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Impacto de la neoadyuvancia en el abordaje axilar en pacientes con cáncer de mama

Sergi Fernández González

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Impacto de la neoadyuvancia en el abordaje axilar en pacientes con cáncer de mama

Memoria de tesis doctoral presentada por Sergi Fernández González para optar al grado de doctor por la Universidad de Barcelona.

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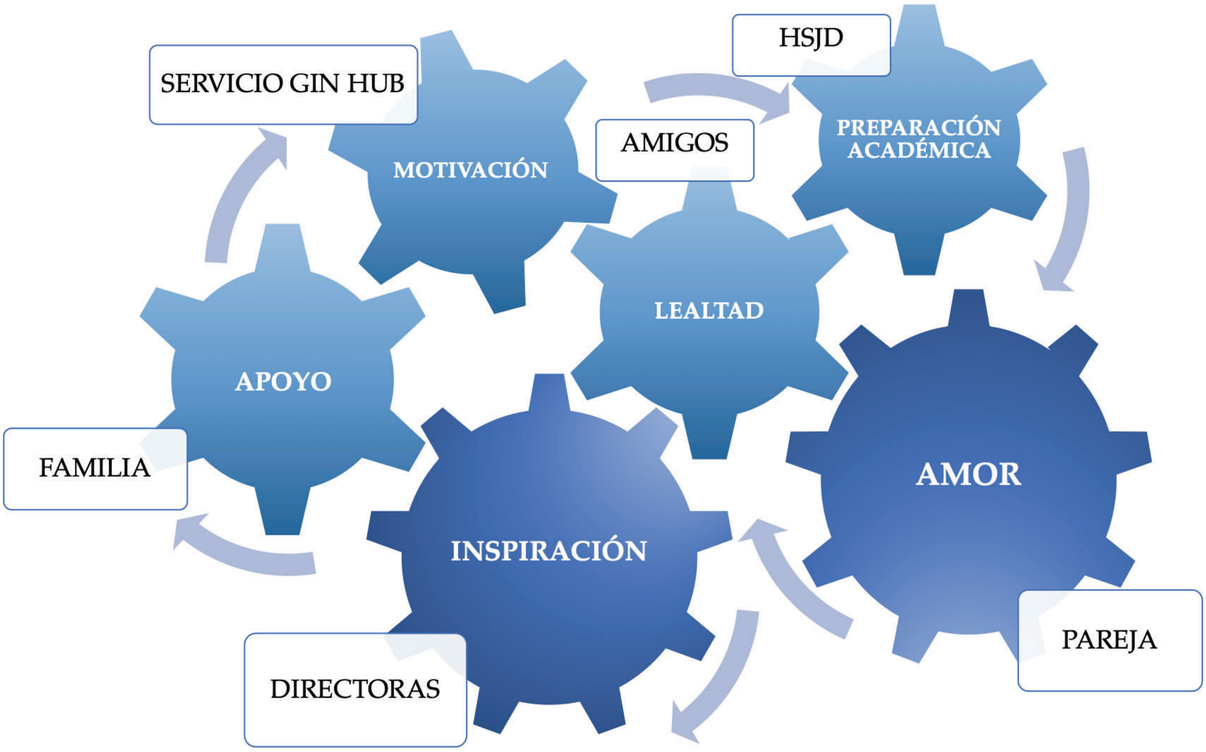
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En agosto del 2023 recibí una llamada del comité de recerca del HUB donde se me notificaba que me habían concedido una intensificación gracias a la Fundació Catalunya La Pedrera. Desde entonces, han sido muchos los momentos en los que me imaginaba redactando este apartado. Sin embargo, ha llegado el día y me cuesta encontrar las palabras apropiadas que transmitan mi agradecimiento a todas las personas implicadas en la elaboración de esta tesis, incluyendo a dicha fundación que sin su generosidad no habría resultado posible presentar esta tesis a día de hoy, mil gracias! Como una imagen vale más que mil palabras, esta figura se aproxima a la idea que quiero expresar y es que para mí, no es posible una progresión académica sin un desarrollo personal.

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Todo este entorno personal hace sinergia con un entorno laboral del que me siento muy afortunado. Desde mi primer año de residencia de ginecología en el Hospital Sant Joan de Déu, he tenido la suerte de contar con grandes mentores que me han enseñado como ser un buen profesional sin olvidar el valor "humano" con las pacientes, marca de la casa. Además, el entusiasmo por la "recerca" se me contagió de R2 tras mi primera publicación gracias al Dr. Amat, ahí se sentaron los fundamentos que han servido hoy en día para la elaboración de esta tesis. Gracias a todos los adjuntos, a mis Co-R y a mis compañeros de residencia por ir sumando fascículos de conocimiento que han servido para llenarme la mochila. Y la guinda laboral se la debo a mis compañeros del servicio de ginecología del Hospital Universitari de Bellvitge. Nuestra vocación por la cirugía y la complejidad pese a las jornadas eternas que ello supone, hacen que nos parezcamos más a una familia que a un servicio hospitalario de tercer nivel. Con ellos he encontrado mi sitio, no sólo para formarme sino también para dedicarme a mi verdadera pasión dentro de la ginecología, la ginecología oncológica. Uno de los grandes responsables de esta pasión es el Dr. Ponce, que desde sus clases en la UB ya me contagió su ambición por seguir aprendiendo y mejorando cada día. Gracias a todo el staff por acogerme y hacer del lugar de trabajo estar como en casa.

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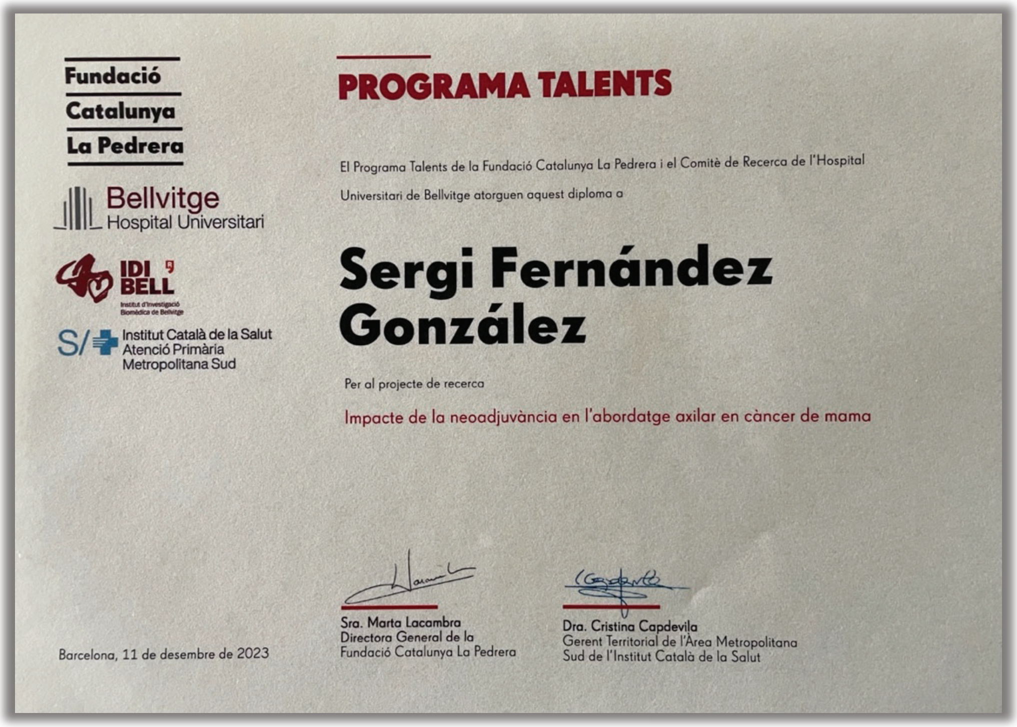

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ABREVIATURAS Y ACRÓNIMOS

ADC: antibody drug conjugates o inmunoconjugados
ALND: Axillary lymph node dissection, linfadenectomía axilar
CI: Confidence intervals, intérvalo de confianza
cN0: Clinically node-negative, pacientes sin enfermedad ganglionar al diagnóstico
cN+: Clinically node-positive, pacientes con enfermedad ganglionar al diagnóstico
cN1: Metastasis to movable ipsilateral level I, II axillary lymph node(s), ganglios sospechosos móviles al diagnóstico
cN2: metastases in ipsilateral axillary lymph nodes fixed or matted, ganglios sospechosos fijos o adheridos entre si al diagnóstico
DDFS: Distant disease free survival, supervivencia libre de enfermedad a distancia
FNR: False negative rate, tasa de falsos negativos
HER2: Human epidermal growth factor receptor 2, receptor 2 del factor de crecimiento epidérmico humano
HR: Hazard ratio
IA: Inhibidores de la aromatasa
IHQ: Inmunohistoquímica
IMC: Índice de masa corporal
IPTW: inverse probability of treatment weighting, probabilidad inversa de ponderación del tratamiento
ITCs: isolated tumor cells, células aisladas en el ganglio centinela
NACT: neoadyuvant chemotherapy, quimioterapia neoadyuvante
NAT: neoadyuvant treatment, tratamiento neoadyuvante
NET: neoadyuvant endocrine therapy, hormonoterapia neoadyuvante
OMS: Organización mundial de la salud
OS: Overall survival, supervivencia global
pCR: Pathological complete response, respuesta patológica completa
RE: Receptor de estrógenos
RRHH: receptores hormonales
RP: Receptor de progesterona
SLN: sentinel lymph node, ganglio centinela
SLNB: sentinel lymph node biopsy, biopsia de ganglio centinela
TDM-1: trastuzumab-emtansina
T-Dxd: trastuzumab-deruxtecan
TILs: Tumor-infiltrating lymphocytes, Infiltrado linfocitario tumoral
TNBC: triple negative breast cancer, cáncer de mama triple negativo

Tesis en formato de compendio por publicaciones.

La tesis consta de 5 objetivos los cuales han sido analizados y documentados en forma de 5 artículos.

ARTÍCULO 1: Q2 en Oncology 2018. IF 3.1

Sergi Fernandez-Gonzalez, Catalina Falo, Maria Jesus Pla, Sonia Pernas, Maite Bajen, Teresa Soler, Raul Ortega, Cecilia Quetglas, Xavier Perez-Martin, Maria Eulalia Fernandez Montoli, Miriam Campos, Mar Varela-Rodriguez, Jordi Ponce, Amparo Garcia-Tejedor.

The Shift From Sentinel Lymph Node Biopsy Performed Either Before or After Neoadjuvant Systemic Therapy in the Clinical Negative Nodes of Breast Cancer Patients. Results, and the Advantages and Disadvantages of Both Procedures.
Clinical Breast Cancer, 2018. Vol. 18, No. 1, 71-7

ARTÍCULO 2: Q2 en Surgery 2020. IF 2.4

Sergi Fernandez-Gonzalez MD, Catalina Falo PhD, Maria J. Pla PhD, Paula Verdaguer MD, Diana Nuñez MD, Anna Guma MD, Teresa Soler MD, Andrea Vethencourt MD, Silvia Vázquez PhD, Maria Eulalia Fernandez-Montoli PhD, Miriam Campos MD, Sonia Pernas PhD, Miguel Gil PhD, Jordi Ponce PhD, Amparo Garcia-Tejedor PhD.

Predictive factors for omitting lymphadenectomy in patients with node-positive breast cancer treated with neo-adjuvant systemic therapy
The Breast Jorunal. 2020 May;26(5):888-896

ARTÍCULO 3: Q1 en Oncology 2021. IF 4.6

Amparo Garcia-Tejedor, **Sergi Fernandez-Gonzalez**, Raul Ortega, Miguel Gil-Gil, Hector Perez-Montero, Eulalia Fernandez-Montoli, Agostina Stradella, Sabela Recalde, Teresa Soler, Anna Petit, Maria Teresa Bajen, Ana Benitez, Anna Guma, Miriam Campos, Maria J. Pla, Evelyn Martinez, Maria Laplana, Sonia Pernas, Diana Perez-Sildekova, Isabel Catala, Jordi Ponce, Catalina Falo

Can we avoid axillary lymph node dissection in N2 breast cancer patients with chemo-sensitive tumours such as HER2 and TNBC?

Breast Cancer Research and Treatment. 2021; 185:657–666

ARTÍCULO 4: Q1 en Oncology 2022. IF 3.8 en 2022

Amparo Garcia-Tejedor, Catalina Falo, **Sergi Fernandez-Gonzalez**, Maria Laplana, Miguel Gil-Gil, Teresa Soler-Monso, Evelyn Martinez-Perez, Iris Calvo1, Hugo Calpelo, Maria-Teresa Bajen, Ana Benitez, Raul Ortega, Anna Petit, Anna Guma, Miriam Campos, Agostina Stradella, Ana Lopez-Ojeda, Jordi Ponce, Maria J. Pla1, Sonia Pernas

Management of the axilla in postmenopausal patients with cN0 hormone receptor-positive/HER2-negative breast cancer treated with neoadjuvant endocrine therapy and its prognostic impact

Breast Cancer Research and Treatment. 2023; 199:445–456

ARTÍCULO 5: Q1 en Oncology 2022. IF 3.8 en 2022

Sergi Fernandez-Gonzalez, Catalina Falo, Maria J. Pla, Miriam Campos, Carlos Ortega, Raul Ortega, Maria Vicente, Ana Petit, Jan Bosch, Maria Teresa Bajen, Gabriel Reyes, Evelyn Martínez, Javier Gonzalez, Judith Peñafiel, Agostina Stradella, Sonia Pernas, Jordi Ponce, Amparo Garcia-Tejedor

Sentinel lymph node biopsy before and after neoadjuvant chemotherapy in cN0 breast cancer patients: impact on axillary morbidity and survival—a propensity score cohort study.

Breast Cancer Research and Treatment. 2024.

Título

Impacto de la neoadyuvancia en el abordaje axilar en pacientes con cáncer de mama.

Introducción

En pacientes con cáncer de mama sin afectación axilar (cN0), la realización de la biopsia del ganglio centinela (SLNB) después de la quimioterapia neoadyuvante (NACT) ha sido preferentemente adoptada en comparación a antes de la NACT debido a sus ventajas. Sin embargo, los resultados de supervivencia asociados a ambas estrategias persisten poco estudiados. Así mismo, el manejo axilar en pacientes tributarias a hormonoterapia neoadyuvante (NET) permanece en estudio y la evidencia actual sobre el efecto del tratamiento en la positividad del ganglio centinela (SLN) es limitada. Finalmente, buscar alternativas a la realización de la linfadenectomía axilar (ALND) en pacientes con afectación axilar (cN1 y cN2) sin comprometer el pronóstico está siendo un área activa de investigación. Identificar los factores tumorales predictores de respuesta patológica axilar (ypN0) permitiría evitar ALND innecesarias y la morbilidad asociada.

Hipótesis

H1: En pacientes cN0, la SLNB post-NACT reduce la tasa de ALND respecto a su realización pre-NACT, manteniendo similares resultados en términos de supervivencia.

H2: En pacientes cN0 con receptores hormonales positivos (RH+) y HER2 negativo, la SLNB post-NET puede ser factible y su positividad podría estar relacionada con el pronóstico.

H3: En pacientes cN1 y cN2 candidatas a NACT, se podrían identificar factores predictores de ypN0 que ayudarían a seleccionar un grupo de pacientes en las que podría evitarse la linfadenectomía axilar.

Objetivos:

O1: Comparar las tasas de ALND y el pronóstico a corto plazo en pacientes cN0 con realización de SLNB post-neoadyuvancia respecto a su realización pre-tratamiento.

O2: Demostrar que, en las pacientes cN0, la realización de la SLNB post-NACT se relaciona con una menor necesidad de ALND sin perjudicar en la supervivencia a medio-largo plazo respecto a su realización pre-NACT.

O3: Comparar la positividad de la SLNB pre-NET versus post-NET en las pacientes cN0 con cáncer de mama RH+/HER2 negativo y su impacto en el pronóstico.

O4: Analizar los factores predictores de ypN0 en pacientes cN+ al diagnóstico tratadas con NACT.

O5: Seleccionar los factores predictores de ypN0 en pacientes cN2 al diagnóstico tratadas con NACT.

Métodos

Esta tesis es el compendio de 5 artículos publicados por nuestro grupo de trabajo, siendo de carácter observacional y retrospectivo. Para los 3 primeros objetivos se analizaron 2 cohortes de pacientes cN0 en las que se realizó la SLNB antes de la NACT (grupo 1: de diciembre 2006 a abril 2014) y después de la NACT (grupo 2: a partir de mayo 2014). En el artículo de 2017 se incluyeron un total de 162 pacientes T1c a T3 y cN0 candidatas a tratamiento neoadyuvante (NACT o NET). En el artículo de 2024 se amplió la cohorte a 310 pacientes que recibieron exclusivamente NACT, aplicando un método de emparejamiento para homogeneizar ambos grupos. En el artículo de 2022 se analizó una cohorte de 91 pacientes posmenopáusicas cN0 y RH+/HER2 negativo que exclusivamente recibió NET. Para los objetivos 4º y 5º, se analizaron a las pacientes cN+ que se sometieron a ALND post-NACT entre junio de 2008 y diciembre de 2016. En el artículo del 2020 se incluyeron 331 pacientes cN1 y cN2. El artículo de 2023 se centró exclusivamente en las pacientes cN2 (≥3 ganglios sospechosos por ecografía al diagnóstico) siendo un total de 221 pacientes. En todos los artículos se evaluaron las respuestas clínicas, radiológicas y patológicas post-NACT, y se realizaron análisis univariados y multivariados mediante regresión logística para determinar los factores predictores de ypN0, así como modelos de regresión de Cox y análisis de supervivencia mediante las curvas de Kaplan-Meier y el test de log-rank. Significación estadística <0.05.

Resultados principales

La tasa de positividad del SLN es del 42.1% pre-NACT frente al 12.5% post-NACT y la tasa de linfadenectomía fue del 29.9% pre-NACT y del 7.4% post-NACT (p<0.001), con un OR de 5.35, IC del 95% (2.7-10.4); p =.002. Tras 4 años de seguimiento, la SLNB post-NACT se asoció con mayor supervivencia libre de enfermedad, 93.1 % (IC 95% 89.3-97) frente a 87.5% (IC95% 81.2-93.9) pre-NACT y una mejor supervivencia global

(OS) [HR 0.21, IC del 95% 0.07–0.67] respecto a la SLNB pre-NACT. Tras el análisis multivariante, los factores pronóstico adversos que impactaron sobre la OS fueron la SLNB pre-NACT [HR 3.095, IC del 95% 2.323-4.123], la falta de respuesta clínica a la NACT [HR 1.702, IC del 95% 1.012-2.861] y el índice de proliferación celular alto [HR 1.889, IC del 95% 1.195-2.985].

En los resultados del estudio sobre la NET, observamos que la positividad del SLN fue del 35.7% pre-NET y 37% post-NET (p=NS). Sólo tres pacientes (18.7%) con macrometástasis en el SLN tuvieron > 3 ganglios positivos tras la ALND. La OS a los 5 años y la supervivencia libre de enfermedad a distancia fueron del 92.4% y 94.8%, respectivamente, sin diferencias significativas según el estado de SLNB (p = 0.5 y p = 0.8, respectivamente).

Entre los resultados de las pacientes cN+, observamos que el 38.7% (128) se convirtieron en ypN0 post-NACT. Los factores predictores independientes de ypN0 fueron Ki67>30 (OR 1.98; IC del 95%, 1.146-3.381), positividad HER2 (OR 2.6; IC del 95%, 1.354-5.108), subtipo molecular no luminal (OR 4.15; IC del 95%, 2.068-5.108), y respuesta clínica completa (OR 2.8; IC del 95%, 1.110-7.081). Al estudiar exclusivamente a las pacientes cN2 observamos que el 40.3% (89) de las pacientes consiguieron ypN0 y se repitieron los mismos factores independientes de ypN0 hallados en las pacientes cN+.

Conclusiones

C1: En pacientes cN0, la SLNB post-NACT reduce significativamente el número de linfadenectomías axilares necesarias sin perjudicar su supervivencia a corto y medio-largo plazo respecto a la SLNB pre-NACT. Por tanto, se podría considerar el reemplazo de la SLNB pre-NACT por la post-NACT.

C2: En pacientes RH+/HER2 negativo y cN0 tratadas con NET, la SLNB es factible ya sea antes o después del tratamiento sistémico sin modificar la tasa de positividad del mismo. Estas pacientes tienen un pronóstico muy favorable independientemente de la afectación axilar evaluada mediante el ganglio centinela.

C3: Los factores predictores de respuesta patológica axilar completa tras la NACT en las pacientes cN+ incluyendo aquellas con menor (cN1) y mayor (cN2) carga tumoral axilar son: la negatividad de los receptores hormonales, la positividad de HER2, un Ki67 > 30% y obtener una respuesta clínica completa. Las pacientes que cumplan estos requisitos, tanto cN1 como cN2, podrían ser consideradas para la realización de una disección axilar dirigida en lugar de una linfadenectomía axilar.

Title

Impact of Neoadjuvant Therapy on Axillary Management in Breast Cancer Patients.

Introduction

In breast cancer patients without axillary involvement (cN0), performing sentinel lymph node biopsy (SLNB) after neoadjuvant chemotherapy (NACT) has been preferentially adopted compared to before NACT due to its advantages. However, the survival outcomes associated with both strategies remain poorly studied. Similarly, axillary management in patients eligible for neoadjuvant hormone therapy (NET) is still under investigation, and current evidence on the effect of treatment on sentinel lymph node (SLN) positivity is limited. Finally, seeking alternatives to axillary lymphadenectomy (ALND) in patients with axillary involvement (cN1 and cN2) without compromising prognosis is an active area of research. Identifying the tumor factors predictive of pathological axillary response (ypN0) would allow for the avoidance of unnecessary ALND and its associated morbidity.

Hypothesis

H1: In cN0 patients, post-NACT SLNB reduces the rate of ALND compared to pre-NACT SLNB with similar survival outcomes.

H2: In cN0 and hormone receptor-positive (HR+) and HER2-negative patients, post-NET SLNB may be feasible, and its positivity could be related to prognosis.

H3: In cN1 and cN2 patients after NACT, predictive factors for ypN0 could be identified to select a group of patients where ALND could be avoided

Objetives:

O1: Compare the rates of ALND and short-term prognosis in cN0 patients with post-neoadjuvant SLNB versus pre-treatment SLNB.

O2: Demonstrate that in cN0 patients, performing post-NACT SLNB is associated with a lower rate of ALND without compromising medium to long-term survival compared to pre-NACT SLNB.

O3: Compare the positivity of SLNB pre-NET vs post-NET in cN0 HR+/HER2-negative breast cancer patients and its impact on prognosis.

O4: Analyze predictive factors for ypN0 in cN+ patients diagnosed and treated with NACT.

O5: Identify predictive factors for ypN0 in cN2 patients diagnosed and treated with NACT.

Methods

This thesis is a compilation of 5 articles published by our research group, being observational and retrospective in nature. For the first 3 objectives, we analyzed 2 cohorts of cN0 patients who underwent SLNB before NACT (group 1: from December 2006 to April 2014) and after NACT (group 2: from May 2014 onwards). In the 2017 article, a total of 162 patients with T1c to T3 and cN0, candidates for neoadjuvant treatment (NACT or NET), were included. In the 2024 article, the cohort was expanded to 310 patients who received exclusively NACT, applying a matching method to homogenize both groups. The 2022 article analyzed a cohort of 91 postmenopausal cN0 and HR+/HER2-negative patients who exclusively received NET. For the 4th and 5th objectives, we analyzed cN+ patients who underwent post-NACT ALND between June 2008 and December 2016. The 2020 article included 331 cN1 and cN2 patients. The 2023 article focused exclusively on cN2 patients (≥3 suspicious nodes on ultrasound at diagnosis), totaling 221 patients. In all articles, post-NACT clinical, radiological, and pathological responses were evaluated, and univariate and multivariate analyses were performed using logistic regression to determine predictive factors for ypN0, as well as Cox regression models and survival analyses using Kaplan-Meier curves and the log-rank test. Statistical significance was set at <0.05.

Main results

The SLNB positivity rate was 42.1% pre-NACT vs. 12.5% post-NACT, and the lymphadenectomy rate was 29.9% pre-NACT and 7.4% post-NACT ($p<0.001$), with an OR of 5.35, 95% CI (2.7-10.4); p=.002. After 4 years of follow-up, post-NACT SLNB was associated with a longer disease-free period, HR 0.42 95% CI (0.17-1.06); p=0.066, and better overall survival (OS), HR 0.21 95% CI (0.07-0.67); p=0.009 compared to pre-NACT SLNB. In multivariate analysis, independent adverse prognostic factors for OS included pre-NACT SLNB, HR 3.095 95% CI (2.323-4.123), lack of clinical response to

NACT, HR 1.702 95% CI (1.012-2.861), and small tumors (cT1) with a high proliferation index, HR 1.889 95% CI (1.195-2.985).

In the NET and SLNB study results, SLNB positivity was 35.7% pre-NET and 37% post-NET (p=NS). Only three patients (18.7%) with macrometastases in SLNB had >3 positive nodes after ALND. OS at 5 years and distant disease-free survival were 92.4% and 94.8%, respectively, with no significant differences based on SLNB status (p=0.5 and p=0.8, respectively).

Among the results for cN+ patients, 38.7% (128) became ypN0 post-NACT. Independent predictors of ypN0 were Ki67>30 (OR 1.98; 95% CI, 1.146-3.381), HER2 positivity (OR 2.6; 95% CI, 1.354-5.108), non-luminal molecular subtype (OR 4.15; 95% CI, 2.068-5.108), and complete clinical response (OR 2.8; 95% CI, 1.110-7.081). In studying cN2 patients exclusively (≥3 nodes at diagnosis), we observed that 40.3% (89) achieved ypN0, with the same independent factors for ypN0 found in cN1patients.

Conclusions

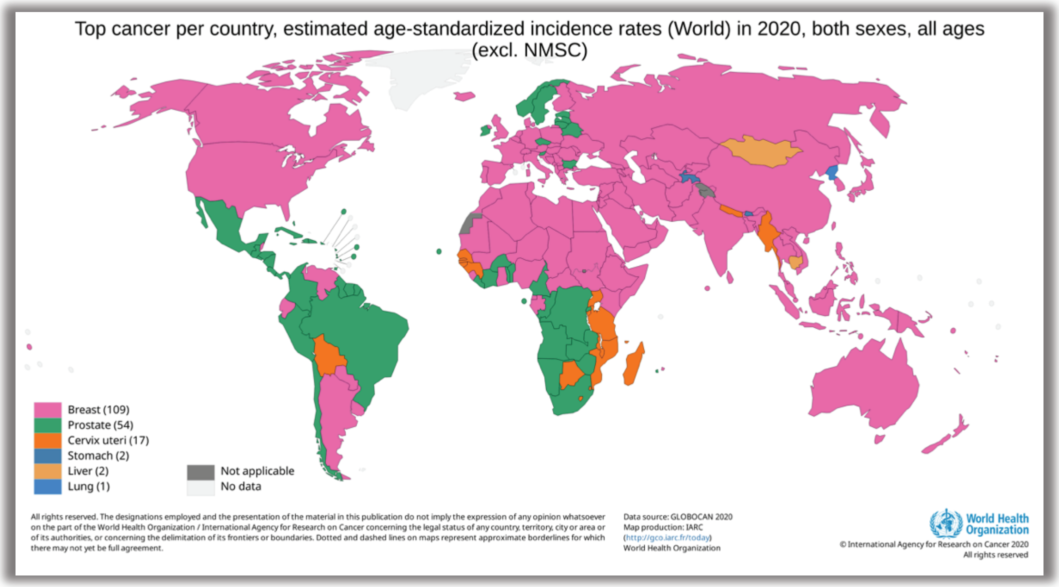
C1: In cN0 patients, post-NACT SLNB significantly reduces the number of axillary lymphadenectomies without compromising short-term and medium to long-term survival compared to pre-NACT SLNB. Therefore, replacing pre-NACT SLNB could be considered.

C2: In HR+/HER2-negative and cN0 patients treated with NET, SLNB is feasible either before or after systemic treatment without altering the positivity rate. These patients have a very favorable prognosis regardless of axillary involvement evaluated by sentinel node.

C3: Predictive factors for complete pathological axillary response after NACT in cN+ patients, including those with lower (cN1) and higher (cN2) axillary tumor burden, are: hormone receptor negativity, HER2 positivity, Ki67 > 30%, and achieving a complete clinical response. Patients meeting these criteria, both cN1 and cN2, could be considered for targeted axillary dissection instead of full axillary lymphadenectomy.

EPIDEMIOLOGÍA

En el año 2020, se diagnosticaron 2.3 millones de casos nuevos de cáncer de mama en todo el mundo (1), convirtiéndolo en la neoplasia con mayor incidencia y prevalencia en ambos sexos a nivel global (Figura 1) (2). Su incidencia es mayor en regiones más desarrolladas, situándose en 70 casos por 100.000 habitantes en América del Norte, Europa Occidental y Australia en contraposición a los 30 casos por 100.000 en el África subsahariana. En España, se estimaron 35.000 nuevos casos para el año 2023, de los cuales 5.500 se diagnosticaron en Cataluña. Se trata de uno de los cánceres con mejores tasas de supervivencia global, estimada para todos los estadios entorno al 80% gracias a los avances científicos que proporcionan la incorporación de nuevos tratamientos y que permiten una reducción de la mortalidad año tras año. Sin embargo, dada su elevada incidencia, en el año 2020 se calculó una mortalidad mundial que afectó a 685.000 personas (1), lo que sitúa al cáncer de mama como un problema con gran impacto en la salud mundial. Cabe destacar que, a pesar de una menor incidencia en países en vías de desarrollo como África, América del Sur y en el sur de Asia; las tasas de mortalidad son más elevadas en estos países (Figura 2) (2) representando 2/3 partes de la mortalidad global.


Top cancer per country, estimated age-standardized incidence rates (World) in 2020, both sexes, all ages (excl. NMSC)

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Data source: GLOBOCAN 2020
Map production: IARC
(http://gco.iarc.fr/today)
World Health Organization

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Figura 1: Tasas estimadas de incidencia estandarizadas por edad a nivel mundial en 2020. Ordenadas según el tipo de neoplasia (2).

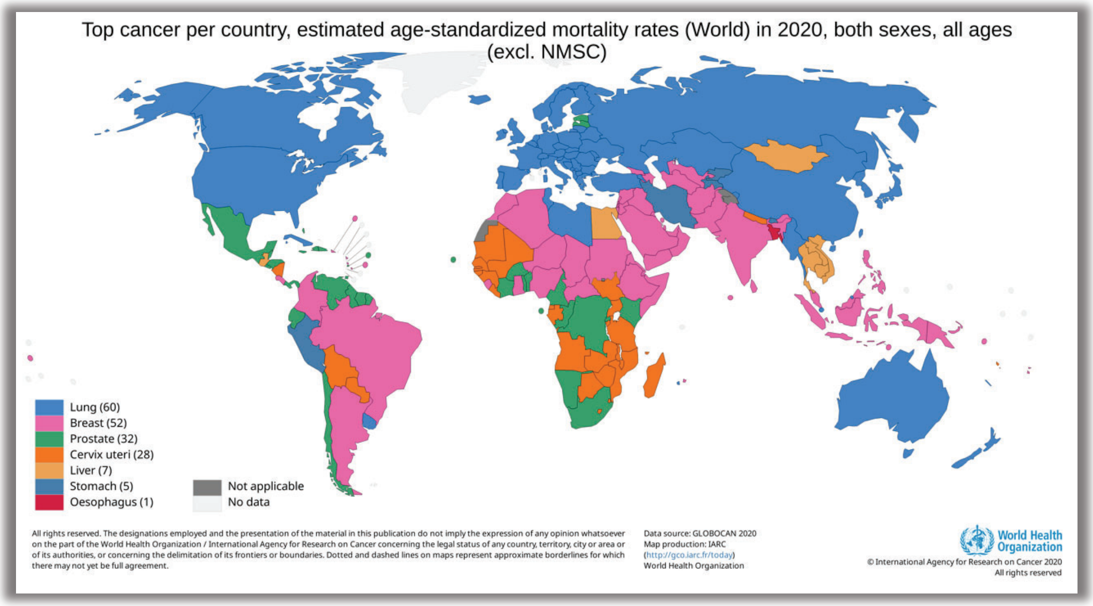
Top cancer per country, estimated age-standardized mortality rates (World) in 2020, both sexes, all ages (excl. NMSC)
🟦 Lung (60)
🟪 Breast (52)
🟩 Prostate (32)
🟧 Cervix uteri (28)
Liver (7)
Stomach (5)
🟥 Oesophagus (1)
Not applicable
No data
All rights reserved. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization / International Agency for Research on Cancer concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate borderlines for which there may not yet be full agreement.
Data source: GLOBOCAN 2020
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Figura 2: Tasas estimadas de mortalidad estandarizadas por edad a nivel mundial en 2020. Ordenadas según el tipo de neoplasia (2).

Estas diferencias entre países, podría ser explicada por una mayor exposición a factores de riesgo que justifican una mayor incidencia en países desarrollados. Entre los factores de riesgo más conocidos de aparición de cáncer de mama se encuentran: una mayor esperanza de vida, la obesidad, el alcohol o una mayor exposición hormonal que sucede en aquellas mujeres con menarquia precoz, menopausia tardía y menor exposición a la lactancia materna (3–5). Por otro lado señalar que, aunque el 80% de los casos de cáncer de mama se clasifican como esporádicos, el 10-15% de los casos tienen una predisposición familiar que involucra factores de riesgo tanto ambientales como genéticos (6). Sabemos que, los genes más frecuentemente asociados al desarrollo de cáncer de mama son BRCA1 y BRCA2, representando el 20-30% de los casos de cáncer hereditario. El riesgo acumulado a los 70 años para portadores/as de variantes patogénicas es del 57% y 49% respectivamente. Sin embargo, también conocemos otros genes frecuentemente implicados en el cáncer de mama hereditario como TP53, PTEN, CDH1, STK11, ATM, PALB2, CHEK2 (7).

Como hemos comentado anteriormente, la supervivencia estimada a 5 años en aquellas pacientes con cáncer de mama en países desarrollados se calcula del 80% (8) en comparación al 70% en la India o incluso del 50% en Sudáfrica (9). En respuesta a estas diferencias, la Organización Mundial de la Salud (OMS) presentó en 2021 “the new Global Breast Cancer initiative” (10) con el objetivo de mejorar las tasas de supervivencia en todo el mundo a través de la promoción de la salud, diagnóstico precoz y tratamiento integral de la paciente con cáncer de mama.

FACTORES PRONÓSTICO EN CÁNCER DE MAMA

El pronóstico de las pacientes con cáncer de mama viene determinado no sólo por la extensión de la enfermedad al diagnóstico sino también, por una serie de factores tumorales que impactan tanto en el riesgo de recidiva como en la supervivencia. Estos factores pronóstico que abarcan desde características tumorales hasta biomarcadores moleculares y respuestas terapéuticas, desempeñan un papel crucial en la predicción del curso de la enfermedad y la selección de tratamientos personalizados. Estas variables pronósticas, se han ido desarrollando a través de la investigación y aunque todavía se siguen considerando una serie de factores más “clásicos” como son los relacionados con la histología o la afectación ganglionsar, cabe destacar el impacto que ha tenido el desarrollo de la medicina molecular en el cáncer de mama. Los principales factores pronóstico del cáncer de mama atendiendo a su relevancia clínica, impacto en la práctica médica y relación con la presente tesis se muestran agrupados en: factores histopatológicos, subtipos moleculares, TNM y afectación ganglionar.

1. Factores histopatológicos

a) Histología

El cáncer de mama se considera una enfermedad heterogénea que reúne múltiples entidades histológicas (11). De hecho, a pesar de originarse en la misma estructura anatómica, el epitelio de la unidad ducto-lobulillar (Figura 3) (12), existen diferencias en cuanto a presentación clínica, pronóstico e incluso diferentes respuestas al tratamiento sistémico en función del patrón de crecimiento de la célula cancerígena. El cáncer de mama se clasifica en distintos tipos histológicos (13) siendo el más frecuente, el carcinoma ductal no especial que representa el 75% de todos los tipos histológicos. El otro 25% lo componen 18 entidades histológicas que desde la última revisión de la OMS en 2019 se clasifican dentro de la categoría especial (14) y por orden de frecuencia lo componen el carcinoma lobulillar (15-8%), el carcinoma medular (<5%) y el carcinoma metaplásico (<5%) entre otros. Característicamente, el carcinoma lobulillar está conformado por células pequeñas y no cohesivas que infiltran el estroma formando una estructura en patrón de fila única. La falta de cohesión es consecuencia de la pérdida de expresión de e-cadherina (15) y ocasiona, entre otras características, una mayor frecuencia de presentación de tumores multifocales o tumores bilaterales respecto al carcinoma ductal. Además, estudios con largo seguimiento en pacientes con tumores lobulillares han observado mayor tendencia a diseminación gastrointestinal, peritoneal y ovárica respecto el carcinoma ductal (16).

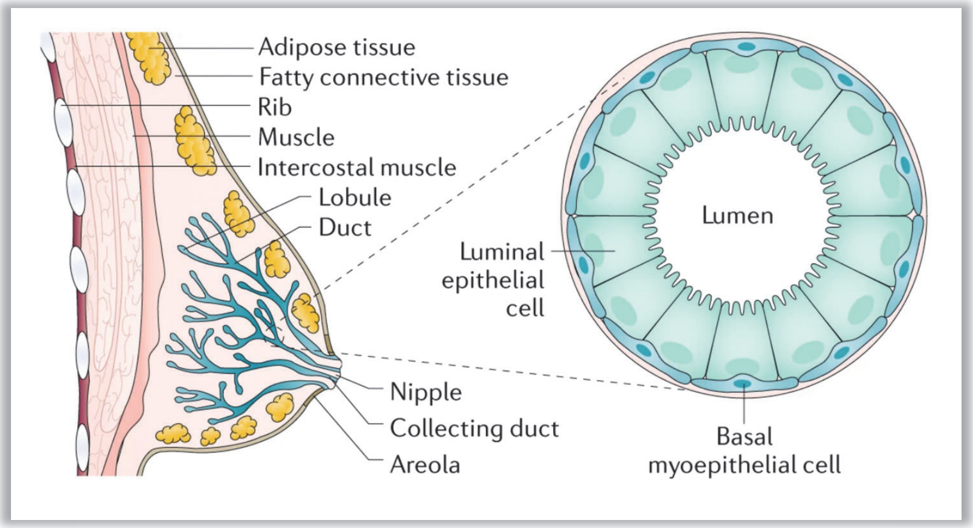


Figura 3: Estructura anatómica del carcinoma ductal y el carcinoma lobulillar (12).

b) Grado

El grado de Nottingham (17) informa del grado de diferenciación celular y tiene en cuenta la atipia nuclear, la formación glandular y el índice mitótico. Los tumores de bajo grado se relacionan con tumores de menor agresividad y mejor pronóstico (18) respecto a aquellos de alto grado con mayor atipia nuclear, desestructuración tubular y mayor índice mitótico. Con todo, la respuesta a la quimioterapia es mejor en los tumores de alto grado, de tal manera que si conseguimos desarrollar esquemas con una mayor eficacia sobre este grupo de pacientes, se podría revertir el mal pronóstico inicial.

c) Proliferación

El índice de proliferación Ki67 responde a una proteína del córtex nuclear que se expresa en las fases del ciclo celular relacionadas con la división (fase G1, S, G2 y M) y por tanto, a mayor expresión de esta proteína mayor actividad mitótica celular y mayor agresividad tumoral. Aunque hay estudios que relacionan índices de Ki67 > 20-30% con peor supervivencia (19,20) todavía no existe un consenso firme para recomendar un punto de corte exacto que determine la toma de decisiones. En esta línea, el International Ki67 in Breast Cancer Working Group publicó un consenso en 2021 sobre la recomendación de usar Ki67<5% o >30% para el manejo clínico (21).

d) Receptores hormonales

En general, el cáncer de mama se ha considerado como una enfermedad hormono-dependiente ya que el 70-80% de las células epiteliales expresan receptores de estrógeno (RE) y/o progesterona (RP) (22); siendo este un biomarcador de mejor pronóstico respecto a aquellos tumores que no expresan receptores hormonales. Su evaluación mediante IHQ es cuantitativa, y habitualmente se expresa con el porcentaje de células tumorales en las cuales se observa una tinción positiva para RE y RP. Clásicamente se consideraba la positividad para el RE una tinción igual o superior al 10% de las células tumorales (23). Sin embargo, en las nuevas clasificaciones se considera positividad a partir del 1% de las células (24). Este corte favorece la selección de tumores considerados RE negativos como criterio de inclusión en estudios de quimiosensibilidad, pero no es tan favorable para determinar los tumores más sensibles al tratamiento hormonal.

e) HER2

Otra proteína importante que se muestra expresada en el 20% de los tumores de cáncer de mama, es la glicoproteína transmembrana del receptor del factor de crecimiento epidérmico humano 2 (HER2) codificada por el gen c-erb2 situado en el brazo corto del cromosoma 17. Los tumores con sobre-expresión/amplificación de HER2, se asocian a una mayor proliferación, motilidad celular, invasión celular, angiogénesis acelerada y reducción de la apoptosis (25). Desde su descubrimiento a mediados de los 80, múltiples estudios han relacionado su expresión como factor de peor pronóstico demostrando hasta el doble de riesgo de recidiva (26) respecto aquellos tumores sin sobre-expresión de HER2. Sin embargo, el desarrollo de tratamientos diana con anticuerpos monoclonales (IgG1) humanizados anti-HER2 como el trastuzumab (aprobado en 2005) y pertuzumab (aprobado en 2015), han demostrado una reducción del 34% en las recidivas y de un 33% de mortalidad cuando se añaden a los esquemas de quimioterapia estándar (27). De hecho, desde la aprobación de la terapia anti-HER2, las pacientes con este tipo de tumores han pasado de tener un pronóstico similar a los triples negativos en la era pre-trastuzumab, a tener un pronóstico similar o incluso mejor que los tumores luminales en series de quimioterapia primaria actuales que incluyen tratamiento anti-HER2 (28).

f) Invasión vascular

La invasión vascular es un factor pronóstico bien conocido desde 1984, cuando Bettelheim et al. (29) encontraron histopatológicamente que la presencia de émbolos tumorales en espacios vasculares asociados con el cáncer de mama primario tenía un pronóstico desfavorable respecto a su ausencia. Varios estudios han observado que la presencia de invasión vascular confiere de manera independiente un mayor riesgo de recidiva local y a distancia (30, 31) consecuentemente, este factor ha ganado importancia con el paso de los años y ha sido progresivamente incorporado en el desarrollo de las nuevas guías clínicas (32,33).

g) Linfocitos infiltrantes del tumor (TILs)

Finalmente mencionar, que en los últimos años se han descubierto nuevos marcadores pronóstico como son la evaluación del infiltrado linfocitario intratumoral estromal. La presencia de TILs se ha observado más frecuentemente en tumores triple negativo y HER2 (34,35) y es un predictor de respuesta al tratamiento con quimioterapia, por lo que el pronóstico de las pacientes con TILs elevados podría mejorar en los próximos años con el desarrollo de la inmunoterapia en cáncer de mama (36).

