
Madrid, 9 de mayo de 2012
USCAP & AACR HIGHLIGHTS
Avances en patología mamaria
Iosu Sola
Clínica Universidad de Navarra
Roche
USCAP & AACR HIGHLIGHTS 2012

Resumen

Temas seleccionados

- Oncotype©
- Neoplasia Lobulillar/Lesión Esclerosante Compleja
- Impacto del ACOSOG Z0011
- CerB-b2/Her2-neu: heterogeneidad/polisomía

RESULTS

Breast Cancer Recurrence Score = 22

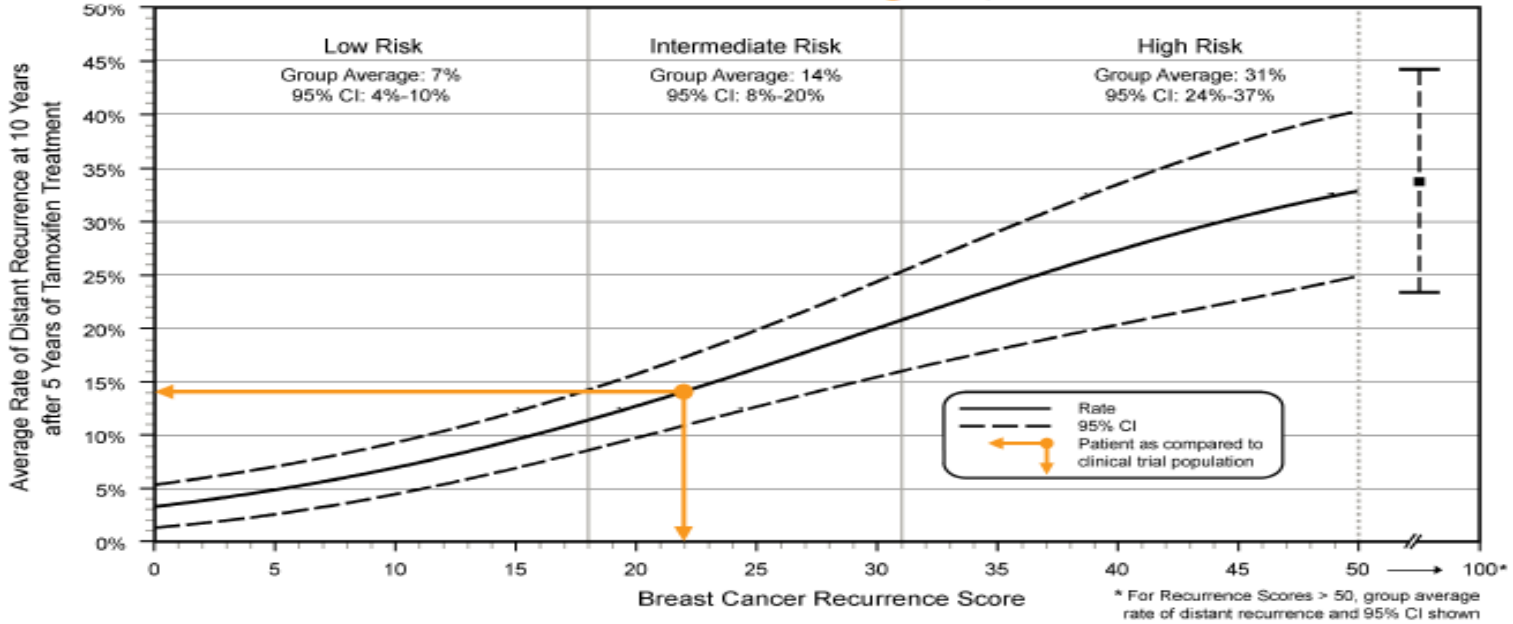
The findings summarized in the Clinical Experience sections of this report are applicable to the patient populations defined in each section. It is unknown whether the findings apply to patients outside these criteria.

CLINICAL EXPERIENCE: PROGNOSIS FOR NODE NEGATIVE, ER-POSITIVE PATIENTS

The Clinical Validation study included female patients with Stage I or II, Node Negative, ER-Positive breast cancer treated with 5 years of tamoxifen. Those patients who had a Recurrence Score of 22 had an Average Rate of Distant Recurrence of **14% (95% CI: 11%-17%)**

The following results are from a clinical validation study of 668 patients from the NSABP B-14 study. *N Engl J Med* 2004; 351: 2817-26.

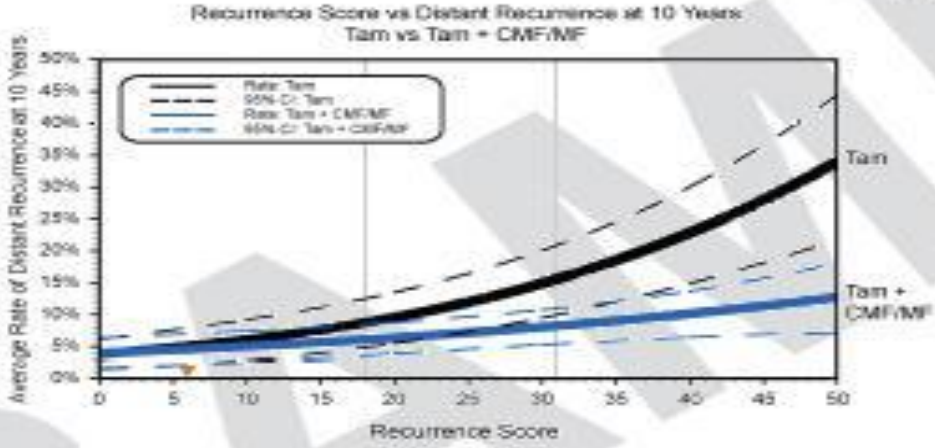
Recurrence Score vs Distant Recurrence in Node Negative, ER-Positive Breast Cancer Prognosis

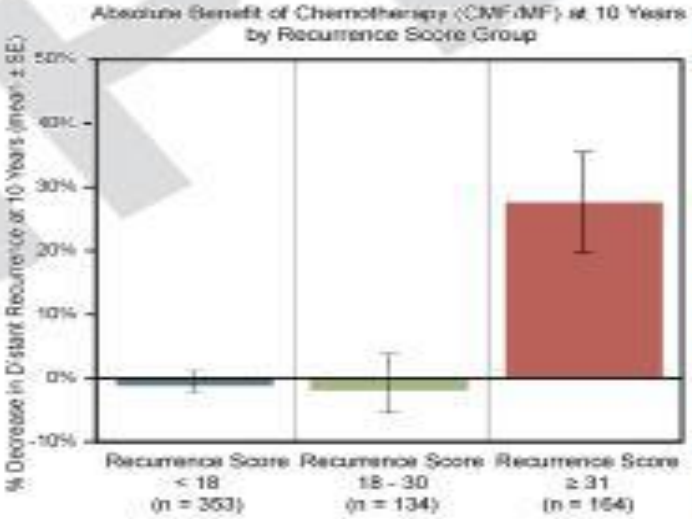


CLINICAL EXPERIENCE: CHEMOTHERAPY BENEFIT FOR NODE NEGATIVE, ER-POSITIVE PATIENTS

The following results are from a clinical study involving 651 patients from the NSABP B-20 Study. The study included female patients with Stage I or II, Node Negative, ER-Positive breast cancer. Patients were randomized to either tamoxifen alone or tamoxifen plus CMF or MF chemotherapy. For patients in the pre-specified group with Recurrence Scores ≥ 31, the group average 10-year rates (95% CI) of distant recurrence were 40% (25%, 54%) for Tam alone and 12% (6%, 18%) for Tam + CMF/MF. *J Clin Oncol*. 2006; 24(23): 3726-34.

