

Neoadjuvant Chemotherapy for Breast Cancer: Who Should Get It?

Nattapong Wisedsook, M.D., Wongsakorn Chaochankit, M.D.

Department of Surgery, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.

ABSTRACT

Neoadjuvant chemotherapy plays a critical role for patients eligible for preoperative therapy; especially for those with HER2-positive or triple-negative breast cancer. Advances in systemic therapy have led to increased rates of pathological complete response (pCR), a key indicator of long-term outcomes and a guide for subsequent adjuvant treatments. pCR also serves as a surrogate marker for the approval of new drugs in breast cancer. Neoadjuvant chemotherapy enhances the feasibility of breast-conserving surgery and sentinel lymph node biopsy for patients showing a clinical response. Effective management requires collaboration with a multidisciplinary team—including medical oncologists, surgical oncologists and radiation oncologists—prior to starting treatment. This is to consider therapy sequencing, its results in various treatment options, and appropriate management of breast and axillary nodes for potential de-escalation. Future advancements in personalized therapy involve identifying patients with exceptional responses to neoadjuvant chemotherapy whom may be able to avoid surgery entirely, and developing strategies to tailor neoadjuvant regimens using predictive biomarkers.

Keywords: biomarkers; breast cancer; HER2-positive; Neoadjuvant chemotherapy; pathological complete response; personalized therapy; triple-negative

INTRODUCTION

Breast cancer is the most common cancer as well as the leading cause of cancer death in women¹. The 5-year survival rates are 76–90% for localized and 47–75% for regional cancer².

The precancerous lesion is known as ductal carcinoma in situ (DCIS). Breast cancer staging ranges from stage I to IV³. Most staging systems have been used by the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control classification

Corresponding author: Wongsakorn Chaochankit, M.D.
Department of Surgery, Faculty of Medicine, Prince of Songkla University,
Hat Yai, Songkhla 90110, Thailand.
E-mail: wongsakorn.c@psu.ac.th
doi: 10.31584/psumj.2025273526
<https://he01.tci-thaijo.org/index.php/PSUMJ/>

PSU Med J 2025;5(3):179–185
Received 1 September 2024
Revised 1 July 2025
Accepted 2 July 2025
Published online 4 December 2025

stage system for Tumor, Nodes, and Metastases (TNM) for treatment planning: as shown in Figure 1³.

Molecular subtypes and biomarkers

Advances in breast cancer biology, alongside the growing validation of biomarkers that assess prognosis and predict treatment response or resistance, highlight the importance of documenting multiple biomarkers at the time of initial diagnosis, whenever feasible³. Molecular classification, based on hormone receptor and HER2 status, has become integral in determining treatment strategies. Table 1 outlines these surrogate molecular subtypes and their biomarker profiles³.

Table 1 summarizes the surrogate molecular subtypes of breast cancer, based on the St. Gallen 2013 consensus, which plays a pivotal role in selecting neoadjuvant and adjuvant systemic therapies.

ER: Estrogen receptor; PgR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; PI: Proliferation index; +: Positive; -: Negative; *: One of these criteria must be met to define luminal B-like breast cancer⁴

Early breast cancer patients will start treatment via surgery, followed by adjuvant therapies that depend on surrogate subtypes. In contrast locally advanced breast cancer patients receive neoadjuvant treatment to control micrometastasis, followed by surgery, while advanced

T	N	M	Stage	
Tis	0	0	0	
1	0	0	IA	
0	1mi	0	IB	
1	1mi	0	IB	
0	1	0	IIA	
1	1	0	IIA	
2	0	0	IIA	
2	1	0	IIB	
3	0	0	IIB	
0	2	0	IIIA	
1	2	0	IIIA	
2	2	0	IIIA	
3	1	0	IIIA	
3	2	0	IIIA	
4	0	0	IIIB	
4	1	0	IIIB	
4	2	0	IIIB	
Any T	N3	M0	IIIC	
Any T	Any N	1	IV	

}

Carcinoma in situ

}

Early

}

Locally advanced

}

Advanced

Figure 1 Illustrates the anatomical staging system according to the 8th edition of the American Joint Committee on Cancer (AJCC), which remains a key framework in guiding breast cancer treatment decisions