2. Subtipos moleculares de cáncer de mama

Uno de los grandes cambios que se han producido en los últimos años en cuanto a la clasificación de los tumores de mama ha sido el desarrollo de los subtipos moleculares tras el trabajo publicado por Perou et al. en el año 2000 (Figura 4) (37). En este estudio se analizaron mediante microarrays de expresión génica el cDNA de 38 cánceres de mama invasivos y se identificaron 4 subtipos moleculares diferentes de cáncer de mama: luminal, normal breast-like, HER2 y “basal-like”. Un año más tarde, este mismo grupo demostró que el grupo luminal, positivo para el RE, podía ser dividido en al menos 2 subgrupos (luminal A y luminal B), cuya relevancia deriva del hecho que cada subtipo presenta diferentes resultados en supervivencia y período libre de enfermedad (38).

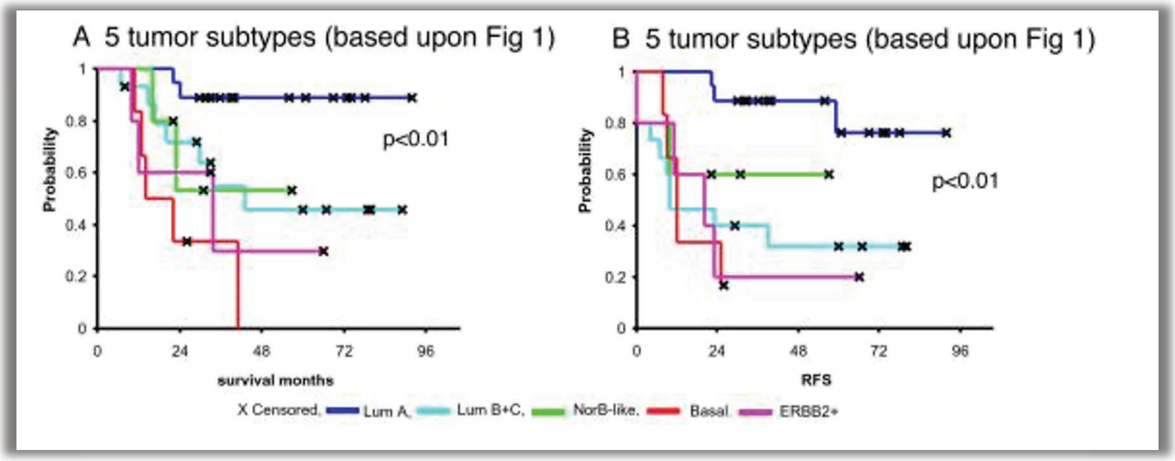


Figura 4: Análisis de la supervivencia global (A) y supervivencia libre de recaídas (B) para los cinco subtipos tumorales basados en la expresión génica (38).

Posteriormente, grupos independientes han reproducido y validado estos resultados confirmando que los tumores originariamente clasificados como luminales A, tienen niveles elevados de expresión de genes activados por el RE, bajos niveles de expresión de genes relacionados con la proliferación y, por tanto, suelen tener un grado histológico bajo y ser de buen pronóstico. Sin embargo, los tumores clasificados como luminales B son más propensos a tener un mayor grado histológico, tasas de proliferación más elevadas, expresión de genes HER2 y un pronóstico significativamente peor que los tumores luminales A. En la rama del clúster negativo para el RE, encontramos los tumores HER2 y triple negativo (basal-like originariamente) con peor pronóstico en cuanto a supervivencia y riesgo de recidiva debido a su mayor agresividad (39). Además, este tipo de cáncer de mama se observa más prevalentemente en mujeres jóvenes (40) y portadoras de variantes patogénicas en los genes BRCA respecto a los tumores luminales.

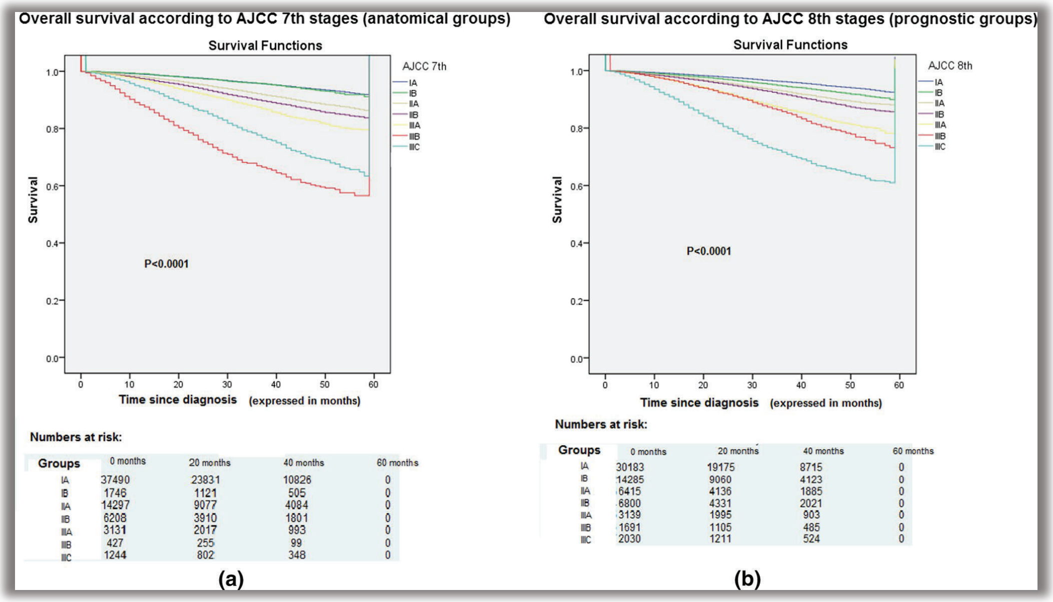
La importancia de la clasificación molecular no sólo radica en aportar información pronóstica sino que actualmente es clave en la decisión terapéutica. Permite orientar tratamientos más dirigidos para cada grupo tumoral debido al desarrollo de esquemas más específicos. Sin embargo, debido a que los microarrays no están disponibles para el diagnóstico asistencial rutinario en muchos de los laboratorios de anatomía patológica, se ha realizado una aproximación a los subtipos intrínsecos a través de los factores pronóstico tradicionales incluyendo los receptores hormonales (RRHH), Ki67 y HER2.

Estos factores son evaluados mediante tinción de inmunohistoquímica realizados en biopsia o en la pieza quirúrgica. Estos subgrupos subrogados se conocen como luminal A-like, luminal B -like , luminal B-like Her2, HER-2 enriched y triple negativo.

Finalmente, sabemos que el patrón de afectación ganglionar y metastásica también es diferente entre los subtipos moleculares. Los tumores triple negativo y HER2 se relacionan con mayor afectación ganglionar y con mayor tendencia a metastatizar a nivel visceral: hepático, cerebral y pulmonar (41,42). Por el contrario, los tumores luminales tienen menos riesgo de afectación linfática y menores tasas de recurrencia loco-regional (43). Su diseminación es predominantemente ósea, pleural y partes blandas (44).

3. TNM

La aplicación del sistema de clasificación TNM (Tumor, Node, Metastasis) permite una evaluación precisa de la extensión de la enfermedad y la estratificación del pronóstico. Desde su introducción por la American Joint Committee on Cancer (AJCC), el TNM ha evolucionado substancialmente. De hecho ha pasado de ser una clasificación puramente anatómica como la que encontramos en la 7ª edición, a integrar en la 8ª edición (45) los biomarcadores mencionados como el grado tumoral, el estatus HER2 y los RRHH para estratificar aún más a las pacientes acorde a su pronóstico (Figura 5).



Overall survival according to AJCC 7th stages (anatomical groups)

Numbers at risk:

Groups	0 months	20 months	40 months	60 months
IA	37490	23831	10826	0
IB	1746	1121	505	0
IIA	14297	9077	4084	0
IIB	6208	3910	1801	0
IIIA	3131	2017	993	0
IIIB	427	255	99	0
IIIC	1244	802	348	0

Overall survival according to AJCC 8th stages (prognostic groups)

Numbers at risk:

Groups	0 months	20 months	40 months	60 months
IA	30183	19175	8715	0
IB	14285	9060	4123	0
IIA	6415	4136	1885	0
IIB	6800	4331	2021	0
IIIA	3139	1995	903	0
IIIB	1691	1105	485	0
IIIC	2030	1211	524	0

Figura 5: Curva de Kaplan-Meier de la supervivencia global según: (a) sistema de estadificación anatómica; (b) sistema de estadificación pronóstica (45).

4. Afectación ganglionar

La afectación ganglionar (axilar y/o cadena mamaria interna) (46) se ha considerado tradicionalmente como el factor pronóstico más importante de recurrencia y supervivencia y está presente en el momento del diagnóstico en el 30-40% de las pacientes con cáncer de mama. Mientras que la tasa de supervivencia a 5 años para pacientes con enfermedad localizada en la mama es del 95%, esta cifra disminuye por debajo del 85% para pacientes con afectación axilar (47). Académicamente la afectación ganglionar se divide en 3 niveles (Figura 6): los ganglios axilares del Nivel I se encuentran inferiores y laterales al borde lateral del músculo pectoral menor; los ganglios axilares del Nivel II se encuentran posterior al músculo pectoral menor e incluyen los ganglios interpectorales de Rotter; y los ganglios axilares del Nivel III se encuentran superiores y mediales al borde medial del músculo pectoral menor. Finalmente, los ganglios mamarios internos se encuentran a lo largo de los espacios intercostales paraesternales. A nivel quirúrgico, la radicalidad de la linfadenectomía axilar (ALND, axillary lymph node dissection) ha ido disminuyendo en extensión quirúrgica en aras de reducir la morbilidad asociada. Hoy en día, en los casos en que está indicado realizar una ALND, se suele realizar la disección y exéresis de los niveles I y II, relegando el nivel III para aquellas pacientes en las que se sospeche enfermedad en dicho nivel.

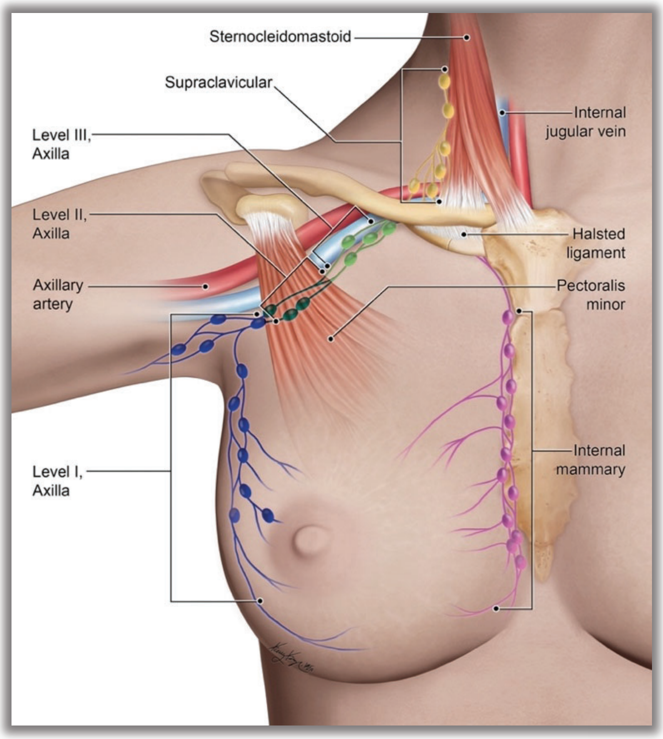

Sternocleidomastoid
Supraclavicular
Internal jugular vein
Level III, Axilla
Level II, Axilla
Halsted ligament
Axillary artery
Pectoralis minor
Internal mammary
Level I, Axilla

Figura 6: Representación del drenaje ganglionar axilar de la mama y los diferentes niveles anatómicos (48).

ESTADIFICACIÓN AXILAR

La ecografía axilar con confirmación citológica/histológica de adenopatías sospechosas permite el diagnóstico de la afectación ganglionar que, como hemos dicho anteriormente, se encuentra presente en el 30-40% del global de las pacientes con cáncer de mama, incluso en algunas pacientes a las que clínicamente no se palpan adenopatías sospechosas al diagnóstico (49). Sin embargo, la ecografía preoperatoria sólo identifica al 50-70% de las pacientes con afectación ganglionar, observándose una tasa de falsos negativos del 25% para esta técnica (50) por lo que la biopsia selectiva de ganglio centinela (SLNB, sentinel lymph node biopsy) se considera el "gold estándar" para la evaluación del estatus ganglionar en pacientes cN0.

1. El paradigma del ganglio centinela

La diseminación ganglionar en las pacientes con cáncer de mama generalmente respeta la migración a través del ganglio centinela (SLN) (51); es decir, el primer ganglio que recibe el drenaje tumoral (Figura 7). Por lo que un resultado negativo en la SLNB descartará enfermedad a este nivel. Sin embargo, hasta la década de los 90' la ALND se consideraba el método de referencia para el diagnóstico de la afectación axilar puesto que además del valor diagnóstico ofrecía control local de la enfermedad y permitía la adecuación del tratamiento adyuvante. No obstante, para pacientes sin afectación axilar inicial (cN0), la supervivencia no se ha visto beneficiada por el hecho de realizar ALND y en cambio puede producir secuelas a largo plazo que se observan hasta en el 40-60% (52,53) de las pacientes con una morbilidad postquirúrgica entorno al 20-50% (54).

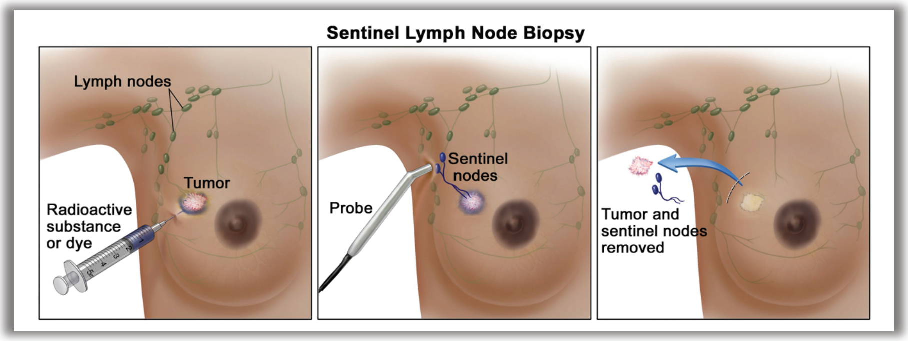

Sentinel Lymph Node Biopsy
Lymph nodes
Tumor
Radioactive substance or dye
Sentinel nodes
Probe
Tumor and sentinel nodes removed

Figura 7. Representación de punción peritumoral y marcaje en piel de la localización del ganglio centinela (55).

2. Desarrollo y evolución de la biopsia del ganglio centinela

Como alternativa a la ALND, la técnica más estandarizada para la realización del estadiaje axilar es la SLNB (Figura 8). Este procedimiento consiste en la inyección peritumoral o peri-areolar preoperatoria de 3 mCi 99mTc-albumina nanocoloide y su posterior detección intraoperatoria con gamma sonda. El acceso a la fosa axilar para la SLNB se puede realizar mediante la incisión mamaria en casos de mastectomía o mediante una incisión independiente axilar de unos 2cm. Al acceder al tejido subcutáneo e incidir en la fascia axilar se accede al tejido linfograso donde la gammasonda es capaz de detectar el mayor contaje procedente de la primera estación ganglionar. También se acepta considerar como ganglios centinelas secundarios aquellos que tengan al menos un 10% respecto la máxima actividad o aquellos que se consideren sospechosos por tamaño o consistencia durante el acto quirúrgico. Otras opciones validadas para la detección del SLN son la inyección de azul patente o el verde de indocianina.

La técnica del SLNB ha demostrado obtener unas tasas de detección cercanas al 100%. Además, en los grandes estudios de validación de la técnica se demostró una precisión diagnóstica (tanto valor predictivo negativo como positivo) entorno al 97% y una tasa de falsos negativos < 9% (56–58). Adicionalmente, se confirmó que las secuelas del SLNB tales como el dolor en extremidad o aparición de linfedema del brazo eran < 8% de las pacientes en comparación al 20% de las pacientes tras ALND (59,60).

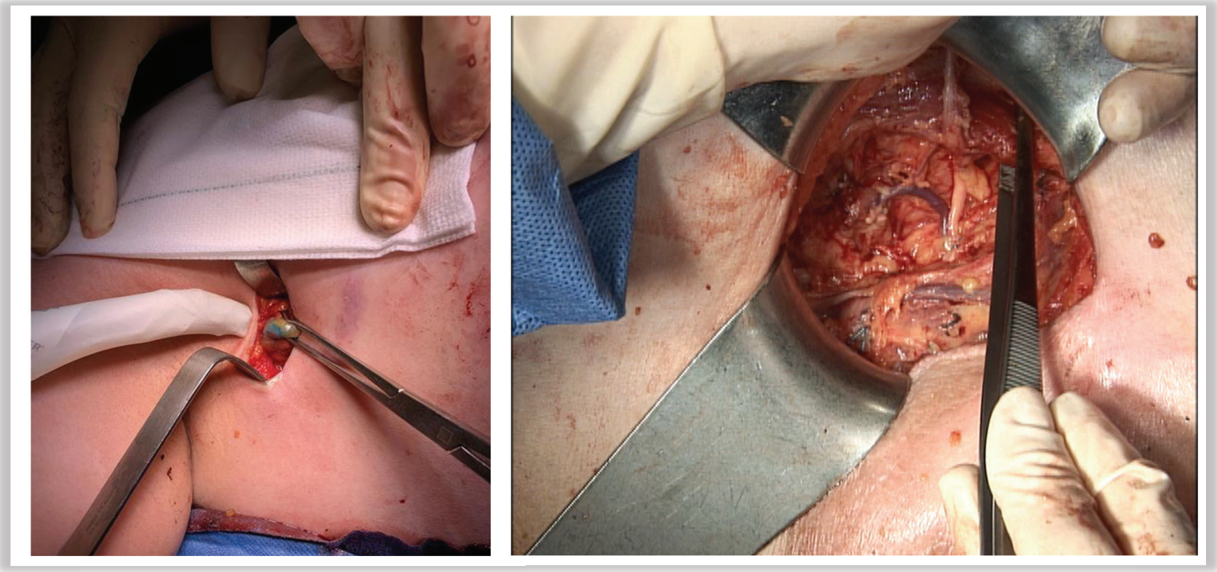


Figura 8. A la izquierda, técnica de biopsia de ganglio centinela. A la derecha, técnica quirúrgica de linfadenectomía axilar. Figura propia.

Entre finales de los ‘90 y principios de los 2000, la seguridad oncológica de la técnica también quedó validada tras demostrar que en las pacientes sin afectación axilar inicial (cN0), la adición de linfadenectomía no impactaba en el pronóstico. En uno de los mayores estudios sobre este tema (NSABP B-32) (61) donde se aleatorizaron a 5.611 pacientes con cáncer de mama sin afectación ganglionar clínica a recibir: SLNB + linfadenectomía axilar (grupo 1) vs únicamente SLNB (linfadenectomía axilar sólo en caso de SLNB positivo) (grupo 2); se demostró que la supervivencia global fue del 91.8% en el grupo 1 y del 90.3% en grupo 2 así como supervivencia libre de enfermedad del 82.4% y 81.5% respectivamente (ambas diferencias no estadísticamente significativas). Por tanto, la técnica SLNB se estableció como “gold estándar” para el diagnóstico de la enfermedad ganglionar en aquellas pacientes con cáncer de mama en estadio inicial cN0.

Con el objetivo de reducir el número de ALND en aquellas pacientes con baja carga tumoral en el SLN, debido a las secuelas asociadas, se diseñó el estudio multicéntrico aleatorizado Z0011(62) que publicó sus resultados en 2011. Demostró que, las pacientes con estadios T1-T2 (<5cm) sin afectación ganglionar inicial candidatas a cirugía conservadora de mama (y radioterapia) y con hallazgo de 1 o 2 SLNB positivos, obtenían mismas tasas de supervivencia global y supervivencia libre de enfermedad aún sin completar la ALND respecto a aquellas que se habían sometido a linfadenectomía axilar. Datos recientes de la misma cohorte con una mediana de seguimiento de 9.25 años, confirmaron una incidencia acumulada a 10 años de recurrencia loco regional del 5.3% en el grupo SLNB exclusivo vs 6.2% en el grupo de SLNB + linfadenectomía ($p = 0.36$). Además, se demostró la no-inferioridad de la SLNB al observar una supervivencia global a 10 años del 86.3% en el grupo SLNB sólo y del 83.6% en el grupo de SLNB + linfadenectomía ($p=0.02$)(63,64). En contrapartida, en el análisis de complicaciones tales como infección de la herida, seromas axilares, parestesias y linfedema; sí se observaron diferencias significativas a favor del grupo del SLNB, observándose en un 70% en el grupo SLNB + ALND vs 25% en el grupo SLNB exclusivo ($p < 0.001$). Consecuentemente, la realización de linfadenectomía axilar como método de estadificación está en declive en las pacientes cN0 (65) debido a las importantes secuelas que puede ocasionar principalmente resultantes del daño en el drenaje linfático del brazo (Figura 9).

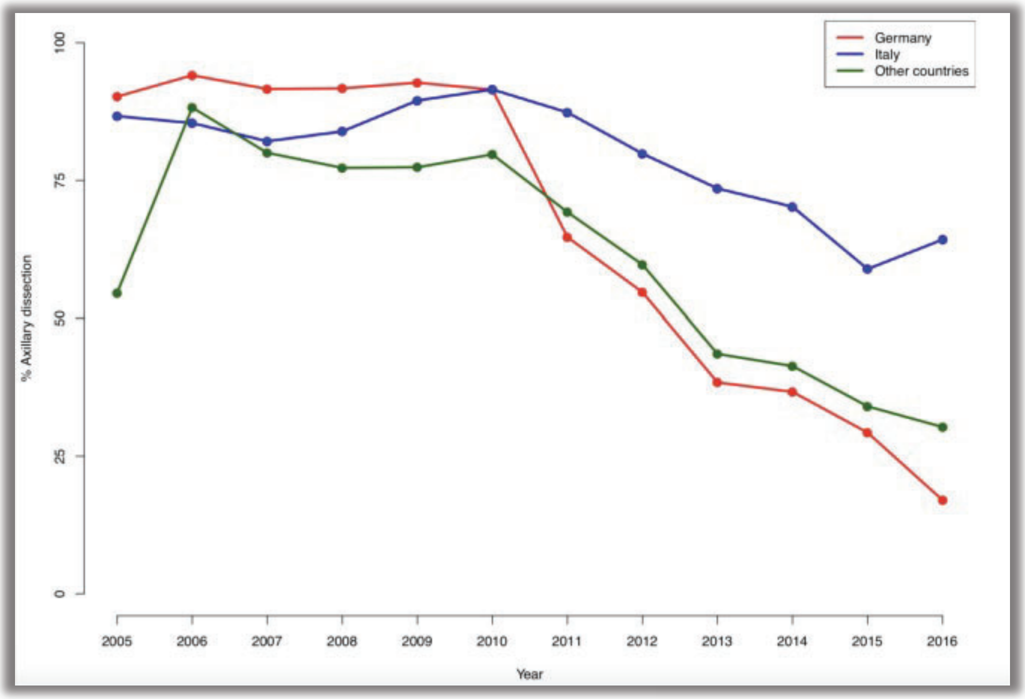


Figura 9. Tasas de linfadenectomía axilar por países desde 2006 hasta 2016 en pacientes con estadios T1-T2 N0 M0 (65).

EFECTOS ADVERSOS DEL ABORDAJE AXILAR

Como ya hemos comentado brevemente, la ALND clásica implicaba la exéresis de ganglios linfáticos en los niveles I, II y III (66). Aunque su radicalidad se ha reducido con el paso de los años y generalmente sólo se abordan el nivel I-II, las complicaciones quirúrgicas y secuelas funcionales continúan afectando a una alta proporción de pacientes repercutiendo significativamente en su calidad de vida. En general, los efectos adversos postoperatorios descritos tras la realización de una linfadenectomía axilar se encuentran entorno al 60% de las pacientes mientras que, para el SLNB se sitúan alrededor del 3-17% (52). Así mismo, varios estudios han demostrado peores resultados en encuestas de satisfacción y calidad de vida en pacientes en las que se realizó una linfadenectomía respecto a aquellas pacientes sometidas a SLNB (67). Entre las complicaciones más frecuentes asociadas a la linfadenectomía se encuentran: el linfedema del brazo, el seroma, la hemorragia post-quirúrgica, la sensación de entumecimiento, la limitación de la movilidad del hombro, las parestesias, el dolor y la infección (68).

1. Complicaciones post-quirúrgicas inmediatas

En la tabla 1 se recogen las complicaciones postquirúrgicas más frecuentemente observadas en función del tipo de abordaje axilar, siendo todas ellas significativamente menos frecuentes en pacientes sometidas a SLNB en comparación con aquellas que se sometieron a SLNB y ALND:

Complicaciones Postquirúrgicas	***SLNB (%)***	***SLNB + ALND (%)***	***p value***
Restricción del rango de movimiento	26.8	50.0	< 0.001
Dolor en hombro/brazo	9.3	22.9	< 0.001
Entumecimiento	6.6	23.3	< 0.001
Dolor axilar	8.2	17.1	< 0.001
Drenaje de seromas	25	81	< 0.001

Tabla 1: Complicaciones postquirúrgicas inmediatas en función del abordaje axilar (52). *SLNB: biopsia de ganglio centinela, ALND: linfadenectomía axilar*.

Es por ello, que la educación sanitaria y la valoración por un fisioterapeuta especializado tras la cirugía axilar después de una linfadenectomía se ha incorporado de forma rutinaria en muchos centros de referencia.

2. Secuelas a medio-largo plazo

La realización de ALND también se ha asociado de manera significativa con una mayor incidencia de secuelas postquirúrgicas a largo plazo, descritas en la tabla 2 (52). Destacar, la aparición del linfedema como una de las más frecuentes e invalidantes para las pacientes. Además, tiene como particularidad que puede aparecer de manera tardía suponiendo aún un mayor reto en su manejo.

Secuelas a Medio-Largo Plazo	*SLNB (%)*	*ALND (%)*	*p value*
Restricción del rango de movimiento	3.5	11.3	< 0.001
Dolor en hombro/brazo	8.1	21.1	< 0.001
Dolor en cicatriz	3.7	13.7	< 0.001
Parestesias en el brazo	10.9	37.7	< 0.001
Linfedema	3.5	19.1	< 0.001

Tabla 2: Secuelas a medio-largo plazo en función del abordaje axilar (52). *SLNB: biopsia de ganglio centinela, ALND: linfadenectomía axilar.*

a) Linfedema

El linfedema es la complicación más frecuente de todas las secuelas asociadas al tratamiento axilar y que ocasiona una mayor incapacidad funcional en las pacientes (Figura 10). Se presenta en el 6-30% (69) de los casos y todavía no existe una terapia curativa realmente eficaz. Consiste en el aumento anormal del líquido linfático en el espacio extracelular debido a una insuficiencia en su capacidad de drenaje. Dicho estancamiento linfático, inicia una cascada inflamatoria que destruye progresivamente la elasticidad celular y provoca una fibrosis e hipertrofia del tejido conectivo exacerbando el circulo de estancamiento-fibrosis (70). A su vez, el linfedema puede dar lugar a otras complicaciones, siendo la linfangitis o infección del linfedema la más común con una incidencia observada hasta en el 62.5% (70) de las pacientes. Desafortunadamente, la "no aparición" del linfedema inmediatamente posterior a la cirugía no excluye su desarrollo. Aunque su incidencia es mayor dentro de los dos primeros años post-cirugía, se han descrito linfedemas de aparición tardía, a los 5 o 10 años tras la cirugía (71).

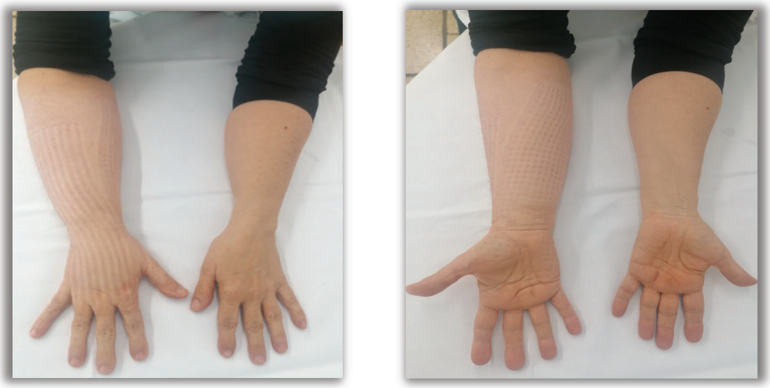


Figura 10. Paciente con linfedema en extremidad superior derecha secundaria a linfadenectomía axilar. Figura propia.

El diagnóstico del linfedema es clínico y por exploración física, por lo que su reconocimiento precoz permite establecer medidas preventivas para evitar la infección así como aumentar los cuidados sobre el brazo afectado. El linfedema se clasifica en una serie de estadios progresivos según la Sociedad de Linfología internacional (72)**:**

-En el *Estadio 0*, se presenta una condición latente donde el deterioro del transporte linfático y los cambios en la composición del tejido y los fluidos empiezan a generar síntomas. Sin embargo, la hinchazón aún no es evidente clínicamente. Esta etapa puede durar meses o años antes de que el edema sea visible.

-El *Estadio I,* se caracteriza por una acumulación temprana de fluido con un alto contenido proteico en comparación con el edema venoso. El edema disminuye con la elevación del miembro y durante el descanso nocturno. En muchas ocasiones, puede observarse el signo de la fóvea.

-En el *Estadio II* (Figura 11A), la elevación del miembro ya no reduce el exceso del volumen de la extremidad de manera efectiva. Aunque el signo de la fóvea es evidente al principio, se va perdiendo a medida que progresa el linfedema debido al aumento del tejido fibroso y la grasa subcutánea.

-En el *Estadio III* (Figura 11B), conocido como elefantiasis, la piel se vuelve dura y escamosa, con cambios tróficos como papilomatosis, acantosis y depósitos grasos. También pueden aparecer vesículas y ampollas, aumentando el riesgo de linfangitis.

-Finalmente, un linfedema crónico puede derivar en un tumor vascular poco común pero muy agresivo, el linfangiosarcoma o síndrome Stewart-Treves, descrito en pacientes post-mastectomía por Stewart y Treves en 1948 (73) (Figura 11C).

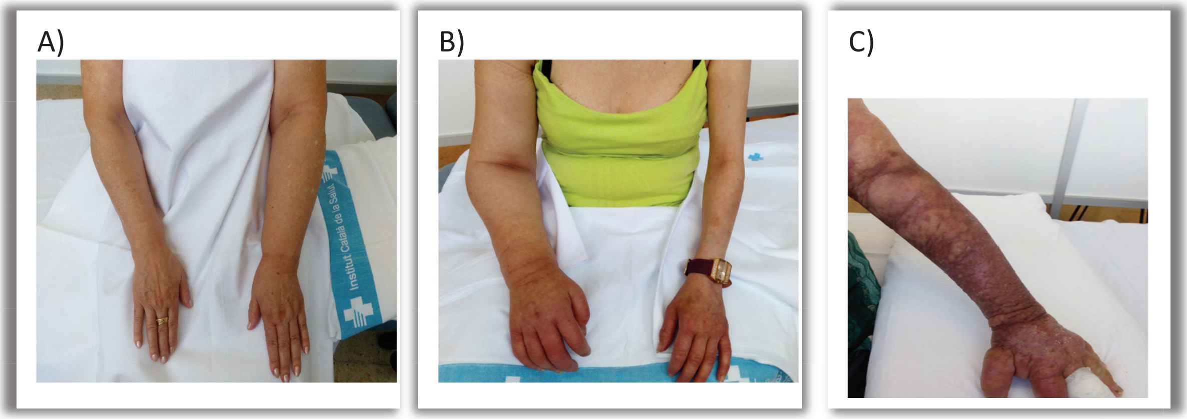


Figura 11. Fotografías de pacientes con linfedema categoría II (A), categoría III (B) y linfangiosarcoma (C). Fotos propias.

Existe consenso en iniciar el tratamiento para el linfedema cuando existe una diferencia de volumen > al 10% respecto al brazo contralateral (74). Los objetivos del tratamiento son principalmente reducir o evitar el aumento del mismo y para ello se recomienda higiene de la piel, drenaje linfático manual o la aplicación de vendas multicapa. Existen otras modalidades de tratamiento como la presoterapia o los sistemas de compresión ajustable que han demostrado su utilidad en la fase descongestiva del tratamiento (Figura 12). Una vez el linfedema se estabiliza, las prendas compresivas ayudan a mantener la reducción de volumen ya que aumentan la presión intersticial, mejoran el drenaje del líquido tisular, estimulan las contracciones linfáticas y rompen el tejido fibro-esclerótico.

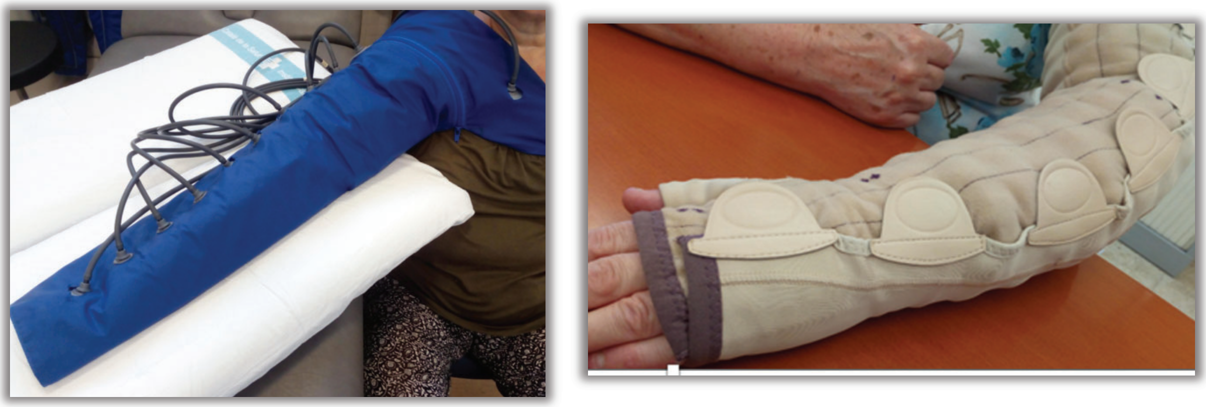


Figura 12. A la izquierda, manguito de presoterapia con 11 cámaras utilizado en la fase descongestiva del linfedema, A la derecha, sistemas de compresión ajustables prefabricados. Figura propia.

Por último, destacar que, aunque el abordaje conservador del linfedema es el más utilizado, el tratamiento quirúrgico ha demostrado ser útil especialmente en casos iniciales cuando todavía no hay fibrosis del tejido subcutáneo y el linfedema es reversible. Dicho tratamiento se ha podido implementar gracias al desarrollo de la microcirugía y los nuevos métodos de visualización con verde de indocianina (75) que permiten un estudio más preciso de la anatomía del sistema linfático (Figura 13). Se han desarrollado diferentes técnicas quirúrgicas que se basan en anastomosar el sistema linfático al sistema venoso o realizar la transferencia de un colgajo de ganglios linfáticos y grasa perinodal que permite aumentar el drenaje de la linfa no-circulante.

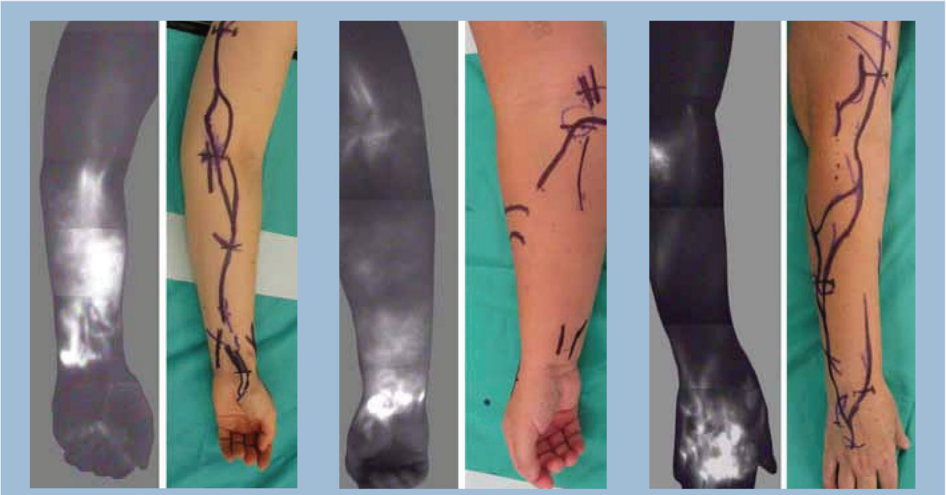


Figure 3. Incocyanine green (ICG) fluorescent lymphography image of the dorsal (left) and volar (centre) sides of a lymphoedema limb; injection sites of ICG and identified collecting lymphatic vessels. (Right) Preoperative view of the patient. Ink marks indicate the positions of the collecting lymphatic vessels found during the surgery.

Figura 13. Linfografía prequirúrgica mediante verde de indocianina para el estudio del defecto del drenaje linfático y su posterior anastomosis intraquirúrgica (76).

b) Dolor e impotencia funcional

El dolor prolongado, definido como el dolor que persiste hasta tres meses después de la cirugía focalizado en la mama, la axila o el brazo, es la segunda secuela en frecuencia tras la ALND y se reporta hasta en el 50% de los pacientes según las series (77,78) al igual que las limitaciones funcionales. La disminución en la calidad de vida secundaria a estas complicaciones son la principal causa de la “no incorporación” laboral. Además del número de ganglios extraídos, también se han observado otros factores de riesgo independiente de aparición de secuelas postquirúrgicas como mayor edad y que la linfadenectomía se haya realizado en el brazo dominante (79).

