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Breast Cancer Outcomes of Neoadjuvant vs Adjuvant Chemotherapy by Receptor Subtype: a Scoping Review

Trista J Stankowski-Drengler, MD, MS¹, Devon Livingston-Rosanoff, MD, PhD¹, Jessica Schumacher, PhD¹, Bret Hanlon, PhD^{1,2}, Mary Hitchcock, MS, MA³, Heather B Neuman, MD, MS^{1,4}

¹Wisconsin Surgical Outcomes Research Program, Department of Surgery, University of Wisconsin, Madison, WI

²Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison, WI

³Ebling Library for the Health Sciences, University of Wisconsin, Madison, WI

⁴Carbone Cancer Center, University of Wisconsin, Madison, WI

Abstract

Introduction: Trials demonstrate equivalent survival for breast cancers treated with neoadjuvant (NAC) or adjuvant chemotherapy (AC). However, these were conducted prior to the recognition of the importance of receptor subtype for survival and chemotherapy response. Therefore, chemotherapy timing may impact survival for certain receptor subtypes. A scoping review of studies assessing outcomes by chemotherapy timing based on receptor subtype was conducted to evaluate gaps in existing literature.

Methods: Three databases were searched in February 2019 with terms related to breast cancer, NAC/AC, and survival. Inclusion criteria were original, peer-reviewed studies published in English after 1989 comparing breast cancer outcomes for females based on chemotherapy timing. Studies/sections of studies lacking outcomes by receptor subtype or including patients missing appropriate targeted therapy were excluded.

Results: Of 7,354 articles, 262 abstracts and 60 full-texts were reviewed. Three studies met criteria. All were single-institution retrospective studies analyzing outcomes for triple negative (TN) patients with one study also examining luminal A patients. Significant differences in clinical characteristics existed between patients selected for NAC vs AC. Two studies demonstrated no

Corresponding Author: Trista Stankowski-Drengler, MD, MS, 600 Highland Avenue, K6/117F, Madison, WI 53792-7375, Phone number: (608) 262-7847, tstankowski-drengler@uwhealth.org.

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survival difference by chemotherapy timing for TN patients, with the third showing improved likelihood of survival after AC for TN patients. No difference was seen for patients with luminal A cancer.

Conclusions: Our scoping review reveals a significant gap in the existing literature regarding optimal timing of chemotherapy for modern-era patients receiving targeted therapy based on receptor subtype. Review of the identified studies identified methodological challenges to answering this question through observational study designs.

Introduction:

Many randomized controlled trials (RCT) have examined the potential benefits associated with neoadjuvant chemotherapy (NAC) versus adjuvant chemotherapy (AC) for women with locally advanced breast cancer, with the rationale that early introduction of systemic therapy in the neoadjuvant setting would translate into improved survival.¹⁻³ Although these RCTs demonstrated equivalent survival regardless of timing of chemotherapy¹⁻³, additional studies have found other advantages associated with NAC. NAC increases the likelihood of patients being candidates for breast conserving surgery³⁻⁵ and may allow select women with a good response to NAC to avoid an axillary dissection and its associated morbidities.⁶⁻⁹ NAC provides key insight into a cancer's biology based on its responsiveness. Importantly, response to therapy is highly prognostic; women with pathologic complete responses (pCR) have significantly higher overall survival and disease-free survival rates compared with women with residual disease.¹⁰⁻²¹ Women who have residual disease after NAC can then be selected for additional systemic therapy following surgery.^{22,23} This is especially pertinent with recent studies such as the KATHERINE and CREATE-X trials finding improved survival with the addition of adjuvant trastuzumab emtansine or capecitabine respectively for women with either residual Her2neu+ (KATHERINE) or Her2neu- (CREATE-X) disease.^{22,23}

