Management of small early-stage HER2-positive breast cancer: Trends and Outcomes

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Background

- Treatment of cT1-2 (≤3 cm) N0 M0 HER2-positive breast cancer has significantly changed over the past several decades.[1]
- This is secondary to advancements in HER2 targeted therapies, expanding benefits of neoadjuvant systemic therapy[2] and clinical trials such as the APT trial supporting abbreviated systemic therapy regimens.[3]
- Current treatment strategies include neoadjuvant systemic therapy (NST) to assess treatment response followed by surgery, or upfront surgery to define pathologic stage followed by systemic therapy, with advantages and disadvantages associated with both approaches.

Study Objectives

- To evaluate the management of small early-stage HER2-positive breast cancer including pathologic, clinical, and oncologic outcomes.
- To evaluate trends in management over time and current practice.

Methods

- An institutional Breast Surgical Oncology database was reviewed from 2015-2020.
- Inclusion criteria:
  - HER2-positive invasive breast cancer
  - cT1-2N0M0 (clinical tumor size ≤3 cm)
  - Received surgery at MD Anderson
- Exclusion criteria:
  - Recurrent breast cancer
  - Concurrent malignancy
- Patient, tumor and treatment characteristics were evaluated and compared for patients who received upfront surgery and NST.
- Statistical analysis: Student *t* test was used to compare the means of continuous variables with equal variances. Wilcoxon rank-sum test was used to compare the medians of continuous variables without equal variances. The X^2 test or Fisher exact test was used for univariate comparison of categorical variables. Multivariate logistical regression models were used to identify factors that significantly predict upgrade to pathologic tumor size (pT) >3 cm or pN1-3 in the upfront surgery group, and residual disease in the breast or ypN1-3 in the NST group. All *P* values were 2 tailed, and $P \leq 0.05$ was considered significant. Kaplan-Meier survival curves were calculated, and log-rank tests were used to compare the overall survival, disease specific survival, local-regional recurrence free survival and distant recurrence free survival between treatment groups.
- Additionally, an electronic survey assessing recommendations for clinical scenarios in management of early-stage HER2-positive breast cancer was sent to MD Anderson medical and surgical oncologists.

Results

- 256 patients met eligibility criteria
  - 170 (66.4%) received upfront surgery
  - 86 (33.6%) received NST

Table 1: Patient demographics

	Overall (N=256)	Upfront surgery (N=170)	NST (N=86)	P value
Age at diagnosis, Years				0.0001
Median	57	59	53	
Mean (range)	57	59.1 (33-85)	52.9 (28-76)	
Gender				0.3
Female	255	170 (100%)	85 (98.8%)	
Male	1	0 (0)	1 (1.2%)	
Race				0.07
White	186	130 (76.5%)	56 (65.1%)	
Others	70	40 (23.5%)	30 (34.9%)	
Asian	18	9	9	
Black	26	17	9	
Declined to answer	2	1	1	
Other	23	13	10	
Unknown	1	0	1	
Ethnicity				0.04
Hispanic or Latino	37	19 (11.2%)	18 (20.9%)	
Not Hispanic or Latino	216	149 (87.7%)	67 (77.9%)	
Declined to Answer	3	2 (1.2%)	1 (1.2%)	
BMI				0.7
Median	27.5	28	27	
Mean (range)	28.5	28.6 (17-63)	28.2 (19-66)	

