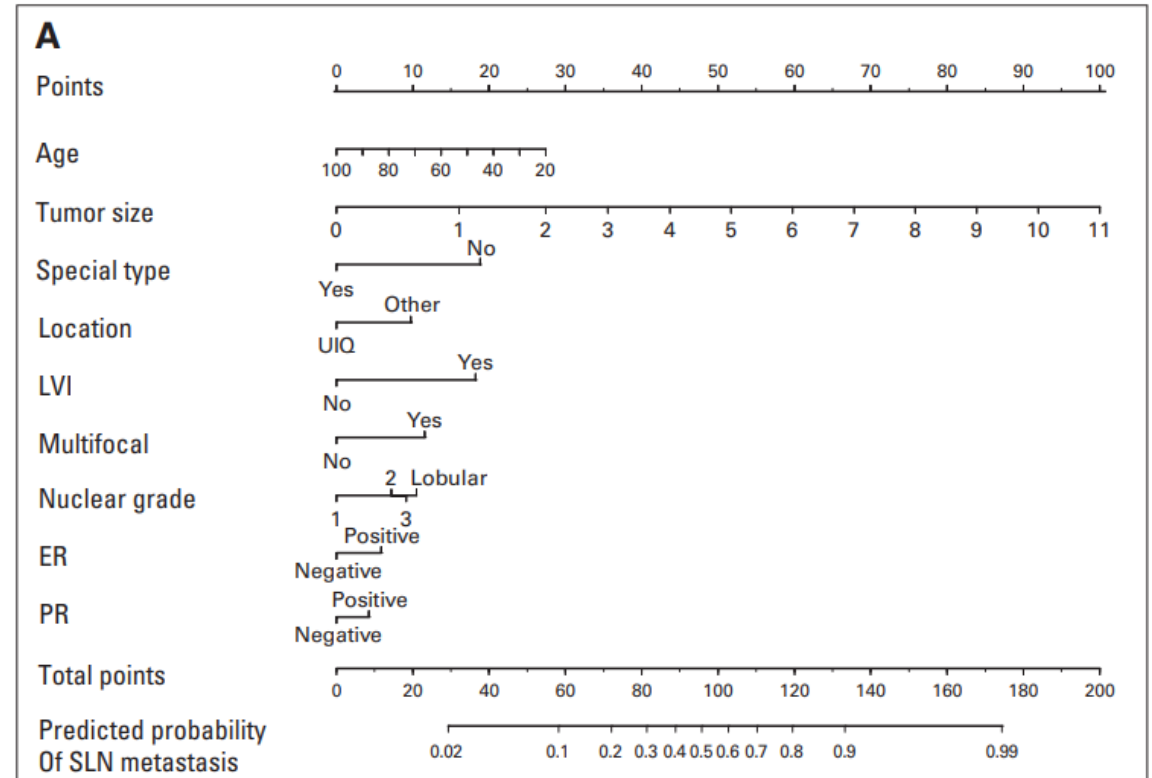
RESEARCH

Open Access

## Impact of tumor chronology and tumor biology on lymph node metastasis in breast cancer

Ann Smeets<sup>1,3†</sup>, Andries Ryckx<sup>1†</sup>, Ann Belmans<sup>2</sup>, Hans Wildiers<sup>1,4</sup>, Patrick Neven<sup>1,5</sup>, Giuseppe Floris<sup>1,6</sup>, Patrick Schöffski<sup>4</sup> and Marie-Rose Christiaens<sup>1,3</sup>

The combination of *T size = chronology* and *tumor biology* is the best prediction model for nodal spread



VOLUME 25 · NUMBER 24 · AUGUST 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## Doctor, What Are My Chances of Having a Positive Sentinel Node? A Validated Nomogram for Risk Estimation

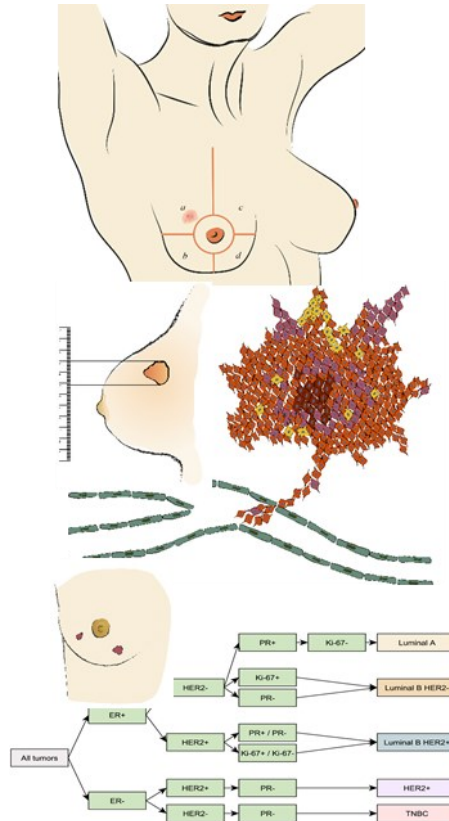
José Luiz B. Bevilacqua, Michael W. Kattan, Jane V. Fey, Hiram S. Cody III, Patrick I. Borgen, and Kimberly J. Van Zee

# Leave the axilla alone with a good prediction model



*1/3 of patients could be classified as having an ultralow risk of nodal metastasis*

- Tumor size
- Age
- Screeningdetection
- Localisation
- Multifocality
- Vascular invasion
- Histopathology
- ER, PR, Ki67



The screenshot shows the NILS calculator interface. The input parameters are: Age at diagnosis (years): 78 years; Screening-detected: No; Localisation of the largest tumor: Laterality: Left, Central in the breast: No, Position in the breast: Undefined; Tumor size (mm): 3 mm; Histopathological type: Ductal (NST); Multifocal or multicentric: No; Vascular invasion: No; ER status: Negative; PR status: Negative; Proliferation index, Ki67 (%): 7%. The results section shows a probability distribution graph with a vertical line at 91% and a "Summary of results" section.