Although existing RCTs have demonstrated equivalent survival between NAC and AC, it is hypothesized that receptor subtypes with a higher likelihood of responding to NAC such as triple negative (estrogen and progesterone receptor negative, Her2neu negative) or Her2neu positive cancers,^{10-14,24-26} may potentially derive a survival benefit from earlier administration of systemic therapy. However, the existing RCTs designed to answer clinical questions regarding timing of chemotherapy are unable to address this question as receptor subtypes, especially Her2neu, were not recognized to be clinically significant at the time the trials were conducted and were not routinely evaluated. Further, targeted therapy for specific receptors was not routinely administered in these trials. Finally, the vast majority of breast cancers are estrogen receptor (ER)+ or progesterone receptor (PR)+/Her2neu-.²⁷ Thus this receptor subtype, which is the least likely to respond to NAC, is likely to be overrepresented in the study samples of trials designed to assess the timing of chemotherapy. For these reasons, it is not possible to know whether there may be potential benefits for NAC versus AC for women with triple negative and Her2neu+ disease. Overall, the lack of available data on receptor subtypes combined with the limited use of targeted therapy in existing studies represents a significant gap in our current understanding of the optimal timing of chemotherapy for women with non-metastatic breast cancer.

To address this gap, we performed a scoping review of the current literature to systematically identify relevant studies that were designed to assess differences in recurrence and mortality by chemotherapy timing based on receptor subtype and evaluate gaps in the existing literature. The following research question was developed: Does NAC have a recurrence and/or survival advantage over AC for certain breast cancer receptor subtypes?

Methods:

This scoping review was conducted according to the Arksey and O'Malley framework²⁸ and conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Review (PRISMA-ScR) standards.²⁹

Database Search

Relevant search terms were identified by the lead author (T.S-D.) and an experienced librarian (M.H.) relating to breast cancer, neoadjuvant chemotherapy, adjuvant chemotherapy, and survival or recurrence. The search also included the terms “preoperative” and “postoperative” to ensure broad capture of relevant studies (Table 1). The following databases were searched on February 21, 2019: PubMed (MEDLINE), Scopus, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Additional studies were found through review of references included in articles returned upon initial search.

Inclusion criteria were original, peer-reviewed studies published in English in 1990 or later that compared breast cancer recurrence and survival outcomes (disease-free survival, overall survival, and distant recurrence), for female patients based on chemotherapy timing. We excluded studies or sections of studies that did not report outcomes by receptor subtype or included patients not treated with the currently recognized appropriate targeted therapy (Her2neu-targeted therapy and endocrine therapy). We also excluded studies that only analyzed recurrence and/or survival outcomes for the NAC cohort based on pathologic response to systemic therapy.

Article Selection

Titles were reviewed (T.S-D.) to identify articles to explore further. Abstracts from these selected articles were then reviewed by two investigators (T.S-D. and D.L-R.) to determine whether they should be included for full review. Any instances of discordance between reviewers resulted in the study being pulled for full article review. Relevant full text articles of abstracts were obtained and read in their entirety (T.S-D.).

Data Extraction

The following elements were abstracted from each full text article: study design, sample size (overall and by treatment arm), years of breast cancer diagnosis included in the study, cancer stage, Her2neu and hormone (ER/PR) receptor status (yes/no, with those that were ‘no’ being excluded), NAC regimen, AC regimen, duration of chemotherapy, disease-free survival, overall survival, distant disease free survival, and distant recurrence. Investigators also documented the rationale for limiting the analysis to certain receptor subtypes only for those studies not including all receptor subtypes.

Scoping Analysis

Study characteristics and recurrence and survival outcomes were summarized for each study and patterns and relationships across included studies were examined. Qualitative content analysis of included articles involved identifying themes for selection of certain receptor subtypes for outcome analyses as well as limitations of all included studies. The lead author (T.S-D.) developed the thematic categories which were verified by a second author (H.B.N).

