Neoadjuvant Chemo-Immunotherapy Yields Survival Comparable to Upfront Surgery in Triple Negative Metaplastic Breast Cancer: A National Cancer Database Analysis

1. Margo Nelis, MD 2. Lily Zhang, MS 3. Vijayakrishna Gadi, MD, PhD 4. Anna Chichura, MD

1. Cleveland Clinic, Cleveland, OH, USA. 2., University of Illinois at Chicago, Chicago, IL, USA. 3. University of Illinois Cancer Center, Chicago, IL, USA. 4. Duly Health and Care, Schamburg, IL, USA

Introduction

Metaplastic breast cancer (MpBC) is a rare and aggressive subtype of breast cancer that frequently exhibits triple-negative receptor status and carries a worse prognosis than other morphologic subtypes of triple-negative breast cancer (TNBC).[1] The standard of care for locally advanced TNBC is neoadjuvant chemotherapy (NAC).[2] Upfront surgery for MpBC has been associated with superior outcomes, particularly when compared to NAC.[3] The addition of immunotherapy to standard chemotherapy has been shown to enhance treatment efficacy in other subtypes of TNBC, but the applicability of these findings to MpBC has yet to be determined.[4]

Purpose

To evaluate overall survival (OS) in patients with TN-MpBC treated with neoadjuvant chemotherapy (NAC) or neoadjuvant chemo-immunotherapy (NACIO) compared to upfront surgery using the National Cancer Database (NCDB).

Methods

- A retrospective cohort analysis was conducted using the NCDB to identify patients diagnosed with stage I-III TN-MpBC between 2010 and 2022 treated with NAC, NACIO, or upfront surgery.
- Primary endpoints included overall survival (OS), pathologic complete response (pCR), and breast conservation rates.
- Continuous variables were analyzed using the Wilcoxon rank-sum test, and categorical variables were assessed with the Chi-square or Fisher's exact test. Survival outcomes were estimated using the Kaplan–Meier method.

Results

Table 1: Patient Demographics

Variable	Surgery-first (n=3,429)	NAC (n=1,232)	NACIO (n=292)	p-value
Age, median (IQR)	61 (53–69)	58 (49–67)	60 (49–67)	<0.001
Race				0.002
– White	2,441 (71%)	837 (68%)	186 (64%)	
– Black	646 (19%)	242 (20%)	62 (21%)	
– Hispanic	191 (5.6%)	101 (8.2%)	24 (8.2%)	
Insurance status				<0.001
– Private / Managed care	1,678 (50%)	645 (53%)	164 (57%)	
– Medicare	1,340 (40%)	384 (31%)	90 (31%)	
– Medicaid	268 (7.9%)	139 (11%)	25 (8.7%)	
– Uninsured	52 (1.5%)	32 (2.6%)	3 (1.0%)	
Median income quartile				0.019
– 1st quartile	491 (17%)	212 (21%)	33 (14%)	
– 2nd quartile	622 (21%)	193 (19%)	48 (20%)	
– 3rd quartile	716 (25%)	237 (23%)	52 (22%)	
– 4th quartile	1,075 (37%)	374 (37%)	105 (44%)	
Facility type				<0.001
– Academic / Research	1,143 (33%)	387 (31%)	106 (36%)	
– Comprehensive community	1,224 (36%)	345 (28%)	92 (32%)	
– Integrated network	682 (20%)	310 (25%)	58 (20%)	
Grade *				0.3
– Grade I	56 (1.8%)	15 (1.4%)	2 (0.8%)	
– Grade II	401 (13%)	124 (11%)	25 (9.5%)	
– Grade III	2,649 (84%)	945 (86%)	236 (89%)	
– Grade IV	39 (1.2%)	14 (1.3%)	1 (0.4%)	
NCDB Analytic Stage				<0.001
– Stage I	1,108 (32%)	268 (22%)	30 (10%)	
– Stage II	1,810 (53%)	643 (52%)	145 (50%)	
– Stage III	511 (15%)	321 (26%)	117 (40%)	
AJCC Clinical Stage				<0.001
– Stage I	1,196 (39%)	130 (11%)	27 (9.3%)	
– Stage II	1,553 (50%)	722 (60%)	147 (51%)	
– Stage III	330 (11%)	354 (29%)	117 (40%)	
AJCC Pathologic Stage				<0.001
– Stage I	1,058 (33%)	186 (29%)	6 (27%)	
– Stage II	1,717 (54%)	321 (50%)	11 (50%)	
– Stage III	390 (12%)	140 (22%)	5 (23%)	
Charlson–Deyo Score ≥1 **	673 (20%)	214 (17%)	54 (18%)	0.5