Las técnicas de bloqueo nervioso paravertebral torácico y la infiltración de anestésicos locales en el lecho quirúrgico son dos técnicas que han demostrado ser útiles en el tratamiento del dolor crónico cuando la analgesia oral convencional no es suficiente. En aquellas pacientes con debilidad de la extremidad o impotencia funcional, los tratamientos de rehabilitación realizados por un/a fisioterapeuta capacitado/a en rehabilitación oncológica durante programas con una duración mínima de 6 semanas, se ha visto que son efectivos para reducir el dolor y para la recuperación funcional del miembro superior. En concreto, los ejercicios miofasciales específicos en la articulación escapulotorácica son de especial utilidad para la recuperación funcional del brazo (80). Finalmente, la adopción de un programa de rehabilitación no intensivo durante el primer año después de una ALND debería ofrecerse a todas las pacientes sometidas a este procedimiento. Esta medida permite mejorar los resultados de la recuperación tanto cualitativa como cuantitativa en la función de la extremidad.

3. Impacto en la calidad de vida

A consecuencia del incremento en supervivencia de las pacientes afectas de cáncer de mama en las últimas décadas, ha surgido la necesidad de prestar especial atención en mejorar la calidad de vida con la que conviven las pacientes, no solo tras los tratamientos recibidos sino también durante el proceso diagnóstico. De tal manera, en los últimos años se ha visto incrementado el número de estudios que tienen como objetivo primario mejorar la calidad de vida y buscar estrategias que permitan una reducción de los efectos secundarios y secuelas quirúrgicas. En este sentido, recientemente se ha publicado una revisión sistemática (81) donde se observa que los principales factores de riesgo para las secuelas a largo plazo en el brazo secundario al tratamiento del cáncer de mama son: la realización de una linfadenectomía axilar, un IMC > 30 y la realización de una mastectomía. Precisamente, la sustitución de la linfadenectomía axilar por la biopsia del ganglio centinela (cuando es oncológicamente factible) es un claro ejemplo de esta evolución y motiva a seguir estudiando diferentes estrategias terapéuticas que permitan reducir el número de procedimientos con elevada morbilidad sin perjudicar la seguridad oncológica.

TRATAMIENTO SISTÉMICO DEL CÁNCER DE MAMA

El desarrollo de la terapia sistémica adyuvante a la cirugía sucedió en la década de los años 50 cuando Bernard Fisher (82) cambió el paradigma de Halsted demostrando que el cáncer de mama era una enfermedad sistémica en lugar de una enfermedad local. Este cambio de paradigma llevó al abandono de las cirugías radicales y, en su lugar, se promovieron cirugías conservadoras de mama especialmente para los carcinomas en etapas tempranas. Se pudo demostrar que las cirugías más conservadoras junto con radioterapia, quimioterapia y hormonoterapia, prolongaban la supervivencia de las pacientes con menor morbilidad asociada (83).

Históricamente, la elección del tratamiento sistémico adyuvante ha sido guiada por la experiencia en el tratamiento de pacientes con enfermedad avanzada. El primer tratamiento sistémico para las pacientes metastásicas de cáncer de mama data de 1896, cuando Beatson (84) informó sobre dos pacientes con estadio avanzado que mejoraron después de la ooforectomía. Este enfoque se convirtió en una terapia común en este subgrupo de pacientes y abrió las puertas para la investigación sobre el tratamiento antihormonal. Sin embargo, no fue hasta la década de 1950 cuando la quimioterapia basada en alquilantes se convirtió en una terapia disponible y reproducible para el manejo de pacientes con neoplasias hematológicas y sólidas, e inmediatamente se integró en el tratamiento postoperatorio de pacientes con cáncer de mama (85).

La terapia sistémica se convirtió en el “estándar de tratamiento” en la década de 1970 cuando se demostró mediante ensayos aleatorizados (86,87) que: la quimioterapia mejoraba las tasas de supervivencia libre de enfermedad y supervivencia global, que la ablación ovárica (88) aumentaba la supervivencia en pacientes premenopáusicas y que el tamoxifeno (89) mejoraba las tasas de supervivencia en mujeres posmenopáusicas.

1. Quimioterapia

El primer esquema de tratamiento quimioterápico utilizado en cáncer de mama incorporaba ciclofosfamida, metotrexato y 5-fluorouracilo (CMF) y demostró (90) que reducía las tasas de recurrencia del 37% al 22% y la mortalidad del 27% al 14% cuando se comparaba con regímenes de monoterapia en pacientes con estadios iniciales.

A finales de los ‘90 se observó, que los regímenes que incluían antraciclinas junto ciclofosfamida podrían mejorar los resultados oncológicos (91). Recientemente en 2023, se ha publicado un meta-análisis (92) donde tras analizar 100.000 pacientes concluyó que los regímenes que incluyen antraciclinas y taxanos reducen significativamente el porcentaje de recidivas en comparación con regímenes de taxanos sin antraciclinas. Se observó que el riesgo de recurrencia a 10 años es del 12.3% con esquemas que incluyen antraciclinas vs 21% sin antraciclinas (RR 0.58, 0.47-0.73; $P<0{,}001$) y la mortalidad se redujo en el grupo con antraciclinas en un 4.2% (0.4-8.1; $p=0.0034$). Además, también observaron que estas reducciones en las recurrencias se mantenían estables independientemente de la edad, de la positividad de los receptores hormonales, del estado de HER2, e incluso en las pacientes sin afectación ganglionar. Sin embargo, es importante balancear el beneficio oncológico que se espera de estos agentes quimioterápicos en relación con sus efectos secundarios. Entre los efectos tóxicos agudos más destacados de las antraciclinas se encuentran la alopecia, las náuseas y vómitos y la neutropenia febril. Como efectos tóxicos a largo plazo se encuentra la aparición de leucemia mieloide aguda estimada en 1/1000 pacientes tratadas y alteraciones en el funcionamiento cardíaco en forma de miocardiopatía que pueden aparecer 4 o 5 años tras finalizar el tratamiento (93). Respecto a los taxanos, los efectos secundarios más frecuentes son las reacciones anafilácticas, por lo que requieren de la administración de premedicación con corticoides y la neuropatía sensitiva periférica que afecta entre el 15-20% de las pacientes (94). Finalmente, destacar que la neuropatía periférica (95) puede persistir a pesar de suspender el tratamiento pudiendo ocasionar un detrimento significativo en la calidad de la vida de las pacientes.

Otros fármacos utilizados predominantemente en cáncer de mama triple negativo son los derivados del platino. La adición de carboplatino en los esquemas de neoadjuvancia de los tumores tiple negativo ha conseguido mejorar las tasas de respuesta patológica del 35% al 50% con una consiguiente mejoría en supervivencia libre de enfermedad (96–98). Por último, mencionar la adición de la capecitabina, un derivado de las fluoropirimidinas de administración oral, como tratamiento adyuvante durante 6-8 ciclos en aquellas pacientes con enfermedad residual tas la quimioterapia neoadyuvante que demostró disminuir las tasas de recidiva con impacto positivo en supervivencia (99).

2. Hormonoterapia

Como hemos comentado previamente, la hormonoterapia fue, probablemente, el primer tratamiento sistémico para el cáncer de mama (84). En la actualidad la base del tratamiento hormonal son los inhibidores de la aromatasa (IA) desarrollados en los ‘90 en mujeres post-menopaúsicas y el tamoxifeno, que se mantiene de elección en pacientes pre-menopaúsicas o en mujeres post-menopaúsicas de buen pronóstico como tratamiento secuencial junto a los IA.

La introducción del tamoxifeno en el tratamiento del cáncer de mama ha representado un hito significativo en la oncología moderna. Como el primer agente de su clase utilizado en esta enfermedad, el tamoxifeno es conocido por su capacidad para modular el receptor de estrógeno (SERM). Su inclusión en el abordaje terapéutico del cáncer de mama ha contribuido a mejorar significativamente las tasas de supervivencia y calidad de vida de las pacientes al reducir tanto el riesgo de recidiva en un 47% como el riesgo de mortalidad en un 26%, respecto a su no administración (100). Además, ofrece un efecto de protección contra la pérdida ósea en pacientes postmenopáusicas gracias a la acción agonista parcial estrogénica y un perfil metabólico también favorable disminuyendo los niveles de colesterol (101). Sin embargo, esta misma acción estrogénica también se ha relacionado con un incremento de riesgo de fenómenos tromboembólicos así como de un incremento de riesgo de aparición de cáncer de endometrio (102,103). Es por ello que en los años ‘90 se desarrollaron los fármacos IA que inhiben la conversión periférica de andrógenos a estrógenos y se han relacionado con un menor efecto tromboembólico, menor prevalencia de cáncer de endometrio y una mayor eficacia respecto al tamoxifeno en cuanto a la reducción de la mortalidad y recidivas (104) a costa de una mayor toxicidad ósea e incremento de la dislipemia, entre otros efectos secundarios debido a su acción antiestrogénica.

Actualmente, la recomendación de tratamiento hormonal se basa en considerar el estado menopaúsico de la paciente y el riesgo de recaída (6). En las pacientes pre-menopáusicas de bajo riesgo la indicación es tamoxifeno 20 mg/día x 5 años, mientras que en las de alto riesgo se recomienda la supresión ovárica junto a exemestano según esquema estudio SOFT (105). En las mujeres postmenopáusicas de bajo riesgo el tratamiento recomendado es tamoxifeno secuencial a IA hasta completar 5 años, mientras que en pacientes de alto riesgo se recomienda IA entre 5 a 10 años (106,107).

3. Terapias dirigidas

Paralelamente, a finales de los ’90 (108) también se desarrollaron los tratamientos dirigidos contra dianas terapéuticas previamente mencionadas como el HER2, trastuzumab y pertuzumab. El estudio HERA (109) demostró que el trastuzumab administrado después de la cirugía y la quimioterapia durante un año para aquellas pacientes con tumores que sobre-expresaban HER2, reducía la tasa de recurrencia; especialmente la recurrencia a distancia en aproximadamente un 50% respecto a su no administración. En enfermedad avanzada la adición de pertuzumab en primera línea de enfermedad metastásica demostró un incremento del tiempo a la progresión de 12.4 meses a 18.5 meses frente al brazo control basado en trastuzumab y paclitaxel (110). Sin embargo, en la adyuvancia el beneficio de añadir pertuzumab sólo se ha demostrado en aquellas pacientes de alto riesgo como las que tienen afectación ganglionar (111). A pesar de que los tratamientos diana tienen menos efectos secundarios que la quimioterapia convencional, no están exentos de toxicidad. El efecto adverso más grave relacionado con estos fármacos es la disfunción ventricular izquierda y se estima que aparece aproximadamente en el 0’5% de las pacientes que reciben este tratamiento, así como las reacciones de anafilaxia puesto que al ser anticuerpos murinos humanizados deben administrarse con premedicación. El pertuzumab además puede producir toxicidad digestiva en forma de diarrea (109).

En los últimos años hemos visto un gran avance en el desarrollo de los inmunoconjugados (antibody drug conjugates o ADC) como trastuzumab-emtansina (TDM-1) o más recientemente trastuzumab-deruxtecan (T-Dxd). TDM-1 cómo adyuvancia ha demostrado mejoras en supervivencia en enfermedad avanzada (112) y en supervivencia libre de progresión en pacientes con tumores HER2. Recientemente, también ha demostrado beneficio en pacientes con enfermedad residual tras la neoadyuvancia basada en trastuzumab y pertuzumab (113). Por otro lado, T-Dxd está suponiendo una revolución en el manejo de la enfermedad avanzada tanto en HER2 positivo (114) como para tumores con baja expresión de HER2 (115) al haber demostrado mejoras en supervivencia libre de progresión y supervivencia global. Como efecto secundario de estos ADCs se debe vigilar especialmente la enfermedad pulmonar intersticial, que si bien ocurre un menos del 5% de los casos puede ser grave, además de la hematológica y la digestiva.

Otros agentes diana destacables en el manejo de las pacientes con cáncer de mama son los fármacos inhibidores de quinasa dependiente de ciclina CDK 4 y CDK 6 (CDKi)(116): palbociclib, ribociclib y abemaciclib. Estos fármacos demostraron un beneficio en tiempo a la progresión de 10 a 24 meses aproximadamente en enfermedad avanzada y ocupan actualmente la primera línea para la enfermedad metastásica luminal. Actualmente abemaciclib tiene aprobación en la adyuvancia de pacientes con tumores luminales de muy alto riesgo (117) y en breve se espera la aprobación de ribociclib en adyuvancia en pacientes de riesgo intermedio/alto (118).

Por último, mencionar los inhibidores de la polimerasa de poli ADP-Ribosa (iPARP)(119). Estos fármacos desarrollados en las pacientes portadoras de la mutación germinal en BRCA 1 y/o BRCA 2, han conseguido resultados prometedores tanto en enfermedad avanzada (120) como en enfermedad precoz (121) con mejoras significativas en supervivencia global.

4. Inmunoterapia

La inmunoterapia basada en inmune checkpoint inhibitors como pembrolizumab (anti-PD-1) o atezolizumab (anti-PDL1) recibieron su aprobación en cáncer de mama avanzado triple negativo PDL-1 positivo en base a los estudios Keynote 355 (122) e Impassion 130 (123), respectivamente. Recientemente pembrolizumab ha recibido la aprobación como tratamiento neoadjuvante en cáncer de mama triple negativo independientemente de PDL1 en base al estudio Keynote 522 junto con la quimioterapia que hoy en dia se considera standard en cáncer de mama triple negativo con paclitaxel-carboplatino semanal x12 seguido e adriamicina-cilofosfamida (AC) cada 21 dias x 4 ciclos todo ello concomitante a pembrolizumab 2 mg/kg cada 21 dias x 8 ciclos neoadjuvante. Con este esquema se ha conseguido aumentar el porcentaje de pCR del 50 al 65%, y mejora en la supervivencia libre de enfermedad estimada a 5 años de 72.3% vs 81.3% con HR: 0.63 (95%IC 0.49-0.81) a favor de pembrolizumab .

El tratamiento sistémico puede implementarse tanto como adyuvancia tras la cirugía como de manera neoadyuvante, proporcionando así un beneficio en aquellas pacientes que respondan al tratamiento en cuanto a pronóstico e incremento de las cirugías conservadoras de mama.

TRATAMIENTO SISTÉMICO NEOADYUVANTE

El tratamiento sistémico preoperatorio o neoadyuvante (NAT, neoadjuvant treatment) incluye tanto quimioterapia (NACT: neoadjuvant chemotherapy) como hormonoterapia (NET: neoadjuvant endocrine therapy). Se considera que la NAT se empezó a utilizar inicialmente en la década de los '70 tras observar altas tasas de recurrencia local y mortalidad en pacientes con carcinoma inflamatorio y tumores localmente avanzados (124) tratados exclusivamente con cirugía. Tras demostrar que existían reducciones significativas del volumen tumoral en un 60-80% (125) de las pacientes tratadas con quimioterapia, el siguiente objetivo de esta nueva modalidad de tratamiento pretendía obtener este efecto beneficioso para plantear una cirugía conservadora mamaria posterior en pacientes que, de entrada, eran candidatas a una cirugía radical.

La valoración de la respuesta "in vivo" a la NACT es otra de las grandes ventajas respecto a su administración tras la cirugía. Esta respuesta, no solo aumenta las posibilidades de realizar una cirugía conservadora de la mama sino que además, ofrece un valor pronóstico dado que las pacientes que responden mejor a la quimioterapia son aquellas que presentarán una mejor supervivencia. Sin embargo, no se han encontrado diferencias en la supervivencia cuando los mismos regímenes de tratamiento sistémico se administran de manera neoadyuvante o adyuvante (126–132). En este sentido, el metaanálisis de Mauri et al. (133) que incluyó un total de 3.946 pacientes, tampoco encontró diferencias significativas en mortalidad global (RR = 1.00, 95% IC = 0.90 a 1.12), progresión de la enfermedad (RR = 0.99, 95% IC = 0.91 a 1.07), ni recurrencias a distancia (RR = 0.94, 95% IC = 0.83 a 1.06). Por otra parte, el tratamiento neoadyuvante, además de permitir una valoración de la respuesta "in vivo" y de reducirlas tasas de mastectomías (134), permite la posibilidad de un abordaje axilar menos radical acorde a la respuesta clínica. Finalmente destacar, que también permite modificar los esquemas de tratamiento en aquellas pacientes donde se observe una respuesta desfavorable (135).

La respuesta patológica completa (pCR) tras la quimioterapia observada en el análisis anatomopatológico tanto de la mama (ypT0) como de los ganglios linfáticos (ypN0), hoy en día se considera como uno de los mejores marcadores pronóstico de supervivencia puesto que se relaciona con tasas más favorables tanto de supervivencia libre de enfermedad como de supervivencia global (Figura 14) (136,137). Las tasas documentadas de pCR en la literatura varían del 20% al 60% (138), dependiendo de varios factores predictores de respuesta, especialmente del subtipo molecular. Está reportado en la literatura que el 60% de las pacientes con tumores HER2 y triples negativo conseguirán pCR después de NACT (139)(140) mientras que, en pacientes con tumores luminales, las tasas de pCR son <10% tanto si se tratan con NACT como NET (141,142).

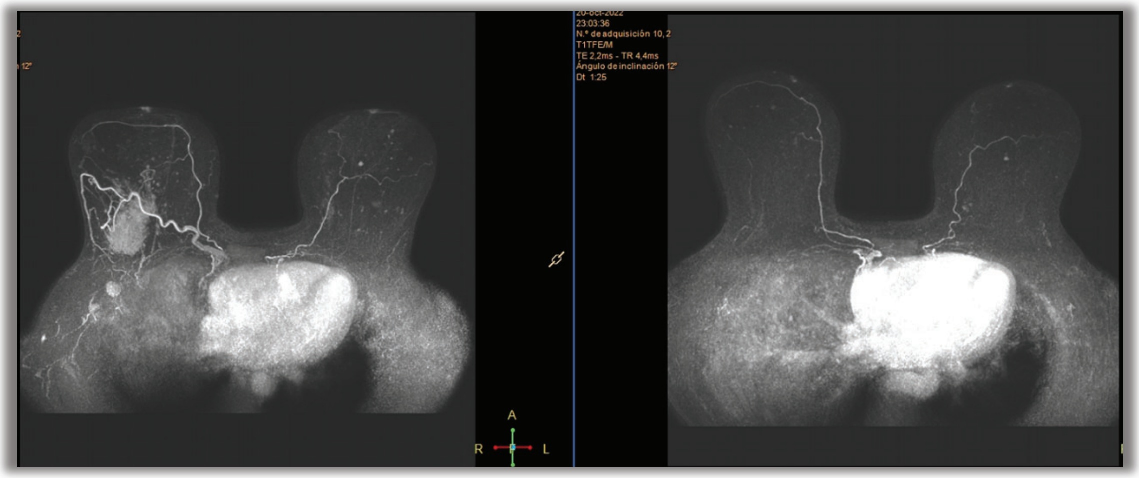


Figura 14. Evaluación por resonancia magnética de un tumor mamario antes y después de quimioterapia neoadyuvante, con respuesta radiológica completa. Figura propia.

Debido a la escasa respuesta de los tumores luminales a la quimioterapia neoadyuvante, la hormonoterapia ha demostrado ser una alternativa útil teniendo en cuenta además, la edad y la fragilidad de este subgrupo de pacientes. Por este motivo, actualmente se recomienda la administración de letrozol neoadyuvante con una duración de al menos 6 meses o incluso duraciones mayores (sin sobrepasar el año de neoadyuvancia) hasta conseguir el máximo de respuesta posible (143) (Figura 15). Tras la cirugía se valora el PEPI score (perioperative endocrine prognostic index) en base al tamaño, la afectació ganglionar, la positividad del RE y el valor del KI 67 en la pieza quirúrgica. En las pacientes con PEPI score de 0 el pronóstico es excelente y se ofrece continuar el tratamiento hormonal hasta completar los 5 años, en las pacientes con PEPI score entre 1-3 el pronóstico es intermedio y se discute el beneficio o no de la quimioterapia adyuvante. Por último, en aquellas pacientes con PEPI score 4 o superior el pronóstico es peor y se recomienda la quimioterapia adyuvante si es factible.

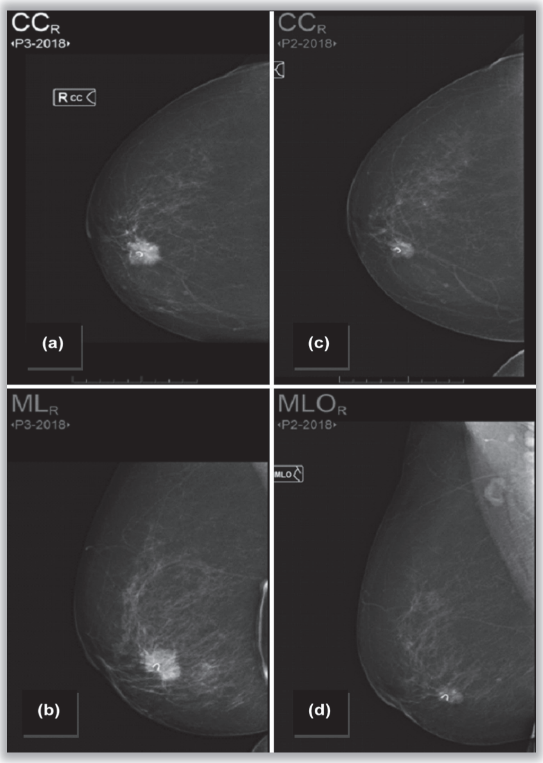


Figura 15: Evaluación mamográfica de un tumor mamario antes y después de la terapia endocrina neoadyuvante, con respuesta parcial. (a, b) Proyección craneocaudal (CC) y proyección oblicua del tumor de cáncer de mama al momento del diagnóstico con marcador metálico en su interior. (c, d) Proyección CC y proyección oblicua 6 meses después de la NET (144). *Figura propia.*

1. Impacto de la NACT en el abordaje axila

El abordaje axilar tras la NACT varía en función de la afectación axilar al diagnóstico.

a) Pacientes sin enfermedad axilar al diagnóstico (cN0)

Como hemos comentado anteriormente, actualmente las pacientes sin enfermedad clínica axilar al diagnóstico (cN0) son tributarias de realizar SLNB como estadiaje ganglionar. Sin embargo, escoger el momento de realización del SLNB en pacientes cN0 que son tributarias de recibir tratamiento neoadyuvante ha resultado muy controvertido en la literatura debido a las ventajas y desventajas de realizar el centinela previo a la neoadyuvancia (SLNB pre-NAT) vs practicar el centinela tras la neoadyuvancia (SLNB post-NAT) (Figura 16).

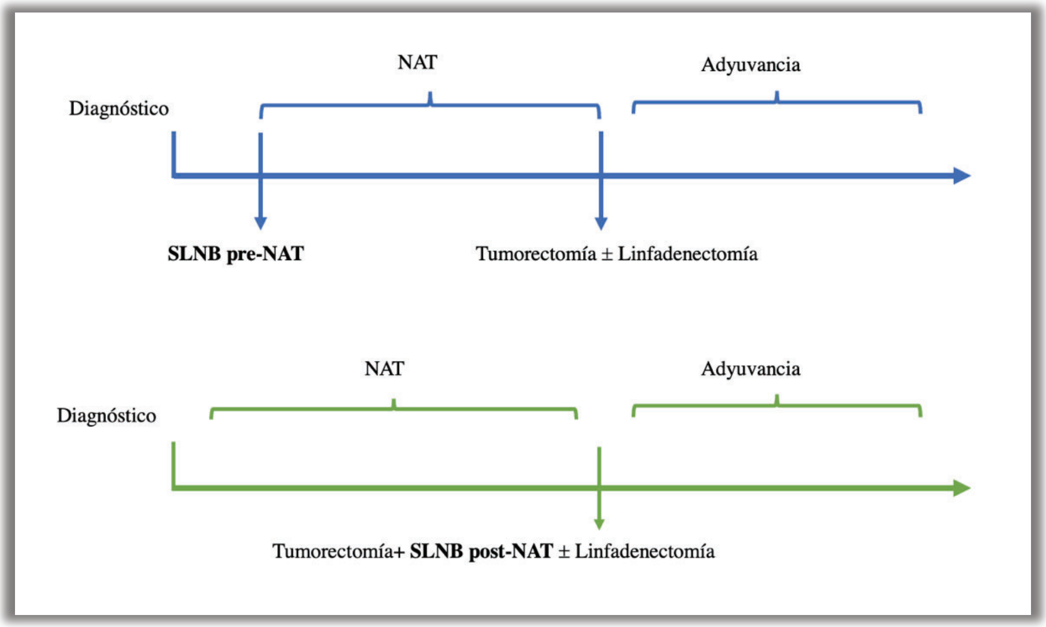

NAT
Adyuvancia
Diagnóstico
SLNB pre-NAT
Tumorectomía ± Linfadenectomía
NAT
Adyuvancia
Diagnóstico
Tumorectomía+ SLNB post-NAT ± Linfadenectomía

Figura 16. Esquemas de realización de ganglio centinela (SLNB) respecto al inicio de tratamiento neoadyuvante (NAT) (figura propia).

La principal ventaja de realizar el SLN pre-NAT es que permite la evaluación "basal" del estado ganglionar (145) demostrando la extensión de la enfermedad al diagnóstico. Además, en los primeros estudios de validación de la técnica se demostraron unas tasas de detección superiores al 95% al no haber recibido ningún efecto de la NAT. Otra de las ventajas que se le atribuye a este "timing" son las tasas de falsos negativos (FNR) <8% dado que no se ha producido ninguna fibrosis secundaria a la neoadyuvancia (146), hecho que podría alterar la precisión diagnóstica del SLNB. Sin embargo, en aquellas pacientes en las que se realiza el SLNB pre-NAT se ha observado una mayor tasa de resultados positivos, lo que conllevaría a una mayor proporción de linfadenectomía axilar respecto a aquellas pacientes en las que el SLNB se ha analizado después de la NAT. Además, se sabe que del 22% al 35% (147) de las pacientes en las que se realiza linfadenectomía axilar por SLNB positivo, no se hallará enfermedad residual en los ganglios por lo que surge la pregunta de si se podría haber evitado la ALND.

En contrapartida, la realización del SLNB post-NACT permite la medición de la respuesta tumoral "in vivo" (148) tanto en la mama como en la axila y en consecuencia el resultado del SLNB podría reflejar de manera más precisa el pronóstico de la paciente e incluso modificar el tratamiento sistémico en función de la respuesta observada.

Además, la realización post-NAT no retrasaría el inicio del tratamiento sistémico y permite realizar la cirugía mamaria y axilar en un mismo acto quirúrgico. Por contra, en los primeros estudios de validación de esta técnica se observaron tasas de detección inferiores a su realización pre-NAT (alrededor del 85%) al igual que tasas de falsos negativos entre el 8-30% según series (149,150). Es por ello, que hasta hace pocos años la mayoría de las guías clínicas recomendaban en primer lugar la realización del SLNB pre-NAT acorde a la evidencia científica disponible (151,152). Sin embargo, recientemente múltiples estudios han reportado tasas de identificación y de falsos negativos similares a realizar el SLNB antes y después de la NACT (153,154) incluyendo un metaanálisis sobre el SLNB post-NACT, que reportó una tasa de identificación del 94% (IC del 95%, 92–96) y un FNR del 7% (IC del 95%, 5–9) (10). En consecuencia, hoy en día el SLNB post-NAT ha sido ampliamente adoptado por la mayoría de centros puesto que en las guías clínicas más actualizadas ya se considera una alternativa igual de válida (155,156). Sin embargo, no existen estudios donde se evalúe el pronóstico de las pacientes entre ambos momentos de realización del ganglio centinela respecto a la neoadyuvancia.

Destacar que, la mayoría de los estudios mencionados en cuanto al abordaje axilar con SLNB pre y post-neoadyuvancia, incluyen a pacientes que recibieron quimioterapia neoadyuvante (NACT) y excluyen a aquellas con tumores luminales que recibieron tratamiento hormonal (NET). Por tanto, su aplicación en este subgrupo de tumores aún permanece en desarrollo. Sabemos que las pacientes con tumores HR+/HER2-, tienen un excelente pronóstico con supervivencias específicas para cáncer de mama > 99% en estadio I (157). Sin embargo, su respuesta a la quimioterapia es 5 veces inferior a otros subtipos moleculares tales como triples negativos o HER2 (158). Incluso las tasas de respuesta patológica tanto en la mama como en la axila, son inferiores en las pacientes que recibieron NET respecto a aquellas que recibieron NACT (159). Además, en las pacientes cN0 y tumores RRHH+, no se han observado diferencias en cuanto a supervivencia global ni supervivencia libre de enfermedad a 6 años entre aquellas en las que se realizó linfadenectomía vs solo cirugía de mama (160). Al igual que tampoco se han observado diferencias en supervivencia respecto a realizar SLNB o ALND post-NET. En consecuencia, la evaluación de la positividad axilar del ganglio centinela respecto a la hormonoterapia neoadyuvante y su impacto en el pronóstico puede proporcionar información de utilidad de cara a entender el comportamiento de estos tumores y ayudar a la toma de decisiones terapéuticas.

b) Pacientes con enfermedad axilar al diagnóstico (cN+)

Para las pacientes con enfermedad axilar inicial (cN+), la terapia neoadyuvante representa el estándar de tratamiento. Por tanto, el planteamiento de "desescalada" quirúrgica axilar está siendo estudiado en los últimos años con el objetivo de disminuir el número de linfadenectomías especialmente en aquellas pacientes donde se objetive una respuesta tumoral. La principal limitación del SLNB en pacientes cN+ son las tasas de falsos negativos reportadas inicialmente entorno al 10-13% (161). Sin embargo, actualmente se han desarrollado otras estrategias para reducir dicha tasa de falsos negativos. Se ha demostrado que el uso de un trazador dual y/o la biopsia de ≥3 ganglios linfáticos centinelas reducen la tasa de falsos negativos a ≤ 10% (162). Otra de las estrategias recientemente descritas es la inserción de un clip o semilla antes de iniciar la NACT, asociando a su vez la SLNB, técnica conocida como TAD (163) (targeted axillary dissection). La exéresis del ganglio marcado junto la exéresis del ganglio centinela permite reducir aún más la tasa de falsos negativos incluso < al 2% (164). De ahí que las guías clínicas internacionales acepten por igual el uso de cualquiera de estas 2 técnicas en pacientes cN1 que se convierten en cN0 tras NACT(6). Sin embargo, en pacientes con enfermedad axilar extensa al diagnóstico (cN2-3) o carcinoma inflamatorio, la linfadenectomía axilar sigue siendo el estándar de tratamiento post-neoadyuvancia debido a la falta de estudios donde se evalúe la seguridad del ganglio centinela en este contexto. El estudio de los factores predictores de respuesta axilar tras NACT nos puede ayudar a identificar a aquellas pacientes tributarias de estas técnicas con menor morbilidad, dado que existiría una baja probabilidad de metástasis axilar después de la NACT y disminuiría aún más el riesgo de dejar enfermedad axilar residual.

JUSTIFICACIÓN DE LA IMPORTANCIA DE LA PRESENTE TESIS

La importancia de esta tesis dónde se investiga el impacto del tratamiento sistémico neoadyuvante sobre el abordaje axilar con datos de pacientes en “condiciones reales de la práctica clínica”, radica en su potencial para mejorar significativamente el manejo de esta enfermedad. Esta investigación podría proporcionar datos muy relevantes sobre el efecto del tratamiento sistémico en cuanto a la identificación y positividad del ganglio centinela y por tanto, qué impacto secundario tiene tanto en el diagnóstico, cómo en la planificación terapéutica y la evolución del paciente. Además, una mejor comprensión de este aspecto podría llevar a una reducción de procedimientos quirúrgicos de elevada morbilidad como la linfadenectomía axilar, minimizando el riesgo de complicaciones y secuelas y permitir una mejoría en la calidad de vida de las pacientes con cáncer de mama sin perjuicio en la supervivencia.

En primer lugar, demostrar que la realización de la biopsia selectiva del ganglio centinela post-neoadyuvancia evita la realización de linfadenectomías axilares innecesarias en un mayor porcentaje de pacientes que cuando se realiza previo al tratamiento sistémico neoadyuvante sin repercutir negativamente en su pronóstico, permitiría poder recomendar con mayor grado de evidencia esta estrategia terapéutica y abandonar su realización pre-quimioterapia. Con este objetivo, se realizó un primer estudio con datos preliminares a corto plazo incluyendo tanto pacientes tratadas con quimioterapia como tratamiento hormonal neoadyuvante. Una vez confirmados los resultados favorables a la hipótesis planteada, se decidió completar dicho estudio hasta obtener 5 años de seguimiento centrado sólo en las pacientes tratadas con quimioterapia neoadyuvante para evaluar los resultados de supervivencia. Al disponer de un mayor seguimiento y un mayor número de casos tras reunir 2 cohortes de pacientes consecutivas en el tiempo, utilizamos métodos estadísticos de macheado de pacientes para obtener así conclusiones de mayor potencia y solidez.

Por otra parte, dado el escaso número de estudios que abordan el efecto de la hormonoterapia neoadyuvante en el manejo axilar, también decidimos investigar paralelamente este aspecto en tumores con RRHH+ y HER2 negativo. Al igual que en otros trabajos de esta tesis, nuestro propósito era evaluar cómo el tratamiento hormonal neoadyuvante impacta según el momento en que se realiza la biopsia del ganglio centinela y su relevancia pronóstica. Además, presentar los resultados de la realización del ganglio centinela en pacientes tratadas con hormonoterapia neoadyuvante podría contribuir a estandarizar esta práctica clínica que aún hoy en día permanece infrautilizada dada la escasez de resultados publicados en la literatura al respecto.

Finalmente, conocer aquellos factores predictores de respuesta axilar a la quimioterapia entre aquellas pacientes con afectación ganglionar inicial, permitiría optimizar la implementación de técnicas de detección axilar post-neoadyuvancia disminuyendo el riesgo de obtener falsos negativos e incluso utilizar éstas mismas técnicas en aquellas pacientes con mayor enfermedad axilar al diagnóstico (cN2). De esta manera, se podría reducir el número de linfadenectomías innecesarias y las secuelas asociadas. Se realizó un estudio inicial sobre los factores predictores de respuesta axilar tras la quimioterapia en pacientes con afectación ganglionar al diagnóstico, donde se identificaron los factores de respuesta axilar y que especialmente aplicaban a las pacientes cN1. Se comprobó que aquellas pacientes con tumores quimio-sensibles como los HER2 y TNBC que conseguían negativizar la axila tras la NACT, tenían un pronóstico excelente y probablemente se podrían haber ahorrado la ALND. Ante estos hallazgos, quisimos comprobar si también se reproducían estos resultados seleccionando exclusivamente a las pacientes con mayor enfermedad axilar al diagnóstico (cN2). De ser así, intentar determinar un subgrupo de pacientes en las que también se pudiera evitar la realización de cirugía axilar radical, independientemente de la carga tumoral al diagnóstico, podría disminuir las secuelas postquirúrgicas mejorando la calidad de vida de estas pacientes.

En resumen, la justificación general de esta tesis se fundamenta en el objetivo primordial de intentar reducir el número de linfadenectomías axilares (debido a su morbilidad asociada) en aquellas pacientes con buena respuesta al tratamiento sistémico, y todo ello sin perjudicar en su supervivencia. Reconociendo que el cáncer de mama es una enfermedad que afecta tanto la salud física como emocional de las pacientes, es imperativo buscar enfoques terapéuticos que no solo prolonguen la vida, sino que también promuevan el bienestar, la funcionalidad y la calidad de vida. Por tanto, esta investigación se centra en identificar y evaluar intervenciones eficaces desde el punto de vista clínico pero con gran impacto a nivel psicológico y social de la enfermedad como es la reducción de linfadenectomías axilares evitables. Todo ello, con el objetivo de lograr altas tasas de supervivencia permitiendo una mejoría en la calidad de vida para las pacientes.

Hipótesis 1

En pacientes con cáncer de mama sin afectación inicial axilar, el ganglio centinela practicado posterior a la quimioterapia neoadyuvante permite reducir la tasa de linfadenectomías respecto a su realización pre-neoadyuvancia con similares resultados en supervivencia a corto y largo plazo.

Hipótesis 2

En pacientes con cáncer de mama receptores hormonales positivos y receptor 2 del factor de crecimiento epidérmico humano negativo sin afectación inicial axilar, la técnica de ganglio centinela posterior a la hormonoterapia puede ser factible y su positividad podría tener relación con el pronóstico.

Hipótesis 3

En pacientes con afectación axilar inicial por cáncer de mama (incluyendo a las de menor y mayor carga tumoral) tratadas con quimioterapia neoadyuvante, se podrían identificar factores predictivos de respuesta axilar completa que ayudarían a seleccionar un grupo específico de pacientes en las que podría evitarse la linfadenectomía post-quimioterapia neoadyuvante.

Objetivo General

Evaluar el impacto del tratamiento neoadyuvante sistémico en la estrategia quirúrgica del abordaje axilar y la afectación de las adenopatías axilares.

Objetivos específicos (O)

O1: Comparar las tasas de linfadenectomía axilar y el pronóstico a corto plazo, en las pacientes con cáncer de mama sin afectación ganglionar al diagnóstico con realización de ganglio centinela posterior al tratamiento neoadyuvante (quimioterapia y hormonoterapia) respecto a su realización pre-tratamiento neoadyuvante.

O2: Demostrar que, en las pacientes con cáncer de mama sin afectación ganglionar al diagnóstico, la realización del ganglio centinela posterior a la quimioterapia neoadyuvante se relaciona con una menor realización de linfadenectomías axilares sin perjudicar en la supervivencia a medio-largo plazo respecto a su realización pre-quimioterapia neoadyuvante.

O3: Comparar la positividad de la biopsia del ganglio centinela realizado previa y posteriormente a la hormonoterapia neoadyuvante administrada en las pacientes con cáncer de mama luminal (receptor de estrógeno positivo y receptor 2 del factor de crecimiento epidérmico humano negativo) sin afectación ganglionar inicial y su impacto en el pronóstico.

O4: Analizar los factores predictores de respuesta patológica axilar completa tras la quimioterapia neoadyuvante en pacientes con afectación axilar inicial.

O5: Analizar los factores predictores de respuesta patológica axilar completa tras la quimioterapia neoadyuvante en pacientes con tumores localmente avanzados a nivel axilar.

Esta tesis es el compendio de 5 artículos publicados por nuestro grupo de trabajo enfocados en analizar el impacto del tratamiento sistémico neoadyuvante sobre el abordaje axilar y su relación con el pronóstico.

A continuación se detallan los artículos de la presente tesis en el orden cronológico en el que se publicaron en relación con el orden en el que se presentan y discuten. Todo ello teniendo en cuenta las hipótesis que se plantearon al inicio (Figura 17):

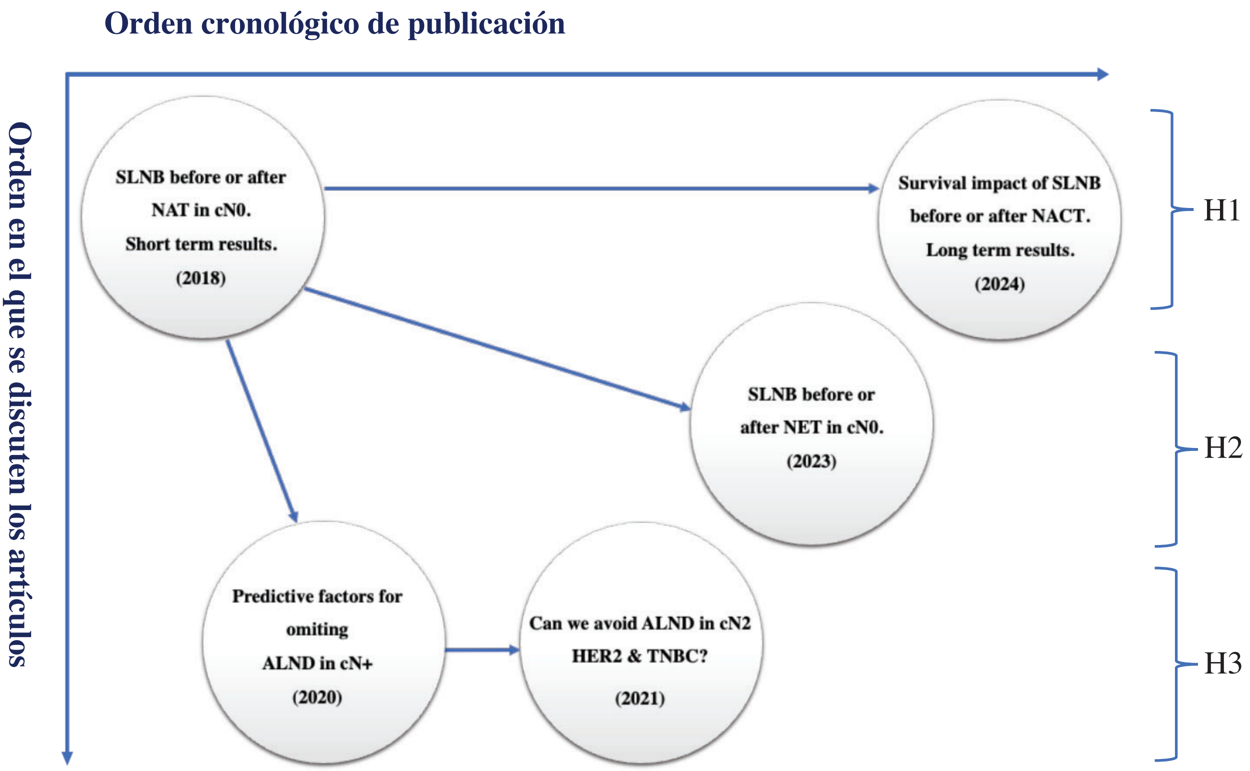

Orden cronológico de publicación
Orden en el que se discuten los artículos
SLNB before or after NAT in cN0. Short term results. (2018)
Survival impact of SLNB before or after NACT. Long term results. (2024)
SLNB before or after NET in cN0. (2023)
Predictive factors for omiting ALND in cN+ (2020)
Can we avoid ALND in cN2 HER2 & TNBC? (2021)
H1
H2
H3

Figura 17: Representación del orden cronológico en el que han sido publicados los 5 artículos de la tesis (eje de las X) y el orden en el que van a ser desarrollados en la tesis tanto en resultados como en la discusión. Todo ello en relación con las tres hipótesis planteadas (H1, H2, H3). Figura propia.

