Neoadjuvant Chemotherapy for T3 tumors in the Era of Precision Medicine – Biology is Still King

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SAN ANTONIO BREAST CANCER SYMPOSIUM®

Presentation ID: P1-11-24, December 11, 2024

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Background

- Clinical T3 (cT3) breast cancer often precludes cosmetically acceptable breast conservation, leading NCCN[1] and ASCO[2] to recommend neoadjuvant chemotherapy (NCT) for downstaging.
- However, response to chemotherapy is dictated by the biological profile regardless of tumor size.
- MammaPrint® risk of recurrence and BluePrint® molecular subtyping genomic signatures have demonstrated high accuracy in predicting chemotherapy response.[3]
- Thus, genomic profiling can potentially enable Choosing Wisely®[4] informed treatment choices and reduced toxicity for patients unlikely to benefit from NCT with cT3 tumors.
- cT3 tumor response to chemotherapy in the context of genomic profiling will inform precision medicine approach for these patients.

Methods

- A pooled analysis from FLEX (NCT03053193), MINT (NCT01501487), and NBRST (NCT01479101) trials was conducted on all cT3 patients who received NCT, had MammaPrint/BluePrint results, and post-surgical pathological Complete Response (pCR) data.
- MammaPrint risk was characterized as Low or High Risk. BluePrint subtype classified tumors as Luminal-Type, HER2-Type, or Basal-Type. Luminal-Type tumors were further classified as Luminal A (MammaPrint Low Risk) or Luminal B (MammaPrint High Risk).
- Tumor pCR rates were analyzed as an outcome measure.
- The association of genomic subtype and clinical features with likelihood of pCR was evaluated by multivariate logistic regression.
- Differences in pCR rates between genomic risk categories were evaluated by two-sided proportional z-test and stratified by nodal status.

References: 1. NCCN 2024 Breast Cancer Guidelines. 2. Korde, et al. JCO. 2021. 3. O'Shaughnessy, et al. ASCO 2024. 4. Shah, et al. BCRT. 2021. 5. Piccart, et al. Lancet Oncol. 2021. 6. Lopes Cardoso, et al. JCO. 2022. 7. van Olmen, et al. Breast. 2024.

Table 1. Clinical Characteristics of patients with cT3 tumors from FLEX, MINT, and NBRST

Characteristic	No. patients (%) (n=404)
Age in years – Mean (SD)	52 (±12)
Menopausal Status	
Pre/Peri	186 (51.7)
Post	209 (46.0)
Unknown	9 (2.2)
Race	
White	293 (72.5)
Black	67 (16.6)
Latin/Hispanic	24 (5.9)
AAPI	12 (2.97)
Other	3 (0.7)
Unknown	5 (1.2)
Histopatholgical Type	
IDC	325 (80.5)
ILC	49 (12.1)
Mixed IDC/ILC	18 (4.5)
Other	10 (2.5)
Unknown	2 (0.5)
Nodal Status	
N0	104 (25.7)
N1	237 (58.7)
N2	38 (9.4)
N3	12 (3.0)
NX	8 (2.0)
Unknown	5 (1.2)
Grade	
G1	20 (5.0)
G2	150 (37.1)
G3	215 (53.2)
GX	13 (3.2)
Unknown	6 (1.5)
Receptor Status	
HR+HER2-	209 (51.7)
HR+HER2+	53 (13.1)
HR-HER2+	50 (12.4)
TNBC	79 (19.6)
Unknown	13 (3.2)
MammaPrint	
Low Risk	65 (16.1)
High 1	167 (41.3)
High 2	172 (42.6)
BluePrint	
Luminal A-Type	64 (15.8)
Luminal B-Type	150 (37.1)
HER2-Type	68 (16.8)
Basal-Type	121 (30.1)
Not Requested	1 (0.3)

Data in **Table 1** presents n (%) unless indicated otherwise. **Figure 2**, 'Overall' includes patients with unknown nodal status. Data in **Table 2** presents OR (95% CI, p-value). p<0.05 indicates significance. Abbreviations; cT3, clinical stage 3 tumor; LN, lymph node; ns, not significant; OR, Odds ratio; CI, Confidence interval.