Results:

A flow diagram for article inclusion is depicted in Figure 1. After removing duplicates, a total of 7,341 articles were initially identified through database review with an additional 13 articles identified through review of the references included in relevant articles. After review of the titles, 262 articles were selected for full abstract review and 60 articles underwent full text review. Overall, three articles met inclusion criteria for analysis after full text review.

A summary of the three articles meeting inclusion criteria for this scoping review are presented in Table 2. All three studies reported outcomes using single institution retrospective study designs. The three studies described outcomes for patients diagnosed with stage I-III breast cancer between 1997 and 2016. All studies analyzed patients with triple negative breast cancer, with one study (Yang, et al.) also reporting outcomes for patients with luminal A cancer (ER+/PR+/Her2neu-/Ki67- as determined by immunohistochemistry). Although the Yang, et al. article also described outcomes for Luminal B (ER+/PR+/Her2neu+ or Ki67+) and Her2neu+ (ER-/PR-/Her2neu+) cohorts, these cohorts were excluded from our analysis as these women did not receive Her2neu targeted therapy. Both studies that limited their cohort to patients with triple negative cancer (Kennedy, et al. and Clifton, et al.) cited the poorer overall prognosis in women with triple negative cancers combined with the fact that targeted therapy options do not exist for these patients. As such, the authors highlighted the importance of optimizing chemotherapy treatment for women with triple negative cancers, specifically focusing on determining the appropriate timing of systemic treatment for this receptor subtype.

Given the observational nature of the studies and the fact that treatment assignment was not randomly determined, there were significant differences in sociodemographic and tumor characteristics between women who received NAC and those who received AC (Table 3). Notable examples include the following: women receiving NAC had larger tumor sizes (Clifton, et al., Kennedy, et al. and Yang, et al.) with more positive lymph nodes (Clifton, et al., Kennedy, et al. and Yang, et al.), were younger (Kennedy, et al.) and were more likely to receive a taxane containing regimen (Clifton, et al.). Importantly these factors are also critical determinants of recurrence and survival. All studies attempted to control for the inherent differences in the cohorts of women who underwent NAC versus AC through statistical modeling. Broadly speaking, these approaches included covariate adjustment in multivariable models (Yang, et al. and Kennedy, et al.) or nearest neighbor matching to achieve balance between the chemotherapy timing comparison groups (Clifton, et al.).

All three studies analyzed overall survival (OS) by chemotherapy timing utilizing Kaplan-Meier and Cox proportional hazard modeling; one study (Clifton, et al.) also analyzed disease-free survival (DFS) defining recurrence as either local or distant. Two studies demonstrated no statistically significant survival difference based on chemotherapy timing for luminal A and/or triple negative cohorts (Yang, et al. and Clifton, et al.) with the third study showing improved likelihood of survival after AC for the triple negative cohort (Kennedy, et al.) (Table 2).

Significant limitations common to all three studies included in the scoping review were: 1) Non-random assignment of treatment and differences in sociodemographic and clinical characteristics of the cohorts of patients undergoing NAC versus AC that leave open the possibility of residual confounding to have influenced study findings; and 2) Relatively small sample size, compromising the statistical power of the study and the ability to detect clinically meaningful differences in survival between NAC and AC groups. The one study that used a matching approach to achieve balance between the comparison groups on measured factors (Clifton et al.) had to drop a number of patients from each cohort (NAC n=132 to n=85 and AC n=187 to n=85), possibly reducing both power and potentially reducing the generalizability of findings given the number of patients that had to be dropped from the analysis to achieve balance.

Discussion:

In this scoping review, we identified three studies that evaluated the impact of the timing of chemotherapy on survival and recurrence in breast cancer patients based on receptor subtype. All studies focused on triple negative cohorts due to the significantly worse prognosis in this cohort relative to other receptor subtypes and the lack of targeted systemic treatment options. Results were mixed, with two studies demonstrating no difference in DFS and/or OS based on chemotherapy timing, while the third found an improved likelihood of OS for those with triple negative cancers who received AC. No study found a statistically significant improvement in survival for patients receiving NAC. The only study examining survival for those with luminal A cancers found no difference in survival based on chemotherapy timing. Unfortunately, all of these studies had significant limitations inherent to the non-random assignment of treatment, which prevented drawing definitive conclusions regarding the optimal timing of chemotherapy treatment based on receptor subtype.