ARTÍCULO 1 – *Cambio de protocolo*

The Shift From Sentinel Lymph Node Biopsy Performed Either Before or After Neoadjuvant Systemic Therapy in the Clinical Negative Nodes of Breast Cancer Patients. Results, and the Advantages and Disadvantages of Both Procedures.

Objetivos: En pacientes con cáncer de mama que son candidatas a neoadyuvancia, el momento en el que realizar la SLNB sigue siendo objeto de debate. El objetivo de este estudio fue comparar las ventajas y desventajas de la SLNB realizada antes y después de la NAT.

Pacientes y Métodos: Se incluyeron 162 pacientes, T1c a T3 y N0 (clínicamente y según la ecografía) candidatas para NAT. Comparamos los resultados de 2 grupos: (1) 122 pacientes de las cuales se realizó la SLNB antes de la NAT (pre-NAT) desde diciembre de 2006 hasta abril de 2014; y (2) 50 pacientes con SLNB realizada después de la NAT (post-NAT) desde mayo de 2014 hasta julio de 2016.

Resultados: Ambos grupos fueron homogéneos en las características basales de las pacientes. La SLNB fue positiva en 50 pacientes (41.7%) [33 macrometástasis (66%) y 17 micrometástasis (34%)] versus 6 pacientes (12%) [5 macrometástasis (83.3%) y 1 micrometástasis (16.7%)] en los grupos pre-NAT y post-NAT, respectivamente. Se realizó la linfadenectomía en 34 pacientes (28.3%) pre-NAT versus 4 pacientes (8%) post-NAT, con una odds ratio (OR) de 3.48 (CI 95%, 1.3-9.3). Las recurrencias en el grupo pre-NAT después de un seguimiento mediano de 62 meses fueron 12 sistémicas, 2 locales y sistémicas, y ninguna axilar. En el grupo post-NAT no hubo recurrencias después de un seguimiento mediano de 16 meses. Finalmente, la SLNB después de la NAT redujo el retraso en el inicio de la NAT de 24 a 14 días (medianas; $P < .001$) respecto al SLNB pre-NAT y la identificación de la SLNB fue elevada en ambos grupos: 122/122 pacientes (100%) versus 49/50 pacientes (98%), respectivamente.

Conclusión: La SLNB realizada después de la NAT reduce significativamente la tasa de linfadenectomías sin ningún aumento en las recurrencias en el seguimiento temprano. Además, permite iniciar el tratamiento sistémico antes sin interferir en la tasa de identificación de la SLNB.

Original Study

The Shift From Sentinel Lymph Node Biopsy Performed Either Before or After Neoadjuvant Systemic Therapy in the Clinical Negative Nodes of Breast Cancer Patients. Results, and the Advantages and Disadvantages of Both Procedures

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Abstract

The clinical consequence of performing sentinel lymph node biopsy (SLNB) before or after neoadjuvant therapy (NAT) in breast cancer patients remains under study. Therefore, we present a comparison between both approaches. The lymphadenectomy rate is reduced by threefold when the SLNB is assessed after NAT with no increase in early recurrences; consequently, it seems that this approach has more advantages for the patients than before NAT.

Background: In patients with breast cancer who are candidates for neoadjuvant therapy (NAT), the timing of when to perform sentinel lymph node biopsy (SLNB) remains under discussion. The aim of this study was to compare the advantages and disadvantages of SLNB performed before and after NAT. **Patients and Methods:** One hundred seventy-two patients, T1c to T3 and N0 (clinically and according to ultrasound) candidates for NAT were included. We compared the outcomes of 2 groups: (1) 122 patients of whom SLNB was performed before NAT (pre-NAT) from December 2006 to April 2014; and (2) 50 patients with SLNB performed after NAT (post-NAT) from May 2014 to July 2016. **Results:** Both groups were homogeneous in baseline patient characteristics. The SLNB was positive in 50 patients [41.7%] (33 macrometastases [66%] and 17 micrometastases [34%]) versus 6 patients [12%] (5 macrometastases [83.3%] and 1 micrometastases [16.7%]) in pre- and post-NAT groups, respectively. The lymphadenectomy was performed in 34 patients [28.3%] versus 4 patients [8%], with an odds ratio of 3.48 (95% confidence interval, 1.3-9.3). The recurrences in the pre-NAT group after a median follow-up of 62 months were 12 systemic, 2 local and systemic, and none axillary. In the post-NAT group were no recurrences after a median follow-up of 16 months. Finally, SLNB after NAT reduces the delay in starting NAT from 24 to 14 days (medians; $P < .001$) and the identification of the SLNB was in 122 patients [100%] versus 49 patients [98%]. **Conclusion:** SLNB performed after NAT significantly reduces the rate of lymphadenectomies without any increase in recurrences at early follow-up. Furthermore, it allows systemic treatment to be started earlier without interfering in the SLNB identification rate.

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Keywords: Axillary lymph node dissection, Follow-up, Lymphadenectomies, Neoadjuvant chemotherapy, Recurrences

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Introduction

In recent years, scientific interest in the effect of neoadjuvant therapy (NAT) in axillary lymph nodes (ALNs) in patients with breast cancer has increased.[1] In most patients with positive ALNs before NAT, it is recommended to subsequently perform an ALN dissection (ALND), despite the fact that 22% to 35% of these patients will have no residual disease in the axilla after NAT.[2] When the ALNs are negative before NAT, sentinel lymph node (SLN) biopsy (SLNB) is recommended according to all international guidelines.[3] However, the timing to perform it remains controversial without any preference as to whether it is better to perform it before or after NAT.

The feasibility and accuracy of SLNB before NAT have already been shown in the literature.[4-6] However, SLNB performed after NAT has shown consistent and reproducible results in the past few years.[7-9] Therefore, the results comparing advantages and disadvantages of performing SLNB either before or after NAT are currently being debated and the time to perform it remains under 2b recommendation according to the levels of the current evidence.[3,10] The biggest advantage of the SLNB before NAT is the assessment of the basal axillary stage. It represents an independent prognostic factor for patient survival and can be used to guide postoperative locoregional treatment decisions. However, there has been no effect of NAT in the axillary nodes,[11,12] and, as a consequence, the rate of ALND might increase compared with SLNB after NAT.

However, an interesting feature attributed to the SLNB after NAT approach is that it allows measurement of the response "in vivo" in the breast[13] as well as in the ALNs, and consequently, SLNB might reflect the patient's prognosis more accurately than does initial assessment of the axilla. This information is relevant in the sense that response to primary therapy is statistically related to patient outcome.[14] Furthermore, it does not interfere with the initiation of NAT and both surgeries (breast and SLNB) are performed in 1 single procedure. However, the false negative rate (FNR) might be increased because of the alteration in lymph drainage by previous systemic therapy, which, as described in the literature, varies from 8% to 30%.[15-18] Therefore, the timing of when to perform SLNB remains unclear and frequently depends on institutional preference.

In our institution SLNB was performed before NAT until 2014. Then, according to the new and promising results from SLNB after NAT, and the international guidelines recommendations, we decided to change our protocol to perform SLNB after NAT.

The aim of this study was to compare the advantages and disadvantages of both procedures. We hypothesized that SLNB after NAT reduces the ALND rate without an increase in the number of axillary recurrences. Additionally, we compared the delay in starting NAT and the identification rate of SLNB.

Patients and Methods

Patients

A retrospective observational study of prospectively collected data including 172 patients diagnosed with breast cancer stages T1c to T3 N0 candidates for NAT at the Hospital Universitari Bellvitge and Institut Català d'Oncologia was performed. SLNB was performed before NAT from December 2006 to April 2014 in 122 cases (the pre-NAT group) and after NAT from May 2014 to July 2016 in 50 patients (the post-NAT group) according to our protocol and with informed consent. The study was approved by the ethics committee of our hospital (247/06).

Inclusion and Exclusion Criteria

Patients were required to meet all of the following eligibility criteria: (1) age 18 to 80 years old; (2) palpable breast tumor with a diameter >10 mm, measured using ultrasound; (3) negative ALNs, assessed using ultrasound; (4) core biopsy result of infiltrating breast carcinoma; (5) candidates to receive chemotherapy or endocrine-therapy before surgery according to our multidisciplinary committee; and (6) provided written informed consent. We excluded the following patients: those who were ALN-positive, identified using fine needle aspiration if suspected on pre-NAT ultrasound; those older than 80 years old, because SLNB is not recommended in elderly individuals according the latest international guides[19]; breast tumors measuring <10 mm; stage T4 tumors; a personal history of ipsilateral breast cancer; and refusal to participate.

Methods

Peritumor injection of 3 mCi/mL 99m-technetium radiocolloid was administered for lymphatic mapping 24 hours before the SLNB. In patients for whom the initial migration was not recorded according the previous gammagraphy map, we performed a second injection with Tc the day before to improve the migration. Radioactivity was detected with an intraoperative gamma probe (Europrobe; Britec, Sheffield, United Kingdom). At the Pathology department, the SLNs were routinely sliced in the short axis in sections of <2 mm thick. Cytological smear and/or frozen section were used to evaluate SLNs intraoperatively. The remainder of the SLN and adipose tissue was fixed at 10% formaldehyde and embedded in paraffin for the definitive pathology assessment. The SLNs were processed in 6 sections of 3 μm, separated by 150 μm, 3 of them stained using either hematoxylin and eosin (H & E) and 3 stained using AE1/AE3 cytokeratin. The SLNs before NAT were processed with the same procedure between 2007 and 2011. However, since 2011 the SLNBs before NAT were processed using 1-step nucleic acid amplification (OSNA).[20] Micrometastasis was defined as a small cluster of cells measuring 0.2 to 2 mm according to H & E immunohistochemistry (IHC) or 251 to 5000 copies using OSNA. Macrometastasis was defined for values >2 mm using H & E IHC or 5000 copies using OSNA.

Neoadjuvant therapy was on the basis of endocrine therapy or chemotherapy according to predictive factors. Endocrine NAT consisted of letrozole at a dose of 2.5 mg/d for 6 to 12 months. Chemotherapy consisted of a regimen that included anthracyclines followed by taxanes for 6 months and including trastuzumab in patients with HER2-positive tumors.

The choice of conservative or radical surgery was decided according to the response to NAT, size, and radiological characteristics of the tumor and predictable aesthetic results. During surgery, complete ALND was performed only when macrometastasis was identified in the SLNB. Patients with negative SLNs or micrometastasis did not undergo further treatment of the axilla.

Pathological complete response was defined as no invasive carcinoma left either in the tumor bed or in the axillary nodes. In terms of fibrosis, we considered a pathologic complete response when the pathologist observed 100% fibrosis replacing the infiltrating carcinoma, a partial response when the pathologist observed >30% of fibrosis, and no response when fibrosis was <30%, according to our previous results.[21]

Adjuvant radiotherapy for the breast was advised after conservative surgery and after mastectomy in patients with T3 tumors. Patients with positive SLNB also received radiotherapy in the supraclavicular and level III lymph nodes. Hormonal adjuvant treatment was delivered to all luminal tumors. Adjuvant chemotherapy was offered to patients who had received hormonal NAT with a preoperative endocrine prognostic index[22] >5 and a good performance status (<2). Adjuvant trastuzumab was delivered to all HER2-positive patients to complete 1 year of treatment.

Patients were followed periodically by an oncologist, radiotherapist, and surgeons, and their current vital status as well as any recurrences were recorded. Recurrences were defined as local when present in the ipsilateral breast or lymph nodes, and systemic when other organs or the contralateral lymph nodes were involved. Clinical and pathologic parameters were recorded, including age, tumor size before and after NAT, histological type, Nottingham histological grade, hormonal receptors, HER2 overexpression/amplification, and proliferative index Ki-67, SLN identification rate, SLN involvement, and ALND rate (contralateral tumors were recorded separately). Estrogen receptor and progesterone receptor status were determined using IHC and were reported as positive when a nuclear staining >10% was found. HER2/*neu* status was assessed using IHC and fluorescence in situ hybridization (FISH) in cases with a 2+ score. Positive cases included overexpressed cases with a 3+ scored using IHC or cases amplified using FISH. According to these parameters and the Ki-67 expression, the samples were classified into 5 surrogate subtypes.[23-26] Luminal A-like, luminal B-like HER2-negative, luminal B-like HER2-positive, HER2-enriched, and triple negative (Table 1 shows the definitions of the subtypes and the baseline patient characteristics in our sample).

Statistical Analyses

Differences between groups were analyzed using χ^2 test or Fisher exact test for categorical variables and Student *t* test or Mann−Whitney *U* test for continuous variables. Progression-free survival was calculated from the date of diagnosis to the date of recurrence or death because of breast cancer progression. Kaplan−Meier survival curves were calculated and the differences assessed using the log rank statistic. These analyses were carried out using IBM SPSS Statistics for Windows, version 19.0 and R version 3.0.3 (The R Project for Statistical Computing), and a 5% level of statistical significance was considered throughout.

Table 1 Baseline Patient Characteristics

	Pre-NAT SLN (n = 122)	Post-NAT SLN (n = 50)	P
Median Follow-up (Range), Months	62 (9-121)	16 (5-57)	**< .001**
Mean Age, Years	52.1 ± 13.4	54.9 ± 14.1	.227
Menopausal Status, %	53.3	56	.745
T Stage at Diagnosis, n (%)			.253
cT1c	2 (1.6)	3 (6)	
cT2	103 (84.4)	42 (84.0)	
cT3	17 (13.9)	5 (10)	
Histological Subtype, n (%)			.892
Invasive ductal carcinoma	114 (93.4)	47 (94)	
Invasive lobular carcinoma	8 (6.6)	3 (6)	
Nottingham Grade, n (%)			.979
1	7 (5.7)	3 (6)	
2	47 (38.5)	20 (40)	
3	68 (55.7)	27 (54)	
Molecular-Like Subtype, n (%)[a]			.344
Luminal A-like	12 (9.8)	5 (10)	
Luminal B-like ($HER2^-$)	30 (24.6)	15 (30)	
Luminal B-like ($HER2^+$)	23 (18.9)	13 (26)	
HER2-enriched (nonluminal)	21 (17.2)	3 (6)	
Triple-negative	36 (29.5)	14 (28)	
Neoadjuvant Treatment, n (%)			
Hormonal therapy	14 (11.5)	8 (16)	.420
Chemotherapy	108 (88.5)	42 (84)	

Data were analyzed using Student *t* test, Mann−Whitney *U* test, Yates corrected χ^2 test, or Fisher exact test, as appropriate. *P* value was in bold when a significant difference was observed.

Abbreviations: ER = estrogen receptor; Post-NAT SLN = sentinel lymph node biopsy performed after chemotherapy treatment; PR = progesterone receptor; Pre-NAT SLN = sentinel lymph node biopsy performed before chemotherapy treatment.

[a] Luminal A-like: ER^+ and PR^+ and Ki-67 <20% and $HER2^-$. Luminal B-like ($HER2^-$): ER^+ and $HER2^-$ (PR <10% or Ki-67 ≥20%) luminal B-like ($HER2^+$): ER^+ and $HER2^+$ (PR <10% or Ki-67 ≥20%). HER2-enriched (nonluminal): ER^- and PR^- and $HER2^+$. Triple-negative: ER^- and PR^- and $HER2^-$.

Results

From December 2006 to July 2016, 172 patients were included: 122 in the pre-NAT group and 50 in the post-NAT group. Both groups were homogeneous in clinical and pathological tumor baseline characteristics (Table 1). In both groups NAT was mostly chemotherapy (108 patients [88.5%] and 42 patients [84%], respectively).

The median time from diagnosis to the start of NAT was 24 (range, 7-70) days in the pre-NAT group and 14 (range, 1-32) days in the post-NAT group ($P < .001$).

The identification rate of the SLNB was >98% in both groups (Table 2). The SLNB was positive in 50 patients [41.7%] before NAT (33 macrometastases [66%] and 17 micrometastases [34%]) versus 6 patients [12%] after NAT (5 macrometastases [83.3%] and 1 micrometastases [16.7%]). Therefore, the lymphadenectomy rate was significantly higher in the pre-NAT group with an odds ratio (OR) of 3.48 (95% confidence interval [CI], 1.3-9.3). The number of lymphadenectomies in the pre-NAT group was 34 even if the number of positive SLNBs with macrometastasis was 33 because in the first patient a complete ALND was performed even when the SLNB result was negative. In the post-NAT group, despite there being 5 patients with macrometastasis, in a patient who was 78 years old we decided not to perform a complete ALND. Among the lymphadenectomies performed (Table 3), there was no residual disease in 20 of 34 patients [58.8%] in the pre-NAT group versus 1 of 4 [25%] in the post-NAT group ($P = .228$).

When pathological changes were analyzed in pre- and post-NAT groups, we observed 100% fibrosis in 38 patients [31.1%] versus 9 [18%] respectively, with no significant differences between them. Noteworthy is that all pathological complete responses were observed after neoadjuvant chemotherapy, none after hormonotherapy.

Breast-conserving surgery was performed without statistically significant differences between the groups (94 patients [77%] vs. 38 patients [76.7%] in the pre- and post-NAT groups, respectively; $P = .924$).

The neoadjuvant and adjuvant treatments are summarized in Table 4. No significant differences were observed between groups among patients who received chemotherapy (with or without trastuzumab) or endocrine therapy as a neoadjuvant treatment nor as an adjuvant treatment. No significant differences were observed when adjuvant radiotherapy was compared between groups.

After a median follow-up of 62 months in the pre-NAT group, 14 recurrences were documented, 12 of them were systemic and 2 local and systemic. No recurrences were documented in the post-NAT group at 16 months of median follow-up (Figure 1).

Discussion

In this cohort study, the SLNB performed after NAT proved to be better than before NAT because it avoids lymphadenectomies, it allows one to start NAT earlier, and it reduces the number of surgical interventions, with a similar identification rate and without an increase in the recurrence rate shown in early follow-ups.

In our records, the rate of ALND decreased in the post-NAT group by approximately 3 times. This is because the rate of SLNB-positive was significantly higher when the mapping of the axilla was assessed before NAT compared with after NAT; 41.7% versus 12%, respectively. Our study shows results consistent with similar trials in which the SLNB, assessed in T2 N0 patients before and after NAT, was positive in 36.5% versus 20.5% of the patients, respectively.[27,28] Consequently, they showed a reduction of 13.5% axillary dissections when the SLNB was performed after NAT. We assume that the reduction of SLNB positivity after NAT is because of the response to systemic treatment; however, it could be also influenced by a higher FNR, which is approximately 15% in some studies.[29] Furthermore, some authors[6] consider that the impairment of SLNB detection is instead related more to the beneficial effect of NAT (fibrosis) than to the tumor burden in the lymph nodes. We support that SLNB before NAT in patients with clinically negative ALN at presentation is a reliable tool for planning postoperative treatment. However, assessing the SLNB after NAT allow us to evaluate the axillary downstaging and several studies suggested that staging the axilla after NAT is a more meaningful predictor of local and regional recurrence than before NAT.[30] Further prospective studies comparing recurrence rates between both groups are needed to evaluate the effect of the FNR of both procedures.

The second point evaluated in our study was the identification rate. It was over 95% in both groups, a result in agreement with recent published series,[31,32] even if the variability of the identification rate after NAT is between 80% to 100% as Mocellin et al

Table 2 Sentinel Lymph Node Biopsy Outcomes

	Pre-NAT SLN (n = 122)	Post-NAT SLN (n = 50)	*P*
Median Dx-NAT Time, Days	24 (7-70)	14 (1-32)	**< .001**
SLN Identification Rate, %	100	98	.118
Patients With SLN-Positive, n (%)	50 (41.7)	6 (12)	**.002**
Macrometastases	33 (66)	5 (83.3)	
Chemotherapy	31	3	
Hormonotherapy	2	2	
Micrometastases	17 (34)	1 (16.7)	
Chemotherapy	14	1	
Hormonotherapy	3	0	
Median SLNs Removed (Range)	2 (1-6)	2 (0-6)	.245

Data were analyzed using Mann–Whitney *U* test, Yates corrected χ^2 test, or Fisher exact test, as appropriate. *P* values were in bold when a significant difference was observed.
Abbreviations: Dx-NAT Time = time between diagnosis and systemic therapy; Post-NAT SLN = sentinel lymph node biopsy performed after chemotherapy treatment; Pre-NAT SLN = sentinel lymph node biopsy performed before chemotherapy treatment; SLN = sentinel lymph node.

Table 3 Neoadjuvant Therapy Outcomes

	Pre-NAT SLN (n = 122)	Post-NAT SLN (n = 50)	P	Odds Ratio
Conservative Breast Surgery	94 (77%)	38 (76%)	.882	
Lymphadenectomy	34 (28.3%)	4 (8%)	**.004**	3.48 CI (1.30-9.3)
No Residual DiseaseAfter ALND	20/34 (58.8%)	1/4 (25%)	.228	

Data were analyzed with $\chi 2$ or Fisher exact test as appropriate. *P* value was in bold when a significant difference was observed.
Abbreviations: ALND = axillary lymph node dissection or lymphadenectomy; CI = confidence interval; Post-NAT SLN = sentinel lymph node biopsy performed after chemotherapy treatment; Pre-NAT SLN = sentinel lymph node biopsy performed before chemotherapy treatment.

summarized in a recent meta-analysis.[33] Our high identification rates might be explained by the patients in whom the initial migration was not recorded according to the previous gammagraphy map. Thus, performing a second injection with Tc the day before improves the migration rate. Therefore, we support that a correct procedure of SLNB including a radiocolloid[34] is recommended to obtain the maximum SLN identification rate.

Another potential advantage of SLNB performed after NAT, which has been evaluated in our study, is the delay in initiating chemotherapy. The NAT was initiated significantly earlier from the diagnosis in the post-NAT group than in the pre-NAT group (median 14 days vs. 24 days, respectively). It is true that the proper time to initiate NAT is unknown; however, <20 days to start adjuvant chemotherapy might be beneficial especially in chemosensitive tumors.[35,36]

The last advantage related to the post-NAT procedure is that the patient must undergo only 1 surgical intervention instead of 2 in the pre-NAT procedure, with the risks that 2 anesthetic procedures involve. It is safer for the patient and more cost-effective for the institution.

In contrast to similar studies such as the study published by Rutgers et al,[37] the 3 major strengths of this report are the inclusion of 2 homogeneous cohorts to compare (in total 172 patients), treated in only 1 center with the same professional team and the longest follow-up described in the literature with a median of 62 months in the pre-NAT group and 16 months in the post-NAT group.

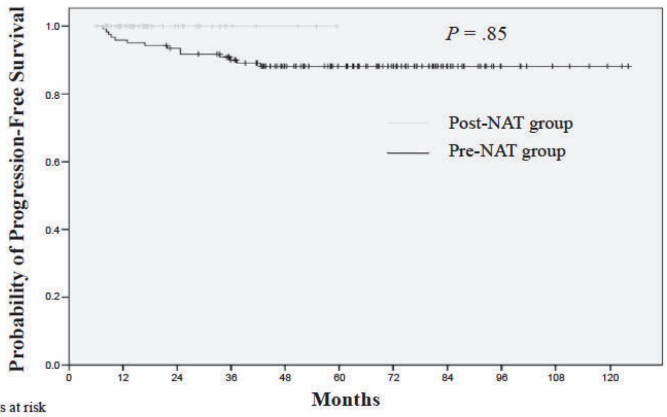
One of the limitations of our study is the small number of patients and shorter follow-up in the post-NAT group. However, we consider that adding the recurrence rate at early follow-up is important to confirm that the SLNB performed after NAT is not a risk factor for early recurrences despite the lower number of ALNDs carried out. The difference between the follow-up is explained by the fact that our SLNB protocol was changed in April 2014, consequently, the medians of follow-ups were 62 and 16 months for the pre-NAT versus post-NAT groups, respectively. To our knowledge, there are no studies with longer follow-ups evaluating the effect in terms of prognosis, depending on the time the SLNB was performed. Longer follow-ups of patients in our series will allow us to elucidate if the recurrence rate might be different between the

Table 4 Adjuvant Treatment

	Pre-NAT SLN (n = 122)	Post-NAT SLN (n = 50)	P
Adjuvant Systemic Therapy			
After neoadjuvant chemotherapy			
Endocrine therapy	53 (49.1%)	21 (50%)	.930
Trastuzumab	43 (39.8%)	16 (39%)	.930
Chemotherapy	8 (7.4%)	7 (17.1%)	.080
None	31 (28.7%)	6 (14.3%)	.066
After neoadjuvant endocrine therapy			
Endocrine therapy	15 (100%)	8 (100%)	1
Chemotherapy	3 (20%)	1 (12.5%)	.651
Trastuzumab	1 (6.7%)	0	.455
Adjuvant Radiotherapy			
Breast	93 (76.2%)	40 (80%)	.296
Alone	73	36	
With SCV&III	19	2	
With SCV&III and Ax*	1	2	
Chest wall	11 (9%)	2 (4%)	.315
Alone	4	1	
With SCV&III	6	0	
With SCV&III and Ax	1	1	

Data were analyzed using χ^2 or Fisher exact test as appropriate.
Abbreviations: Ax = axillary lymph nodes; Post-NAT SLN = sentinel lymph node biopsy performed after chemotherapy treatment; Pre-NAT SLN = sentinel lymph node biopsy performed before chemotherapy treatment; SCV&III = supraclavicular and level III lymph nodes.

Figure 1 Probability of Progression-Free Survival, Using Kaplan–Meier Analysis



Patients at risk	0	12	24	36	48	60	72	84	96	108	120
Post-NAT group	50	38	16	6	4	0					
Pre-NAT group	122	117	112	100	81	67	47	24	10	5	2

Abbreviation: NAT = neoadjuvant therapy.

2 procedures and which approach is best in relation to patient prognosis. It is worth noting that in a previous study of our Breast Cancer Unit[38] the positivity of SLNB pre-NAT was not related to the patient's prognosis, probably because the response to NAT overcame the initially bad prognosis.

Taking into account the results of our study, it can be proposed that SLNB performed after NAT presents several advantages and makes it more suitable than SLNB performed before NAT.

Conclusion

Sentinel lymph node biopsy after NAT reduces by 3 times the lymphadenectomy rate with no increase in early recurrences. In addition, the identification rate is not reduced by assessing the SLNB after NAT; it allows the systemic treatment to be started twice as quickly and it saves patients a second surgery. Consequently, to perform SLNB after NAT seems to have more advantages for the patients than before NAT at early follow-up.

Clinical Practice Points

- Among patients diagnosed with breast cancer with negative axillary nodes who are candidates to receive NAT, SLNB is the gold standard technique to assess the axillary stage. However, the timing of when to perform the SLNB remains controversial between before or after NAT.
- This lack of consensus has prompted our study in which 122 patients in the pre-NAT group were compared with 50 patients in the post-NAT group. All 172 patients diagnosed with breast cancer stages T1c to T3 N0 were candidates for NAT. The SLNB was positive in 41.7% (66% macrometastases) versus 12% (83% macrometastases) in the pre- and post-NAT groups, respectively. Therefore, the lymphadenectomy rate was 28.3% versus 8% respectively, with an OR of 3.48 (95% CI, 1.3-9.3). However, the recurrences in the pre-NAT group after a median follow-up of 62 months were 12 systemic, 2 local and systemic, and none axillary; and in the post-NAT group, there were no recurrences after a median follow-up of 16 months.
- Our results confirm that performing the SLNB after NAT does not increase the rate of recurrences in short-term follow-up, however, it allows a decrease of 3 times in the rate of lymphadenectomies performed. We believe that our positive results can promote some institutions to change the timing of performing SLNB and we will confirm our outcomes after 5 years of follow-up.

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Disclosure

The authors have stated that they have no conflicts of interest.

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ARTÍCULO 2 – *Impacto en supervivencia del centinela post-neoadyuvancia*

Sentinel Lymph Node Biopsy Before and After Neoadjuvant Chemotherapy in cN0 Breast Cancer Patients: Impact on Axillary Morbidity and Survival. A Propensity Score Cohort Study.

Objetivo: En pacientes con cáncer de mama sin afectación axilar (cN0), realizar la biopsia del ganglio linfático centinela (SLNB) después de la quimioterapia neoadyuvante (NACT) ha sido preferentemente adoptado en comparación a antes de la NACT. Sin embargo, los resultados de supervivencia asociados a ambas estrategias persisten poco estudiados. Nuestro objetivo fue comparar la tasa de linfadenectomía axilar (ALND), la supervivencia libre de enfermedad (DFS) y la supervivencia global (OS) entre las dos estrategias.

Métodos: Incluimos 310 pacientes en un estudio observacional retrospectivo. La SLNB se realizó antes de la NACT de diciembre de 2006 a abril de 2014 (grupo 1= 107 pacientes) y después de la NACT de mayo de 2014 a mayo de 2020 (grupo 2= 203 pacientes). Se aplicó un método de emparejamiento por probabilidad inversa de tratamiento (IPTW) para homogeneizar ambos grupos. Se informan las razones de riesgo (HR) y las razones de probabilidad (OR) con intervalos de confianza del 95% (95% CI).

Resultados: La tasa de linfadenectomía fue del 29.9% antes de la NACT y del 7.4% después de la NACT (p<0.001), con un OR de 5.35, IC del 95% (2.7-10.4); p =.002. Después de 4 años de seguimiento, la SLNB después de la NACT se asoció con un menor riesgo de DFS, HR 0.42 IC del 95% (0.17-1.06); p=0.066 y una mejor OS, HR 0.21 CI del 95% (0.07-0.67); p=0.009 respecto a la SLNB antes de la NACT. Después del análisis multivariado, los factores pronóstico adversos independientes para la OS incluyeron la SLNB antes de la NACT, HR 3.095 IC del 95% (2.323-4.123), la falta de respuesta clínica a la NACT, HR 1.702 IC del 95% (1.012-2.861) y tumores pequeños (cT1) con un índice de proliferación alto, HR 1.889 IC del 95% (1.195-2.985).

Conclusión: Realizar la SLNB antes de la NACT resulta en mayor tasa de realización de linfadenectomías y no demuestra beneficios para la supervivencia de las pacientes. Estos hallazgos respaldan la interrupción de la práctica clínica de SLNB antes de la NACT en pacientes con cáncer de mama cN0 a favor de practicarlo post-NACT.

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RESEARCH

Sentinel lymph node biopsy before and after neoadjuvant chemotherapy in cN0 breast cancer patients: impact on axillary morbidity and survival—a propensity score cohort study

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Abstract

Purpose In patients with clinically lymph node-negative (cN0) breast cancer, performing sentinel lymph node biopsy (SLNB) after neoadjuvant chemotherapy (NACT) has been preferentially embraced in comparison to before NACT. However, survival outcomes associated with both strategies remain understudied. We aimed to compare the axillary lymphadenectomy (ALND) rate, disease-free survival (DFS), and overall survival (OS), between two strategies.

Methods We included 310 patients in a retrospective observational study. SNLB was performed before NACT from December 2006 to April 2014 (107 cases) and after NACT from May 2014 to May 2020 (203 patients). An inverse probability of treatment weighting (IPTW) method was applied to homogenize both groups. Hazard ratios (HR) and odd ratios (OR) are reported with 95% confidence intervals (95%CI).

Results The lymphadenectomy rate was 29.9% before NACT and 7.4% after NACT ($p < 0.001$), with an OR of 5.35 95%CI (2.7–10.4); $p = .002$. After 4 years of follow-up, SLNB after NACT was associated with lower risk for DFS, HR 0.42 95%CI (0.17–1.06); $p = 0.066$ and better OS, HR 0.21 CI 95% (0.07–0.67); $p = 0.009$ than SLNB before NACT. After multivariate analysis, independent adverse prognostic factors for OS included SLNB before NACT, HR 3.095 95%CI (2.323–4.123), clinical nonresponse to NACT, HR 1.702 95% CI (1.012–2.861), and small tumors (cT1) with high proliferation index, HR 1.889 95% (1.195–2.985).

Conclusion Performing SLNB before NACT results in more ALND and has no benefit for patient survival. These findings support discontinuing the practice of SLNB before NACT in patients with cN0 breast cancer.

Keywords Breast cancer · Neoadjuvant chemotherapy · Sentinel lymph node biopsy · Axillary lymph node dissection

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Abbreviations

cN0	Clinically lymph node negative
SLNB	Sentinel lymph node biopsy
NACT	Neoadjuvant chemotherapy
ALND	Axillary lymphadenectomy
DFS	Disease-free survival
OS	Overall survival
FNR	False-negative rate
OSNA	One-step nuclei acid amplification
ypT0	Pathologic complete response in breast
ypTis	Pathologic residual in situ carcinoma in breast
ER	Estrogen receptor
PR	Progesterone receptor
IPTW	Inverse probability of treatment weighting
CI	Confidence intervals
HR	Hazard ratios
SI	Supplementary Information
NS	No statistical significance

Introduction

Sentinel lymph node biopsy (SLNB) has been proven equally safe and accurate compared to axillary lymph node dissection (ALND) [1, 2] when evaluating axillary status in cN0 patients, while also benefiting from less morbidity and better quality of life outcomes for patients [3]. Until 2015, performing SLNB before NACT was recommended as it enables the basal assessment of nodal status [4]. However, SLNB before NACT has been associated with higher rates of positive SLNB and consequently, higher rates of ALND [5]. In addition, with evidence that 22% to 35% of patients will have no residual disease in the axilla after NACT [6, 7], this raises the question of whether ALND could have been avoided.

Multiples studies in the last decade have reported similar identification rates and false-negative rates (FNRs) when performing SLNB before and after NACT [8, 9]. Regarding the latter, a recent meta-analysis found an identification rate of 94% (95%CI, 92–96) and an FNR of 7% (95%CI, 5–9) [10]. Additional advantages, such as the assessment of "in vivo" tumoral response, prompt initiation of NACT, and the simultaneous performance of both SNLB and breast surgery, are associated with SLNB after NACT. Consequently, this timing has been preferentially embraced in comparison to before NACT but the latter still remains optional in accordance with the latest guidelines [11–13].

Although the advantages and disadvantages of performing SLNB before or after NACT are well known in patients with cN0 disease, comparison of the long-term oncological survival outcomes remains understudied to date. To provide results in survival outcomes following SLNB before and after NACT, it may help the scientific community to homogenize clinical practice [14, 15]. This study aimed to compare ALND rates when SLNB is performed before and after NACT. The impact of these strategies on disease-free survival (DFS) and overall survival (OS) are then assessed in a series of breast cancer patients' cN0 disease treated by NACT after 4 years of follow-up.

Methods

Study design and participants

Consecutive patients with breast cancer and negative axillary lymph nodes (cN0) from our Breast Cancer Unit (Hospital Universitari Bellvitge & Institut Català d'Oncologia) who were candidates for NACT were enrolled for retrospective analysis from a prospectively maintained database. Patients were divided into two cohorts. Cohort A included patients who underwent SLNB before NACT between December 2006 and April 2014, whereas Cohort B included patients who underwent SLNB after NACT between May 2014 and May 2020. Patients were required to meet all the inclusion criteria: age 18–80 years old; negative axillary lymph nodes after ultrasound assessment, core biopsy showing an infiltrating breast carcinoma; stage > cT1b; and candidates for chemotherapy before surgery (according to our multidisciplinary committee). Exclusion criteria were age > 80 years, pathologically confirmed clinically positive axillary lymph node and a personal history of ipsilateral breast cancer. The ethics committee of our hospital approved the study (247/06). All patients gave written informed consent for NACT and surgical procedures. No large language models were used in the preparation of this manuscript.

Treatment protocol

Between 18 and 24 h before surgery, 3 mCi 99mTc-albumin nanocolloids were injected in breast for lymphatic mapping. Intraoperative gamma probe (Europrobe; Britec; Sheffield; UK) was used for SLN identification. The SLN before NACT performed between 2007 and 2011 and all SLN after NACT were processed histologically. They were cut into 1–2-mm-thick slices and were formalin fixed and paraffin embedded. From each slice, 6 consecutive series of microtome sections with gaps of 150 µm between them were prepared. They were stained alternatively by Hematoxilin-eosin and AE1–AE3 cytokeratin (DAKO IR053/IS053) immunohistochemistry.

However, the SLN before NACT between 2011 and April 2014 was studied by one-step nuclei acid amplification (OSNA) [16]. Isolated tumor cells (ITCs) were defined as small clusters of cells not greater than 0.2 mm or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross section by HE/IHC or less than 160 copies by OSNA. Micrometastasis was defined as a small tumor cluster of cells measuring 0.2–2 mm by HE/IHC or 251–5000 copies by OSNA. Macrometastasis was defined for values greater than either 2 mm by HE/IHC or more than 5000 copies by OSNA.

NACT included anthracyclines followed by taxanes for 6 months, and adding trastuzumab in HER2-positive tumors. Since October 2016, pertuzumab was added to trastuzumab and chemotherapy in patients with human epidermal growth factor receptor (HER2)-positive tumors. Breast conservative or radical surgery was decided considering response to NACT, tumor size, predictable esthetic results, and initial tumor characteristics. Complete ALND was performed only when macrometastasis was identified in the SLNB. Patients with negative SLNB, isolated tumoral cells, or micrometastasis did not undergo further axillary treatment. During the time period covered by this study, the indication for axillary lymphadenectomy has remained consistent in both time periods that is for macrometastasis in the sentinel node. Adjuvant radiotherapy was indicated whether breast-conserving surgery, tumoral margins affected or ink margins, T3–T4 tumors, and/or positive SLNBs. Endocrine therapy was indicated in receptor hormonal-positive tumors. Trastuzumab was completed up to one year in those HER2-positive ones according to international guidelines. Since 2017, in patients with TN and residual invasive disease following tumors NACT, 6–8 cycles of Capecitabine were added [17].

Pathological complete response (pCR) was defined as the absence of invasive carcinoma in both the tumor bed and the axillary nodes with a 100% of fibrosis replacing the invasive carcinoma (ypT0 or ypTis). Pathological partial response was characterized by the pathologist observing more than 30% fibrosis replacing the infiltrating carcinoma, while no response was indicated when fibrosis was less than 30%.

Data collection

Clinical and pathologic variables of interest included age, tumor size before and after NACT, histological type, Nottingham histological grade, estrogen and progesterone receptors (ER, PR), immunohistochemical expression, HER2 status, Ki67 proliferative index, and the sentinel lymph node identification rate and involvement. The clinical imaging-based tumor response was classified according to the WHO criteria [18]. Cases were classified according to immunohistochemical determination of ER, PR, and HER2 status into four subtypes [19, 20]: ER+/HER2(−), ER+/HER2+, ER(−)/HER2+, and Triple Negative (ER(−)/HER2(−)). Disease-free survival (DFS) was defined as the time from starting NACT to disease recurrence or death due to any cause, and overall survival (OS) was defined as the time from starting NACT to death due to any cause.

Statistical analyses

A descriptive analysis was performed to characterize clinical profile of subjects included in this study. Mean and standard deviation were used for continuous variables, and median and interquartile range for those variables with a non-normal distribution. The number of cases and percentages were presented for categorical variables.