Table 2: Clinical tumor characteristics

	Overall (N=256)	Upfront surgery (N=170)	NST (N=86)	P value
Largest Clinical tumor size (cm)				<0.0001
Median	-	1.5	2.5	
Mean (range)	-	1.6 (0.1-3)	2.3 (0.9-3)	
Clinical T stage				<0.0001
T1	167	145 (85.3%)	22 (25.6%)	
T1mic	6	6	0	
T1a	9	9	0	
T1b	35	34	1	
T1c	110	90	20	
T2	89	25 (14.7%)	64 (74.4%)	
Tumor palpable				<0.0001
Yes	140	70 (41.2%)	70 (81.4%)	
No	113	98 (57.7%)	15 (17.4%)	
Unknown	3	2 (1.2%)	1 (1.2%)	
Hormone receptor status				0.2
HR+	198	136 (80%)	62 (72.9%)	
HR-	57	34 (20%)	23 (27.1%)	
Grade				0.04
G1	9	9 (5.3%)	0 (0%)	
G2	109	75 (44.1%)	34 (39.5%)	
G3	86	86 (50.6%)	52 (60.5%)	
Ki67 (%)				<0.0001
Median	33	30	40	
Mean (range)	61.4	33.7 (1-80)	45.9 (7-99)	
DCIS present				<0.0001
Yes	206	148 (87.1%)	58 (67.4%)	
No	50	22 (12.9%)	28 (32.6%)	
Multi-focal/multicentric				0.09
Yes	77	45 (26.5%)	32 (37.2%)	
No	179	125 (73.5%)	54 (62.8%)	

Pathology Predictors

Upfront surgery: Pathologic upgrade

- 4 (2.4%) patients had upgrade to pT >3 cm
- 18 (10.6%) patients had upgrade to pN1-3
- None of the demographic, clinical tumor, or treatment factors significantly predicted upgrade to pT >3 cm or pN1-3.

NST: Pathologic response to therapy

- 47 (54.6%) patients had a pathologic complete response (pcR)
- Older age at diagnosis (OR 1.08, *P* = 0.004) and HR-positive status (OR 7.07, *P* = 0.002) were significant predictors of residual disease (breast) or upgrade to ypN1-3.

Oncologic Outcomes

- 10 (3.9%) patients had any recurrence
  - Local and regional: 1 (0.4%)
  - Regional and distant: 2 (0.8%)
  - Local and distant: 3 (1.2%)
  - Distant only: 4 (1.6%)
- 5 (2.0%) patients died

Figure 1: Survival by treatment groups

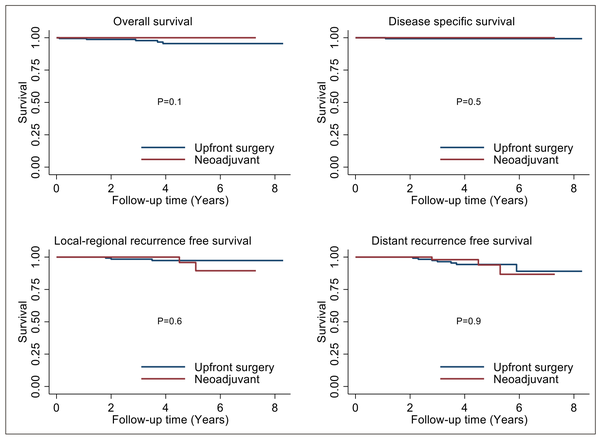


Table 3: Treatment received

	Overall (N=256)	Upfront surgery (N=170)	NST (N=86)	P value
Breast surgery				0.4
Segmental mastectomy	168	114 (68.3%)	54 (62.8%)	
Total mastectomy	85	53 (31.7%)	32 (37.2%)	
ALND				0.7
Yes	8	6 (3.5%)	2 (2.3%)	
No	248	164 (96.5%)	84 (97.7%)	
Adjuvant radiation				0.4
Yes	168	114 (67.5%)	54 (63.5%)	
No	82	51 (30.2%)	31 (36.5%)	
Unknown	4	4 (2.4%)	0 (0%)	
Adjuvant endocrine therapy				0.9
Yes	183	122 (71.8%)	61 (70.9%)	
No	73	48 (28.2%)	25 (29.1%)	
Margin status				0.01
Negative	198	124 (72.9%)	74 (86.1%)	
Close (< 2 mm)	57	46 (27.1%)	11 (12.8%)	
Unknown	1	0 (0%)	1 (1.2%)	
Surgery complications				0.8
Yes	29	20 (11.8%)	9 (10.5%)	
No	226	150 (88.2%)	76 (88.4%)	
Unknown	1	0 (0%)	1 (1.2%)	