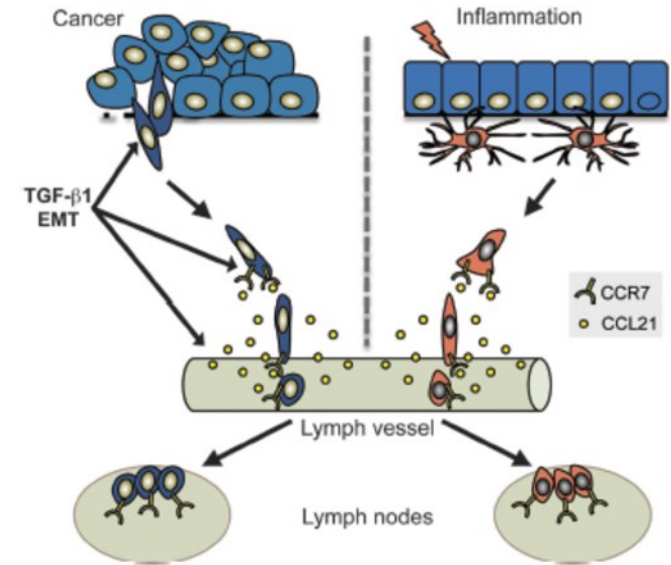
**Results**

91%

**Summary of results**  
Here, we will provide a textual summary of the analysis results, to ensure that the interpretation is correct.



# Tumor related factors and lymphatic spread

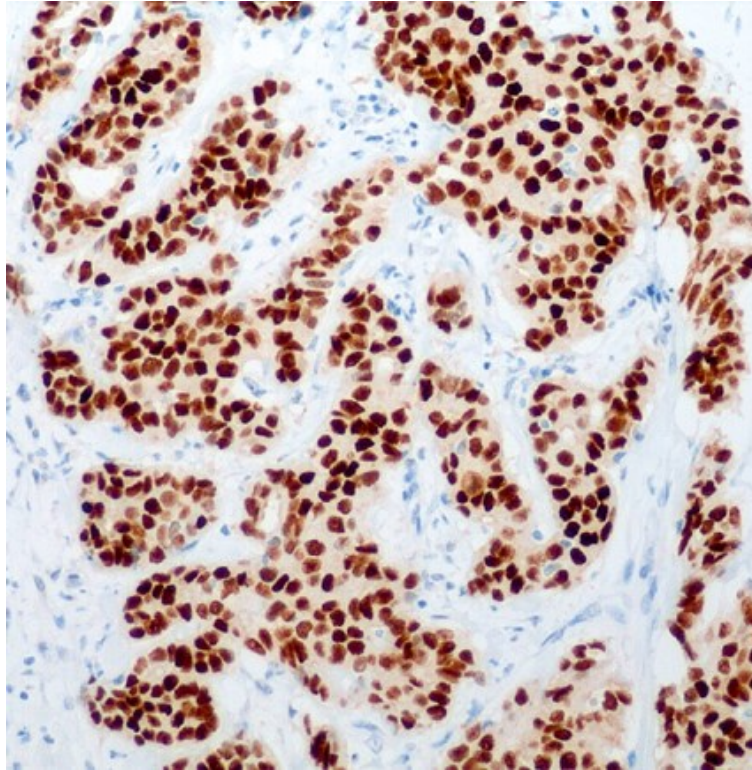


- **Histopathology - Lobular cancers** have more nodal metastasis, **medullary** less
- **Molecular subtypes – TNBCs** have a low risk of nodal metastasis, **luminal** a higher risk
- **Immune response; Tumor infiltrating lymphocytes** and **Immune signatures** are associated with less nodal metastasis
- **Growth factors and cytokines are** related to nodal metastasis



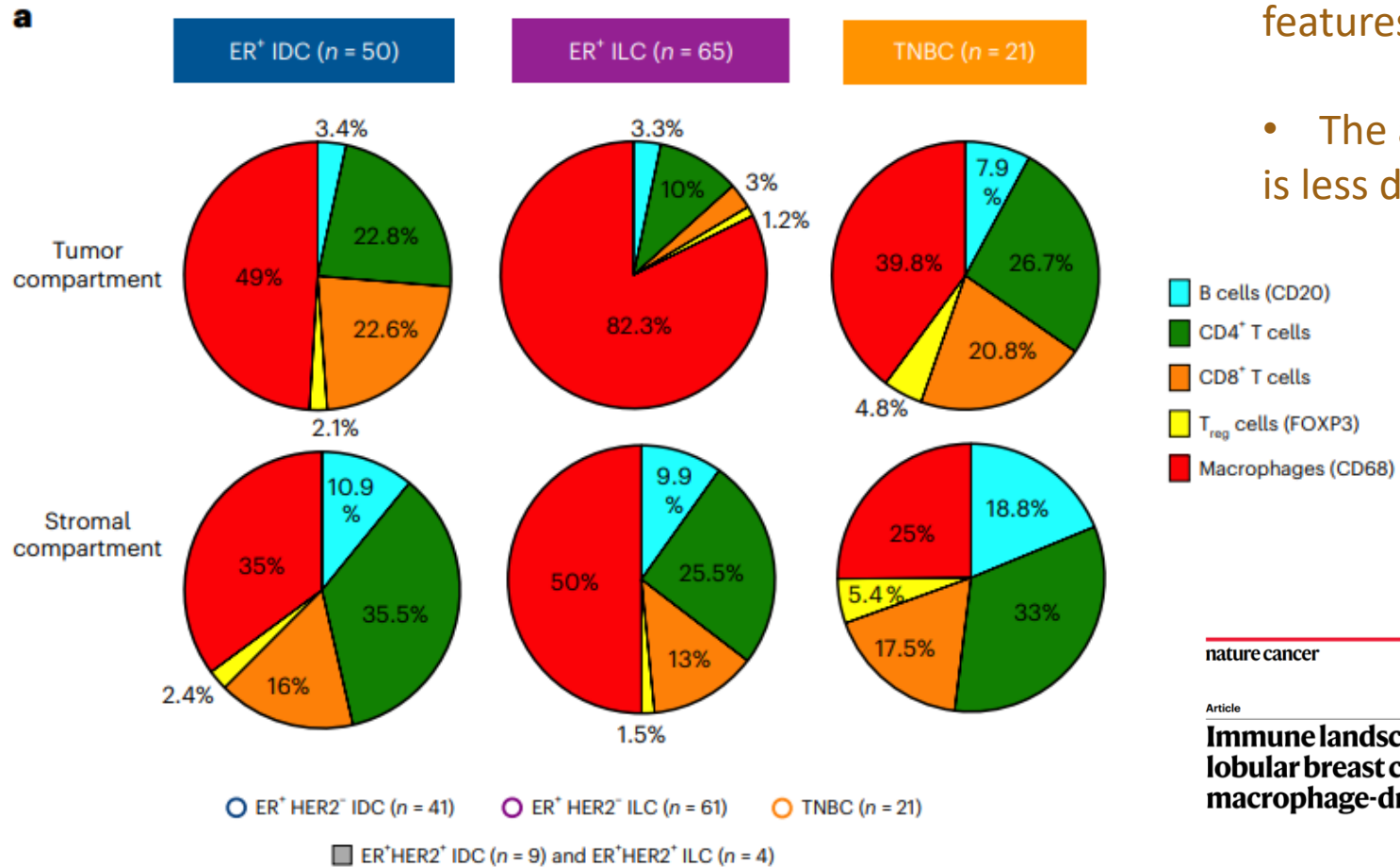
# Luminal tumors compared with TNBC and lymphatic spread