To assess heterogeneity in baseline characteristics between the timing of sentinel node removal (SLN pre-NACT and post-NACT), we used absolute standardized differences, defined as the absolute standardized mean difference for continuous variables and the absolute raw difference for categorical variables. A covariate was considered heterogeneous between groups if the absolute standardized differences were > 0.1. The inverse probability of treatment weights (IPTW) approach was used to create a pseudo-population in which the groups were balanced on baseline characteristics (IPTW dataset). Stabilized weights were calculated using propensity scores obtained from logistic regression adjusted for age, T stage at diagnosis, breast cancer subtype, menopausal status, and clinical imaging response. To assess heterogeneity in baseline characteristics between groups in the IPTW dataset, absolute standardized differences were also calculated (Fig. 2). After IPTW balancing, all covariates were homogeneous (< 0.1).

The Kaplan–Meier method was used to estimate probability of survival, while log-rank test was applied to compare groups. The relative risk and 95% confidence intervals (CI) were estimated to compare DFS and OS between groups. Cox-proportional hazards models were used to calculate hazard ratios (HR) and the 95% CI of each prognostic factor by univariate and multivariate analyses. All these analyses were performed in the original dataset and including propensity score calculated with IPTW method.

All of the analyses were performed with the statistical software package R version 4.1.0 for Windows (http://www.R-project.org, The R Foundation).

RESULTS

In total, data were collected for 310 patients (Fig. 1) and divided into Cohort A (SLNB before NACT) and Cohort B (SLNB after NACT) with 107 and 203 patients, respectively. The clinical characteristics of patients with an absolute mean

Fig. 1 Flow chart

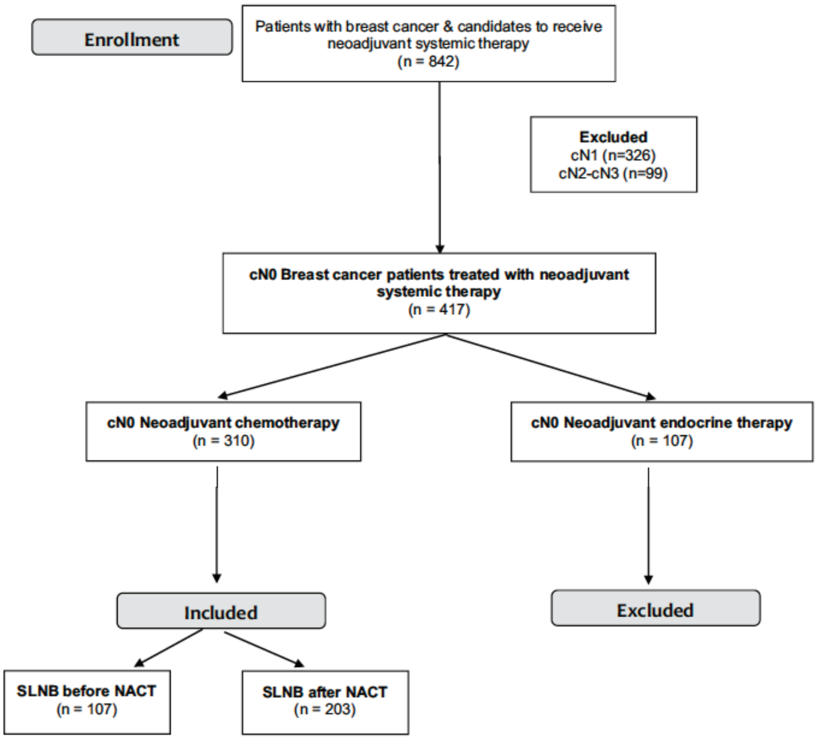
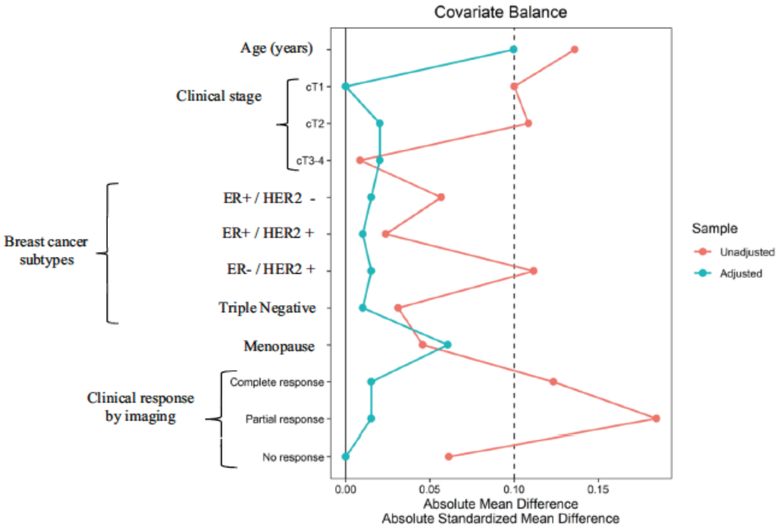

Enrollment
Patients with breast cancer & candidates to receive neoadjuvant systemic therapy (n = 842)
Excluded
cN1 (n=326)
cN2-cN3 (n=99)
cN0 Breast cancer patients treated with neoadjuvant systemic therapy (n = 417)
cN0 Neoadjuvant chemotherapy (n = 310)
cN0 Neoadjuvant endocrine therapy (n = 107)
Included
Excluded
SLNB before NACT (n = 107)
SLNB after NACT (n = 203)

Fig. 2 Baseline characteristics before and after balancing by IPTW



or standardize difference > 0.1 between groups were considered covariates unwell balanced. After applying IPTW balancing, all covariates show < 0.1 absolute mean or standardize difference, and they were considered well-balanced covariates (Fig. 2). Results are shown in Table 1 before and after the IPTW analysis.

Table 1 Results of clinical characteristics and distribution of breast cancer subtypes

	Original sample		IPTW data	
	pre-NACT SLN ($n=107$)	post-NACT SLN ($n=203$)	pre-NACT SLN ($n=103.82$)	post-NACT SLN ($n=202.94$)
Age (mean, years, SD)	49.9 ± 12.7	51.6 ± 12.6	50.61 ± 13.02	50.94 ± 12.46
Menopausal status (%)	51 (47.7)	106 (52.2)	52.3 (50.4)	103.1 (50.8)
T stage at diagnosis (%)				
cT1	1 (0.09)	23 (11.3)	4.8 (4.7)	15.7 (7.7)
cT2	86 (92)	152 (74.9)	83.7 (80.6)	158.9 (78.3)
cT3	14 (13.1)	24 (11.8)	15.3 (14.7)	28.4 (14)
cT4	0	4 (2)	1.6 (1.5)	3.3 (1.6)
Histological subtype (%)				
Invasive ductal carcinoma	103 (96.3)	185 (91.1)	- -	
Invasive lobular carcinoma	4 (3.7)	12 (5.9)	–	–
Nottingham grade (%)				
G1	3 (2.8)	6 (3)		–
G2	38 (35.5)	65 (32)		–
G3	66 (61.7)	132 (65)		–
Breast cancer subtype ** (%)				
Hormone receptor + Her2−	28 (26.2)	64 (31.5)	30 (28.9)	60 (29.6)
Hormone receptor + Her2 +	23 (21.5)	49 (24.1)	21.4 (20.5)	45.6 (22.5)
HER2 pure	21 (19.6)	17 (8.4)	16.1 (15.5)	26.8 (13.2)
Triple negative	35 (32.7)	73 (36)	36.4 (35)	70.6 (34.8)
Clinical response by imaging				
Complete response	51 (47.7)	73 (36)	37.7 (36.3)	80.3 (39.6)
Partial response	42 (39.3)	116 (57.1)	56.2 (54.2)	103. (50.9)
No response	14 (13.1)	14 (6.9)	9.9 (9.5)	19.4 (9.5)

IPW Inverse probability weighting, *pre-NACT SLN* Sentinel Lymph Node performed before chemotherapy treatment, *post-NACT SLN* Sentinel Lymph Node performed after chemotherapy treatment. **Hormone receptor + HER2 -: ER + and Ki67 < 20% and HER2 -. Hormone receptor + HER2 +: ER + and Ki67 ≥ 20% and HER2 +. HER2 +: ER—and PR—and HER2 +. Triple Negative: ER—and PR—and HER2 -

Figure 2 A covariate was considered heterogeneous between groups if the absolute standardized differences were > 0.1. The inverse probability of treatment weights (IPTW) approach was used to create a pseudo-population in which the groups were balanced on baseline characteristics (IPTW dataset). After IPTW balancing, all covariates were homogeneous (< 0.1)

The SLN identification rate was 100% (107 cases) in the pre-NACT group and 97.5% (198 out of 203 cases) in the post-NACT group, without statistical significance difference. However, sentinel lymph node positivity rates differed significantly at 42.1% for SLNB before NACT and 12.5% for SLNB after NACT ($p=0.0001$; Table 2). The lymphadenectomy rate for SLNB before NACT was 29.9% (32 patients) compared with 7.4% (15 patients) for SLNB after NACT ($p<0.001$; Table 2). The odds ratio (OR) for performing lymphadenectomy before NACT was 5.35 (95%CI, 2.7–10.4; $p=0.002$). Furthermore, the rates of achieving complete response in both the breast and axilla (ypT0–N0) were 24.3% (26 patients) when SLNB was before NACT and 33.5% (68 patients) when it was after NACT ($p=0.094$). A detailed analysis of all pathological responses is shown in the Supplementary Information (Figure SI-1) and rates of positive SLN according breast cancer subtype are also shown in Supplementary Information (Table SI-1).

Median follow-up periods were 64 months (range, 12–164 months) for SLNB before NACT and 44 months (range, 7–97 months) for SLNB after NACT. The 4-year OS rates were as follows: 88.4% (95%CI, 82.3–94.6; 12 deaths) for SLNB before NACT and 95.7% (95%CI, 91.5–99.9; 5 deaths) for SLNB after NACT. After applying IPTW to balance the groups, SLNB after NACT was associated with a significantly better OS for any cause of death (HR, 0.21; 95%CI, 0.07–0.67; $p=0.009$), as shown in Fig. 3B.

Table 2 Surgical and adjuvant treatment

	pre-NACT SLN ($n=107$)	post-NACT SLN ($n=203$)	*p* value
Dx-NAT time* (median, range), days	25 (13–92)	24 (5–64)	0.456
Breast conservative surgery (%)	81 (75.7)	141 (69.5)	0.436
SLN identification rate (%)	107 (100)	198 (97.5)	0.675
Patients with SLN positive (%)	45 (42.1)	25 (12.5)	**0.001**
Macrometastases (%)	31 (68.9)	11 (44)	
Micrometastases (%)	14 (32.1)	14(46)	
SLN removed (median, range)	2 (1–6)	2 (0–6)	0.158
Lymphadenectomy (%)	32 (29.9)	15 (7.4)	**<0.001**
LN removed (median, range)	15 (6–27)	15 (10–31)	0.334
No residual disease (%)	21 (65.6)	8 (53.3)	0.419
Radiotherapy (%)			0.352
Breast RT	81 (75.7)	143 (70.4)	
Nodal RT	24 (22.7)	27 (13.3)	
Adjuvant treatment (%)			
Chemotherapy	8 (7.5)	33 (16.3)	0.03
Endocrine	54 (50.5)	117 (57.6)	0.228

* Time between diagnosis and systemic therapy. *SLN* Sentinel Lymph Node

The 4-year DFS rates were 87.5% (95%CI, 81.2–93.9; 13 events) for SLNB before NACT and 93.1% (95%CI, 89.3–97; 12 events) for SLNB after NACT. Following IPW balancing, SLNB after NACT was associated with a reduced risk of disease recurrence or death from any cause compared to SLNB before NACT (HR, 0.42; 95%CI, 0.17–1.06; $p=0.066$), as shown in Fig. 3D. Local or systemic recurrence occurred in 12.1% for SLNB before NACT and 6.5% for SLNB after NACT ($p=0.083$). Table 3 details the patterns of recurrence and cause of death.

Figure 3 Kaplan–Meier curves for overall survival (Survival) and disease-free survival in original and IPW datasets are presented. Post-NACT group was associated with better OS for any cause of death (HR, 0.21 95%CI, 0.07–0.67; $p=0.009$) and better DFS, HR 0.42 CI (0.17–1.06) (*p* value 0.066) (Fig. 3D).

Multivariate analysis for prognostic factors of OS revealed that T1 stage, no response to NACT, and SLNB before NACT significantly and negatively affected OS (Table 4). T1 stage and SLNB before NACT remained independent factors contributing to a worse DFS. In the global cohort, there were no significant differences in DFS by SLNB involvement (Figure SI-2). Sensitivity statistical analysis is shown in figure SI-3 after the exclusion of 44 patients in post-NACT group, 9 for receiving Capecitabine and 35 for receiving trastuzumab + Pertuzumab. Post-NACT group was associated with better OS for any cause of death (HR, 0.19 95%CI, 0.06–0.65; $p=0.008$) and better DFS, HR 0.45 CI (0.18–1.13) (*p* value 0.087).

Discussion

In this study, we observed that patients with cN0 breast cancer who underwent SLNB after NACT had lower rates of ALND and improved DFS and OS rates compared with patients who underwent SLNB before NACT. According to our knowledge, this first IPTW study design to evaluate oncological outcomes before and after NACT found no clinical benefit when performing SLNB before NACT based not only on the similar recurrence and mortality rates but also on the higher rates of axillary lymph node dissection compared to performing SLNB after NACT. Greater ALND-associated morbidity has already been established in previous studies by our group [21]. This is further supported by the results of a meta-analysis published by Bromham N et al. [22], who demonstrated that compared to ALND, patients undergoing SLNB had a lower risk of lymphedema after < 12 months (OR, 0.33; 95%CI, 0.23–0.47; $p<0.0001$), a lower risk of paresthesia (OR, 0.15; 95%CI, 0.09–0.23; $p<0.0001$), and a lower risk of arm numbness (OR, 0.43; 95%CI, 0.34–0.54; $p<0.0001$).

For almost a decade, the detection rate and FNR were major concerns when assessing SLNB after NACT. In 2022, three meta-analyses were published that offered more evidence on these issues for patients with cN0 and cN + breast cancer when comparing single and dual tracers [23–25]. In cN0 disease, the sentinel node detection rate exceeded 95% with no significant differences between single- and dual-tracer mapping: blue dye only, 96% (95%CI, 91–100); radiocolloid only, 96% (95%CI, 94–99); and both blue dye

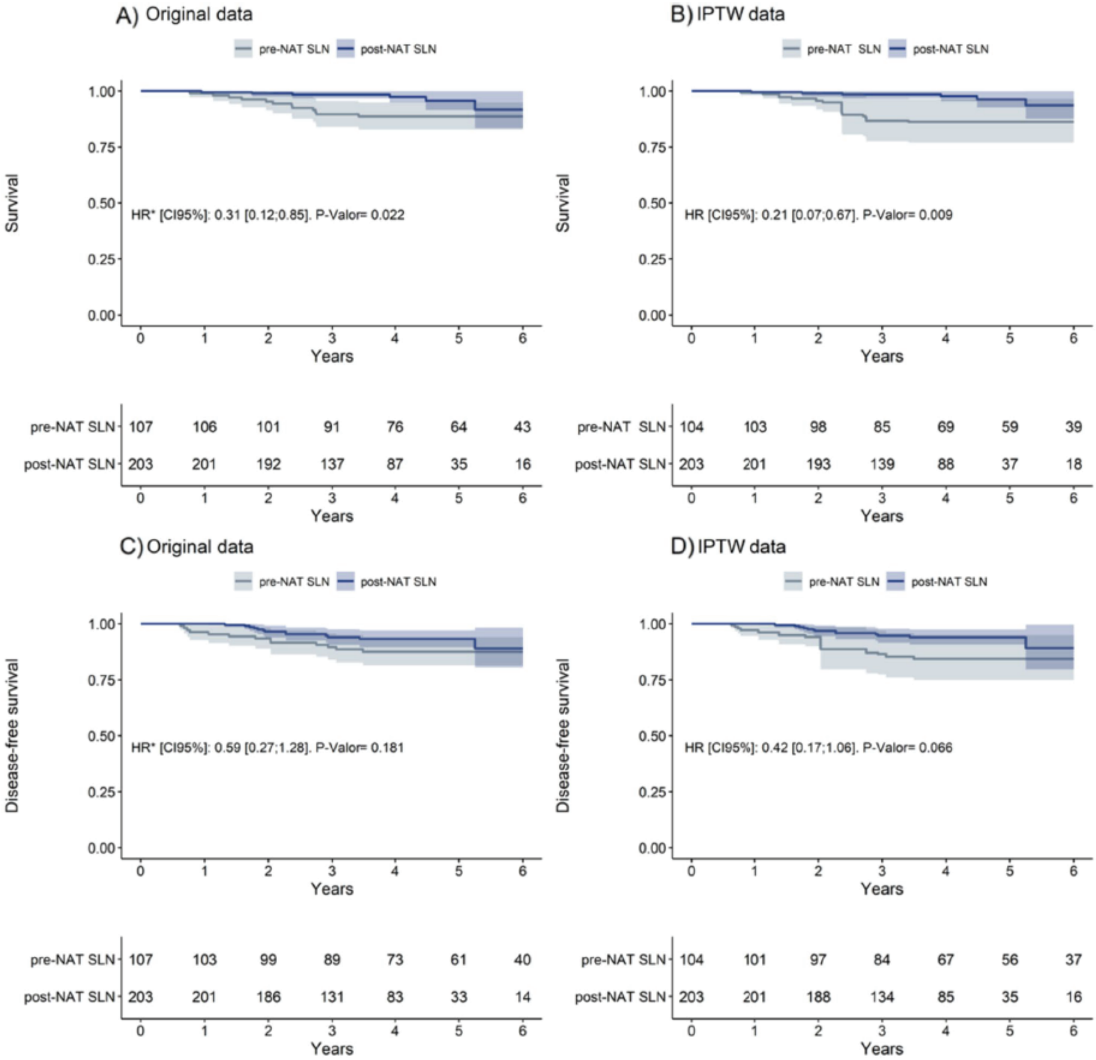


Fig. 3 Overall Survival (Survival) and Disease-free survival in original data and after IPTW

and radiocolloid, 97% (95%CI, 96–98) [26]. Those results are consistent with our data showing a detection rate of 97.5% for SLNB after NACT and 100% for SLNB before NACT (not significant) with radiocolloid. By contrast, a recent meta-analysis reported that the sentinel node FNR was 7%–12% after NACT [23–25] compared to 10%–13% before NACT [26, 27]; consequently SLNB is an accurate method for assessing axillary status after NACT. SLNB is, therefore, an accurate method for assessing axillary status after NACT. Although we could not calculate the FNR, our sentinel node-positive rates among patients after NACT were 12.5% (25/203) compared with 42.1% (45/107) before NACT, which agrees with existing data [28, 29].

Axillary recurrences were not observed with SLNB performed either before or after NACT in this study. Similarly, after 36 months of median follow-up, the GANEA2 study only reported one case of axillary recurrence among 419 patients with cN0 disease [30]. Interestingly, our

Table 3 Pattern of recurrences

	pre-NACT SLN (n = 107)	post-NACT SLN (n = 203)	p value
No recurrence (%)	94 (87.9)	190 (93.5)	0.083
Local recurrences (%)	1 (0.9%)	4 (2)	
Axillary (%)	0	0	
Systemic recurrence (%)	12 (11.2)	9 (4.4)	
Deaths from breast cancer (%)	13 (12.1)	4 (2)	0.001
Deaths from any cause (%)	16 (14.9)	6 (2.9)	0.001

In pre-NACT 2/12 patients experienced local + distant recurrence

In post-NACT: 5/ 9 patients experienced local + distant recurrence

multivariate analysis also showed that findings of macrometastasis or micrometastasis results on SLNB were not independent risk factors for a worse prognosis in our select sample of patients with cN0 breast cancer receiving NACT. However, patients who underwent SLNB before NACT had worse OS (HR, 3.098; 95%CI, 2.323–4.123; $p < 0.001$) and worse DFS (HR, 2.788; 2.095–3.790; $p < 0.001$) compared with those who underwent SLNB after NACT. The risk of macrometastasis at SLNB in patients with cN0 breast cancer decreased markedly after NACT in our series. We observed macrometastasis in 28% and micrometastasis in 13.1% when performing SLNB before NACT, versus macrometastasis in 5.5%, micrometastasis in 14%, and isolated tumor cells in 2.5% when performing SLNB after NACT. Kaplan–Meier analysis identified no significant differences between negative SLNB, macrometastasis, or micrometastasis in either study cohort. This can be explained by the small sample size (few micrometastases), lack of follow-up, or higher impact of molecular subtype on prognosis (rather than SLNB results) in cN0 breast cancer. In contrast, Wong et al. [31] from Dana-Farber Cancer Institute in boston (MA) analyzed 967 patients retrospectively and observed that patients with SLNypN1mi/i(+) have a worse prognosis compared to those with SLNypN0 over 5 years of median follow-up. They found a proportional decrease in survival related to the amount of residual disease in the lymph nodes after NACT, indicating 5-year OS of 88.8%, 82.8%, 79.5%, and 77.6%, for ypN0, ypNo(i+), ypN1mic, and ypN1, respectively.

The role of ALND in the presence of a macrometastasis at SLNB after NACT appears to be well defined, but uncertainties persist regarding the potential benefits of performing axillary lymphadenectomy for SLNypN1mi/i(+). This question is expected to be addressed by Tinterri et al. in the ongoing NEONOD 2 [32]. In this regard, the IBCSG 23–01 trial [33, 34] has already demonstrated no clinical benefit in terms of OS or DFS when performing ALND in patients with early-stage breast cancer with ≥ 1 micrometastasic sentinel node. This rationale was adopted in our institution, and it was applied in patients with cN0 disease who received NACT. Note that, only 39% of the panelists in the last St. Gallen consensus [12] voted in favor of performing ALND for micrometastasis and instead suggested axillary radiotherapy as valid alternative for these patients. At the present, the standard of care entails conducting ALND upon encountering macrometastasis in the post-neoadjuvant SLNB. However, there are two ongoing studies where patients who have SLNB positive after NACT are being randomized to receive either ALND or axillary radiotherapy. The results of the Alliance A011202 and the ADARNAT trial NCT04889924 [35] will be crucial to determine whether radiotherapy is non-inferior to ALND in terms of DFS and OS in patients with a positive SLNB after NACT. Research is ongoing in two trials: the Alliance A011202 and the ADARNAT trial NCT04889924.

Despite being limited to a retrospective analysis, we used clear objectives and a good quality of the study design may overcome the retrospective nature of the present study. By balancing the two study cohorts using IPTW, we could reduce the bias introduced by confounders and to evaluate whether SLNB performed before or after NACT-affected survival. On the other hand, the improvement over time in the standard of care may positively influence better outcomes in the earlier cohort. However, this fact does not impact the reduction of axillary lymphadenectomies occurring in this group. After the exclusion of those patients who received latest systemic therapies such as Capecitabine and Trastuzumab, we still observe better oncological outcomes after IPTW sensitivity analysis. Consistent with our results, performing the SLNB technique after NACT carries a reduced risk of ALND, and at the very least, provides equivalent OS and DFS.

Table 4 Multivariate analysis of Prognostic Factors for Overall Survival (OS) and Disease-Free Survival (DFS)

Characteristic	OS and HR (95%CI)	P value	DFS and HR (95%CI)	P value
Menopausal status				
Pre-menopause	Ref		Ref	
Menopause	1.064 (0.82–1.381)	0.641	1.028 (0.788–1.341)	0.837
T stage at diagnosis (%)				
cT1	1.889 (1.195–2.985)	0.006	2.037 (1.287–3.223)	0.002
cT2	.Ref		Ref	
cT3	1.373 (0.946–1.993)	0.095	1.232 (0.886–1.702)	0.218
cT4	2.56 (0.802–8.173)	0.112	2.94 (0.916–9.432)	0.07
Breast cancer subtype ** (%)				
Hormone receptor+ Her2–	Ref		Ref	
Hormone receptor+ Her2+	1.07 (0.77–1.487)	0.688	1.228 (0.886–1.702)	0.218
HER2 pure	0.66 (0.433–1-008)	0.055	0.613 (0.399–0.943)	0.026
Triple negative	0.813 (0.602–1.097)	0.176	0.776 (0.571–1.056)	0.107
Clinical response by imaging				
Complete response	Ref		Ref	
Partial response	1.58 (0.961–2.598)	0.071	1.456 (0.897–2.364)	0.128
No response	1.702 (1.012–2.861)	0.045	1.442 (0.866–2.401)	0.160
SLNB timing				
pre-NACT SLN	3.095 (2.323–4.123)	<0.001	2.788 (2.095–3.709)	<0.001
post-NACT SLN	Ref		Ref	
SLNB results				
Negative	Ref		Ref	
Macrometastasis	0.506 (0.14–1.829)	0.299	0.699 (0.184–2.651)	0.598
Micrometastasis	1.172 (0.722–1.9)	0.521	1.06 (0.653–1.721)	0.813
Isolated tumor cells	0.760 (0.247–2.392)	0.65	0.969 (0.311–3.018)	0.957
Breast pathological response				
Complete	Ref			
Partial	0.896 (0.644–1.245)	0.511	0.971 (0.695–1.356)	0.863
No response	0.952 (0.636–1.424)	0.810	1.03 (0.684–1.551)	0.887
Breast radiotherapy				
No	Ref		Ref	
Breast radiotherapy	0.841 (0.601–1.178)	0.314	0.787 (0.57–1.087)	0.146
Breast+chest wall	1.466 (0.823–2.611)	0.194	1.326 (0.795–2.212)	0.279
Axillary radiotherapy				
No	Ref		Ref	
Supraclavicular and level III	1.098 (0.58–2.078)	0.774	1.09 (0.569–2.088)	0.795
Axilla+supraclavicular+level III	1–224 (0.67–2.234)	0.511	1.335 (0.733–2.431)	0.345

OS Overall Survival, *DFS* Disease-free Survival, *Pre-NACT SLN* Sentinel Lymph Node performed before chemotherapy treatment, *post-NACT SLN*: Sentinel Lymph Node performed after chemotherapy treatment. **Hormone receptor+HER2 -: ER+and Ki67 < 20% and HER2 -. Hormone receptor+HER2+: ER+and Ki67 ≥ 20% and HER2+. HER2+: ER—and PR—and HER2+. Triple Negative: ER—and PR—and HER2 -

Conclusion

In conclusion, performing SLNB after NACT is associated with less axillary lymphadenectomy, lower recurrences rate, and no detrimental effect on survival. Therefore, in the absence of no clinical benefit, our results indicate that SLBV should no longer be recommended before NACT in patients with clinically node-negative breast cancer.

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Data availability The datasets generated during the current study are no publicly available due to protect study participant privacy but they are available from the corresponding author on reasonable request.

Declarations

Competing interests S. Fernandez-Gonzalez, C. Falo, M.J Pla, M. Campos, C. Ortega, R. Ortega, M. Vicente, A. Petit, J. Bosch, M.T Bajen, G. Reyes, E. Martínez, J. Gonzalez, J. Ponce and A. Garcia-Tejedor do not have any financial/non-financial interest.A.Stradella declares:•Speaker's bureau: Daiichi, Novartis, Astra Zeneca•Travel, accommodations or expenses paid: Eisai, Novartis, and Pfizer•Advisory role: Astra Zeneca, Boehringer Ingelheim, Novartis, Seagen and Gilead•Non-financial disclosure: member of GEICAM's Executive BoardS. Pernas declares:•Advisor/Consultant: AstraZeneca-Daiichi; Gebro; Pfizer; Pierre-Fabre; SeaGen•Speaker honoraria: AstraZeneca-Daiichi; Eisai; Gilead; Lilly; Novartis; Roche;•Travel grants from AstraZeneca-Daiichi; Pfizer; Gilead; Roche•Non-financial disclosure: member of SOLTI's Executive Board and Scientific Committee

Conflict of interest All authors declare that they have no financial interest.

Ethical approval The study was approved by the ethics committee from our hospital (247/06).

Informed consent Informed consent was obtained from all individual participants included in the study to be treated and analyzed in our institution.

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ARTÍCULO 3 – *Centinela tras hormonoterapia neoadyuvante*

Management of the axilla in postmenopausal patients with cN0 hormone receptor-positive/HER2-negative breast cancer treated with neoadjuvant endocrine therapy and its prognostic impact.

Objetivo: Evaluar las diferencias en positividad de la biopsia del ganglio centinela (SLNB) al realizarse antes o después de la terapia endocrina neoadyuvante (NET) en pacientes con cáncer de mama, y su impacto en el pronóstico.

Métodos: Se realizó un estudio de cohortes retrospectivo en un único centro que incluyó 91 casos de pacientes posmenopáusicas con cáncer de mama sin afectación axilar y receptores hormonales positivos con HER2 negativo (HR+/HER2−), tratados con NET y SLNB. La SLNB se realizó antes de la NET hasta el año 2014, y después de la NET a partir de entonces. La disección de ganglios linfáticos axilares (ALND) sólo se indicó en caso de macrometástasis en SLNB. En pacientes seleccionadas de edad avanzada también se omitió la ALND. Se estimaron curvas de supervivencia de Kaplan–Meier en relación con el estado de la axila, y se evaluaron las diferencias utilizando la prueba de log-rank.

Resultados: Entre diciembre de 2006 y marzo de 2022, se realizó la SLNB antes de la NET en 14 casos y después de la NET en 77. Ambos grupos fueron similares en características basales del tumor y del paciente. La positividad de SLNB fue similar independientemente de si se realizó antes (5/14, 35.7%) o después de la NET (27/77, 37%), con 2/14 macrometástasis en la cohorte pre-NET y 17/77 en la cohorte post-NET. Solo tres pacientes (18.7%) con macrometástasis en el SLNB tuvieron > 3 ganglios positivos tras ALND. La supervivencia global a los 5 años y la supervivencia libre de enfermedad a distancia fueron del 92.4% y 94.8%, respectivamente, sin diferencias significativas según el estado de SLNB ($p = 0.5$ y $p = 0.8$, respectivamente).

Conclusión: La tasa de positividad del SLNB no difirió según su momento de realización, antes o después de la NET. Por tanto, la NET no parece tener un efecto en la negativización de los ganglios linfáticos. Dado que en este subgrupo de pacientes se observa muy buen pronóstico independientemente de la afectación axilar, deberían tenerse en cuenta otros factores pronóstico más allá de la afectación ganglionar para la toma de decisiones, como por ejemplo la disminución del Ki67 incorporado en el PEPI score (post-neoadjuvant prognostic index).

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CLINICAL TRIAL

Management of the axilla in postmenopausal patients with cN0 hormone receptor-positive/HER2-negative breast cancer treated with neoadjuvant endocrine therapy and its prognostic impact

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Abstract

Purpose To evaluate the differences in nodal positivity if the sentinel lymph node biopsy (SLNB) is performed before or after neoadjuvant endocrine therapy (NET) in breast cancer patients, and its impact on prognosis.

Methods A retrospective cohort study was performed in a single center including 91 postmenopausal cases with clinically node-negative and hormone receptor-positive/HER2-negative (HR+/HER2−) breast cancer, treated with NET and SLNB. SLNB was done pre-NET until 2014, and post-NET thereafter. Axillary lymph node dissection (ALND) was indicated only in SLNB macrometastasis, although in selected elderly patients, it was omitted. Kaplan–Meier survival curves were estimated in relation to the status of the axilla, and the differences assessed using the log-rank test.

Results Between December 2006 and March 2022, SLNB was performed pre-NET in 14 cases and post-NET in 77. Both groups were similar in baseline tumor and patient characteristics. SLNB positivity was similar regardless of whether SLNB was performed before (5/14, 35.7%) or after NET (27/77, 37%), with 2/14 SLN macrometastases in the pre-NET cohort and 17/77 in the post-NET cohort. Only three patients (18.7%) with SLN macrometastasis had > 3 positive nodes following ALND. The 5-year overall survival and distant disease-free survival were 92.4% and 94.8%, respectively, with no significant differences according to SLNB status (p 0.5 and 0.8, respectively).

Conclusion SLN positivity did not differ according to its timing (before or after NET). Therefore, NET has no effect on lymph node clearance. Furthermore, the prognosis is good regardless of the axillary involvement. Therefore, factors other than axillary involvement may affect the prognosis in these patients.

Keywords Neoadjuvant endocrine therapy · Sentinel lymph node biopsy · Hormone-receptor-positive breast cancer · Axillary management · Axillary node dissection · De-escalation

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Introduction

Hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR +/HER2−) tumors are the most common type of breast cancer, accounting for approximately 75% of women over 50 years old [1]. In a recent review of Waks and Winer [2], the 5-year breast cancer-specific survival in stage I for HR +/HER2− tumors was > 99%, while for HER2 + was > 94% and for triple negatives was > 85%. Furthermore, Gianni et al [3] have found a significant correlation between HR + and low response to chemotherapy, in a large series of cases with breast cancer, where HR + patients achieve a complete pathological response between 5 and 6 times less than the rest. Therefore, this subgroup of tumors has a better prognosis than others [2], is less sensitive to chemotherapy [3, 4], and requires different therapeutic approaches. In contrast, current axillary management guidelines for these patients does not differ from that applied in other more aggressive subtypes.

Several clinical trials have demonstrated that neoadjuvant endocrine therapy (NET) in postmenopausal patients can downsize HR +/HER2− tumors and facilitate breast-conserving surgery [5]. Aromatase inhibitors are the treatment of choice [6]. However, axillary management strategies are underreported in these patients; indeed, they have been excluded not just from the large trials evaluating the feasibility of sentinel lymph node biopsy (SLNB) after preoperative therapy [7] but also from most of the ongoing clinical trials investigating regional nodal radiation after positive SLNB and neoadjuvant systemic therapy (NST). As a result, information on axillary management in the NET setting is lacking.

Neoadjuvant chemotherapy (NAC) has been shown to reduce the requirement for axillary lymph node dissection (ALND) in clinically node-positive (cN +) patients, since it achieves a complete pathological axillary response (pCR) in more than 60% of cases, especially for HER2-positive and triple negative tumors [8, 9]. By contrast, the incidence of axillary pCR after NET is much lower (< 10%) [10]. Moreover, in node-negative (cN0) disease, ALND rates also fell from 42% when performed before NAC to 12% following NAC [11], thanks to the downstaging of the undetectable lymph nodes involved. However, no data on SLNB before or after NET were reported.

The lack of significant differences in survival outcomes observed in patients aged ≥ 60 years with HR +/HER2− disease treated with or without ALND [12] suggests an opportunity to de-escalate treatment when patients have limited residual nodal disease. In fact, information from the National Cancer Database after examining patterns of axillary management in patients with cN0 HR +/HER2− disease revealed that those who had a positive SLNB after NET were less likely to complete ALND, thus favoring the adoption of less aggressive management strategies by this group [13]. Nevertheless, the long-term impact of omitting ALND in this setting remains unknown.

The efficacy and tolerability of NET have been widely reported, especially in elderly patients, and its superior cost-efficacy balance compared with NAC has been stressed [14]. However, it is not widely used in clinical practice [15]. Given the limited data available for axillary management after NET, the present study aimed to evaluate the differences in nodal positivity if the SLNB is performed before or after NET in patients with cN0 HR +/HER2− breast cancer, as well as its impact on adjuvant chemotherapy decision-making and prognosis.

Material and methods

Study design and patients

This retrospective cohort study of a prospectively maintained database included cN0 breast cancer patients treated with NET at Institut Català d'Oncologia-Hospital Universitari Bellvitge, between December 2006 and March 2022. In that period, 522 patients were identified as candidates for NST, and 91 were finally treated with NET (17.4%) (see Fig. 1). The Hospital Universitari Bellvitge Institutional Review Board approved the study (247/06), and all patients signed informed consent forms. The anonymization of all patient data was ensured, and their confidential information was protected in accordance with the national regulations.

Patients were required to meet all the following eligibility criteria: (1) postmenopausal women, or men; (2) tumor size > 2 cm or palpable breast tumor; (3) clinical and radiological cN0 at diagnosis (by axillary ultrasound); (4) invasive breast carcinoma in tumor core biopsy, estrogen receptor (ER) > 50% and HER2-negative tumors; (5) treated with NET; and (6) willingness to undergo surgery following NET. We excluded patients who had axillary lymph node (ALN) positive disease at diagnosis by fine-needle aspiration, treated with NAC, and HER2-positive tumors.

Treatments and cohorts

NET was indicated in patients with HR +/HER2− in which primary surgery could be less esthetic, trying to downstaging the tumor and thus improve surgery, knowing that this type of tumor does not respond well to neoadjuvant chemotherapy, or older patients in whom chemotherapy would ideally be avoided, to test endocrine sensitivity in vivo according to our multidisciplinary committee. Treatment consisted of 2.5 mg letrozole in women and 20 mg tamoxifen in men for

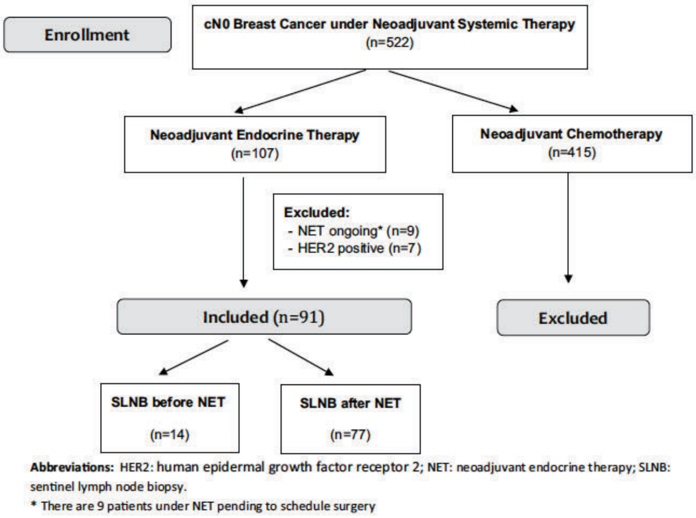

Enrollment
cN0 Breast Cancer under Neoadjuvant Systemic Therapy (n=522)
Neoadjuvant Endocrine Therapy (n=107)
Neoadjuvant Chemotherapy (n=415)
Excluded:
- NET ongoing* (n=9)
- HER2 positive (n=7)
Included (n=91)
Excluded
SLNB before NET (n=14)
SLNB after NET (n=77)
Abbreviations: HER2: human epidermal growth factor receptor 2; NET: neoadjuvant endocrine therapy; SLNB: sentinel lymph node biopsy.
* There are 9 patients under NET pending to schedule surgery

Fig. 1 Study flow chart HER2: human epidermal growth factor receptor 2; NET: neoadjuvant endocrine therapy; SLNB: sentinel lymph node biopsy. * There are 9 patients under NET pending to schedule surgery

6–12 months, depending on response. Conservative breast surgery or mastectomy following NET was decided according to tumor response, tumor size, and predictable esthetic results.

Cases were distributed into two cohorts based on when they underwent SLNB before (pre-NET) and after NET (post-NET). SLNB was performed before NST from December 2006 to April 2014 and following NST thereafter according to our breast cancer guidelines. Peritumor injection of 3 mCi/mL 99 m-technetium radiocolloid (99 m-Tc) was administered for lymphatic mapping 24 h before the SLNB. When initial migration had not been observed on a previous gammagraphic map, we performed a second injection with 99 m-Tc the day before to improve migration. Radioactivity was detected with an intraoperative gamma probe (Europrobe; Britec, Sheffield, United Kingdom).

In the pathology department, the SLN and adipose tissue were fixed in 10% formaldehyde and completely embedded in paraffin, and processed in 3-mm sections, separated by 150 mm, three stained using hematoxylin and eosin and three stained using AE1/AE3 cytokeratin. Micrometastasis was defined as a small cluster of cells measuring 0.2–2 mm, and macrometastasis as > 2 mm. In both cohorts, deferred ALND was performed in patients with SLNB macrometastasis, except in selected elderly women in whom it was omitted in accordance with the Rudenstam et al. guidelines [12]. Patients with negative SLNs or with SLN micrometastasis did not undergo further treatment of the axilla.

Adjuvant chemotherapy was offered to patients with a postoperative endocrine prognostic index [16] (PEPI score) > 3 if they were aged < 80 years and had a good performance status (< 2). Most of the schemas included taxanes; however, therapy was adapted to each patient depending on their associated comorbidities prior to oncogeriatric screening. All patients received the same adjuvant endocrine therapy as in the neoadjuvant setting (2.5 mg letrozole, except in cases of progression during NET) to complete a minimum of five years. All patients had radiotherapy of the breast or chest wall according to our institutional guidelines after breast-conserving surgery and in cases with cT3-T4 tumors after mastectomy. Patients with SLNB-positive disease also received supraclavicular radiotherapy, including level III-ALN.

