LA ECOGRAFÍA INTRAOPERATORIA COMO TÉCNICA PARA GUIAR Y REDUCIR LA CIRUGÍA AXILAR EN LOS PACIENTES CON CÁNCER DE MAMA DESPUÉS DE TRATAMIENTO SISTÉMICO PREOPERATORIO

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Tesis doctoral por compendio de artículos

Universitat Autònoma de Barcelona

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Índice

Resumen 5
English abstract 6
Introducción 8
PAPEL DEL TRATAMIENTO SISTÉMICO PRIMARIO (TSP) EN CÁNCER DE MAMA 9
Evolución histórica 9
Indicaciones 9
Objetivos 10
Esquemas de tratamiento neoadyuvante 12
MANEJO AXILAR TRAS TSP 13
Valoración clínica de la axila 13
Axila Clínicamente Negativa (cN0) 14
Axila Clínicamente Positiva (cN+) 16
Hipótesis y objetivos 26
Hipótesis 27
Objetivos 27
Publicaciones 28
1ª publicación 29
Resumen y discusión de 1ª publicación 39
Cirugía mamaria 39
Cirugía axilar 40
Pronóstico 41
2ª publicación 43
Resumen y discusión de 2ª publicación 51
Respuesta al tratamiento 51
Valoración clínica axila 52
Estadificación quirúrgica axila 53
Pronóstico 54
Manejo axilar 54
Conclusiones 56
Anexos 58
(A) Algoritmo A 59
(B) Algoritmo B. 60
(C) Artículo anexo: descripción TAD guiado por ecografía intraoperatoria. 61
Listado de abreviaturas 70
Referencias bibliográficas 71

Resumen

El estado ganglionar constituye uno de los factores pronósticos más relevantes en cáncer de mama. Durante muchas décadas se consideró la linfadenectomía axilar como el tratamiento imprescindible para el control de la enfermedad a nivel regional. Sin embargo, el conocimiento de la biología tumoral, las mejoras de las pruebas de imagen y, los avances en el tratamiento sistémico, radioterápico y de las técnicas quirúrgicas han hecho que la cirugía axilar sea más personalizada. Se ha reducido la linfadenectomía axilar sin afectar a los resultados oncológicos, reduciendo la morbilidad y mejorando la calidad de vida de los pacientes con cáncer de mama.

Numerosos estudios han demostrado que, en pacientes con estadios iniciales de cáncer de mama, no hay beneficio en extirpar ganglios axilares negativos, y que, en situación de baja carga tumoral en los ganglios axilares, la linfadenectomía no mejora el resultado oncológico. De igual manera, en pacientes con tratamiento sistémico primario (TSP), el incremento en las respuestas patológicas completas ha favorecido la introducción de técnicas innovadoras en la cirugía axilar, facilitando en muchos casos la utilización de la biopsia de ganglio centinela y de la disección axilar dirigida (TAD, Targeted Axillary dissection).

La mejora en los tratamientos sistémicos primarios y las terapias dirigidas (inmunoterapia) ha incrementado las respuestas patológicas completas en los diferentes subtipos moleculares y ha puesto de manifiesto también la importancia de la biología tumoral y la correlación de la respuesta al tratamiento, a la hora de determinar la cirugía de la mama y la axila.

En los pacientes con TSP, la decisión quirúrgica se toma basada en la estadificación inicial antes de la TSP y, en la respuesta clínica y radiológica antes de la cirugía. En función de esta valoración, y según la axila fuera clínicamente positiva o negativa al diagnóstico, las diferentes técnicas quirúrgicas para la cirugía axilar se evalúan. En esta tesis, se presenta la validación quirúrgica y oncológica de una técnica innovadora para la cirugía axilar en pacientes con cáncer de mama después de TSP. Esta técnica consiste en la utilización de la ecografía intraoperatoria para guiar la cirugía axilar y realizar la disección axilar dirigida adaptada a cada paciente en función de las características tumorales y las características de las pacientes. La cirugía en el cáncer de mama seguirá evolucionando con los resultados de los diferentes ensayos clínicos que permitirán optimizar la cirugía mejorando los resultados oncológicos y reduciendo la morbilidad de los tratamientos.

En esta tesis se pone de manifiesto que, en las pacientes con cáncer de mama, la interrelación de los diferentes tratamientos en el manejo multidisciplinar del cáncer de mama consigue los mejores resultados oncológicos

English abstract

Nodal status is one of the most important prognostic factors in breast cancer. For many decades, axillary lymphadenectomy was considered the essential treatment for regional disease control. However, knowledge of tumor biology, improvements in imaging and advances in systemic treatment, radiotherapy and surgical techniques have made axillary surgery more personalized. Axillary lymphadenectomy has been spared without compromising oncological outcomes, and with reduced morbidity and improved quality of life for breast cancer patients.

Numerous studies have shown that in patients with early-stage breast cancer, there is no benefit in removing negative axillary nodes, and that in low tumor burden in the axillary nodes, lymphadenectomy does not improve oncological outcome. Similarly, in patients with primary systemic treatment (PST), the increased rate of complete pathological responses has favored the

introduction of innovative techniques in axillary surgery, facilitating the use of sentinel node biopsy and targeted axillary dissection (TAD) in many cases.

Improved primary systemic treatments and targeted therapies (immunotherapy) have increased the number of complete pathological responses in the different molecular subtypes and have also highlighted the importance of tumor biology and correlation with treatment response in determining breast and axillary surgery.

In patients with PST, the surgical decision is based on the initial staging prior to PST and the clinical and radiological response prior to surgery. Based on this assessment, and depending on whether the axilla was clinically positive or negative at diagnosis, different axillary surgical techniques may be evaluated. This thesis presents the surgical and oncological validation of an innovative technique for axillary surgery in breast cancer patients after PST. This technique consists of the use of intraoperative ultrasound to guide axillary surgery and to perform a targeted axillary dissection adapted to each patient according to tumor and patient characteristics. Breast cancer surgery will continue to evolve with the results of the various clinical trials, which will make possible to optimize surgery, improve oncological outcomes and reduce treatment morbidity.

This work shows that the best oncological outcomes in breast cancer patients are achieved by combining different treatments in a multidisciplinary breast cancer management approach.

Introducción

PAPEL DEL TRATAMIENTO SISTÉMICO PRIMARIO (TSP) EN CÁNCER DE MAMA

El cáncer de mama es una enfermedad con una historia natural de larga evolución cuya mortalidad viene dada por las metástasis a distancia más que por la enfermedad local. Por ese motivo, incluso un tratamiento local agresivo parece ser insuficiente para lograr una supervivencia a largo plazo en los casos en que ya existe diseminación micrometastásica a distancia en el momento del diagnóstico.

Evolución histórica

En los años '70, los primeros ensayos clínicos en cáncer de mama conducidos por Bernard Fisher revelaron una supervivencia a los 10 años de tan sólo un 25% en las pacientes con afectación ganglionar, a pesar de haber recibido una cirugía radical [1]. Esto fue el origen para la búsqueda de nuevos tratamientos sistémicos en forma de quimioterapia [2] y hormonoterapia [3], que demostraron en estos estudios pioneros mejorar el pronóstico de estas pacientes, especialmente aquellas con peor pronóstico con afectación ganglionar. En la misma época, en modelos experimentales murinos se demostró como el uso de adriamicina administrada antes de la cirugía conseguía la remisión completa de las células malignas mamarias trasplantadas a los ratones en un 80% de los casos y, adicionalmente, se confirmó como una buena respuesta del tumor primario se relacionaba estrechamente con una buena respuesta de la metástasis a distancia [4].

Una década más tarde, en los años '80, se iniciaron los primeros ensayos no aleatorizados en humanos con TSP con el objetivo principal de reconvertir la cirugía de mastectomía en cirugía conservadora, en una época en que la mastectomía solía ser el tratamiento estándar [5,6]. En los años '90, tuvieron lugar dos grandes estudios aleatorizados fase 3, NSABP B-18 y NSABP B-27, los cuáles demostraron la ausencia de diferencias en supervivencia libre de enfermedad (SLE) y supervivencia global (SG) entre pacientes que recibían la quimioterapia preoperatoria o postoperatoria. Además, en el primero de ellos NSABP B-18, obtuvieron otras conclusiones de interés; por un lado, la tasa de cirugía conservadora fue significativamente mayor en el grupo de neoadyuvancia, y por otro lado, el lograr una respuesta patológica completa se asociaba a un mejor pronóstico global. De hecho, existía una tendencia a favor de una mejor SLE y SG tras quimioterapia preoperatoria en mujeres menores de 50 años [7]. En el subsiguiente ensayo NSABP B-27, sin demostrar un beneficio en supervivencia entre quimioterapia pre- y posquirúrgica, se confirmó un beneficio significativo en términos de SLE y SG de hasta un 20% en aquellas pacientes que lograban una respuesta patológica completa (pCR) tras tratamiento neoadyuvante y, el hecho de añadir al esquema preoperatorio el docetaxel al AC se mejoraba de forma significativa la tasa de pCR [8].

Todo esto ha contribuido a la tendencia al alza del uso de TSP en los últimos años, pasando del 4% en 2010 al 17% en 2015, según la National Cancer Database (NCDB) [9].

Indicaciones

El TSP se ha convertido no sólo en un tratamiento estándar de los tumores inoperables o localmente avanzados (incluyendo el cáncer de mama inflamatorio), sino también de tumores pequeños (cT1c; 1.5 cm-<2cm) y subtipos agresivos de cáncer de mama (subtipos triple negativo y HER2+), donde se ha observado la mayor tasa de respuesta. En términos generales, la TSP debe

plantearse en todos aquellos casos en que se plantea sin dudas el mismo tratamiento sistémico en el contexto adyuvante, en casos que puede favorecer la cirugía más conservadora o, en aquellos casos, en que se disponga de una plataforma genómica que sugiera que existe beneficio de la terapia citotóxica.

Objetivos

Los tres principales objetivos de la TSP son:

1.- Facilitar el tratamiento quirúrgico. En los tumores inicialmente operables pero con indicación clara de quimioterapia adyuvante, diferir la cirugía a después de realizar el mismo tratamiento sistémico preoperatoriamente, favorece poder confirmar histológicamente la buena respuesta tumoral a los tratamientos sistémicos recibidos dejando la paciente libre de enfermedad y, favorecer la cirugía más conservadora de la mama y la axila. En pacientes muy seleccionadas, en un futuro quizás no hacer cirugía ante respuestas excepcionales [10,11].

Por otro lado, en los tumores inicialmente inoperables o localmente avanzados, el TSP puede facilitar las opciones quirúrgicas del paciente, permitiendo una reducción en la extensión de la cirugía, facilitando el rescate quirúrgico en tumores inicialmente inoperables o, reconvirtiendo una mastectomía a una cirugía conservadora en los tumores localmente avanzados y, indirectamente mejorando el resultado cosmético de la cirugía.

2.- Determinar la respuesta al TSP. Numerosos estudios han demostrado que la pCR constituye un marcador subrogado de supervivencia a largo plazo de cáncer de mama, especialmente en tumores triple negativo y HER2 positivo [12,13]. De hecho, se acepta la pCR como un criterio de valoración relevante por las autoridades reguladoras, como la FDA ("Food and Drug Administration") de EEUU, a la hora de aprobar nuevos agentes terapéuticos.

Sin embargo, existe una gran variabilidad en la probabilidad y validez pronóstica de lograr una pCR entre los diferentes subtipos intrínsecos de cáncer de mama; mientras la pCR es un importante factor pronóstico en pacientes con subtipos de alto riesgo (triple negativo y HER2 no luminal), otros subtipos de bajo riesgo (luminal A/B) pueden tener un pronóstico favorable a pesar de presentar enfermedad residual tras la cirugía. Dada la heterogeneidad en la respuesta y con el objetivo de poder cuantificar la respuesta a la quimioterapia, el grupo de MD Anderson diseñó un sistema de puntuación llamado *"Residual Cancer Burden (RCB)"*, con capacidad predictiva del riesgo de recaída a 10 años en función de su valor simplificado en 4 categorías (RCB 0,I,II,III; donde 0 corresponde a pCR) [14,15]. Esta herramienta incluso es capaz de estratificar el riesgo en función de la enfermedad residual entre los 4 diferentes subtipos biológicos (triple negativo, RRHH negativo/HER2 negativo, RRHH positivo/HER2 positivo y RRHH positivo/HER2 negativo) [16].

En cuanto a la definición de pCR, durante años existió una controversia en la definición a la hora de incluir en la definición la presencia de carcinoma ductal in situ (CDIS) en la mama o la respuesta a nivel ganglionar. Se ha demostrado que la presencia de carcinoma ductal in situ residual no parece impactar en valor pronóstico de una pCR [17], en cambio, la respuesta ganglionar completa si tiene un valor pronóstico relevante,

independientemente del tipo de respuesta en mama [18]. Por lo tanto, la definición más aceptada como pCR es ypT0/is ypN0 [12].

3.- Personalizar el tratamiento en función de la respuesta al TSP. Ante el creciente número de pacientes que reciben TSP se plantea un nuevo desafío terapéutico, en concreto en aquellas pacientes en las que queda enfermedad residual tras un tratamiento sistémico primario con múltiples agentes. Estas pacientes con pronóstico desfavorable, sobre todo en aquellos casos con extensa enfermedad residual o progresión de la enfermedad durante el tratamiento sistémico, se debe buscar una alternativa terapéutica para revertir el curso de la enfermedad.

En los últimos años diversos estudios fase III aleatorizados han demostrado que la incorporación de nuevos tratamientos adyuvantes tras la cirugía, en pacientes con enfermedad residual, mejoran la SLE y, en algunos casos, la SG. Incluso esta nueva ventana terapéutica ha contribuido en la ampliación de la recomendación de TSP a tumores más pequeños (cT1c) triple negativos y HER2 positivos, ante el potencial beneficio de tratamientos adicionales en adyuvancia en caso de no lograr una pCR.

Los estudios más importantes y con resultados alentadores son: en tumores triple negativo añadiendo capecitabina *(Create-X trial [19]),* en tumores HER2 añadiendo T-DM1 *(Katherine trial [20]),* pacientes portadoras de mutación BRCA1/2 añadiendo olaparib *(OlympiA trial [21]).* Por otro lado, en el caso de tumores luminal HER2 negativo con enfermedad residual no parece que se beneficien de la introducción de inhibidores de CDK4/6 *(Penelope B trial [22])*, a pesar de sí haberse demostrado beneficio la adición en adyuvancia de abemaciclib a la hormonoterapia convencional en estadios iniciales de alto riesgo (≥ 4 ganglios positivos o 1-3 ganglios positivos asociado a G3 o tamaño tumoral ≥ 5cm) *(MonarchE [23]).*

Otra de las ventajas de la TSP son la obtención de tiempo para poder completar un estudio genético, ya que los pacientes con cáncer de mama y portadoras de una mutación BRCA pueden beneficiarse de tratamientos loco-regionales y sistémicos diferentes que mejoran su pronóstico. Una reciente publicación ha demostrado que pacientes portadoras de mutación en BRCA se pueden beneficiar de la adición de olaparib adyuvante para prolongar su SLE [21]. Que la mastectomía bilateral en estadios iniciales de cáncer de mama disminuya el riesgo de morir por cáncer de mama en comparación con la realización exclusivamente de la mastectomía unilateral continúa siendo un tema controvertido [24]. No obstante, la ventaja temporal que ofrece un TSP para la obtención del resultado del estudio genético no es tal con la aparición de sistemas integrados de test genético rápido con obtención de resultados en 2-3 semanas (fast-track), que también parecen tener influencia en la elección del tipo de cirugía por parte de la paciente [25].

Asimismo, el TSP hace que la paciente sea testigo en primera persona de la involución del tumor teniendo un efecto psicológico positivo, ofreciendo un mayor tiempo a la paciente para aceptar su diagnóstico reduciendo así su distrés emocional perioperatorio [26].

Por el contrario, el TSP también puede tener aspectos negativos. La incertidumbre en el manejo terapéutico en caso que se produzca una progresión de la enfermedad bajo el tratamiento neoadyuvante (incidencia <5% casos)[27], potencial riesgo de sobre- o infratratamiento quirúrgico

por una sobre- o subestimación de la enfermedad residual por las pruebas de imagen de reestadificación tras finalizar el TSP [28].

Esquemas de tratamiento neoadyuvante

Prácticamente todas las modalidades de tratamiento sistémico (quimioterapia, hormonoterapia y terapia dirigida) utilizados en adyuvancia se han demostrado útiles en la TSP [29-36]. En el caso de la quimioterapia se recomienda administrar todo el tratamiento planificado inicialmente sin interrupciones y sin dividirlo entre antes y después de la cirugía, siempre y cuando no exista progresión de enfermedad, con el objeto de aumentar la probabilidad de lograr una pCR [37] y lograr reducir la incidencia de recaída local [8].

MANEJO AXILAR TRAS TSP

El estado de los ganglios linfáticos regionales ha constituido la variable clínico-patológica con mayor significado pronóstico en términos de supervivencia en cáncer de mama [38]. La controversia acerca del impacto de la linfadenectomía en la supervivencia de los pacientes con cáncer de mama se despejó después de los resultados del ensayo NSBAP B-04, que demostró que en las pacientes con cáncer de mama sin afectación axilar clínica por palpación (cN0), el tipo de manejo de la axila ya fuese en forma de linfadenectomía axilar o radioterapia axilar en comparación con no hacer tratamiento activo de la axila hasta la aparición de recaída, se traducía en una diferencia significativa en la incidencia de recaídas axilares a 10 años del 1.4%, 3.1% o 18%, respectivamente. No obstante, dichas diferencias en el control regional de la enfermedad no tuvieron un impacto en la supervivencia, siendo la supervivencia en los 3 grupos similar [39]. Una de las críticas a este ensayo B-04 fue la falta de potencia estadística para descartar una ventaja en términos de supervivencia asociada a la linfadenectomía axilar (LDNA). Un meta-análisis intentó mostrar un beneficio medio de supervivencia del 5.4% con la linfadenectomía en pacientes con axila clínicamente negativa y tumores operables (estadios I-II) durante el tiempo de seguimiento (5-10 años), pero con la importante limitación de la ausencia de uso de tratamientos sistémicos, en contraste a la práctica clínica actual [40].

Uno de los efectos secundarios de la LDNA que más impacta en la calidad de vida de los pacientes, es el riesgo inherente de linfedema de la extremidad superior que llega a manifestarse hasta en un 10%-25% de las mujeres tras este tipo de cirugía [41-44]. Esta tasa de linfedema puede llegar a un 25%- 40% si se asocia radioterapia axilar con LDNA [43], pero se reduce a un 15% tras RDT axilar exclusivamente [41,42] o, menos del 5% en caso de realizarse la biopsia de ganglio centinela exclusivamente [44,45]. En términos de rigidez de hombro y molestias en el brazo también parece que cuanto menor sea el intervencionismo sobre la axila, menor es su frecuencia de aparición [46].

Valoración clínica de la axila

La valoración de la axila en pacientes con cáncer de mama se realiza mediante exploración física y ecografía axilar. Se puede asociar a punción aspiración con aguja fina (PAAF) o a biopsia con aguja gruesa (BAG) en caso de ganglios axilares sospechosos.

Exploración física

La palpación manual de la axila no es sensible ni fiable para determinar el estado de los ganglios linfáticos axilares, porque los ganglios linfáticos metastásicos no suelen ser palpables y los ganglios linfáticos reactivos pueden confundirse con metástasis. El valor predictivo positivo de la palpación clínica se estima que puede oscilar entre el 61-84%, mientras que, en pacientes sin palpación axilar sospechosa entre el 26-40% se presenta enfermedad metastásica en los ganglios axilares [47,48].

Ecografía axilar

La ecografía constituye la herramienta no invasiva de cribado más efectiva para la detección de metástasis a nivel ganglionar, aunque su eficacia es operador dependiente. Para confirmar la sospecha de un ganglio anormal se practica una PAAF o BAG ecoguiados. La ecografía patológica se correlaciona muy bien con la identificación de pacientes con elevada carga de enfermedad en la axila (≥ 3 ganglios metastásicos, afectación extranodal o afectación hasta nivel III) [49].

Todas aquellas pacientes con indicación de TSP, necesitan una ecografía axilar de estadificación, ya que el estado ganglionar puede impactar en la decisión quirúrgica [50] y sistémica [33]. En un subgrupo del ensayo Z1071, la ecografía axilar posneoadyuvancia predecía con mayor precisión qué pacientes presentarían ganglios positivos en el estudio anatomo-patológico definitivo (72% vs 57% en caso de ecografía axilar negativa), al igual que predecían casos con mayor número de ganglios positivos y mayor tamaño de las metástasis ganglionares. En caso de que la ecografía axilar no visualizará ganglios sospechosos antes de proceder a la LDNA, dicha prueba asociada a la biopsia de ganglio centinela (GC) hubiese logrado reducir la tasa de falsos negativos (TFN) del GC del 12.6% a 9.8% [51].

Otra indicación de la ecografía axilar, como se describirá más adelante, es la posibilidad de realizar el marcaje del ganglio inicialmente confirmado como metastásico, en concreto a las pacientes con carga de enfermedad limitada en la axila (cN1). Este marcaje, que puede ser de diferentes materiales, facilita la localización y exéresis tras finalizar el TSP. En caso de asociarse la exéresis del ganglio marcado a la biopsia del ganglio centinela, este procedimiento es conocido como disección axilar dirigida (TAD "Targeted Axillary Dissecction"). Su ventaja respecto al GC exclusivo es la menor tasa de falsos negativos, cuya explicación viene dada por la no coincidencia del ganglio centinela con el ganglio marcado en un 23% de los casos [50,52].

Axila Clínicamente Negativa (cN0)

Incluye a todos aquellos pacientes con cáncer de mama en que inicialmente no existía evidencia de enfermedad axilar, ni por exploración física ni ecografía axilar, o, el resultado de la PAAF o BAG del ganglio sospechoso resultó negativa.

Momento realización GC

Inicialmente, existió la controversia de cuando debía realizarse el GC, si antes o después del TSP.

La ventaja del GC después de TSP es el ahorro de una posible segunda intervención quirúrgica axilar en caso de GC positivo. Pero la ventaja más relevante es la posibilidad de disminuir el porcentaje de LDNA, dado que un porcentaje de las pacientes negativizarán la axila. Las pacientes sometidas a un GC posTSP tienen mayor probabilidad de presentar un resultado negativo (67% vs 54%; p=0.001) y menor probabilidad de acabar con una LDNA en comparación con GC preTSP (33% vs 45%, p=0.001) [53]. La prevalencia GC positivo en función de su momento de realización, también se relaciona con el estadio tumoral (cT), siendo más frecuente si se realiza antes del TSP (T1: 19.0% vs 12.7%, p= 0.2; T2: 36.5% vs 20.5% p < 0.001; T3: 51.4% vs. 30.4%, p= 0.04) [54].

Por otro lado, la ventaja de proponer su realización antes del TSP es conocer el estado ganglionar inicial, pudiendo incluir esta información en la toma de decisiones del tratamiento loco-regional, especialmente en relación a la radioterapia y cuya indicación tiene implicaciones en el tipo de reconstrucción mamaria tras mastectomía. No obstante, diversos estudios señalan que la respuesta al tratamiento sistémico constituye un factor predictor de mayor peso de recaída loco-regional en comparación con la estadificación preneoadyuvancia [12,55,56]. En caso de GC preTSP positivo, en el ensayo multicéntrico SENTINA [57] el hecho de intentar un segundo GC tras TSP para valoración de respuesta, mostró una tasa de identificación del 61.0% y una tasa de falsos negativos del 51.6%. Incluso en caso de ausencia de ganglios positivos adicionales tras la LDNA, tampoco se podía concluir que había tenido lugar una respuesta completa axilar.

Por todo ello, la guía clínica de la "National Comprehensive Cancer Network (NCCN)" recomienda el uso de GC después de TSP [58].

Validación GC posTSP en cN0

La cirugía axilar posTSP es tan precisa para la estadificación axilar como en preTSP. Tanto en estudios unicéntricos de centros con amplia experiencia en GC tras neoadyuvancia, como en meta-análisis, se han publicado tasas de identificación de GC en pacientes con axila cN0 entre 85% y 97%, y tasas de falsos negativos entre 6% y 12% *(tabla 1)*. Al igual que con la validación del GC en cirugía primaria, existe una curva de aprendizaje en el contexto del GC posTSP, confirmando unos mejores resultados de la técnica con el paso del tiempo, pasando de tasas de identificación GC del 88.9% al 98.1% tras varios años de experiencia [54]. En diversas publicaciones recientes [59], la tasa de identificación del GC posTSP se mantiene en valores altos, similares a los estudios de validación del GC en cirugía primaria de estadios iniciales cáncer de mama sin TSP [60], confirmando la idea de que el tratamiento sistémico no interfiere en la anatomía del drenaje linfático. La tasa de falsos negativos se ve influenciada por la tasa de identificación de GC, cuanto mayor es esta menor es la TFN [61], y por el número de ganglios centinelas, siendo la TFN en caso de resecar un único GC o ≥ 2 GCs del 14.3% y 4.3%, respectivamente [62]. En cambio, la TFN no parece verse influenciada por el uso de técnicas de inmunohistoquímica en la evaluación del GC [59,63] ni por el tipo de técnica de marcaje del GC (radioisótopo y/o colorante) [59,63].

Tabla 1. Resultados de diversos estudios para valorar el GC posTSP en pacientes cN0.

Autor	Pacientes cN0 (n)	**Posneoadyuvancia**			**Preneoadyuvancia**		
		Tasa identificación (%)	Tasa falsos negativos (%)	Recaída regional (%)	Tasa identificación (%)	Tasa falsos negativos (%)	Recaída regional (%)
Hunt [54]	3746	97.4%	5.9%	1.2%	98.7%	4.1%	0.9%
Mamoumas (NSABP B-27) [64]	428	85%	11%	N/A			
Classe (GANEA) [65]	195	95%	9%	N/A			
Xing (meta-análisis 2006) [66]	1273	91%	12%	N/A			
Kelly (meta-análisis 2009) [67]	1799	90%	8%	N/A			
Van Deurzen (meta-analisis 2009) [68]	2148	91%	11%	N/A			
Tan (meta-análisis 2011) [63]	449	94%	7%	N/A			
Geng (meta-análisis 2016) [59]	1456	96%	6%	N/A			

Cirugía axilar en función del resultado del GC posTSP

A pesar de la falta de ensayos aleatorizados, actualmente se acepta que pacientes cN0 que reciben TSP y permanecen cN0 se pueden estadificar únicamente con ganglio centinela. El porcentaje de pacientes cN0 en que el GC resulta negativo tras neoadyuvancia es del 79-91%

[54,69], mientras que la tasa de recaída regional es anecdótica, situándose entre 0.2%-1.2% [54,69,70]. En caso de que el GC posTSP resulte positivo, la probabilidad de encontrar ganglios positivos adicionales es del 47% [71], probabilidad mayor que en los ensayos de GC en cirugía primaria como ACOSOG Z0011 y AMAROS [41,72]. Esta probabilidad se mantiene independientemente del tamaño de la metástasis hallada en el GC posTSP (micro o macrometástasis) [73].

En conclusión, en caso de GC posTSP negativo (ypN0), no se precisa completar la LDNA. En caso de no localizarlo o resultado positivo (ypN+) se recomienda completar la LDNA. Actualmente, tampoco existen datos que apoyen una equivalencia entre LDNA y radioterapia axilar en este contexto en particular (cN0-ypN+).

Axila Clínicamente Positiva (cN+)

La axila clínicamente positiva se define como afectación axilar limitada *(cN1),* dicho estadio no viene dado por el número de ganglios sospechosos visualizados por las pruebas de imagen y, se diferencia de otros estadios por la ausencia de ganglios fijos o conglomerado adenopático *(cN2)* o por su localización infra/supraclavicular *(cN3).*

Validación del GC posTSP en axila cN+

Tradicionalmente la presencia de enfermedad axilar en el momento del diagnóstico era indicación directa de proceder a una LDNA tras finalizar el TSP. La razón de intentar un GC posTSP en este grupo de pacientes es poder identificar las pacientes en que se ha negativizado la axila con el tratamiento sistémico, permitiendo así omitir la LDNA y, consecuentemente, disminuir la morbilidad de este tipo de cirugía y mejorar la calidad de vida de estas pacientes.

A falta de seguimiento a largo plazo de las pacientes cN+ con buena respuesta clínica al TSP en las que se ofreció la realización de un GC posTSP, se adoptó inicialmente como valor límite de TFN el 10% para poder validar la técnica, basándose en el diseño de los estudios de GC en cirugía primaria en cN0 [74,75]. No obstante, en el ensayo de validación del GC en cirugía primaria NSABP B-32, dicha asociación entre TFN y recaída axilar no pareció del todo definida, dado que una TFN del 9.8% se tradujo en una tasa de recaída axilar de tan sólo el 0.7% [47]. Incluso en el ensayo ACOSOG Z0011, las pacientes tratadas con cirugía conservadora, radioterapia, tratamiento sistémico y GC positivo sin LDNA en cirugía primaria, a pesar que en un 27% de las pacientes se estimaba que quedaba enfermedad residual axilar no resecada, esto no supuso un detrimento en la supervivencia o en el control loco-regional de la enfermedad [72,76]. Este hecho hace suponer que el tratamiento sistémico contribuye a disminuir el riesgo de recaída regional. En cambio, de qué forma en neoadyuvancia, la TFN y el riesgo de permanecer enfermedad axilar residual resistente al tratamiento sistémico puede influir en las recaídas regionales no está del todo claro.

Existen cuatro grandes estudios prospectivos pioneros que han intentado proporcionar una visión real de la temática. Es importante remarcar que dichos estudios fueron diseñados exclusivamente para valorar el GC en pacientes cN+ tras TSP, pero en ningún caso la seguridad oncológica de dicho procedimiento quirúrgico *(tabla 2)*:

- ACOSOG Z1071 trial [77]. Estudio multicéntrico prospectivo de un único brazo incluyendo 756 pacientes (T0-T4, cN1-2, M0) sometidas a GC posTSP previa realización de LDNA. La tasa de identificación de GC fue del 92.5% con una TFN del 12.6%. En caso de resecar 2 GCs la TFN se situaba en el 21.1%, mientras que se lograba reducir a 9.1% en caso de resecar ≥3 GCs. En los casos en que se usó un doble mapeo del GC (radioisótopo + colorante) la TFN fue del 10.8%.