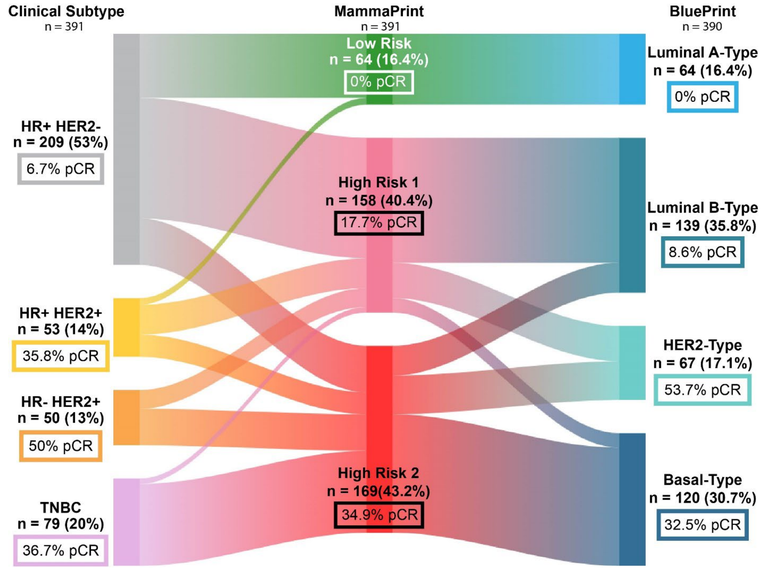

Figure 1. pCR rates by clinical and genomic subtypes. Patients with unknown receptor status (n=13) and not requested BluePrint (n=1) were excluded. Abbreviations: pCR, pathological Complete Response; HR, hormone receptor; HER2, human epidermal growth factor; TNBC, triple negative breast cancer

Figure 2. pCR rates by nodal status and MammaPrint for patients with HR+HER2- disease

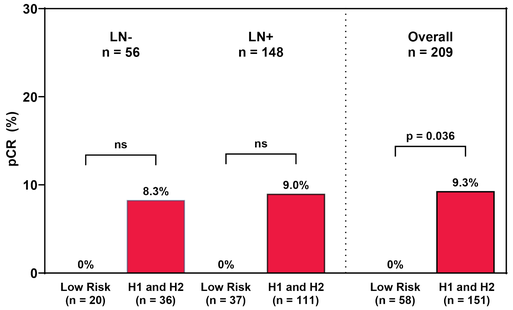

Table 2. Multivariate analysis of predictive factors for pCR

Characteristic	Odds Ratio	95% CI	P-value
BluePrint Subtype			
Luminal (n=214)	1.00		
Basal (n=121)	3.06	[1.15, 8.19]	**0.025**
HER2 (n=68)	6.27	[2.19, 19.38]	**0.001**
Menopausal Status			
Pre/Peri (n=186)	1.00		
Post (n=209)	0.66	[0.36, 1.19]	0.173
Receptor Status			
HR+HER2- (n=209)	1.00		
HR+HER2+ (n=53)	2.91	[0.97, 8.23]	**0.048**
HR-HER2+ (n=50)	2.59	[0.82, 8.05]	0.101
TNBC (n=79)	2.33	[0.91, 6.34]	0.085
Lymph Node Stage			
LN- (n=104)	1.00		
LN+ (n=287)	1.08	[0.55, 2.18]	0.816
Grade			
G1 (n=20)	1.00		
G2 (n=150)	2.77	[0.39, 56.98]	0.380
G3 (n=215)	4.49	[0.66, 91.11]	0.191

Results

- A total of 404 patients (FLEX, n=123; MINT, n=67; NBRST, n=214) with cT3 breast cancer underwent NCT followed by resection and 87 (21.5%) achieved pCR (**Table 1**).
- pCR by receptor status vs MammaPrint/BluePrint (**Figure 1**):
  - Of the 209 (51.7%) patients with HR+HER2- disease, 6.7% achieved pCR.
  - No pCR was achieved for any MammaPrint Low Risk T3 tumor (n=64). In contrast, 34.9% of High Risk 2 tumors achieved pCR.
  - By molecular subtype, pCR was achieved for 8.6% of Luminal B-Type and 32.5% of Basal-Type, cT3 tumors.
- Among patients with HR+HER2- tumors, no pCR was achieved for MammaPrint Low Risk, regardless of nodal involvement. In contrast, HR+HER2- MammaPrint High Risk had significantly higher rates of pCR compared to Low Risk (p=0.036) (**Figure 2**).
- Logistic regression revealed that MammaPrint/BluePrint subtyping showed significantly higher odds ratios for pCR in High Risk Basal-Type (p=0.025) and HER2-Type (p=0.001), compared to Luminal-Type (**Table 2**).
  - Only clinical subtype HR+HER2+ exhibited a higher likelihood of pCR (p=0.048).
  - Menopausal status, nodal status, and grade were not significantly associated with likelihood of pCR.

Conclusion

- These data suggest that patients with MammaPrint Low Risk, cT3 tumors are unlikely to have a pCR with NCT.
- Additionally, long-term follow-up, level 1A evidence from MINDACT shows that patients with clinically high risk, MammaPrint Low Risk, HR+HER2-, LN+/- tumors may safely omit chemotherapy.[5,6]
- Alternatively, long-term outcome data demonstrating endocrine therapy (ET) benefit for MammaPrint Low-Risk tumors may suggest these patients are better candidates for NET.[7]
- Intuitively, NET for downstaging or proceeding to definitive surgery should be considered for genomically low-risk, cT3 cancers.