Table 1 Definitions of molecular subtypes and surrogate subtypes in breast cancer

Molecular subtype	Surrogate subtype	ER	PgR	HER2	PI (Ki-67)
Luminal A	Luminal A-like	+	≥20%	-	<20%
Luminal B	Luminal B-like (HER2-negative)	+	<20%*	-	≥20%*
	Luminal B-like (HER2-positive)	+	Any	+	Any
HER2-overexpression	HER2-positive	-	-	+	Any
Basal-like	Triple negative	-	-	-	Any

*=One of these criteria must be met to define luminal B-like breast cancer; ER=estrogen receptor; PgR=progesterone receptor; HER2=human epidermal growth factor receptor 2; PI=proliferation index; +=positive; -=negative

breast cancer patients aim for palliative care. In recent years, the term 'neoadjuvant systemic treatment (NST)' has emerged to encompass a broader range of preoperative therapies; including chemotherapy, endocrine therapy and targeted agents; such as trastuzumab or immune checkpoint inhibitors. However, for this review, we use the term 'neoadjuvant chemotherapy (NAC)' to specifically refer to cytotoxic chemotherapy, which remains the most established and widely studied approach in this context.

Neoadjuvant chemotherapy has become increasingly important, providing valuable information on tumor biology and response to therapies⁵. As a result, AJCC has clarified the staging of post-neoadjuvant therapy⁵. Staging after neoadjuvant treatment is denoted with a "yc" or "yp" prefix to the T and N classification⁵.

Historically, Neoadjuvant therapy (NAC) has been initially used for locally advanced or unresectable breast cancer patients⁶, with the main goal of reducing tumor size to enable breast-conserving surgery or, in some cases, to avoid axillary dissection in patients that prefer less extensive procedures⁶. At that time, the main indication for NAC was to convert inoperable tumors into operable ones. However, with increasing evidence of its benefits, NAC has been gradually adopted for operable breast cancer cases as well; particularly in triple-negative and HER2-positive subtypes. This is due to its role in improving breast conservation rates and assessing tumor chemosensitivity via pathologic complete response (pCR). Nowadays, NAC has been broadened to patients with early-stage breast cancer⁶. Hence, NAC allows for promotion in oncologic and cosmetic outcomes and decreases postoperative complications⁶.

Concept and rationale of neoadjuvant chemotherapy

The concept of NAC originated from the treatment results of adjuvant chemotherapy (AC), which can reduce recurrence and mortality. The golden era of AC began in the early 1970s⁷. In AC, the initiating time is shifted from treating macrometastases to treating micrometastases. Adjuvant chemotherapy is effective in eliminating micrometastases

that may be present before or at the time of surgery, resulting in a corresponding survival benefit. This raises the question of whether minor adjustments in the timing of starting adjuvant treatment could further impact treatment outcomes and survival⁷⁻⁹. Neoadjuvant chemotherapy was introduced in 1973 as part of a multidisciplinary approach. This condition has been defined in various ways, but generally refers to patients with large tumors (involvement of the overlying breast skin or attachment to the underlying chest wall)¹⁰. It includes the matted or fixed axillary lymph nodes or supraclavicular lymphadenopathy¹⁰. Patients in this stage showed poor long-term prognosis after locoregional therapy alone⁸. Not only do distant metastases frequently occur, but also the primary tumor is often difficult to control⁸.

The following is the rationale for neoadjuvant chemotherapy.

1. Kinetic changes: Occult micrometastases will be stimulated to increase through the process of angiogenesis once the tumor is removed¹¹⁻¹².

2. Resistance to chemotherapy: Tumors exhibit varying levels of resistance in cancer cells. A brief delay in starting chemotherapy can negatively impact outcomes by promoting resistance¹¹⁻¹².

3. Opportunity to deliver cytotoxic agent to the tumor with intact native vasculature: Given that blood flow is considerably greater in tumor tissue compared to normal breast tissue, the tumor's vascular system could potentially be utilized to enhance the delivery of cytotoxic agents, targeting both the tumor itself and any micrometastases prior to surgical removal¹¹⁻¹².

The initial use of neoadjuvant chemotherapy was confined to patients with unresectable breast cancer, typically those at very high risk of metastasis and mortality, even following an initial surgical resection¹³. These neoadjuvant chemotherapy regimens achieved high rates of objective response, reducing the size of the tumor and lymph node metastases by at least 50%¹⁴.