Variables

We recorded the following clinical and pathologic variables: age, tumor size before and after NET, histological type, Nottingham histological grade, lympho-vascular invasion, hormonal receptors status, proliferative index by Ki-67 staining, percentage of TILs (considered negative if < 5% of stromal TILs), treatment duration, type of breast and axillary surgery, SLN identification rate, SLN involvement, ALND rate, and any adjuvant treatments. Samples were divided into two surrogate subtypes according to PR and Ki-67 expression [17]: Luminal A-like, for progesterone receptor (*PR*) > 20%, and Ki-67 < 20%; and Luminal B-like (HER2−), for *PR* < 20% or Ki-67 > 20%. The Ki-67 proliferative index was grouped as > 30% or < 30% based on the results from a receiver operating characteristic curve (data not shown) at diagnosis and > 10% or < 10% after NET. Evaluation of clinical and radiological responses was grouped according to World Health Organization criteria, as complete response, partial response, no response, or progression [18]. Pathological complete response was considered when the pathologist observed 100% fibrosis replacing the invasive carcinoma and no axillary involvement, partial response if > 30% of fibrosis, and no response if < 30% fibrosis.

Follow-up

The patients were evaluated clinically and radiologically every three months before surgery. Radiological assessment included mammography and ultrasound of the breast and axilla in all cases, with magnetic resonance imaging reserved for selected cases. After surgery, patients were followed clinically every six months, with an annual mammography. Recurrences were defined as local when present in the ipsilateral breast or lymph nodes and systemic when they involved contralateral lymph nodes or other organs. Contralateral tumors were recorded separately.

Statistical analysis

Categorical variables are presented as the number of cases and proportions, whereas normally distributed continuous variables are presented as means and standard deviations (SD). Differences between the pre-NET and post-NET groups were analyzed by the chi-square test or Fisher's exact test for categorical variables and by the student t-test for continuous variables. The level of statistical significance was arbitrarily set at 5%. Statistical analyses were performed using IBM SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Distant disease-free survival (DDFS) was defined as the time from diagnosis to distant recurrence, a second primary invasive cancer, or death from any cause. Breast cancer-specific survival (BCSS) was calculated from diagnosis until death from breast cancer, and overall survival (OS) was calculated from diagnosis until death from any cause. OS, BCSS, and DDFS were calculated at 5 years with their 95% confidence intervals (95%*CIs*). Kaplan–Meier survival curves of DDFS and OS were obtained in relation to the status of the axilla, which was grouped as ypN0 or ypN+, to assess the impact of affected lymph nodes in the context of HR+HER2− tumors, and the differences were computed by the log-rank test. Patients without events were censored at the time of the last follow-up.

Results

From December 2006 to March 2022, we included 89 patients who underwent NET and SLNB (88 women and 1 man); two of the patients had bilateral synchronous disease, so the final sample comprised 91 cases. The man included in the study was 93 years old and presented a cT4bN0 invasive ductal carcinoma at diagnosis with partial response after NET (ypN2ypN0). The PEPI score after NET was 1, so adjuvant CT could be safely avoided. After 13 months of follow-up, the patient is still alive and free of disease.

SLNB was performed before NET in 14 cases (pre-NET cohort) and following NET in 77 (post-NET cohort). Table 1 shows the baseline characteristics of the patients and tumors, as well as the clinical-radiological response in the overall sample and comparing both cohorts pre- vs post-NET. There are no significant differences between both cohorts in the baseline description The seven cT1N0 cases included were due to bilateral tumors ($n=1$), comorbidity associated with the diagnosis ($n=4$), or COVID infection requiring surgical delay ($n=2$). Mammographic evaluation of a breast tumor before and after NET, with partial response, is shown in Fig. 2.

Median months under NET were 7.6 (ranged 4.8–12.4) in the pre-NET group and 7.7 (ranged 4.1–13.6) in the post-NET group. SLNB identification rate was higher before NET although non-significant ($p=1$): 100% versus 94.5% after NET (Table 2). In three of the four undetectable cases, ALND was omitted because the patients were elderly. SLNB positivity was similar whether performed before or after NET (35.7% versus 37%, respectively) and the rate of omission of ALND was similar in the two cohorts (85.7% pre-NET and 88.2% post-NET, $p=1$). Note that only three of the 17 ALND performed (17.6%) had > 3 positive nodes in the final pathology report and that all these cases had more than one positive SLNB.

Table 3 details the local and systemic adjuvant therapy and the results of pathological specimen evaluation. Interestingly, pathological complete response was observed in one patient with a cT2N0 luminal B-like tumor. Ki-67 staining after NET fell to < 10% in most patients (60.4%). The PEPI score was not evaluated until 2014, since then 20 out of 77 patients (26%) have had a PEPI score of ≥ 4; only four of these did not receive adjuvant chemotherapy due to low performance status or comorbidities.

After a mean follow-up of 50 months (standard deviation, 38; range 9–174 months), five recurrences and four deaths were reported (Table 3). A locoregional recurrence occurred in one patient with pN1mi disease (pre-NET cohort), contralateral breast cancer in one patient with ypN1a disease (post-NET cohort), and distant recurrences in three patients with pN0/ypN0 disease (one in the pre-NET cohort and two in the post-NET cohort). Of the four patients who died, only one was due to breast cancer. The 5-year OS was 92.4% (95%*CI* 84.5–100%), the BCSS was 98.3% (95%*CI* 94.9–100%), and the DDFS was 94.8% (95%*CI* 87.4–100%) in the overall sample (Fig. 3). When comparing DDFS and OS, no significant differences were found between positive

Table 1 Patient and tumor characteristics*

	Total	Pre-NET ($n=14$)	Post-NET ($n=77$)	*p*
Age, years, mean (SD)	69.5 (7.9)	68.6 (4.3)	69.6 (8.4)	0.5
cT (%)				0.7
1	7 (7.7%)	1 (7.1%)	6 (7.8%)	
2	57 (62.6%)	10 (71.4%)	47 (61%)	
3	20 (22%)	3 (21.4%)	17 (22.1%)	
4	7 (7.7%)	–	7 (9.1%)	
Tumor size, mm**	39.8 (20)	42.6 (19.9)	39.3 (20.1)	0.6
Histology (%)				0.8
No special type (Ductal)	64 (70.3%)	10 (71.4%)	54 (70.1%)	
Lobular	25 (27.5%)	4 (28.6%)	21 (27.3%)	
Other	2 (2.2%)	–	2 (2.6%)	
Nottingham histological grade				0.9
1	26 (28.6%)	4 (28.6%)	22 (28.6%)	
2	58 (63.7%)	9 (64.3%)	49 (63.6%)	
3	6 (6.6%)	1 (7.1%)	5 (6.5%)	
Not evaluable	1 (1.1%)	–	1 (1.3%)	
Ki-67				0.6
$\leq 30\%$	80 (87.9%)	12 (85.7%)	68 (88.3%)	
$> 30\%$	11 (12.1%)	2 (14.3%)	9 (11.7%)	
Molecular surrogate subtype				0.5
Luminal A-like	39 (42.9%)	7 (50%)	32 (41.6%)	
Luminal B-like	52 (57.1%)	7 (50%)	45 (58.4%)	
Vascular invasion				NA
Yes	0 (0%)	–	–	
No	70 (76.9%)	–	70 (90%)	
Missing	21 (23.1%)	14 (100%)	7 (10%)	
TILs				NA
Positive	16 (17,6%)	–	16 (20.8%)	
Negative	52 (57.1%)	–	52 (67.5%)	
Missing	23 (25.3%)	14 (100%)	9 (11.7%)	
Clinical-radiological response				0.6
Complete	6 (6.6%)	1 (7.1%)	5 (6.5%)	
Partial > 50%	73 (80.2%)	10 (71.4%)	63 (81.8%)	
No response	11 (12.1%)	3 (21.4%)	8 (10.4%)	
Progression	1 (1.1%)	–	1 (1.1%)	

SD standard deviation; %, percentage of patients; *TILs* tumor-infiltrating lymphocytes, *NA* not applicable

*Data related to 91 tumors in 89 patients

**Tumor size measured by magnetic resonance imaging in 58 cases and ultrasounds in 33

and negative SLNB (Fig. 4). Long rank for DDFS was 0.07, $p=0.8$, and for OS was 0.4, $p=0.5$.

Discussion

In our sample of 91 cN0 breast tumors from 89 patients under neoadjuvant endocrine therapy, SLNB was positive in 35.7% of cases when performed pre-NET and in 37% of cases post-NET. The overlap of pre- and post-NET results indicates that endocrine therapy has no effect on subclinical SLN-positive disease. In contrast, previous studies by our team on SLNB before and after neoadjuvant chemotherapy observed that NAC reduces SLNB involvement threefold in cN0 patients (from 42% pre-NAC to 12% post-NAC), indicating that NAC provides a benefit in subclinical SLN-positive disease [11]. There are few studies evaluating SLNB in the setting of NET [19] but, based on the overlap of our results before and after NET, it appears that the effect on lymph nodes differs substantially between chemotherapy and endocrine therapy. Seeking to answer this question, Friedman et al [20] evaluated axillary downstaging in HR+/

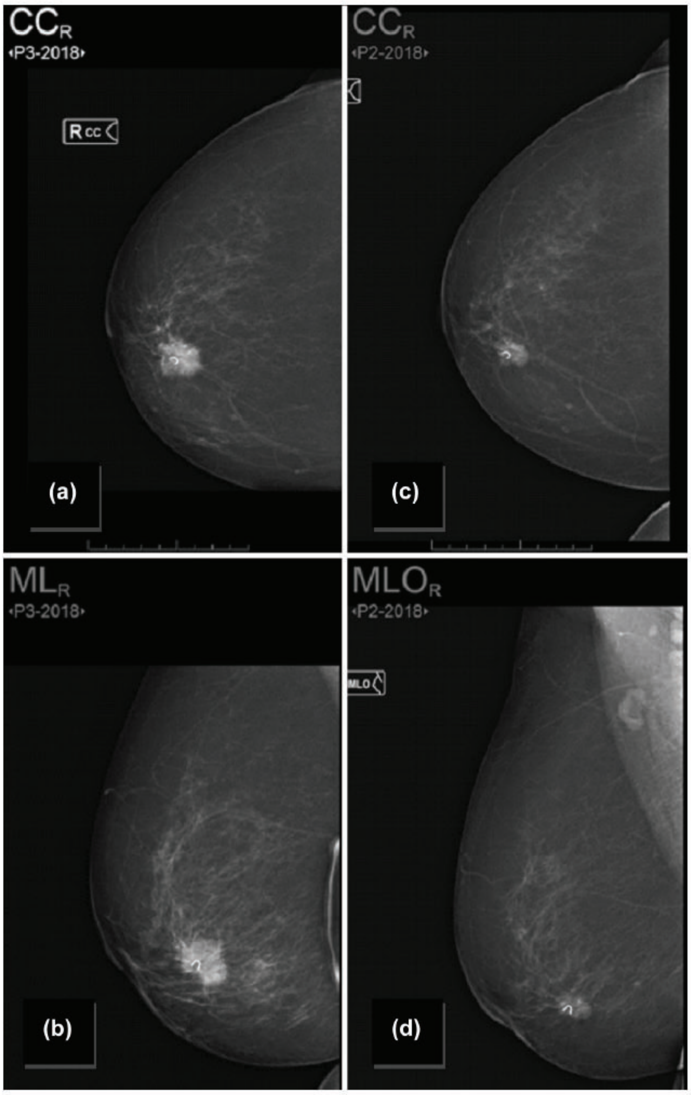


Fig. 2 Mammographic evaluation of a breast tumor before and after neoadjuvant endocrine therapy (NET), with partial response. (**a**,**b**) Craniocaudal (CC) and oblique projection of breast cancer tumor at diagnosis with metallic marker inside (**c**,**d**) CC and oblique projection 6 months after NET

Her2−cN + tumors after neoadjuvant systemic treatment comparing the two therapies, and observed pathological complete response after NAC in 19 out of 137 cases (13.9%) versus three out of 41 (7.3%) after NET. Therefore, lymph node disease in HR +/Her2− tumors appears to be resistant to any systemic treatment, with very poor responses regardless of whether the systemic treatment administered is chemotherapy or endocrine therapy.

The proportion of micrometastases/macrometastases in SLNB and in ALND was higher before NET than after,

Table 2 Outcomes of axillary surgery

	Pre-NET (n = 14)	Post-NET (n = 77)	p
SLN Identification Rate (%)	14 (100%)	73 (94.8%)	1
SLN removed, mean (SD)	1.7 (0.9)	1.8 (0.9)	0.85
SLN pathological result			1
-Positive	5 (35.7%)	27 (37%)	
-Negative	9 (64,3%)	46 (63%)	
SLN-positive (%)			0.48
-Macrometastases	2 (14,3%)	17 (23.3%)	
-Micrometastases	3 (21,4%)	7 (9.6%)	
-Isolated Tumoral Cells	–	3 (4.1%)	
Lymphadenectomy			1
Yes	2 (14.3%)	15 (19.5%)	
Not	12 (85.7%)	62 (88.2%)	
Lymphadenectomy outcomes			
-LN removed, mean (SD)	20.5 (6.3)	19.9 (4.6)	0.33
-Number of positive LN	–		0.89
0	–	4 (26.7%)	
<3	2 (100%)	8 (53.3%)	
≥3	–	3 (20%)	
ypN*			0.45
-ypN0	9 (64.3%)	49 (63.6%)	
-ypN1	5 (35.7%)	21 (27.3%)	
-ypN2	–	2 (2.6%)	
-ypN3	–	2 (2.6%)	
-ypNx	–	3 (3.3%)	

LN lymph nodes; n, number of patients; *NET* neoadjuvant endocrine therapy; *SD* standard deviations; *SLN* sentinel lymph node

*ypN summarized the number of positive SLN and positive LN at lymphadenectomy

although the sample is very small. These results are consistent with those previously published by our group [11]. NET decreases the proliferation of tumor cells as it is seen in the decrease in KI67, but rarely converts a positive axilla into a negative one after NET, neither after NAC in luminal cases as the ones reported in this series. Perhaps the effect of NST could be easier when the SLN has micrometastases at diagnosis, managing to clean the affected node, but it would be more difficult when there is a greater tumor burden, so the disease would persist in a higher proportion of cases with macrometastasis afterward of the NST, but this hypothesis cannot be proved.

Lymph node disease in HR+/Her2− tumors is not usually very extensive. In our study, only three patients with SLN macrometastases (17.6%) had > 3 positive nodes in the final pathology study. Similarly, Kantor et al. observed the presence of ≤ 3 positive nodes in surgery in 90% of patients with cN0 after NET [21]. These results suggest that most patients with cN0 disease treated with NET have a low nodal disease burden, and therefore, might be spared the morbidity associated with ALND. In the United States National Cancer Database, no significant differences in 5-year OS were observed when comparing patients with residual isolated tumor cells or micrometastasis with those who had no residual nodal disease after NET [22]. Our findings support these data, with DDFS and OS at 5 years unrelated to SLNB involvement and both exceeding 95%. Therefore, NET does not seem to carry the same prognostic significance as the residual nodal disease reported after NAC by Fisher et al [23].

Despite the behavioral differences between breast cancer surrogate molecular subtypes and the impact of different types of neoadjuvant systemic therapy (NAC or NET), axillary management after NET is currently extrapolated from NAC, meaning that patients who are cN0 at diagnosis and SLNB-positive after NET will undergo ALND [6]. Emerging data suggest that the residual nodal disease burden for cN0 HR+/HER2− after NET should be similar to that for cT1–T2N0 after primary surgery, and that this may be an opportunity to extrapolate management strategies used in the upfront surgery setting. Both ACOSOG Z0011 [24, 25] and AMAROS studies [26, 27] have shown that cN0 patients undergoing primary surgery with one or two positive SLNBs did not benefit from ALND in terms of DDFS and OS. Thus,

Table 3 Local and systemic adjuvant therapy and outcomes

	Mean (SD)	N° of patients (%)
Surgical procedures		
Breast Surgery		
Lumpectomy		49 (53.8%)
BCS + Oncoplasty		17 (18.7%)
Mastectomy		19 (20.9%)
Mastectomy + Reconstruction		6 (6.6%)
Axillary Lymph Node Dissection		
Yes		17 (18.7%)
Not		74 (81.3%)
Specimen pathological evaluation		
ypT		
0		1 (1.1%)
1		26 (28.6%)
2		44 (48.4%)
3		20 (22%)
Tumor size (mm), mean (SD)	37 (25.6)	
Ki-67 after NET		
< 10		55 (60.4%)
≥ 10		21 (23.1%)
Missing		15 (16.5%)
Pathological response		
Complete		1 (1.1%)
Partial > 30%		63 (69,2%)
No response		27 (29.7%)
PEPI score		
0		24 (26.4%)
1–3		33 (36.3%)
≥4		20 (22%)
Missing		14 (15.4%)
Radiotherapy		
Breast Radiotherapy		
Not		11 (12.1%)
Breast		66 (72.5%)
Thoracic wall		14 (15.4%)
Axillary Radiotherapy		
None		69 (75.8%)
Level III and Supraclavicular		8 (8.8%)
All levels		14 (15.4%)
Systemic adjuvant therapy		
Chemotherapy		
Yes		18 (19.8%)
Not		73 (80.2%)
Endocrine therapy		
Tamoxifen		1 (1.1%)
Letrozole		90 (98.9%)
Follow-up outcomes		
Recurrences		
Local ipsilateral (breast)		1 (1.1%)
Contralateral Breast Cancer		1 (1.1%)
Systemic		3 (3.4%)
Death		4 (4.5%)
Cancer progression		1 (1.1%)
Other causes		3 (3.4%)

Table 3 (continued)

%, percentage of patients; *BCS* breast conservative surgery; *PEPI* postoperative endocrine prognostic index; *SD* standard deviation

it might be possible to consider de-escalating axillary management strategies after NET, subject to the results of further studies that are needed to standardize surgical management.

Regarding adjuvant systemic therapy in HR +/HER2− disease, one of the most important questions is who will benefit from chemotherapy and endocrine therapy. Nitz et al. observed that patients with ypN0–1 disease (≤ 3 lymph nodes) and low Ki-67 after a short NET can safely receive adjuvant ET alone [28]. Another tool for deciding the need for adjuvant chemotherapy is the PEPI score, based on residual tumor size and Ki-67 after NET, but the value for lymph node involvement is the same regardless of the number of positive nodes [16]. Interestingly, the POETIC trial demonstrated that Ki-67 measured two weeks after preoperative NET was able to predict survival outcomes, providing a basis for simple and inexpensive testing that could personalize adjuvant treatment in HR +/HER2− disease regardless of the axillary involvement [29]. Another useful test to predict the NET response and help us select the target patients is the OncotypeDX© Recurrence Score (RS) multigene panel [30]. In a recent review, they noted that breast cancers with low-intermediate RS on core biopsy are four times more likely to respond to NET than those with high-risk RS.

No randomized controlled trials have been reported on neoadjuvant endocrine treatment in man with breast cancer due to its low incidence. In clinical practice, the same management is offered to men than to women according to the TNM and molecular surrogate subtype [31]. In consequence, the male case reported in our series meet clinical criteria to receive NET and, in fact, his evolution has been like their counterpart female patients.

Limitations of the study include the retrospective design which has an inherent selection bias for those patients chosen for this approach versus initial surgery or neoadjuvant chemotherapy, so these results may be different prospectively or in a clinical trial. Furthermore, the small number of pre-NET SLNBs, however it provides an understanding of the low effect of NET on axillary tumor burden. Another limitation of our study is the relatively short follow-up (50 months) given that recurrences in HR +/HER2− disease may occur beyond 5 or 10 years from surgery. Despite these limitations, our study is one of the few to have exclusively analyzed the effect of NET on patients with cN0 disease at a single institution.

Another important consideration is that most patients undergoing NET were over the age of 70, and in these patients, survival depended more on other associated comorbidities than on breast cancer diagnosis (e.g., only

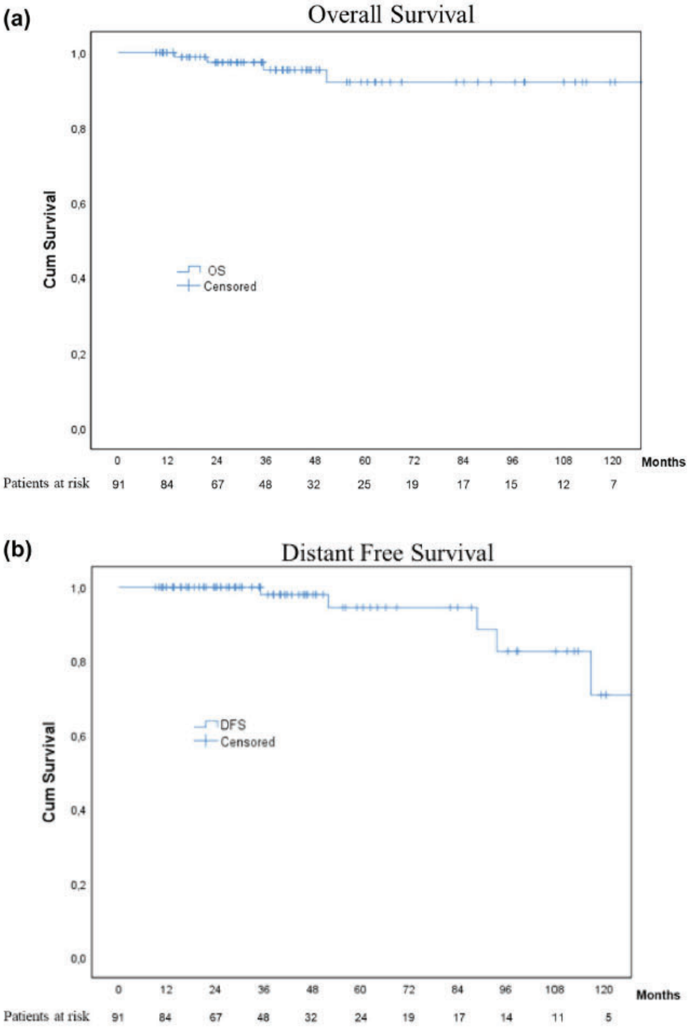
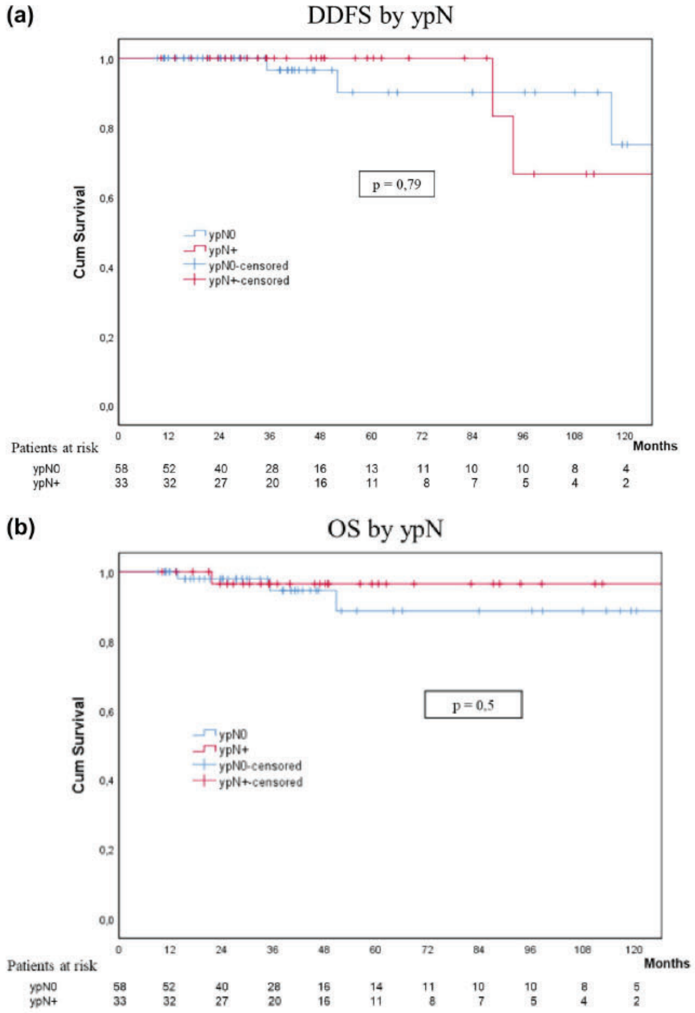


Fig. 3 Survival curves **a**. overall survival **b**. distant disease-free survival

one out of four deaths was related to breast cancer). In fact, in 2006, a clinical trial showed that avoiding axillary clearance in clinically node-negative women aged ≥ 60 years receiving NET had the same prognosis with better early quality of life than ALND; therefore, even SLNB could have been avoided for this population with HR +/HER2− disease [12]. Nevertheless, since life expectancy has risen over the years, SLNB was performed in most of these patients, and if positive, ALND might be offered.

According to all data collected related to NET, Kantor et al. proposed a new tailored approach to axillary management after NET [32] based on performing an axillary ultrasound evaluation at the time of diagnosis to enumerate the suspicious lymph nodes. Then, for candidates for NET

Fig. 4 Survival curves according to axillary involvement; (a) Distant disease-free survival (DDFS); (b) overall survival (OS)



who had cN0 disease at diagnosis and ≤ 3 SLNB-positive nodes following NET, those authors recommend routinely omitting ALND. For patients who have biopsy-proven cN1 disease with ≤ 2 suspicious nodes by axillary ultrasound following NET, they recommend performing SLNB in addition to the clipped biopsy-proven node, only omitting ALND when 1–2 positive nodes are found. This approach may reduce axillary morbidity in a significant proportion of patients treated with NET, but to date, there are no studies that have demonstrated its safety.

Further prospective studies on the axillary management approach after NET are needed to establish consensus management of the axilla in patients with HR+/HER2– disease. Our group has designed a phase 3 randomized multicenter clinical trial (Axillary Lymph Node Dissection Versus Axillary Radiotherapy in Patients with Positive Sentinel Node after Neoadjuvant Therapy: ADARNAT, NCT04889924), to demonstrate whether ALND can be safely omitted in patients with ≤ 3 SLN macrometastases following NAC or NET in order to reduce the morbidity associated with ALND (recruitment is ongoing).

Conclusion

More than 30% of cN0 HR +/HER2− breast cancer patients treated with NET have a positive SLNB, irrespective of whether assessment is performed before or after neoadjuvant therapy. This suggests that the therapy has little effect on the axilla. In addition, survival may not be related to axillary involvement in these patients, who tend to present with low residual axillary disease burden. Therefore, future efforts should focus on de-escalating ALND after NET.

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Data availability Data were collected from computerized medical histories and the Catalan Public Health computerized network. The system was accessed with non-transferable passwords, ensuring patient confidentiality and privacy. The patient data were also anonymized for the analysis. All confidential patient data were protected according to national standards.

Declarations

Conflict of interest S.P. has served as an advisor/consultant for AstraZeneca, Daiichi Sankyo Eisai, Novartis, Polyphor, Roche, Pierre-Fabre, Pfizer, and SeattleGenetics. All other authors declare that they have no conflict of interest.

Ethical approval The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board of Hospital Universitari de Bellvitge (protocol code 247/06, approved in November 2006).

Informed consent Informed consent was obtained from all study participants.

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ARTÍCULO 4 – *Factores predictores de respuesta axilar*

Predictive factors for omitting lymphadenectomy in patients with node-positive breast cancer treated with neo-adjuvant systemic therapy

Introducción: En las pacientes con afectación inicial axilar por cáncer de mama, la respuesta patológica completa (pCR) en la axila ocurre en el 30%-40% de las pacientes tras haber recibido quimioterapia neoadyuvante (NACT). Persiste el debate sobre si realizar la linfadenectomía axilar sistemática (ALND) en pacientes con enfermedad inicialmente positiva en los ganglios linfáticos con respuesta clínica completa después de la NACT. Nuestro objetivo fue identificar factores predictivos de la pCR axilar (ypN0) después de la NACT.

Métodos: Este estudio retrospectivo se analizaron los datos de todos los pacientes con enfermedad inicialmente positiva en los ganglios linfáticos confirmada por biopsia que se sometieron a ALND después de la NACT entre junio de 2008 y diciembre de 2016 en nuestra institución. Se compararon las características clínicas y patológicas, las tasas de recurrencia y mortalidad específica entre los pacientes que lograron una pCR axilar y aquellos que no lo hicieron (ypN0 frente a ypN+, respectivamente).

Resultados: Se incluyeron un total de 331 pacientes, de las cuales 128 (38.7%) se convirtieron en ypN0 después de la NACT. Entre las pacientes con >2 ganglios linfáticos axilares sospechosos antes del tratamiento, 54 (38%) lograron el estado de ypN0. Los predictores independientes de ypN0 fueron Ki67 > 30 (OR 1.98; IC del 95%, 1.146-3.381), positividad para HER2 (OR 2.6; IC del 95%, 1.354-5.108), subtipo molecular no luminal (OR 4.15; IC del 95%, 2.068-5.108), y respuesta clínica completa, definida como la no evidencia de enfermedad ni clínica ni ecográfica (OR 2.8; IC del 95%, 1.110-7.081). Después de un seguimiento medio de 61 meses, las tasas de supervivencia libre de enfermedad a distancia y supervivencia global fueron mayores en pacientes con estadio ypN0 (HR 4.14; IC del 95%, 2.03-8.43) que en pacientes ypN+.

Conclusiones: La respuesta clínica completa y la presencia de subtipos moleculares no luminales predijeron de forma independiente la respuesta patológica completa axilar (ypN0). Las pacientes que cumplen con estos criterios podrían ser adecuados para omitir la ALND y simplemente realizar procedimientos axilares dirigidos reduciendo así una morbilidad evitable.

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ORIGINAL ARTICLE

Predictive factors for omitting lymphadenectomy in patients with node-positive breast cancer treated with neo-adjuvant systemic therapy

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Abstract

A pathologic complete response (pCR) in the axilla occurs in 30%-40% of patients with initially node-positive breast cancer after neo-adjuvant chemotherapy (NACT). Debate persists about whether to perform systematic axillary lymphadenectomy (ALND) in patients with initial node-positive disease and clinical complete response after NACT. We aimed to identify predictive factors of axillary pCR (ypN0) after NACT. This retrospective study analyzed data for all patients with initial biopsy-proven node-positive disease who underwent ALND after NACT between June 2008 and December 2016 at our institution. Clinical and pathologic features, recurrence and specific mortality rates were compared between patients who achieved an axillary pCR and those who did not (ypN0 vs ypN+, respectively). A total of 331 patients were included, of whom 128 (38.7%) became ypN0 after NACT. Among patients with >2 suspicious axillary lymph nodes before treatment, 54 (38%) achieved ypN0 status. The independent predictors of ypN0 were Ki-67 > 30 (OR 1.98; 95% CI, 1.146-3.381), HER2 positivity (OR 2.6; 95% CI, 1.354-5.108), nonluminal molecular-like subtype (OR 4.15; 95% CI, 2.068-5.108), and clinical complete response, defined as negative clinical and ultrasonographic findings (OR 2.8; 95% CI, 1.110-7.081). After a mean follow-up of 61 months, distant disease-free and overall survival rates were higher in patients with ypN0 disease (HR 4.14; 95% CI, 2.03-8.43) than ypN+ patients. Complete clinical response and the presence of nonluminal molecular-like subtypes independently predicted ypN0. Patients meeting these criteria might be suitable form omitting ALND and just performing targeted axillary procedures to patients meeting these criteria.

Abbreviations: ALND, axillary lymph node dissection; cN+, node-positive; DDFS, distant disease-free survival; DFS, disease-free survival; NACT, neo-adjuvant chemotherapy; OS, overall survival; pCR, pathologic complete response; SLNB, sentinel lymph node biopsy; ypN0, pathologic complete response in lymph nodes; ypT0, pathologic complete response in breast.

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KEYWORDS

axillary lymph node dissection, breast cancer, neo-adjuvant chemotherapy, targeted axillary lymph node dissection

1 | INTRODUCTION

Although the management of stage II-III breast cancer is continuously developing, the use of neo-adjuvant chemotherapy (NACT) has become a standard of care. NACT allows for breast-conserving surgery and for evaluation of the in vivo response of the primary tumor and metastatic lymph nodes.[1] Achieving pathologic complete response (pCR), either in the breast (ypT0) or lymph nodes (ypN0), has been shown to produce better disease-free survival (DFS) and overall survival (OS) rates.[2,3] Therefore, pCR has become a primary end point of most NACT trials, representing one of the best surrogate markers of survival. Documented pCR rates in the literature range from 20% to 60% depending on the molecular subtype.[2,4,5]

In node-positive (cN+) disease, axillary lymph node dissection (ALND) has also become a standard surgery. However, new strategies that avoid ALND are being studied to reduce the morbidity associated with ALND.[6] In recent years, the introduction of sentinel lymph node biopsy (SLNB) for patients with initial cN+ breast cancer before NACT has been used to tailor disease management.[7] The main limitation of SLNB in cN+ cases is the high rate of false negatives, which is reported to be 13%.[8] An accurate SLNB technique is therefore needed. The use of a dual tracer and examination of ≥2 sentinel lymph nodes has been shown to reduce the false-negative rate to ≤10%.[8,9] Clip or iodine seed insertion before initiating NACT in patients with cN+ disease also allows targeted axillary dissection,[10] with SLND and the selective removal of clipped nodes further reducing the false-negative rate to 2%.[11] Nevertheless, these techniques are emerging and are not universally used.

The St. Gallen 2017 consensus stated that controversy remained about the role of SLNB in patients with cN+ disease, though it was agreed such a procedure could be considered adequate if ≥3 sentinel lymph nodes were identified.[12] To ensure a low false-negative rate, we must be able to identify those patients with a low likelihood of axillary metastasis after NACT. In the current study, we analyze the factors predicting ypN0 status after NACT in patients with cN+ disease and present the outcomes in terms of DDFS and OS after long-term follow-up.

2 | MATERIALS AND METHODS

2.1 | Study design and participant selection

This was a retrospective observational cohort study of real-world data for patients with breast cancer and positive axillary lymph nodes treated by NACT between June 2008 and November 2016 at the Hospital Universitari Bellvitge & Institut Català d'Oncologia. Patients were required to meet the following eligibility criteria: (a) core biopsy indicating infiltrating breast carcinoma; (b) positive axillary lymph nodes proved by fine-needle aspiration; (c) stages II-III disease; (d) received NACT before surgery, based on the decision of a multi-disciplinary committee; and (e) complete ALND performed after NACT. We excluded patients with clinical N3 disease.

2.2 | Treatment protocol

All patients were preoperatively assessed by axillary and breast ultrasound, and the core biopsy was obtained from every suspicious lesion. Once the breast cancer was pathologically confirmed, a clip was routinely placed in the tumor.

The NACT regimen comprised anthracyclines followed by taxanes for 6 months, with trastuzumab added in cases of HER2-positive tumors. After NACT, complete ALND was performed in all patients. For analysis, patients were divided into two cohorts according to the axillary response: (a) ypN0, which included ypN0 and ypN0(i+); and (b) ypN+, which included ypN1mi to ypN3.

The factors analyzed for their utility to predict ypN0 were as follows: clinical and pathologic parameters, including age, body mass index, percentage of NACT administered, and clinical breast cancer stage; radiologic imaging grouped by nodule, nonmass distortion, or extensive microcalcifications (when microcalcifications were >50% of tumor length); radiologic tumor size and number of suspicious axillary lymph nodes assessed by ultrasound; and histopathological criteria, including the histological subtype, Nottingham histological grade, and vascular invasion. The Ki-67 proliferation index was grouped as >30 or <30 for receiver operating curve analysis. Immunohistological staining was based on receptor status, Ki-67 proliferative index, and HER2 overexpression, and the results were classified into five subtypes[13-16]: luminal A-like, luminal B-like Her2 negative, luminal B-like Her2 positive, Her2 positive, and triple negative.

Complete clinical response was defined as the clinical absence of all evidence of active invasive tumor in the breast and lymph nodes. Partial response was defined as a ≥50% reduction in the product of the perpendicular diameters of the measurable lesion(s) without progression of any lesion or the appearance of new disease. Stable disease was defined as no change, or as a decrease in tumor measurements that was insufficient to qualify as a partial remission. Disease progression was defined as a 25% increase in size of (any) tumor and/or the appearance of new lesions. Combined clinical response was based on mammographic and ultrasonic evaluations of the tumor(s) and axillary nodes, plus physical examination, based on the WHO criteria.[17]

TABLE 1 Predictive factors for ypN0. Univariate analysis

	N	Overall	YpN0 (n = 128)	YpN+ (n = 202)	P value
Age (years), mean ± DS	330	57.7 ± 12.7	58.5 ± 13.19	57.2 ± 12.30	.364
BMI, mean ± DS	330	27.7 ± 5.40	27.7 ± 5.40	27.8 ± 5.38	.770
Dosis of QT, mean ± DS	330	95.3 ± 12.4	96.8 ± 13.3	94.3 ± 11.7	.083
Clinical stage (%)					
II	330	200 (60.7)	77 (38.5%)	123 (61.5%)	.894
III		130 (39.3)	51 (39.2%)	79 (60%)	
T at diagnosis, n (%)					
T0	330	4 (1.2)	0	4 (100)	.446
T1		20 (6.5)	9 (45)	11 (55)	
T2		191 (57.6)	72 (37.7)	119 (62.3)	
T3		61 (18.4)	23 (37.7)	38 (62.3)	
T4		54 (16.3)	24 (44.4)	30 (55.5)	
Node at diagnosis, n (%)					
N1	330	291 (88.2)	115 (39.5)	176 (60.5)	.457
N2		39 (8.8)	13 (33.3)	26 (66.7)	
Histological subtype, n (%)					
Invasive ductal carcinoma	330	312 (94.6)	124 (39.7)	188 (60.3)	.566
Invasive lobular carcinoma		10 (3)	2 (20)	8 (80)	
Others**		8 (2.4)	3 (37.5)	5 (62.5)	
Nottingham grade, n (%)					
G1	319	16 (5)	1/122 (6.2)	15/196 (93.8)	<.001
G2		146 (45.7)	39/122 (26.7)	107/196 (73.3)	
G3		157 (49.2)	86/122 (52.6)	75/196 (47.4)	
HER-2, n (%)					
HER-2 positive	329	114 (34.7)	76 (66.7)	38 (33.33)	<.001
HER-2 negative		211 (64.1)	49 (23.3)	162 (76.8)	
Ki-67, n (%)					
<30%	331	160 (48.3)	47 (29.4)	113 (70.6)	.001
>30%		171 (51.7)	81 (47.4)	89 (52.6)	
Molecular-like subtype*, n (%)					
Luminal A-like	331	36 (10.9)	1 (2.8)	35 (97.2)	<.001
Luminal B-like (Her2-)		115 (34.7)	21(18.3)	94 (81.7)	
Luminal B-like (Her2+)		62 (18.7)	39 (62.9)	23 (37.1)	
HER-2 enriched		53 (16)	38 (71.7)	15 (28.3)	
Triple Negative		65 (19.6)	29 (45.3)	35 (54.7)	
Vascular invasion, n (%)	234	40 (17.1)	16/88 (40)	24/146 (61.4)	.724
Radiologic image, n (%)					
Nodule	331	279 (84.3)	110/128 (39.8)	168/202 (60.2)	.897
Others		49 (15.7)	17/128 (34.7)	32/202 (65.3)	
Radiologic size (median)	316	30 (0-106)	32.2 (0-115)	30.9 (0-130)	.498
Suspicious LN by US, n (%)					
<2	289	147 (50.9)	73/186 (39.2)	113/186 (60.8)	.909
>2		146 (49.1)	54/142 (38)	88/142 (62)	

(Continues)

TABLE 1 (Continued)

	N	Overall	YpN0 (n = 128)	YpN+ (n = 202)	P value
Clinical response, n (%)					
Complete	331	79 (23.9)	58 (73.4)	21 (26.6)	<.001
Partial		215 (65)	64 (29.8)	151 (70.2)	
No response		30 (9)	6 (20.7)	24 (79.3)	
Progression		7 (2.1)	0	7 (100)	

Notes: Data are presented as mean ± SD, median with range or n (%). Analysis was by Student's test, Mann-Whitney U-test, Yates corrected chi-square test or Fisher's exact test as appropriate.
YpN0 includes ypN0 and ypN(i+). YpN+ includes ypN1-N3.
N column means the total data available and analyzed. One patient was exclude due to YpNx.
HER2 cases were considered HER2 enriched + luminal B HER2+.
All categories were analyzed from all patients except when denominator was added.
*Percentage are given per row (risk factor between ypN0 vs ypN+).
**Others include nonmass distorsion, microcalcifications, and no image.