- SENTINA trial [57]. Estudio multicéntrico prospectivo con cuatro brazos comparando diferentes momentos de realización del GC. En pacientes cN0 con GC preTSP positivo se sometieron a un segundo GC posTSP (brazo B con 360 pacientes) y pacientes cN1-2 con respuesta clínica al TSP se sometieron a GC posTSP seguido de LDNA (brazo C con 592 pacientes). La tasa de identificación y TFN del segundo GC en el brazo B fue del 61% y 52%, respectivamente. En el GC posTSP en el brazo C la tasa de identificación fue del 80.1% y, la TFN fue del 24.3% en caso de encontrar un único GC o <10% en caso de resecar ≥ 3 GCs. Una diferencia significativa en comparación con el ACOSOG Z1071 fue la no obligación de la confirmación patológica de la afectación inicial ganglionar, siendo sólo necesario la sospecha ecográfica.
- SN FNAC study [78]. Estudio que englobó 153 pacientes con confirmación citológica de afectación axilar (cN1-2). La tasa de identificación y la TFN fueron del 87.6% y 9.6%, respectivamente. La introducción de técnicas IHQ para la detección de CTAs (ypN0(+i)) logró disminuir la TFN a 8.4%. Al igual que los estudios previos, el hecho de resecar ≥ 2 GCs lograba una TFN del 4.9%.
- GANEA 2 [70]. Ensayo que englobó 307 pacientes con confirmación citológica de enfermedad axilar (cN1-2). Como mínimo se localizó 1 GC en el 79.5% con una TFN del 11.9%, que disminuía al 7.8% en caso de identificar ≥ 2 GCs. Dado que no se puede predecir el número de GCs, los autores describen un modelo predictivo (AUC de curva ROC=0.834) que estima que el riesgo de ganglios positivos no centinelas es de tan sólo el 3.7%; en aquellos casos con GC negativo independientemente de su número, ausencia de invasión linfo-vascular y enfermedad mamaria residual <5mm.

La conclusión de estos estudios prospectivos es que una técnica estandarizada del GC posTSP es fundamental, siendo recomendable para maximizar la tasa de detección y minimizar la TFN: hacer uso de una doble técnica de marcaje, localizar ≥ 3 GCs y valorar el uso de técnicas de IHC en el estudio anatomo-patológico del GC. La siguiente cuestión es averiguar la frecuencia en que se lograron localizar 3 o más GCs durante el procedimiento en estos ensayos, siendo esta del 34-56% [57,77], asimismo, la media/mediana de ganglios extirpados tampoco superó el umbral de los 3 ganglios [57,78]. Teniendo en cuenta que para disminuir la TFN por debajo de 10% suele ser necesario obtener 3 o más GCs, parecería que la técnica de GC posTSP en este grupo de pacientes no es del todo precisa. Aunque en ninguno de los ensayos se evaluó realizar un sampling ganglionar a ciegas para aumentar el número de GCs, no existe evidencia que ello disminuya la TFN, por lo que no debe convertirse en una recomendación. También es importante recalcar, que el uso de la inmunohistoquímica en el estudio intraoperatorio es técnicamente complejo y, raramente se encuentra disponible en la mayoría de centros sanitarios.

Tabla 2. Resultados de ensayos de evaluación de GC posneoadyuvancia en pacientes inicialmente cN1-2.

	ACOSOG Z1071[77]	**SENTINA[57]**	**SN FNAC[78]**	**GANEA 2 [70]**	**Total**
Nº pacientes	663	592	153	307	1715
Estadio	cT0-4 cN1-2	cN0-1-2	cT0-3 cN1-2	cT1-3 cN0-1-2	-
Tasa detección GC (%)	92.7%	80.1%	87.6%	79.5%	85.0%
TFN global (%)	12.6%	14.2%	13.3%	11.9%	10.5%

TFN marcaje único (%)	20.3%	16.0%	4.9%	N/A	13.7%
TFN doble marcaje (%)	10.8%	8.6%	5.2%	N/A	8.2%
TFN incluyendo ypN0(+i) (%)	8.7%	N/A	8.4%	N/A	8.6%
TFN con 2 GCs (%)	21.1%	18.5%	4.9% (≥2 GCs)	7.8% (≥2 GCs)	-
TFN ≥3 GCs (%)	9%	5%	N/A	N/A	-
Nº GCs	N/A	2.0 (mediana)	2.7 (media)	2.0 (media)	-
GCs ≥3ggs (%)	56.3%	33.9%	N/A	N/A	45.1%

¿Cómo mejorar la precisión dl GC después de TSP en axila cN1?

Una propuesta para mejorar la fiabilidad del GC posTSP surgió del ensayo ACOSOG Z1071. En 141 pacientes del estudio se procedió al marcaje con un clip radiopaco el ganglio inicialmente metastásico antes de iniciar el TSP con posterior confirmación de su extirpación. Tras la cirugía se realizaba una radiografía de los especímenes (ganglio centinela y LDNA). En los casos en que el ganglio centinela coincidía con el ganglio clipado, la tasa de fasos negativos fue del 6.8%. Mientras que en los casos en que el centinela no coincidía con el ganglio clipado (24% de los casos) y radiológicamente ese clip se encontraba en la pieza de LDNA, la tasa de falsos negativos aumentaba hasta el 19.0% [79].

Al mismo tiempo otro grupo holandés describió una nueva técnica que bautizaron como "MARI procedure" probada en 100 sujetos, que consistía en el marcaje del ganglio afecto, pero en este caso con una semilla de yodo radioactivo I^{125}, que se dejaba durante todo el transcurso del TSP, y posteriormente se extirpaba con la ayuda de una gammasonda previo a la realización de la LDNA. El ganglio marcado fue identificado exitosamente en un 97% de los casos y arrojó una tasa de falsos negativos del 7% [80].

El grupo MD Anderson perfeccionó esta técnica acuñando el nombre de disección axilar dirigida (también conocido como **TAD "Targeted Axillary Dissection"**). Este procedimiento implicaba la extirpación del ganglio marcado, en su caso también con una semilla radioactiva, pero a su vez se localizaba y extirpaba el ganglio centinela marcado con doble trazador. En este estudio se vino a confirmar que en un 23% de las ocasiones se tratan de ganglios diferentes. En 85 pacientes en que se realizó el procedimiento TAD seguido de LDNA, se demostró que dicho procedimiento presentaba una TFN de tan sólo un 2.0% [50]. A raíz de este estudio han surgido diferentes modalidades de marcaje y resección del ganglio axilar positivo.

Pero sin duda, con la llegada de nuevos tratamientos sistémicos cada vez más eficaces en la erradicación de la enfermedad axilar, asistiremos a una mejora directamente proporcional en la precisión de las técnicas de estadificación axilar de estas pacientes, al aumentar el número de pCR axilares.

Técnicas de marcaje del ganglio axilar positivo

Clip ecovisible

La aparición de la ecografía intraoperatoria en cirugía mamaria ha demostrado ser una herramienta más precisa y efectiva en comparación con la cirugía guiada por guías metálicas/arpones [81,82] o guiada por palpación [83]. Con la introducción de los marcadores ecovisibles, la ecografía intraoperatoria se ha podido extender a la cirugía conservadora tras TSP

[84]. La ecografía también ha facilitado la programación quirúrgica y reducción de forma significativa de los costes sanitarios relacionados con otras técnicas quirúrgicas [82,85]. Asimismo, se ha publicado que para la adquisición de las competencias necesarias para un uso adecuado de la técnica quirúrgica ecoguiada en cirugía mamaria se precisa de una breve curva de aprendizaje de menos de 10 procedimientos [86], siendo así una técnica de rápida y fácil asimilación por el cirujano.

En 2018 se publicó por primera vez el TAD mediante técnica ecoguiada [52] *(anexo C).* Dicho procedimiento consiste en el uso de un **clip** de titanio incrustado en un polímero de hidrogel que se expande tras absorber agua de su entorno una vez implantado, que a su vez hace que adquiera la propiedad de ser **ecovisible** (HydroMARK™, Devicor Medical Products Inc.). Esta visibilidad perdura durante muchos meses tras su colocación mientras la paciente se somete a TSP [87]. Dicha ecovisibilidad facilita la localización y extirpación del ganglio marcado mediante ecografía intraoperatoria en el momento de realización del TAD. Su gran ventaja radica en la posibilidad de colocar el marcador en el ganglio afecto en el momento del diagnóstico, obviando la necesidad de un proceso separado de localización previa a la cirugía contribuyendo a una mejor experiencia del paciente. Además, este marcador ecovisible es de bajo coste y se trata de un material inerte que puede permanecer de forma indefinida en el cuerpo al no emitir radiación. Por el contrario, sus mayores desventajas son dos: la necesidad de experiencia en ecografía intraoperatoria por parte del cirujano para evitar su extrusión inadvertida y, la pérdida de visibilidad del clip por reabsorción del hidrogel por adelgazamiento de la cortical ganglionar o migración del clip por falta de adherencia a los tejidos circundantes. En este primer estudio de factibilidad se incluyeron 35 pacientes con una tasa de falsos negativos del 4.1% [52] .

Otras técnicas

Se han desarrollado otras técnicas para la realización de TAD tras el TSP. La mayoría de estas técnicas han sido adaptadas a la axila tras una amplia experiencia en la localización de lesiones mamarias.

Describimos algunas de ellas junto a sus ventajas y desventajas *(tabla 3 y 4):*

- Localización con **semillas radioactivas** utiliza un pellet de titanio recubierto de I^{125}. Se considera seguro para la exposición humana (1,85-5,55 MBq)[88]. La manipulación de material radioactivo requiere la aprobación de un Comité de Seguridad Radiológica tras documentar formación y experiencia de todo el personal implicado (cirujanos, radiólogos, patólogos), lo que puede contribuir a aumentar el coste de la aplicación. La Comisión Reguladora Nuclear (NRC) limita el tiempo de permanencia en el paciente a 5-7 días [89]. La semilla se despliega mediante una aguja de 18G bajo guía ecográfica y se localiza durante la cirugía mediante un gammasonda de baja energía para detectar el I^{125} (27 keV). El precio de la semilla es bajo y es posible utilizar la misma sonda y consola utilizadas para la detección del ganglio centinela (Tc-99m), siempre y cuando, esté optimizada para localización de I^{125}. El procedimiento implica un proceso en dos pasos, primero la inserción de un clip en el ganglio metastásico en el momento del diagnóstico y, después, la colocación de una semilla de I^{125} en el ganglio clipado unos pocos días antes de la intervención quirúrgica. Tras la extracción de la semilla, ésta debe almacenarse a largo plazo durante casi 2 años para que se descomponga. La combinación de ganglio centinela y escisión de ganglio clipado han mostrado una tasa de falsos negativos de 2.0% [50]. La principal preocupación de las semillas radioactivas es la radiación del paciente y del personal médico, que parece ser insignificante. Se estima que la dosis residual en la mama tras la resección de un espécimen mamario de 2 cm de diámetro después de la implantación de una semilla de 3,7 MBq daría lugar a una dosis residual máxima en la mama de 2.8cGy (comparable a la de una mamografía de dos incidencias) [88]. Otros inconvenientes son: riesgo de extrusión de la semilla durante la

cirugía cuando la semilla se colocó periféricamente al ganglio o dentro del hidrogel del clip hidrófilo, extravío de la semilla al no poder reposicionarla o extraerla percutáneamente o, pérdida o daño de la semilla durante el procesamiento de la muestra en el laboratorio de patología.

- Localización con **semillas magnéticas** utiliza una pequeño pellet paramagnético libre de radiación de acero inoxidable (Magseed®, Sysmex S.L.) o titanio (Sirius Pintuition®, Sirius Medical Inc.). Han sido aprobados por las autoridades sanitarias para su uso sin restricción de tiempo o hasta 180 días de implantación, respectivamente. La implantación de la semilla se realiza de forma ecoguiada mediante punción y, para su localización en el momento de la cirugía debe usarse una sonda superparamagnética que guía la extracción mediante retroalimentación sonora y visual (Sentimag®, Sysmex o TargetLOC™, Sirius Medical Inc.). En el caso de Magseed® este tiene una estructura acanalada que está diseñada para promover el crecimiento del tejido durante la implantación para evitar su migración. Además, no presentan decaimiento de la señal con el tiempo, lo que permite la colocación de la semilla antes de la cirugía desacoplando los flujos de trabajo de radiología y cirugía. La semilla magnética es visible con ultrasonidos y rayos X, aunque genera un artefacto en las secuencias de RM que puede ocultar la enfermedad axilar residual tras el TSP. También existen limitaciones quirúrgicas, como la necesidad de varias calibraciones de la sonda durante la cirugía y la necesidad de utilizar herramientas poliméricas no magnéticas. En un estudio reciente con Magseed® se demostró la viabilidad del uso de un sistema de localización magnética en la axila, documentando una tasa de identificación de 37 de 38 Magseeds (97%), que se recuperaron con éxito en el quirófano [90].

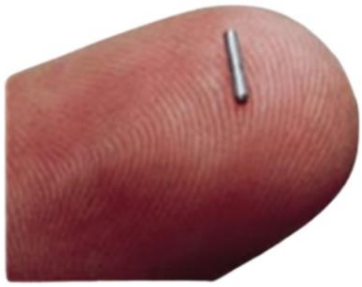
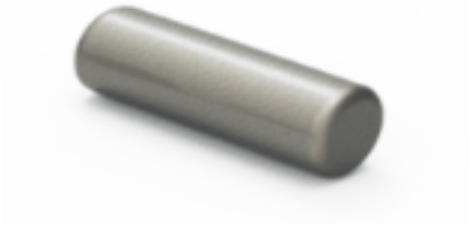
- Localización con **arpón** (Duo System®, Somatex Medical Technologies GmbH) tiene la ventaja de utilizar un material de bajo precio con el que la mayoría de cirujanos de mama están habituados a trabajar. El arpón se visualiza fácilmente saliendo de la piel y facilita reseguir su recorrido hasta el ganglio de interés durante la cirugía. El arpón puede colocarse bajo guía ecográfica, mamográfica, guiado por resonancia magnética o tomografía computarizada. Este procedimiento supone un problema de programación de agendas, dado que la colocación del arpón por el radiólogo y su retirada por el cirujano deben realizarse el mismo día, lo que provoca retrasos en el quirófano. Los radiólogos tienen también preocupación por riesgo de lesionar estructuras axilares críticas como los vasos axilares, el plexo braquial o la punción de estructuras más profundas (pleura, corazón) [91,92]. La migración axilar del arpón podría ser más pronunciada en la axila que en la mama, debido al movimiento del brazo o a la contracción muscular, dificultando la localización del ganglio clipado. En un estudio con 24 pacientes con nódulo clipado visible tras TSP se logró una retirada selectiva del arpón señalando el ganglio clipado en el 71% (17/24) de las pacientes. Los autores concluyeron que el arpón se desplazó debido al movimiento del paciente tras la inserción antes de la intervención o a la manipulación del cirujano durante el procedimiento quirúrgico [93]. Posteriormente, otros grupos han presentado series de pacientes con tasas de localización y extirpación exitosa en el 92% (23/25) de los pacientes, mediante uso del arpón en la localización prequirúrgica del ganglio marcado [94].

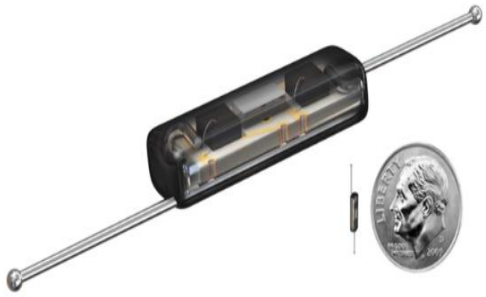
- Localización basada en el **tatuaje del ganglio mediante una suspensión de carbono** (Spot Ex®, GI Supply Inc)**.** Es una técnica barata que consiste en inyectar la tinta en la corteza del ganglio linfático en el momento del diagnóstico vía punción ecoguiada. La experiencia reportada confirma que es una técnica con tasas de identificación excelentes del 100% [95,96]. A pesar de ello, existen algunas dudas importantes en relación a esta técnica como son: el riesgo de confundir los ganglios tatuados con ganglios teñidos

debido a la migración de la tinta de eventuales tatuajes cutáneos de la paciente o, confundirlo con un posible ganglio centinela en caso de haber utilizado un colorante (azul isosulfán o azul patente). También existe el riesgo de migración de la tinta a ganglios no tatuados o, la no visualización del ganglio tatuado por encontrarse en la profundidad de la axila o haber utilizado un volumen de inyección mínimo.

Otros métodos de marcaje que han demostrado ser útiles hacen uso de dispositivos más sofisticados que se implantan en el ganglio y tras el TSP se pueden localizar de forma muy precisa con la ayuda de sondas específicas. Las tecnologías usadas se fundamentan en radar/infrarojos (SCOUT®, Merit Medical Systems) [97] y radiofrecuencia (LOCalizer™, Hologic Inc.) [98]. El mayor inconveniente de estos es su elevado precio de venta.

Tabla 3. Muestra iconográfica de los diferentes métodos usados en la localización del ganglio metastático.

 **Clip ecovisible** (HydroMARK™)	 **Semilla radioactiva** (I^{125})
 **Semilla magnética** (Magseed®)	 **Semilla magnética** (Sirius Pintuition®)
 **Arpón** (Duo System®)	 **Suspensión de carbón negro** (Spot Ex®)



Reflector radar (Scout®)

Dispositivo radiofrecuencia (LOCalizer™)

Tabla 4. Resultados publicados de las diferentes técnicas utilizadas para TAD.

Autor	Técnica	Producto	Pacientes	Estadios clínicos	Tasa identificación (%)	Tasa falsos negativos (%)
Sisó (ILINA) [52]	Ecografía intraoperatoria	Clip ecovisible (HydroMARK™)	35	cT1-4 cN1	100%	4.1%
Caudle [50]	Medicina nuclear	Semilla radioactiva (I^{125})	85	cT0-4 cN1	96%	2.0%
Greenwood [90]	Paramagnética	Magseed®	35	N/A	97%	N/A
Balasubramian [94]	Arpón	N/A	25	N/A	92%	N/A
Patel [96]	Tatuaje percutáneo	Spot Ex®	47	cT0-4 cN1-3	100%	N/A
Baker [97]	Radar	Scout®	23	Estadio II/III	100%	N/A
Lowes [98]	Radiofrecuencia	LOCalizer™	75	N/A	100%	N/A

Manejo quirúrgico

Pacientes con extensa afectación ganglionar *(cN2 o cN3)* previo inicio de tratamiento (estadios iniciales III), independientemente del tipo de respuesta que hagan en axila, presentan un mayor riesgo de recaída loco-regional a 5 años en comparación con un estadio I/II (10.6% vs 3.2%) [99], siendo estas pacientes las menos indicadas para plantear una reducción de la cirugía axilar. Sin embargo, hasta un 75% de las pacientes cN+ diagnosticadas y tratadas con TSP en la práctica asistencial [100] presentan una carga de enfermedad axilar limitada (cN1), siendo las candidatas ideales para plantear una estadificación quirúrgica axilar menos invasiva que la LDNA.

El manejo axilar en este grupo de pacientes cN+ vendrá dado

por:

- **Desaparición clínica de la enfermedad axilar (ycN0).** Aunque la tendencia actual es plantear un GC contemplando todos los aspectos técnicos para disminuir la TFN, no existe un claro consenso sobre el manejo axilar. En una encuesta realizada en 2022 por la European Breast Cancer Research Association of Surgical Trialists, la cirugía axilar

posneoadyuvancia más común en este grupo de pacientes cN1 que se convierte a ycN0 fue la disección axilar dirigida (TAD) (54%), seguido de GC (21%), la LDNA de niveles I-II (18%), la LDNA de niveles I-III (4%) y la biopsia exclusiva del ganglio marcado (2,5%) [101].

Actualmente, en el ensayo EUBREAST 3 o AXSANA se están recogiendo prospectivamente los datos de diferentes abordajes axilares para definir sus resultados oncológicos y de calidad de vida *(clinicaltrials.gov: NCT04373655).*

- **Persistencia de enfermedad clínica a nivel de la axila (ycN+).** Actualmente se les ofrece una LDNA seguido de radioterapia sobre áreas ganglionares, dado que existe un mayor riesgo de recaída loco-regional y peor supervivencia libre de enfermedad [99,102] .

Pronóstico según el resultado de la respuesta axilar

La presencia de mínima enfermedad residual axilar, ya sea en forma de micrometástasis o células tumorales aisladas, supone persistencia de enfermedad resistente al TSP, que constituye un factor pronóstico importante para supervivencia libre de enfermedad (SLE a 5 años del 87% si ypN0 vs 51% si ypN+) [102,103]. En función del resultado:

- **Confirmación patológica de erradicación de la enfermedad axilar (ypN0).**
  No existen ensayos prospectivos aleatorizados que aporten evidencia robusta en esta situación particular. Pero sí que disponemos de series retrospectivas de pacientes cN1-2 con GC posneoadyuvancia negativo que muestran tasas de recaída axilar del orden de 0.4-2.3% [54,69,104,105], similares al GC preneoadyuvancia [54]. Estos resultados deben someterse a una lectura cautelosa ante posibles factores de confusión, como presencia de una proporción importante de pacientes con tumores especialmente sensibles al TSP (HER2 y TN), uso de radioterapia sobre áreas ganglionares o estadificación axilar en el momento del diagnóstico con PET-TC sin confirmación histológica [105] *(tabla 5).*

Tabla 5. Estimación de la tasa de recaída axilar en pacientes con cN1-2 con GC posTSP (sin TAD).

Autor	**Wong** [69]	**Barrio** [104]	**Kahler-Ribeiro-Fontana** [105]
Pacientes (nº)	132	610	222
Estadio tumoral	cT1-3 cN1-2	cT1-3 cN1	cT1-3 cN1-2
GC negativo (%)	45.5%	38.4%	55.4%
GC exclusivamente (%)	77.3%	38.4%	59.5%
Radioterapia áreas ganglionares (%)	71% GC negativo 100% GC positivo	70% GC negativo exclusivo	23.4%
Recaídas axilares (%)	2.3%	0.4% GC negativo exclusivo	1.8%
Supervivencia libre enfermedad a 5 años (%)	N/A	92.7% GC negativo exclusivo	87.7% sin LDNA 81.3% con LDNA
Tiempo seguimiento (mediana)	36 meses	40 meses	9.2 años

- **Confirmación patológica de persistencia de enfermedad axilar (ypN+).**
  En una revisión de la National Cancer Database (NCDB) que incluyó 12.965 pacientes entre 2012-15 con afectación axilar previo inicio TSP, se reportaron tasas de omisión de LDNA en el 37% de los casos con CTAs y en el 24% de casos con micrometástasis en el ganglio centinela [106]. Una explicación plausible de este suceso, podría ser la suposición que pacientes con excelente respuesta en la mama al tratamiento sistémico (HER2+ y TN), el hecho de presentar una baja carga de enfermedad en el GC, se debía correlacionar con una nula/baja carga de enfermedad residual ganglionar, apoyando la decisión de omitir la LDNA. Estudios retrospectivos llevados a cabo en el Memorial Sloan Kettering Cancer Center han evidenciado que la presencia de micrometástasis o macrometástasis en el GC se relacionan con una probabilidad mayor de encontrar ganglios positivos no centinelas en la axila, con una probabilidad del 64% y 62% [73], respectivamente, el doble que en el contexto de GC en cirugía primaria en pacientes cN0 [72]. En estos estudios, el valor de CTAs en el ganglio centinela para predecir ganglios positivos adicionales no se pudo estimar con exactitud, dado el bajo número de pacientes con tal hallazgo, posiblemente por un infradiagnóstico al no utilizar habitualmente técnicas de IHQ en la evaluación del GC [73,107]. Otro hallazgo relevante, fue que en los casos de no pCR axilar, la probabilidad de hallar ganglios metastásicos en la LDNA continuó siendo alta, independientemente del subtipo biológico, excediendo en todos los subtipos el 40% [107]. En base a estos datos, se debe ser precavido a la hora de proponer la omisión de cirugía tanto en mama como axila, incluso en las pacientes con sospecha de pCR en mama a través de los hallazgos radiológicos o de biopsia mamaria posneoadyuvancia, dado que una baja carga de enfermedad axilar en el GC puede asociarse a una cantidad sustancial de enfermedad axilar.

  En relación al pronóstico de pacientes con persistencia de enfermedad axilar se dispone de datos muy heterogéneos con bajo nivel de evidencia. Según otra revisión del National Cancer Database (NCDB), la omisión de LDNA en este grupo de pacientes se tradujo en un detrimento en la supervivencia. En 1617 pacientes cN1-ypN+ diferenciadas entre tipo de cirugía GC vs LDNA, todas ellas con posterior radioterapia sobre áreas ganglionares, se reportó una supervivencia global a 5 años significativamente inferior en grupo de GC (71% vs 77%, p=0.01) [108]. Tampoco está claro el papel de la radioterapia sobre áreas ganglionares. En una revisión retrospectiva del ensayo ACOSG Z1071 incluyendo 506 pacientes con enfermedad axilar residual tratadas con LDNA y, posteriormente radiación sobre áreas ganglionares a discreción del médico especialista, mostró que la radioterapia no aporta un claro beneficio en el control de recaída loco-regional en pacientes con enfermedad axilar residual (HR 1.80, IC 95% 0.89-3.65), al igual que tampoco impacta en términos de supervivencia global y supervivencia libre de enfermedad [109].

  Se espera que en pocos años se publiquen los esperados resultados de dos grandes ensayos prospectivos multicéntricos que intentarán responder sendas cuestiones: el papel de la radioterapia sobre áreas ganglionares en caso de pCR axilar (NRG 9354 o NSABP B-51; *ClinicalTrials.gov, NCT01872975*) y, la equivalencia entre radioterapia y LDNA para el control loco-regional en caso de no lograr una pCR axilar (Alliance A011202; *ClinicalTrials.gov, NCT01901094*).

Hipótesis y objetivos

Hipótesis

1. La respuesta a los tratamientos sistémicos preoperatorios en cáncer de mama está en función de los subtipos moleculares e influye en las opciones de cirugía axilar post-tratamiento.

2. La utilización de la ecografía intraoperatoria para guiar la cirugía axilar en pacientes con cáncer de mama y tratamiento sistémico preoperatorio es una técnica segura y efectiva.

3. La técnica permite reducir las tasas de linfadenectomía axilar en el grupo de pacientes con cáncer de mama y axila clínicamente positiva que tienen una respuesta patológica completa al TSP.

4. La reducción de la linfadenectomía axilar en este contexto no empeora los resultados oncológicos de las pacientes.

Objetivos

La finalidad de esta tesis por compendio de artículos es aportar nuestra experiencia clínica en poder avanzar en el propósito de reducir la radicalidad de la cirugía axilar y, consecuentemente, mejorar la calidad de vida de las pacientes sin ponerlas en riesgo desde el punto de vista de seguridad oncológica.

Ambos artículos escogidos para este trabajo incluyen pacientes con cáncer de mama tratadas con terapia neoadyuvante, cuya información se ha utilizado para resolver dudas de situaciones concretas en la cirugía de estadificación axilar.

1ª publicación: *Esgueva A, Siso C, Espinosa-Bravo M, et al.* Leveraging the increased rates of pathologic complete response after neoadjuvant treatment in breast cancer to de-escalate surgical treatments. *J Surg Oncol. 2021*

- ¿Se puede diferenciar el manejo quirúrgico axilar en función del subtipo biológico?
- ¿La respuesta patológica de la mama puede guiar la cirugía de la axila?
- El lugar de respuesta patológica completa (mama y/o axila) tiene un impacto pronóstico diferenciado?

2ª publicación: *Siso C, Esgueva A, Rivero J, et al.* Feasibility and safety of targeted axillary dissection guided by intraoperative ultrasound after neoadjuvant treatment. *Eur J Surg Oncol. 2023*

- ¿La técnica de TAD axilar guiado por ecografía intraoperatoria es un procedimiento fiable y reproducible?
- ¿Se puede desescalar en la cirugía axilar de pacientes cN1 con buena respuesta clínica a la TSP?
- ¿Cuál es la mejor estrategia de estadificación axilar en pacientes cN1: LDNA, BGC, exéresis ganglio marcado, TAD axilar?

Publicaciones

1ª publicación

Esgueva A, Siso C, Espinosa-Bravo M, et al.

Leveraging the increased rates of pathologic complete response after neoadjuvant treatment in breast cancer to de-escalate surgical treatments.

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RESEARCH ARTICLE

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Leveraging the increased rates of pathologic complete response after neoadjuvant treatment in breast cancer to de-escalate surgical treatments

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Abstract

Introduction: Breast conservative surgery (BCS) and sentinel lymph node biopsy (SLNB) after neoadjuvant treatment (NAT) is safe and effective for selected patients. This aim of this study is to evaluate the impact of anatomic site of response on outcomes and to assess the real population who may benefit from nonsurgical approaches after NAT.

Material and Methods: From a prospectively maintained database, patients with T1-4 N0-2 breast cancer undergoing NAT were identified. Clinicopathological and survival rates were compared in relation to response and anatomic site of response.

Results: Six hundred and forty-six patients were included in the study. Pathologic complete response (pCR) was an independent factor for BCS and SLN. HER2 positive and TN tumors with cN0 achieving a breast pCR remain ypN0 ($p = .002$). Residual axillary disease was associated with breast residual tumor ($p = .05$) and subtype ($p = .001$). With a median follow up of 35.25 months, patients with any pCR had improved survival when compared with partial response, but not significant differences between pCR, axillary pCR, or breast pCR.

Conclusion: Achieving a pCR increases BCS and SLN. In selected subgroups, sparing any axillary surgery after NAT maybe feasible. In cN+ patients, any pCR was associated with survival, but not the anatomic site of response.

KEYWORDS
breast neoplasms, de-escalation, neoadjuvant therapy, pathologic complete response, survival

1 | INTRODUCTION

Neoadjuvant treatment (NAT) has increasingly being used in early stage breast cancer and the introduction of new effective systemic treatments has changed the surgical approach in this setting. Downsizing the tumor has enabled surgeons to increase rates of breast conserving therapy (BCS),[1,2] and downstaging has enabled to lessen axillary surgery while associating with better prognosis. The controversy on the safety of BCS after NAT reported by the EBCCTC meta-analysis requires careful interpretation.[3] There is no doubt that nowadays, BCS after NAT is performed in a more accurate way than it was performed in some of the randomized clinical trials included in the meta-analysis.[4] The use of different methods of guiding BCS have decreased re-excision rates, reduced volume of healthy tissue excised, and have supported the concept that there is no need to excise the pretreatment volume of tumor.[5,6] It is also important to realize that

many of the risk factors for locoregional recurrence (LRR) after BCS also predict for LRR after mastectomy.[7,8] Rates of BCS after NAT have increased in HER2 positive and TN breast cancer who achieve an excellent response,[9] rates that historically had been the lowest.[10] There is now enough evidence to suggest that, in the multidisciplinary management of breast cancer, BCS after NAT is safe and effective for adequately selected patients.[2,9]

The NSABP B18 trial introduced the concept that NAT decreased the incidence of nodal metastasis and showed that the use of sentinel lymph node biopsy (SLNB) after NAT could spare axillary node dissection (ALND) in patients with clinically negative axilla.[11] Several studies have shown that in clinically negative axilla, SLNB achieves high identification rates (>90%) and low false negative rates (<10%), and it has become a standard procedure.[12,13] In clinically positive axilla, three prospective, single-arm studies have reported an overall false-negative rate from 8% to 14% for SLN after NAT.[14–16] Refinement of surgical techniques has reduced false negative rates to less than 5%. It includes placing a marker in the positive node at the time of diagnosis and excising it at the time of the axillary surgery with or without SLN.[17–20] All these findings have reflected in a substantially decreased rates of ALND over the last years.[21]

As effective systemic therapy increases pathologic complete response (pCR) rates in HER2 and TN breast cancer (up to 50%), and breast imaging improves the accuracy in detecting residual disease, the surgical community have investigated whether it is feasible to go from less surgery to no surgery. In HER2 positive and TN subtypes, there are several ongoing trials looking at no breast surgery[22,23] or no axillary surgery in patients with cN0 at diagnosis. (https://clinicaltrials.gov/ct2/show/NCT04101851). Studies have shown that it is very unlikely, in clinically negative axilla in HER2 positive and TN breast cancer, to have a positive SLN if the breast achieves a pCR.[24,25] The implications of these surgical de-escalation on LRR or survival are still unknown, with few retrospective studies showing low LRR in selected patients.[26] Besides, if de-escalation approaches and survival outcomes are influenced by the anatomic site of response still remain largely unexplored.[27]

The aim of this study is to evaluate the impact of anatomic site of response on surgical treatments and outcomes and to assess the real population who may benefit from nonsurgical approaches after NAT.