* Grade IV refers to undifferentiated tumors

**Charlson-Deyo score, primary site, laterality, and location were not found to be statistically significant

Figure 1: Outcomes Based on Treatment Sequence

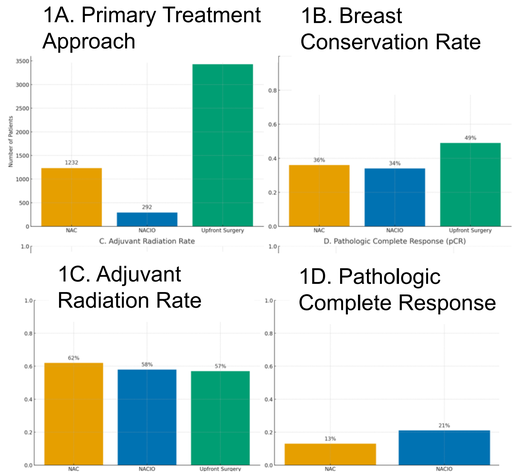


Figure 2: Treatment Type by Year

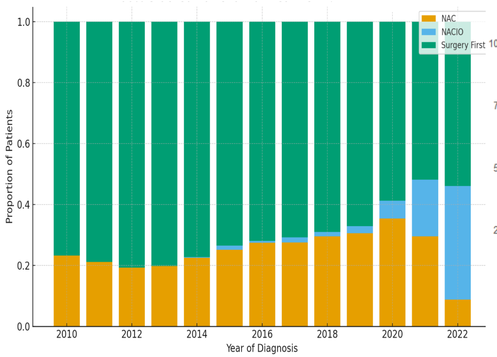


Figure 3: Kaplan-Meier Curve of OS by Group

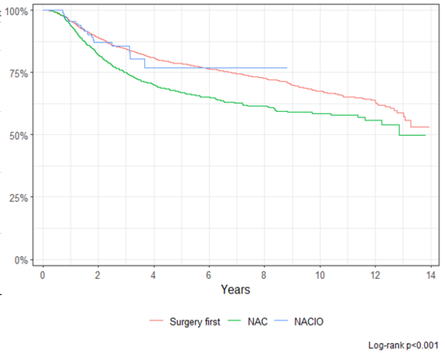
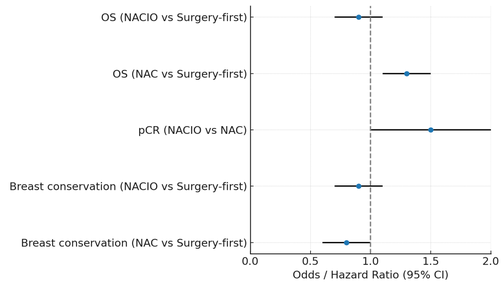


Figure 4: Multivariable Regression Estimates for Surgical and Oncologic Outcomes



Conclusions

- No significant difference in OS was observed between NACIO and surgery-first approaches (HR = 0.80, 95% CI: 0.51-1.27; $p = 0.3$)
- NAC was associated with a 37% increased risk of mortality compared to upfront surgery (HR = 1.37, 95% CI: 1.21-1.56; $p < 0.001$).
- NACIO was associated with a 62% higher likelihood of achieving pCR compared to NAC (OR = 1.62, 95% CI: 1.11-2.38; $p = 0.013$).
- The rate of breast conservation was not significantly different between NACIO and upfront surgery (OR = 0.8, 95% CI: 0.61-1.05; $p = 0.11$), but patients receiving NAC were 27% less likely to undergo breast-conserving surgery compared to those undergoing surgery first (OR - 0.73, 95% CI: 0.63-0.84; $p < 0.001$).
- These findings align with emerging data from KEYNOTE-522 and other TNBC trials showing enhanced response with immunotherapy

Contact
Margo Nelis, MD
Cleveland Clinic Foundation
Email: nelism2@ccf.org
Phone: 216-870-0511

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