NODE NEGATIVE, ER-Positive Breast Cancer
Chemotherapy Benefit





Node Negative

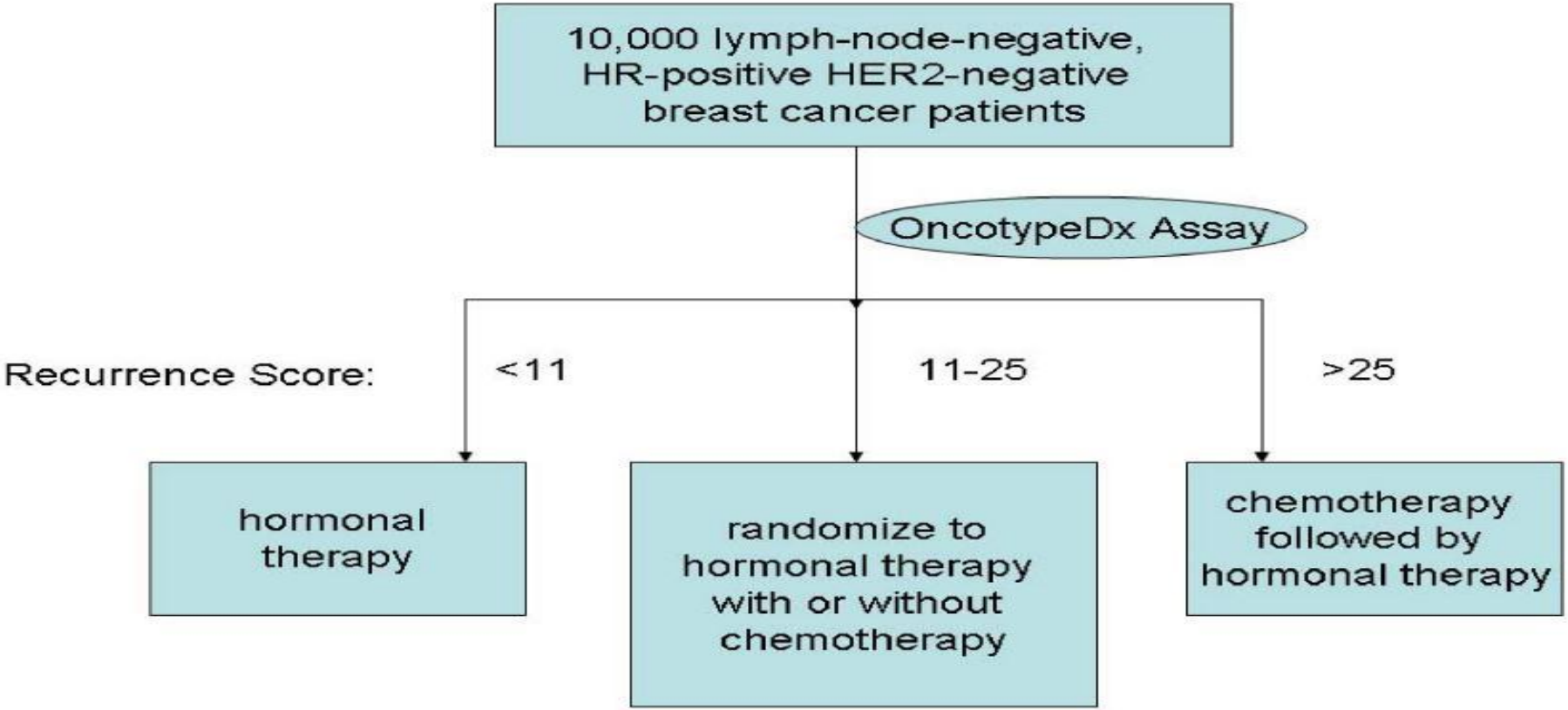
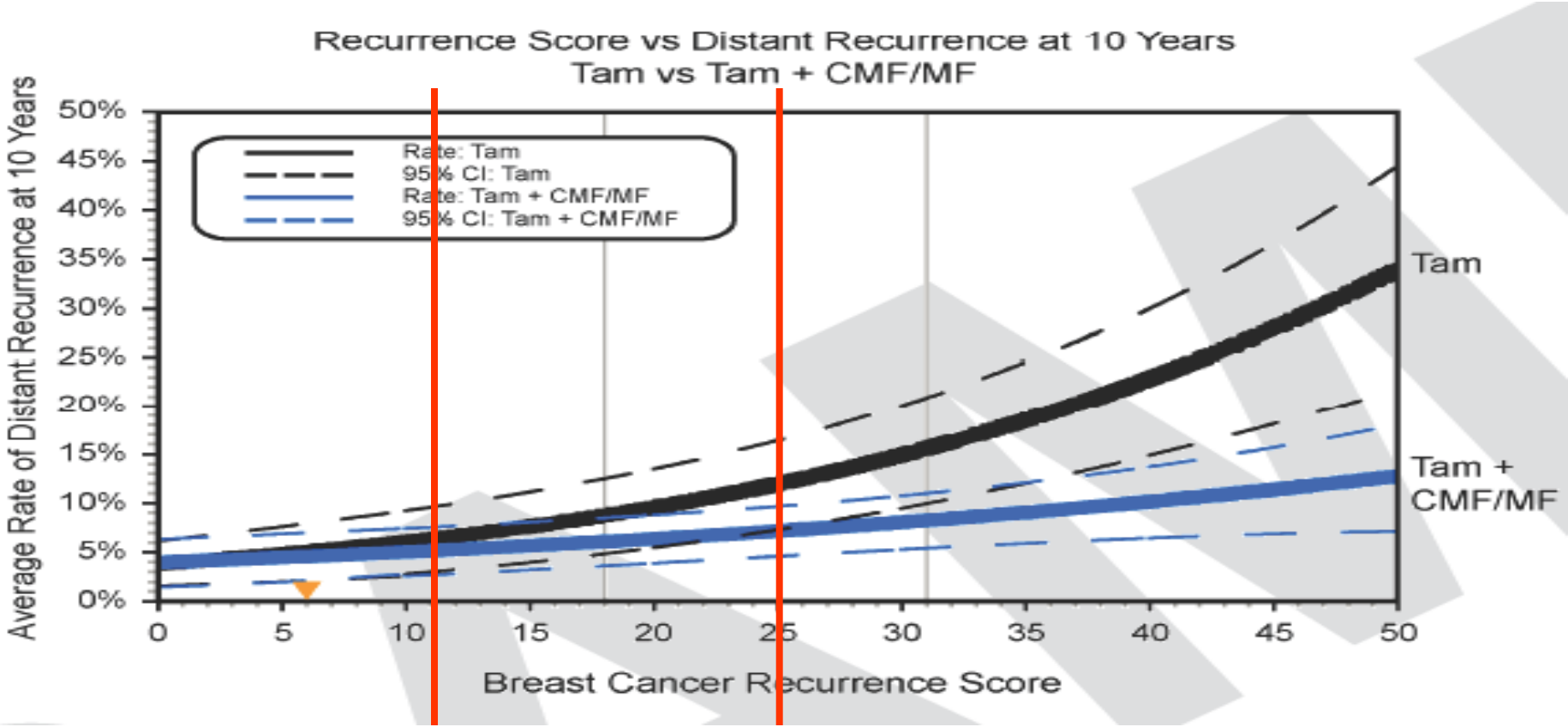


Figure 3.
TAILORx Treatment Schema (Modified from Sparano, 2007[26])



- Modificaciones del TAYLORx

Ann Oncol. 2012 Mar;23(3):625-31. Epub 2011 Jun 6.

Prospective transGEICAM study of the impact of the 21-gene Recurrence Score assay and traditional clinicopathological factors on adjuvant clinical decision making in women with estrogen receptor-positive (ER+) node-negative breast cancer.

Albanell J, González A, Ruiz-Borrego M, Alba E, García-Saenz JA, Corominas JM, Burgues O, Furio V, Rojo A, Palacios J, Bermejo B, Martínez-García M, Limon ML, Muñoz AS, Martín M, Tusquets I, Rojo F, Colomer R, Faull I, Lluch A.

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Abstract

BACKGROUND: This study examined the impact of the Recurrence Score (RS) in Spanish breast cancer patients and explored the associations between clinicopathological markers and likelihood of change in treatment recommendations.

PATIENTS AND METHODS: Enrollment was offered consecutively to eligible women with estrogen receptor-positive; human epidermal growth factor receptor 2-negative, node-negative breast cancer. Oncologists recorded treatment recommendation and confidence in it before and after knowing the patient's RS.

RESULTS: Treatment recommendation changed in 32% of 107 patients enrolled: in 21% from chemohormonal (CHT) to hormonal therapy (HT) and in 11% from HT to CHT. RS was associated with the likelihood of change from HT to CHT ($P < 0.001$) and from CHT to HT ($P < 0.001$). Confidence of oncologists in treatment recommendations increased for 60% of cases. Higher tumor grade ($P = 0.007$) and a high proliferative index (Ki-67) ($P = 0.023$) were significantly associated with a greater chance of changing from HT to CHT, while positive progesterone receptor status ($P = 0.002$) with a greater probability of changing from CHT to HT.

CONCLUSIONS: Results from the first prospective European study are consistent with published experience and use of the RS as proposed in European clinical practice guidelines and provide evidence on how Oncotype DX and clinicopathological factors are complementary and patient selection may be improved.

ONCOTYPE

Factores morfológicos e inmunohistoquímicos que permitan seleccionar casos en los que Oncotype aporte información relevante (predecir resultados Oncotype)

[102] Patterns of Oncotype DX Recurrence Scores – Analysis Based on Levels of ER & PR Expression and Proliferation Markers

[138] Do Combined Histopathological Features of ER Positive Breast Carcinoma Correlate with OncotypeDx Recurrence Score?

[153] The University of Kentucky Model for Selecting Breast Cancer Patients for Oncotype DX Testing

[182] Prediction of Oncotype DX Recurrence Score: Use of Equations Derived by Linear Regression Analysis

[271] Progesterone Receptor and Ki-67 Immunohistochemistry Predict Oncotype Dx® Recurrence Score in Lymph Node Negative and Positive Breast Cancers

[183] Can GP88 Expression Serve as an Additional Surrogate Marker for Oncotype DX Recurrence Score?

ONCOTYPE

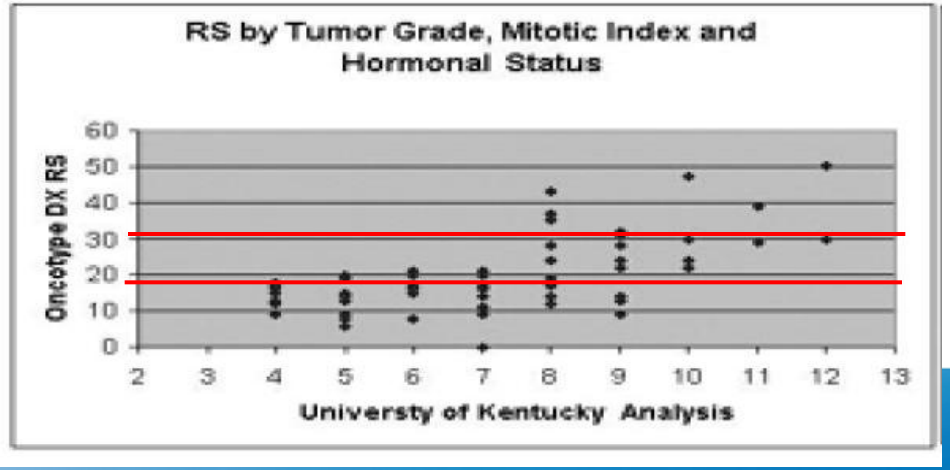
[153] The University of Kentucky Model for Selecting Breast Cancer Patients for Oncotype DX Testing