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- Tumor size ↓
- Proliferation ↓ ↑ (grade and Ki67 matters)
- Tumor infiltrating lymphocytes ↓
- Tumor mutational burden ↓
- **Nodal metastasis** ↑
- Late recurrences ↑

# The immune landscape of ER+/HER2-



- Macrophages are dominating features in luminal breast cancer
- The adaptive immune response is less dominant in ILCs

nature cancer

Article

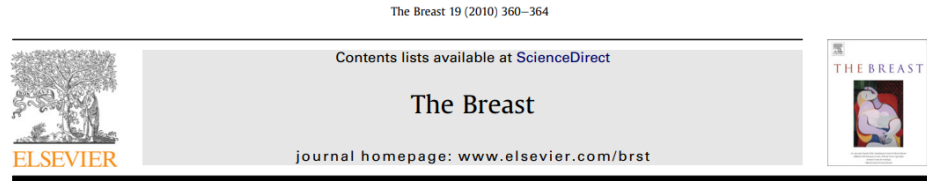
<https://doi.org/10.1038/s43018-023-00527-w>

**Immune landscape in invasive ductal and lobular breast cancer reveals a divergent macrophage-driven microenvironment**



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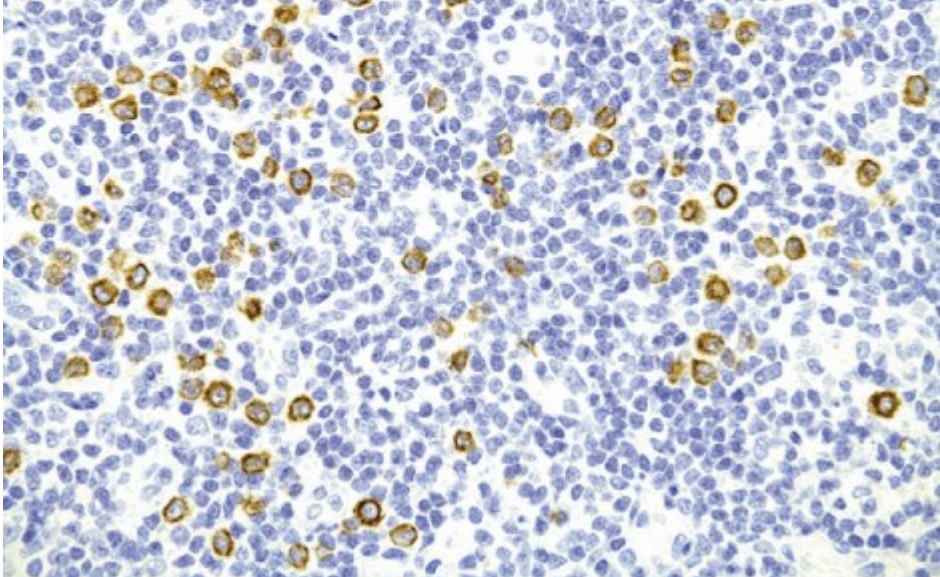
# Diagnosis of nodal involvement in sentinel node biopsy in invasive lobular cancers



Original article

Accurate classification of sentinel lymph node metastases in patients with lobular breast carcinoma

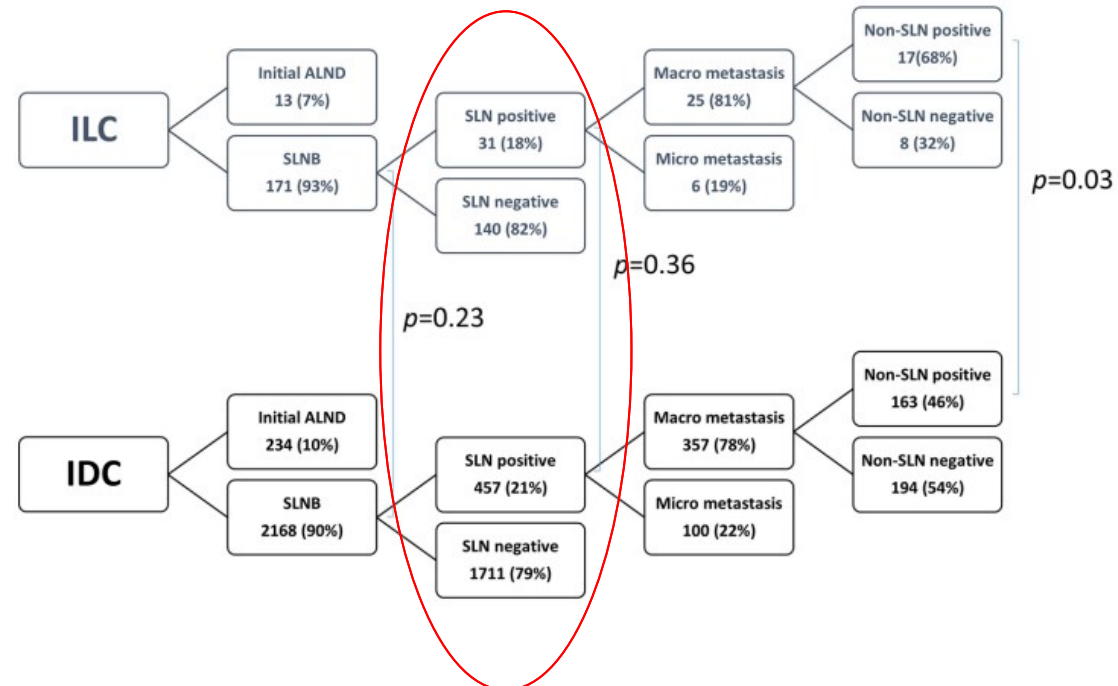
Sophia K. Apple<sup>b,1</sup>, Neda A. Moatamed<sup>c,2</sup>, Rachel H. Finck<sup>d,3</sup>, Peggy S. Sullivan<sup>a,\*</sup>