2 | MATERIALS AND METHODS

2.1 | Study population

A prospectively maintained database included 646 women undergoing NAT from January 2010 to December 2018 in two Spanish hospitals (Hospital Vall d'Hebron, Barcelona and Clínica Universidad de Navarra, Madrid). Patients were assessed by a multidisciplinary team at diagnosis. All women underwent clinical staging that included mammogram, breast, and axillary ultrasound at diagnosis and after NAT. MRI was performed in the majority of patients. A single marker was placed in the tumor at diagnosis (Hydromark, Mammotome). All suspicious axillary lymph nodes underwent fine needle aspiration biopsy for diagnosis and an US visible marker was placed in the positive axillary node (mainly after 2015). Patients were classified as luminal A, B, HER2 positive and triple negative cancer based on immunohistochemistry assessment. This study was approved by the Institutional Review Board.

2.2 | Study protocol

At the end of the NAT, patients were assessed by the same radiological imaging as used for diagnosis. BCS was decided based on baseline characteristics and response to treatment. BCS included resection of the residual tumor or the clip with a rim of tissue around it guided by intraoperative ultrasound (IOUS). All patients with BCS underwent radiation therapy to the breast as part of the locoregional treatment. Radiation therapy to the mastectomy site and nodal basins was delivered at the discretion of the radiation oncologist and following national guidelines. For cN0 patients, axillary surgery generally consisted in SLN alone, or SLN + ALND as part of the initial validation trials. Similarly, in cN+ patients, SLN + ALND was usually performed as part of the validation trials, and in those with a marker in the positive axillary node, an IOUS guided excision of the clipped node was performed. SLN was done using dual tracer (radioisotope + blue dye).

Intraoperative pathologic assessment of margins was performed by a dedicated breast pathologist in all cases as well as intraoperative assessment of SLNs by frozen section.

pCR was defined as the absence of invasive tumor in both the breast and axilla. Axillary pCR (AXpCR) as the absence of invasive tumor in the axilla and breast pCR (BrpCR) as absence of invasive tumor in the breast.

Chemotherapy regimens were dictated by ongoing clinical trials or at the discretion of the medical oncologist. Anti-HER2 treatment was administered to all HER2 positive breast cancer patients and depending on the period and clinical trial it included different antibodies.[28,29] Patients with hormone receptor–positive disease received adjuvant endocrine therapy.

2.3 | Endpoints and statistical methods

Data assessed included age, date of diagnosis, histology, clinical stage, nuclear grade, estrogen receptor (ER), progesterone receptor (PR), HER2 status, and pathological stage.

Events were evaluated from the date of diagnosis. Distribution of clinical factors between groups were compared using the *U* Mann–Whitney test for continuous and χ^2 test for categorical variables. Differences between different groups were performed using the analysis of variance test. Survival curves were compared with the Kaplan–Meier method. Multivariate regression was employed for comparison and to explore the effect of confounding factors.

TABLE 1 Baseline characteristics

	Total
N	646
Age, years (range)	53.8 (24–95)
Histological type	
IDC	573 (88.7%)
ILC	49 (7.59%)
Other	24 (3.72%)
Grade	
I	28 (4.33%)
II	344 (53.25%)
III	268 (41.49%)
Missing	6 (0.93%)
Estrogen status	
Negative	177 (27.4%)
Positive	469 (72.6%)
Progesterone stats	
Negative	272 (42.11%)
Positive	374 (57.89%)
HER2 status	
Negative	504 (78.02%)
Positive	142 (21.98%)
Ki67 status (%)	
≤20	144 (22.29%)
>20	502 (77.71%)
Molecular subtype	
Luminal A	101 (15.63%)
Luminal B HER2 negative	271 (41.95%)
HER2 positive	142 (21.99%)
Triple negative	132 (20.43%)
Breast surgery	
BCS	370 (57.28%)
Mastectomy	276 (42.72%)
Axilar surgery	
SLNB	235 (36.38%)
SLNB + ALND	179 (27.71%)
ALND	228 (35.29%)
Missing	4 (0.62%)
Initial T stage	
cT1	29 (6.97%)
cT2	410 (63.47%)
cT3	124 (19.2%)
cT4	62 (9.60%)
cTx	1 (0.15%)
Missing	4 (0.62%)
Initial N stage	
cN0	265 (41.02%)
cN1	285 (44.12%)
cN2	36 (5.57%)
cN3	59 (9.13%)
Missing	1 (0.15%)
Initial TN stage	
I	16 (2.48%)
II	429 (66.41%)
III	197 (30.5%)
Unknown	4 (0.62%)
pCR	
No	510 (79.57%)
Yes	136 (21.05%)

Abbreviations: ALND, axillary node dissection; BCS, breast conservative surgery; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; pCR, pathologic complete response; SLNB, sentinel lymph node biopsy.

All calculations were performed with Stata software (Stata/SE 14; Stata Corp). Two-tailed p values .05 or less were considered statistically significant.

3 | RESULTS

3.1 | Overview

Six hundred and forty-six patients were included in the analysis. Mean patient age at diagnosis was 53.8 years (range, 24–95), most tumors were Grade II (53.25%), ER+ (72.6%), PR+ (57.89%), and had a Ki67 >20% (77.71%). Among these, 534 patients (82%) had clinical T2 and T3 tumors and 380 patients (59%) were cN+ at presentation. Clinicopathologic characteristics of the study population are listed in Table 1.

Overall pCR (breast + axilla) was achieved in 131 patients (21.05%), while BrpCR in 152 patients (23.57%) and AxpCR in 105 patients (36.84%). There were significant differences on pCR depending on molecular subtype, with the highest rates occurring in HER2 positive patients (45.07%), followed by TN tumors (33.3%), 10.33% in luminal B HER2 negative, and no pCR in luminal A ($p = .001$).

3.2 | Breast surgery

Overall, 370 patients (57.28%) underwent BCS while 276 patients (42.72%) underwent mastectomy. Women receiving BCS were significantly younger, had cN0 and achieved higher rates of pCR (23.78 vs. 15.94%). Characteristics related to type of surgery are shown in Table 2. In those patients who achieved a pCR, rates of BCS increased significantly in all subgroups from 54.86% to 66.67% ($p = .01$), but especially in luminal B HER2 negative. Multivariate analysis showed that pCR is and independent factor for patients

TABLE 2 Comparison between surgical groups

	BCS	Mastectomy	p
N	370	276	
Age, mean (range)	56.26 (29–87)	52.66 (24–95)	.004
Histological type			.02
CDI	339 (91.62%)	234 (84.78%)	
CLI	20 (5.41%)	29 (10.51%)	
Other	11 (2.97%)	13 (4.71%)	
Grade			.9
I	15 (4.05%)	28 (4.71%)	
II	197 (53.24%)	147 (53.26%)	
III	155 (41.89%)	113 (40.94%)	
Missing	3 (0.81%)	3 (0.81%)	
Estrogen status			.23
Negative	108 (29.19%)	69 (25%)	
Positive	262 (70.81%)	207 (75%)	
Progesterone stats			.89
Negative	155 (41.89%)	117 (42.39%)	
Positive	215 (58.11%)	159 (57.61%)	
HER2 status			.86
Negative	290 (78.38%)	214 (77.82%)	
Positive	80 (21.62%)	61 (22.18%)	
Ki67 status (%)			.3
≤20	77 (20.81%)	67 (24.28%)	
>20	293 (79.19%)	209 (75.72%)	
Molecular subtype			.89
Luminal A	56 (15.14%)	45 (16.30%)	
Luminal B	155 (41.89%)	116 (42.03%)	
HER2 positive	80 (21.62%)	62 (22.47%)	
Triple negative	79 (21.35%)	53 (19.2%)	
Axillar surgery			.0001
SLNB	177 (47.84%)	58 (21.01%)	
SLNB + ALND	111 (30%)	68 (24.64%)	
ALND	79 (21.35%)	149 (53.99%)	
Missing	3 (0.81%)	1 (0.36%)	
Initial T stage			.85
cT1	29 (7.84%)	16 (5.8%)	
cT2	234 (63.24%)	176 (63.77%)	
cT3	69 (18.65%)	55 (19.93%)	
cT4	35 (9.46%)	27 (9.78%)	
cTx	1 (0.27%)	0	
Missing	2 (0.54%)	2 (0.72%)	
Initial N stage			.001
cN0	190 (51.35%)	75 (27.17%)	
cN1	149 (40.27%)	136 (49.28%)	
cN2	16 (4.32%)	20 (7.25%)	
cN3	15 (4.05%)	44 (15.94%)	
Missing	0	1 (0.36%)	
Pathological T stage			.001
ypT0	119 (32.16%)	72 (26.09%)	
ypT1	215 (58.11%)	130 (47.1%)	
ypT2	36 (9.73%)	55 (19.93%)	
ypT3	0	13 (4.71%)	
ypT4	0	5 (1.81%)	
Missing		1 (0.36%)	
Pathological N stage			.001
ypN0	233 (62.97%)	122 (44.20%)	
ypN0 (itc)	0	4 (1.45%)	
ypN1mi	22 (5.95%)	16 (5.8%)	
ypN1	87 (23.51%)	79 (28.62%)	
ypN2	25 (6.76%%)	45 (16.3%)	
ypN3	3 (0.81%)	9 (3.26%)	
Missing	0	1 (0.36%)	
pCR			.01
No	280 (75.67%)	230 (83.33%)	
Yes	90 (24.32)	46 (16.67%)	
Initial stage			.0001
I	13 (3.51%)	3 (1.09%)	
II	265 (71.62%)	164 (59.42%)	
III	90 (24.32%)	107 (38.77%)	
Unknown	2 (0.54%)	2 (0.72%)	

Abbreviations: ALND, axillary node dissection; BCS, breast conservative surgery; CDI, invasive ductal carcinoma; CLI, invasive lobular carcinoma; pCR, pathologic complete response; SLNB, sentinel lymph node biopsy.

undergoing BCS (hazards ratio = 1.64 [95% confidence interval: 1.1–2.45], $p = .01$) and cN+ is a significant factor for receiving a mastectomy compared with cN0 ($p = .001$).

Only 142 patients with HER2 breast tumors were assessed for BCS eligibility before starting NAT. Of this, 115 (81%) had an indication for mastectomy before NAT with conversion to BCS in 53 patients (46.09%), increasing the BCS rates up to 56.34% in the whole cohort.

3.3 | Axillary surgery

Three hundrd and eighty (58.97%) patients presented with clinically positive axilla (cN+) and 265 patients (41.02%) with cN0. There were significant differences in axillary involvement at diagnosis among subtypes with the highest involvement in luminal B HER2 negative (64.94%) ($p = .002$) as well as significant differences in AxpCR with the highest pathologic response in HER2 positive patients (75.86%) ($p < .001$). In univariate analysis, ER negative ($p = .006$), mastectomy ($p > .001$), and higher clinical stage were risk factors for ALND, regardless of type of response ($p = .0001$). In multivariate analysis, cT4, mastectomy, cN, and ypN remain as independent factors for undergoing an ALND.

3.4 | Pathologic axillary response in cN0 patients

Of 265 patients with cN0, 214 patients (80.7%) remained as ypN0 and 51 (19.3%) had a positive SLN at final pathology. Patients who presented with initial cN0 disease but did not achieve a BrpCR had a 5.8% chance of having positive nodal disease at final pathology. All HER2 positive and TN tumors presenting as cN0 and achieving a BrpCR remain pN0 at final pathology ($p = .002$) (Table 3). Of 265 patients, 217 (82%) patients had a preoperative axillary ultrasound, yielding a sensitivity and specificity of 28% and 94% respectively. Of 51 patients with a positive axilla, 24 (47%) patients had macrometastasis, 23 (45%) micrometastasis, and 4 (0.7%) isolated tumor cells.

According to breast residual disease, 68 (25.66%) women achieved BrpCR. Of them, a positive axillary node was found in four patients (5.88%), two of them were luminal A tumors and the other two were luminal B HER2 negative tumors.

The majority of cN0 patients (79.25%) underwent a SLN after NAT as axillary treatment.

3.5 | Pathologic axillary response in cN1 patients

Of 380 patients with cN+, 141(37.1%) achieved an AxpCR. Patients who presented with initial cN+ but did not achieve a BrpCR had a higher risk of having positive nodal disease at final pathology ($p < .001$) (Table 3). Eighty-four (22.1%) patients achieved a BrpCR, of them 68 patients (80.95%) had an AxpCR. On the other hand, of the 296 (77.9%) women that did not achieve a BrpCR, only 73 (24.66%) had an AxpCR. The majority of patients (57%) underwent an ALND while 36% underwent SLN + ALND. Patients with complete radiologic response were allocated to SNLB + ALND surgery as part of the validation protocol. HER2+ and TN patients were more likely to receive only a SLNB than Luminal A or B tumors ($p = .001$) if SLN would have been done as the only procedure. False negative rate of SLN was 2.94% (4/136). Interestingly, only one SLN was excised in all four patients. Average number of excised nodes was 2.77, with a median of 3 (range, 1–10). Residual axillary disease was significantly associated with residual tumor in the breast ($p = .05$) and with subtype ($p = .001$).

3.6 | Local recurrences and metastasis

Mean follow up was 35.25 months (range, 1.8–85.6 months). Forty-one patients (6.43%) developed LRR. Those patients achieving a pCR developed significantly less LRR compared with pathologic partial response (pPR), respectively (1.5% vs. 7.58%) ($p = .002$). Consequently, disease-free survival (DFS) was significantly better for those who achieved a pCR versus no pCR (96.97% vs. 86.2%) ($p = .001$). Multivariate analysis showed that cT3/4, cN2/3, negative ER or PR status, ypT stage, and ypN3 were significant factors for pCR.

TABLE 3 Pathologic node status by response, stratified by cTN category

Breast pCR			Breast pPR		
Subtype	ypN0, *n* (%)	ypN + *n* (%)	Subtype	ypN0, *n* (%)	ypN + *n* (%)
Luminal A					
cT1N0	0	0	cT1N0	4 (100)	0
cT1N+	0	0	cT1N+	0	5 (100)
cT2N0	0	2 (100)	cT2N0	14 (58.33)	10 (41.67)
cT2N+	0	0	cT2N+	2 (7.14)	26 (92.86)
cT3N0	0	0	cT3N0	10 (62.5)	6 (37.5)
cT3N+	0	1 (100)	cT3N+	0	10 (100)
cT4N0	0	0	cT4N0	3 (60)	2 (40)
cT4N+	0	0	cT4N+	1 (20)	4 (80)
Total	0	3 (100)	Total	34 (35.05)	63 (64.95)
Luminal B HER2 negative					
cT1N0	0	0	cT1N0	3 (75)	1 (25)
cT1N+	1 (100)	0	cT1N+	4 (26.67)	11 (73.33)
cT2N0	11 (100)	0	cT2N0	40 (74.07)	14 (25.93)
cT2N+	4 (50)	4 (50)	cT2N+	24 (25)	72 (75)
cT3N0	3 (60)	2 (40)	cT3N0	10 (71.43)	4 (28.57)
cT3N+	3 (75)	1 (25)	cT3N+	5 (17.86)	23 (82.14)
cT4N0	2 (100)	0	cT4N0	2 (66.67)	1 (33.33)
cT4N+	0	1 (100)	cT4N+	5 (22.73)	17 (77.27)
Total	24 (75)	8 (25)	Total	93 (39.41)	143 (60.59)
Luminal B HER2 positive					
cT1N0	2 (100)	0	cT1N0	2 (66.67)	1 (33.33)
cT1N+	1 (100)	0	cT1N+	2 (66.67)	1 (33.33)
cT2N0	13 (100)	0	cT2N0	16 (88.89)	2 (11.11)
cT2N+	14 (100)	0	cT2N+	7 (28)	18 (72)
cT3N0	1 (100)	0	cT3N0	1 (100)	0
cT3N+	6 (100)	0	cT3N+	3 (50)	3 (50)
cT4N0	1 (100)	0	cT4N0	2 (66.67)	1 (33.33)
cT4N+	3 (100)	0	cT4N+	2 (66.67)	1 (33.33)
Total	41 (100)	0	Total	35 (56.45)	27 (43.55)
HER2 positive					
cT1N0	0	0	cT1N0	0	0
cT1N+	1 (100)	0	cT1N+	0	0
cT2N0	4 (100)	0	cT2N0	5 (100)	0

(Continues)

TABLE 3 (Continued)

Breast pCR			Breast pPR		
Subtype	ypN0, *n* (%)	ypN + *n* (%)	Subtype	ypN0, *n* (%)	ypN + *n* (%)
cT2N+	11 (91.67)	1 (8.33)	cT2N+	4 (44.44)	5 (55.56)
cT3N0	0	0	cT3N0	0	0
cT3N+	5 (100)	0	cT3N+	0	0
cT4N0	1 (100)	0	cT4N0	0	0
cT4N+	1 (100)	0	cT4N+	0	1 (100)
Total	23 (95.83)	1 (4.17)	Total	9 (60)	6 (40)
Triple negative					
cT1N0	2 (100)	0	cT1N0	1 (100)	0
cT1N+	0	1 (100)	cT1N+	0	3 (100)
cT2N0	20 (100)	0	cT2N0	23 (88.46)	3 (11.54)
cT2N+	11 (73.33)	4 (26.67)	cT2N+	10 (38.46)	16 (61.54)
cT3N0	3 (100)	0	cT3N0	10 (90.91)	1 (9.09)
cT3N+	4 (66.67)	2 (33.33)	cT3N+	3 (42.86)	4 (57.14)
cT4N0	1 (100)	0	cT4N0	3 (100)	0
cT4N+	3 (75)	1 (25)	cT4N+	0	3 (100)
Total	44 (84.62)	8 (15.38)	Total	50 (62.5)	30 (37.5)

Abbreviations: cTN, cardiac troponin; pCR, pathologic complete response; pPR, pathologic partial response.

3.7 | Overall survival

During follow up, 42 patients (6.5%) developed metastasis, including 34 patients (80%) with both LRR and distant metastasis. Patients with pCR had significantly better survival. (98.5% vs. 92.22%, $p = .01$). There were no differences in overall survival (OS) related to the type of axillary surgery ($p = .35$). Multivariate analysis showed that mastectomy does not remain as an independent factor for survival. Only cT4, cN+, PR, ypT, and ypN3 remain as independent factors for worse prognosis.

3.8 | Differences in DFS or OS regarding the site of response in cN+ patients

Of 380 patients with cN+, 68 (17.89%) patients achieved a pCR, 73 patients (19.21%) AxpCR, and 16 patients (4.21%) a BrpCR. Univariate analysis did not show significant differences related to initial cT or cN status, although women achieving pCR at any site were younger, had higher nuclear grade tumors, ER or PR negative, HER2 positive tumors and Ki67 >20% ($p < .001$). Patients achieving pCR or AxpCR significantly had SLNB performed ($p < .001$). There were no differences in DFS or OS among pCR (breast and axilla), AxpCR and BrpCR ($p = .30$), although there were differences when pPR was included, with pPR having worse outcomes ($p = .05$) (Figures 1 and 2). Multivariate analysis showed that initial N3 lymph status was a significantly predictor of worse prognosis.

4 | DISCUSSION

Our study shows that the high rates of response seen in patients with triple-negative and HER2-positive cancers receiving NAT make these patients ideal candidates for NAT to allow more conservative breast and axillary surgery. The finding that BrpCR is highly correlated with nodal status after NAT, and that all HER2 positive and TN cancers presenting as cN0 who achieve a BrpCR remain ypN0, confirm that this is the selected group for no axillary surgery in future clinical trials.

In this cohort, achieving pCR increases rates of BCS and/or SLNB (especially in certain subtypes) and achieving any type of pCR correlates with survival outcomes.

4.1 | Breast surgery

Our data demonstrated that pCR is an independent factor for patients undergoing BCS and rates of BCS are increased across all subgroups. Similarly, to other studies, one of the limitations has been that some patients were candidates for BCS before NAT, so the true rate of downstaging cannot be determined.[30] In our study, only type of surgery in HER2 positive cancers were assessed before NAT, and it showed a conversion to BCS in 46% of patients who were eligible for mastectomy before NAT. This clearly explain the need for breast surgeons to participate in the design of neoadjuvant clinical trials that includes BCS as an end-point.[31] Institutional studies have shown a conversion rate of 75% from BCS-ineligible to BCS-eligible when assessment of BCS is done before starting NAT.[32]

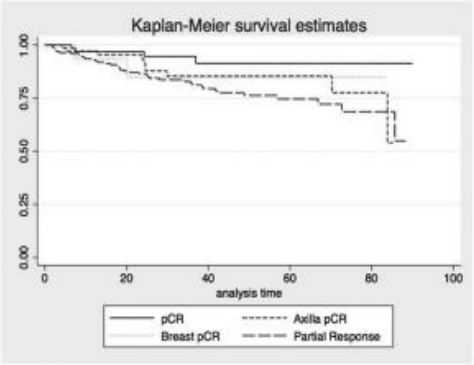

FIGURE 1 Disease-free survival regarding anatomic site of response. pCR, pathologic complete response [Color figure can be viewed at wileyonlinelibrary.com]

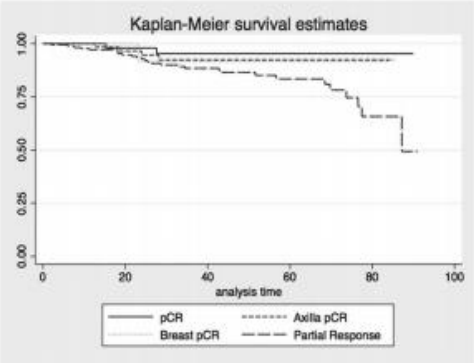

FIGURE 2 Overall survival regarding anatomic site of response. pCR, pathologic complete response [Color figure can be viewed at wileyonlinelibrary.com]

Women having BCS were significantly younger, and whether this was related to specific patient, tumor, or surgeon factor that affect the decision-making process is unknown. It also may reflect trends in Europe as mastectomy rates have not increased parallel to the increase in USA.[33]

At present, prospective clinical trials, where breast surgery is omitted in patients with HER2 positive and TN tumors with an excellent response to NAT and who achieve a BrpCR by image-guided biopsy of the tumor bed, are ongoing.[23]

4.2 | Axillary surgery

One of the benefits of NAT is the ability to downstage axillary status enabling the possibility of performing SLNB and sparing an ALND in selected groups. The rate of axillary nodal response depends on tumor biology, with higher rates in HER2 positive and TN tumors, as shown in our study. Rates of AxpCR in HER2 positive tumors reaches 76%. This is consistent with other studies in the era of modern neoadjuvant antiHer2 therapies.[34] But even in the other subgroups, as luminal B HER2 negative tumors, 28% of cN1 patients could spare an ALND. Clinical and pathological axillary status as well as cT4 and mastectomy are independent factors for ALND, although not tumor subtype. Therefore, selection of patients for this approach is crucial to de-escalate the axillary surgery.

Correlation between BrpCR and AxpCR has been studied when considering de-escalation approaches to the breast and/or the axilla. BrpCR is highly correlated with nodal status after NAT. In patients with cN+, 81% of women achieving BrpCR also achieve an AXpCR. This rate is lower than the 90% rate in the study by Tadros,[24] which includes only HER2 positive and TN tumors, and higher than the 45% of AxpCR reported by Saimei et al.[35] including all tumor subtypes. Tadros et al.[24] reported a relative risk for positive nodal metastases after NAT of 7.4%, in HER2+ or TN patients without a BrpCR compared with BrpCR, and similar to the 5.8% chance reported in our study. It is clear that patients without BrpCR do not seem to be appropriate for omission of axillary surgery after NAT.

In cN0 patients, BrpCR achieved after NAT is strongly correlated with ypN0, especially in HER2 positive (regardless of ER status) and TN subtypes. In these two subtypes, our data show that 100% of patients with cN0 who achieve BrpCR present with ypN0, similar to the 97.7% in the study by from Samiei et al.[35] and the 98% in patients with BrpCR in the study by Barron et al.,[36] which supports consideration of omission of axillary surgery in this subset of patients.

Adequate SLN mapping post-NAC, defined as the identification and excision of the clipped nodes along with greater than 2 SLNs, has yield a FN rate below 5% in different prospective studies.[17,18,20] Among patients with adequate mapping, 37% achieved AxpCR and could have been spared an ALND. These rates are consistent with the results of the ACOSOG Z1071 trial.[20] In our study, the majority of patients had a completion ALND as part of the validation trial, although nowadays, those patients would have not had an ALND.

Results from this study and others support the ongoing clinical trial where patients who had cN0 disease at presentation and no residual breast disease by percutaneous biopsy after NAT, may undergo no axillary surgery (https://clinicaltrials.gov/ct2/show/NCT04101851) and those with cN1 disease at presentation undergo SLNB with resection of the clipped node proceeding to axillary lymph node dissection if any axillary lymph node is positive.

4.3 | Anatomic site of response

As others, we have confirmed in this study that pCR is associated with improved DFS and OS as well as BrpCR and/or AxpCR when compared with partial pathologic response. Node-positive patients with BrpCR only or AxpCR only had improved survival compared to those with pPR, but no differences with those experiencing pCR (both breast and axilla). Similar findings have been reported by Lee et al.,[27] where any pCR was associated with improved survival versus partial response and that any excellent response to NAC has prognostic value. These results contrast with the study by Fayanju et al.[37] where a subset of node-positive patients with BrpCR or AxpCR had improved survival compared to those experiencing no change in stage but had worse survival compared to those experiencing pCR in both the breast and axilla. Different length in follow up may be one of the reasons for these differences.

We also evaluated the impact of type of surgery on outcomes. In our cohort, patients achieving pCR or AxpCR were more likely to have a SLNB and also patients achieving a pCR had increased rates of BCS. In multivariate analysis, mastectomy and ALND were not independent factors for survival. Contrary to this finding, Fayanju et al.[37] found that mastectomy was associated with worse adjusted OS, association that the authors admit, may be due to variables that could not be adjusted for in the multivariate analysis.

4.4 | Locoregional recurrence and survival rates

As expected, and similarly to other reported studies,[38] more advanced disease at presentation correlated with worse DFS and OS, with TN breast cancer having the worse prognosis. For a relatively short median F/U of 35 months, DFS and OS rate in those patients achieving a pCR were excellent (96.9% and 98.5%, respectively) and correlates with other studies. The reason for the excellent outcome is related to the introduction in routine clinical practice of highly effective treatments in specific subtypes of breast cancer, in particular anti-HER2 agents. Five-year LRR rates in our study were similar to other reported cohorts.[8,30]

5 | CONCLUSION

Additional step forward towards optimal selection of patients who will benefit from de-escalating in locoregional treatments after NAT is ongoing. It will impact on reducing morbidity while achieving equal or better long-term outcomes, and reflects the real multidisciplinary breast cancer care at the Institutional level. Our study proves that achieving a pCR increases BCS as well as the use of SLNB and that in selected subgroups, as HER2 positive and TN patients with cN0, sparing any axillary surgery after NAT maybe an option, as it is extremely unlikely, to have a positive SLN if the breast achieves a pCR.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Resumen y discusión de 1ª publicación

Esgueva A, Siso C, Espinosa-Bravo M, et al.* Leveraging the increased rates of pathologic complete response after neoadjuvant treatment in breast cancer to de-escalate surgical treatments. *J Surg Oncol. 2021

El estudio recoge prospectivamente los datos de 646 pacientes con cáncer de mama cT1-4 cN0-3 tratadas con TSP en el periodo comprendido entre 2011-2018. Las características de las pacientes se pueden consultar en el artículo. En las pacientes cN0 la estadificación axilar se realizó mediante GC, mientras que en las pacientes cN+ se procedió con LDNA, aunque en un 36% de los casos se realizó previamente GC en vistas a validar la técnica en este subgrupo de pacientes cN+.

A continuación, se muestra una tabla resumen con las frecuencias de pCR en función de localización anatómica y subtipo biológico del tumor. Estos resultados son consistentes con otros estudios contemporáneos con uso de terapia antiHER2 [110].

pCR	N (%)	Global	Mama	Axila
General	642*	21 %	24%	37%
HER2+ no luminal	39 (6%)	59%	62%	76%
Triple negativo	132 (20%)	33%	40%	49%
Luminal B HER2 +	103 (16%)	40%	40%	62%
Luminal B HER2 -	268 (42%)	10%	12%	26%
Luminal A	100 (16%)	0%	3%	6%

*4 pacientes missing

Cirugía mamaria

Del total del grupo, 370 pacientes (53%) fueron tratadas con cirugía conservadora mientras las 276 pacientes (47%) restantes se sometieron a una mastectomía. La pCR se relacionó significativamente con acabar con cirugía conservadora en todos los grupos de tumores, siendo la tasa de cirugía conservadora 67% tras pCR vs 55% en el grupo no pCR *(p=0.01).* En el análisis multivariado la pCR también se confirmó como un factor independiente de cirugía conservadora *(HR=1.64, IC 95% 1.1-2.45*). En general, no se recogió inicialmente si las pacientes hubiesen sido candidatas a cirugía conservadora, por lo que no se pudo realizar un cálculo de reconversión de mastectomía a cirugía conservadora tras finalizar la neoadyuvancia. Una excepción, fueron las 142 pacientes HER2+, en que si se recogió la impresión inicial del clínico pudiendo establecer una reconversión de mastectomía a cirugía conservadora en 53 de 115 pacientes (tasa de conversión 46%). En otros estudios se ha demostrado la posibilidad de reconvertir a cirugía conservadora hasta un 75% de las pacientes inicialmente no candidatas a ello, especialmente en el grupo de triple negativo y HER2+ [111].