Design: Recurrence Scores (RS) from 72 randomly selected N0 patients were compared to levels (%) of ER, Progesterone Receptors (PR), Ki – 67, Cyclin A, Mitotic Index (MI) and Tumor Grade (TG) using univariate regression analyses. Although no one variable showed a significant R value, the ones that correlated the most were selected and

Univeristy of Kentucky Model for Oncotype DX testing

	1	2	3	4	5
ER expression %	>90	<90			
PR expression %	90 - 100	70 - 90	30 - 70	1 - 30	0
Mitotic Index*	I	II	III		
Tumor Grade*	1	2	3		

Based on the modified combined Bloom Richardson Score



ONCOTYPE

[182] Prediction of Oncotype DX Recurrence Score: Use of Equations Derived by Linear Regression Analysis

Design: We used a dataset of over 800 cases to formulate three new RS equations, then used each equation to calculate a RS for an independent set of 162 cases.
new Magee Equation 1 (nME1): RS = 15.31385 + Nottingham score*1.4055+ ER H-score*(-0.01924) + PR H-Score* (-0.02925) + (0 for HER2 negative, 0.77681 for equivocal, 11.58134 for positive) + Tumor size*0.78677 + Ki-67*0.13269.
nME2: RS = 18.8042+ Nottingham score*2.34123 + ER H-Score*(-0.03749) + PR H-Score*(-0.03065) + (0 for HER2 negative, 1.82921 for equivocal, 11.51378 for positive) + Tumor size*0.04267.
nME3: RS = 24.30812+ ER H-Score*(-0.02177) + PR H-Score*(-0.02884) + (0 for HER2 negative, 1.46495 for equivocal, 12.75525 for positive) + Ki-67*0.18649.
Results: The concordance between RS category by Oncotype DX® and Magee equations was 54.6% (88/161), 55.7% (87/156), 59.7% (95/159), and 54% (86/159) for oME, nME1, nME2, and nME3 respectively. When the IR category was eliminated, the concordance increased to 95.4% (62/65), 100% (52/52), 98.1% (52/53), and 98.1% (53/54) for oME, nME1, nME2, and nME3 respectively. The mean (median) RS for Oncotype DX® was 20 (19), compared to 17.5 (16) for oME, 19.9 (18.8) for nME1, 19.8 (19.6) for nME2 and 19.3 (18.5) for nME3.
Conclusions: Any of the four equations may be used to calculate a RS, using reported pathologic findings. When the calculated RS is LR or HR, the concordance with the Oncotype DX® RS is very high, and Oncotype DX® testing may even be avoided. Conversely, pathologists should investigate any Oncotype DX® RS that is dramatically different than expected based on pathologic findings, to ensure accuracy of the Oncotype DX® result.

ONCOTYPE

[271] Progesterone Receptor and Ki-67 Immunohistochemistry Predict Oncotype Dx® Recurrence Score in Lymph Node Negative and Positive Breast Cancers

Design: Our objective was twofold: 1) to test whether routinely performed histology and immunohistochemical studies could be used to predict the RS in a cohort of lymph node negative and lymph node positive patients, and 2) to assess the prediction of recurrence using both the standard RS and the modified TAILORx RS. H&E stained slides were used to assess morphology including the components of the Nottingham combined histologic grade. Immunohistochemistry was used to assess hormone receptor expression, Ki-67 positivity, and Her-2/neu expression.

Results: The most recent 92 cases with invasive carcinoma and Oncotype DX® results were evaluated. Of those, 69 cases were node negative and 23 were node positive. Using the standard RS, 56 cases were low risk, 26 were intermediate risk, and 10 were high risk. Using the modified TAILORx stratification, 19 cases were low risk, 57 were intermediate risk, and 16 were high risk. Bivariate analysis demonstrated that PR status, Nottingham grade, nuclear score, mitotic rate, and Ki-67% were significantly associated with RS using both the standard and modified TAILORx risk stratifications. However, multivariate logistic regression analysis demonstrated that only a positive PR status and low Ki-67% were predictive of a low RS using the standard risk stratification. None of the variables remained predictive of RS when the modified TAILORx values were applied.

ONCOTYPE

Conclusiones

- La combinación de factores morfológicos e inmunohistoquímicos convencionales permite seleccionar/predecir resultados de Oncotype
- La expresión de receptores de progesterona y la actividad proliferativa (mitosis, ki67%) son, en la mayoría de los casos, los datos determinantes
- Mantengamos unos criterios estables…..

Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis

A Randomized Clinical Trial

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Context Sentinel lymph node dissection (SLND) accurately identifies nodal metastasis of early breast cancer, but it is not clear whether further nodal dissection affects survival.

Objective To determine the effects of complete axillary lymph node dissection (ALND) on survival of patients with sentinel lymph node (SLN) metastasis of breast cancer.

Design, Setting, and Patients The American College of Surgeons Oncology Group Z0011 trial, a phase 3 noninferiority trial conducted at 115 sites and enrolling patients from May 1999 to December 2004. Patients were women with clinical T1-T2 invasive breast cancer, no palpable adenopathy, and 1 to 2 SLNs containing metastases identified by frozen section, touch preparation, or hematoxylin-eosin staining on permanent section. Targeted enrollment was 1900 women with final analysis after 500 deaths, but the trial closed early because mortality rate was lower than expected.

Interventions All patients underwent lumpectomy and tangential whole-breast irradiation. Those with SLN metastases identified by SLND were randomized to undergo ALND or no further axillary treatment. Those randomized to ALND underwent dissection of 10 or more nodes. Systemic therapy was at the discretion of the treating physician.

Main Outcome Measures Overall survival was the primary end point, with a noninferiority margin of a 1-sided hazard ratio of less than 1.3 indicating that SLND alone is noninferior to ALND. Disease-free survival was a secondary end point.

Results Clinical and tumor characteristics were similar between 445 patients randomized to ALND and 446 randomized to SLND alone. However, the median number of nodes removed was 17 with ALND and 2 with SLND alone. At a median follow-up of 6.3 years (last follow-up, March 4, 2010), 5-year overall survival was 91.8% (95% confidence interval [CI], 89.1%-94.5%) with ALND and 92.5% (95% CI, 90.0%-95.1%) with SLND alone; 5-year disease-free survival was 82.2% (95% CI, 78.3%-86.3%) with ALND and 83.9% (95% CI, 80.2%-87.9%) with SLND alone. The hazard ratio for treatment-related overall survival was 0.79 (90% CI, 0.56-1.11) without adjustment and 0.87 (90% CI, 0.62-1.23) after adjusting for age and adjuvant therapy.

Conclusion Among patients with limited SLN metastatic breast cancer treated with breast conservation and systemic therapy, the use of SLND alone compared with ALND did not result in inferior survival.

Trial Registration clinicaltrials.gov Identifier: NCT00003855

JAMA. 2011;305(6):569-575 www.jama.com

AXILLARY LYMPH NODE DISSECTION (ALND) has been part of breast cancer surgery since the description of the radical mastectomy.[1] ALND reliably identifies nodal metastases and maintains regional control,[2,3] but the contribution of local therapy to breast cancer survival is controversial.[4,5] The Early Breast Cancer Trialists' Collaborative Group synthesized findings from 78 randomized controlled trials, concluding that local control of breast cancer was associated with improved disease-specific survival.[6]

ALND, as a means for achieving local disease control, carries an indisputable and often unacceptable risk of complications such as seroma, infection, and lymphedema.[7-9] Sentinel lymph node dissection (SLND) was therefore devel-

ACOSOG Z0011

"Among patients with limited SLN metastatic breast cancer treated with breast conservation and sistemic therapy, the use of SNLD alone compared with ALND did not result in inferior survival"

[169] Internal Impact of ACOSOG Z0011 at a Tertiary Academic Center

[223] Applying the American College of Surgeons Oncology Group Z0011 Trial; Can Histological Parameters Predict Axillary Nodal Understaging in Breast Carcinomas ?

[228] Impact of ACOSOG Trial Results in the Practice of Breast Cancer Surgery in Long Island: Survey of 19 Hospitals

ACOSOG Z0011

¿Pueden los resultados de este estudio modificar las prácticas relacionadas con el SNL?

