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Role of breast MRI in predicting pathologically negative nodes after neoadjuvant chemotherapy in cN0 patients in the I-SPY 2 trial

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BACKGROUND AND AIMS

- In patients with clinically node-negative (cN0) breast cancer with triple negative (TN) or HER2+ disease who achieve a breast pathological complete response (pCR) after neoadjuvant chemotherapy (NAC), low rates of nodal positivity have been demonstrated.
- In these patients, the omission of surgical axillary staging has been proposed. However, breast pCR information is not known preoperatively.
- Aims of this study:
  - To validate the correlation between breast pCR and pathologically negative nodes after NAC (ypN0)
  - To evaluate the correlation between response of the tumor in the breast on MRI and nodal status in cN0 patients in the I-SPY 2 trial.

ELIGIBILITY AND METHODS

In the I-SPY 2 study, eligible tumors must meet one of the following criteria: Stage II or III, or T4, any N, M0, including clinical or pathologic inflammatory cancer or Regional Stage IV, where supraclavicular lymph nodes are the only sites metastasis.

For this study, we identified all patients with cT1-4 cN0 breast cancer at presentation from all closed experimental and control arms in the I-SPY2 trial.

•Absence of residual breast disease post-NAC on MRI was defined as longest diameter (LD) of 0 mm (LD=0)
•Residual disease post-NAC on MRI was defined as LD of >0 mm (LD>0)
•Breast pCR: absence of invasive tumor in the breast at surgery
•Associations between ypN0 and patient, MRI, and tumor characteristics were assessed using chi-square tests, univariate regression and Venn diagrams
•The distribution of nodal status in correlation to LD and RCB was assessed using a scatter box plot

I-SPY2's ADAPTIVE TRIAL DESIGN

I-SPY 2 is a multicenter, phase 2 trial using response-adaptive randomization within biomarker subtypes to evaluate a series of novel agents when added to standard neoadjuvant therapy for women with high-risk stage II/III breast (FIG.1). Within each patient subtype, participants are assigned to one of several investigational therapies or the control regimen (4:1). Randomization probabilities are weighed by the probability of achieving a pCR within each subtype for each agent and adapts over the course of the trial. *The primary endpoint is pathologic complete response (pCR, no residual disease in breast or nodes) at surgery.*

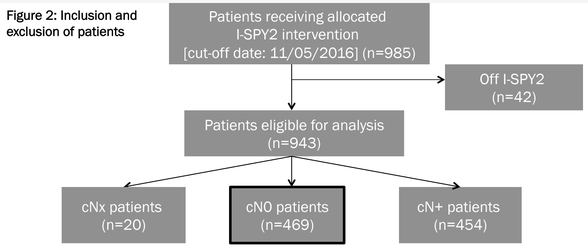
The goal is to identify/graduate regimens that have ≥85% Bayesian predictive probability of success (statistical significance) in a 300-patient phase 3 neoadjuvant trial, defined by hormone-receptor (HR) & HER2 status & MammaPrint (MP).

Regimens may leave the trial for one of four reasons: Graduate, Drop for futility (< 10% probability of success), Drop for safety issues, or accruing maximum sample size (10%< probability of success <85%).

Figure 1: I-SPY2 study schema and adaptive randomization based on probabilities of agents of achieving pCR within a given subtype

ENROLLMENT

Figure 2: Inclusion and exclusion of patients



RESULTS

Table 1: Proportion of patients with pathologic negative nodes in patients with and without breast pCR, and with and without residual disease on MRI

	Response of the breast at pathology		Response of the breast on MRI	
Subtype	ypN0 in pts with breast pCR (%)	ypN0 in pts without breast pCR (%)	ypN0 in pts with LD=0 (%)	ypN0 in pts LD>0 (%)
HR+/HER2- (n=162)	35/41 (85%)	78/121 (65%)	36/48 (75%)	74/108 (69%)
HR+/HER2+ (n=77)	30/31 (97%)	26/46 (54%)	26/31 (84%)	28/43 (65%)
HR-/HER2+ (n=39)	28/29 (97%)	10/10 (100%)	19/20 (95%)	18/18 (100%)
TN (n=191)	92/96 (96%)	76/95 (80%)	68/72 (94%)	97/116 (84%)