Estudios clásicos como el ensayo NSABP B-18 al comparar entre grupo con quimioterapia neoadyuvante vs adyuvante también se constató que el tratamiento sistémico primario elevaba la tasa de cirugía conservadora (67% vs 60%, *p<0.02*) [112]. Un metaanálisis de la EBCTCG en 2018, cuyos resultados requieren una interpretación cautelosa, comparó los resultados a largo plazo de quimioterapia neoadyuvante vs adyuvante, concluyendo que la neoadyuvancia logró mayor tasa de cirugía conservadora (65% tratados con neoadyuvancia vs 49% tratados en adyuvancia) a expensas de un aumento pequeño en las recaídas loco-regionales (aumento del 5.5% a 15

años), pero sin que ello impactase en las recaídas a distancia ni en la supervivencia de estas pacientes [113]. Actualmente disponemos de métodos más fiables de guiado en la cirugía conservadora [84] que sumados a la irrupción de técnicas quirúrgicas oncoplásticas han permitido ofrecer una cirugía conservadora con garantías en muchas más pacientes que en épocas anteriores hubiesen terminado con una mastectomía [114].

En el presente estudio, las mujeres jóvenes (<50 a) mostraron mayor probabilidad de cirugía conservadora y mayor tasa de pCR. Esto concuerda con otros autores que defienden que las mujeres jóvenes presentan tumores más agresivos (triple negativo y HER2+), que a su vez son más quimiosensibles [115,116]. Asimismo, también puede haber influido la tendencia europea a intentar contener las tasas de mastectomía en favor de la cirugía conservadora en los casos oncológicamente factibles, en contraposición a la inclinación a la mastectomía que sucede en EEUU, en especial con la mayor indicación de mastectomías bilaterales en pacientes jóvenes [117,118].

La excelente respuesta al TSP de los tumores triple negativo y HER2+, ha abierto la puerta a diferentes autores a contemplar la omisión de la cirugía mamaria en función de la respuesta al tratamiento. Hace unos años, en un ensayo de viabilidad que incluía tumores cT1-3 cN0-3 triple negativo y HER2, se demostró como la biopsia asistida por vacío guiada por imagen del lecho tumoral tras la neoadyuvancia antes de la cirugía podía predecir con exactitud la pCR con una tasa de falsos negativos del 5% y un valor predictivo negativo del 95% [119]. Recientemente, se han publicado los primeros datos de un ensayo fase II incluyendo tumores con la misma biología tumoral cT1-2 cN0-1 *(ClinicalTrials.gov, NCT02945579),* en que se ha omitido la cirugía mamaria en un total de 31 pacientes sin enfermedad residual en la biopsia percutánea, recibiendo exclusivamente como tratamiento local la radioterapia externa con sobreimpresión. Tras una mediana de seguimiento a 26 meses no se ha reportado ninguna recaída local [120].

Cirugía axilar

En las 380 pacientes (59%) inicialmente **cN+**, la erradicación de la enfermedad a nivel axilar se logró en el 37%. Es notoria la diferencia de pCR axilar en función de la respuesta patológica en la mama. En caso de darse una pCR en mama, en el 81% de estas pacientes no se hallaba enfermedad en la axila. Por el contrario, en caso de persistir enfermedad en la mama, sólo en el 25% de las pacientes desaparecía la enfermedad de la axila.

	cN1
Respuesta completa mama (ypCR)	81% ypN0
Respuesta parcial mama (ypPR)	25% ypN0

Una correcta técnica de estadificación axilar podría haber identificado a 1 de cada 3 pacientes con afectación metastásica axilar inicial (cN+) con el objetivo de desestimar la LDNA en los casos de respuesta completa al TSP. Las pacientes cN1, que representan el 75% del grupo cN+ en esta cohorte de neoadyuvancia, se podrían haber beneficiado de una disección axilar dirigida (TAD), técnica validada posteriormente en nuestro centro [121].

Entre las 265 pacientes (41%) inicialmente **cN0,** en el 19% se halló enfermedad en el ganglio centinela. Dentro de este grupo, en caso de confirmación de ausencia de enfermedad en mama a nivel patológico, en tan sólo 4 pacientes (5.8%) se encontró enfermedad en axila. En caso de tratarse de un tumor buen respondedor a TSP, como son los triple negativo y HER2+, no se dio

ningún caso de ganglio centinela positivo (0%). Este hallazgo abriría el marco a plantear la no cirugía de estadificación axilar en este grupo de pacientes.

	cN0
Respuesta completa mama (ypCR)	5.8% ypN+ 0% TN y HER2+

A continuación, mostramos una tabla con los porcentajes de respuesta completa axilar (ypN0) en función del estadio clínico axilar inicial y la respuesta patológica en mama. En la tabla se comparan los resultados del presente estudio y otros similares, en los que se incluyen sólo tumores cT1-2 cN0-1 con biología de triple negativo y HER2+.

ypN0 **TN y HER2**	**cN0**		**cN1**	
	ypCR mama	**ypPR mama**	**ypCR mama**	**ypPR mama**
Tadros et al. 2017 [122]	100%	94%	90%	43%
Samiei et al. 2020* [123]	98-100%	85-90%	47-52%	16-30%
Barron et al. 2018 [124]	96%	67%	70%	17%
Presente estudio	100%	89%	79%	37%

*Incluye dentro del grupo de HER2+ también los que expresan RE.

En resumen, el conocimiento del tipo de respuesta en mama supone una valiosísima información para poder plantear la omisión de la cirugía axilar en pacientes cN0 con perfil triple negativo y HER2+. No obstante, tales hallazgos se deben refrendar en un ensayo clínico prospectivo, como es el estudio europeo de reciente inicio EUBREAST-01 *(ClinicalTrials.gov, NCT04101851) (consultar algoritmo anexo B).*

Pronóstico

Tras una media de seguimiento de 35 meses (rango 1.8-85.6 meses) se confirmaron unos datos excelentes en cuanto intervalo libre de enfermedad y supervivencia global en aquellas pacientes que mostraron una pCR, en gran medida facilitados por la introducción en la clínica asistencial de tratamientos sistémicos altamente efectivos, como pueden ser los agentes antiHER2. Los factores que se asociaron a peor pronóstico fueron los casos con más carga de enfermedad en el momento del diagnóstico (cT3-4, cN2-3) y los tumores triple negativos, concordante con lo reportado por otros estudios [125,126].

	ypCR	**ycPR**
Recaída loco-regional	1.5%	7.6%
Supervivencia libre enfermedad	97.0%	86.2%
Supervivencia global	98.5%	92.2%

En nuestro estudio al igual que en otros [127], la localización anatómica donde tenga lugar la pCR en mama o axila, no difiere en términos de mejora en supervivencia en comparación con pacientes que han presentado una pCR global (mama y axila). En otros estudios, se ha descrito un comportamiento diferente, en especial, en el grupo de cN+, al objetivar un valor pronóstico mayor de la pCR global en comparación con una localización anatómica concreta (mama o axila), concluyendo que ante determinados subtipos biológicos la persistencia de enfermedad, en alguna de las 2 localizaciones, pueden traducirse en un peor pronóstico, sobretodo aquellas pacientes en que se espera una gran respuesta al TSP (triple negativo y HER2+). Según el autor Fayanju et al, este sería un punto importante a tener en cuenta a la hora de diseñar los nuevos

protocolos de estudio que buscan omitir la cirugía en grandes respondedoras (TN y HER2+). No obstante, es probable que las diferencias se deban al diferente patrón de recaídas entre los diferentes subtipos, siendo habitualmente más precoz en TN y HER2, explicando así el origen de las diferencias [128].

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Feasibility and safety of targeted axillary dissection guided by intraoperative ultrasound after neoadjuvant treatment

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ABSTRACT

Background: Axillary management in cN + axillary nodes after neoadjuvant systemic therapy (NST) in breast cancer (BC) remains under research with the aim of de-escalation of axillary node dissection (ALND). Several axillary guided localization techniques have been reported. This study evaluates the safety of intraoperative ultrasound (IOUS) guided targeted axillary dissection (TAD) in a large sample after the results of ILINA trial.

Materials: Prospective data have been collected from October 2015 to June 2022 in patients with cT0-T4 and positive axillary lymph nodes (cN1) treated with NST. Before NST, an ultrasound visible marker was placed into the positive node. After NST, IOUS guided TAD was performed including sentinel node biopsy (SLN). Until December 2019, all patients underwent an ALND after TAD procedure. From January 2020, ALND was spared in those patients with an axillary pathological complete response (pCR).

Results: 235 patients were included. pCR (ypT0/is ypN0) was achieved in 29% patients. Identification rate (IR) of the clipped node by IOUS was 96% (95% IC, 92.5–98.1%) and IR of SLN was 95% (95% IC, 90.8–97.2%). False negative rate (FNR) for TAD procedure (SLN + clipped node) was 7.0% (95% IC, 2.3–15.7%), which decreased to 4.9% when a total of 3 or more nodes were removed. Axillary ultrasound before surgery assessed residual disease with an AUC of 0.5241. Residual axillary disease tend to be the most significant factor for axillary recurrences.

Conclusions: This study confirms the feasibility, safety and accuracy of IOUS guided surgery for axillary staging after NST in node positive BC patients.

1. Introduction

In the last decade several clinical trials have evaluated the feasibility of a less invasive surgical axillary staging strategy after neoadjuvant systemic therapy (NST) for clinically node-positive patients who converted to cN0. The routinely axillary lymph node dissection (ALND), that has been standard in positive axillary nodes before NST, causes sequelae (i.e. lymphedema, loss of nerve sensory) that decrease quality of life in breast cancer patient [1]. Nowadays, targeted therapy has increased rates of axillary pathological complete response (pCR) up to 74%, and in such cases, ALND may turn to be an unnecessary surgery [2]. Sentinel node (SLN) biopsy being a less extensive axillary surgery with lower risk of morbidity, still rise concerns as the only axillary surgery due to the very few long term results [3], as well as the awaiting results of the role of radiation therapy in this setting. Several trials (SENTINA [4], Z1071 [5], SN FNAC [6], GANEA 2 [7]) of SLNB with subsequent ALND have settled the FNR in the range of 10–14%. This FNR was considered too high in order to detect patients with residual disease after NST who could benefit from the addition of adjuvant treatments, such as radiotherapy and new systemic treatments (capecitabine [8], T-DM1 [9]) with impact on oncological outcomes.

Abbreviations: NST, Neoadjuvant systemic treatment; pCR, Pathologic Complete Response; ALND, Axillary Lymph Node Dissection; SLNB, Sentinel Node Biopsy; TAD, Targeted axillary dissection; IOUS, Intraoperative Ultrasound.

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Different strategies have been proposed to decrease the FNR below the target of 10%. Removal of 3 or more SLN, the use of dual tracer techniques (radioactive and dyes), immunohistochemistry (IHC) lymph node evaluation and removal of the initially biopsied positive lymph node. Even though, studies have shown that removing ≥3 SLNs may not be achievable in the vast majority of patients [4,5] and in around 25% of cases the clipped node is not the SLN [10]. The latter could be solved marking the positive lymph node before initiate NST and removing it at the time of surgery besides the SLN, procedure which has been called targeted axillary dissection (TAD) [10]. Several methods for marking the positive axillary node have been described, such as wire localization, radioactive seeds, carbon dye, magnetic seeds, radar reflector or radiofrequency tag. Identification rates (IR) and FNR published varies between 92-100% and 2.0–7.0%, respectively [10–12]. Nevertheless, there are no studies comparing the different techniques, and the majority of them are chosen depending on the surgeon's discretion, or institutional resources available. Our group have already published the use of intraoperative ultrasound (IOUS) for excising the clipped axillary node with a FNR of 4% [13].

The aim of the study is to update the results of the prospective study ILINA, using IOUS for excising the clipped node in cN + breast cancer patients after NST as part of the TAD procedure as well as identifying accuracy of radiological response and results of oncological outcomes with the omission of ALND.

2. Material & Methods

From October 2015 to June 2022, patients with cytologically-proven axillary metastasis undergoing NST followed by surgery were included in this prospective study. Until December 2019, patients were included in a prospective study named ILINA study [13] approved by the Institutional Ethics Committee, which entailed TAD followed by ALND. From January 2020, patients were offered TAD and omission of ALND in case of having both negative SLNs and clipped node.

All patients had a mammogram and an US of the breast and axilla, and, in some cases, MRI. If suspicious axillary nodes were found on US, a fine-needle aspiration (FNA) was performed. Lymph nodes were considered suspicious if they showed a focal or diffuse cortical thickening (>3 mm thick) or loss of the fatty hilum. Number of suspicious nodes and morphological alteration according to BEDI criteria [14] were also recorded in each patient. In patients with cytologically-proven positive axillary nodes, a US-visible hydrogel polymer metal marker (Hydromark; Devicor Medical Products, Inc., Cincinnati, OH, USA) was placed into the biopsied node before initiating NST.

2.1. Neoadjuvant treatments

NST was administered according to institutional protocols at the discretion of the treating oncologist. Chemotherapy included anthracycline (four cycles of adriamycin + cyclophosphamide) plus a weekly (x12) taxane-based regimen. Endocrine therapy was based on aromatase inhibitors. Targeted therapy included (neo) adjuvant anti-HER2 therapy with trastuzumab ± pertuzumab when indicated or CDK 4/6 inhibitors inside a clinical trial. The time interval from placement of the clip to surgery was recorded in all patients.

Patient's response to NST was assessed by mammogram, breast and axillary US (AUS), and an MRI examination (only for patients who underwent diagnostic MRI). As mentioned above, patients with radiologic complete response by US were triaged to SLNB, IOUS-guided excision of the clipped node, and ALND inside ILINA protocol study. Since 2020, ALND was spared in some patients who had a negative clipped node and SLNs. For patients with suspicious axillary nodes after NST, an FNA was performed and, if positive, patients were triaged to ALND. In case the clip was not clearly visualized, an attempt was made to place another US hydrogel marker close to the first marker to facilitate IOUS-guided surgical excision. Although, in few cases where the clip was not visible by ultrasound, patients undergone ALND. All patients with IOUS-guided excision of the clipped node were evaluated for assessing the feasibility of the IOUS procedure, regardless of the type of axillary surgery performed.

2.2. Surgical procedure

The ILINA trial involved IOUS-guided excision of the clipped node, followed by SLNB and ALND. Most patients underwent a dual technique for SLN localization, i.e., Tc99 and blue dye (Patent Blue V, ACROS OrganicsTM or methylene blue). Blue dye was injected subareolar prior to surgery, as described elsewhere [15]. If the SLN or clipped node were not localized during surgery, a direct ALND was performed. In some cases where the SLN was not identified during surgery or the clipped node was confirmed to be positive by a preoperative FNA, the clipped node excision was attempted. Before the incision, US with a high frequency probe (7–15 MHz; MyLabTM, Esaote, Genova, Italy) was performed in multiple planes to localize the hydrogel marker. The incision was made just over the area where the clip was localized, and the distance from the skin to the clip was measured by US. IOUS-guided excision of the clip was then performed as previously described [13]. Prior to resecting the clip, the area was checked with the gamma probe to ascertain that the clipped node was the SLN. Once the clipped node was excised, we confirmed the presence of the clip by ultrasound prior to the node being sent for pathologic examination. Mammogram of the clipped node was not systematically performed if breast surgeon felt confident having excised the clip. All radioactive and blue nodes found in the axilla after removal of the clipped node were excised as SLNs.

After surgery all patients with residual axillary disease received regional node irradiation (RNI). In those patients with cN1 and a complete pathological response (ypT0/is ypN0), RNI was performed only if it was considered high risk (grade 3, initial tumor size >2 cm, <50y/o, triple negative o HER2 overexpression).

2.3. Pathological evaluation

All fresh lymph nodes were sent to the Pathology Department for intraoperative assessment. The clipped node was analyzed separately from the SLN when no concordance was found, which was specified in the pathology report. Frozen section analysis was performed on SLNs, and stained with hematoxylin and eosin. Immunohistochemical staining for cytokeratins was limited to selective use at the discretion of the pathologist. Staging of the axillary nodes was performed according to the 7th edition of the American Joint.

2.4. Statistical analysis

Statistical analysis was performed using STATA software 14.2 (StataCorp, College Station, TX, USA). AUS findings to predict axilla pathologic status was calculated with a Wilcoxon rank sum test. Response assessment by AUS was evaluated calculating AUC and NPV, defined as the number of true negatives divided by the total number of negative results. FNR of SLN and/or clipped node was defined as the number of cases where the SLN or clipped node did not show metastasis even though residual disease was present, divided by the total number of cases with persistent disease in

axillary lymph nodes. Logistic regression was used to identify features associated with the inability to identify the clipped node as SLN and to identify factors associated to disease recurrence. All tests were two-sided, with a significance level of .05. CIs for different measures were calculated using the Clopper–Pearson exact method.

3. Results

3.1. Patient characteristics

A total of 235 patients were included. Median age at the time of enrollment was 51 years (range, 28–85 years). Infiltrating ductal carcinoma was the most frequent histology in 198 (84%) patients. Almost 60% of patients were classified as stage cT2. 118 (50%) patients had palpable axillary nodes and 161 (69%) patients had 3 or less suspicious nodes on initial AUS evaluation. Neoadjuvant chemotherapy was administered in 208 (89%) patients. Breast and axilla complete clinical complete response was reported in 85 (36%) and 223 (95%) patients, respectively. Patient and tumour characteristics are specified in Table 1.

3.2. Tumour response to NST

After NST, breast conservation was performed in 151 (64%) patients. Pathological complete response (pCR) was achieved in 69 (29%) patients. Breast and axillary pathologic complete response were achieved in 78 (33%) and 92 (39%) patients, respectively. None of luminal A breast cancers achieved a pCR neither in breast nor axilla. The highest rates of pCR were in pure HER2 positive and triple negative breast cancers, reaching a breast pCR of 97% and 67% and an axilla pCR of 94% and 62%, respectively.

Median number of positive nodes was higher in ER/PR + Her2 negative tumors, as well as risk of axilla upstaging (ypN2a-3a), with a probability of 35% in luminal A and 14% in luminal B, of upstaging respectively (Table 2).

Among all patients who underwent an ALND, additional axillary positive nodes were found in patients with a previous positive TAD, regardless of type of metastasis. At least one additional positive node where found at ALND in 50% patients (3 of 6) with ITCs, 24% (5 of 21) with micrometastases and 54% (50 of 93) with macrometastases detected in either the SLN and/or clipped node.

Table 1
Patient and tumour characteristics.

	No of patients (%)
Number patients	235
Median age (years)	51 (range: 28–85)
Tumour histology	
Ductal	198 (84%)
Lobular	22 (9%)
Others	15 (6%)
Biologic subtype	
Luminal A	51 (22%)
Luminal B HER2-negative	94 (40%)
Luminal B HER2-positive	36 (15%)
HER2 positive no luminal	33 (14%)
Triple negative	21 (9%)
Clinical T stage	
Tx	2 (1%)
T1	22 (9%)
T2	142 (60%)
T3	63 (27%)
T4	6 (3%)
Clinical N stage	
N1	231 (98%)
N2	1 (0.5%)
N3	3 (1.5%)
Initial axilla physical examination	
Negative	117 (50%)
Positive	118 (50%)
Suspicious nodes on initial AUS	
<3 nodes	161 (69%)
≥3 nodes	74 (31%)
Type of neoadjuvant therapy	
Chemotherapy	131 (56%)
Chemotherapy + targeted therapy	77 (33%)
Endocrine	19 (8%)
Endocrine + targeted therapy	8 (3%)
Clinical tumour response after NST	
ycT0	85 (36%)
ycT+	150 (64%)
Clinical node response after NST	
ycN0	223 (95%)
ycN+	12 (5%)
Type of breast surgery	
BCT	151 (64%)
Mastectomy	84 (36%)

3.3. Accuracy of axillary imaging for response assessment

Initial assessment by AUS before NST, including number of initial suspicious nodes and cortical morphologic features (BEDI 4–6), was not a good predictor of pathological nodal status (*Wilcoxon test*, p = 0.21 and 0.59, respectively).

After NST, an axillary restaging by imaging was conducted to predict correlation with pCR. Axillary ultrasound was used to assess residual disease in the axilla showing an AUC of 0.5241.

After NST, 27 patients had suspicious nodes by AUS, before surgery an FNA was done in all that confirmed residual disease in 11 patients. After ruling out these patients, clinical complete response *(ycN0)* by imaging showed a negative predictive value (NPV) for axilla pCR of 40% (95% IC, 33.9–47.1%). Assuming that breast response could be another good surrogate of axilla response, clinical breast complete response *(ycT0)* was evaluated showing also a NPV for axilla pCR of 61% (95% IC, 50.0–72.0%).

3.4. Accuracy of TAD

A total of 141 patients were included in the ILINA trial to validate IOUS guided TAD. Besides, 94 patients with cALND for residual disease were also added to this group. After NST, patients with clinical axillary disease, loss of US visibility of the clipped node or SLN and/or clipped node not identified during surgery were excluded of analysis. A median number of 11 nodes were excised (range: 1–33) (Fig. 1).

3.4.1. SLN plus clipped node (TAD)

Median number of nodes excised was 3 (range: 1–14). FNR rate was 7.0% (5/71), which decreased to 4.9% when a total of 3 or more nodes were removed. Clipped node was not a SLN in 25% of the patients. Presence of ≥3 suspicious lymph nodes on initially ultrasound, removal of >2 SLNs, dual tracer technique for SLN localization, presence of residual nodal disease, or presence of metastases on clipped node did not predict the clipped node to be a SLN, although retrieval of 3 or more SLNs showed a trend to statistically association (p = 0.06) (Table 4).

3.4.2. Clipped node

Visualization and excision of the clipped node was done by IOUS (Fig. 2). The clipped node was not visualized after NST in 4 patients and, its visualization was lost during surgery in another 5 patients. Identification rate of the clipped node by IOUS was 96% (95% IC, 92.5–98.1%). In 9 patients the clipped node was negative with additional positive axillary nodes making a FNR of 12.7% for the clipped node only.

In 16 patients (7.8%) no evidence of foreign body changes were

Table 2
Response to neoadjuvant therapy according to breast cancer subtype.

	Luminal A	Luminal B HER2 neg	Luminal B HER2+	HER2+ pure	Triple negative	Global
Global pCR (ypT0/is ypN0)	0% (0/51)	7.4% (7/94)	58.3% (21/36)	93.9% (31/33)	47.6% (10/21)	29.4% (69/235)
Breast pcR (ypT0/ypTis)	0% (0/51)	9.6% (9/94)	63.9% (23/36)	97.0% (32/33)	66.7% (14/21)	33.2% (78/235)
Axillary pCR (ypN0)	0% (0/51)	25.5% (24/94)	66.7% (24/36)	93.9% (31/33)	61.9% (13/21)	39.2% (92/235)
Median residual positive nodes	3 nodes (range: 1–11)	2 nodes (range: 1–23)	1 node (range: 1–7)	1 node	1 node (range: 1–6)	2 nodes (range: 1–23)
Upstaging to ypN2-3	35.3% (18/51)	14.9% (14/94)	16.7% (6/36)	0% (0/33)	4.8% (1/21)	16.6% (39/235)

seen on pathological examination of the clipped node. In such cases, mammographic axillary views and AUS scanning were performed postoperatively, but no residual clipped nodes were identified, suggesting clip dislodgement. No association was found between pathological nodal status and absence/presence of pathological changes secondary to clip on node *(Fisher's exact test, $p = 0.37$)*.

3.4.3. SLN biopsy

To identify SLN, radiolabelled Tc99 was used in all patients and, additionally, blue dye in 90% patients (dual tracer technique). Lymphoscintigraphy was unsuccessful for SLN identification in 16 patients. SLN was not surgically identified in 12 patients. Identification rate for SLN was 95% (95% IC, 90.8–97.2%) with a median number of 3 nodes removed (range: 1–8). FNR of SLN alone was 22.5% (Table 3).

3.5. Preliminary oncological outcomes

After a median follow-up of 31 months (range: 1–75 months), 2 patients developed local recurrence, 7 (2.9%) developed locoregional + distant metastasis and 16 (6.8%) developed distant metastasis. Axillary recurrences in 6 patients, all with distant metastasis. All patients with axillary recurrences had previously an ALND for positive axillary nodes and had received RNI. Recurrences were not significantly associated to the number of suspicious axillary nodes on initial AUS (≥3 nodes) or initially locally advanced tumour stage cT3-T4, although the presence of residual axillary nodal disease showed a statistically significance trend (HR 2.38, p = 0.079).

4. Discussion

IOUS guided targeted axillary surgery has been demonstrated to be a feasible method to de-escalate axillary staging surgery in node positive breast cancer patients who undergo NST. Identification rate of the clipped node was 96% and FNR for TAD procedure was 7.0%, both figures comparable to other localization techniques for TAD (wire localization [16], radioactive seed [10], carbon tattooing [17], magnetic seed [12], radiofrequency tag [18] or radar reflector [19]) described in literature.

Our study confirms the need for surgical axillary staging that cannot be yet substituted by radiological response to NST. Current breast and axillary imaging techniques are not enough accurate to be a good predictor tool to detect nodal residual disease. A large discrepancy between AUS after neoadjuvant therapy and the pathology results of the axillary nodes was evident. One explanation could be that 35% of patients with ycN0 had limited residual disease defined as isolated tumor cell or micrometastasis, increasing the false negative results of AUS. Other problem, expressed by the radiologist, is sometimes the difficulty for differentiating between the peripheral anechoic hydrogel of the marker and the length of the cortical thickness of the lymph node that can also influence these results. In summary, AUS examination is far from considering it as a good screening method for residual disease.

Similar to previous findings [20,21], none of patients with luminal A tumors achieved a pCR, or an axillary pCR, being the group with higher risk of axillary upstaging (ypN2-3), probably reflecting the inaccurate results of axillary staging prior to systemic treatment. Better selection of patients for NST in this subgroup would be desirable. Nevertheless in neoadjuvant endocrine (NET) setting, Kantor et al. [22] have hypothesized that leaving behind a low volume of axillary disease after NET is potentially less important than after neoadjuvant chemotherapy, as NET patients have only received a small fraction of their overall endocrine therapy in the preoperative setting and no differences in OS were seen when compared this patients with upfront surgery patients with nodal disease [23]. They proposed to omit ALND in patients with fewer than three suspicious nodes before neoadjuvant endocrine therapy If only one or two nodes are positive after removal of the clipped node and two additional SLNs, the recurrence rates and survival following this Z011 like strategy are awaited.

In Her2 positive and TN negative BC, systemic treatments have contributed to an increase in pCR up to 90% in HER2 pure breast cancers in our study, similar to other published reports [24]. Tadros et al. published that nearly 90% early stage (cT1-2 cN1) HER2 and TN breast cancers, who had documented nodal metastasis before NST, were not found any residual axillary metastases when a breast pCR was confirmed. Meanwhile in the same study, patients who did not achieve a breast pCR had only a 40% probability to become node negative [25]. New strategies searching to improve preoperative identification of patients who achieved breast pCR are raising, in the aim to omit breast surgery [26]. However, any residual disease in HER2 and TN subtypes, regardless of size, is relevant to define the need of additional adjuvant treatments with survival impact [8,9]. In line with other authors [27], low volume SLN disease after NAC is not an indicator of a low risk of additional positive axillary nodes and remains an indication for cALND outside a clinical trial.

According to our results, TAD is the method that yields the lowest FNR (7%) after NST, compared to SLN biopsy or clipped node excision individually. A systematic review and pooled analysis comparing biopsy of the initial metastatic lymph node and SLN biopsy showed that both approaches were highly accurate with a FNR of 6.28% (95% CI, 3.98–9.43) and 5.18% (95% CI, 3.41–7.54), respectively [28]. This study concluded that biopsy of the clipped node alone represents a valid alternative to ALND in those node positive breast cancer patients who have responded well to upfront systemic treatment. These FNRs are significantly below the FNR for SLNB alone (13%) in the same setting [29]. Other authors advocate the optimization of SLNB procedure with dual tracer and retrieval of ≥3 SLNs, presuming the clipped node is an SLN in the majority of cases and, in the few cases the clipped node was not identified it seems not to increase the risk of developing an axillary recurrence [30]. In our study, no significant factor was found to predict concordance of SLN and clipped node, including the number of initially suspicious nodes, number of SLNs, localization technique of SLN or clipped node or axilla status after NST. This suggest again that nor SLN or clipped node must be omitted from TAD.

One concern when omitting ALND in those cN + who convert to ypN0 is the risk of regional recurrences. Retrospective studies have

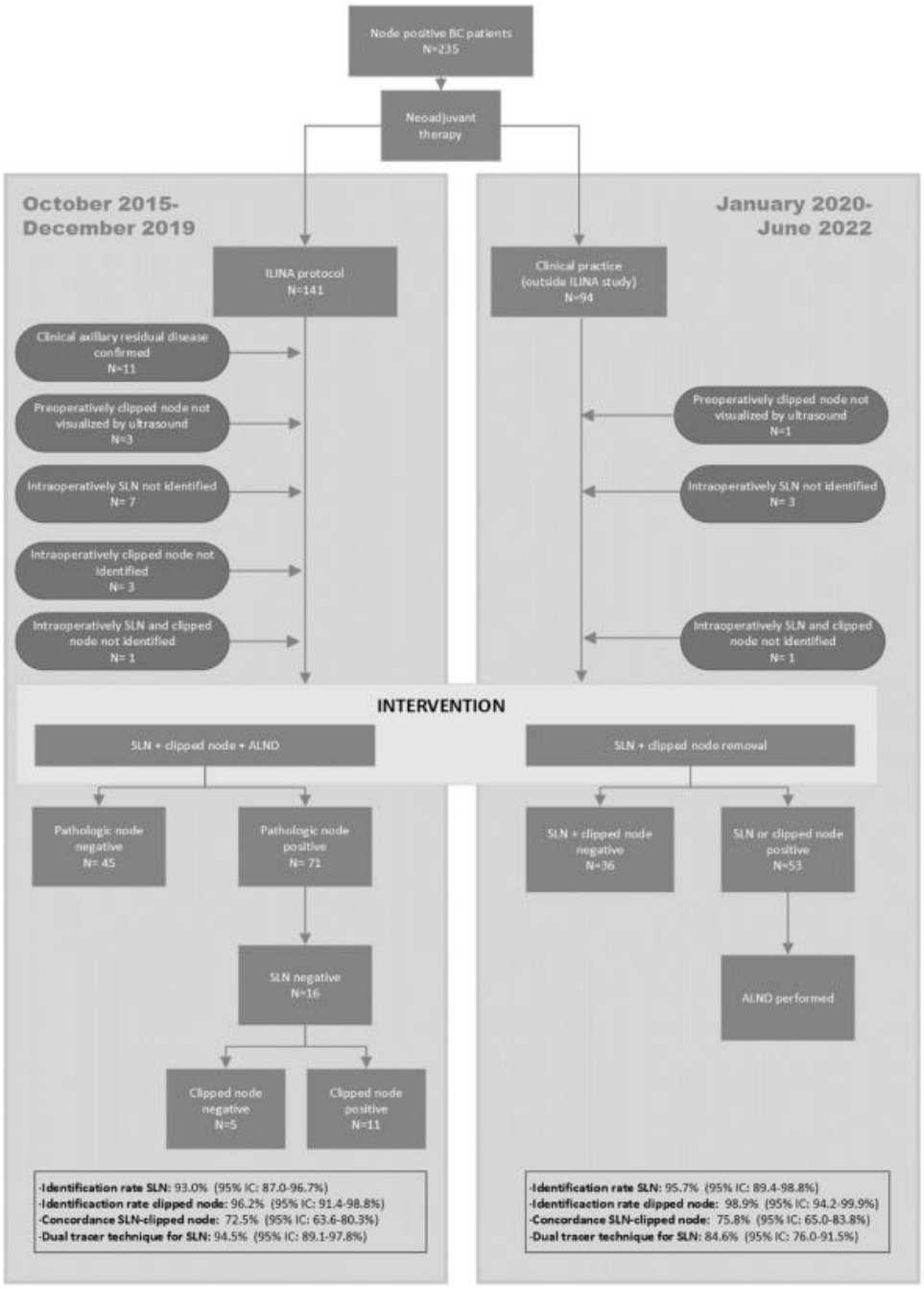

Fig. 1. Diagram of all patients included in the study. ALND axillary lymph node dissection, SLN sentinel lymph node.

shown a very low risk of nodal recurrence (0–0.5%) [31,32]. In our cohort 2/6 regional recurrences occurred after a negative TAD, but in both cases with positive nodes in the ALND. This remarks how important is an accurate axillary staging in these group of patients.