[169] Internal Impact of ACOSOG Z0011 at a Tertiary Academic Center

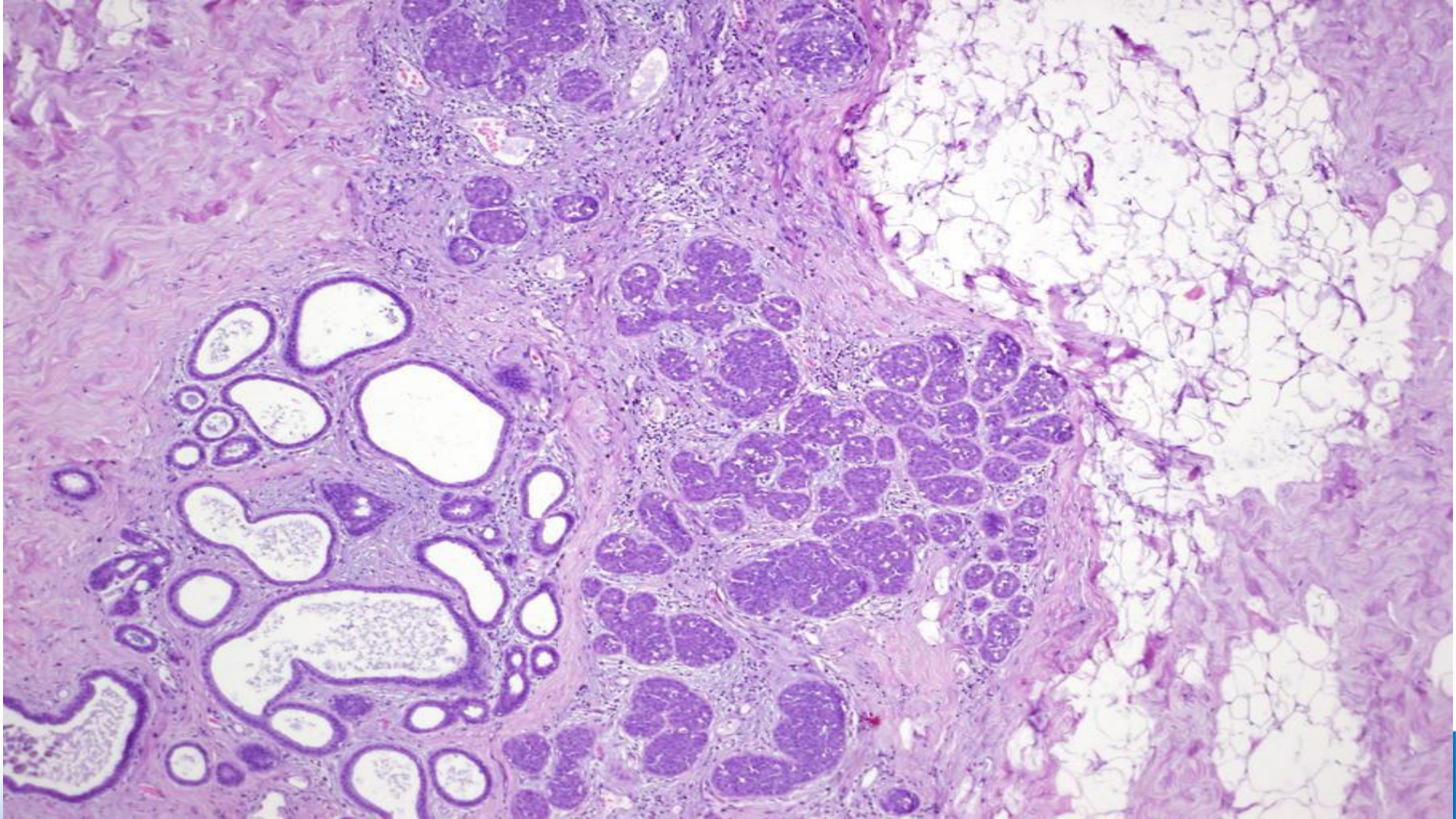
The ACOSOG Z011 trial has impacted the surgical practice and treatment of breast cancer patients in some academic institutions. At our institution there has been a dramatic increase and trend towards non-frozen rather that frozen SLNBs, although there still remains individual variability among surgeons.

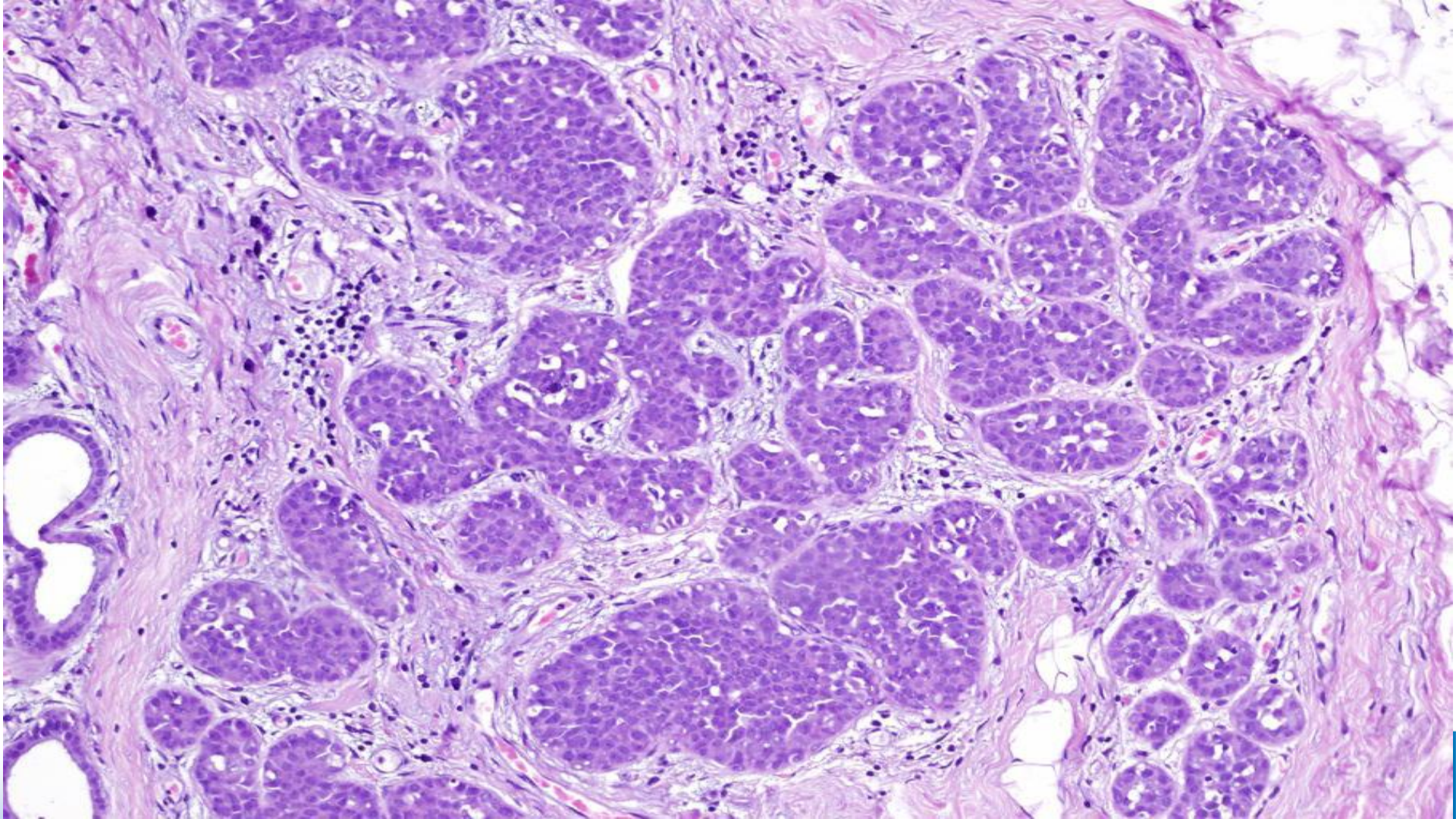
[223] Applying the American College of Surgeons Oncology Group Z0011 Trial; Can Histological Parameters Predict Axillary Nodal Understaging in Breast Carcinomas ?

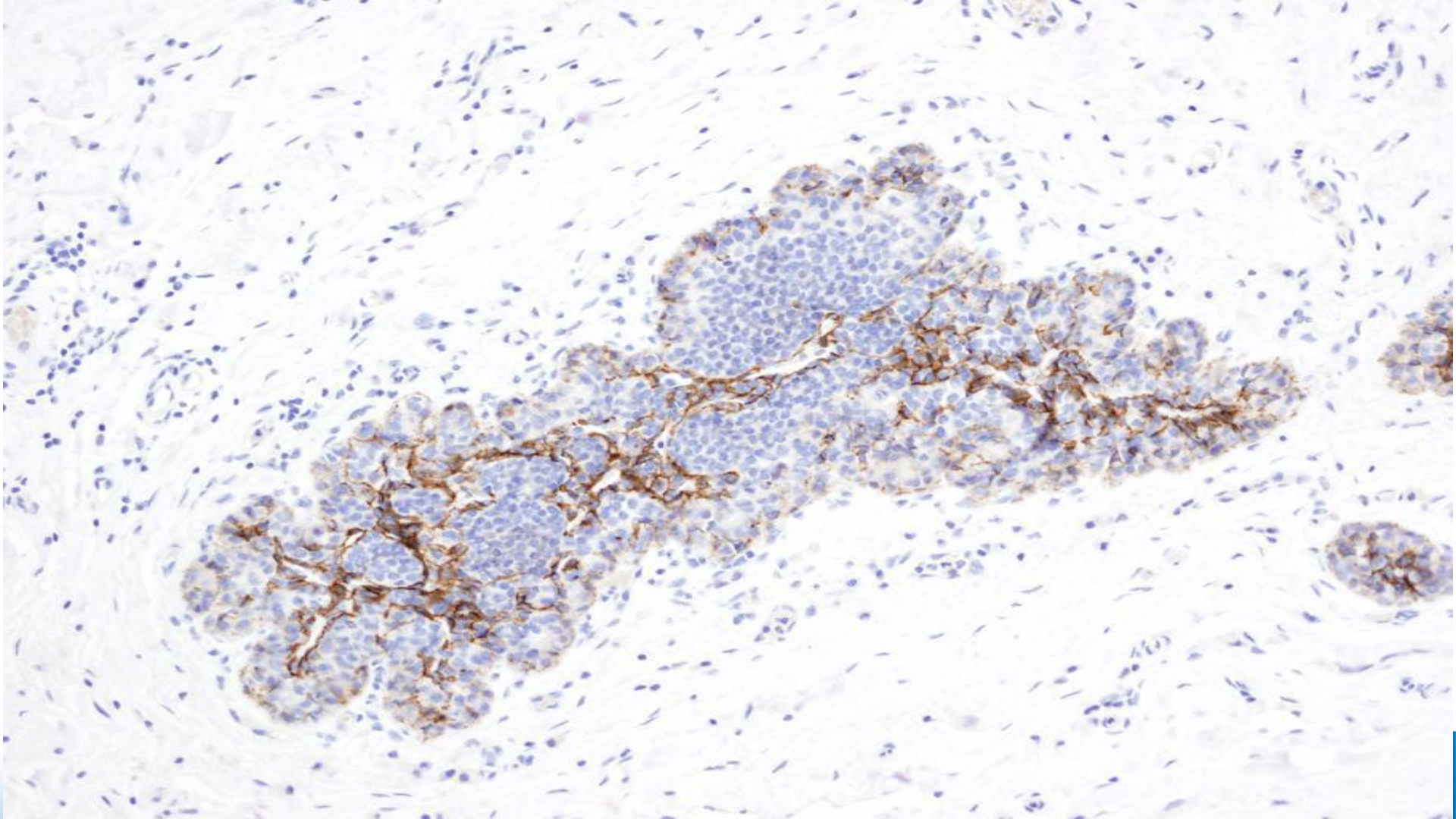
Conclusions: If the results of the Z0011 trial are applied as currently suggested a significant number of patients will be understaged by omission of axillary clearance (12%). Tumour size is larger in these understaged patients, suggesting further analysis of this parameter in predicting non sentinel lymph node metastasis in T1- T2 tumours with one or two positive sentinel lymph nodes is warranted.