RESULTS continued

- Overall, 375/469 patients (80%) were ypN0
- The strongest correlation between ypN0 and breast pCR was observed in patients with HR+HER2+, HR-HER2+ and TN tumors (respectively 97%, 97%, 96%) [table 1]
- The strongest correlation between ypN0 and LD=0 on MRI was observed in patients with HR-/HER2+ and TN tumors (respectively 95% and 94%)
- Significant predictors for ypN0 at univariate regression (table 2) were:
  - Tumor subtype
  - MammaPrint classification
  - Tumor grade
  - Breast MRI findings pre-surgery
  - Pathologic response breast tumor

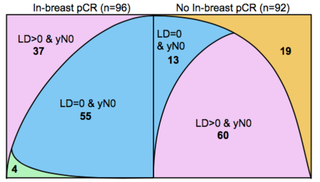
Table 2 - Predictors for ypN0 at univariate regression

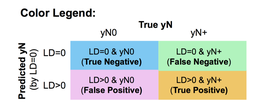
Characteristic	Total	ypN0 (%)	p-value
All patients	469	375 (80)	n.a.
Subtype			
HR+HER2-	162	113 (70)	
HR+HER2+	77	56 (73)	<0.001
HR-HER2+	39	38 (97)	
TN	191	168 (88)	
MammaPrint Classification			
High Risk 1	221	155 (70)	<0.001
High Risk 2	247	219 (89)	
Unknown	1		
Grade			
I	7	4 (57)	
II	83	59 (71)	0.001
III	234	200 (86)	
Unknown	145		
T-category			
T1	20	17 (85)	
T2	342	278 (81)	0.059
T3	98	75 (77)	
T3	9	5 (56)	
Breast MRI findings pre-surgery			
LD=0 (imaging breast CR)	171	149 (87)	0.005
LD > 0	285	217 (76)	
Unknown	13		
Breast pathologic complete response			
Breast pCR (ypT0)	197	185 (94)	<0.001
no breast pCR (ypTis/ypT1)	272	190 (70)	

- In patients with LD=0 on MRI who achieved breast pCR, the strongest correlation between LD=0 and ypN0 was observed in HR-HER2+ patients (figure 3)
- Patients with LD=0 had significantly lower RCB index than those with LD>0
- ypN0 patients with LD=0 on MRI had lower RCB scores compared to patients with LD>0 on MRI (figure 4)
- ypN+ patients with LD=0 on MRI had lower RCB scores compared to patients with LD>0 on MRI

Figure 3: Association between breast pCR, LD on MRI and ypN

TN tumors





HER2+ HR- tumors

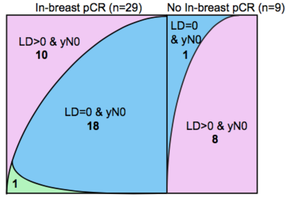
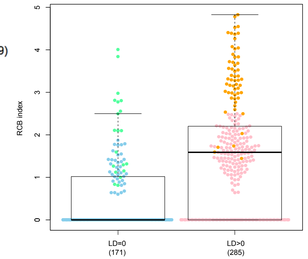


Figure 4: Distribution of nodal status based on LD and RCB



CONCLUSIONS

- Overall, 80% of cT1-4 cN0 patients were ypN0 after NAC; 80% was ypN+
- In cT1-4 cN0 breast cancer patients with HR+HER2+, HR-HER2- and TN tumors and a breast pCR, ypN0 rates after NAC are very high (96-97%)
- In HR- (HER2+/-) patients with no residual disease in the breast on MRI after NAC, ypN0 rates are high at 94-95%. Consideration of omission of axillary surgery in these patients is warranted.
- In patients with LD=0 on MRI who achieved breast pCR, the strongest correlation between LD=0 and ypN0 was observed in HR-/HER2+ patients
- Breast MRI after NAC (prior to surgery) can be used to assess for residual breast disease and predict pathologic breast pCR.
- In HR+ patients, breast MRI is insufficiently predictive for pCR and can not be used to identify ypN-patients at high likelihood of ypN0.
- In HR+/HER2- patients, pCR in the breast is associated with 15% ypN+

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