TABLE 2 Outcomes (n = 330)

Pathologic node response after neo-adjuvant chemotherapy	
YpN0	114 (34.5%)
YpN0i(+)	14 (4.2%)
YpN1Mic	9 (2.7%)
YpN1	113 (34.1%)
YpN2	56 (16.9%)
YpN3	24 (7.3%)
Events	
Local recurrences	8 (2.4%)
Axillary recurrences	3 (0.9%)
Local + distant recurrences	14 (4.2%)
Distant recurrences	43 (13%)
Specific mortality	37 (11.2%)

TABLE 3 Multivariate analysis of clinical predictive factors of ypN0

	OR	95% confidence interval	P
Ki-67			
>30 vs <30	1.98	1.146-3.381	.014
HER 2			
Positive vs negative	2.6	1.354-5.108	.004
Molecular-like subtype			
No luminal vs luminal	4.15	2.068-5.108	<.001
Clinical response			
Response vs nonresponse	2.8	1.110-7.081	.029

Note: HER2 were considered HER2 enriched + luminal B HER2 +.

2.3 | Statistical analyses

The primary objective was to assess the impact of predictive factors on ypN0 compared with ypN+ after NACT. Differences between groups were analyzed by chi-squared or Fisher tests for categorical variables and by Student *t*-tests for continuous variables. Logistic regression analysis was used in the multivariate analysis to assess the association of predictive factors with ypN0 status, and the odds ratios (ORs) and 95% confidence interval (CIs) were calculated. We also specifically analyzed the axillary response to NACT when >2 lymph nodes were previously involved. Survival was measured in terms of OS and the distant DFS (DDFS). OS was calculated from the date NACT was started until death from any cause, and breast-specific OS was defined as that until death due to breast cancer progression. DDFS was defined as the time from starting NACT until distant recurrence of breast cancer, a second primary invasive cancer (nonbreast), or death due to any cause. Kaplan-Meier survival curves were calculated, and the differences were assessed using the log rank statistic. Patients without events were censored at the date of last follow-up. DDFS an OS analyses were based on the status of the axilla after NACT and were grouped by ypN0 and ypN+ status and by the molecular-like subtype. Statistical analyses were performed using IBM SPSS Version 23.0 and R 3.0.3. Statistical significance was accepted at the 5% level for all analyses.

3 | RESULTS

Over the study period, 331 patients with cN+ breast cancer were treated with NACT and included in our analysis. The demographic and clinical characteristics are summarized in Table 1. After NACT, 128 patients (38.8%) had axillary pCR (ypN0) and 202 (61.2%) had axillary residual disease (ypN+) (Table 2).

Univariate analysis indicated that the tumor Nottingham grade, molecular-like subtype, HER2 status, Ki-67 level, and clinical response to the NACT were significant predictors of ypN0 (Table 1). In the multivariate analysis, Ki-67 level, HER2 status, molecular-like

TABLE 4 Pathologic response among patients with >2 suspicious a-LN by US

	YpN0 (n = 54)	YpN+ (n = 88)	*P* value
Ki-67			
<30	12 (20%)	48 (80%)	<.001
>30	42 (52.1%)	40 (48.8%)	
HER2			
Negative	22 (24.7%)	67 (75.3%)	<.001
Positive	32 (61.5%)	20 (38.5%)	
Molecular-like subtype*			
Luminal A-like	1 (7.7)	12 (92.3)	<.001
Luminal B-like (Her2 -)	11(22)	39 (78)	
Luminal B-like (Her2 +)	15 (68.2)	7 (31.8)	
HER-2 enriched (nonluminal)	17 (56.7)	13 (43.3)	
Triple negative	10 (37)	17 (63)	
Clinical response	51 (39.5%)	78 (69.5%)	.370
Not clinical response	3 (23.1%)	10 (76.9%)	

Notes: Data are presented as n (%) and were analyzed using Mann-Whitney U-test, Yates corrected chi-square test or Fisher's exact as appropriate.

YpN0 includes ypN0 and ypN(i+). YpN1 includes ypN1-N3.

HER2 cases were considered HER2 enriched + luminal B HER2+.

One patient was exclude due to YpNx.

The significant *P* values are indicated in bold.

*Percentage are given per row.

subtype, and clinical response to the NACT remained independent predictors of ypN0 (Table 3). Among patients with >2 suspicious axillary lymph nodes by ultrasound before NACT, 54 (38%) achieved ypN0 status (Table 4).

As shown in Table 2, there were 68 recurrences and 38 deaths (37 due to breast cancer) after a median follow-up of 61 months (range, 9-118 months). The DDFS and OS were significantly superior for patients achieving ypN0 status after NACT compared with those achieving ypN+ status, with a hazard ratio of 4.14 (95% CI, 2.03-8.43) (Figure 1), but they were similar when comparing ypN0 and ypN0i+ statuses (Figure 2). According to the molecular-like subtype, the DDFS and OS in Figure 2 were also significantly different ($P < .001$, both). Finally, the DDFS ($P = .05$) and OS ($P = .012$) are shown in Figure 3 by molecular-like subtype between the ypN0 and ypN+ groups. When stratified by molecular-like subtype, the differences in DDFS and OS between subtypes were minimized in patients who became ypN0.

4 | CONCLUSION

In this cohort study of patients with cN+ breast cancer, 37.8% had no residual disease in the lymph nodes after NACT, thus corroborating previous results.[18] Therefore, complete ALND after NACT could have been avoided in nearly 40% of patients with cN+ disease based on this approach. Moreover, we identified four independent predictors of pCR in the axilla (ypN0), namely the molecular-like subtype, the clinical response, the HER2 status, and the Ki-67 level.

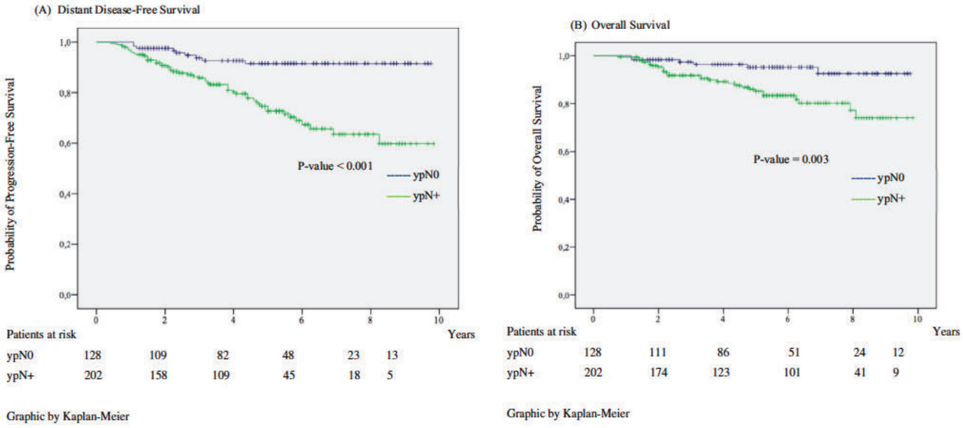
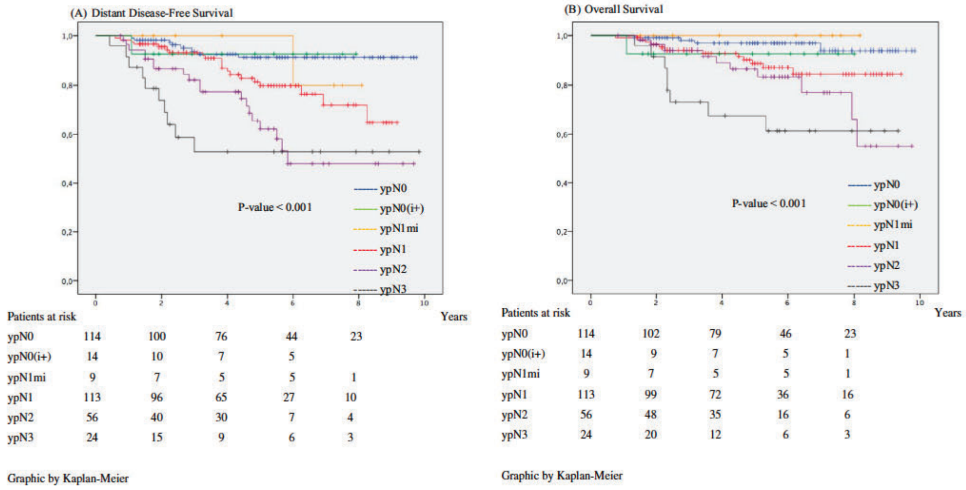


FIGURE 1 DDFS and OS by ypN0 and ypN+ status of the axilla after NACT. Patients were divided in two cohorts according to the axillary response: (a) ypN0, which included ypN0 and ypN0(i+); and (b) ypN+, which included ypN1mi to ypN3. Abbreviations: DDFS, distant disease-free survival; NACT, neo-adjuvant chemotherapy; OS, overall survival



Patients at risk					
ypN0	114	100	76	44	23
ypN0(i+)	14	10	7	5	
ypN1mi	9	7	5	5	1
ypN1	113	96	65	27	10
ypN2	56	40	30	7	4
ypN3	24	15	9	6	3

Graphic by Kaplan-Meier

Patients at risk					
ypN0	114	102	79	46	23
ypN0(i+)	14	9	7	5	1
ypN1mi	9	7	5	5	1
ypN1	113	99	72	36	16
ypN2	56	48	35	16	6
ypN3	24	20	12	6	3

Graphic by Kaplan-Meier

FIGURE 2 DDFS an OS by pathologic status of the axilla after NACT. Patients were divided in two cohorts according to the axillary response: (a) ypN0, which included ypN0 and ypN0(i+); and (b) ypN+, which included ypN1mi to ypN3. Abbreviations: DDFS, distant disease-free survival; NACT, neo-adjuvant chemotherapy; OS, overall survival

The molecular-like subtype was shown to be the most predictive factor for ypN0, with an OR of 4.15 (CI 95%, 2.068-5.108), which is again consistent with that reported in other studies.[2,19,20] In the GEPARDUO study,[21] negative hormonal receptor status was described to have an OR of 3.23 (CI 95%, 1.91-5.46, P = .0001) for predicting pCR. In the GEPARTRIO study,[22] negative hormonal receptor status also had an OR of 5.5 (95% CI, 3.8-8; P = .0001). Cases associated with higher rates of ypN0 status in our study were those with HER2 overexpression (66.7%) and those who were triple negative (45.3%). Boughev et al[23] described similar results. Patients with these subtypes should be considered most suitable for SLNB when the goal is to reduce the likelihood of false negatives.

Although the predictive value of the Ki-67 has been well documented, no consensus has formed about the optimal cutoff point to include in treatment decision strategies.[24-28] We could find no reports indicating that a Ki-67 level > 30% results in an almost two-fold increased probability of ypN0, as we have shown.[29] Recently, Resende et al [18] found that a Ki-67 ≥ 50% predicted clinical complete response in the breast (OR 2.00; 95% CI, 1.31-3.06) and both the breast and axilla (OR 1.67; 95% CI, 1.10-1.45). In patients with clinical stage II or III breast cancer, Wang et al [30] also observed that pCR rates were significantly higher among patients with Ki-67 levels > 40% compared with <40%, with pCR rates of 33.3% and 8.1%, respectively (P < .001).

We observed that ypN0 was achieved in 70% of patients with complete clinical response but in only 30% of patients with partial clinical response. We therefore propose that partial clinical response in the breast should not prevent assessment by SLNB after NACT when axillary complete response is achieved. In addition, some studies have shown that cN1 stage disease was associated with an increased chance of pCR when compared with cN2 stage disease.[8,31] On the other hand, some studies have found a RR of 7.4 (95% CI, 3.7-14.8; P < .001) of nodal metastases in patients without a pCR in the breast.[32] As detailed in Table 3, neither the clinical stage nor the number of suspicious axillary lymph nodes by ultrasound were associated with increased rates of ypN+ in our analyses. Therefore, the decision to offer SLNB in cN+ disease should depend less on the initial clinical stage and more on the molecular-like subtype, the Ki-67 index, the HER2 status, and the clinical response.

An interesting finding of our study was that 38% of patients with >2 suspicious axillary lymph nodes before treatment achieved ypN0 status. Therefore, we also consider it appropriate to review the need for SLNB in those patients. Consistent with this, some institutions have already reported including patients with cN2 disease who are downstaged to cN0 after NACT, as we now advocate. Galimberti et al [33] published an OS of 93.3% (95% CI, 90.0%-96.6%) in those initially diagnosed with cN0 disease and 86.3% (95% CI, 80.6%-92.1%) in those initially diagnosed as cN1/2 disease (P = .12). They concluded that SLNB was acceptable in patients with cN1/2 disease who are downgraded to cN0 after NACT.

Finally, it is well documented that the pCR in invasive lobular carcinomas is around 10% or less.[34] In our series, we indicated NACT in 10 patients affected by lobular carcinoma with two purposes: to start immediately the systemic treatment or to reduce the tumoral volume with the aim to perform a conservative breast surgery.

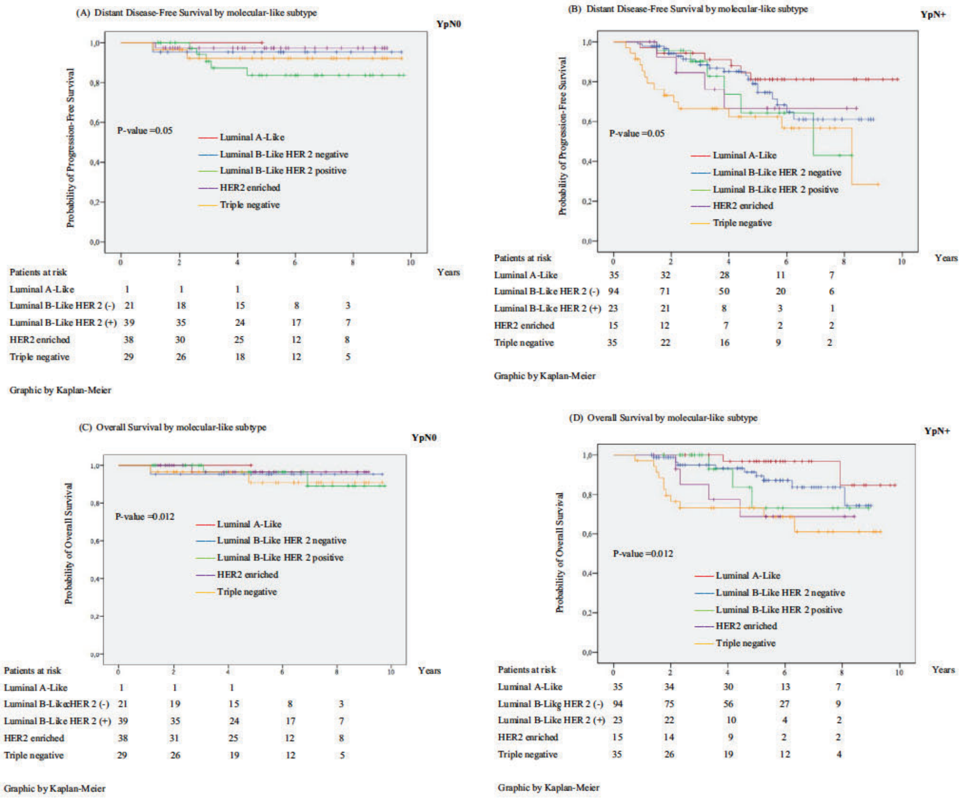


FIGURE 3 DDFS and OS by molecular-like subtype in the ypN0 and ypN+ groups. Patients were divided in two cohorts according to the axillary response: (a) ypN0, which included ypN0 and ypN0(i+); and (b) ypN+, which included ypN1mi to ypN3. Abbreviations: DDFS, distant disease-free survival; OS, overall survival

A limitation of our study was the retrospective approach, even though we reduced the risk of bias by selecting all consecutive patients diagnosed and treated with NACT in a single institution. This approach also allowed us to analyze long-term outcomes, which uncovered significant differences when the OS and DDFS (Figures 1-3) were compared between the ypN0/N0(i+) and ypN+ groups after 61 months. In contrast to the FNAC study,[9] patients affected by ypN0(i+) were also considered to be ypN0 because both groups had similar DDFS and OS rates (Figure 2). Our data indicate that patients with ypN0(i+) disease have an excellent prognosis and may not require ALND. In contrast, the retrospective series published by Choi et al [35] showed a worse DDFS in YpN0(i+) patients compared with not metastatic LNs (5-year DDFS: ypT0 ypN0, 92.1%; ypT0 ypN ≥ 0(i+), 68.6%; $P = .036$). Finally, according to our data, when both groups ypN0 and ypN+ were compared by molecular-like subtype strata, the differences in DDFS and OS between subtypes were minimal in patients who were downgraded to ypN0. Therefore, as we have published elsewhere,[36] the response to NACT significantly affected the initially different prognosis of each molecular subtype (Figure 3).

In conclusion; in this cohort of patients with cN+ breast cancer treated with NACT, a nonluminal molecular subtype, a KI-67 level > 30, HER2 overexpression, and complete clinical response emerged as reliable predictors of cases in which ALND can be safely avoided. Patients presenting these factors are candidates fora more targeted axillary approach after NACT.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest except author Miguel Gil who has remuneration by Pfizer, Novartis, Daiichi, and Roche.

AUTHOR CONTRIBUTIONS

Sergi Fernandez-Gonzalez involved in conceptualization, methodology, formal analysis, data curation,and writing of the manuscript. Catalina Falo and Amparo Garcia-Tejedor involved in conceptualization, methodology, writing, and supervision of the manuscript. Maria J Pla, Anna Guma, Teresa Soler, Andrea Vethencourt, Silvia Vázquez, Maria Eulalia Fernandez-Montoli, Miriam Campos, Sonia Pernas, Miguel Gil, and Jordi Ponce contributed to visualization and supervision of the manuscript. Verdaguer Paula and Diana Nuñez involved in data curation and visualization of the manuscript.

ETHICAL APPROVAL

This study was observational; therefore, no ethical approval was needed.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study to analyze her information.

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ARTÍCULO 5 – *Linfadenectomía en afectación axilar extensa, siempre?*

Can we avoid axillary lymph node dissection in N2 breast cancer patients with chemo-sensitive tumours such as HER2 and TNBC?

Objetivo: Encontrar un grupo de pacientes cN2 o pacientes con una alta carga axilar que se convierten en ypN0 después de la quimioterapia neoadyuvante (NACT) y que puedan beneficiarse de evitar una linfadenectomía.

Métodos: Se realizó un estudio de cohorte observacional retrospectivo con 221 pacientes estadificados clínicamente como N2 o pacientes con al menos 3 ganglios linfáticos sospechosos encontrados por ecografía al diagnóstico. Se analizaron los factores predictivos para ypN0, como la edad, el tamaño tumoral determinado por resonancia magnética, el subtipo histológico, el grado histológico de Nottingham, el subtipo molecular y la invasión vascular. También se evaluaron las respuestas clínicas y radiológicas después de la NACT. Se realizaron análisis univariados y multivariados mediante regresión logística. La supervivencia libre de enfermedad a distancia (DDFS) se calculó en relación con el estado de los ganglios linfáticos axilares después de la NACT.

Resultados: Después de la NACT, 89 pacientes (40.3%) tuvieron una respuesta patológica completa axilar (ypN0) y 132 (59.7%) tuvieron enfermedad axilar residual (ypN+). El subtipo molecular, la expresión de Ki67 y las respuestas clínicas y radiológicas a la NACT fueron los únicos factores independientes asociados con ypN0. La respuesta patológica completa axilar se observó con más frecuencia en tumores HER2 positivo (67.9%) y triple negativo (45.2%) que en los luminales (16.8%) (OR 7.5 y 3.6, respectivamente). La DDFS fue del 88.7% (IC del 95%, 80.7–96.7%) para ypN0 y del 56.2% (IC del 95%, 32.1–80.3%) para ypN+ (p = 0.09).

Conclusiones: En pacientes con cáncer de mama HER2 positivo y triple negativo estadificados como cN2 o con una alta carga axilar antes de la NACT, también podría recomendarse una biopsia del ganglio linfático centinela después de la NACT si hay respuesta clínica y radiológica.

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CLINICAL TRIAL

Can we avoid axillary lymph node dissection in N2 breast cancer patients with chemo-sensitive tumours such as HER2 and TNBC?

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Abstract

Purpose To find a group of cN2 patients or patients with high axillary burden who become ypN0 after neoadjuvant chemotherapy (NACT) and who may benefit from avoiding a lymphadenectomy.

Methods A retrospective observational cohort study was conducted with 221 clinically staged N2 patients or patients with at least 3 suspicious lymph nodes found by ultrasound at diagnosis. The predictive factors for ypN0 analysed were age, MRI-determined tumour size, histological subtype, the Nottingham histologic grade, surrogate molecular subtype, ki-67 and vascular invasion when present. Clinical and radiological responses after NACT were also evaluated. Univariate and multivariate analyses by logistic regression were performed. Distant disease-free survival (DDFS) was calculated in relation to the status of the axillary lymph nodes after NACT.

Results After NACT, 89 patients (40.3%) had axillary pathologic complete response (pCR) (ypN0) and 132 (59.7%) had residual axillary disease (ypN+). Molecular surrogate subtype, Ki-67 expression, and the clinical and radiological responses to NACT were the only independent factors associated with ypN0. Axillary pCR was observed more often in HER2-positive and triple-negative tumours than in luminal ones (OR 7.5 and 3.6, respectively). DDFS was 88.7% (95% CI 80.7–96.7%) for ypN0 and 56.2% (95% CI 32.1–80.3%) for ypN+ ($p = 0.09$).

Conclusions In HER2-positive and triple-negative breast cancer patients staged as cN2 or with high axillary burden before NACT, a sentinel lymph node biopsy after NACT could be recommended if there is a clinical and radiological response.

Keywords Neoadjuvant chemotherapy · Sentinel lymph node · Axillary pathologic complete response · Distant disease-free survival · High axillary tumour burden

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Introduction

An axillary lymphadenectomy (ALND) has been the standard surgical approach in clinically node-positive patients. However, this is associated with significant morbidity [1] and there are questions about its benefits in those who achieve axillary pathologic complete response (pCR) after neoadjuvant chemotherapy (NACT) [2]. Sentinel lymph node (SLN) surgery provides reliable information on node staging with less morbidity than ALND for patients with clinically node-negative (cN0) breast cancer [3–5]. However, the use of SLN surgery following NACT in patients with nodal positive disease has been questioned because the available data have reported FNRs ranging from 7 to 25% [6–11]. Therefore, the 2014 American Society of Clinical Oncology recommendations considered the FNR of SLN reported after NACT unacceptable in patients with axillary node involvement [12].

Subsequently, prospective trials have been developed to improve FNR in this setting. In the multicentric SN FNAC trial [13], they found that the FNR was reduced to 8.4% compared with 13.3% if immunohistochemistry had been used. In the Z1071 trial of the American College of Surgeons Oncology Group (ACOSOG) [14,] the overall FNR was 12.6% but it was reduced to 10.8% when mapping with the combination of blue dye and radiolabeled colloid, and to 9.1% by examination of at least 3 SLNs. Similarly, in the multi-institutional French cohort study GANEA2 [15,] the global FNR in pN1 cases was 11.9%, but it was reduced from 19.3 to 7.8% in those cases with more than one SLN analysed. Simultaneously, MD Anderson's group developed a novel surgical technique, the targeted axillary dissection (TAD) [2], which consists of removing the SLNs as well as removing the clipped lymph node, achieving a FNR of 2.0%. A similar technique for locating lymph nodes has been reported from the Netherlands, marking the axillary lymph node with radioactive seed (MARI procedure) [16], with a 7% FNR.

Finally, the 2019 St. Gallen conference panel concluded that, for patients with clinically positive axilla and down staged to a clinically negative after NACT, SLN after NACT might be appropriate. In such instances, the panel proposed that SLN biopsies can be performed instead of ALNDs, provided that three or more SLNs are identified and all are negative or TAD approaches are undertaken including the clipping of positive nodes at diagnosis. However, patients who present with cN2 disease are excluded and should undergo complete axillary dissection, regardless of the response to NACT, and receive regional nodal irradiation [17].

In recent years, the biological characteristics of tumours have become more relevant in refining breast cancer treatment. The pioneering studies on molecular classification by Perou and Sorlie et al. in the 2000s identified five subtypes of invasive breast cancer with differing incidences, survival rates and responses to therapy [18]. HER2-positive tumours and triple-negative breast cancer (TNBC), which are known to have a worse prognostic outcome, present the highest rates of pCR to NACT [19], which promotes disease-free survival [20]. Due to improvements in systemic therapies, pCR rates have increased up to 65% with anti-HER2 therapies in HER2 tumours [21–23] and nearly 60% in TNBC with the addition of carboplatin to the standard anthracycline-taxane combination [24, 25]. Furthermore, promising results have been achieved in trials with immune checkpoint inhibitors [26].

Decisions about optimal surgeries, radiation therapy and medical treatments are becoming increasingly tailored based on the initial response to NACT [17]. In the ACOSOG Z1071 trial, the authors stated that the most appropriate candidates for SLN surgery may be those with the highest likelihood of nodal response and the lowest likelihood of residual nodal disease and those with normalization of the nodal architecture on an ultrasound scan [14].

In a previous study, we found that Her2, TNBC and radiologic complete response in the breast were independent predictive factors for axillary pCR (ypN0). Therefore, patients meeting these criteria could be suitable for ALND omission and be offered TAD procedures [27]. In that study, cN2 patients represented only 9% of the sample, but their ypN0 rates were similar to those of cN1 patients (33.3% vs 39.5%, $p = 0.49$).

The aim of the present study was to focus on cN2 patients or those with high axillary burden to determine whether they could also benefit from avoiding ALND after NACT, despite the high axillary tumour burden. The predictive factors for ypN0 in this selected group of patients were evaluated to identify a group who could avoid ALNDs after NACT.

Materials and methods

A retrospective observational cohort study was conducted at the University Hospital of Bellvitge-Institut Català d'Oncologia with 221 clinically staged N2 patients or patients with at least 3 suspicious lymph nodes found by ultrasound at diagnosis. From June 2008 to December 2019, all consecutive patients treated with NACT at our institution, referred from our area of influence as a third-level university hospital, who met all the inclusion criteria, were recorded.

Patient selection

Patients were required to meet all of the following eligibility criteria to participate in the study: (1) have biopsy or cytology-proven axillary nodal metastasis; (2) present a clinically staged N2 disease or at least 3 suspicious lymph nodes found by ultrasound at diagnosis; (3) receive NACT before surgery according to our multidisciplinary committee; and (4) complete ALND after NACT. We excluded patients with fewer than 3 suspicious lymph nodes, those presenting cN3 disease, patients undergoing neoadjuvant endocrine therapy, or patients with local recurrences and metastatic tumours. To homogenize the sample, cN3 and cN1 patients with less than 3 suspicious lymph nodes were excluded, especially those cN1 patients in whom SLN was already accepted after NACT. Conventional endocrine therapy has been estimated to be ineffective in achieving lymph node pCR [28, 29], so SLN should be avoided in cN+ patients after this therapy.

Treatment and cohorts

NACT included anthracyclines followed by taxanes over a total duration of 6 months, with trastuzumab and, since 2015, pertuzumab also provided to patients with HER2-positive tumours. Mammography, ultrasound and magnetic resonance imaging (MRI) were carried out pre- and post-NACT for the radiological evaluation of the response. Surgery was performed by 4 gynaecologist and 3 plastic surgeons, 3 to 4 weeks after the last cycle of NACT (breast conservation or mastectomy when appropriate, with axillary dissection). Patients were divided into two cohorts based on the axillary pathologic response: (1) **ypN0** (including ypN0i+) and (2) **ypN+** (ypN1mi-ypN3).

Radiation therapy (RT) was administered to the breast or chest wall according to our institutional protocol in all the cases after breast-conserving surgery or mastectomy. Nodal RT was also given in all cases due to the high axillary burden at diagnosis.

Recorded variables

Data were collected by AG, SF and CF from medical records, including radiology reports, and pathology reports. The predictive factors for ypN0 analysed were age, the TNM stage, number of suspicious lymph nodes found by ultrasound, tumour size determined by MRI, histological subtype, the Nottingham histologic grade, vascular invasion, the presence of tumour-infiltrating lymphocytes (TILs), hormonal receptors, Ki-67 expression and molecular surrogate subtype at the diagnostic core biopsy obtained before NACT, and the clinical and radiological response after NACT. The evaluation of the clinical and radiological responses was performed according to the criteria of the World Health Organization [30], by the clinician and the radiologist before knowing the final pathological result, taking into account the calliper measurements in each cycle, a radiological assessment at 3 months, and mammography, ultrasound and MRI of the breast before surgery, as part of the standard tumour board.

Definitions

High axillary burden was considered when cN2 by clinical examination according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual [31] or cN1 with at least 3 suspicious lymph nodes by ultrasound. According to the cortical morphological features described by Bedi [32], types 4, 5 and 6 were considered as suspicious lymph nodes. Generalized lobulated hypoechoic cortex in type 4, focal hypoechoic cortical lobulation in type 5, and totally hypoechoic node with no hilum in type 6. The number of suspicious lymph nodes was collected mainly from axillary ultrasound and MRI when necessary.

Hormonal receptor (HR) status was defined as positive when at least 10% of the tumour nuclei stained positively for it. The Ki-67 proliferative index was grouped as $>$ or $<$ 30% based on our ROC curve results (data not shown). HER2-positive status was defined as an immunohistochemistry overexpression of 3+ or a fluorescence in situ hybridisation (FISH) amplification according to international consensus guidelines [33]. Immunohistochemical staining was used to classify the tumour samples into three surrogate molecular subtypes based on HR status and HER2 overexpression: (a) HR+HER2− (HR-positive and HER2-negative); (b) HER2+ (HER2-positive tumours regardless of the HR status); and (c) TNBC (HR- and HER2-negative) [34–36].

Evaluation of the clinical and radiological responses was grouped according to the criteria of the World Health Organization [30] as (a) complete response; (b) partial response; and (c) no response (including stable disease or progression). A complete clinical and radiological response was defined as an absence of all evidence of the tumour in the breast and lymph nodes. Partial response was defined as $\geq$ 50% reduction in the perpendicular diameters of the measurable lesion(s), without progression of any of the lesions or appearance of any new disease. Stable disease was defined as no change or a decrease in tumour size that was insufficient to qualify as a partial remission. Progression of disease was defined as a 25% increase in size of (any) tumour and/or the appearance of new lesions.

Ethical approval

Informed consent was waived because of the retrospective nature of this observational study. The data of the patients were anonymized for the purposes of this analysis. The confidential information of the patients was protected according national normative. This paper has been revised for its publication by the Research Ethics Committee of Bellvitge University Hospital.

Statistical analysis

Categorical variables are presented as the number of cases and proportions, while continuous variables following a normal distribution are presented as means and standard deviations (SD). Differences between the groups were analysed by Chi-square test or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. Logistic regression analysis was used in the multivariate analysis to assess the association of the significant predictive factors with ypN0. Odds ratio (OR) and 95% confidence interval (CI) were calculated. The level of statistical significance was arbitrarily set at 5%. Statistical analyses were performed using SPSS version 23.0.

Distant disease-free survival (DDFS) was defined as the time from the start of NACT until the distant recurrence of disease, second primary invasive cancer, or death due to any cause. Breast cancer-specific survival (BCSS) was calculated from the start date of the NACT until death from breast cancer. Kaplan–Meier survival curves were obtained and the differences assessed using the log-rank test. Patients without events were censored at the time of the last follow-up. DDFS and BCSS curves were obtained in relation to the status of the axilla after NACT, which was grouped as ypN0 or ypN+.

Results

From June 2008 to December 2019, 842 breast cancer patients were treated with NACT in our institution. In this period, 532 (63%) had positive lymph nodes at diagnosis and 221 (26%) met all the inclusion criteria of our study (see flow chart in Fig. 1). Table 1 shows the patient and tumour characteristics of our sample at diagnosis and the clinical and radiological responses before surgery. After NACT, 89 patients (40.3%) had axillary pCR (ypN0) and 132 (59.7%) had residual axillary disease (ypN+). Table 2 shows the nodal pathologic response after NACT in all the categories.

The predictive factors for ypN0 as assessed with the univariate and multivariate analyses are described in Table 3. The Nottingham histologic grade and the presence of TILs were significant only in the univariate analyses. The molecular surrogate subtype, Ki-67 expression, and the clinical and radiological response to NACT were the only independent factors associated with ypN0. Patients with HER2+ tumours achieved complete response in the axillary lymph nodes 7.5 times more often than those with luminal tumours, while TNBC patients achieved this response 3.6 times more often.

Fig. 1 Flow chart diagram

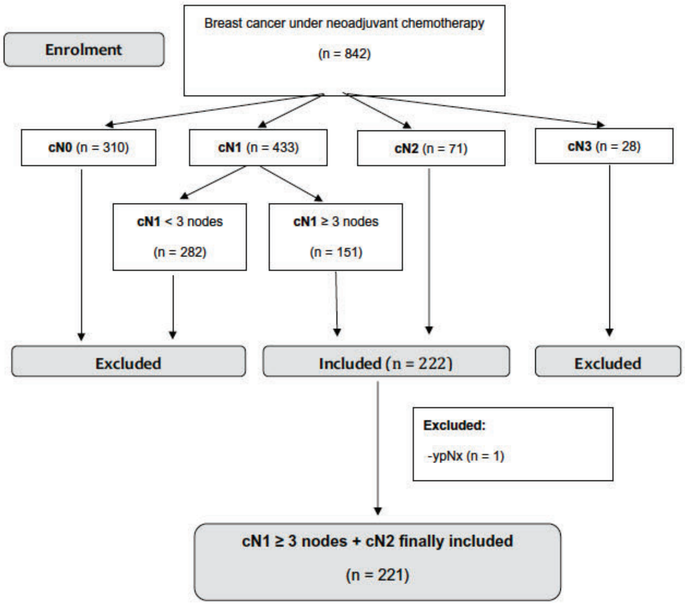


Table 1 Baseline patient and tumour characteristics as well as the clinical-radiological response before surgery

	Mean (SD)	No of patients (%)
Age, years	56.8 (13.8)	221
cT		
0		6 (2.7)
1		17 (7.7)
2		101 (45.7)
3		46 (20.8)
4		51 (23.1)
cN		
cN1		151 (68.3)
cN2		70 (31.7)
No. of suspicious lymph nodes		
< 5		197 (76.5)
≥ 5		24 (23.5)
MRI tumour size, mm	43.4 (24)	215[b]
Histology		
Ductal		205 (92.8)
Lobular		7 (3.2)
Others		7 (3.2)
Not evaluable[a]		2 (0.9)
Nottingham grade		
1		13 (5.9)
2		92 (41.6)
3		114 (51.6)
Not evaluable[a]		2 (0.9)
Ki-67		
≤ 30		83 (37.6)
> 30		138 (62.4)
Molecular subtype		
HR+ HER2(−)		101 (45.7)
HER2		78 (35.3)
Triple-negative		42 (19)
Vascular invasion		
Yes		36 (16.3)
No		148 (67)
Not evaluable		37 (16.7)
TILs		
Yes		96 (43.4)
No		95 (43)
Not evaluable		30 (13.6)
Clinical-radiological response		
Complete		60 (27.1)
Partial > 50%		110 (49.8)
No response		51 (23.1)

SD, standard deviation; %, percentage of patients; cN, clinical axillary nodes; MRI, magnetic resonance image; HR, hormonal receptor; TILs, *tumour-infiltrating lymphocytes*

[a] Histological and Nottingham grades were not evaluated in two T0N2 patients who had been diagnosed by fine-needle axillary biopsy instead of a core-needle biopsy

[b] Tumour size was not evaluable by MRI in six T0 patients

Table 2 Pathological response in the nodes after NACT

	n = *221*
Pathological node response after NACT	
ypN0	86 (38.9%)
ypN0i+	3 (1.4%)
ypN1Mic	4 (1.8%)
ypN1	64 (29%)
ypN2	46 (20.8%)
ypN3	18 (8.1%)

NACT neoadjuvant chemotherapy, *n* number of patients

Patients with cCR showed a complete response in the lymph nodes that was 4.8 times more frequent than that observed in cases without a response in the breast. Even a partial clinical-radiological response increased the axillary response 2.5 times more.

The median follow-up was 36 months, ranging from 23 months in quartile 1 to 62 months in quartile 3. Survival curves according to axillary response are shown in Fig. 2. Axillary pCR was associated with better overall DDFS and BCSS although the differences were not statistically significant. DDFS was 88.7% (95% CI 80.7–96.7%) for ypN0 and 56.2% (95% CI 32.1–80.3%) for ypN+ ($p = 0.09$), while BCSS was 92.7% (95% CI 85.6–99.9%) for ypN0 and 59.3% (95% CI 23–95.6%) for ypN+ ($p = 0.2$).

Discussion

In the current study, in a selected group of women with high axillary burden before NACT, ypN0 was achieved in 40% of the patients, 68% in HER2–positive cases and 45% in TNBC cases. However, according to international guidelines, these patients were surgically overtreated with the lymphadenectomy. The main strength of this study is to focus exclusively on cN2+ patients or patients with more than 3 suspicious lymph nodes at diagnosis because these patients are underrepresented in the SLN literature.

Targeted axillary dissection (TAD) is the preferred technique after NACT in cN1 patients. This includes an SLN biopsy and the selective localisation and removal of clipped nodes, which has been reported to have a false-negative rate of 2% [2]. In that report, 45% of the patients had 3 or more suspicious nodes before NACT. Therefore, if SLN biopsies are accepted in N1 patients, why are they not in some N2 patients with cCR after NACT?

Patients with clinically node-positive breast cancer often receive NACT, which can eradicate nodal disease in 40% to 75% of patients [35, 37–39]. Despite this high rate of nodal pCR, standard practice includes ALND in N2 patients or in patients with more than 2 suspicious lymph nodes found

Table 3 Predictive factors for ypN0. Univariate and Multivariate analyses

	Univariate analyses			Multivariate analyses*		
	YpN0 ($n = 89$)	YpN+ ($n = 132$)	p value	OR	95% CI	p value
Age (years), mean ± DS	55 ± 14	58 ± 14	0.14			
cT at diagnosis n (%)			0.89			
T0	2 (33.3%)	4 (66.7%)				
T1	8 (47.1%)	9 (52.9%)				
T2	42 (41.6%)	59 (58.4%)				
T3	16 (34.8%)	30 (65.2%)				
T4	21 (41.2%)	30 (58.8%)				
cN at diagnosis			0.73			
N1 ≥ 3 lymph nodes	62 (41.1%)	89 (58.9%)				
N2	27 (38,6%)	43 (61.4%)				
N of suspicious lymph nodes			0.19			
< 5 lymph nodes	76 (38.6%)	121 (61.4%)				
≥ 5 lymph nodes	13 (54.2%)	11 (45.8%)				
Radiological size (mm), mean ± DS	41.2 ± 23.7	44.9 ± 24.5	0.27			
Histological subtype (%)			0.37			
Invasive ductal carcinoma	84 (41%)	121 (59%)				
Invasive lobular carcinoma	1 (14,3%)	6 (85,7%)				
Others**	3	4				
Nottingham grade (%)			< 0.001			
G1	1 (6.7%)	14 (93.3%)				
G2	27 (29.3%)	65 (70.7%)				
G3	60 (53.1%)	53 (46.9%)				
Ki-67			< 0.001			
$< 30\%$	17 (20.5%)	66 (79.5%)		Ref.		
$\geq 30\%$	72 (52.2%)	66 (47.8%)		2.8	1.3–6.3	0.01
Biologic subtype			< 0.001			< 0.001
HR+Her2–	17 (16.8%)	84 (83.2%)		Ref.		
Her2+	53 (67.9%)	25 (32.1%)		7.5	3.4–16.8	< 0.001
Triple negative	19 (45.2%)	23 (54.8%)		3.6	1.4–8.9	0.007
Vascular invasion			0.36			
Yes	15 (41.7%)	21 (58.3%)				
Not	59 (39.9%)	89 (60.1%)				
TILs						
Yes	49 (51%)	47 (49%)	0.001			
Not	24 (25.3%)	71 (74.7)				
Clinical and radiological response			< 0.001			0.01
Complete response	37 (61.7%)	23 (38.3%)		4.8	1.7–13.8	0.004
Partial response $> 50\%$	43 (39.1%)	67 (60.9%)		2.5	0.9–6.5	0.06
No response	9 (17.6%)	42 (82.4%)		Ref.		

