The impact of local therapy on locoregional recurrence in women with high risk breast cancer in the neoadjuvant I-SPY2 TRIAL

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BACKGROUND

In women with breast cancer receiving neoadjuvant chemotherapy, residual cancer burden (RCB) predicts distant recurrence and survival. In those with high risk and locally advanced tumors, locoregional recurrence (LRR) remains a concern, and has been associated with type of local therapy received. We evaluated the impact of local therapy on LRR in the ISPY-2 TRIAL.

TRIAL ELIGIBILITY & STUDY METHODS

- Clinical Eligibility 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 of metastasis
- Molecular Eligibility Criteria: Triple Negative, or HER2+, or MammaPrint High risk HR+HER2-
- Data were analyzed in Stata 14.2, using Chi2 test, log rank test, and a Cox proportional hazards model. Primary endpoint was LRR.
- RCB was considered a categorical variable (0/1 versus 2/3).
- Breast surgery categories were lumpectomy or mastectomy

ADVOCATE'S PERSPECTIVE

This study highlights the importance of neoadjuvant trials to discover important findings, including, in this case, safely undergoing less extensive surgery. Despite many trials showing no difference in distant recurrence and long term survival, with breast conservation vs mastectomy, this study now allows even women with high risk tumors who have a good response to therapy, to feel confident about choosing lumpectomy in terms of LRR. RCB as one of two key determinants of LRR underscores that low RCB is a reliable biomarker for long term outcomes. We need to continue to work to get all women to an RCB of 0/1.

LOCAL THERAPY

	BCS rate	Mastectomy rate	P value
Age			
<40 years	40 (30.5%)	91 (69.5%)	<0.001
≥40 years	243 (48.7%)	256 (51.3%)	
Tumor Grade			
1	4 (66.7%)	2 (33.3%)	
2	54 (41.5%)	76 (58.5%)	0.348
3	139 (46.8%)	158 (53.2%)	
Tumor subtype			
HR+Her2-	94 (39.7%)	143 (60.3%)	
Her2+	85 (48.3%)	91 (51.7%)	0.113
Triple negative	104 (48.2%)	112 (51.9%)	
Clinical stage			
I	132 (55%)	108 (45%)	
II	81 (43.8%)	104 (56.2%)	<0.001
III	19 (23.8%)	61 (76.3%)	
RCB			
0/1	150 (51.2%)	143 (48.8%)	0.002
2/3	113 (38.7%)	179 (61.3%)	

Table 1. Factors associated with breast conserving surgery (BCS) versus mastectomy
Young age, higher clinical stage, and more residual disease (RCB 2/3) were significantly associated with higher rates of mastectomy.

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 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%).

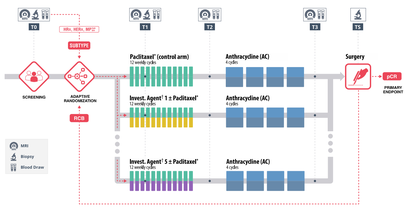

Figure 1: I-SPY2 study schema and adaptive randomization based on probabilities of agents of achieving pCR within a given subtype

RESULTS

Table 3. Factors associated with locoregional recurrence (LRR)

	Frequency	LRR rate (%)	P value
Age			
<40 years	131 (20.8%)	12.2	0.052
≥40 years	499 (79.2%)	7.0	
Clinical stage			
I	240 (47.5%)	7.0	
II	185 (36.6%)	9.7	0.598
III	80 (15.8%)	7.5	
Tumor subtype			
HR+Her2-	237 (37.7%)	5.9	
Her2+	176 (28.0%)	6.3	0.033
Triple negative	216 (34.3%)	12.0	
Tumor Grade			
1	6 (1.4%)	0.0	
2	130 (30.0%)	4.6	0.215
3	297 (68.6%)	9.1	
Local therapy			
Lumpectomy alone	24 (3.8%)	12.5	
Lumpectomy + radiation	259 (41.1%)	8.1	0.511
Mastectomy	144 (22.9%)	5.6	
Mastectomy + radiation	203 (32.2%)	9.4	
RCB			
0/1	293 (50.1%)	4.1	0.001
2/3	292 (49.9%)	11.6	

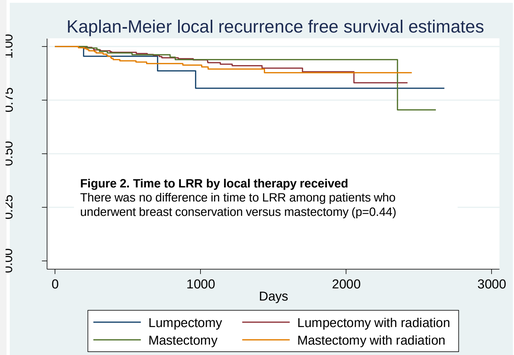

Figure 2. Time to LRR by local therapy received
There was no difference in time to LRR among patients who underwent breast conservation versus mastectomy (p=0.44)

RESULTS

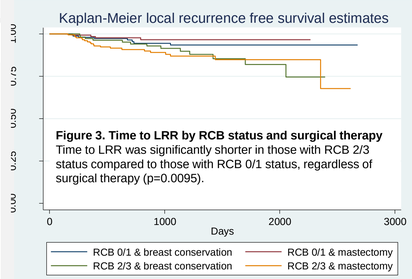

Figure 3. Time to LRR by RCB status and surgical therapy
Time to LRR was significantly shorter in those with RCB 2/3 status compared to those with RCB 0/1 status, regardless of surgical therapy (p=0.0095).

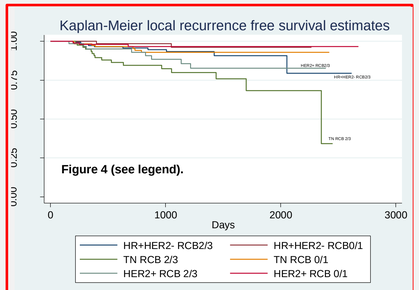

Figure 4 (see legend).

Table 2. Cox proportional hazards model for LRR including local therapy, tumor subtype, clinical stage, age, tumor grade, RCB status.

On multivariate analysis, only RCB status and tumor subtype were associated with LRR. The effect of tumor subtype appeared predominantly in those with RCB 2/3 status (see Figure 4).

	HR	95% CI	P value
RCB 0/1	0.33	0.12-0.89	0.029
HR+ HER2-	Baseline		
HER2+	3.13	0.95-10.29	0.061
Triple negative	3.6	1.14-11.47	0.029

Figure 4. Time to LRR by RCB status and tumor subtype

Tumors of the HER2+ or triple negative (TN) subtype had significantly shorter time to LRR than tumors of the HR+HER2- subtype, particularly among those with RCB2/3 status (p=0.0001). Surgical therapy (lumpectomy versus mastectomy) was not associated with LRR regardless of tumor subtype or RCB.

CONCLUSIONS

- Extent of surgical therapy was not associated with local tumor control, regardless of advanced tumor stage at presentation.
- Response to therapy (RCB) was the best predictor of LRR. Within those with RCB 2/3 status, HER2+ and triple negative tumor subtype had shorter time to LRR.
- For those with residual disease, BCS particularly in those who will need adjuvant radiation regardless of surgical therapy, can minimize complications without impacting LRR.
- **These data highlight the opportunity to minimize the morbidity of extensive surgical therapy for patients with excellent response to systemic therapy.**

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