Axillary residual disease seems to be the most robust risk factor for recurrence ahead of the burden of disease both in the breast and axilla. If ALND omission after an involved SLN post-NST may have an adverse effect on prognosis is still uncertain. A study analyzing National Cancer Database (NCDB) patients with residual disease in 1–3 lymph nodes (ypN1), SLNB was associated with significantly

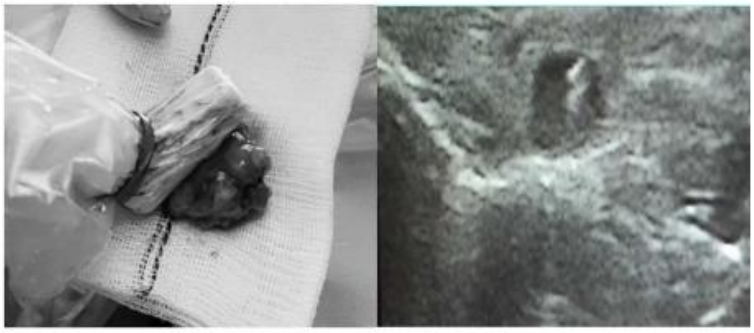

Fig. 2. Pictures of intraoperative verification of clipped node removal by ultrasound.

Table 3
False negative rates (FNR) depending on number of nodes excised.

Surgical procedure	False negative rate (%)
SLN biopsy only	FNR: 22.5% (95% IC, 13.5–33.9%) • SLNs ≤2 nodes: 26.7% (95% IC, 12.3–45.9%) • SLNs ≥3 nodes: 19.5% (95% IC, 8.8–34.9%)
Clipped node excision only	FNR: 12.7% (95% IC, 6.0–22.7%)
SLN + Clipped node excision	FNR: 7.0% (95% IC, 2.3–15.7%) • Nº nodes ≤2 nodes: 10.0% (95% IC, 2.1–26.5%) • Nº nodes ≥3 nodes: 4.9% (95% IC, 0.6–16.5%)

Table 4
Analysis of possible factors associated with concordance of clipped node and sentinel lymph node.

Variable	OR (95% CI)	P
Num. of lymph nodes suspicious initially on ultrasound		
< 3	–	0.98
≥ 3	1.01 (0.49–2.04)	
Num. of SLN removed.		
≤ 2	–	0.06
≥ 3	1.86 (0.97–3.56)	
SLN localization technique		
Tc99	–	0.58
Tc99 + blue dye (dual tracer)	0.73 (0.23–2.29)	
Presence of residual nodal disease		
Node negative	–	0.61
Node positive	0.66 (0.13–3.28)	
Metastasis in clipped node		
Absent	–	0.43
Present	1.92 (0.38–9.67)	

lower 5-year overall survival compared to ALND group (71% vs 77%, p = 0.01) [33]. Ongoing prospective randomized trials will respond the need of nodal radiation after SN negative (NSBAP B51) and the role of ALND in addition to nodal radiation after SN positive (A011202) in initially node positive breast cancer patients after neoadjuvant chemotherapy.

The use of US- visible markers has made feasible the IOUS technique for excising the clip node. It can be placed directly within the cortex of axillary positive node at initial diagnosis workup, providing an exceptional visibility up to 12 months after placement in all imaging modalities (mammogram, ultrasound, MRI) [34]. It eliminates the need for a separate location procedure prior surgery creating a better patient experience.

It is the most inexpensive technique considering that other techniques demand a new and costly implantable device and a console for its localization. Reference It can be deployed after ultrasound-guided biopsy and can easily be placed inside the metastatic node, favored for its tiny size. This biopsy marker is also inert and could be left indefinitely in the body, unlike what is allowed to the radioactive seeds where is a strict time for removal according to the nuclear regulatory protocols. Contrary to magnetic seeds, it does not require non-magnetic surgical tools during surgery and does not generate an artifact in MRI sequences, which can difficult axillary or upper outer quadrant breast assessment of response.

The downside of this technique is the occasionally difficulty in visualization of the clip after NST. Clip's visibility could be compromise in case it ends within a node deep in the axilla. Loss of ultrasound visibility over time is also possible, due to reabsorption of polyethylene glycol (PEG) hydrogel coverage at the same time as lymph node cortical thickening disappears in response to systemic therapy. In that case, a new marker may be placed before surgery by the radiologist. The clip's migration is another relevant concern, consequence of an initially wrong placement by radiologist or displacement during induction therapy due to shrinkage of the metastatic node. As described previously in breast surgery, clip dislodgement during surgery is also possible [35], although uncommon, most probably because a poor tissue adherence of the hydrogel substance to fatty-lymphatic tissue, sometimes also associated to a narrow transection with electrocautery during clipped node removal.

The surgeon expertise in ultrasound guided surgery is crucial to be confident removing the clipped node without extrusion of the clipped. A surgical mammogram of the surgical specimen to confirm the presence of the clip is recommended in case of uncertainty with no clear visualization of the clip by ultrasound. It is also important to reconsider that any preoperative loco-regional anesthetic blockade in the axillary region, may interfere with the clipped node visualization. Future research may be focused on quality of life, particularly arm lymphedema rate using the TAD procedure.

5. Conclusions

In clinically node positive BC patients, IOUS guided axillary surgery after NST is feasible, safe, and an accurate method for de-escalation of axillary surgery without compromising oncologic outcomes in those patients with a pCR.

CRediT authorship contribution statement

Christian Siso: Study concepts, Study design, Funding acquisition, Quality control of data and algorithms, Formal analysis, and interpretation, Statistical, Formal analysis, Manuscript preparation, Writing – review & editing. **Antonio Esgueva:** Funding acquisition. **Joaquin Rivero:** Funding acquisition. **Clara Morales:** Funding acquisition. **Ignacio Miranda:** Funding acquisition. **Vicente Peg:** Funding acquisition. **Antonio Gil-Moreno:** Funding acquisition. **Martin Espinosa-Bravo:** Funding acquisition. **Isabel T. Rubio:** Study concepts, Funding acquisition, Formal analysis, and interpretation, Writing – review & editing, Manuscript review.

Declaration of competing interest

All authors declare that they have no potential conflicts of interest to declare.

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Resumen y discusión de 2ª publicación

Siso C, Esgueva A, Rivero J, et al. **Feasibility and safety of targeted axillary dissection guided by intraoperative ultrasound after neoadjuvant treatment.** ***Eur J Surg Oncol. 2023***

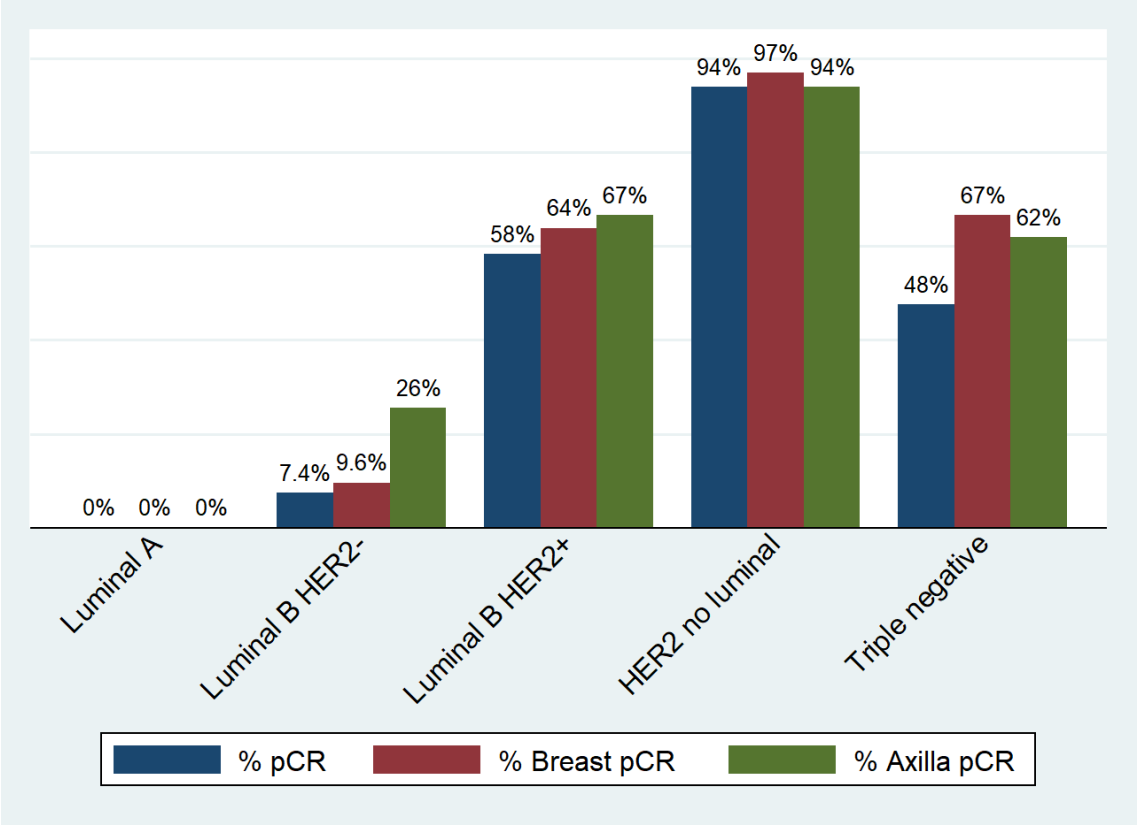
Para este estudio se recogieron datos de forma prospectiva de 235 pacientes en el período comprendido entre 2015-22. Las características de los pacientes se pueden consultar en el artículo. Los principales criterios de inclusión eran haber sido diagnosticado de cáncer de mama con afectación axilar limitada cN1 y ser candidata a tratamiento sistémico neoadyuvante, incluyendo quimioterapia, terapia dirigida y/o hormonoterapia, según los criterios del oncólogo médico tratante. La confirmación de la afectación axilar se realizó habitualmente con PAAF ecoguiada y, posteriormente se procedió al marcaje del mismo con un marcador hidrófilo ecovisible (HydroMARK^{TM}). Al finalizar el TSP se repitieron las pruebas de reestadificación para valorar la respuesta clínica del tumor y, confirmando la correcta visualización del clip hidrófilo en el ganglio axilar. Una vez descartada la permanencia de ganglios sospechosos o, en tal caso, después de haberse descartado su afectación mediante nueva PAAF; las pacientes se programaron para realización de una disección axilar dirigida (TAD) guiada por ecografía. La TAD ecoguiada consistió en la escisión del ganglio centinela localizado mediante doble técnica mayoritariamente (Tc99-Alb y azul patente) junto a la exéresis mediante ecografía intraoperatoria del ganglio marcado con clip ecovisible. En una primera fase del estudio (2015-19), independientemente del resultado de TAD, se procedía posteriormente a la realización de la LDNA, en un intento de validar la técnica y fijar la seguridad oncológica del procedimiento definiendo la tasa de falsos negativos de la técnica. En una segunda fase del estudio (2020-22), en caso de obtener un resultado negativo para enfermedad residual con la técnica TAD, se desestimaba la realización de la LDNA. Las pacientes con enfermedad axilar residual recibieron radioterapia en las áreas ganglionares. En las pacientes cN1 y una respuesta patológica completa (ypT0/is ypN0), se realizó radioterapia sólo si se consideraban casos de alto riesgo (grado 3, tamaño inicial del tumor >2 cm, <50 años, triple negativo o sobreexpresión de HER2).

Respuesta al tratamiento

La **pCR** global se logró en el 29% de las pacientes, mientras que la pCR mama y axila fueron del 33% y 39%, respectivamente. Por subtipos biológicos, los tumores que mostraron mejores tasas de pCR globales fueron los HER2+ puro y triple negativo, 94 y 48% respectivamente, mientras que no hubo ningún caso de luminal A que alcanzó la pCR. Tras haber recibido el tratamiento neoadyuvante, el hallazgo de ≥4 ganglios metastásicos en la axila (ypN2a-3a), se dio con mayor frecuencia en los tumores luminales A (35%), en contraste a ningún caso reportado entre los tumores HER2 puros (0%).

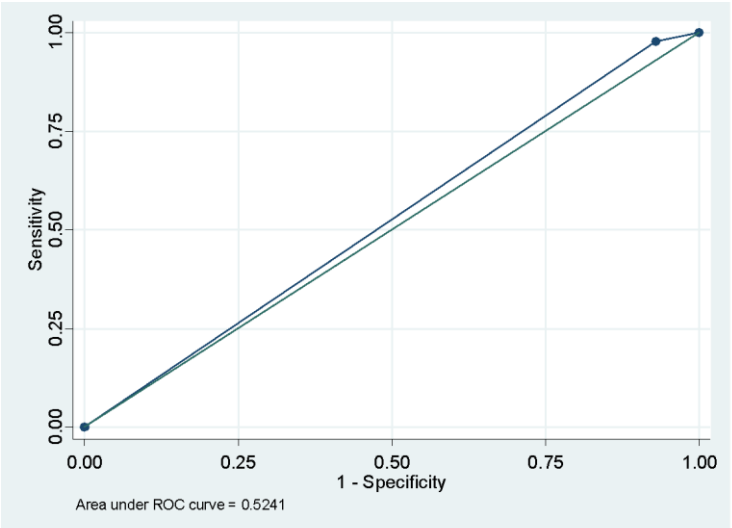
	Luminal A	Luminal B HER2-	Luminal B HER2+	HER2+ pure	Triple negativo	Global
Global pCR (ypT0/is ypN0)	0% (0/51)	7.4% (7/94)	58.3% (21/36)	93.9% (31/33)	47.6% (10/21)	29.4% (69/235)
Breast pcR (ypT0 / ypTis)	0% (0/51)	9.6% (9/94)	63.9% (23/36)	97.0% (32/33)	66.7% (14/21)	33.2% (78/235)
Axillary pCR (ypN0)	0% (0/51)	25.5% (24/94)	66.7% (24/36)	93.9% (31/33)	61.9% (13/21)	39.2% (92/235)

Upstaging a ypN2-3	35.3% (18/51)	14.9% (14/94)	16.7% (6/36)	0% (0/33)	4.8% (1/21)	16.6% (39/235)



Valoración clínica axila

En el mismo estudio se valoró la precisión de la ecografía axilar en la detección de enfermedad axilar residual tras TSP, mostrando esta una fiabilidad diagnóstica con un área bajo la curva (ROC) de 0.5241, comportándose como una herramienta diagnóstica con valores propios del efecto del azar.



Se intentó correlacionar la respuesta clínica completa (ycN0) con el valor predictivo negativo (VPN) de la ecografía axilar para estimar la pCR axilar, siendo está de tan sólo el 40% *(IC 95%, 33.9-47.1%)*. Asumiendo que la respuesta de la mama podía ser un marcador subrogado de respuesta en axila, se utilizó la respuesta clínica en mama (ycT0) para estimar el VPN de la ecografía axilar siendo también de tan sólo el 61% *(IC 95%, 50.0-72.0%).* Una explicación plausible de esta baja rentabilidad diagnóstica podría ser que el 35% de las pacientes ycN0 presentaban mínima enfermedad en los ganglios, en forma de CTAs o micrometástasis. También dudas en la interpretación del grosor cortical por la interposición del clip hidrófilo, podría haber contribuido a aumentar la tasa de falsos negativos (FN).

Estadificación quirúrgica axila

La técnica de TAD ecoguiada ha demostrado ser un método fiable y reproducible para la estadificación de pacientes cN1 sometidas a TSP. Su tasa de identificación fue del 96% y la tasa de FN del 7.0%, comparable a otras técnicas de TAD [50,93,96,129]. En la siguiente tabla mostramos resultados resumidos de TAD.

	GC	**Ganglio clipado**
Tasa identificación	95%	96%
Doble técnica localiz. GC	90%	-
Discordancia GC-GClip	25%	
TFN por separado	22.5%	12.7%
TFN combinado	7.0% (si ≥3 ggs: 4.9%)	

TFN. Tasas de falsos negativos.

La presencia de ≥ 3 adenopatías patológicas inicialmente, la extirpación de > 2 GCs, el uso de doble trazador para el ganglio centinela, la presencia de enfermedad residual axilar o en el ganglio clipado; no pudieron predecir que el ganglio clipado fuese a coincidir con el GC, aunque la presencia de 3 o más GCs presentó una asociación con tendencia a la significación *(p=0.06).* Este hecho resalta la importancia de incluir en la TAD tanto el ganglio centinela como el ganglio marcado, siendo ambos necesarios para una correcta valoración axilar posneoadyuvancia.

En 16 (7.8%) pacientes el informe anatomo-patológico no reportó cambios secundarios al clip hidrófilo, no obstante, en todas ellas se realizó un rastreo ecográfico y mamográfico de la axila en el posoperatorio para descartar persistencia del ganglio clipado en la axila. La explicación a tal suceso se ha relacionado con la implantación perinodal del clip en lugar de intranodal o, a la probable extrusión del clip durante la cirugía, hecho habitual cuando se procede con una disección con electrocauterio muy cercana al componente de hidrogel del clip.

Entre las pacientes que se sometieron a una LDNA con TAD positiva, se encontraron ganglios axilares positivos adicionales, independientemente del tipo de metástasis detectada en los ganglios TAD. En aquellos casos en que se detectó una CTA, micrometástasis o macrometástasis; se halló al menos un ganglio axilar positivo adicional en el 50% (3/6), 24% (5/21) y 54% (50/93) de los pacientes, respectivamente. Esto demuestra que un pequeño volumen de enfermedad

residual en los ganglios TAD no es un indicio de bajo riesgo de ganglios axilares adicionales positivos, por lo que se debe continuar considerando una indicación de LDNA[73].

La aparición de nuevos estudios que muestran significativas mejoras en la supervivencia en pacientes con enfermedad residual con la introducción de tratamientos sistémicos en adyuvancia [19-21], intensifica la importancia de poder ofrecer a estas pacientes la estadificación más fiable posible para evitar situaciones de enfermedad residual inadvertida.

Pronóstico

Tras una mediana de seguimiento de 31 meses (rango: 1-75 meses), un total de 6 pacientes padecieron una recidiva axilar y, en todos los casos acompañada de una recaída a distancia. Todas ellas tenían en común haberse identificado en la estadificación axilar persistencia de enfermedad axilar tras TSP (ypN+) y, habiendo recibido en todos los casos una cirugía en forma de LDNA y radioterapia de áreas ganglionares. Otro escenario son las pacientes que experimentan una negativización de la axila (ypN0), siendo en este grupo el riesgo de recaída regional excepcional (0-0.5%) [69,104].

Manejo axilar

Según los resultados de nuestro estudio, el TAD es el método de estadificación axilar en cN1 que muestra una menor tasa de FN (7%) tras TSP, en comparación con el GC o ganglio clipado por separado, 22.5% y 12.7%, respectivamente. En caso de confirmarse un TAD negativo (ypN0) se pueda evitar la LDNA, con la tranquilidad de que dichas pacientes tienen unos resultados excelentes de supervivencia global y supervivencia libre de enfermedad [130].

Para considerar una técnica TAD representativa y válida, consideramos necesario la obtención de un mínimo de 2 ganglios TAD, siendo uno de ellos el ganglio marcado [80,131] *(consultar algoritmo anexo A).* Normalmente, en muchos de estos casos se procederá a radioterapia sobre áreas ganglionares (aunque la necesidad de este tratamiento también está siendo evaluada por ensayos en curso).

En situaciones donde sólo se recuperen uno o dos ganglios TAD pero sin coincidir con el ganglio marcado, el tratamiento óptimo no está claro, dada la mayor probabilidad de un falso negativo [57,70,77,78]. Existen grupos que han reportado tasas de FN del 7% con la escisión exclusiva del ganglio clipado [80], aunque en nuestro estudio el valor de la tasa de FN alcanzaba el 12.7% con la exéresis exclusiva del ganglio clipado. Otros autores han propuesto optimizar la técnica del GC con el uso de una técnica de doble marcaje y la obtención de un mínimo de ≥ 3 GCs, asumiendo que el ganglio marcado será uno de los GCs en la mayoría de los casos y, en los casos en que no coincida parece no aumentar el riesgo de recaída axilar [132]. En nuestra cohorte de pacientes cumpliendo el requisito de ≥ 3 GCs, independientemente del ganglio marcado, la tasa de FN continuaba siendo elevada, con un valor del 19.5%. En estas situaciones existe la duda de pasar por alto enfermedad axilar residual, sabiendo que constituye el factor pronóstico más robusto para recaída. Saber que impacto pronóstico puede tener omitir la LDNA en pacientes con un TAD positivo se desconoce actualmente, pero en un estudio retrospectivo de pacientes de la National Cancer Database (NCDB) se ha observado que en los pacientes con GC positivo pero sin LDNA presentan una supervivencia global a 5 años inferior (71% vs 77%, *p=0.01*) [108] .

La respuesta a cuál es el manejo correcto de la axila en estas pacientes cN1 tras TSP no la obtendremos hasta 2028-29 con la publicación de dos ensayos multicéntricos muy esperados. Uno de los cuáles busca valorar la necesidad de radioterapia en áreas ganglionares después de un GC negativo (NSBAP B-51 trial; *ClinicalTrials.gov, NCT01872975*) y, el otro, valorar el papel de la LDNA sumada a la radioterapia de áreas ganglionares después de un GC positivo (ALLIANCE A11202 trial; *ClinicalTrials.gov, NCT01901094*) *(consultar algoritmo anexo B).*

Al igual que vimos en la anterior publicación, la probabilidad de pCR en el grupo de HER2 positivo y triple negativo es muy elevada, pudiendo llegar al 90% en el caso de los HER2 puro en esta cohorte, similar a otros estudios publicados [133]. Tadros et al. publicaron que casi el 90% de los cánceres de mama en estadio inicial (cT1-2 cN1) HER2 positivo y triple negativo, no presentaban metástasis axilares residuales cuando se confirmó una pCR de mama. Mientras que, en el mismo estudio, las pacientes que no alcanzaron una pCR de mama tenían sólo un 40% de probabilidad de convertirse en ganglios negativos [122]. En vías de optimizar la valoración de la pCR de mama para en un futuro omitir la cirugía, existen múltiples ensayos clínicos que están usando la biopsia guiada por imagen tras finalizar el TSP [119,120,134,135].

Otro grupo donde el manejo axilar podría personalizarse seria en el grupo de los tumores luminales A sometidos a neoadyuvancia. En este grupo de pacientes la probabilidad de pCR axilar es muy baja, así como su valor pronóstico no es tan importante como en otro tipo de tumores, aunque la no negativización de la axila tiene impacto en el tratamiento de la axila en forma de indicación de LDNA [12]. En pacientes RE+/RP+ HER2- las tasas de pCR axilar tras quimioterapia o hormonoterapia neoadyuvante son muy similares, 11% vs 18% respectivamente *(p=0.37)* [136]. En este grupo de pacientes, el uso de tratamiento neoadyuvante parece multiplicar por tres el riesgo de recibir una LDNA en comparación con haber realizado una cirugía primaria aplicando los criterios de Z0011 *(HR=3.35; P<0.01)* [137]. Por todo ello, en un intento de desescalar tratamiento, el grupo de Dana Farber [138] ha planteado una hipótesis basada en el concepto de que dejar atrás un bajo volumen de enfermedad axilar tras hormonoterapia neoadyuvante (NHT) es potencialmente menos importante que tras la quimioterapia neoadyuvante, ya que las pacientes NHT sólo han recibido una pequeña parte de su terapia endocrina global en el preoperatorio y, no se observaron diferencias en la SG al comparar a estas pacientes con pacientes con cirugía primaria con enfermedad ganglionar [139]. Su propuesta a falta de confirmación con más estudios, sería la omisión de la LDNA en pacientes siempre y cuando: hayan sido tratadas con NHT, hubiesen <3 ganglios sospechosos inicialmente y, sólo si son positivos 1-2 ganglios en el TAD; debiendo incluir este el ganglio clipado y al menos dos ganglios centinelas adicionales.

Conclusiones

- El tratamiento sistémico primario (TSP) aumenta la tasa de cirugía conservadora en mama y axila debido a la respuesta del tumor al tratamiento, en todos los subtipos biológicos de cáncer de mama, aunque mayoritariamente en los subtipos Her2 positivo y triple negativo. La afectación axilar es el lugar de mayor probabilidad de pCR en dichos subtipos tumorales.

- La pCR es un marcador subrogado de buen pronóstico en términos de intervalo libre de recaída loco-regional, supervivencia libre de enfermedad y supervivencia global. La presentación de una pCR disociada (mama o axila) no parece que se traduzca en un peor pronóstico en comparación con una pCR global (mama y axila).

- La valoración ecográfica de la axila y la confirmación citológica/histológica de los ganglios sospechosos antes del inicio de TSP es crucial. En los casos de baja carga de enfermedad axilar (cN1) el marcaje del ganglio metastásico biopsiado reduce la tasa de falsos negativos en la cirugía axilar tras neoadyuvancia.

- La estadificación axilar en pacientes cN+ tras TSP debe ser quirúrgica, dada la alta probabilidad de enfermedad residual no detectada por las pruebas de imagen convencionales utilizadas en la valoración clínica de la axila.

- La técnica TAD guiada por ecografía intraoperatoria es una técnica fiable y reproducible en el desescalaje en la cirugia axilar en pacientes cN1 sometidas a TSP, con tasas de identificación del 96% y tasas de falsos negativos del 7.0%.

- La técnica TAD es superior a la biopsia de ganglio centinela en términos de tasa falsos negativos en pacientes cN1 sometidas a TSP. Es importante tenerlo en cuenta en los casos en que se pretenda omitir la LDNA.

- Para una correcta estadificación con TAD es preciso obtener un mínimo de 2 ganglios, uno de los cuáles tiene que ser el ganglio marcado previo al TSP.

- Independientemente del tamaño de la metástasis en los ganglios del TAD, completar la linfadenectomía axilar es el tratamiento estándar ya que la afectación de ganglios axilares no centinela es alta y la linfadenectomía axilar favorece el control regional.

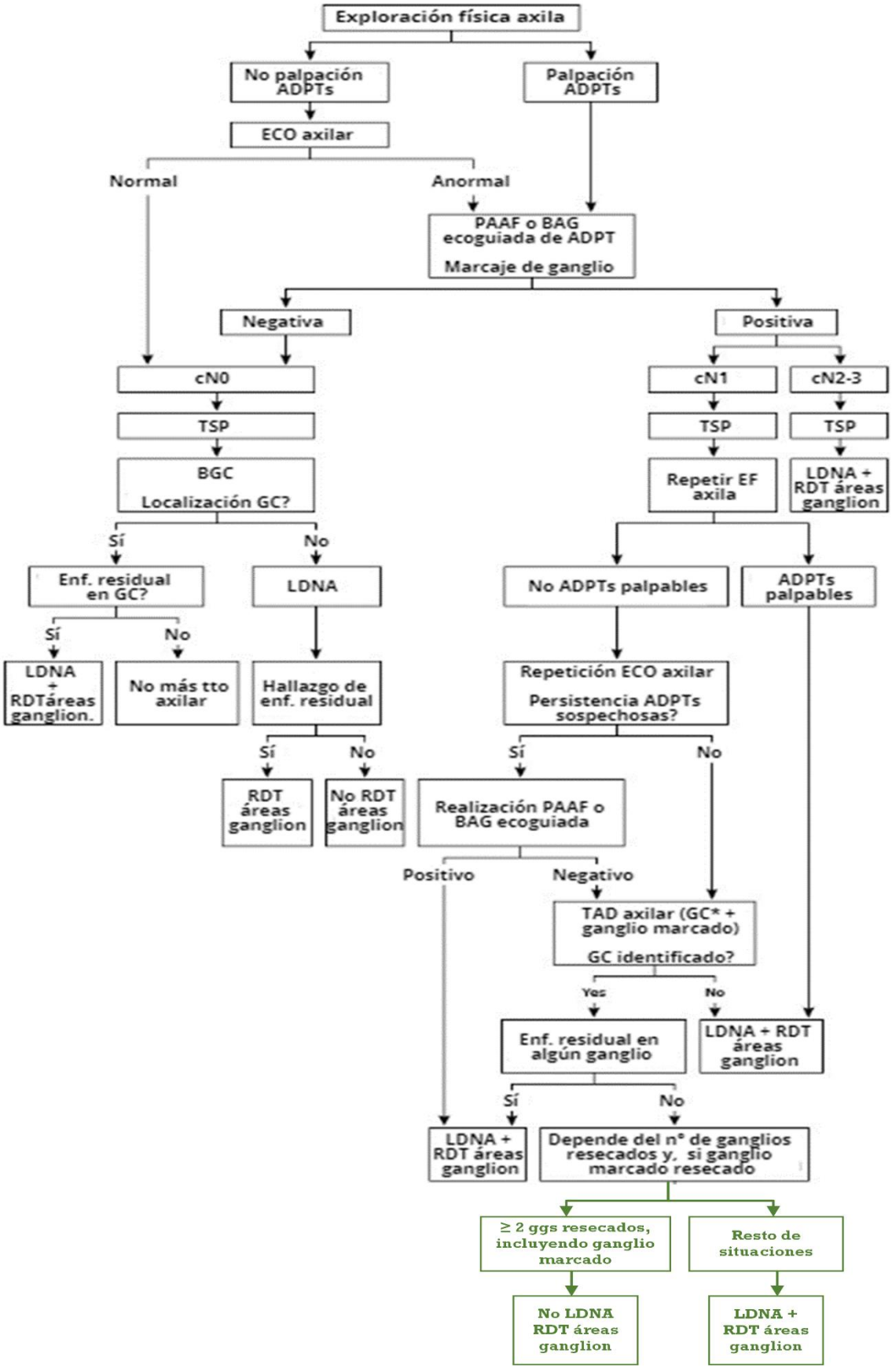
- Los datos preliminares de recidiva loco-regional y supervivencia parecen confirmar que las pacientes cN1 con negativización de la axila (ypN0), objetivada con TAD y sin LDNA, tienen similar pronóstico a aquellas pacientes con una linfadenectomía.