- The growth pattern of invasive lobular cancer poses classification problems
- Isolated tumor cells might represent micro- or macrometastasis
- The consistent use of cytokerating staining has improved the classification of nodal spread in invasive lobular cancer

# Invasive lobular cancer and sentinel node metastasis

- A clinically healthy axilla can be associated with nodal metastasis especially in invasive lobular cancer
- The risk of sentinel node metastasis is not higher in invasive lobular cancer



# St Gallen 2019 guidelines understage the axilla in lobular breast cancer: a population-based study

U. Narbe <sup>1,2</sup>, P.-O. Bendahl<sup>1</sup>, M. Fernö<sup>1</sup>, C. Ingvar <sup>3,4</sup>, L. Dihge <sup>3,5</sup> and L. Rydén<sup>3,4,\*</sup>

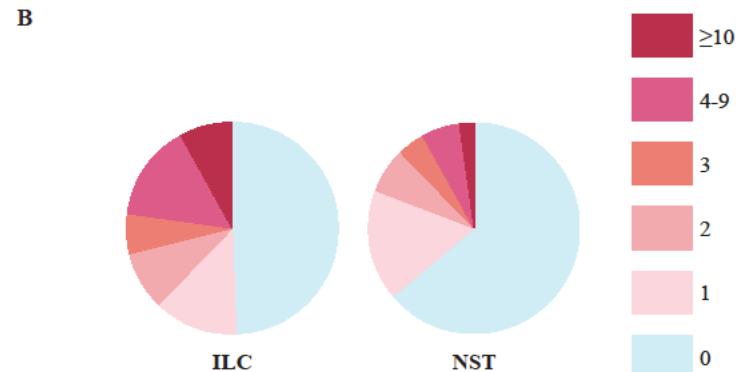
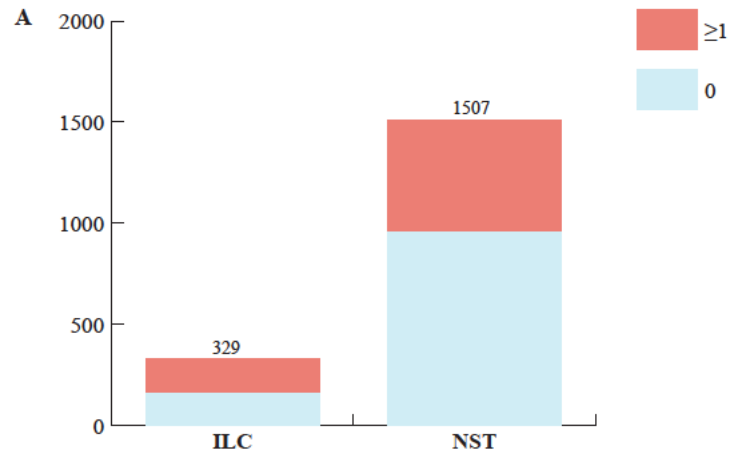
- Data from NKBC 2014-2017 (ALND was still performed in patients with SLNMs)
- Patients with ILC, NST and mixed ILC/NST type were included (n=1886) and those fulfilling the criteria for omission of cALND according to the St Gallen 2019 and Z0011 constituted the study population
- The aim was to decipher the nodal metastatic load in patients fulfilling the criteria for cALND omission stratified by surrogate molecular subtype as an indicator of understaging



# Lobular breast cancer has an increased risk of non-sentinel node metastasis

ILC has a higher proportion of patients with non-sentinel node metastasis

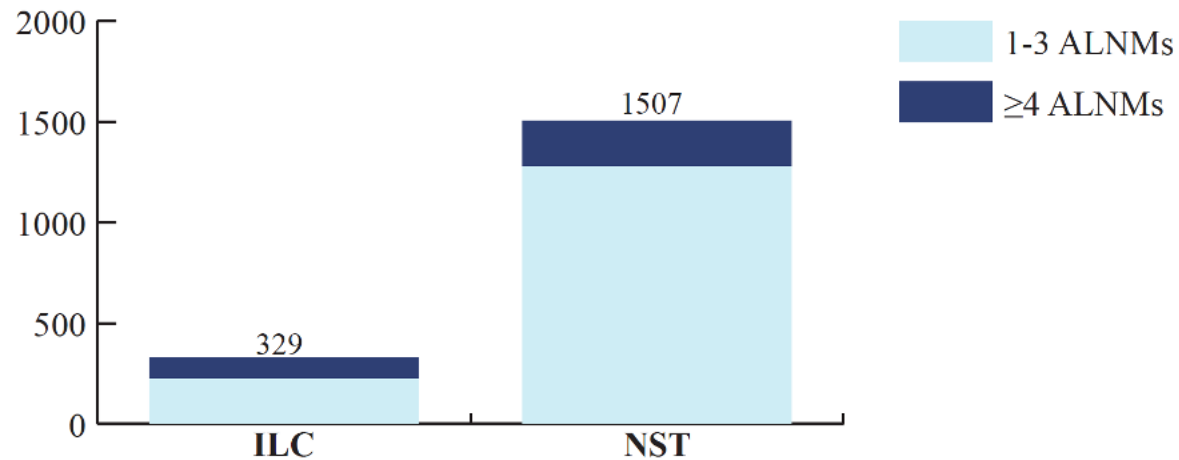
Non-sentinel node metastases in the St. Gallen 2019 cohort