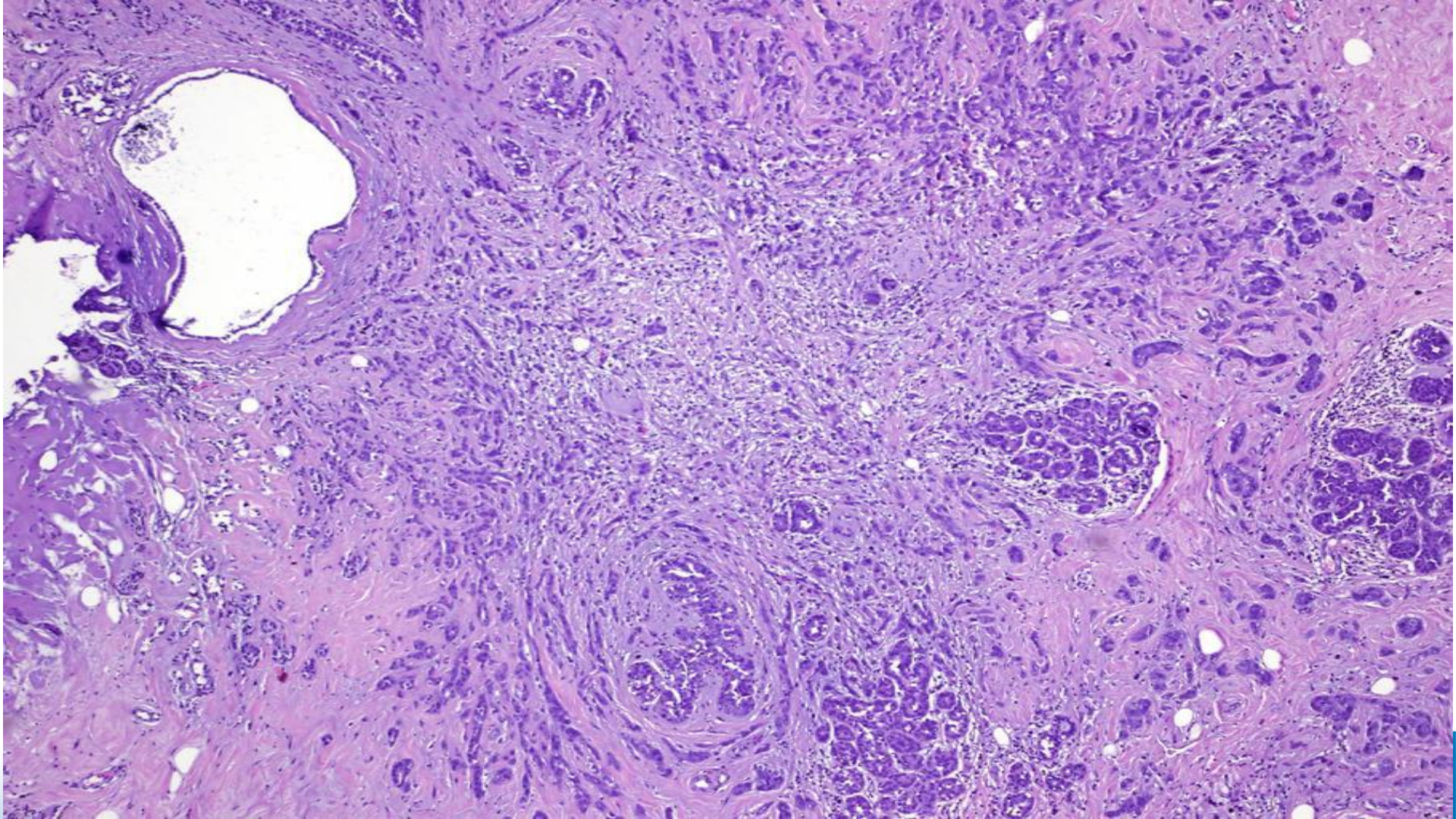
[228] Impact of ACOSOG Trial Results in the Practice of Breast Cancer Surgery in Long Island: Survey of 19 Hospitals

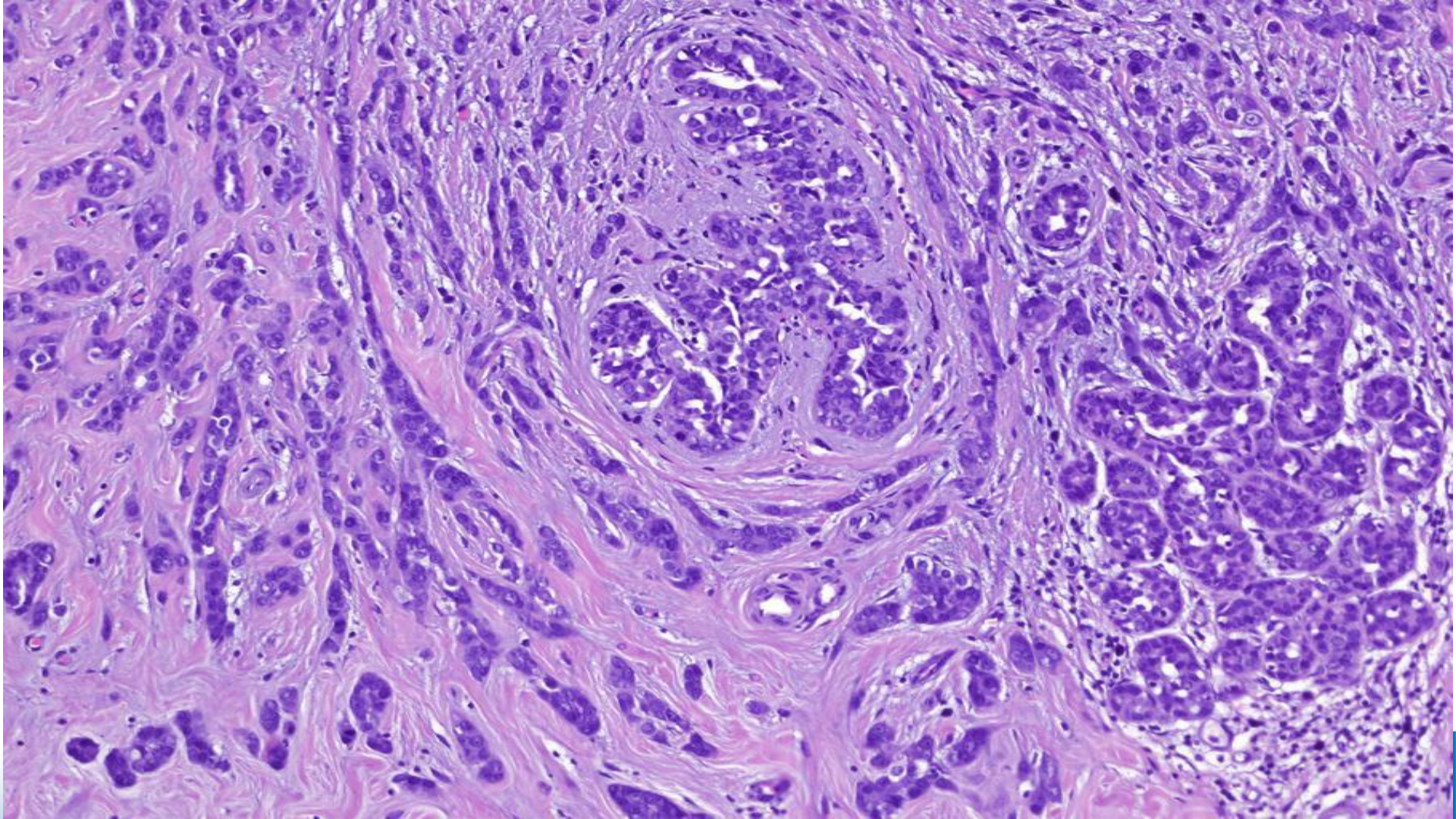
Conclusions: Long Island hospitals treat approximately 2,400 new cases a year. Despite these numbers, and despite the presence of one academic institution in the survey, only one surgeon in one community hospital has made changes in the daily practice of SLNB. Pathology work up of SLN in all hospitals remains unchanged.