- En pacientes cN1, que presentan enfermedad residual axilar, los ensayos aleatorizados nos darán la respuesta de cuál es el tratamiento óptimo regional (si es radioterapia o linfadenectomía o RDT + LDNA).

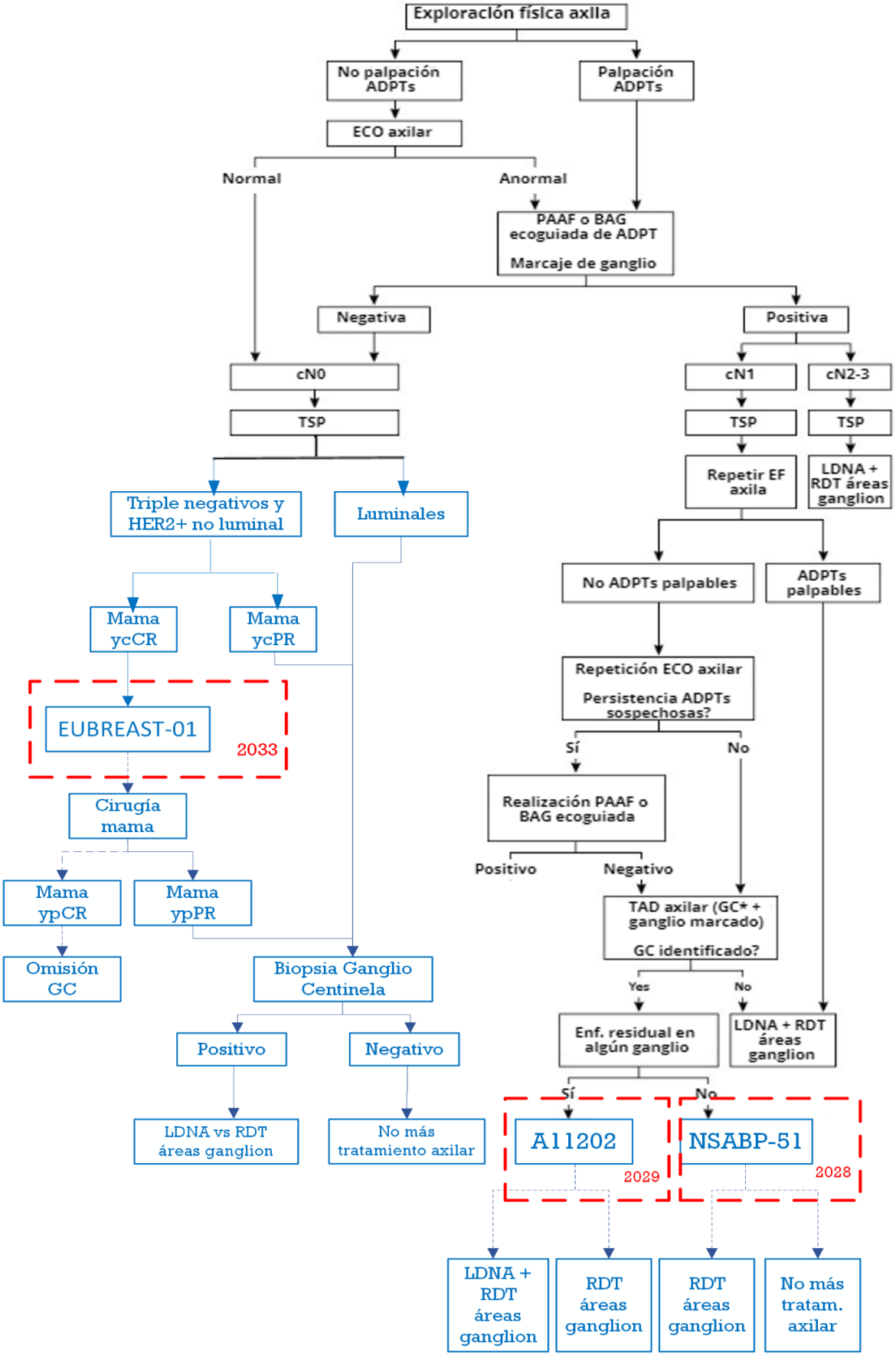
- Existe una clara correlación entre pCR en mama y axila. Las pacientes cN0 con tumores triple negativo y HER2 que presentan pCR en mama permanecen como ypN0. Estos resultados abren la puerta a plantear la omisión de cirugía axilar en este grupo de pacientes dentro ensayos clínicos.

Anexos

(A) Algoritmo A. Manejo axilar tras TSP. Doble técnica de marcaje de ganglio centinela.



(B) Algoritmo B. Manejo axilar con aspectos susceptibles de cambio con ensayos en curso.



(C) Artículo anexo: descripción TAD guiado por ecografía intraoperatoria.

Siso C, de Torres J, Esgueva-Colmenarejo A, et al.

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Intraoperative Ultrasound-Guided Excision of Axillary Clip in Patients with Node-Positive Breast Cancer Treated with Neoadjuvant Therapy (ILINA Trial)

A New Tool to Guide the Excision of the Clipped Node After Neoadjuvant Treatment

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ABSTRACT

Background. The accuracy of sentinel lymph node biopsy (SLNB) after neoadjuvant therapy (NAT) has been improved with the placement of a clip in the positive node prior to treatment. Several methods have been described for clipped node excision during SLNB after NAT. We assessed the feasibility of intraoperative ultrasound (IOUS)-guided excision of the clipped node during SLNB and investigated whether the accuracy of SLNB is improved.

Methods. After approval by the Institutional Ethics Committee, all breast cancer patients undergoing NAT had an US-visible clip placed in the positive node. The ILINA trial consisted of IOUS-guided excision of the clipped node along with SLNB and axillary lymph node dissection (ALND).

Results. Forty-six patients had a clip placed in the positive node. In two (4.3%) cases, the clip could not be seen prior to surgery and the patient underwent ALND; however, the clipped node was successfully removed by IOUS-guided excision in 44 patients. Thirty-five patients (79.5%) underwent SLNB along with IOUS-guided excision of the clipped node and ALND, and were subsequently included in the ILINA trial. Nine patients were not included (five patients with SLNB only and four patients with ALND without SLNB). SLNB matched the clipped node in 27 (77%) patients. The false negative rate for the ILINA protocol was 4.1% (95% confidence interval 0.1–21.1%).

Conclusions. IOUS-guided excision of the axillary clipped node after NAT was feasible, safe, and successful in 100% of cases. The ILINA trial is accurate in predicting axillary nodal status after NAT.

In the era of minimally invasive surgery, breast surgeons have focused their attention on reducing the number of surgical procedures performed. The increased use of neoadjuvant therapies (NATs) in breast cancer, together with improved response rates, have encouraged surgeons to adopt a more conservative surgical approach with similar oncological outcomes.[1–4] In patients with nodal metastases before NAT, nodal disease is eradicated in 23–74% of patients.[5,6]

At present, the current challenge is to be able to design individualized locoregional treatment strategies for patients who downstage the axilla after NAT. Although patients are likely to achieve complete axillary response (pCR), they have to bear the morbidities associated with an axillary lymph node dissection (ALND).[7,8]

Physical examination and imaging studies such as ultrasound (US), magnetic resonance imaging (MRI), or positron emission computed tomography are not helpful in distinguishing residual disease from pCR in the axilla.[9,10] Even all three tests combined have a sensitivity of 81% and a 28–48% negative predictive value.[11]

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Initial studies such as ACOSOG,[7] SENTINA,[12] and the SN FNAC[8] have reported false negative rates (FNRs) of sentinel lymph node biopsy (SLNB) from 8 to 14.2%. To reduce this FNR, novel techniques have been developed that involve marking the positive lymph node and excising the clipped node after NAT. The ACOSOG Z1071 trial showed that the FNR dropped to 7.4% when the clipped node was removed at the time of SLNB.[13] A similar technique, but without SLNB—the marking axillary lymph nodes with radioactive iodine seeds (MARI) procedure—has reported an FNR of 7% (95% confidence interval, CI 2–16%).[14] The MD Anderson Group refined this technique and developed the targeted axillary dissection (TAD). Clipped node removal resulted in an FNR of 4.2% for residual axillary metastases, and 2.0% when combined with SLNB.[15]

Other labeling techniques have been described, such as injecting a black carbon suspension to tattoo positive axillary nodes.[16] The aim of this study was to assess the feasibility of intraoperative US (IOUS)-guided excision of the clipped nodes after NAT and to investigate whether the accuracy of SLNB is improved.

MATERIALS AND METHODS

From October 2015 to July 2017, patients with cytologically-proven axillary metastasis undergoing NAT followed by surgery were included in this prospective study approved by the Institutional Ethics Committee.

Tumor staging was performed by mammogram, US of the breast and axilla, and, in some cases, MRI. If suspicious axillary nodes were found on US, a fine-needle aspiration (FNA) was performed. Lymph nodes were considered suspicious if they showed a focal or diffuse cortical thickening ($\geq$ 3 mm thick) or loss of the fatty hilum (Fig 1a). In patients with cytologically-proven positive axillary nodes, a US-visible hydrogel polymer metal marker (Hydromark; Devicor Medical Products, Inc., Cincinnati, OH, USA) was placed into the biopsied node, and US was performed 1 week after insertion to test for visibility.

Neoadjuvant Treatments

NAT was administered according to institutional protocols at the discretion of the treating oncologist. Chemotherapy included anthracycline (four cycles of adriamycin + cyclophosphamide) plus a weekly ($\times$ 12) taxane-based regimen. Endocrine therapy was based on aromatase inhibitors. In tumors with human epidermal growth factor receptor 2 (HER2) overexpression, anti-HER2 therapy with trastuzumab $\pm$ pertuzumab was added. The time interval from placement of the clip to surgery was recorded in all patients.

Patient's response to NAT was assessed by mammogram, breast and axillary US, and an MRI examination (only for patients who underwent diagnostic MRI). Patients with US pCR were triaged to SLNB, IOUS-guided excision of the clipped node, and ALND. For patients with suspicious axillary nodes after NAT, an FNA was performed and, if positive, patients had ALND. All patients with IOUS-guided excision of the clipped node were evaluated for assessing the feasibility of the IOUS procedure, regardless of the type of axillary surgery performed.

Surgical Procedure

Most patients underwent a dual technique for SLN localization, i.e., Tc99 and blue dye (Patent Blue V, ACROS Organics™). Patent blue was injected subareolarly prior to surgery, as described elsewhere.[17] Careful examination with axillary US was also performed prior to surgery to adequately visualize the clip (Fig. 1b). In case the clip was not clearly visualized, an attempt was made to place another US hydrogel marker close to the first marker to facilitate IOUS-guided surgical excision. If the clip could be not visualized or localized by imaging studies, a direct ALND was performed. The ILINA trial involved IOUS-guided excision of the clipped node, followed by SLNB and ALND. Before the incision, US with a high frequency probe (7–15 MHz; MyLab™, Esaote, Genoa, Italy) was performed in multiple planes to localize the hydrogel marker. The incision was made just over the area where the clip was localized, and the distance from the skin to the clip was measured by US. IOUS-guided excision of the clip was then performed as previously described.[18] Prior to resecting the clip, the area was checked with the gamma probe to ascertain that the clipped node was the SLN. Once the clipped node was excised, we confirmed the presence of the clip prior to the node being sent for pathologic examination. All radioactive and blue nodes found in the axilla after removal of the clipped node were excised as SLNs.

Pathological Evaluation

All fresh lymph nodes were sent to the Pathology Department for intraoperative assessment. The clipped node was analyzed separately from the SLN when no concordance was found, which was specified in the pathology report. Frozen section analysis was performed on SLNs, and stained with hematoxylin and eosin. Immunohistochemical staining for cytokeratins was also performed. Staging of the axillary nodes was performed according to the 7th edition of the American Joint

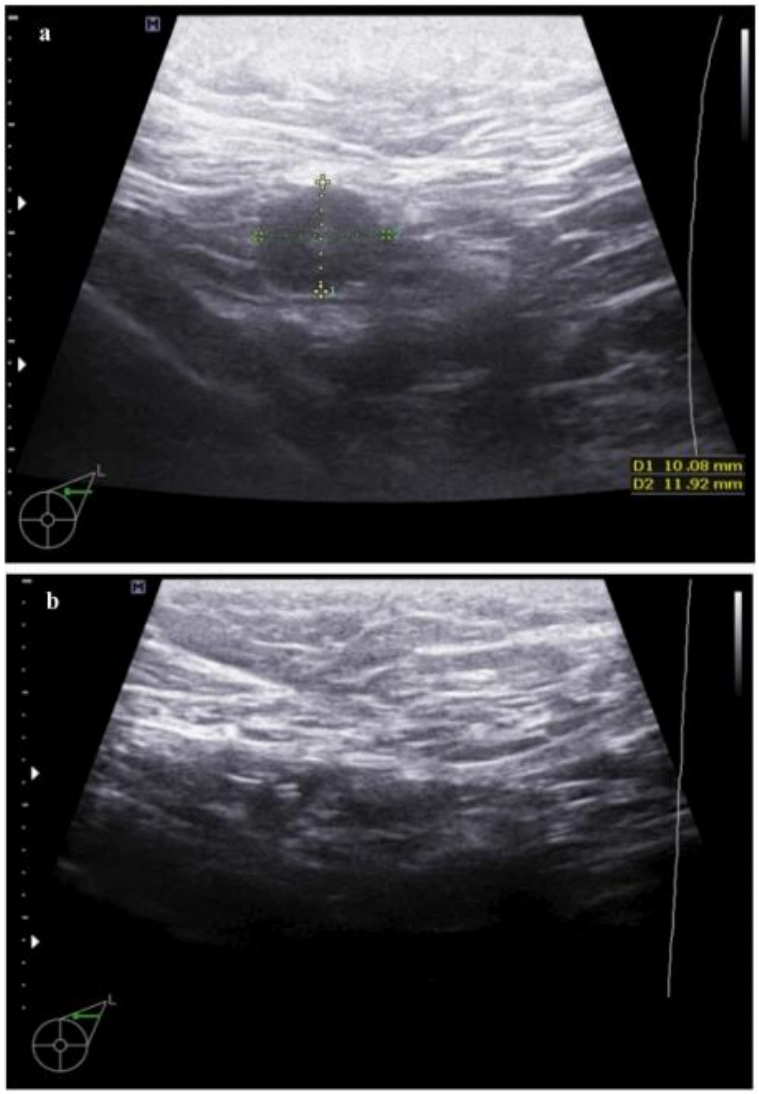

FIG. 1 Ultrasound images of an axillary lymph node. **a** Metastatic lymph node confirmed by biopsy. **b** Normal appearance of initially metastatic lymph node after neoadjuvant therapy marked with an ultrasound-visible device

Committee on Cancer.[19] Isolated tumor cells (ITCs) in the SLN or clipped node were considered positive for false negative purposes.

Statistical Analysis

Statistical analysis was performed using STATA software 14.2 (StataCorp, College Station, TX, USA). FNR was defined as the number of cases where the SLN or clipped node did not show metastasis even though residual disease was present, divided by the total number of cases with persistent disease in axillary lymph nodes. CIs for FNRs were calculated using the Clopper–Pearson exact method.

RESULTS

Patient Characteristics

Forty-six patients with a median age of 49.5 years (range 32–84) had an axillary clip placed and were treated with NAT followed by surgery. Almost 70% of patients were classified as stage T2, and 23 patients (50%) had only one positive node on US. Forty patients (87%) received chemotherapy as NAT. After NAT, breast conservation was performed in 26 (56.5%) patients, and axillary pathologic complete response was achieved in 18/46

TABLE 1 Patient and tumor characteristics

	N (%)
No. of patients	46
Median age (years)	49.5 (range 32–84)
Tumor histology	
Ductal	42 (91.3)
Lobular	4 (8.7)
Intrinsic subtypes	
Luminal A	4 (8.7)
Luminal B HER2-negative	27 (58.7)
Luminal B HER2-positive	6 (13.0)
HER2, no luminal	5 (10.8)
Triple negative	4 (8.7)
Clinical T stages	
T1	4 (8.7)
T2	30 (65.2)
T3	11 (23.9)
T4	1 (2.2)
No. of abnormal nodes on ultrasound at diagnosis	
1	23 (50.0)
2	9 (19.6)
3	9 (19.6)
> 3	5 (10.9)
Type of neoadjuvant therapy	
Endocrine	6 (13.0)
Chemotherapy	29 (63.0)
Chemotherapy + anti-HER2	11 (23.9)
Type of breast surgery	
BCT	26 (56.5)
Mastectomy	20 (43.5)
Breast pCR	14 (30.4)
Axillary pCR	13 (31.7)[a]

pCR pathological complete response, *BCT* breast-conserving therapy, *HER2* human epidermal growth factor receptor

[a]Patients without axillary lymph node dissection were excluded

patients (39%). Patient and tumor characteristics are specified in Table 1.

Preoperative Clip Visualization

Preoperative axillary US was performed in all patients. In two patients (4.4%), the clip could not be seen prior to surgery after a careful search using US. In one of these patients, a second clip was placed close to the first clip, although the mammogram for confirmation showed that it was 2 cm apart. These two patients underwent ALND as part of the planned treatment, and no IOUS excision was attempted.

Intraoperative Ultrasound-Guided Excision of the Clipped Node

Forty-four patients underwent successful IOUS-guided excision of the clipped node, 35 (76%) of whom were included in the ILINA trial as they had a clipped node excised along with SLNs, followed by ALND (Fig. 2). Nine of the 44 patients were excluded from the ILINA trial, of whom 5 did not have ALND performed after extensive discussion about the benefits and risks of sparing ALND if the SLN and clipped node were negative. The four remaining patients underwent ALND only, as a result of failure of lymphatic mapping in two patients and for cytologically positive axillary nodes prior to surgery in the remaining two patients.

When analyzing different types or duration of NAT, there were no statistically significant differences between those patients either included or excluded from the trial. Table 2 compares the characteristics, tumors, and treatment for patients included in the trial versus those excluded.

ILINA Protocol

The median number of SLNs removed in the 35 patients included in the trial was three. The SLN was localized using the dual tracer technique in 30 patients (85.7%), and axillary pCR was achieved in 11 (31.4%) of the 35 patients. SLN matched the clipped node in 27 (77%) patients. A total of 24 patients (68.6%) had axillary residual disease, in 18 (75%) of whom the SLN matched the clipped node.

In six patients, the clipped node did not match the SLN. Of these six patients, the SLN was negative, and the clipped node was positive in three patients. The mean number of SLNs excised in these three patients was 3.3, using the dual technique. For the other three patients where the SLN and the clipped node did not match, the SLN and the clipped node were positive.

In one case, a false negative was reported where the clipped node and SLN were negative but a positive axillary node was found during ALND. In this case, only an SLN was excised and the clipped node was coincident with the SLN, which yielded an FNR of 4.1% (95% CI 0.1–21.1%). The ILINA protocol predicted axillary nodal status after NAT in 34 of the 35 patients (overall accuracy 97.1%, 95% CI 85.1–100).

The overall axillary pCR for all patients with a clipped node was 39%. pCR by subtypes was 63% for HER2-positive patients and 26% for luminal B HER2-negative patients.

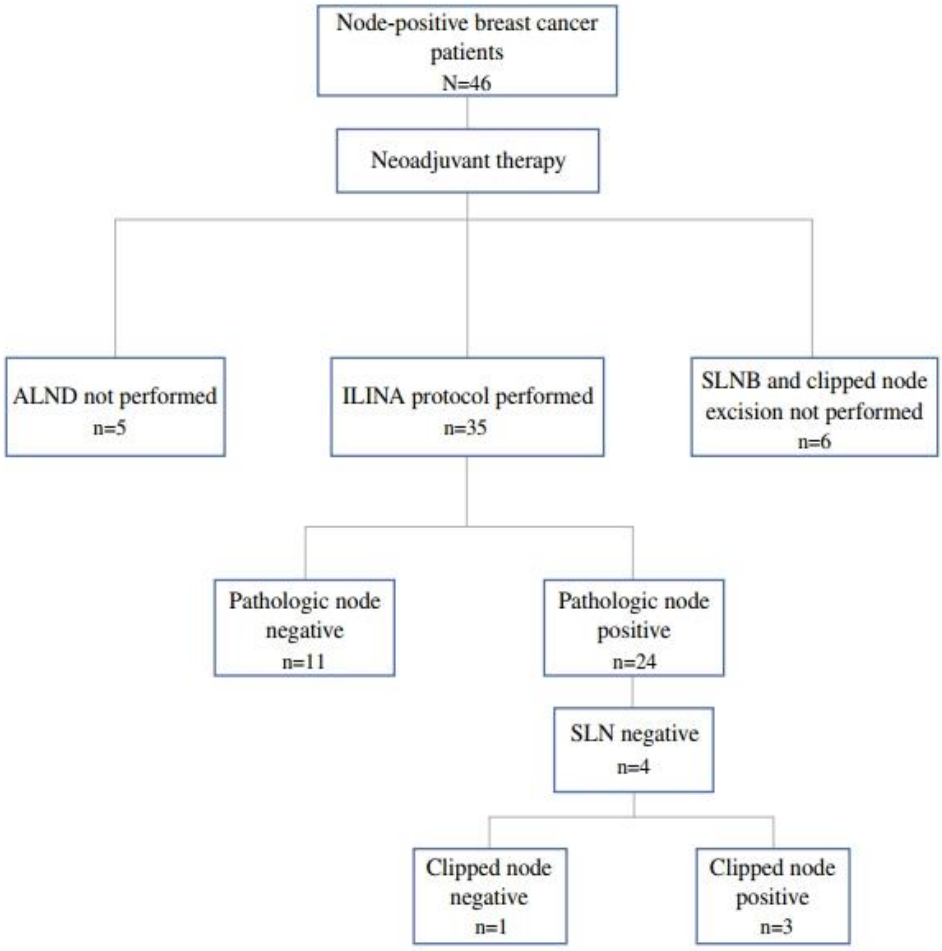

FIG. 2 Flowchart of all patients included in the study. *ALND* axillary lymph node dissection, *SLNB* sentinel lymph node biopsy

DISCUSSION

According to the results obtained, IOUS-guided excision of the clipped node can be performed successfully after NAT without complications, as long as the clip is US-visible prior to surgery.

IOUS has been widely demonstrated to be a more accurate and effective tool compared with wire localization[20] and palpation-guided surgery.[21] Moreover, since the introduction of US-visible markers, IOUS has been extended to breast-conserving surgery after NAT.[18,22] IOUS eases the surgical schedule and significantly reduces the healthcare costs related to other localization techniques.[23] Using IOUS in the axilla allows the surgeon to verify the resected clip without having to send the specimen to the Radiology Department.

IOUS-guided resection of the clipped node was performed in all patients regardless of the type of axillary surgery, as part of the learning curve. Breast surgeons need to have expertise in IOUS to perform IOUS-guided clipped node excision as this technique is more challenging than IOUS-guided breast lumpectomy. Although < 10 breast US-guided procedures seem to be enough to reach expertise,[24] the number of procedures required to excise the axillary clip after NAT is currently being explored.

The increasing use of NAT has brought SLNB after NAT to the front line. Prospective studies, such as ACOSOG Z1071,[7] the SENTINA trial,[12] and the SN FNAC study,[8] have shown that an FNR < 10% can be achieved if more than two SLNs are excised, a dual tracer technique is used, and ITCs are considered positive nodes. In order to decrease the FNR, placing a marker into the positive node prior to NAT has been explored. First described by Donker

TABLE 2 Characteristics of patients included in the trial versus patients excluded

	Patients included ($n = 35$) (%)	Patients excluded ($n = 11$) (%)	p Values
ALND not performed		5 (45.5)	
SLNB not performed (+ FNA)		2 (18.2)	
SLN not localized		2 (18.2)	
Clip not preoperatively seen		2 (18.2)	
Molecular subtypes			0.266
Luminal A	2 (5.7)	2 (18.2)	
Luminal B HER2-negative	23 (65.7)	4 (36.4)	
Luminal B HER2-positive	4 (11.4)	2 (18.2)	
HER2, no luminal	3 (8.6)	2 (18.2)	
Triple negative	3 (8.6)	1 (9.1)	
Clinical T stages			0.387
T1	3 (8.6)	1 (9.1)	
T2	24 (68.6)	6 (54.5)	
T3	8 (22.9)	3 (27.3)	
T4	0 (0)	1 (9.1)	
Number of abnormal nodes on ultrasound at diagnosis			0.329
1	16 (45.7)	7 (63.4)	
2	7 (20.0)	2 (18.2)	
3	8 (22.9)	1 (9.1)	
> 3	4 (11.4)	1 (9.1)	
Type of neoadjuvant therapy			0.011
Endocrine	3 (8.6)	3 (27.3)	
Chemotherapy	26 (74.3)	3 (27.3)	
Chemotherapy + anti-HER2	6 (17.1)	5 (45.5)	
Median time interval (weeks)[a]	31.9	32.0	0.728

ALND axillary lymph node dissection, *SLNB* sentinel lymph node biopsy, *FNA* fine-needle aspiration, *SLN* sentinel lymph node, *HER2* human epidermal growth factor receptor 2

[a]Time interval from placement of the clip to intraoperative ultrasound-guided excision of the clipped node

et al., who named it the 'MARI procedure', the technique consisted of placing a 125-iodine seed on the biopsy-proven node positive at the time of diagnosis, left in place throughout NAT, and excised during completion ALND. However, no SLNB was performed. In a group of 100 patients, the marked node was identified and surgically excised prior to ALND, with a reported FNR of 7% (95% CI 2–16),[14] which is higher than the reported rates for other clipped procedures. Recently, Caudle et al. published data for the TAD procedure.[15] This procedure involves inserting a clip at diagnosis and a 125-iodine seed into the clipped node a few days prior to surgery. Clipped node excision, SLNB, and completion ALND were then performed. The detection rate of SLN was 94.9%, using dual tracers in 55% of patients, with a mean number of SLNs removed of 2.7. Of the 120 patients with residual nodal disease, the FNR for the clipped node alone was 4.2% (95% CI 1.4–9.5), and in 85 patients evaluable for the TAD procedure, the FNR for SLNB alone was 10.6% (95% CI 3.6–23.1). For the combination of SLNB and clipped node excision, the FNR decreased to 2.0% (95% CI 0.05–10.7), although a statistical significance was not attained ($p = 0.13$), presumably because of the small size of the cohort.[15] These results are similar to those of our study, with an FNR for the ILINA protocol of 4.1% (95% CI 0.1–21.1%), which makes this technique useful after NAT.

Nguyen et al.[25] reported the use of IOUS with radioactive seed placed on the clipped node. US guidance was used in 18 of the 25 patients included in the study. IOUS localization was performed by a breast imaging radiologist, which is different from our study where the procedure was performed by breast surgeons.

Theoretically, Hydromark clips are visible for 6 months, which is more or less the duration of NAT treatments; however, sometimes they cannot be identified after NAT, as previously described.[18] In our study, there were no differences between the duration of treatment and clip visibility, but visibility of the Hydromark clip will worsen

the longer it is placed in the axilla. In cases where US cannot identify the clip, it can be localized with a needle localization, but, even without localization, 77% of cases will be removed using the SLNB procedure. Due to these issues, we are exploring other US visible clips that may retain US visibility for more than 6 months.

An important aspect to be considered when a Hydromark is employed is that the pathologist needs to be informed that the node sent for intraoperative pathology examination includes the Hydromark. Lymph nodes marked with the Hydromark show a pseudocystic lesion lined by histiocytes and foreign body reaction that can be misinterpreted as granulomatous changes, or even neoplastic cells and reported as a positive node, as Nguyen et al. have also shown.[25]

The number of SLNs excised in the presence of a clipped node is still unknown. In most of the reported series, the SLN does not correspond to the clipped node in almost 23% of patients. This occurs mainly in patients with a high metastatic burden in the axilla, as suspected by the presence of $\geq$ 4 abnormal nodes on initial US.[15] In our study, a median of 3.3 SLNs was excised; the only FN was in a patient who had 1 SLN excised.

IOUS-guided clip excision has some advantages over other methods. In most cases, no other interventions need to be performed prior to surgery, and the clip is verified intraoperatively by US. The use of Hydromark clips does not pose any problems related to radioactivity as it occurs with iodine seed and does not create additional costs. Due to the low FNR obtained in our study, the next step will be to spare ALND for patients with a clipped node and negative SLNs after NAT.

CONCLUSION

IOUS-guided excision of the axillary clipped node during the SLNB procedure is feasible, safe, and accurate in axillary staging and may be an excellent alternative to surgery based on radioactive seeds.

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Listado de abreviaturas

TAD	Disección axilar dirigida	**BAG**	Biopsia aguja gruesa
TSP	Tratamiento sistémico primario	**PAAF**	Punción aspiración aguja fina
SLE	Supervivencia libre enfermedad	**BGC o GC**	Biopsia del ganglio centinela
SG	Supervivencia global	**VPN**	Valor predictivo negativo
pCR	Respuesta patológica completa	**FN**	Falsos negativos
RCB	Residual Cancer Burden	**NHT**	Hormonoterapia neoadyuvante
LDNA	Linfadenectomía axilar	**NA**	Neoadyuvancia

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RESEARCH ARTICLE

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Leveraging the increased rates of pathologic complete response after neoadjuvant treatment in breast cancer to de-escalate surgical treatments

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Abstract

Introduction: Breast conservative surgery (BCS) and sentinel lymph node biopsy (SLNB) after neoadjuvant treatment (NAT) is safe and effective for selected patients. This aim of this study is to evaluate the impact of anatomic site of response on outcomes and to assess the real population who may benefit from nonsurgical approaches after NAT.

Material and Methods: From a prospectively maintained database, patients with T1-4 N0-2 breast cancer undergoing NAT were identified. Clinicopathological and survival rates were compared in relation to response and anatomic site of response.

Results: Six hundred and forty-six patients were included in the study. Pathologic complete response (pCR) was an independent factor for BCS and SLN. HER2 positive and TN tumors with cN0 achieving a breast pCR remain ypN0 ($p = .002$). Residual axillary disease was associated with breast residual tumor ($p = .05$) and subtype ($p = .001$). With a median follow up of 35.25 months, patients with any pCR had improved survival when compared with partial response, but not significant differences between pCR, axillary pCR, or breast pCR.

Conclusion: Achieving a pCR increases BCS and SLN. In selected subgroups, sparing any axillary surgery after NAT maybe feasible. In cN+ patients, any pCR was associated with survival, but not the anatomic site of response.