Although previous randomized control trials demonstrated equivalent survival with NAC and AC, these studies were conducted in a time period that preceded much of our current understanding about the importance of receptor subtype on breast cancer treatment and prognosis.¹⁻³ There is a strong theoretical rationale for a potential difference in recurrence and survival for NAC for certain receptor subtypes, especially triple negative tumors. Triple negative cancers have a relatively high rate of pCR (38%)³³ and the worst prognosis compared to other receptor subtypes.²⁰ Further, patients with triple negative breast cancers rely on chemotherapy to reduce their risk of recurrence and improve survival, with no other targeted systemic therapy options. In current clinical practice, known advantages of NAC influence clinical decision making, including higher rates of breast conservation, de-escalation of axillary surgery, and assessing tumor response to treatment.^{4,5,7-21}

Additionally, for women with residual cancer following NAC, newer studies such as the KATHERINE (Her2neu+ patients) and CREATE-X (triple negative patients) trials have demonstrated a survival benefit for women when given adjuvant trastuzumab emtansine or capecitabine respectively. This realization may direct clinicians towards NAC for most Her2neu+ and triple negative patients. However, this potential benefit also needs to be weighed against the toxicities associated with additional systemic therapy, especially for those with smaller tumors. As such, understanding whether a survival benefit exists based on chemotherapy timing for specific cohorts of breast cancer patients could help further optimize personalized cancer care.

Our scoping review was conducted to identify any existing research that addresses this important question. We did not identify any RCTs which specifically evaluated the benefits of NAC versus AC for different receptor subtypes. The three studies we did identify were all observational, retrospective analyses, where clinicians made the determination of whether patients received NAC or AC based on clinical characteristics using their own judgement as opposed to treatment being randomly assigned. As such, we found significant differences in cancer characteristics such as tumor size and lymph node status based on chemotherapy timing. As these factors are strongly associated with prognosis, it is critical that these clinical factors are adequately controlled for in the outcome analyses. Unsurprisingly all studies found critical sociodemographic and clinical factor differences between the comparison groups that are also associated with survival. While all studies attempted to control for these differences through a number of statistical techniques, there is always the potential for residual confounding to have influenced study findings and only one of the studies utilized a rigorous matching approach. However, in the study using nearest neighbor matching authors reported likely being underpowered to detect a clinically significant difference based on chemotherapy timing.

While a prospective study examining breast cancer outcomes by chemotherapy timing for patients with known receptor subtypes receiving appropriate targeted therapy would provide conclusive answers to the question of optimal chemotherapy timing, the cost, resources, and volume of patients needed for an RCT is prohibitive. However, a review of clinicaltrials.gov was able to locate a randomized control trial currently recruiting in China (NCT03011060) which aims to assess timing of chemotherapy for women with breast cancer. This study is administering chemotherapy in either the neoadjuvant or adjuvant setting to women with stage I-IIIa breast cancer with those who do not achieve a pCR with neoadjuvant chemotherapy planned to undergo a course of adjuvant capecitabine. Primary outcomes include OS and DFS with an expected study completion of February 2025. While these results are highly anticipated, the racial/ethnic difference of this patient population will need to be taken into account. Alternatively, retrospective studies using a large, multicenter database may be able to help answer this important question if rigorous matching approaches are used.