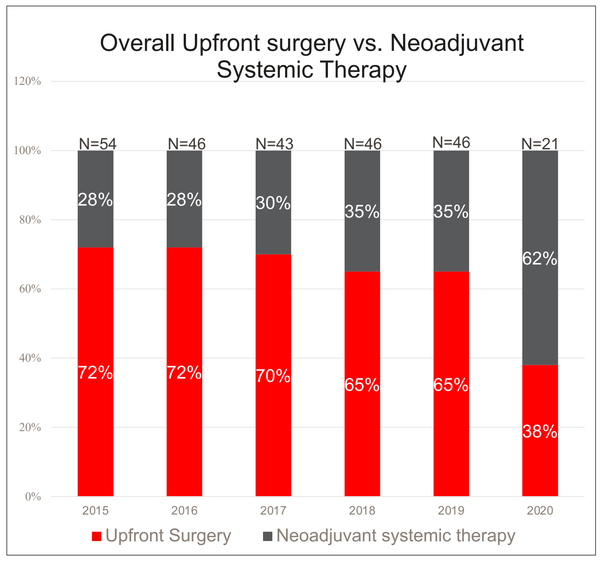
Table 4: Pathologic tumor characteristics

	Overall (N=256)	Upfront surgery (N=170)	NST (N=86)	P value
pcR				
Yes	47	N/A	47 (54.7%)	
No	39	N/A	39 (45.3%)	
pT size				<0.0001
Median	0.90	1.3	0	
Mean (range)	0.99	1.3 (0-4.3)	0.6 (0-4.8)	
SLN positive				0.02
Yes	24	21 (12.4%)	3 (3.5%)	
No	232	149 (87.7%)	83 (96.5%)	
Number of positive SLN				0.09
0	231	148 (87.6%)	83 (96.5%)	
1	21	18 (10.6%)	3 (3.5%)	
2	3	3 (1.8%)	0 (0%)	
Max positive SLN size (mm)				0.08
Median	0.13	0.2	0.08	
Mean (range)	0.26	1.3 (0.02-7%)	0.08 (0.05-0.12%)	
pN stage				0.1
N0	233	150 (89.3%)	83 (96.5%)	
N1	20	17 (10.0%)	3 (3.5%)	
N3	1	1 (0.6%)	0 (0%)	

Management Trends

- NST rates increased from 28% to 62% (2015-2020)
- cT1mic, cT1a and cT1b tumors almost always received upfront surgery compared to 81.8% of cT1c and 28% of cT2 (≤3 cm) tumors.

Figure 2: Proportion of patients receiving upfront surgery vs. NST by year, 2015-2020



Current Practice: Survey Results

Response rate was 39.3% overall (34.2% medical oncologists, 45.8% surgical oncologists). Agreement was 100% for treating cT1aN0 patients with upfront surgery, and cT2N0 (3-5 cm) and cT1-2N1 patients with NST. There was near agreement (92%) for treating cT1bN0 patients with upfront surgery. For cT1cN0 patients, 45% of physicians recommended upfront surgery, and for cT2N0 (<3 cm) patients, 71% recommended NST. These findings were similar to the retrospective review.

Conclusion

- Majority of cT1-2 (≤3 cm) N0 HER2-positive breast cancer patients received upfront surgery.
- Rates of NST increased over time.
- Low rates of pathologic upgrade were observed after upfront surgery.
- Older age and HR-positive status were predictors of residual disease (breast) and ypN1-3 disease after NST.
- No difference in surgical management or oncologic outcomes was observed between the two groups.
- Future studies may consider focusing on cT1c patients to assist in guiding oncologists in the management of this population.

References

1) Zeridman et al. Trends in neoadjuvant chemotherapy versus surgery-first in stage I HER2-positive breast cancer patients in the National Cancer Database (NCDB). Breast Cancer Research and Treatment. 2021; 187:177-85
2) Von Minckwitz et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med. 2019;380(7):617-28
3) Tolaney et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med. 2015;372(2):134-141.