KEYWORDS

breast neoplasms, de-escalation, neoadjuvant therapy, pathologic complete response, survival

1 | INTRODUCTION

Neoadjuvant treatment (NAT) has increasingly being used in early stage breast cancer and the introduction of new effective systemic treatments has changed the surgical approach in this setting. Downsizing the tumor has enabled surgeons to increase rates of breast conserving therapy (BCS),[1,2] and downstaging has enabled to lessen axillary surgery while associating with better prognosis. The controversy on the safety of BCS after NAT reported by the EBCCTC meta-analysis requires careful interpretation.[3] There is no doubt that nowadays, BCS after NAT is performed in a more accurate way than it was performed in some of the randomized clinical trials included in the meta-analysis.[4] The use of different methods of guiding BCS have decreased re-excision rates, reduced volume of healthy tissue excised, and have supported the concept that there is no need to excise the pretreatment volume of tumor.[5,6] It is also important to realize that

many of the risk factors for locoregional recurrence (LRR) after BCS also predict for LRR after mastectomy.[7,8] Rates of BCS after NAT have increased in HER2 positive and TN breast cancer who achieve an excellent response,[9] rates that historically had been the lowest.[10] There is now enough evidence to suggest that, in the multidisciplinary management of breast cancer, BCS after NAT is safe and effective for adequately selected patients.[2,9]

The NSABP B18 trial introduced the concept that NAT decreased the incidence of nodal metastasis and showed that the use of sentinel lymph node biopsy (SLNB) after NAT could spare axillary node dissection (ALND) in patients with clinically negative axilla.[11] Several studies have shown that in clinically negative axilla, SLNB achieves high identification rates (>90%) and low false negative rates (<10%), and it has become a standard procedure.[12,13] In clinically positive axilla, three prospective, single-arm studies have reported an overall false-negative rate from 8% to 14% for SLN after NAT.[14–16] Refinement of surgical techniques has reduced false negative rates to less than 5%. It includes placing a marker in the positive node at the time of diagnosis and excising it at the time of the axillary surgery with or without SLN.[17–20] All these findings have reflected in a substantially decreased rates of ALND over the last years.[21]

As effective systemic therapy increases pathologic complete response (pCR) rates in HER2 and TN breast cancer (up to 50%), and breast imaging improves the accuracy in detecting residual disease, the surgical community have investigated whether it is feasible to go from less surgery to no surgery. In HER2 positive and TN subtypes, there are several ongoing trials looking at no breast surgery[22,23] or no axillary surgery in patients with cN0 at diagnosis. (https://clinicaltrials.gov/ct2/show/NCT04101851). Studies have shown that it is very unlikely, in clinically negative axilla in HER2 positive and TN breast cancer, to have a positive SLN if the breast achieves a pCR.[24,25] The implications of these surgical de-escalation on LRR or survival are still unknown, with few retrospective studies showing low LRR in selected patients.[26] Besides, if de-escalation approaches and survival outcomes are influenced by the anatomic site of response still remain largely unexplored.[27]

The aim of this study is to evaluate the impact of anatomic site of response on surgical treatments and outcomes and to assess the real population who may benefit from nonsurgical approaches after NAT.

2 | MATERIALS AND METHODS

2.1 | Study population

A prospectively maintained database included 646 women undergoing NAT from January 2010 to December 2018 in two Spanish hospitals (Hospital Vall d'Hebron, Barcelona and Clínica Universidad de Navarra, Madrid). Patients were assessed by a multidisciplinary team at diagnosis. All women underwent clinical staging that included mammogram, breast, and axillary ultrasound at diagnosis and after NAT. MRI was performed in the majority of patients. A single marker was placed in the tumor at diagnosis (Hydromark, Mammotome). All suspicious axillary lymph nodes underwent fine needle aspiration biopsy for diagnosis and an US visible marker was placed in the positive axillary node (mainly after 2015). Patients were classified as luminal A, B, HER2 positive and triple negative cancer based on immunohistochemistry assessment. This study was approved by the Institutional Review Board.

2.2 | Study protocol

At the end of the NAT, patients were assessed by the same radiological imaging as used for diagnosis. BCS was decided based on baseline characteristics and response to treatment. BCS included resection of the residual tumor or the clip with a rim of tissue around it guided by intraoperative ultrasound (IOUS). All patients with BCS underwent radiation therapy to the breast as part of the locoregional treatment. Radiation therapy to the mastectomy site and nodal basins was delivered at the discretion of the radiation oncologist and following national guidelines. For cN0 patients, axillary surgery generally consisted in SLN alone, or SLN + ALND as part of the initial validation trials. Similarly, in cN+ patients, SLN + ALND was usually performed as part of the validation trials, and in those with a marker in the positive axillary node, an IOUS guided excision of the clipped node was performed. SLN was done using dual tracer (radioisotope + blue dye).

Intraoperative pathologic assessment of margins was performed by a dedicated breast pathologist in all cases as well as intraoperative assessment of SLNs by frozen section.

pCR was defined as the absence of invasive tumor in both the breast and axilla. Axillary pCR (AXpCR) as the absence of invasive tumor in the axilla and breast pCR (BrpCR) as absence of invasive tumor in the breast.

Chemotherapy regimens were dictated by ongoing clinical trials or at the discretion of the medical oncologist. Anti-HER2 treatment was administered to all HER2 positive breast cancer patients and depending on the period and clinical trial it included different antibodies.[28,29] Patients with hormone receptor–positive disease received adjuvant endocrine therapy.

2.3 | Endpoints and statistical methods

Data assessed included age, date of diagnosis, histology, clinical stage, nuclear grade, estrogen receptor (ER), progesterone receptor (PR), HER2 status, and pathological stage.

Events were evaluated from the date of diagnosis. Distribution of clinical factors between groups were compared using the *U* Mann–Whitney test for continuous and χ^2 test for categorical variables. Differences between different groups were performed using the analysis of variance test. Survival curves were compared with the Kaplan–Meier method. Multivariate regression was employed for comparison and to explore the effect of confounding factors.

TABLE 1 Baseline characteristics

	Total
N	646
Age, years (range)	53.8 (24–95)
Histological type	
IDC	573 (88.7%)
ILC	49 (7.59%)
Other	24 (3.72%)
Grade	
I	28 (4.33%)
II	344 (53.25%)
III	268 (41.49%)
Missing	6 (0.93%)
Estrogen status	
Negative	177 (27.4%)
Positive	469 (72.6%)
Progesterone stats	
Negative	272 (42.11%)
Positive	374 (57.89%)
HER2 status	
Negative	504 (78.02%)
Positive	142 (21.98%)
Ki67 status (%)	
≤20	144 (22.29%)
>20	502 (77.71%)
Molecular subtype	
Luminal A	101 (15.63%)
Luminal B HER2 negative	271 (41.95%)
HER2 positive	142 (21.99%)
Triple negative	132 (20.43%)
Breast surgery	
BCS	370 (57.28%)
Mastectomy	276 (42.72%)
Axilar surgery	
SLNB	235 (36.38%)
SLNB + ALND	179 (27.71%)
ALND	228 (35.29%)
Missing	4 (0.62%)
Initial T stage	
cT1	29 (6.97%)
cT2	410 (63.47%)
cT3	124 (19.2%)
cT4	62 (9.60%)
cTx	1 (0.15%)
Missing	4 (0.62%)
Initial N stage	
cN0	265 (41.02%)
cN1	285 (44.12%)
cN2	36 (5.57%)
cN3	59 (9.13%)
Missing	1 (0.15%)
Initial TN stage	
I	16 (2.48%)
II	429 (66.41%)
III	197 (30.5%)
Unknown	4 (0.62%)
pCR	
No	510 (79.57%)
Yes	136 (21.05%)

Abbreviations: ALND, axillary node dissection; BCS, breast conservative surgery; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; pCR, pathologic complete response; SLNB, sentinel lymph node biopsy.

All calculations were performed with Stata software (Stata/SE 14; Stata Corp). Two-tailed *p* values .05 or less were considered statistically significant.

3 | RESULTS

3.1 | Overview

Six hundred and forty-six patients were included in the analysis. Mean patient age at diagnosis was 53.8 years (range, 24–95), most tumors were Grade II (53.25%), ER+ (72.6%), PR+ (57.89%), and had a Ki67 >20% (77.71%). Among these, 534 patients (82%) had clinical T2 and T3 tumors and 380 patients (59%) were cN+ at presentation. Clinicopathologic characteristics of the study population are listed in Table 1.

Overall pCR (breast + axilla) was achieved in 131 patients (21.05%), while BrpCR in 152 patients (23.57%) and AxpCR in 105 patients (36.84%). There were significant differences on pCR depending on molecular subtype, with the highest rates occurring in HER2 positive patients (45.07%), followed by TN tumors (33.3%), 10.33% in luminal B HER2 negative, and no pCR in luminal A ($p = .001$).

3.2 | Breast surgery

Overall, 370 patients (57.28%) underwent BCS while 276 patients (42.72%) underwent mastectomy. Women receiving BCS were significantly younger, had cN0 and achieved higher rates of pCR (23.78 vs. 15.94%). Characteristics related to type of surgery are shown in Table 2. In those patients who achieved a pCR, rates of BCS increased significantly in all subgroups from 54.86% to 66.67% ($p = .01$), but especially in luminal B HER2 negative. Multivariate analysis showed that pCR is and independent factor for patients

TABLE 2 Comparison between surgical groups

	BCS	Mastectomy	*p*
N	370	276	
Age, mean (range)	56.26 (29–87)	52.66 (24–95)	.004
Histological type			.02
CDI	339 (91.62%)	234 (84.78%)	
CLI	20 (5.41%)	29 (10.51%)	
Other	11 (2.97%)	13 (4.71%)	
Grade			.9
I	15 (4.05%)	28 (4.71%)	
II	197 (53.24%)	147 (53.26%)	
III	155 (41.89%)	113 (40.94%)	
Missing	3 (0.81%)	3 (0.81%)	
Estrogen status			.23
Negative	108 (29.19%)	69 (25%)	
Positive	262 (70.81%)	207 (75%)	
Progesterone stats			.89
Negative	155 (41.89%)	117 (42.39%)	
Positive	215 (58.11%)	159 (57.61%)	
HER2 status			.86
Negative	290 (78.38%)	214 (77.82%)	
Positive	80 (21.62%)	61 (22.18%)	
Ki67 status (%)			.3
≤20	77 (20.81%)	67 (24.28%)	
>20	293 (79.19%)	209 (75.72%)	
Molecular subtype			.89
Luminal A	56 (15.14%)	45 (16.30%)	
Luminal B	155 (41.89%)	116 (42.03%)	
HER2 positive	80 (21.62%)	62 (22.47%)	
Triple negative	79 (21.35%)	53 (19.2%)	
Axillar surgery			.0001
SLNB	177 (47.84%)	58 (21.01%)	
SLNB + ALND	111 (30%)	68 (24.64%)	
ALND	79 (21.35%)	149 (53.99%)	
Missing	3 (0.81%)	1 (0.36%)	
Initial T stage			.85
cT1	29 (7.84%)	16 (5.8%)	
cT2	234 (63.24%)	176 (63.77%)	
cT3	69 (18.65%)	55 (19.93%)	
cT4	35 (9.46%)	27 (9.78%)	
cTx	1 (0.27%)	0	
Missing	2 (0.54%)	2 (0.72%)	
Initial N stage			.001
cN0	190 (51.35%)	75 (27.17%)	
cN1	149 (40.27%)	136 (49.28%)	
cN2	16 (4.32%)	20 (7.25%)	
cN3	15 (4.05%)	44 (15.94%)	
Missing	0	1 (0.36%)	
Pathological T stage			.001
ypT0	119 (32.16%)	72 (26.09%)	
ypT1	215 (58.11%)	130 (47.1%)	
ypT2	36 (9.73%)	55 (19.93%)	
ypT3	0	13 (4.71%)	
ypT4	0	5 (1.81%)	
Missing		1 (0.36%)	
Pathological N stage			.001
ypN0	233 (62.97%)	122 (44.20%)	
ypN0 (itc)	0	4 (1.45%)	
ypN1mi	22 (5.95%)	16 (5.8%)	
ypN1	87 (23.51%)	79 (28.62%)	
ypN2	25 (6.76%%)	45 (16.3%)	
ypN3	3 (0.81%)	9 (3.26%)	
Missing	0	1 (0.36%)	
pCR			.01
No	280 (75.67%)	230 (83.33%)	
Yes	90 (24.32)	46 (16.67%)	
Initial stage			.0001
I	13 (3.51%)	3 (1.09%)	
II	265 (71.62%)	164 (59.42%)	
III	90 (24.32%)	107 (38.77%)	
Unknown	2 (0.54%)	2 (0.72%)	

Abbreviations: ALND, axillary node dissection; BCS, breast conservative surgery; CDI, invasive ductal carcinoma; CLI, invasive lobular carcinoma; pCR, pathologic complete response; SLNB, sentinel lymph node biopsy.

undergoing BCS (hazards ratio = 1.64 [95% confidence interval: 1.1–2.45], $p = .01$) and cN+ is a significant factor for receiving a mastectomy compared with cN0 ($p = .001$).

Only 142 patients with HER2 breast tumors were assessed for BCS eligibility before starting NAT. Of this, 115 (81%) had an indication for mastectomy before NAT with conversion to BCS in 53 patients (46.09%), increasing the BCS rates up to 56.34% in the whole cohort.

3.3 | Axillary surgery

Three hundrd and eighty (58.97%) patients presented with clinically positive axilla (cN+) and 265 patients (41.02%) with cN0. There were significant differences in axillary involvement at diagnosis among subtypes with the highest involvement in luminal B HER2 negative (64.94%) ($p = .002$) as well as significant differences in AxpCR with the highest pathologic response in HER2 positive patients (75.86%) ($p < .001$). In univariate analysis, ER negative ($p = .006$), mastectomy ($p > .001$), and higher clinical stage were risk factors for ALND, regardless of type of response ($p = .0001$). In multivariate analysis, cT4, mastectomy, cN, and ypN remain as independent factors for undergoing an ALND.

3.4 | Pathologic axillary response in cN0 patients

Of 265 patients with cN0, 214 patients (80.7%) remained as ypN0 and 51 (19.3%) had a positive SLN at final pathology. Patients who presented with initial cN0 disease but did not achieve a BrpCR had a 5.8% chance of having positive nodal disease at final pathology. All HER2 positive and TN tumors presenting as cN0 and achieving a BrpCR remain pN0 at final pathology ($p = .002$) (Table 3). Of 265 patients, 217 (82%) patients had a preoperative axillary ultrasound, yielding a sensitivity and specificity of 28% and 94% respectively. Of 51 patients with a positive axilla, 24 (47%) patients had macrometastasis, 23 (45%) micrometastasis, and 4 (0.7%) isolated tumor cells.

According to breast residual disease, 68 (25.66%) women achieved BrpCR. Of them, a positive axillary node was found in four patients (5.88%), two of them were luminal A tumors and the other two were luminal B HER2 negative tumors.

The majority of cN0 patients (79.25%) underwent a SLN after NAT as axillary treatment.

3.5 | Pathologic axillary response in cN1 patients

Of 380 patients with cN+, 141(37.1%) achieved an AxpCR. Patients who presented with initial cN+ but did not achieve a BrpCR had a higher risk of having positive nodal disease at final pathology ($p < .001$) (Table 3). Eighty-four (22.1%) patients achieved a BrpCR, of them 68 patients (80.95%) had an AxpCR. On the other hand, of the 296 (77.9%) women that did not achieve a BrpCR, only 73 (24.66%) had an AxpCR. The majority of patients (57%) underwent an ALND while 36% underwent SLN + ALND. Patients with complete radiologic response were allocated to SNLB + ALND surgery as part of the validation protocol. HER2+ and TN patients were more likely to receive only a SLNB than Luminal A or B tumors ($p = .001$) if SLN would have been done as the only procedure. False negative rate of SLN was 2.94% (4/136). Interestingly, only one SLN was excised in all four patients. Average number of excised nodes was 2.77, with a median of 3 (range, 1–10). Residual axillary disease was significantly associated with residual tumor in the breast ($p = .05$) and with subtype ($p = .001$).

3.6 | Local recurrences and metastasis

Mean follow up was 35.25 months (range, 1.8–85.6 months). Forty-one patients (6.43%) developed LRR. Those patients achieving a pCR developed significantly less LRR compared with pathologic partial response (pPR), respectively (1.5% vs. 7.58%) ($p = .002$). Consequently, disease-free survival (DFS) was significantly better for those who achieved a pCR versus no pCR (96.97% vs. 86.2%) ($p = .001$). Multivariate analysis showed that cT3/4, cN2/3, negative ER or PR status, ypT stage, and ypN3 were significant factors for pCR.

TABLE 3 Pathologic node status by response, stratified by cTN category

Breast pCR			Breast pPR		
Subtype	ypN0, *n* (%)	ypN + *n* (%)	Subtype	ypN0, *n* (%)	ypN + *n* (%)
Luminal A					
cT1N0	0	0	cT1N0	4 (100)	0
cT1N+	0	0	cT1N+	0	5 (100)
cT2N0	0	2 (100)	cT2N0	14 (58.33)	10 (41.67)
cT2N+	0	0	cT2N+	2 (7.14)	26 (92.86)
cT3N0	0	0	cT3N0	10 (62.5)	6 (37.5)
cT3N+	0	1 (100)	cT3N+	0	10 (100)
cT4N0	0	0	cT4N0	3 (60)	2 (40)
cT4N+	0	0	cT4N+	1 (20)	4 (80)
Total	0	3 (100)	Total	34 (35.05)	63 (64.95)
Luminal B HER2 negative					
cT1N0	0	0	cT1N0	3 (75)	1 (25)
cT1N+	1 (100)	0	cT1N+	4 (26.67)	11 (73.33)
cT2N0	11 (100)	0	cT2N0	40 (74.07)	14 (25.93)
cT2N+	4 (50)	4 (50)	cT2N+	24 (25)	72 (75)
cT3N0	3 (60)	2 (40)	cT3N0	10 (71.43)	4 (28.57)
cT3N+	3 (75)	1 (25)	cT3N+	5 (17.86)	23 (82.14)
cT4N0	2 (100)	0	cT4N0	2 (66.67)	1 (33.33)
cT4N+	0	1 (100)	cT4N+	5 (22.73)	17 (77.27)
Total	24 (75)	8 (25)	Total	93 (39.41)	143 (60.59)
Luminal B HER2 positive					
cT1N0	2 (100)	0	cT1N0	2 (66.67)	1 (33.33)
cT1N+	1 (100)	0	cT1N+	2 (66.67)	1 (33.33)
cT2N0	13 (100)	0	cT2N0	16 (88.89)	2 (11.11)
cT2N+	14 (100)	0	cT2N+	7 (28)	18 (72)
cT3N0	1 (100)	0	cT3N0	1 (100)	0
cT3N+	6 (100)	0	cT3N+	3 (50)	3 (50)
cT4N0	1 (100)	0	cT4N0	2 (66.67)	1 (33.33)
cT4N+	3 (100)	0	cT4N+	2 (66.67)	1 (33.33)
Total	41 (100)	0	Total	35 (56.45)	27 (43.55)
HER2 positive					
cT1N0	0	0	cT1N0	0	0
cT1N+	1 (100)	0	cT1N+	0	0
cT2N0	4 (100)	0	cT2N0	5 (100)	0

(Continues)

TABLE 3 (Continued)

Breast pCR			Breast pPR		
Subtype	ypN0, *n* (%)	ypN + *n* (%)	Subtype	ypN0, *n* (%)	ypN + *n* (%)
cT2N+	11 (91.67)	1 (8.33)	cT2N+	4 (44.44)	5 (55.56)
cT3N0	0	0	cT3N0	0	0
cT3N+	5 (100)	0	cT3N+	0	0
cT4N0	1 (100)	0	cT4N0	0	0
cT4N+	1 (100)	0	cT4N+	0	1 (100)
Total	23 (95.83)	1 (4.17)	Total	9 (60)	6 (40)
Triple negative					
cT1N0	2 (100)	0	cT1N0	1 (100)	0
cT1N+	0	1 (100)	cT1N+	0	3 (100)
cT2N0	20 (100)	0	cT2N0	23 (88.46)	3 (11.54)
cT2N+	11 (73.33)	4 (26.67)	cT2N+	10 (38.46)	16 (61.54)
cT3N0	3 (100)	0	cT3N0	10 (90.91)	1 (9.09)
cT3N+	4 (66.67)	2 (33.33)	cT3N+	3 (42.86)	4 (57.14)
cT4N0	1 (100)	0	cT4N0	3 (100)	0
cT4N+	3 (75)	1 (25)	cT4N+	0	3 (100)
Total	44 (84.62)	8 (15.38)	Total	50 (62.5)	30 (37.5)

Abbreviations: cTN, cardiac troponin; pCR, pathologic complete response; pPR, pathologic partial response.

3.7 | Overall survival

During follow up, 42 patients (6.5%) developed metastasis, including 34 patients (80%) with both LRR and distant metastasis. Patients with pCR had significantly better survival. (98.5% vs. 92.22%, $p = .01$). There were no differences in overall survival (OS) related to the type of axillary surgery ($p = .35$). Multivariate analysis showed that mastectomy does not remain as an independent factor for survival. Only cT4, cN+, PR, ypT, and ypN3 remain as independent factors for worse prognosis.

3.8 | Differences in DFS or OS regarding the site of response in cN+ patients

Of 380 patients with cN+, 68 (17.89%) patients achieved a pCR, 73 patients (19.21%) AxpCR, and 16 patients (4.21%) a BrpCR. Univariate analysis did not show significant differences related to initial cT or cN status, although women achieving pCR at any site were younger, had higher nuclear grade tumors, ER or PR negative, HER2 positive tumors and Ki67 >20% ($p < .001$). Patients achieving pCR or AxpCR significantly had SLNB performed ($p < .001$). There were no differences in DFS or OS among pCR (breast and axilla), AxpCR and BrpCR ($p = .30$), although there were differences when pPR was included, with pPR having worse outcomes ($p = .05$) (Figures 1 and 2). Multivariate analysis showed that initial N3 lymph status was a significantly predictor of worse prognosis.

4 | DISCUSSION

Our study shows that the high rates of response seen in patients with triple-negative and HER2-positive cancers receiving NAT make these patients ideal candidates for NAT to allow more conservative breast and axillary surgery. The finding that BrpCR is highly correlated with nodal status after NAT, and that all HER2 positive and TN cancers presenting as cN0 who achieve a BrpCR remain ypN0, confirm that this is the selected group for no axillary surgery in future clinical trials.

In this cohort, achieving pCR increases rates of BCS and/or SLNB (especially in certain subtypes) and achieving any type of pCR correlates with survival outcomes.

4.1 | Breast surgery

Our data demonstrated that pCR is an independent factor for patients undergoing BCS and rates of BCS are increased across all subgroups. Similarly, to other studies, one of the limitations has been that some patients were candidates for BCS before NAT, so the true rate of downstaging cannot be determined.[30] In our study, only type of surgery in HER2 positive cancers were assessed before NAT, and it showed a conversion to BCS in 46% of patients who were eligible for mastectomy before NAT. This clearly explain the need for breast surgeons to participate in the design of neoadjuvant clinical trials that includes BCS as an end-point.[31] Institutional studies have shown a conversion rate of 75% from BCS-ineligible to BCS-eligible when assessment of BCS is done before starting NAT.[32]

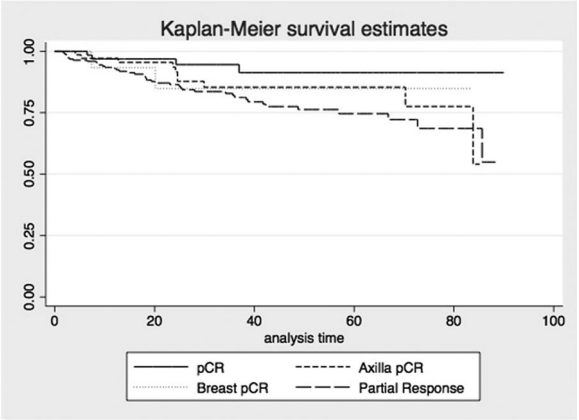

FIGURE 1 Disease-free survival regarding anatomic site of response. pCR, pathologic complete response [Color figure can be viewed at wileyonlinelibrary.com]

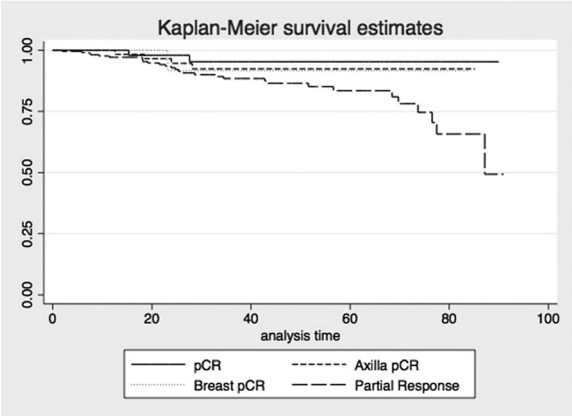

FIGURE 2 Overall survival regarding anatomic site of response. pCR, pathologic complete response [Color figure can be viewed at wileyonlinelibrary.com]

Women having BCS were significantly younger, and whether this was related to specific patient, tumor, or surgeon factor that affect the decision-making process is unknown. It also may reflect trends in Europe as mastectomy rates have not increased parallel to the increase in USA.[33]

At present, prospective clinical trials, where breast surgery is omitted in patients with HER2 positive and TN tumors with an excellent response to NAT and who achieve a BrpCR by image-guided biopsy of the tumor bed, are ongoing.[23]

4.2 | Axillary surgery

One of the benefits of NAT is the ability to downstage axillary status enabling the possibility of performing SLNB and sparing an ALND in selected groups. The rate of axillary nodal response depends on tumor biology, with higher rates in HER2 positive and TN tumors, as shown in our study. Rates of AxpCR in HER2 positive tumors reaches 76%. This is consistent with other studies in the era of modern neoadjuvant antiHer2 therapies.[34] But even in the other subgroups, as luminal B HER2 negative tumors, 28% of cN1 patients could spare an ALND. Clinical and pathological axillary status as well as cT4 and mastectomy are independent factors for ALND, although not tumor subtype. Therefore, selection of patients for this approach is crucial to de-escalate the axillary surgery.

Correlation between BrpCR and AxpCR has been studied when considering de-escalation approaches to the breast and/or the axilla. BrpCR is highly correlated with nodal status after NAT. In patients with cN+, 81% of women achieving BrpCR also achieve an AXpCR. This rate is lower than the 90% rate in the study by Tadros,[24] which includes only HER2 positive and TN tumors, and higher than the 45% of AxpCR reported by Saimei et al.[35] including all tumor subtypes. Tadros et al.[24] reported a relative risk for positive nodal metastases after NAT of 7.4%, in HER2+ or TN patients without a BrpCR compared with BrpCR, and similar to the 5.8% chance reported in our study. It is clear that patients without BrpCR do not seem to be appropriate for omission of axillary surgery after NAT.

In cN0 patients, BrpCR achieved after NAT is strongly correlated with ypN0, especially in HER2 positive (regardless of ER status) and TN subtypes. In these two subtypes, our data show that 100% of patients with cN0 who achieve BrpCR present with ypN0, similar to the 97.7% in the study by from Samiei et al.[35] and the 98% in patients with BrpCR in the study by Barron et al.,[36] which supports consideration of omission of axillary surgery in this subset of patients.

Adequate SLN mapping post-NAC, defined as the identification and excision of the clipped nodes along with greater than 2 SLNs, has yield a FN rate below 5% in different prospective studies.[17,18,20] Among patients with adequate mapping, 37% achieved AxpCR and could have been spared an ALND. These rates are consistent with the results of the ACOSOG Z1071 trial.[20] In our study, the majority of patients had a completion ALND as part of the validation trial, although nowadays, those patients would have not had an ALND.

Results from this study and others support the ongoing clinical trial where patients who had cN0 disease at presentation and no residual breast disease by percutaneous biopsy after NAT, may undergo no axillary surgery (https://clinicaltrials.gov/ct2/show/NCT04101851) and those with cN1 disease at presentation undergo SLNB with resection of the clipped node proceeding to axillary lymph node dissection if any axillary lymph node is positive.

4.3 | Anatomic site of response

As others, we have confirmed in this study that pCR is associated with improved DFS and OS as well as BrpCR and/or AxpCR when compared with partial pathologic response. Node-positive patients with BrpCR only or AxpCR only had improved survival compared to those with pPR, but no differences with those experiencing pCR (both breast and axilla). Similar findings have been reported by Lee et al.,[27] where any pCR was associated with improved survival versus partial response and that any excellent response to NAC has prognostic value. These results contrast with the study by Fayanju et al.[37] where a subset of node-positive patients with BrpCR or AxpCR had improved survival compared to those experiencing no change in stage but had worse survival compared to those experiencing pCR in both the breast and axilla. Different length in follow up may be one of the reasons for these differences.

We also evaluated the impact of type of surgery on outcomes. In our cohort, patients achieving pCR or AxpCR were more likely to have a SLNB and also patients achieving a pCR had increased rates of BCS. In multivariate analysis, mastectomy and ALND were not independent factors for survival. Contrary to this finding, Fayanju et al.[37] found that mastectomy was associated with worse adjusted OS, association that the authors admit, may be due to variables that could not be adjusted for in the multivariate analysis.

4.4 | Locoregional recurrence and survival rates

As expected, and similarly to other reported studies,[38] more advanced disease at presentation correlated with worse DFS and OS, with TN breast cancer having the worse prognosis. For a relatively short median F/U of 35 months, DFS and OS rate in those patients achieving a pCR were excellent (96.9% and 98.5%, respectively) and correlates with other studies. The reason for the excellent outcome is related to the introduction in routine clinical practice of highly effective treatments in specific subtypes of breast cancer, in particular anti-HER2 agents. Five-year LRR rates in our study were similar to other reported cohorts.[8,30]

5 | CONCLUSION

Additional step forward towards optimal selection of patients who will benefit from de-escalating in locoregional treatments after NAT is ongoing. It will impact on reducing morbidity while achieving equal or better long-term outcomes, and reflects the real multidisciplinary breast cancer care at the Institutional level. Our study proves that achieving a pCR increases BCS as well as the use of SLNB and that in selected subgroups, as HER2 positive and TN patients with cN0, sparing any axillary surgery after NAT maybe an option, as it is extremely unlikely, to have a positive SLN if the breast achieves a pCR.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Feasibility and safety of targeted axillary dissection guided by intraoperative ultrasound after neoadjuvant treatment

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ABSTRACT

Background: Axillary management in cN + axillary nodes after neoadjuvant systemic therapy (NST) in breast cancer (BC) remains under research with the aim of de-escalation of axillary node dissection (ALND). Several axillary guided localization techniques have been reported. This study evaluates the safety of intraoperative ultrasound (IOUS) guided targeted axillary dissection (TAD) in a large sample after the results of ILINA trial.