The role of NAC in resectable breast cancer increased the rate of breast-conserving therapy and

was used for patients with unresectable breast cancer¹⁵. Investigators have also since used NAC as an in vivo test for chemosensitivity by assessing pathologic complete response¹⁵. The pCR refers to the absence of invasive/in situ cancer in the breast and/or axillary lymph nodes that could affect the overall survival¹⁵.

Key clinical trials of NAC

The clinical trial involving preoperative chemotherapy was shown in 1981 by a team at the Milan Cancer Institute¹⁶. The results showed no significant difference in clinical outcomes or local control between the two treatment groups¹⁶. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial, conducted in 1997, was the first study to compare neoadjuvant and adjuvant chemotherapy using the same regimen in operable breast cancer¹⁷. Moreover, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 trial examined the effect of adding docetaxel (T) to preoperative chemotherapy¹⁸. The results showed that adding T to AC did not significantly improve disease-free survival (DFS) or overall survival (OS)¹⁸. In both treatment groups, patients that achieved a pCR continued to show significantly better DFS and OS outcomes compared to those that did not achieve a pCR¹⁸. The European Organization for Research and Treatment of Cancer (EORTC) trial in early breast cancer showed preoperative chemotherapy was associated with an increase in BCT rates.

However, there was no significant difference between the two groups in OS, DFS, or locoregional recurrence¹¹. Patients having received neoadjuvant chemotherapy and achieved a pCR continued to experience significantly better DFS and OS¹⁹. Additionally, neoadjuvant chemotherapy helps identify patients with chemotherapy-resistant disease, providing the opportunity to customize systemic therapy based on the disease subtype¹⁹. A meta-analysis from the National Cancer Institute studied neoadjuvant versus adjuvant systemic treatment in breast

cancer in nine randomized studies²⁰. A total of 3,946 breast cancer patients; including those with both early-stage and locally advanced breast cancer, were enrolled in a study comparing neoadjuvant therapy with adjuvant therapy²⁰. The results showed no statistically significant difference between the two treatment arms regarding death, disease, or recurrence of distant disease²⁰. Overall, neoadjuvant therapy was found to be equivalent to adjuvant therapy in terms of survival and disease progression²⁰. A 2005 meta-analysis and systematic review of randomized trials comparing neoadjuvant and adjuvant chemotherapy for early breast cancer included 14 studies, with a total of 5,500 women¹³. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) compared long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer. Patients receiving NAC had a higher rate of breast-conserving therapy compared to those receiving adjuvant chemotherapy (1,504 out of 2,320, or 65% for NAC vs 1,135 out of 2,318, or 49% for adjuvant chemotherapy)²¹. [Table 2](#) summarizes the major clinical trials evaluating the efficacy of neoadjuvant chemotherapy in breast cancer, comparing designs, interventions, and key oncologic outcomes. These studies form the evidence base for the current role of NAC in treatment guidelines.

Current clinical practice and outcome of neoadjuvant chemotherapy for early breast cancer

The clinical applications of NAC increased from 5% in 2007 to levels of about 18% in 2017²². Based on the findings from two randomized trials, patients with TNBC that do not achieve pCR after NAC had the benefit from adjuvant capecitabine, while those with HER2-positive breast cancer, who do not achieve pCR after NAC, had the benefit from adjuvant trastuzumab emtansine (T-DM1)²³⁻²⁵.

Who should receive the neoadjuvant chemotherapy?

- To convert from an inoperable case to an operable case

Table 2 Summary of key clinical trials in Neoadjuvant chemotherapy

Trial	Design	Intervention	Main outcomes
NSABP B-18	RCT, operable breast cancer	Pre-op vs post-op AC	No significant DFS/OS difference; ↑BCT rate
NSABP B-27	RCT in neoadjuvant setting	AC+docetaxel vs. AC	↑pCR with T, no OS/DFS benefit
EORTC 10902	RCT, early BC	Pre-op vs. adjuvant chemo	↑BCT rate, no difference in DFS/OS
Meta-analysis (EBCTCG)	Meta-analysis of 10 RCTs, NAC vs. AC	Various regimens	↑BCT rate in NAC (65% vs 49%), equivalent survival