Multivariate analyses included all the significant variables identified by the previously performed univariate analyses

Data are presented as mean ± SD, median with range or n (%) and were analysed using Student's t-test

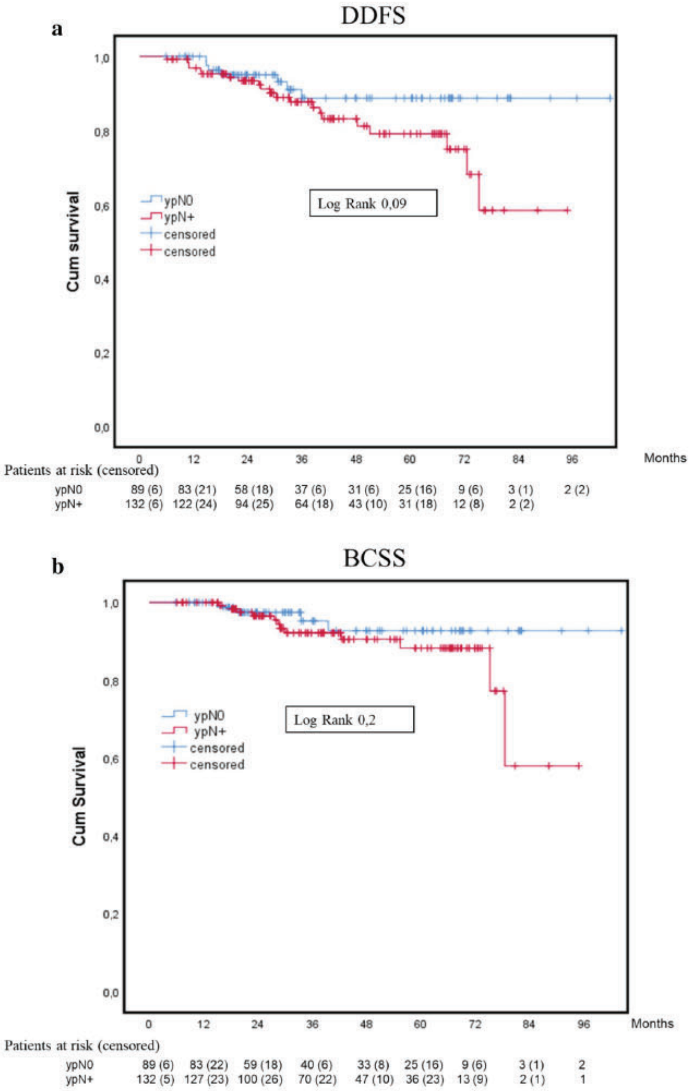
YpN0 includes ypN0 and ypN0(i+)

YpN+ includes ypN1–N3

Percentages are given per row (risk factor between ypN0 vs ypN+)

N number of cases, *OR* odds ratio, *CI* confidence interval, *TILs* tumour-infiltrating lymphocytes

Fig. 2 **a** Distant disease-free survival (DDFS) and **b** breast cancer-specific survival (BCSS) according to the axillary response



by ultrasound at diagnosis. However, it is very unlikely that extensive axillary surgery in patients without residual nodal disease improves their prognosis. In addition, ALND is associated with lymphedema in approximately one out of five patients treated for breast cancer, which is increased to one out of four when radiotherapy is added because of the initial high axillary burden. This has a significant negative impact on the patient's quality of life [40].

To identify patients who may not require ALND has been problematic. It is well known that breast cancer molecular subtypes respond differently to NACT. Rouzier et al. demonstrated that the highest rates of CR were achieved in the basal-like and Her2 subgroups (45% in both cases), whereas the luminal tumours had a low CR rate of 6% [41]. Concordantly, other studies have found that the rate of ypN0 is 0–29% in luminal tumours, 45–82% in HER2+ tumours and 47–67% in TNBC [19, 35, 37–39]. In our series, we observed similar results, with only 17% of the cases with luminal tumours achieving ypN0 in contrast to 68% of those with HER2+ tumours and 45% of those with TNBC. New therapies could improve these results [24, 26]. We observed that the number of affected lymph nodes pre-NACT was not associated with the final axillary response. Patients with more than 5 suspicious lymph nodes, some with more than 8, presented similar complete responses in their nodes as the others in our series. Thus, axillary response is not related to the number of suspicious lymph nodes at diagnosis and this number should not have any influence on surgical decisions after NACT. Accordingly, our question was why not select these good responders for ALND omission even in cN2 patients?

The main reason for excluding N2 patients from SLN biopsies after NACT were the initial reports of high false-negative rates (FNRs) ranging from 5 to 20% [2, 13, 42, 43]. There was great concern that fibrosis in the lymphatic channels after NACT and the extended lymph node burden could alter lymphatic drainage, thereby increasing the FNR risk [44]. Enokido et al., using the dual technique with a blue dye and radiolabelled colloid agents, found an overall FNR of 16%. Furthermore, the FNR in each clinical subtype was inversely related with the likelihood of pCR: 42.1% in luminal tumours, 16.7% in luminal-HER2 cases, 3.2% in HER2-enriched tumours, and 10.5% in TNBC [43]. However, they had removed more than 2 SLNs in only 14% of the cases. Therefore, their FNRs could have been reduced to 2–9% by removing more than 3 SLNs or using TAD [2, 13, 42, 44]. In our opinion, in patients with cN+ disease, modification of the SLN biopsy technique is needed to minimize the FNR. Therefore, to include all the new techniques, such as TAD and dual-tracer mapping, the removal of more than 2 SLNs might be required.

Furthermore, the clinical and radiological responses in the breast do not always correlate well with the axillary response. In our series, ypN0 was achieved in 62% of the cases with cCR, 39% of the cases with partial response and 18% of the non-responders. In fact, the sensitivity of ultrasound in predicting residual node metastasis has been reported to be higher than that of clinical examinations and MRI/PET in most studies. However, its specificity has been reported to range from 37 to 92% and to depend on the tumour subtype, with the positive predictive value highest for luminal tumours and the negative predictive value highest for TNBC tumours [45]. Kim et al. [46] described a predictive model that incorporated the lymph node status, ultrasound findings, MRI response, and molecular receptor status to estimate the residual axillary LN metastases after NACT in patients with clinically node-positive breast cancer. In that study, the N2 staging was grouped with N3 and considered to be independent predictors of residual axillary LN metastasis. However, axillary pCR was achieved in 43% of the cN2 patients. Although all this information could be used to plan surgical approaches, further investigations are required about the axillary response after NACT.

The main limitations of our study were the lack of an SLN procedure in our series and the retrospective study design. However, we reduced the risk of bias by selecting all consecutive patients diagnosed and treated with NACT at our single institution. Another limitation was the lack of standardized measures to classify a patient to have high axillary tumour burden. The cut-off point was not well established in the number of suspicious lymph nodes in which SLN might be appropriate after NACT. Furthermore, other authors analysed cN2 and cN3 patients together, which makes it difficult to compare our data across different studies.

Based on our results, prospective studies of TAD in N2 patients are required to demonstrate its efficacy after NACT in Her2 and TNBC. This change in the clinical management of these patients could prevent more than 50% of lymphadenectomies, avoiding the possible morbidity of ALND, improving the quality of life and a better working life for patients, as well as reducing the surgical time and the hospital stage and, presumably, no decrease in survival. It is clear that NACT offers the only possibility of avoiding ALND in these patients [44], with prognosis probably associated more with distant metastases (based on other parameters such as the neoadjuvant response index of Rodenhuis et al. [47], the residual cancer burden of Symmnans et al. [34], vascular invasion and nodal downstaging) than with the risk of local regional recurrences.

Conclusion

Due to the knowledge of biological differences between breast cancer tumours, the pCR rates after NACT are currently increasing. Therefore, FNRs in SLN biopsies will reduce in the near future. HER2-positive and TNBC patients with cN2 disease or with high axillary burden before NACT could safely avoid ALND if a clinical and radiological response is achieved. Further prospective studies on SLN biopsies in N2 patients are needed to gain further knowledge.

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Compliance with ethical standards

Conflict of interest All the authors declare that we have no conflict of interest. The authors alone are responsible for the content and writing of the paper.

Ethical approval All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. As a retrospective study, the patient did not receive any specific informed consent for the study. The patients signed the informed consent for the usual procedure.

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Acorde a nuestros estudios, la realización del SLNB post-neoadyuvancia en pacientes sin enfermedad ganglionar al diagnóstico (cN0) ha demostrado obtener las mismas tasas de detección respecto a su realización pre-neoadyuvancia con una significativa reducción de ganglios afectos, lo que permite reducir el número de linfadenectomías realizadas mediante esta estrategia terapéutica. Hemos podido confirmar que esta reducción en la tasa de linfadenectomías no compromete la supervivencia ni a corto ni a largo plazo. Por otra parte, hemos observado que en más del 40% de las pacientes con enfermedad axilar confirmada en el momento del diagnóstico (cN+) y con marcadores de proliferación celular elevados como el Ki67 o con subtipos moleculares no luminales (HER2 positivo y triple negativo), se produce una respuesta axilar completa después de la terapia neoadyuvante, tanto en pacientes cN1 como en cN2 al diagnóstico. Estos hallazgos respaldan la aplicación de la disección axilar selectiva en lugar de la linfadenectomía completa en estos subgrupos de pacientes.

1. Ventajas inmediatas del centinela post-neoadyuvancia

En concreto, hemos demostrado en nuestro primer artículo que, la realización de SLNB post-NAT permite evitar alrededor de un 20% de linfadenectomías en aquellas pacientes con cáncer de mama cN0 en comparación con su realización pre-NAT. Estos datos los hemos consolidado con el último artículo en publicarse cronológicamente al disponer de un mayor seguimiento y mayor número de pacientes que recibieron exclusivamente quimioterapia neoadyuvante. En este último artículo, también hemos confirmado que esta reducción en linfadenectomías no comporta ningún detrimento ni en la supervivencia global ni en la supervivencia libre de enfermedad para las pacientes. Estos resultados han sido evaluados después de una media de seguimiento de 4 años y tras comparar los resultados de ambos grupos mediante metodología de emparejamiento por IPTW.

La positividad del SLNB post-NACT en nuestra serie final, seleccionando pacientes cuyo tratamiento ha sido quimioterapia neoadyuvante, es de 12.5% (25/203) en comparación con el 42.1% (45/107) del grupo pre-NACT, resultados muy consistentes en relación con otros estudios publicados donde el SLNB se realizó en pacientes T2N0 y obtuvieron resultados positivos en el 20.5% y 36.5% post y pre-NACT respectivamente

(165,166). En consecuencia, las pacientes en las que se realiza el SLNB pre-NACT tienen aproximadamente cinco veces más riesgo de obtener un resultado positivo con la consiguiente realización de linfadenectomía axilar y, por tanto, el riesgo de un incremento de secuelas asociadas a esta técnica con un detrimento considerable de su calidad de vida. Datos recientes publicados en la literatura al respecto, demuestran que las pacientes en las que se realizó el centinela en lugar de una linfadenectomía tenían un menor riesgo de: linfedema a 12 meses (OR, 0.33; IC del 95%, 0.23–0.47; $p < 0.0001$), parestesias en extremidad superior (OR, 0.15; IC del 95%, 0.09–0.23; $p < 0.0001$) y entumecimiento del brazo (OR, 0.43; IC del 95%, 0.34–0.54; $p < 0.0001$).

Existen numerosos estudios que no han encontrado diferencias significativas entre la realización del SLNB pre-neoadyuvancia respecto a su realización post-neoadyuvancia en cuanto a la tasa de detección, a la sensibilidad para diagnosticar enfermedad axilar y a la tasa de falsos negativos (167–170). De hecho, un meta-análisis reciente ha reportado una FNR del 7-12% post-NACT (171) vs 10-13% pre-NACT. De igual forma, las tasas de detección del centinela descritas en la literatura con radiocoloide son superiores al 95% para ambas estrategias (168)(171,172). Estos datos también están en consonancia con nuestros resultados al observar una tasa de detección del 97.5% en el grupo SLNB post-NACT vs 100% SLNB pre-NACT. Finalmente, destacar una mayor proporción de linfadenectomías realizadas en el grupo SLNB pre-NAT sin hallar enfermedad residual siendo un total del 58.8% respecto al 25% del grupo post-NAT. Esta menor proporción de linfadenectomías innecesarias junto con la posibilidad de realizar la cirugía de la mama y de la axila en el mismo acto quirúrgico demuestra los grandes beneficios a corto plazo de realizar el SLNB post-neoadyuvancia.

2. Supervivencia en centinela pre y post-neoadyuvancia

Una vez comprobadas las ventajas a corto plazo de la realización del ganglio centinela tras la quimioterapia, es necesario evaluar el impacto en el pronóstico de las pacientes de ambas estrategias. Acorde a nuestro conocimiento, en el artículo más recientemente publicado de esta tesis se presenta el primer diseño de estudio con apareamiento específico mediante IPTW para evaluar la supervivencia global y el periodo libre de enfermedad en las pacientes a las que se realiza el SLNB antes y después de la NACT. Tras el análisis, no hemos observado ningún beneficio en cuanto al pronóstico de las pacientes al realizar SLNB pre-NACT. De hecho, el grupo SLNB post-NACT se asoció incluso a una mejor supervivencia global por cualquier causa de muerte HR 0.21; IC del 95%, (0.07-0.67); (p= 0.009) y una mejor supervivencia libre de enfermedad HR 0.42; IC del 95%, (0.17-1.06); (valor p 0.066) respecto al grupo de SLNB pre-NACT.

Cabe considerar, que al ser dos cohortes secuenciales en el tiempo, quisimos descartar que la mejora con el tiempo del "standard of care" con la adición de nuevos tratamientos en los últimos años tales como: 1) la capecitabina en adyuvancia tras la enfermedad residual en los tumores triples negativo (173), 2) la adición del pertuzumab en los esquemas de neoadyuvancia en los tumores HER2 positivo (174), 3) la indicación de trastuzumab-emtansina en aquellas pacientes con tumores HER2 con enfermedad residual tras la neoadyuvanica (113) o 4) la reciente aprobación de la inmunoterapia con Pembrolizumab en los tumores triples negativo (175), pudieran haber influido positivamente en observar mejores resultados oncológicos en la cohorte del SLNB post-NACT. Para reducir este sesgo, realizamos un análisis de sensibilidad excluyendo un total de 44 pacientes del grupo post-NACT (9 pacientes que recibieron capecitabina y 35 que recibieron pertuzumab, ninguna paciente recibió T-DM1 adyuvante o pembrolizumab). Al reanalizar la OS y DFS antes y después del emparejamiento utilizando IPTW y tras la exclusión de estas pacientes, seguimos observando una mejor OS en el grupo post-NACT. Por lo tanto, a pesar de la limitación en nuestro estudio respecto al efecto temporal en la mejora del estándar de tratamiento que podría explicar la mejoría pronóstica en el grupo post-NACT, seguimos pudiendo afirmar que la realización del SLNB post-neoadyuvancia reduce significativamente el número de linfadenectomías axilares sin tener un impacto negativo en la supervivencia.

En cuanto a las recurrencias locales, después de 4 años de seguimiento no hemos observado ninguna recidiva axilar en ninguno de los dos grupos. De manera similar después de 36 meses de seguimiento medio, el estudio GANEA2 informó de solo un caso de recurrencia axilar entre 419 pacientes con enfermedad cN0 (176). Curiosamente en nuestra serie, las pacientes con enfermedad mínima residual axilar post-NACT (ypN1mi) han tenido un pronóstico excelente. Probablemente por este motivo no hemos encontrado diferencias estadísticamente significativas entre los subgrupos según su afectación ganglionar post-NACT. Sin embargo, Wong et al. (31) del Dana-Farber Cancer Institute en Boston, analizaron retrospectivamente a 967 pacientes y observaron que las pacientes con SLNypN1mi/i(+) presentaban un peor pronóstico en comparación con aquellas con SLNypN0 tras más de 5 años de seguimiento. Encontraron una disminución proporcional en la supervivencia relacionada con la cantidad de enfermedad residual en los ganglios linfáticos después de la NACT, indicando una supervivencia a 5 años del 88.8%, 82.8%, 79.5% y 77.6%, para ypN0, ypN0(i+), ypN1mic, y ypN1, respectivamente. Estos resultados respaldan otro de los beneficios teóricos de realizar el SLNB post-NACT y es que la evaluación del "downstaging" axilar post-NACT podría ser un predictor pronóstico de la supervivencia y recurrencia local más significativo respecto a su evaluación basal (177). El hecho de no observar estas diferencias en nuestra serie podría explicarse por tener menor tamaño muestral en cuanto a micrometástasis (28/310), por un menor periodo de seguimiento o el mayor impacto del subtipo molecular como factor pronóstico independiente de supervivencia en el cáncer de mama cN0.

En esta línea cabe destacar que el papel de la linfadenectomía en presencia de células tumorales aisladas o una micrometástasis en el SLNB post-NACT está siendo muy debatido en los últimos años. Deberemos esperar a los resultados del estudio NEONOD 2 actualmente en marcha donde se compararán los resultados de pacientes cT1-cT3 y cN+ al diagnóstico que después de neoadyuvancia tengan como resultado: un SLNB negativo (ypN0) vs SLNB con micrometástasis (ypN1mic, hasta 3 ganglios con micrometástasis) (178). Datos del ensayo IBCSG 23-01 (33,34) ya demostraron la ausencia de beneficio clínico en términos de OS o DFS al realizar linfadenectomía axilar en pacientes con cáncer de mama en etapa temprana con ≥ 1 ganglio centinela con micrometástasis sin haber recibido NACT. Este racional de evitar la linfadenectomía en pacientes cN0 y con mínima afectación ganglionar tras la cirugía (pN1mi), fue adoptado en nuestra institución tanto en las pacientes con cirugía primaria como tras la neoadyuvancia, a diferencia de otros centros donde se sigue practicando la linfadenectomía axilar es este último escenario. Recientemente en el último consenso de St. Gallen(179) solo el 39% de los panelistas votaron a favor de realizar ALND para micrometástasis en este subgrupo de pacientes.

En esta línea, mencionar que en el pasado congreso "Sant Antonio Breast Cancer Symposium" 2023 se presentaron los datos del estudio ICARO (OPBC05/EUBREAST-14R) con 694 pacientes estadio T1-T4N0-3 de las cuales 583 presentaban ITCs en el ganglio centinela post-NACT, dichas pacientes fueron aleatorizadas a recibir o no una linfadenectomía axilar completa posterior (180). En aquellas pacientes donde se realizó la ALND se hallaron otros ganglios afectos en un 29.5% de los casos (7.5% macrometástasis, 6.2% micormetástasis y 15.8% ITCs). Sin embargo, destacar que a pesar de estos hallazgos y tras una mediana de seguimiento de 3.2 años, no hubo diferencias significativas en la tasa de recidiva axilar entre el grupo sin linfadenectomía vs el grupo con linfadenectomía (1.1% vs 1.7%, p=0.7, respectivamente), ni en metástasis a distancia (4.6% vs 4.1%, p=0.8, respectivamente). Estos resultados también cuestionan el beneficio de realizar una linfadenectomía axilar en pacientes con células tumorales aisladas en el centinela post-NACT. Como alternativa a la linfadenectomía y con el objetivo de disminuir la morbilidad quirúrgica, la radioterapia axilar está siendo evaluada para demostrar su no-inferioridad respecto a la ALND en términos de DFS y OS en pacientes con SLNB positivo después de la NACT, incluyendo a las pacientes con ganglios afectos tanto por macrometástasis como micrometástasis. En este contexto, tendremos que esperar a los resultados de dos ensayos "on going": A011202 (181) y ADARNAT NCT04889924 (182), este último liderado por nuestro grupo de investigación.

3. Impacto del ganglio centinela post-hormonoterapia

Por otra parte, dado que actualmente hay muy pocos estudios publicados sobre el tratamiento hormonal neoadyuvante y su efecto sobre el abordaje axilar, generalmente se asumen los mismos criterios quirúrgicos que tras la quimioterapia neoadyuvante. Sin embargo, los tumores luminales presentan un comportamiento tumoral particular y su pronóstico es mejor respecto al resto de tumores. La primera de las particularidades que encontramos en nuestro artículo basado en la neoadyuvancia hormonal es la frecuencia similar de encontrar ganglios centinelas positivos post-tratamiento hormonal respecto a las que han recibido quimioterapia. Tras comparar pacientes con SLNB pre-NET vs post-NET observamos una tasa de centinelas positivos similar entre ambos grupos, siendo del 35.7% vs 37% respectivamente, mientras que en la serie de pacientes tratadas con NACT era del 42.1% pre-NACT vs 12.5% post-NACT. Esto indica que la terapia endocrina no parece tener un efecto significativo sobre la enfermedad subclínica de ganglios centinelas positivos. Nuestros resultados son similares a estudios recientes (183) que han tratado de evaluar el "downstaging axilar" en pacientes HR+/HER2- tratadas mediante quimioterapia o tratamiento endocrino. En concreto, se observó una respuesta patológica completa axilar en el 13.9% (19/137 casos) que recibieron NACT vs en el 7.3% (3/41 casos) después de la NET. Por lo tanto, la enfermedad axilar en este subtipo de tumores parece ser resistente a cualquier tratamiento sistémico y con respuestas muy escasas, independientemente de si el tratamiento sistémico administrado es quimioterapia o terapia endocrina.

Tras analizar los resultados de nuestro artículo en relación a la hormonoterapia neoadyuvante, hemos podido confirmar que pese a esta persistencia de positividad tras la terapia hormonal, en la mayoría de las pacientes con RRHH+/HER2- la enfermedad ganglionar no es muy extensa y se suele focalizar únicamente en el ganglio centinela. En nuestra cohorte de 91 pacientes, sólo tres pacientes con macrometástasis en el SLNB (17.6%) tuvieron más de 3 ganglios positivos en el estudio anatomopatológico final. En otra cohorte similar en pacientes cN0 con tumores HR+, Kantor et al. (184) observaron la presencia de ≤ 3 ganglios positivos en el 90% de los pacientes con cN0 después de la NET.

Otro hecho destacable es que la supervivencia de nuestra serie es excelente con una supervivencia global estimada a los 5 años del 92.4%, supervivencia especifica por cáncer de mama del 98.3% y supervivencia libre de enfermedad a distancia del 94.8%. Tampoco hemos encontrado diferencias entre aquellas pacientes con resultado de centinela positivo vs centinela negativo tras la NET en cuanto a la supervivencia libre de enfermedad a distancia (p=0.79), ni en supervivencia global (p=0.5). En consonancia con nuestros resultados, en un estudio publicado sobre la base de Datos Nacional del Cáncer de Estados Unidos (184) tampoco se observaron diferencias significativas en la supervivencia a los 5 años al comparar pacientes con micrometástasis o células tumorales aisladas residuales respecto a aquellas pacientes sin enfermedad residual tras NET. Teniendo en cuenta la limitación que supone un seguimiento sólo a 5 años en los tumores luminales, podríamos deducir que la enfermedad residual axilar post-NET no parece demostrar la misma importancia pronóstica respecto a la enfermedad axilar post-NACT previamente mencionada. Consecuentemente, considerar una "desescalada" en el abordaje axilar de estas pacientes con el objetivo de reducir la morbilidad asociada parece muy razonable, y más teniendo en cuenta que suelen ser de edad más avanzada y con mayor proporción de comorbilidades asociadas que condicionan una mayor mortalidad por otras causas más allá del cáncer de mama. Una muestra de ello es la recomendación de las guías internacionales como la NCCN (185) o el último consenso de St. Gallen (156) donde para pacientes >70 años con tumores HR+/HER2- y cN0, se omita la realización de SLNB.

En esta misma línea, se ha publicado recientemente el estudio SOUND (186), en el que no se han observado diferencias ni en supervivencia ni tasa de recurrencias en pacientes con tumores T1N0, con ecografía axilar negativa al diagnóstico, preferentemente luminales, en las que se realizó la técnica de ganglio centinela (n=708) respecto aquellas en las que no se realizó ningún abordaje ganglionar (n=697). Estos resultados pioneros, ponen de manifiesto que en las pacientes con estas características probablemente se podría evitar la realización del SLNB sin impactar en el pronóstico. Sin embargo, son necesarios más estudios prospectivos para la estandarización del manejo quirúrgico axilar tras hormonoterapia en pacientes HR+/HER2- en función de factores pronóstico que tengan un mayor impacto en la supervivencia. Un ejemplo de ello fue el desarrollo del PEPI score (187) que clasifica a las pacientes en 3 grupos de riesgo de recidiva tras considerar en la pieza quirúrgica el pT, pN, el Ki67 y la expresión del receptor de estrógenos. La validación de dicho modelo sobre las pacientes del estudio IMPACT (188) abrió la puerta a la investigación sobre la aplicación de dicho modelo en otras cohortes. De hecho, en nuestros resultados encontramos la evaluación del PEPI score en 77 pacientes, de las cuales 20 (26%) fueron clasificadas en el grupo de peor pronóstico con la consiguiente administración de quimioterapia en 16/20 (4 pacientes fueron excluidas debido a comorbilidades asociadas).

En esta línea de búsqueda de biomarcadores pronóstico en el contexto de hormonoterapia, cabe destacar el estudio fase III de hormonoterapia perioperatoria POETIC (189) donde se aleatorizaron pacientes con tumores RRHH+ a recibir 14 días de hormonoterapia neoadyuvante a la cirugía respecto a no recibirla. A pesar de no demostrarse ningún beneficio de la hormonoterapia perioperatoria en cuanto a supervivencia, sí que se observó que aquellas pacientes RRHH+/HER2- con un Ki67 basal < 10% y que lo mantenían bajo tras la hormonoterapia perioperatoria mostraban un pronóstico excelente con un riesgo de recidiva a 5 años del 4.3%. Mientras que dentro del grupo de pacientes con un Ki67 basal >10%, en aquellas en las que el Ki67 bajó < 10% tenían un pronóstico mejor que las pacientes en que persistía un Ki67 post-cirugía >10%, (riesgo de recidiva a 5 años de 8.4% vs 21.5% respectivamente), recomendando en este último grupo un cambio de estrategia en la adyuvancia quimioterapia o inclusión en ensayo clínico. A pesar de que en nuestra serie el 27.6% de las pacientes obtuvieron un Ki67≥10%, no hemos podido reproducir estos resultados debido al escaso número de eventos. Sin embargo, sí que hemos podido observar una leve tendencia a un mayor número de recidivas en estas pacientes en comparación con el grupo de pacientes con Ki67<10%. Esperamos confirmar estos resultados en futuros estudios donde dispongamos de una cohorte mayor y un periodo de seguimiento más prolongado.

4. Factores predictores de respuesta axilar

Por otra parte, en cuanto a la investigación sobre los factores pronóstico en las pacientes con enfermedad axilar al diagnóstico (cN+) que reciben quimioterapia neoadyuvante, la respuesta patológica completa (pCR, ausencia de células malignas residuales en el lecho del tumor primario y axilar) ha demostrado ser el de mayor impacto (190). De ahí que obtener una pCR tras neoadyuvancia sea un objetivo principal del tratamiento. En consecuencia, dos de los artículos de esta tesis tuvieron como objetivo demostrar aquellos factores predictores de respuesta axilar a la quimioterapia con el consiguiente impacto en el pronóstico de las pacientes. Tras analizar las 331 pacientes cN+ tratadas con NACT en nuestra serie, hemos observado que el 38.8% no tenía enfermedad residual axilar (pCR) en la linfadenectomía post-NACT y por lo tanto, se podría haber evitado la disección axilar completa. Además, hemos confirmado que las pacientes con respuesta patológica axilar completa (ypN0) mantienen un pronóstico excelente observando una OS del 96.3% a 4 años para ypN0 vs el 85.9% en ypN1, p=0.003. Finalmente, hemos identificado cuatro factores predictores independientes de la respuesta patológica completa axilar: 1) el subtipo molecular subrogado, 2) el estado de HER2, 3) el nivel de Ki67 y 4) la respuesta clínica. Como veremos posteriormente, todos estos factores se comportan de forma similar tanto en las pacientes cN1 como en las pacientes con mayor carga tumoral axilar al diagnóstico (cN2).

A continuación desarrollaremos cada uno de estos factores independientes de forma más detallada:

a) Receptores hormonales y expresión de HER2

Los tumores con receptores hormonales negativos y los tumores con sobre-expresión de HER2 han demostrado ser los más sensibles a la quimioterapia observando en nuestra serie, una tasa de respuesta patológica completa (pCR) con una OR de 4.15 en los triple negativo y OR de 2.6 para los HER2 frente al resto de subtipos de cáncer de mama. Estos hallazgos, son consistentes con lo reportado en otros trabajos. En el estudio GEPARDUO (191) donde se analizaron los resultados de 913 pacientes (50.5% cN+ y 49.5% cN0) tras recibir NACT (Doxorubicina y Ciclofosfamida seguida de Docetaxel), el estatus hormonal negativo también demostró ser predictor para pCR con una OR de 3.23. Además, se observó una respuesta completa tanto axilar como mamaria en el 22.8% de los tumores con receptores negativos respecto el 6.2% cuando estos eran positivos. En nuestra serie, hemos observado unas cifras incluso superiores de respuestas patológicas completas axilares siendo del 45.3% en los tumores triples negativo y del 71.7% en los HER2. Estos resultados refuerzan el hecho que la sobre-expresión de HER2 también ha de ser considerada como un factor predictor robusto de respuesta axilar a la quimioterapia.

En la misma línea, en el estudio ACOSOG Z1071 (192) donde evaluaron los resultados de 756 pacientes cN+ que recibieron NACT, la tasa global de pCR en axila y mama fue del 28%, observándose en mayor proporción en los tumores triple negativo con un 38.2% y en el 45.4% de los HER2+. Además, observaron que en pacientes con estos subtipos moleculares se realizó en una mayor proporción la cirugía conservadora de la mama demostrando así, el impacto que puede tener el subtipo molecular en cuanto al planteamiento de cirugía mamaria y axilar post-neoadyuvancia. En contrapartida, también demostraron ser los tumores de peor pronóstico especialmente en aquellas pacientes con persistencia de enfermedad axilar tras la neoadyuvancia (ypN+). Hecho que también hemos podido corroborar en nuestra serie siendo los dos subtipos de cáncer de mama con peor supervivencia global dentro de las 202 pacientes ypN+ .

b) Ki67

Tras considerar los RRHH y el HER2 como primer y segundo factor predictor, el tercero de los factores relacionado de manera independiente con la respuesta patológica completa fue el Ki67. Acorde a nuestros resultados, el 52.1% de las pacientes con Ki67 > 30% obtuvieron ypN0 respecto al 20% de las pacientes con Ki67 < 30%. Gracias al diseño de una curva ROC (gráfica no mostrada en el artículo), pudimos establecer que el umbral del 30% representaba el punto de corte de mayor discriminación para la respuesta axilar completa demostrando una OR de 1.98 (p=0.014). En el momento de la publicación de nuestro segundo artículo donde revelábamos este dato, no existían otros artículos que defendieran dicho punto de corte del Ki67 en relación con la respuesta patológica axilar completa. En su lugar, Resende et al. (193) encontraron que un Ki67 ≥ 50% predecía una respuesta completa clínica en la mama con una OR 2.00 y tanto en la mama como en la axila con una OR 1.67. En pacientes con cáncer de mama en estadio clínico II o III, Wang et al. (194) también observaron que las tasas de pCR fueron significativamente más altas entre pacientes con niveles de Ki67 > 40% en comparación con < 40%, con tasas de pCR del 33.3% y 8.1%, respectivamente ($p < 0.001$). Hay que considerar que hasta la fecha, la valoración del Ki67 es muy variable dependiendo del laboratorio en el que se realice. Tanto es así, que se ha recomendado utilizar rangos específicos independientes para cada uno de los centros en base a la mediana de Ki67 hallada en cada laboratorio. Tal es la dificultad de establecer un umbral clínicamente relevante, que el International Ki67 in Breast Cancer Working Group (IKWG) publicó un consenso en 2021 sobre la recomendación de usar Ki67< 5% o > 30% para el manejo clínico (21), cuyo valor es concordante con nuestros resultados respecto a mayor pCR cuando el Ki67 es > 30%. Concluyendo al igual que nosotros que, para la mayoría de los tumores, un mayor índice de proliferación conllevaría una mejor respuesta a la quimioterapia.

c) Respuesta clínica

El cuarto factor predictor de respuesta axilar completa patológica fue la respuesta clínica a la neoadyuvancia. Cabe destacar que en nuestra serie observamos ypN0 en el 70% de los pacientes con respuesta clínica completa y en el 30% de las pacientes con respuesta clínica parcial. Esta relación entre respuesta clínica y respuesta patológica fue independiente de la carga tumoral inicial, a destacar que, el 38% de las pacientes con ≥ 3 ganglios linfáticos axilares sospechosos antes del tratamiento lograron una respuesta patológica axilar completa. En consonancia con estos resultados, Galimberti et al. (195) publicaron una supervivencia global del 93.3% en aquellas pacientes inicialmente diagnosticadas con enfermedad cN0 y del 86.3% (IC del 95%, 80.6%-92.1%) en aquellas inicialmente diagnosticadas como enfermedad cN1/2 ($P = .12$). Concluyeron, que el SLNB también era aceptable en pacientes con enfermedad cN1/2 que se reclasificaron como ycN0 después de la quimioterapia neoadyuvante. Por lo tanto, la decisión de ofrecer TAD/SLNB en la enfermedad cN+ debería depender menos del estadio clínico inicial y más del subtipo molecular, el índice de Ki67, el estado de HER2 y la respuesta clínica, especialmente considerando que la linfadenectomía axilar no ha demostrado mejorar el control local ni la supervivencia en las pacientes con respuesta axilar completa.

5. Manejo de las pacientes con elevada carga axilar

Estos resultados motivaron el estudio específico de las 221 pacientes de nuestra cohorte con ≥ 3 ganglios sospechosos al diagnóstico (cN2 radiológico) donde pudimos confirmar por una parte que el porcentaje de ypN0 era del 40.3%, similar que en las pacientes cN1 (38.8%) y por otra parte, que se reafirmaban los mismos factores predictores de respuesta axilar que en la cohorte cN1. Además, también observamos que las pacientes que lograron una respuesta clínica completa tenían 4.8 veces más probabilidades de tener ypN0, y que incluso en pacientes con respuestas clínicas parciales, se observaron 2.5 veces más probabilidades de ypN0 en comparación con aquellas pacientes sin respuesta alguna a la quimioterapia. En consonancia, Guo et al. (196) tras estudiar a 709 pacientes cN2, también observaron que aquellas pacientes que lograban respuestas completas mamarias tenían un 80% de probabilidad de conseguir una respuesta patológica completa axilar. Por lo tanto, consideramos que estas pacientes también deberían incluirse para una valoración mediante TAD/SLNB después de la NACT, incluso siendo cN2 al diagnóstico. De hecho en el SN FNAC trial (197), considerado como uno de los grandes estudios de validación del SLNB en pacientes cN+, las pacientes cT0-3 cN1-2 recibieron tanto SLNB como ALND post-NACT y observaron una tasa de identificación de SLNB del 87.6% y una FNR del 8.4%. A pesar de que las pacientes cN2 solo fueron 7 en esta serie de 153 pacientes, el VPN fue del 100%. Por el contrario, en el estudio GANEA-2 sólo evaluaron el SLNB post-NACT en pacientes cN0-cN1. Sin embargo, en el estudio ACOSOG Z1071 (192) sí que incluyeron 26 pacientes cN2 con ≥ 2 SLNB y la FNR fue del 0%. Por tanto, teniendo en cuenta que actualmente se utilizan nuevas técnicas de disección axilar dirigida (TAD) que han demostrado obtener unas tasas de falsos negativos inferiores al 5% en pacientes con enfermedad axilar al diagnóstico, demostrar que es seguro evitar la linfadenectomía axilar en pacientes cN2-cN3 es uno de los retos de los próximos estudios prospectivos puesto que hoy en día persiste la recomendación en la práctica clínica de realizar linfadenectomía en estas pacientes (6). Precisamente, destacar que actualmente hay 2 estudios en fase de reclutamiento que han sido diseñados para resolver este enigma: el estudio TAXIS (198) y el estudio de validación del TAD en tumores localmente avanzados tras neoadyuvancia (NCT05763641) (199). El estudio TAXIS diseñado en pacientes con enfermedad axilar al diagnóstico (cN1-N3), pretende demostrar la no-inferioridad de realizar únicamente la exéresis del SLNB junto a la exéresis de ganglios palpables (procedimiento conocido como TAS, tailored axillary surgery) en el grupo experimental respecto a la TAS junto con linfadenectomía en el grupo control (incluye pacientes tanto de cirugía primaria como tras neoadyuvancia). El segundo estudio que precisamente está liderado por nuestro equipo de investigación, consiste en un estudio aleatorizado y multicéntrico para validar el TAD en tumores localmente avanzados cN2 tras neoadyuvancia (NCT05763641).

6. Relevancia y proyecciones futuras de esta tesis

Por tanto, consideramos que esta tesis puede inspirar en primer lugar, a seguir con la investigación en cuestiones relacionadas con disminuir el número de linfadenectomías axilares manteniendo la seguridad oncológica y, por tanto, reducir los efectos adversos secundarios de este procedimiento sin ningún detrimento en la supervivencia. Así lo demuestran dos estudios prospectivos aleatorizados multicéntricos en marcha que pretenden evaluar la no-inferioridad de la radioterapia axilar respecto a la linfadenectomía en términos de DFS y OS en pacientes con SLNB positivo después de la NACT, incluyendo a las pacientes con ganglios afectos tanto por macrometásasis como micrometástasis. Actualmente en fase de reclutamiento encontramos el estudio ADARNAT NCT04889924 (182) liderado por nuestro grupo de investigación y el estudio A011202 (181) del grupo americano Alliance. Derivado de esta tesis también surgió la necesidad de elaborar un estudio prospectivo exclusivo de N2, mencionado anteriormente. En el campo de la hormonoterapia neoadyuvante, dado el excelente pronóstico de las pacientes con RRHH+ y valorando el menor impacto en el pronóstico del resultado del centinela, se podrían diseñar estudios futuros para considerar una "desescalada" en el abordaje axilar de estas pacientes con el objetivo de reducir la morbilidad asociada. Sin embargo, hacen falta más datos centrados exclusivamente en este grupo de pacientes y con mayor seguimiento para obtener datos más robustos. Finalmente destacar que esta tesis también ha servido para confirmar la seguridad oncológica que se le presuponía a la realización del SLNB post-NACT en comparación con su realización pre-NACT en las pacientes sin enfermedad ganglionar axilar. A pesar de las limitaciones referidas anteriormente, hemos podido demostrar que la técnica del SLNB post-NACT reduce la tasa de linfadenectomías sin impactar negativamente en el pronóstico de las pacientes, por lo que nuestros resultados nos conducen a recomendar la substitución del SLNB pre-NACT a favor de su realización post-NACT.

Tras 6 años de investigación desde la publicación del primer artículo, aquí presentamos las conclusiones de la presente tesis:

1) En pacientes con cáncer de mama sin afectación ganglionar al diagnóstico, la biopsia selectiva del ganglio centinela practicada tras la quimioterapia neoadyuvante reduce más de 3 veces la probabilidad de realizar una linfadenectomía axilar en comparación a su realización previa a la quimioterapia. Sin embargo, esta reducción en linfadenectomías no impacta negativamente en el pronóstico ni a corto ni a medio plazo puesto que se observó una supervivencia global tras 4 de seguimiento del 95.7% en las pacientes con centinela post-quimioterapia respecto al 88.4% en el grupo pre-quimioterapia. Por tanto, sería apropiado considerar el reemplazo de la práctica clínica del ganglio centinela antes de la quimioterapia neoadyuvante a favor de su realización post-tratamiento en este subgrupo de pacientes.

2) En pacientes con cáncer de mama con receptores de estrógeno positivos y HER2 negativo sin afectación ganglionar inicial tratadas con hormonoterapia neoadyuvante, la positividad del ganglio centinela se observó en un tercio de las pacientes independientemente de que su realización sea anterior o posterior al inicio del tratamiento. Además, hemos observado un pronóstico muy favorable con una supervivencia global entorno al 90% tanto en las pacientes con centinela positivo como negativo; por tanto, la afectación axilar no es un factor determinante en el pronóstico de este subgrupo de pacientes.

3) Los factores predictores de respuesta patológica axilar completa tras la quimioterapia neoadyuvante en las pacientes con afectación ganglionar al diagnóstico son: la negatividad de los receptores hormonales, la positividad de HER2, un índice de proliferación elevado definido como un Ki67 mayor del 30% y obtener una respuesta clínica completa. Estos factores se observan tanto en las pacientes con menor carga tumoral axilar inicial como en las pacientes con tumores localmente avanzados a nivel axilar; por tanto, ambos grupos podrían ser considerados idóneos para la realización de una disección axilar dirigida en lugar de una linfadenectomía axilar completa.

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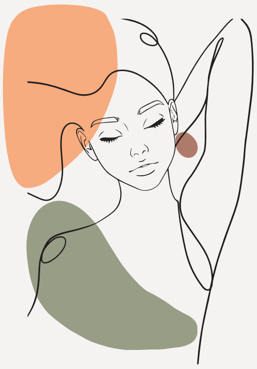
Memoria de tesis doctoral

Impacto de la neoadyuvancia en el abordaje axilar en pacientes con cáncer de mama



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