Materials: Prospective data have been collected from October 2015 to June 2022 in patients with cT0-T4 and positive axillary lymph nodes (cN1) treated with NST. Before NST, an ultrasound visible marker was placed into the positive node. After NST, IOUS guided TAD was performed including sentinel node biopsy (SLN). Until December 2019, all patients underwent an ALND after TAD procedure. From January 2020, ALND was spared in those patients with an axillary pathological complete response (pCR).

Results: 235 patients were included. pCR (ypT0/is ypN0) was achieved in 29% patients. Identification rate (IR) of the clipped node by IOUS was 96% (95% IC, 92.5–98.1%) and IR of SLN was 95% (95% IC, 90.8–97.2%). False negative rate (FNR) for TAD procedure (SLN + clipped node) was 7.0% (95% IC, 2.3–15.7%), which decreased to 4.9% when a total of 3 or more nodes were removed. Axillary ultrasound before surgery assessed residual disease with an AUC of 0.5241. Residual axillary disease tend to be the most significant factor for axillary recurrences.

Conclusions: This study confirms the feasibility, safety and accuracy of IOUS guided surgery for axillary staging after NST in node positive BC patients.

1. Introduction

In the last decade several clinical trials have evaluated the feasibility of a less invasive surgical axillary staging strategy after neoadjuvant systemic therapy (NST) for clinically node-positive patients who converted to cN0. The routinely axillary lymph node dissection (ALND), that has been standard in positive axillary nodes before NST, causes sequelae (i.e. lymphedema, loss of nerve sensory) that decrease quality of life in breast cancer patient [1]. Nowadays, targeted therapy has increased rates of axillary pathological complete response (pCR) up to 74%, and in such cases, ALND may turn to be an unnecessary surgery [2]. Sentinel node (SLN) biopsy being a less extensive axillary surgery with lower risk of morbidity, still rise concerns as the only axillary surgery due to the very few long term results [3], as well as the awaiting results of the role of radiation therapy in this setting. Several trials (SENTINA [4], Z1071 [5], SN FNAC [6], GANEA 2 [7]) of SLNB with subsequent ALND have settled the FNR in the range of 10–14%. This FNR was considered too high in order to detect patients with residual disease after NST who could benefit from the addition of adjuvant treatments, such as radiotherapy and new systemic treatments (capecitabine [8], T-DM1 [9]) with impact on oncological outcomes.

Abbreviations: NST, Neoadjuvant systemic treatment; pCR, Pathologic Complete Response; ALND, Axillary Lymph Node Dissection; SLNB, Sentinel Node Biopsy; TAD, Targeted axillary dissection; IOUS, Intraoperative Ultrasound.

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Different strategies have been proposed to decrease the FNR below the target of 10%. Removal of 3 or more SLN, the use of dual tracer techniques (radioactive and dyes), immunohistochemistry (IHC) lymph node evaluation and removal of the initially biopsied positive lymph node. Even though, studies have shown that removing ≥3 SLNs may not be achievable in the vast majority of patients [4,5] and in around 25% of cases the clipped node is not the SLN [10]. The latter could be solved marking the positive lymph node before initiate NST and removing it at the time of surgery besides the SLN, procedure which has been called targeted axillary dissection (TAD) [10]. Several methods for marking the positive axillary node have been described, such as wire localization, radioactive seeds, carbon dye, magnetic seeds, radar reflector or radiofrequency tag. Identification rates (IR) and FNR published varies between 92-100% and 2.0–7.0%, respectively [10–12]. Nevertheless, there are no studies comparing the different techniques, and the majority of them are chosen depending on the surgeon's discretion, or institutional resources available. Our group have already published the use of intraoperative ultrasound (IOUS) for excising the clipped axillary node with a FNR of 4% [13].

The aim of the study is to update the results of the prospective study ILINA, using IOUS for excising the clipped node in cN + breast cancer patients after NST as part of the TAD procedure as well as identifying accuracy of radiological response and results of oncological outcomes with the omission of ALND.

2. Material & Methods

From October 2015 to June 2022, patients with cytologically-proven axillary metastasis undergoing NST followed by surgery were included in this prospective study. Until December 2019, patients were included in a prospective study named ILINA study [13] approved by the Institutional Ethics Committee, which entailed TAD followed by ALND. From January 2020, patients were offered TAD and omission of ALND in case of having both negative SLNs and clipped node.

All patients had a mammogram and an US of the breast and axilla, and, in some cases, MRI. If suspicious axillary nodes were found on US, a fine-needle aspiration (FNA) was performed. Lymph nodes were considered suspicious if they showed a focal or diffuse cortical thickening (>3 mm thick) or loss of the fatty hilum. Number of suspicious nodes and morphological alteration according to BEDI criteria [14] were also recorded in each patient. In patients with cytologically-proven positive axillary nodes, a US-visible hydrogel polymer metal marker (Hydromark; Devicor Medical Products, Inc., Cincinnati, OH, USA) was placed into the biopsied node before initiating NST.

2.1. Neoadjuvant treatments

NST was administered according to institutional protocols at the discretion of the treating oncologist. Chemotherapy included anthracycline (four cycles of adriamycin + cyclophosphamide) plus a weekly (x12) taxane-based regimen. Endocrine therapy was based on aromatase inhibitors. Targeted therapy included (neo) adjuvant anti-HER2 therapy with trastuzumab ± pertuzumab when indicated or CDK 4/6 inhibitors inside a clinical trial. The time interval from placement of the clip to surgery was recorded in all patients.

Patient's response to NST was assessed by mammogram, breast and axillary US (AUS), and an MRI examination (only for patients who underwent diagnostic MRI). As mentioned above, patients with radiologic complete response by US were triaged to SLNB, IOUS-guided excision of the clipped node, and ALND inside ILINA protocol study. Since 2020, ALND was spared in some patients who had a negative clipped node and SLNs. For patients with suspicious axillary nodes after NST, an FNA was performed and, if positive, patients were triaged to ALND. In case the clip was not clearly visualized, an attempt was made to place another US hydrogel marker close to the first marker to facilitate IOUS-guided surgical excision. Although, in few cases where the clip was not visible by ultrasound, patients undergone ALND. All patients with IOUS-guided excision of the clipped node were evaluated for assessing the feasibility of the IOUS procedure, regardless of the type of axillary surgery performed.

2.2. Surgical procedure

The ILINA trial involved IOUS-guided excision of the clipped node, followed by SLNB and ALND. Most patients underwent a dual technique for SLN localization, i.e., Tc99 and blue dye (Patent Blue V, ACROS OrganicsTM or methylene blue). Blue dye was injected subareolar prior to surgery, as described elsewhere [15]. If the SLN or clipped node were not localized during surgery, a direct ALND was performed. In some cases where the SLN was not identified during surgery or the clipped node was confirmed to be positive by a preoperative FNA, the clipped node excision was attempted. Before the incision, US with a high frequency probe (7–15 MHz; MyLabTM, Esaote, Genova, Italy) was performed in multiple planes to localize the hydrogel marker. The incision was made just over the area where the clip was localized, and the distance from the skin to the clip was measured by US. IOUS-guided excision of the clip was then performed as previously described [13]. Prior to resecting the clip, the area was checked with the gamma probe to ascertain that the clipped node was the SLN. Once the clipped node was excised, we confirmed the presence of the clip by ultrasound prior to the node being sent for pathologic examination. Mammogram of the clipped node was not systematically performed if breast surgeon felt confident having excised the clip. All radioactive and blue nodes found in the axilla after removal of the clipped node were excised as SLNs.

After surgery all patients with residual axillary disease received regional node irradiation (RNI). In those patients with cN1 and a complete pathological response (ypT0/is ypN0), RNI was performed only if it was considered high risk (grade 3, initial tumor size >2 cm, <50y/o, triple negative o HER2 overexpression).

2.3. Pathological evaluation

All fresh lymph nodes were sent to the Pathology Department for intraoperative assessment. The clipped node was analyzed separately from the SLN when no concordance was found, which was specified in the pathology report. Frozen section analysis was performed on SLNs, and stained with hematoxylin and eosin. Immunohistochemical staining for cytokeratins was limited to selective use at the discretion of the pathologist. Staging of the axillary nodes was performed according to the 7th edition of the American Joint.

2.4. Statistical analysis

Statistical analysis was performed using STATA software 14.2 (StataCorp, College Station, TX, USA). AUS findings to predict axilla pathologic status was calculated with a Wilcoxon rank sum test. Response assessment by AUS was evaluated calculating AUC and NPV, defined as the number of true negatives divided by the total number of negative results. FNR of SLN and/or clipped node was defined as the number of cases where the SLN or clipped node did not show metastasis even though residual disease was present, divided by the total number of cases with persistent disease in

axillary lymph nodes. Logistic regression was used to identify features associated with the inability to identify the clipped node as SLN and to identify factors associated to disease recurrence. All tests were two-sided, with a significance level of .05. CIs for different measures were calculated using the Clopper–Pearson exact method.

3. Results

3.1. Patient characteristics

A total of 235 patients were included. Median age at the time of enrollment was 51 years (range, 28–85 years). Infiltrating ductal carcinoma was the most frequent histology in 198 (84%) patients. Almost 60% of patients were classified as stage cT2. 118 (50%) patients had palpable axillary nodes and 161 (69%) patients had 3 or less suspicious nodes on initial AUS evaluation. Neoadjuvant chemotherapy was administered in 208 (89%) patients. Breast and axilla complete clinical complete response was reported in 85 (36%) and 223 (95%) patients, respectively. Patient and tumour characteristics are specified in Table 1.

3.2. Tumour response to NST

After NST, breast conservation was performed in 151 (64%) patients. Pathological complete response (pCR) was achieved in 69 (29%) patients. Breast and axillary pathologic complete response were achieved in 78 (33%) and 92 (39%) patients, respectively. None of luminal A breast cancers achieved a pCR neither in breast nor axilla. The highest rates of pCR were in pure HER2 positive and triple negative breast cancers, reaching a breast pCR of 97% and 67% and an axilla pCR of 94% and 62%, respectively.

Median number of positive nodes was higher in ER/PR + Her2 negative tumors, as well as risk of axilla upstaging (ypN2a-3a), with a probability of 35% in luminal A and 14% in luminal B, of upstaging respectively (Table 2).

Among all patients who underwent an ALND, additional axillary positive nodes were found in patients with a previous positive TAD, regardless of type of metastasis. At least one additional positive node where found at ALND in 50% patients (3 of 6) with ITCs, 24% (5 of 21) with micrometastases and 54% (50 of 93) with macrometastases detected in either the SLN and/or clipped node.

Table 1
Patient and tumour characteristics.

	No of patients (%)
Number patients	235
Median age (years)	51 (range: 28–85)
Tumour histology	
Ductal	198 (84%)
Lobular	22 (9%)
Others	15 (6%)
Biologic subtype	
Luminal A	51 (22%)
Luminal B HER2-negative	94 (40%)
Luminal B HER2-positive	36 (15%)
HER2 positive no luminal	33 (14%)
Triple negative	21 (9%)
Clinical T stage	
Tx	2 (1%)
T1	22 (9%)
T2	142 (60%)
T3	63 (27%)
T4	6 (3%)
Clinical N stage	
N1	231 (98%)
N2	1 (0.5%)
N3	3 (1.5%)
Initial axilla physical examination	
Negative	117 (50%)
Positive	118 (50%)
Suspicious nodes on initial AUS	
<3 nodes	161 (69%)
≥3 nodes	74 (31%)
Type of neoadjuvant therapy	
Chemotherapy	131 (56%)
Chemotherapy + targeted therapy	77 (33%)
Endocrine	19 (8%)
Endocrine + targeted therapy	8 (3%)
Clinical tumour response after NST	
ycT0	85 (36%)
ycT+	150 (64%)
Clinical node response after NST	
ycN0	223 (95%)
ycN+	12 (5%)
Type of breast surgery	
BCT	151 (64%)
Mastectomy	84 (36%)

3.3. Accuracy of axillary imaging for response assessment

Initial assessment by AUS before NST, including number of initial suspicious nodes and cortical morphologic features (BEDI 4–6), was not a good predictor of pathological nodal status (*Wilcoxon test,* $p = 0.21$ and 0.59, respectively).

After NST, an axillary restaging by imaging was conducted to predict correlation with pCR. Axillary ultrasound was used to assess residual disease in the axilla showing an AUC of 0.5241.

After NST, 27 patients had suspicious nodes by AUS, before surgery an FNA was done in all that confirmed residual disease in 11 patients. After ruling out these patients, clinical complete response *(ycN0)* by imaging showed a negative predictive value (NPV) for axilla pCR of 40% (95% IC, 33.9–47.1%). Assuming that breast response could be another good surrogate of axilla response, clinical breast complete response *(ycT0)* was evaluated showing also a NPV for axilla pCR of 61% (95% IC, 50.0–72.0%).

3.4. Accuracy of TAD

A total of 141 patients were included in the ILINA trial to validate IOUS guided TAD. Besides, 94 patients with cALND for residual disease were also added to this group. After NST, patients with clinical axillary disease, loss of US visibility of the clipped node or SLN and/or clipped node not identified during surgery were excluded of analysis. A median number of 11 nodes were excised (range: 1–33) (Fig. 1).

3.4.1. SLN plus clipped node (TAD)

Median number of nodes excised was 3 (range: 1–14). FNR rate was 7.0% (5/71), which decreased to 4.9% when a total of 3 or more nodes were removed. Clipped node was not a SLN in 25% of the patients. Presence of ≥3 suspicious lymph nodes on initially ultrasound, removal of >2 SLNs, dual tracer technique for SLN localization, presence of residual nodal disease, or presence of metastases on clipped node did not predict the clipped node to be a SLN, although retrieval of 3 or more SLNs showed a trend to statistically association ($p = 0.06$) (Table 4).

3.4.2. Clipped node

Visualization and excision of the clipped node was done by IOUS (Fig. 2). The clipped node was not visualized after NST in 4 patients and, its visualization was lost during surgery in another 5 patients. Identification rate of the clipped node by IOUS was 96% (95% IC, 92.5–98.1%). In 9 patients the clipped node was negative with additional positive axillary nodes making a FNR of 12.7% for the clipped node only.

In 16 patients (7.8%) no evidence of foreign body changes were

Table 2
Response to neoadjuvant therapy according to breast cancer subtype.

	Luminal A	Luminal B HER2 neg	Luminal B HER2+	HER2+ pure	Triple negative	Global
Global pCR (ypT0/is ypN0)	0% (0/51)	7.4% (7/94)	58.3% (21/36)	93.9% (31/33)	47.6% (10/21)	29.4% (69/235)
Breast pcR (ypT0/ypTis)	0% (0/51)	9.6% (9/94)	63.9% (23/36)	97.0% (32/33)	66.7% (14/21)	33.2% (78/235)
Axillary pCR (ypN0)	0% (0/51)	25.5% (24/94)	66.7% (24/36)	93.9% (31/33)	61.9% (13/21)	39.2% (92/235)
Median residual positive nodes	3 nodes (range: 1–11)	2 nodes (range: 1–23)	1 node (range: 1–7)	1 node	1 node (range: 1–6)	2 nodes (range: 1–23)
Upstaging to ypN2-3	35.3% (18/51)	14.9% (14/94)	16.7% (6/36)	0% (0/33)	4.8% (1/21)	16.6% (39/235)

seen on pathological examination of the clipped node. In such cases, mammographic axillary views and AUS scanning were performed postoperatively, but no residual clipped nodes were identified, suggesting clip dislodgement. No association was found between pathological nodal status and absence/presence of pathological changes secondary to clip on node *(Fisher's exact test, $p = 0.37$)*.

3.4.3. SLN biopsy

To identify SLN, radiolabelled Tc99 was used in all patients and, additionally, blue dye in 90% patients (dual tracer technique). Lymphoscintigraphy was unsuccessful for SLN identification in 16 patients. SLN was not surgically identified in 12 patients. Identification rate for SLN was 95% (95% IC, 90.8–97.2%) with a median number of 3 nodes removed (range: 1–8). FNR of SLN alone was 22.5% (Table 3).

3.5. Preliminary oncological outcomes

After a median follow-up of 31 months (range: 1–75 months), 2 patients developed local recurrence, 7 (2.9%) developed locoregional + distant metastasis and 16 (6.8%) developed distant metastasis. Axillary recurrences in 6 patients, all with distant metastasis. All patients with axillary recurrences had previously an ALND for positive axillary nodes and had received RNI. Recurrences were not significantly associated to the number of suspicious axillary nodes on initial AUS (≥3 nodes) or initially locally advanced tumour stage cT3-T4, although the presence of residual axillary nodal disease showed a statistically significance trend (HR 2.38, p = 0.079).

4. Discussion

IOUS guided targeted axillary surgery has been demonstrated to be a feasible method to de-escalate axillary staging surgery in node positive breast cancer patients who undergo NST. Identification rate of the clipped node was 96% and FNR for TAD procedure was 7.0%, both figures comparable to other localization techniques for TAD (wire localization [16], radioactive seed [10], carbon tattooing [17], magnetic seed [12], radiofrequency tag [18] or radar reflector [19]) described in literature.

Our study confirms the need for surgical axillary staging that cannot be yet substituted by radiological response to NST. Current breast and axillary imaging techniques are not enough accurate to be a good predictor tool to detect nodal residual disease. A large discrepancy between AUS after neoadjuvant therapy and the pathology results of the axillary nodes was evident. One explanation could be that 35% of patients with ycN0 had limited residual disease defined as isolated tumor cell or micrometastasis, increasing the false negative results of AUS. Other problem, expressed by the radiologist, is sometimes the difficulty for differentiating between the peripheral anechoic hydrogel of the marker and the length of the cortical thickness of the lymph node that can also influence these results. In summary, AUS examination is far from considering it as a good screening method for residual disease.

Similar to previous findings [20,21], none of patients with luminal A tumors achieved a pCR, or an axillary pCR, being the group with higher risk of axillary upstaging (ypN2-3), probably reflecting the inaccurate results of axillary staging prior to systemic treatment. Better selection of patients for NST in this subgroup would be desirable. Nevertheless in neoadjuvant endocrine (NET) setting, Kantor et al. [22] have hypothesized that leaving behind a low volume of axillary disease after NET is potentially less important than after neoadjuvant chemotherapy, as NET patients have only received a small fraction of their overall endocrine therapy in the preoperative setting and no differences in OS were seen when compared this patients with upfront surgery patients with nodal disease [23]. They proposed to omit ALND in patients with fewer than three suspicious nodes before neoadjuvant endocrine therapy If only one or two nodes are positive after removal of the clipped node and two additional SLNs, the recurrence rates and survival following this Z011 like strategy are awaited.

In Her2 positive and TN negative BC, systemic treatments have contributed to an increase in pCR up to 90% in HER2 pure breast cancers in our study, similar to other published reports [24]. Tadros et al. published that nearly 90% early stage (cT1-2 cN1) HER2 and TN breast cancers, who had documented nodal metastasis before NST, were not found any residual axillary metastases when a breast pCR was confirmed. Meanwhile in the same study, patients who did not achieve a breast pCR had only a 40% probability to become node negative [25]. New strategies searching to improve preoperative identification of patients who achieved breast pCR are raising, in the aim to omit breast surgery [26]. However, any residual disease in HER2 and TN subtypes, regardless of size, is relevant to define the need of additional adjuvant treatments with survival impact [8,9]. In line with other authors [27], low volume SLN disease after NAC is not an indicator of a low risk of additional positive axillary nodes and remains an indication for cALND outside a clinical trial.

According to our results, TAD is the method that yields the lowest FNR (7%) after NST, compared to SLN biopsy or clipped node excision individually. A systematic review and pooled analysis comparing biopsy of the initial metastatic lymph node and SLN biopsy showed that both approaches were highly accurate with a FNR of 6.28% (95% CI, 3.98–9.43) and 5.18% (95% CI, 3.41–7.54), respectively [28]. This study concluded that biopsy of the clipped node alone represents a valid alternative to ALND in those node positive breast cancer patients who have responded well to upfront systemic treatment. These FNRs are significantly below the FNR for SLNB alone (13%) in the same setting [29]. Other authors advocate the optimization of SLNB procedure with dual tracer and retrieval of ≥3 SLNs, presuming the clipped node is an SLN in the majority of cases and, in the few cases the clipped node was not identified it seems not to increase the risk of developing an axillary recurrence [30]. In our study, no significant factor was found to predict concordance of SLN and clipped node, including the number of initially suspicious nodes, number of SLNs, localization technique of SLN or clipped node or axilla status after NST. This suggest again that nor SLN or clipped node must be omitted from TAD.

One concern when omitting ALND in those cN + who convert to ypN0 is the risk of regional recurrences. Retrospective studies have

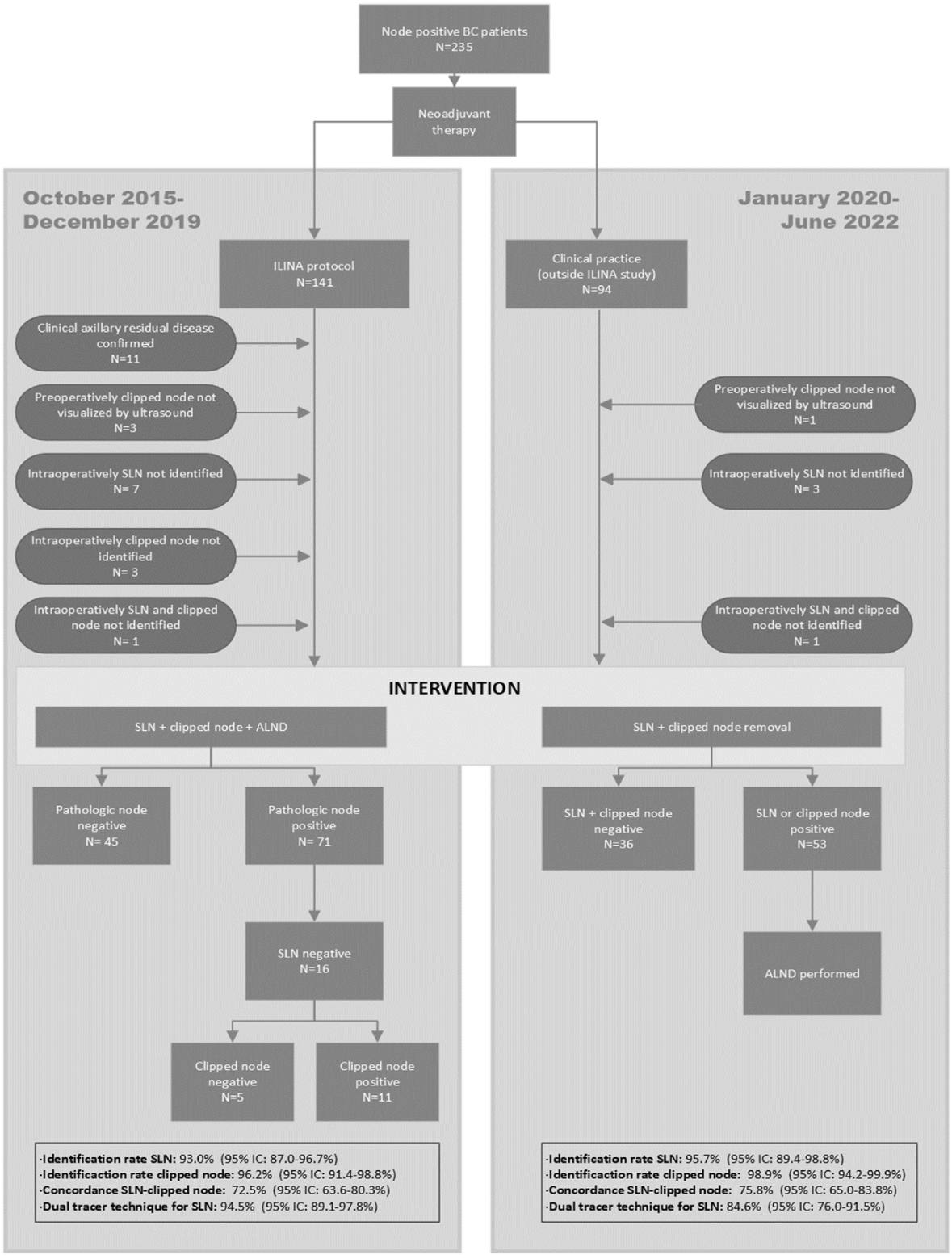

Fig. 1. Diagram of all patients included in the study. ALND axillary lymph node dissection, SLN sentinel lymph node.

shown a very low risk of nodal recurrence (0–0.5%) [31,32]. In our cohort 2/6 regional recurrences occurred after a negative TAD, but in both cases with positive nodes in the ALND. This remarks how important is an accurate axillary staging in these group of patients.

Axillary residual disease seems to be the most robust risk factor for recurrence ahead of the burden of disease both in the breast and axilla. If ALND omission after an involved SLN post-NST may have an adverse effect on prognosis is still uncertain. A study analyzing National Cancer Database (NCDB) patients with residual disease in 1–3 lymph nodes (ypN1), SLNB was associated with significantly

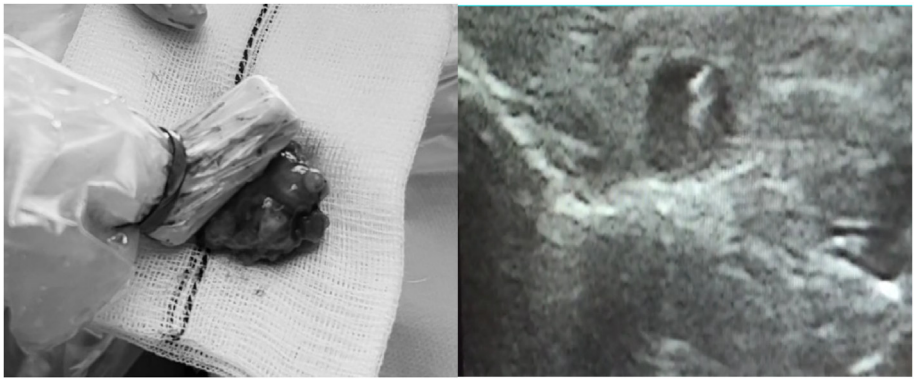

Fig. 2. Pictures of intraoperative verification of clipped node removal by ultrasound.

Table 3
False negative rates (FNR) depending on number of nodes excised.

Surgical procedure	False negative rate (%)
SLN biopsy only	FNR: 22.5% (95% IC, 13.5–33.9%) • SLNs ≤2 nodes: 26.7% (95% IC, 12.3–45.9%) • SLNs ≥3 nodes: 19.5% (95% IC, 8.8–34.9%)
Clipped node excision only	FNR: 12.7% (95% IC, 6.0–22.7%)
SLN + Clipped node excision	FNR: 7.0% (95% IC, 2.3–15.7%) • Nº nodes ≤2 nodes: 10.0% (95% IC, 2.1–26.5%) • Nº nodes ≥3 nodes: 4.9% (95% IC, 0.6–16.5%)

Table 4
Analysis of possible factors associated with concordance of clipped node and sentinel lymph node.

Variable	OR (95% CI)	P
Num. of lymph nodes suspicious initially on ultrasound		
< 3	–	0.98
≥ 3	1.01 (0.49–2.04)	
Num. of SLN removed.		
≤ 2	–	0.06
≥ 3	1.86 (0.97–3.56)	
SLN localization technique		
Tc99	–	0.58
Tc99 + blue dye (dual tracer)	0.73 (0.23–2.29)	
Presence of residual nodal disease		
Node negative	–	0.61
Node positive	0.66 (0.13–3.28)	
Metastasis in clipped node		
Absent	–	0.43
Present	1.92 (0.38–9.67)	

lower 5-year overall survival compared to ALND group (71% vs 77%, p = 0.01) [33]. Ongoing prospective randomized trials will respond the need of nodal radiation after SN negative (NSBAP B51) and the role of ALND in addition to nodal radiation after SN positive (A011202) in initially node positive breast cancer patients after neoadjuvant chemotherapy.

The use of US- visible markers has made feasible the IOUS technique for excising the clip node. It can be placed directly within the cortex of axillary positive node at initial diagnosis workup, providing an exceptional visibility up to 12 months after placement in all imaging modalities (mammogram, ultrasound, MRI) [34]. It eliminates the need for a separate location procedure prior surgery creating a better patient experience.

It is the most inexpensive technique considering that other techniques demand a new and costly implantable device and a console for its localization. Reference It can be deployed after ultrasound-guided biopsy and can easily be placed inside the metastatic node, favored for its tiny size. This biopsy marker is also inert and could be left indefinitely in the body, unlike what is allowed to the radioactive seeds where is a strict time for removal according to the nuclear regulatory protocols. Contrary to magnetic seeds, it does not require non-magnetic surgical tools during surgery and does not generate an artifact in MRI sequences, which can difficult axillary or upper outer quadrant breast assessment of response.

The downside of this technique is the occasionally difficulty in visualization of the clip after NST. Clip's visibility could be compromise in case it ends within a node deep in the axilla. Loss of ultrasound visibility over time is also possible, due to reabsorption of polyethylene glycol (PEG) hydrogel coverage at the same time as lymph node cortical thickening disappears in response to systemic therapy. In that case, a new marker may be placed before surgery by the radiologist. The clip's migration is another relevant concern, consequence of an initially wrong placement by radiologist or displacement during induction therapy due to shrinkage of the metastatic node. As described previously in breast surgery, clip dislodgement during surgery is also possible [35], although uncommon, most probably because a poor tissue adherence of the hydrogel substance to fatty-lymphatic tissue, sometimes also associated to a narrow transection with electrocautery during clipped node removal.

The surgeon expertise in ultrasound guided surgery is crucial to be confident removing the clipped node without extrusion of the clipped. A surgical mammogram of the surgical specimen to confirm the presence of the clip is recommended in case of uncertainty with no clear visualization of the clip by ultrasound. It is also important to reconsider that any preoperative loco-regional anesthetic blockade in the axillary region, may interfere with the clipped node visualization. Future research may be focused on quality of life, particularly arm lymphedema rate using the TAD procedure.

5. Conclusions

In clinically node positive BC patients, IOUS guided axillary surgery after NST is feasible, safe, and an accurate method for de-escalation of axillary surgery without compromising oncologic outcomes in those patients with a pCR.

CRediT authorship contribution statement

Christian Siso: Study concepts, Study design, Funding acquisition, Quality control of data and algorithms, Formal analysis, and interpretation, Statistical, Formal analysis, Manuscript preparation, Writing – review & editing. **Antonio Esgueva:** Funding acquisition. **Joaquin Rivero:** Funding acquisition. **Clara Morales:** Funding acquisition. **Ignacio Miranda:** Funding acquisition. **Vicente Peg:** Funding acquisition. **Antonio Gil-Moreno:** Funding acquisition. **Martin Espinosa-Bravo:** Funding acquisition. **Isabel T. Rubio:** Study concepts, Funding acquisition, Formal analysis, and interpretation, Writing – review & editing, Manuscript review.

Declaration of competing interest

All authors declare that they have no potential conflicts of interest to declare.

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