- Mostly luminal A tumors
- Loss of E-cadherin
- Scattered infiltrative tumor growth in files
- Highly estrogen responsive
- Low proliferation
- Increased risk of late recurrences
- High stroma content

# Patients with ILC have a higher nodal metastatic burden (stage III and beyond)

1-3 and  $\geq 4$  ALNMs by histological subtype



31% ILC vs. 15% NST

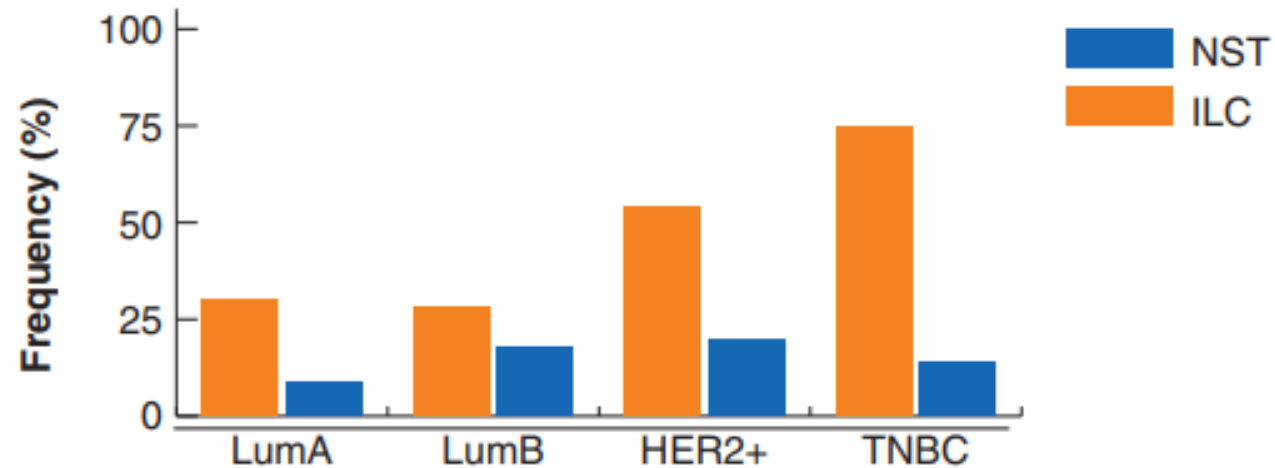
ILS was an independent predictor of high nodal burden





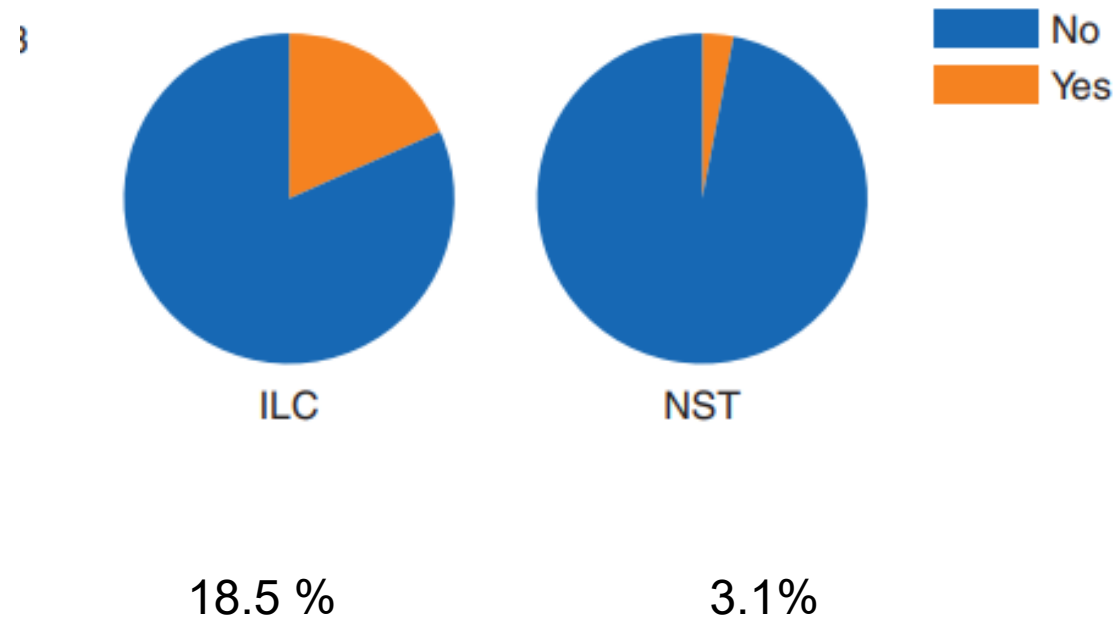
# The risk of high nodal burden is independent of molecular subtype

**c** Frequency of four or more ALN metastases by surrogate molecular subtype



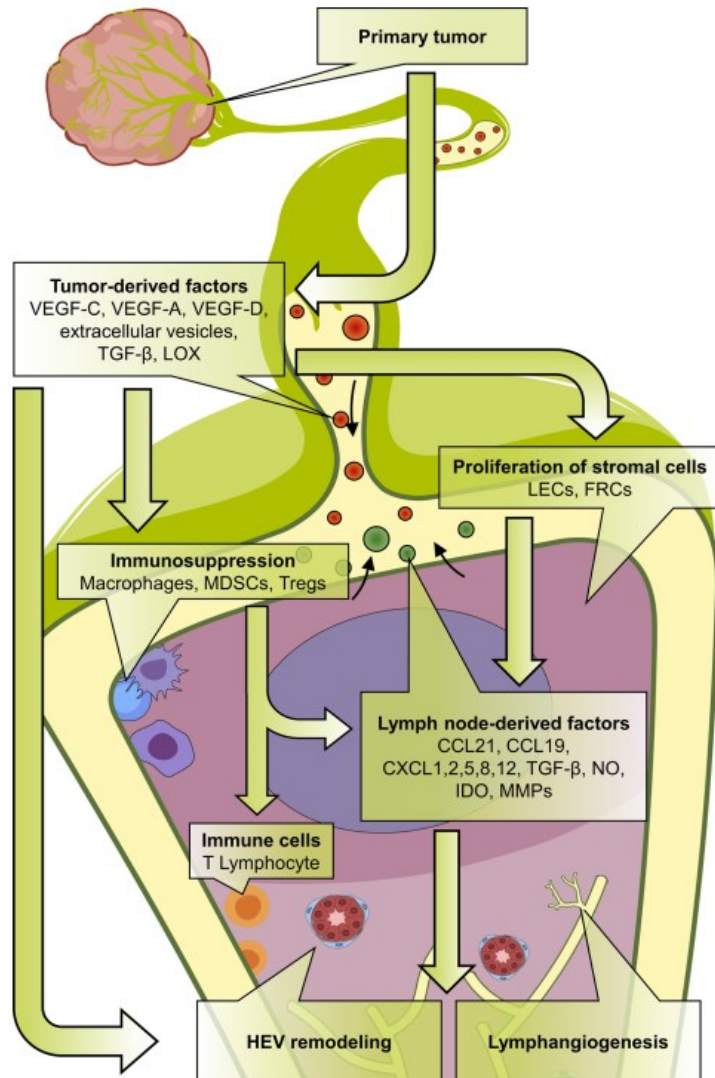
# Luminal A-like ILC has a higher proportion of stage N2