RCT=randomized controlled trial; BC=breast cancer; NAC=neoadjuvant chemotherapy; AC=adjuvant chemotherapy; BCT=breast-conserving therapy; pCR=pathological complete response; DFS=disease-free survival; OS=overall survival; EBCTCG=Early Breast Cancer Trialists' Collaborative Group; EORTC=European Organization for Research and Treatment of Cancer

• Inflammatory breast cancer or unresectable locally advanced disease

- To decrease the extent of surgery

• Increasing the rate of breast-conserving surgery and sentinel lymph node biopsy

- To acquire a pathological complete response

• HER2-positive or triple-negative breast cancer patients

- Delay in surgery: requires genetic testing for decision making, or in some situations; such as COVID infection

Although current guidelines recommend considering NAC for tumors larger than 2 cm in size, there remains an ongoing debate regarding its use in operable small tumors, particularly in patients with triple-negative or HER2-positive subtypes. Some studies suggest that even small tumors in these aggressive subtypes may derive survival benefit or achieve higher pCR rates with NAC; however, definitive conclusions are yet to be drawn. Therefore, individualized decision-making through multidisciplinary discussion remains essential in such cases.

The future of neoadjuvant chemotherapy and breast cancer

The development of clinical, genetic, and biomarkers has had an impact on breast cancer²⁶. Higher rates of

tumor-infiltrating lymphocytes (TILs) were associated with higher pCR rates in non-luminal subtypes of breast cancer²⁶. Gaining insight into molecular, genetic, and clinical profiles, combined with the use of prognostic and predictive modalities, will improve decision-making, leading to more effective strategies and advancing precision medicine²⁷. Future biomarker-focused clinical trials will help in laying the groundwork for the adoption of biomarker-driven personalized medicine; especially with genomic prognostic panels²⁷.

Limitations and challenges

Despite the expanding role of NAC in personalized treatment strategies, several limitations remain. The predictive accuracy of biomarkers; such as hormone receptor status, HER2 expression and tumor-infiltrating lymphocytes, can vary significantly across patient subgroups²⁶. Additionally, the use of pCR as a surrogate endpoint for long-term outcomes remains debated, particularly in hormone receptor-positive cancers; wherein, the correlation with survival is less robust. Another important consideration is the disparity in access to advanced diagnostic tools and genomic testing platforms, which may hinder the global implementation of precision NAC strategies. Addressing these challenges is crucial for optimizing patient selection and ensuring equitable care²⁷.

CONCLUSION

Neoadjuvant chemotherapy has become a cornerstone in the management of breast cancer. The ability to achieve a pCR is a critical indicator of prolonged survival and can guide treatment decisions; including potential de-escalation of surgery and adjuvant therapies. The advancements in systemic treatment have improved pCR rates, offering new opportunities for breast conservation and less invasive procedures. A multi-disciplinary approach to treatment planning is vital to ensure that the sequencing of therapies is optimized, while also enabling the integration of novel biomarkers to better predict treatment responses. Moving forward, personalizing NAC through the identification of patients that respond exceptionally well and those most likely to achieve a pCR will be essential in refining therapeutic strategies and potentially eliminating the need for surgery in select cases. Ultimately, continued research into predictive biomarkers and tailored regimens will help shape the future of breast cancer treatment, improving outcomes and minimizing unnecessary interventions for patients.