A few limitations to this scoping review should be discussed. First, search terms to capture studies utilizing neoadjuvant chemotherapy included “neoadjuvant chemotherapy” and “preoperative chemotherapy.” In the process of reviewing pertinent studies, it was discovered that additional terms included “induction chemotherapy” and “primary

chemotherapy;” however, many of the studies utilizing these terms were found to be published prior to the use of Her2neu-targeted therapies, excluding their pertinence to our review. As such, our search terms were not updated to include these variations. Second, due to time and available resources, we limited our search to only those articles published in English. As such, we may have excluded pertinent, non-English articles. Additionally, our search was focused on outcomes associated with the timing of chemotherapy and does not capture studies assessing outcomes by timing of other systemic therapies such as endocrine or Her2neu-targeted therapies. Lastly, it is important to note that the articles included in our analysis treated women prior to the recognition of survival benefit found in the CREATE-X and Katherine trials. These newer trials has since changed the way many providers think about the timing of chemotherapy.

Conclusion:

This scoping review on the impact of chemotherapy timing on survival and recurrence in breast cancer patients based on receptor subtypes found limited literature addressing this question in modern cohorts. The identified retrospective studies had variable results and inherent weakness to their analysis, limiting the ability to draw definitive conclusions regarding the relative benefits of AC versus NAC. Importantly, the studies all reported significant differences in the clinical characteristics of patients undergoing NAC versus AC, making it challenging to isolate the effects of chemotherapy timing from other patient or tumor characteristics. These findings highlight a significant gap in the current literature regarding optimal timing of chemotherapy for modern-era patients receiving targeted therapy based on receptor subtype and identifies challenges inherent to answering this question through observational study designs.

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Figure 1:

Flow diagram of inclusion/exclusion for search of articles published after 1989 comparing breast outcomes by chemotherapy timing

Table 1:

Database Search Terms for Literature Review

<i>PubMed (MEDLINE) search terms and filters applied</i>	<p>(((((breast[tiab] OR mamma*[tiab])) AND (cancer[tiab] OR neoplasm[tiab] OR tumor[tiab] OR malignan*[tiab] OR carcinoma[tiab])) AND (“neoadjuvant chemotherapy”[tiab] OR “preoperative chemotherapy”[tiab] OR “adjuvant chemotherapy”[tiab] OR “postoperative chemotherapy”[tiab])) AND (surviv*[tiab] OR recurren*[tiab]) AND (woman OR women OR female)))</p> <p>Filters: female sex, time frame (01/01/1990-02/21/2019), English language, human species</p>
<i>CINAHL search terms and limiters applied</i>	<p>((“neoadjuvant chemotherapy” OR “preoperative chemotherapy” OR “adjuvant chemotherapy” OR “postoperative chemotherapy”) AND (breast) AND (cancer OR neoplasm OR carcinoma OR malignan*) AND (recurren* OR surviv*) AND (women OR woman OR female)) NOT (veterinary OR mouse OR mice OR rat OR murine OR cat OR dog OR horse OR pig OR porcine OR equine OR feline OR canine OR animal)</p> <p>Limiters: published date (01/01/1990-02/21/2019), English language, human</p>
<i>Scopus search terms</i>	<p>TITLE –ABS-KEY (“neoadjuvant chemotherapy” OR “preoperative chemotherapy” OR “adjuvant chemotherapy” OR “postoperative chemotherapy”) AND TITLE-ABS-KEY ((breast OR mamm*) W/2 (cancer OR neoplasm OR carcinoma OR malignan*)) AND TITLE-ABS-KEY (women OR woman OR female) AND TITLE-ABS-KEY (recurren* OR surviv*) AND DOCTYPE (ar) AND PUBYEAR >1989 AND (LIMIT-TO (LANGUAGE, “English”))</p>

Table 2:

Outcomes based on timing of chemotherapy in articles included for analysis

Author, year	Study Methodology	Country of Origin	Receptor Subtype(s)	Diagnosis Dates	N	Stage	Statistical Modeling Used to Account for Differences in NAC and AC Cohorts	Outcomes
Kennedy, 2010 ³¹	Retrospective	USA	Triple Negative	2000-2008	493	I-III	Multivariable Cox Regression Model	OS: aHR 0.480 (95% CI 0.298-0.774) in favor of AC
Clifton, 2018 ³²	Retrospective	USA	Triple Negative	1997-2016	319	I-II	Nearest Neighbor Matching	OS: HR 1.25 (95% CI 0.336-4.655, p=0.739) DFS: HR 1.25 (95% CI 0.493-3.167, p=0.637)
Yang, 2018 ³⁰	Retrospective	China	Triple Negative, Luminal A	2000-2008	Total: 406 Triple Negative=67 Luminal A=169	II-III	Multivariable Cox Regression Model	Triple Negative OS: HR 1.00 (95% CI 0.27-3.73, p>0.99) Luminal A OS: HR 1.14 (95% CI 0.53-2.43, p=0.74)

NAC=neoadjuvant chemotherapy DFS=disease-free survival HR=hazard ratio AC=adjuvant chemotherapy aHR=adjusted hazard ratio CI=confidence interval OS=overall survival

Table 3:

Sociodemographic and tumor characteristics with significant differences based on chemotherapy timing

Author, year	Characteristics	NAC cohort	AC cohort	P-value
Kennedy, 2010 ³¹	Age	N=154	N=251	<0.0001
	<50	62% (96)	42% (105)	
	50	38% (58)	58% (146)	
	T Stage			<0.0001
	T1	2% (3)	35% (89)	
	T2	52% (80)	40% (101)	
	T3	28% (43)	8% (19)	
	T4	13% (20)	2% (5)	
	Unknown	5% (8)	15% (37)	
	N Status			<0.0001
	N0	19% (30)	50% (126)	
	N1	59% (91)	42% (105)	
	N2	13% (19)	4% (9)	
	N3	8% (12)	1% (2)	
	Unknown	1% (2)	3% (9)	
Clifton, 2018 ³² <i>Unmatched cohort</i> [*]	Age	N=132	N=187	0.95
	<50	77% (102)	77% (144)	
	>50	23% (30)	23% (43)	
	T Stage			<0.0001
	T1	18% (24)	62% (116)	
	T2	82% (108)	38% (71)	
	N Status			0.03
	N0	59% (78)	71% (132)	
	N1	41% (54)	29% (55)	
Clifton, 2018 ³² <i>Matched cohort</i> ^π	Age	N=85	N=85	0.86
	<50	76% (65)	75% (64)	
	>50	24% (20)	25% (21)	
	T Stage			0.69
	T1	28% (24)	34% (29)	
	T2	72% (61)	66% (56)	
	N Status			0.15
	N0	58% (49)	68% (58)	
	N1	42% (36)	32% (27)	
Yang, 2018 ^{7,30}		N=201	N=205	

Author, year	Characteristics	NAC cohort	AC cohort	P-value
	Age			0.23
	50	47% (96)	53% (116)	
	>50	53% (105)	47% (89)	
	T Stage			<0.0001
	<2	9% (19)	12% (25)	
	2-5	59% (118)	85% (174)	
	>5	32% (64)	3% (6)	
	N Status			0.003
	Negative	54% (109)	69% (141)	
	Positive	46% (92)	31% (64)	
	Receptor Subtype			0.001
	Luminal A	50% (100)	34% (69)	
	Luminal B	25% (50)	44% (90)	
	Her2neu+	7% (15)	7% (15)	
	Triple Negative	18% (36)	15% (31)	

* Data represents cohort prior to nearest neighbor matching based on chemotherapy timing; demographic information collapsed to combine BRCA +/- cohorts based on chemotherapy timing with recalculation of p-values

π Data represents matched cohort using nearest neighbor matching based on chemotherapy timing; important to note 40% of patients were BRCA+

$\dagger$ Data for entire cohort including luminal B and Her2neu+ which were excluded from our review