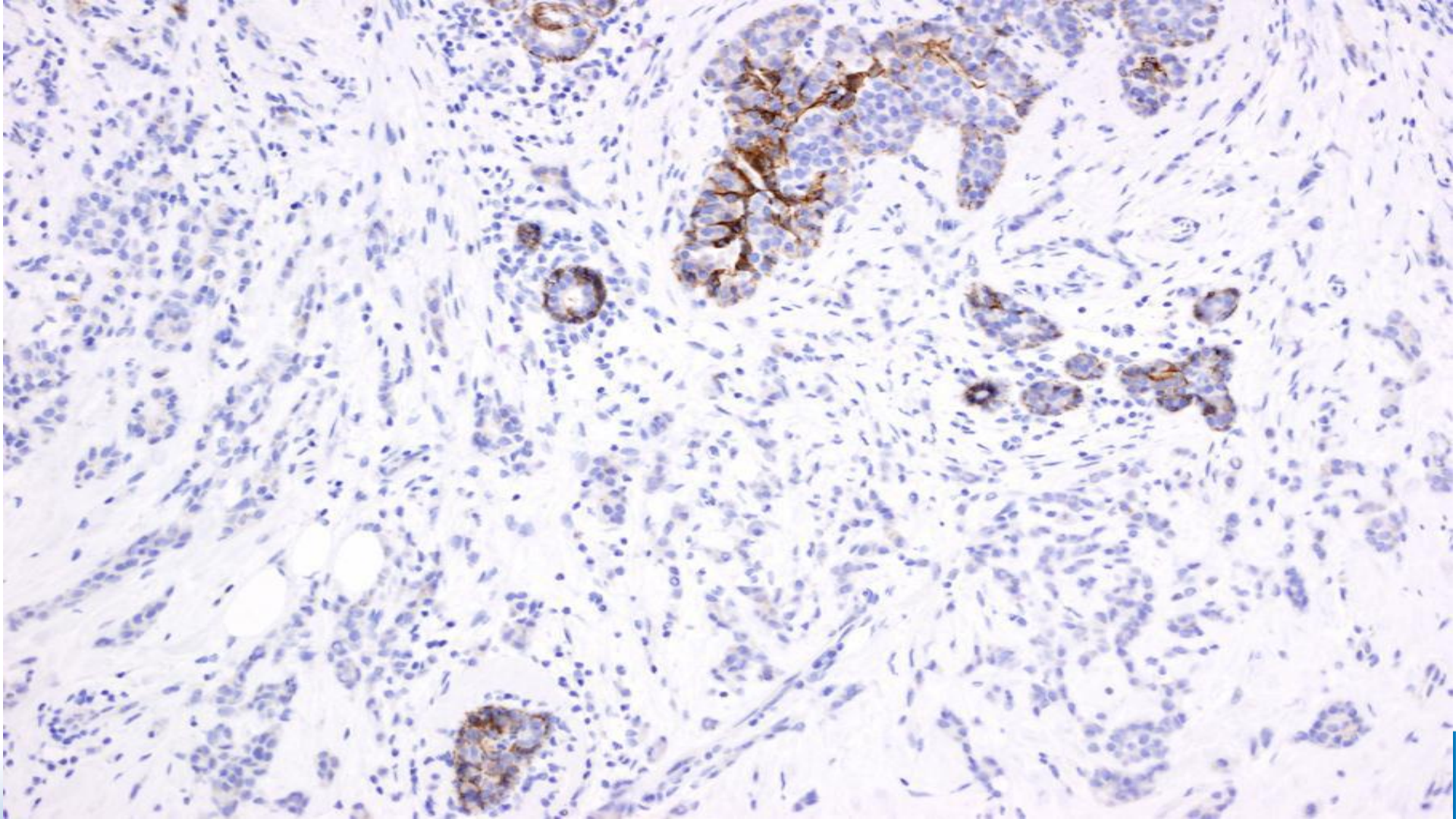


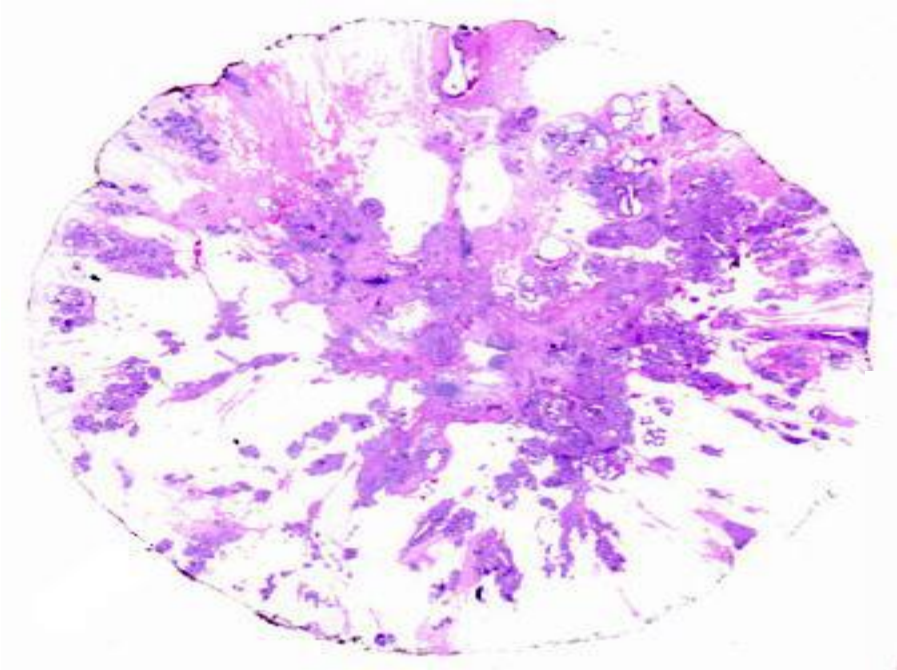


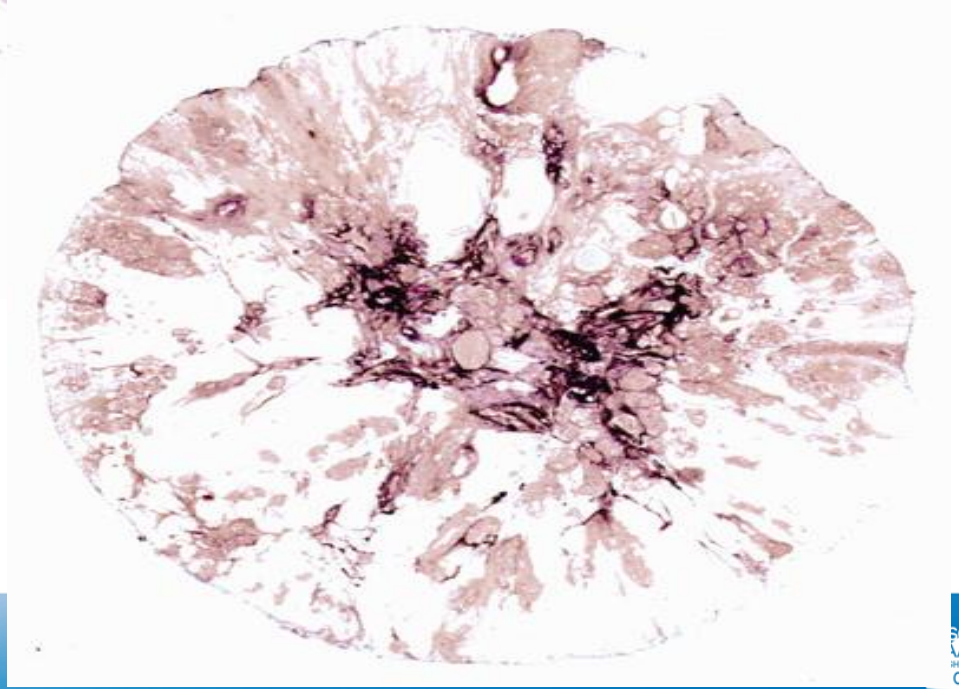


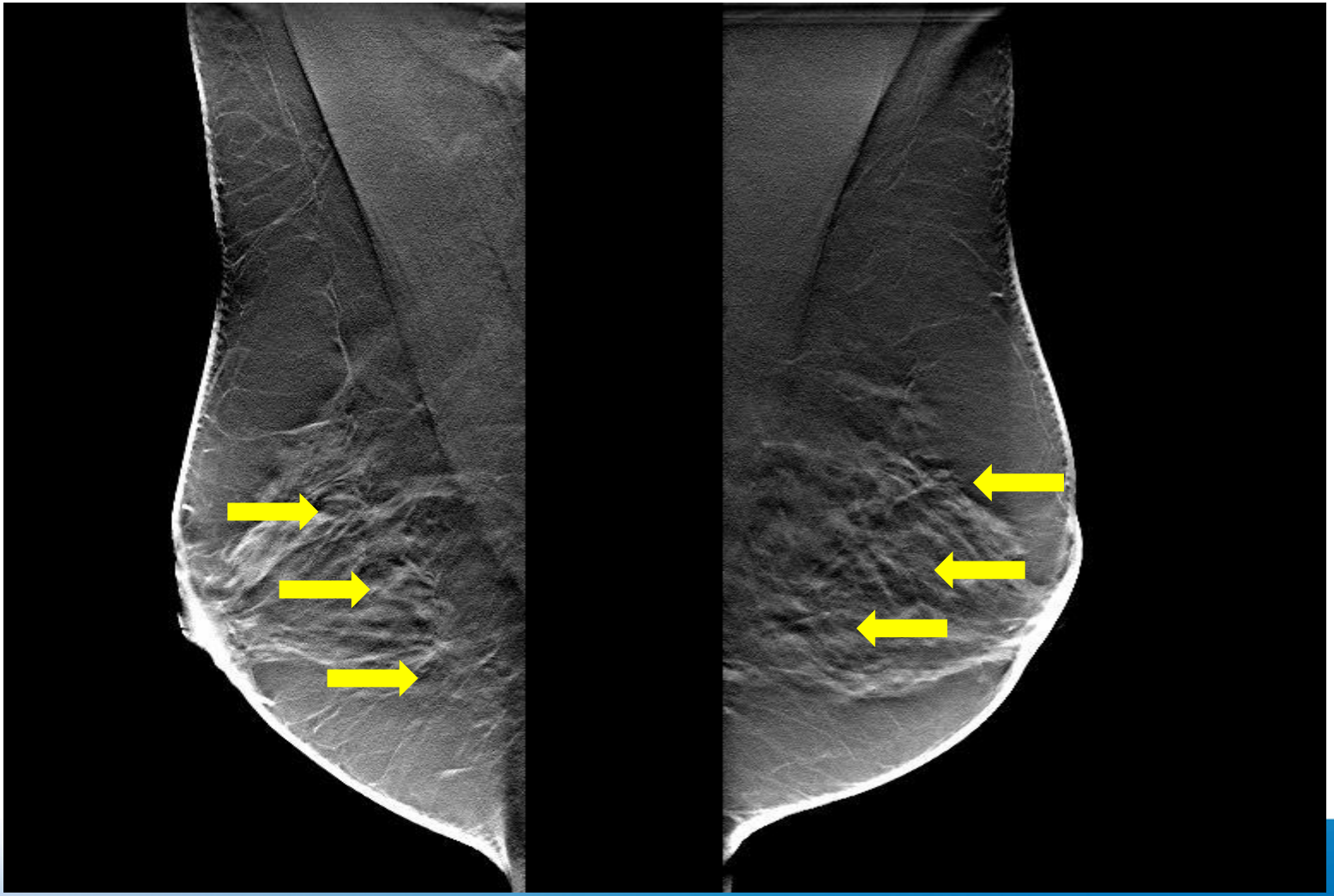












Neoplasia Lobulillar/Lesión Esclerosante Compleja

¿Su diagnóstico en BAG implica la resección quirúrgica posterior?

[106] Lobular Neoplasia on Core Needle Biopsy: Clinical and Radiopathologic Correlation Study with Follow-Up Excision Biopsy of 87 Cases

[121] Pathologic Upgrade (PU) Rates on Subsequent Excisional Biopsy (EXBX) When Lobular Carcinoma In Situ (LCIS) Is Found in a Needle Core Biopsy (NCB) with Emphasis on Radiologic Correlation

[130] Routine Excision Is Necessary for Lobular Neoplasia Detected on Breast Core Needle Biopsy: Experience from a Large Women's Health Center

[161] High Grade Lobular Carcinoma In Situ in Breast Excision: Potential for Misdiagnosis as Solid Type DCIS or Classical LCIS

[220] Clinical Outcome in Pleomorphic Lobular Carcinoma

[124] Radial Scar at Image-Guided Needle Biopsy: Is Follow-Up Excision Always Necessary?

[264] Upgrade Rates on Surgical Excision for Targeted vs. Incidental Radial Scars/Complex Sclerosing Lesions (RS/CSLs) Identified on Core Needle Biopsy (CNB)

[308] The Management of Radial Sclerosing Lesions/Radial Scars Diagnosed in Core Biopsy: Excision or Not?

Neoplasia Lobulillar

[130] Routine Excision Is Necessary for Lobular Neoplasia Detected on Breast Core Needle Biopsy: Experience from a Large Women's Health Center

Results: 807 cases of LN were identified out of 20260 breast core biopsies (4%). 240 cases were excluded due to history or synchronous IC or DCIS (29.7%). Among the remaining 567 cases, 466 (82.2%) with FUE were included in the study. Patients were divided into groups as follow: ALH (235; 50%), LCIS (125; 27%), ALH+ADH (80; 17%) and LCIS+ADH (26; 6%). LN was confirmed by E-cad/P120 dual stain (263/466; 56.4%) or E-cad (70; 15%). The radiological abnormalities were calcification (78.5%), mass (14.2%) or other in 7.3%. The BI-RADS for group 1 were: score 4 in 256/260 (98.5% only 1 case score 5), and scores 3&5 in 4 cases (1.5%). For group 2, the BIRADS were: 4 in 78/80 (97.5%) and score 3 in 2 cases (2.5%) with no significant difference in relation to upstaging. The time interval between the core biopsy and FUE range from 0.3-7 month (mean 1.4) with significant difference in relation to upstaging in group 2. 28/360 (7.8%) and 17/106 (16.0%) of group 1 and group 2 cases upstaged to IC or DCIS (Table 1).

Table (1) Upstaging of LN on surgical follow-up excision

	ALH (%)	LCIS (%)	ALH+ADH (%)	LCIS+ADH (%)	Total (%)
IC	5 (2.1)	8 (6.4)	6 (7.5)	5 (19.2)	24 (5.2)
DCIS	8 (3.4)	7 (5.6)	3 (3.8)	3 (11.5)	21 (4.5)