**b** Luminal A-like subtype and four or more ALN metastases



Any consequence for patients with ILC receiving adjuvant chemotherapy??

# No increased risk of sentinel node metastasis in ILC but of non-sentinel node metastasis – WHY???



- Immune competence of sentinel node metastasis in NST compared to ILC?
- Pre-metastatic niche?
- Simply a matter of understaging of sentinel nodes in ILC???

Cellular and Molecular Life Sciences (2021) 78:5987–6002  
<https://doi.org/10.1007/s00018-021-03873-z>

Cellular and Molecular Life Sciences

REVIEW



The pre-metastatic niche in lymph nodes: formation and characteristics

Lionel Gillot<sup>1</sup> · Louis Baudin<sup>1</sup> · Loïc Rouaud<sup>1</sup> · Frédéric Kridelka<sup>2</sup> · Agnès Noël<sup>1</sup>

# Oncological treatment decisions and nodal metastasis

- Nodal status is of importance for oncological treatment decision especially in postmenopausal patients with luminal A tumors and a positive sentinel node
- The higher risk of non-sentinel node metastasis in ILC of the luminal A subtype might be translated into systemic under-treatment
- Does this matter in terms of survival given that all of them will receive adjuvant radiotherapy and ten years of endocrine treatment?



# Axillary dissection to determine nodal burden

## to inform systemic therapy recommendations in patients with clinically node-positive breast cancer:

### Pre-planned substudy of TAXIS (OPBC-03, SAKK 23/16, IBCSG 57-18, ABCSG-53, GBG 101)

Walter P. Weber, MD<sup>1,2</sup>; Zoltan Matrai, MD, PhD<sup>3</sup>; Stefanie Hayoz, PhD<sup>4</sup>; Christoph Tausch, MD<sup>5</sup>; Guido Henke, MD<sup>6,7</sup>; Daniel R. Zwahlen, MD<sup>8</sup>; Günther Gruber, MD<sup>9</sup>; Frank Zimmermann, MD<sup>2,10</sup>; Thomas Ruhstaller, MD<sup>11</sup>; Simone Muenst, MD<sup>2,12</sup>; Markus Ackermann, PhD<sup>2,13</sup>; Sherko Kueffel, MD, PhD<sup>14</sup>; Vesna Bjelic-Radisic, MD<sup>15</sup>; Viktor Smánykó, MD<sup>16</sup>; Conny Vrieling, MD, PhD<sup>17</sup>; Rok Sattler, MD<sup>18</sup>; Inna Meyer, MD<sup>19</sup>; Charles Becciolini, MD<sup>20</sup>; Susanne Bucher, MD<sup>21</sup>; Colin Simonson, MD<sup>22</sup>; Peter M. Fehr, MD<sup>23</sup>; Natalie Gabriel, MD<sup>24</sup>; Robert Maráz, MD<sup>25</sup>; Dimitri Sarlos, MD<sup>26</sup>; Konstantin J. Dedes, MD<sup>27</sup>; Cornelia Leo, MD<sup>28</sup>; Gilles Berclaz, MD<sup>29</sup>; Hisham Fansa, MD<sup>30</sup>; Christopher Hager, MD<sup>31</sup>; Klaus Reisenberger, MD<sup>32</sup>; Ákos Sávólt, MD, PhD<sup>33</sup>; Christian F. Singer, MD<sup>34</sup>; Roland Reitsamer, MD<sup>35</sup>; Jelena Winkler, MD<sup>36</sup>; Giang Thanh Lam, MD<sup>37</sup>; Mathias K. Fehr, MD<sup>38</sup>; Tatiana Naydina, MD<sup>39</sup>; Magdalena Kohlik, MD<sup>40</sup>; Karine Clerc, MD<sup>41</sup>; Valerijus Ostapenko, MD<sup>42</sup>; Florian Fitzal, MD<sup>43</sup>; Martin Heideringer, MD<sup>1,2</sup>; Nadia Maggi, MD<sup>1,2</sup>; Alexandra Schulz<sup>2,44</sup>; Pagona Markellou, MD<sup>45</sup>; Loïc Lelièvre, MD<sup>46</sup>; Daniel Egle, MD<sup>47</sup>; Jörg Heil, MD<sup>47</sup>; Michael Knauer, MD, PhD<sup>47</sup>; Andreas Mueller, MD<sup>4</sup>; Christian Kurzeder, MD<sup>1,2</sup>