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, et al. Cancer statistics for the year 2020: an overview. *Int J Cancer* 2021.
2. Łukasiewicz S, Czezelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast cancer–epidemiology, risk factors, classification, prognostic markers, and current treatment strategies—an updated review. *Cancers* 2021;13:4287.
3. Kalli S, Semine A, Cohen S, Naber SP, Makim SS, Bahl M. American joint committee on cancer's staging system for breast cancer, eighth edition: what the radiologist needs to know. *Radiographics* 2018;38:1921–33.
4. Harbeck N, Thomssen C, Gnant M. St. Gallen 2013: brief preliminary summary of the consensus discussion. *Breast Care* 2013;8:102–9.
5. Masood S. Neoadjuvant chemotherapy in breast cancers. *Womens Health* 2016;12:480–91.
6. Burotto M, Wilkerson J, Stein WD, Bates SE, Fojo T. Adjuvant and neoadjuvant cancer therapies: a historical review and a rational approach to understand outcomes. *Semin Oncol* 2019;46:83–99.
7. Raut NV, Chordiya N. NEO adjuvant chemotherapy in breast cancer: what have we learned so far? *Indian J Med Paediatr Oncol* 2010;31:8–17.
8. Bonadonna G. Evolving concepts in the systemic adjuvant treatment of breast cancer. *Cancer Res* 1992;52:2127–37.
9. Anampa J, Makower D, Sparano JA. Progress in adjuvant chemotherapy for breast cancer: an overview. *BMC Med* 2015;13:195.
10. Zhang BN, Cao XC, Chen JY, Chen J, Fu L, Hu XC et al. Guidelines on the diagnosis and treatment of breast cancer (2011 edition). *Gland Surg* 2012;1:39–61.
11. Ragaz J, Baird R, Rebbeck P, Goldie J, Coldman A, Spinelli J. Neoadjuvant (preoperative) chemotherapy for breast cancer. *Cancer* 1985;56:719–24.
12. Fisher B, Gunduz N, Coyle J, Rudock C, Saffer E. Presence of a growth-stimulating factor in serum following primary tumor removal in mice. *Cancer Res* 1989;49:1996–2001.
13. Wang M, Hou L, Chen M, Zhou Y, Liang Y, Wang S, et al. Neoadjuvant chemotherapy creates surgery opportunities for inoperable locally advanced breast cancer. *Sci Rep* 2017;7:44673.
14. Mieog JS, van der Hage JA, van de Velde CJ. Preoperative chemotherapy for women with operable breast cancer. *Cochrane Database Syst Rev* 2007;2007:CD005002.
15. Kaufmann M, von Minckwitz G, Mamounas EP, Cameron D, Carey LA, Cristofanilli M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. *Ann Surg Oncol* 2012;19:1508–16.
16. De Lena M, Varini M, Zucali R, Rovini D, Viganotti G, Valagussa P, et al. Multimodal treatment for locally advanced breast cancer. Result of chemotherapy–radiotherapy versus chemotherapy–surgery. *Cancer Clin Trials* 1981;4:229–36.
17. E Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 1998;16:2672–85.
18. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, et al. Preoperative chemotherapy: updates of national surgical adjuvant breast and bowel project protocols b–18 and b–27. *J Clin Oncol* 2008;26:778–85.
19. van Nes JG, Putter H, Julien JP, Tubiana-Hulin M, van de Vijver M, Bogaerts J, et al. Preoperative chemotherapy is safe in early breast cancer, even after 10 years of follow-up; clinical and translational results from the EORTC trial 10902. *Breast Cancer Res Treat* 2009;115:101–13.
20. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst* 2005;97:188–94.
21. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of

- individual patient data from ten randomised trials. *Lancet Oncol* 2018;19:27–39.
22. Ortmann O, Blohmer JU, Sibert NT, Brucker S, Janni W, Wöckel A, et al. Current clinical practice and outcome of neoadjuvant chemotherapy for early breast cancer: analysis of individual data from 94,638 patients treated in 55 breast cancer centers. *J Cancer Res Clin Oncol* 2022.
 23. Masuda N, Lee SJ, Ohtani S, Im YH, Lee ES, Yokota I, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. *N Engl J Med* 2017;376:2147–59.
 24. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, et al. KATHERINE Investigators. Trastuzumab emtansine for residual invasive her2-positive breast cancer. *N Engl J Med* 2019;380:617–28.
 25. Hensing W, Santa-Maria CA, Peterson LL, Sheng JY. Landmark trials in the medical oncology management of early stage breast cancer. *Semin Oncol* 2020;47:278–92.
 26. Herrera Juarez M, Tolosa Ortega P, Sanchez de Torre A, Ciruelos Gil E. Biology of the triple-negative breast cancer: immunohistochemical, RNA, and DNA features. *Breast Care* 2020;15:208–16.
 27. Leon-Ferre RA, Hieken TJ, Boughey JC. The landmark series: neoadjuvant chemotherapy for triple-negative and her2-positive breast cancer. *Ann Surg Oncol* 2021;28:2111–9.