ADH	47 (20)	25 (20)	40 (50)	7 (26.9)	119 (25.5)
Not upstaged	175 (74.5)	85 (68)	31 (38.7)	11 (42.4)	302 (64.8)
Total	235	125	80	26	466

Chi square test, P=0.0001

Conclusions: 1. This is the largest study on patients with diagnosis of LN on core biopsy and FUE.
2. LN with or without ADH is a definite risk factor for upstaging to IC and/or DCIS.
3. The risk of upstaging on FUE for LCIS is more than that of ALH (15.2% vs. 7.0%) (p=0.0001).
4. Our data indicate that excision of the biopsy site is prudent for all patients with LN on core biopsy due to the significant percentage of cases which found to be upgraded to IC or DCIS.

Neoplasia Lobulillar

[106] Lobular Neoplasia on Core Needle Biopsy: Clinical and Radiopathologic Correlation Study with Follow-Up Excision Biopsy of 87 Cases

Design: The data base was searched for breast core biopsies from Jun 06- Jun 11 with the diagnosis of LCIS/ALH. Any case with coexistent pleomorphic LCIS, ADH, flat epithelial atypia, papilloma or radial scar was excluded from the study. Core and excision biopsy slides of all cases were reviewed using Page's criteria. Radiopathologic correlation was done for all cases. 87 cases with follow up excision biopsy qualified for study. Presence of invasive carcinoma/DCIS in direct correlation to initial biopsy site with LN defined the lesion as upgrade. The proportion of upgrade on excision and 95% confidence intervals (CI) were calculated.

Results: Our study consisted of 83 females, mean age 55 yrs (age range=37-88yrs) with 87 core biopsies showing isolated LN (22 ALH, 44 LCIS and 21 ALH&LCIS). Of these, 13 had family history and 28 had history of breast cancer (2 bilateral, 16 contralateral and 10 ipsilateral). Core biopsy indication included calcification in 36 (41%), non mass like enhancements in 17 (20%) and solid nodules or mass enhancement 34 (39%). 3/87 (3.4%) cases upgraded on excision biopsy. The upgraded lesions included low grade invasive ductal carcinoma (6mm), invasive lobular carcinoma (4mm) and pleomorphic LCIS with focal low grade DCIS. 2 of the upgraded cases were BIRADS 6 and 1 was BIRADS 4a. LCIS extent and associated microcalcifications showed no correlation with upgrade.

Conclusions: With a good sample size and radiopathologic correlation, our study showed a 3.4%(95%CI, 1-10%) upgrade on follow up excision for core biopsy with isolated LN. Our study essentially highlights benign outcome for isolated ALH/LCIS on core biopsy and gives a valid reason for rethinking the current practice of surgical excision for these patients.

Lesión esclerosante compleja

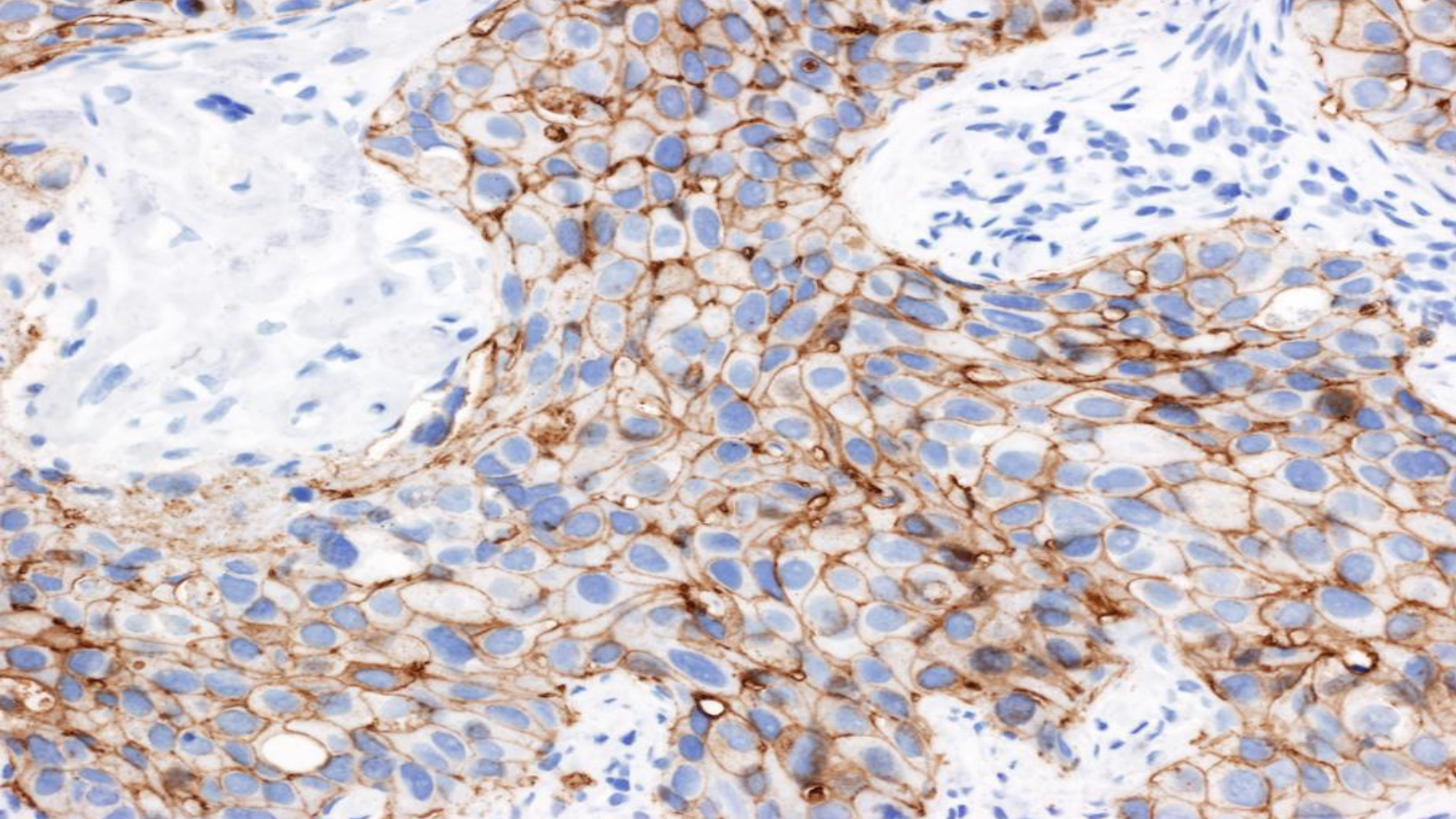
[124] Radial Scar at Image-Guided Needle Biopsy: Is Follow-Up Excision Always Necessary?