1 Breast Center, University Hospital Basel, Basel, Switzerland, 2 University of Basel, Basel, Switzerland, 3 Hamad Medical Corporation, General Surgery, Doha, Qatar, 4 SAKK Coordinating Center, Bern, Switzerland, 5 Breast Center Zurich, Zurich, Switzerland, 6 Department of Radiation Oncology, St. Gallen Cantonal Hospital, St. Gallen, Switzerland, 7 Breast Center, St. Gallen Cantonal Hospital, St. Gallen, Switzerland, 8 Department of Radiation Oncology, Cantonal Hospital Winterthur, Winterthur, Switzerland, 9 Institute of Radiotherapy, Klinik Hirslanden, Zurich, Switzerland, 10 Department of Radiation Oncology, University Hospital Basel, Basel, Switzerland, 11 Tumor and Breast Center Eastern Switzerland, St. Gallen, Switzerland, 12 Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland, 13 Department of Biomedicine, University Hospital Basel, Basel, Switzerland, 14 Breast Unit, Kliniken Essen-Mitte, Essen, Germany, 15 Breast Unit, Helios University Clinic, University Witten/Herdecke, Germany, 16 Centre of Radiotherapy, National Institute of Oncology, Budapest, Hungary, 17 Department of Radiation Oncology, Hirslanden Clinique des Granges, Geneva, Switzerland, 18 Breast Center, Cantonal Hospital Winterthur, Winterthur, Switzerland, 19 Lindenhof Hospital, Praxis Frauenzentrum, Bern, Switzerland, 20 Breast Center, Réseau Hospitalier Neuchâtelais, La Chaux-de-Fonds, Switzerland, 21 Breast Center, Cantonal Hospital Lucerne, Lucerne, Switzerland, 22 Department of Gynecology, Centre Hospitalier du Valais Romand (CHVR), Hôpital de Sion, Switzerland, 23 Breast Center Graubünden, Cantonal Hospital Graubünden, Chur, Switzerland, 24 Breast Center, City Hospital Triemli, Zurich, Switzerland, 25 Department of Oncology, Bacs-Kiskun County Hospital, Kecskemet, Hungary, 26 Breast Center, Cantonal Hospital Aarau, Aarau, Switzerland, 27 Breast Center, University Hospital of Zurich, Zurich, Switzerland, 28 Breast Center, Cantonal Hospital Baden, Baden, Switzerland, 29 Breast Center, Unterhof group, Bern, Switzerland, 30 Breast Center Zurich, Dornbirn, Austria, 31 Department of Gynecology and Obstetrics, City Hospital, Dornbirn, Austria, 32 Department of Gynecology and Obstetrics, Klinikum Weis-Grieskirchen, Weis, Austria, 33 Department of Breast and Sarcoma Surgery, National Institute of Oncology, Budapest, Hungary, 34 Department of Gynecology and Obstetrics and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria, 35 Breast Center, Paracelsus Medical University of Salzburg, Salzburg, Austria, 36 Breast Center, Basel Bethesda Hospital, Basel, Switzerland, 37 Breast Center, University Hospital of Geneva, Geneva, Switzerland, 38 Breast Center Thurgau, Münstertal, Switzerland, 39 Spital Linthmatt, Schlieren, Switzerland, 40 Breast Center GSKM, Clinique de Genolier, Genolier, Switzerland, 41 Brustzentrum Freiburg, Centre du sein Fribourg, Fribourg, Switzerland, 42 National Cancer Institute, Vilnius, Lithuania, 43 Department of Surgery and Breast Health Center, Medical University of Vienna, Vienna, Austria, 44 Department of Clinical Research, University Hospital Basel, Basel, Switzerland, 45 Breast Center, CHUV, Lausanne, Switzerland, 46 Breast Center Tirol, Department of Gynecology, Medical University Innsbruck, Innsbruck, Austria, 47 Breast Center Heidelberg, Heidelberg, Germany

### ABSTRACT

#### Introduction

Chemotherapy is recommended for patients with luminal breast cancer and more than three positive nodes. In addition, recent landmark trials raised the question if the exact number of positive nodes is required to indicate genomic testing. In the neoadjuvant setting, response-driven therapy is increasingly used and may be influenced by surgical staging of the axilla. The present study addressed the role of axillary lymph node dissection (ALND) as decision aid for systemic therapy in a contemporary cohort of patients with clinically node-positive breast cancer in the adjuvant and neoadjuvant setting.

#### Methods

The study was pre-planned in the international multicenter phase-III OPBC-03/TAXIS trial<sup>1</sup> (ClinicalTrials.gov Identifier: NCT03513614). The first 500 patients with clinically node-positive breast cancer who were randomized after tailored axillary surgery (TAS) to undergo ALND or axillary radiotherapy (ART) without ALND in the context of extended regional irradiation were included from August 2018 to June 2022. Clinically node-positive breast cancer was defined by confirmed nodal disease at the time of initial diagnosis; in case of neoadjuvant therapy, the finding of residual nodal disease was mandatory for randomization. TAS consisted of removal of palpably suspicious findings and the sentinel nodes with the option of image guidance. In the ART arm, the total number of positive nodes was not known. We analyzed the impact of ALND on rate and type of systemic therapy.



**Figure 1.** 44 study centers are located in six European countries

#### Axillary treatment of HR+ / Her2- breast cancer patients with upfront surgery

	n = 297		
	TAS+ART	ALND	
Number of patients (%)	145 (48.8)	152 (51.2)	
Median number of removed lymph nodes [IQR]	5 [4-8]	19 [14-26]	<b>p-value</b>
Median number of positive lymph nodes [IQR]	3 [1-4]	4 [2-9]	<0.001

**Table 2.** Surgical characteristics using tailored axillary surgery (TAS) and axillary radiotherapy (ART) or axillary lymph node dissection (ALND) in patients with upfront surgery

HR – hormone receptor; Her2 – human epidermal growth factor receptor 2; IQR – interquartile range

#### Axillary treatment of breast cancer patients after neoadjuvant systemic treatment

	n = 143		
	TAS+ART	ALND	
Number of patients (%)	71 (49.7)	72 (50.3)	
Median number of removed lymph nodes [IQR]	4 [3-6]	16 [12-19]	<b>p-value</b>
Median number of positive lymph nodes [IQR]	1 [1-3]	2 [1-5]	<0.001

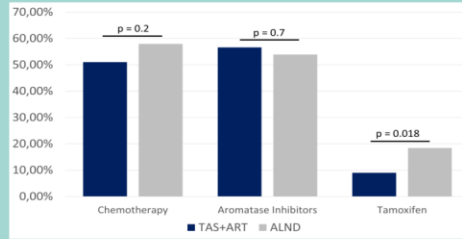
**Table 3.** Surgical characteristics using tailored axillary surgery (TAS) and axillary radiotherapy (ART) or axillary lymph node dissection (ALND) in patients after neoadjuvant systemic treatment