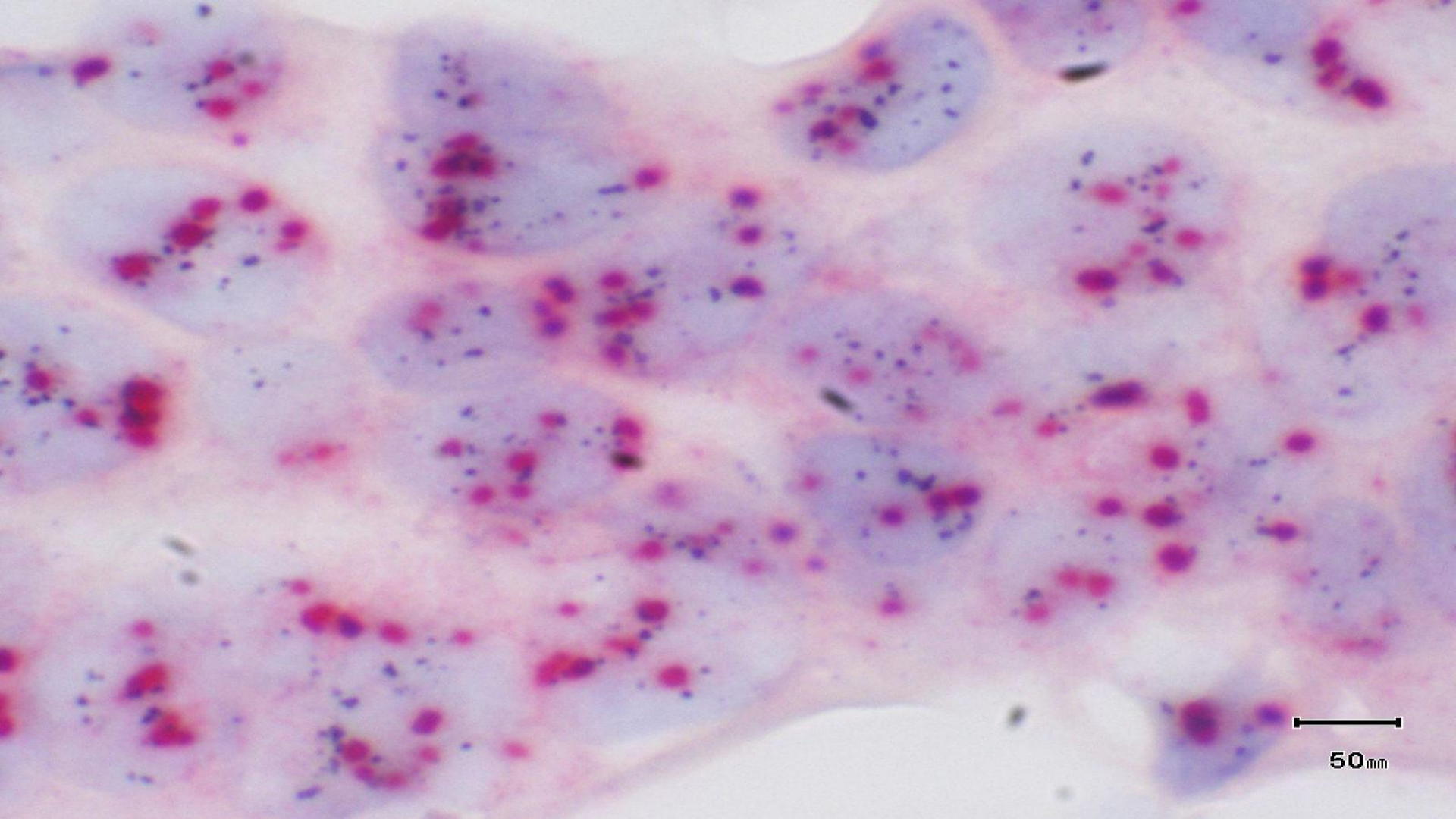
Design: With IRB approval, we performed a retrospective review of CNBs with a benign diagnosis obtained at our center from 1996 to 2011. We identified 55 cases in which CNB yielded a diagnosis of RS with no other associated high risk lesion (ie, ductal or lobular atypia). Biopsy guidance was ultrasound in 27 cases, stereotactic in 20, and MRI

Conclusions: Among lesions yielding RS as the highest risk lesion at CNB, surgery yielded cancer in 4/52 (8%; 95%CI 2-19%). Most cancers were DCIS and occurred in lesions evident as Ca2+. Our data support surgical excision of lesions yielding RS as the highest risk lesion at percutaneous image-guided needle biopsy.

[308] The Management of Radial Sclerosing Lesions/Radial Scars Diagnosed in Core Biopsy: Excision or Not?

Design: Retrospective data were collected from women with a histological diagnosis of RSL/RS in needle core biopsies over an 11-year period from 2000 to 2011 in our institution. Patients with invasive carcinoma, ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), or any type of atypia, as well as papilloma, in the same needle biopsies were excluded from this study. The histological findings of the initial biopsies and the following surgical excisions were analyzed to evaluate the necessity of open surgical excisions following a diagnosis of RSL/RS in core biopsy.
Results: 48 cases of RSL/RS on core biopsies were identified, and 34 of these 48 underwent surgical excisions. One (3%) had a small invasive ductal carcinoma in the surgical excision. None of the excision had DCIS. 4 cases showed atypia (12%) (including one atypical papilloma, one flat epithelial atypia, one with both ADH and ALH and one with ALH). The excisions in 15 of 34 cases had residual RSL/RS, and the remaining 14 cases had non-RSL/RS type benign findings on excision.
Conclusions: Surgical excisions following the diagnosis of RSL/RS on core biopsies had a very low rate of malignancy at our institution (3%). Surgical excision of RSL/RS may not be warranted in all cases.

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CerB-b2/Her2-neu: heterogeneidad/polisomía

¿Qué significan? ¿Cómo manejarlos?

[86] Breast Cancer HER2 Heterogeneity by FISH Pre and Post Neoadjuvant Chemotherapy: A Pilot Study

[90] CEP17 "Polysomy" (CEP17P): Definition and Impact on *HER2* Copy Number (CN) in Breast Carcinoma

[91] Breast Carcinomas with Equivocal *HER2/Neu* Amplification: Morphologic Features, CEP17 Polysomy and *HER2* Genetic Heterogeneity

[139] Chromosome 17 Polysomy and Monosomy as Predictive Markers of Complete Pathological Response (pCR) in Women with Locally Advanced Breast Cancer (LABC)

[191] HER2/Neu Gene Amplification Heterogeneity: The Significance of Cells with a 3:1 HER2/CEP17 Ratio

[225] Chromosome 17 Polysomy: Correlation with Histological Parameters and HER2/Neu Gene Amplification

[237] Utilization of Dual ISH and RT-PCR Enhances Resolution of IHC and FISH Double Equivocal Testing Results in Breast Carcinoma

[239] The Use of Tumor Heterogeneity Scoring in Determining the Amount of Tissue Required for HER2 Diagnosis in Breast Cancer

[274] HER2 Heterogeneity by FISH in Breast Cancers and Matched Lymph Node Metastases: A Pilot Study

CerB-b2/Her2-neu: heterogeneidad

- Añaden nuevos criterios para definir heterogeneidad en la amplificación (señales individuales por célula #86, células con índice 3:1 #191, nº absoluto copias #274)
- Se detectan variaciones, a veces notables, entre el tumor primario y la metástasis, en ámbos sentidos # 274
- La neoadyuvancia origina incremento en la detección de heterogeneidad (63%), incluso con cambios de categoría #86
- Confusión.....

CerB-b2/Her2-neu: Polisomía

- Más frecuente en casos sin amplificación o equívocos, 70% vs 30% (#139, #225)
- Marcada asociación con factores morfológicos clásicos de mal pronóstico (#90,#91,#225) y subtipo intrínseco luminal B (#91)
- Posible predictor de respuesta a neoadyuvancia : 29% vs. 13% vs. 0% (# 139)
- A seguir.....

¡¡¡Gracias por su atención!!!

Clínica Universidad de Navarra

USCAP & AACR HIGHLIGHTS 2012