IQR – interquartile range

n = 500	
Characteristics	
Age, median [IQR]	57 [48-69]
Subtype	
HR+ / Her2-	80.0%
HR+ / Her2+	10.6%
HR- / Her2+	1.0%
HR- / Her2-	6.9%

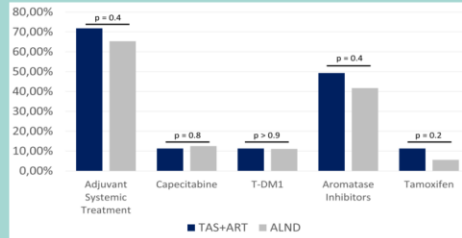
**Table 1.** Patient and tumor characteristics

IQR – interquartile range; HR – hormone receptor; Her2 – human epidermal growth factor receptor 2



**Figure 2.** Adjuvant systemic therapy in HR+ / Her2 - patients with upfront surgery using TAS and ART compared to ALND

TAS – tailored axillary surgery; ART – axillary radiotherapy; ALND – axillary lymph node dissection  
HR – hormone receptor; Her2 – human epidermal growth factor receptor 2



**Figure 3.** Adjuvant systemic therapy after neoadjuvant systemic treatment using TAS and ART compared to ALND

TAS – tailored axillary surgery; ART – axillary radiotherapy; ALND – axillary lymph node dissection

### DISCUSSION

- Both, in patients with neoadjuvant systemic treatment and those with upfront surgery, significantly more positive lymph nodes were removed by axillary lymph node dissection compared to tailored axillary surgery.
- However, this did not have a relevant impact on rate and type of adjuvant systemic therapy.

### REFERENCES

1. Henke, Guido et al. "Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer (TAXIS): study protocol for a multicenter, randomized phase-III trial." *Trials* vol. 19, 1 667. 4 Dec. 2018. doi:10.1186/s13063-018-3021-9

# What about outcome by type of axillary surgery in ILC?

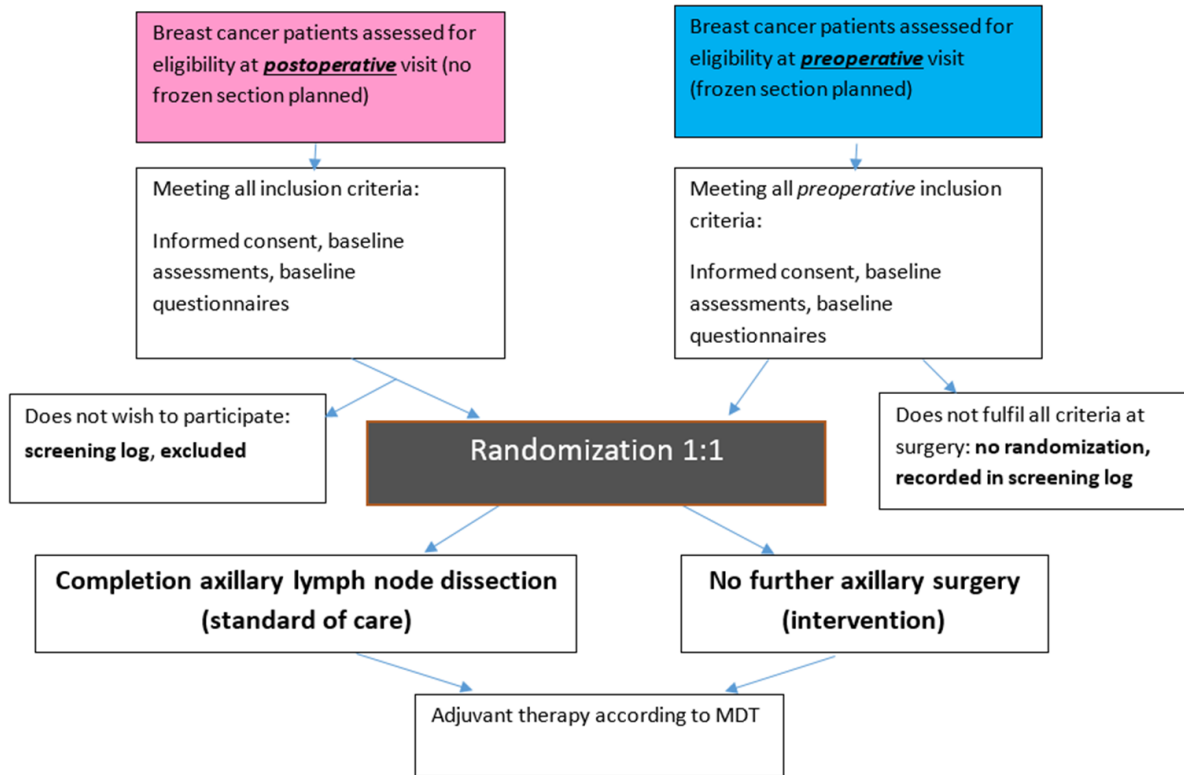
**Table 2** Results of multivariate logistic regression analysis that included a time-varying regression coefficient to account for non-proportional hazards in the entire cohort

	Hazard ratio	95% CI	<i>p</i> value
ALND	0.53	0.17–1.64	0.27
Node status			
0 positive nodes	Ref		
1–2 positive nodes	1.86	0.52–6.68	0.34
≥ 3 positive nodes	25.72	3.46–191.23	0.002

**Conclusions** These findings support the safety of omitting ALND in selected patients with ILC. Further studies of axillary management in ILC and imaging tools to predict nodal involvement and therapeutic response are warranted.

# The SENOMAC trial will shed light on the value of cALND in ILC

SENOMAC trial flow chart



- 2759 randomized between 2015 and 2021
- Sweden, Denmark, Germany, Italy and Greece
- 1-2 macrometastases with clinical stage cN0
- > 800 patienter underwent mastectomy

• *Initiala resultats in 2024*

• *An ideal setting to study impact i ALND in ILC*



# Take-home message



- Invasive lobular cancers have a higher nodal burden irrespective of molecular subtyping
- In patients with luminal A subtyping this will be associated with systemic undertreatment
- The consequences of surgical and systemic de-escalation in terms of outcome is yet to be determined





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