**Original Article**

Eur J Breast Health 2024; 20(4): 277-283
*DOI: 10.4274/ejbh.galenos.2024.2024-6-3*

# Pathologic Complete Response After Neoadjuvant Chemotherapy in Breast Cancer Patients Treated With Mastectomy: Indications for Treatment and Oncological Outcomes

Corrado Tinterri[1,2], Shadya Sara Darwish[3], Erika Barbieri[1], Andrea Sagona[1], Valeriano Vinci[2,4], Damiano Gentile[1,2]

[1]Clinic of Breast Unit, IRCCS Humanitas Research Hospital, Milan, Italy
[2]Department of Biomedical Sciences, Humanitas University Faculty of Medicine, Milan, Italy
[3]Department of Breast Unit, Humanitas Gavazzeni Clinical Institute, Bergamo, Italy
[4]Department of Plastic and Reconstructive Surgery, Humanitas Clinical and Research Center-IRCCS, Milan, Italy

## ABSTRACT

**Objective:** The aim of this study was to evaluate the clinical outcomes of breast cancer (BC) patients treated with neoadjuvant chemotherapy (NAC) followed by mastectomy, focusing on cases achieving pathologic complete response (pCR). The implications of residual ductal carcinoma *in situ* (DCIS) on prognosis and survival were examined.

**Materials and Methods:** A retrospective cohort study included BC patients treated with NAC followed by mastectomy at the breast unit of IRCCS Humanitas Research Hospital between March 2010 and October 2021. Patients were sub-grouped into two: Those with residual DCIS (ypTis) and those with complete response without residual tumor (ypT0). Key variables such as demographics, tumor characteristics, treatment regimens, and survival outcomes were analyzed.

**Results:** Of 681 patients treated with NAC, 175 achieved pCR, with 60 undergoing mastectomy. Among these 60 patients, 24 had residual DCIS (ypTis) while 36 had no residual invasive or *in situ* disease (ypT0). Patients with ypTis had higher rates of multifocal disease (62.5% *vs.* 27.8%, $p = 0.006$) and stage III disease (37.5% *vs.* 11.1%, $p = 0.046$). Triple-negative breast cancer was more prevalent in the ypT0 group (55.6% *vs.* 20.8%, $p = 0.005$). During a mean follow-up of 47 months, 11 patients experienced recurrence, with no significant differences in disease-free survival (DFS) and overall survival (OS) between the groups ($p = 0.781$, $p = 0.963$, respectively).

**Conclusion:** Residual DCIS after NAC did not significantly impact DFS or OS compared to complete pathologic response without residual DCIS. This study underscores the need for further research to refine pCR definitions and improve NAC's prognostic and therapeutic roles in BC management.

**Keywords:** Breast cancer; neoadjuvant chemotherapy; pathologic complete response; mastectomy; ductal carcinoma *in situ*

**Cite this article as:** Tinterri C, Darwish SS, Barbieri E, Sagona A, Vinci V, Gentile D. Pathologic Complete Response After Neoadjuvant Chemotherapy in Breast Cancer Patients Treated With Mastectomy: Indications for Treatment and Oncological Outcomes. Eur J Breast Health. 2024; 20(4): 277-283

## Key Points

- Neoadjuvant chemotherapy (NAC) can lead to a pathologic complete response (pCR) in breast cancer (BC) patients, offering potential for better long-term outcomes.
- Among patients achieving pCR, those undergoing mastectomy were analyzed for prognosis, focusing on the presence or absence of residual ductal carcinoma *in situ* (DCIS).
- Residual DCIS (ypTis) after NAC did not significantly affect disease-free survival or overall survival compared to patients with complete pathologic response without DCIS (ypT0).
- Patients with ypTis had higher rates of multifocal disease and advanced stage III disease, whereas triple-negative BC was more prevalent in patients with ypT0.
- The presence of residual DCIS should be considered in surgical and adjuvant therapy planning, but it does not necessarily indicate a poorer prognosis.

**Corresponding Author:**
**Damiano Gentile; damiano.gentile@humanitas.it**

Received: 26.06.2024
Accepted: 31.07.2024
Available Online Date: 26.09.2024

## Introduction

Breast cancer (BC) is one of the most prevalent forms of cancer affecting women worldwide. Traditionally, the standard treatment for BC involved surgery as the primary intervention, followed by adjuvant therapies. However, advances in cancer research and treatment modalities have led to the development of neoadjuvant chemotherapy (NAC), which refers to administering systemic treatment before surgery (1-3). This approach has revolutionized the management of BC and offers several advantages, including the opportunity to assess treatment response, which has been found to correlate with survival outcomes, the potential for breast-conserving surgery (BCS), and the downstaging of advanced tumors (4-7). In recent years, the concept of pathological complete response (pCR) after NAC has garnered significant attention in the field of BC treatment. The achievement of pCR has been associated with improved long-term outcomes and a higher likelihood of disease-free survival (DFS) (6, 8, 9). For this reason, many studies have focused on increasing the achievement of pCR (10, 11).

Understanding the factors associated with reaching pCR and its impact on long-term outcomes has become an area of significant interest in BC research. However, there is no single definition of pCR, as different working groups consider various aspects. Focusing on the surgical approach, mastectomy has historically been the preferred method for BC treatment. However, with the advent of neoadjuvant therapy and the growing evidence supporting the effectiveness of this treatment modality, BCS has become a viable option for patients who achieve pCR (12-14). In some selected cases, mastectomy remains the preferred approach (15-17). This is true when oncological radicality cannot be achieved with BCS, the disease burden is still high compared to the breast volume, or there is an extensive component of residual microcalcifications. In a few selected cases, mastectomy may also be performed based on the patient's preference. In the present article, we evaluated BC treated with neoadjuvant therapy, focusing specifically on cases where patients achieved pCR and were surgically treated with mastectomy. We explored the implications of achieving pCR in terms of prognosis and survival outcomes, depending on the presence or absence of the residual ductal carcinoma *in situ* (DCIS) component. In addition, we analyzed the differences between the two DCIS subgroups from a demographic and cancer-specific perspectives, aiming to explain the different outcomes and survival benefits, if present.

## Materials and Methods

### Study Design

A retrospective cohort study was conducted to investigate the clinical outcomes of BC patients treated with NAC followed by mastectomy, specifically focusing on cases with a pCR. The study included patients diagnosed with BC of any biological subtype who underwent NAC and subsequent mastectomy between March 2010 and October 2021 at the breast unit of IRCCS Humanitas Research Hospital in Rozzano (Milan, Italy). Medical records of patients from a prospectively maintained institutional database were reviewed to identify eligible participants. Inclusion criteria comprised patients >18 years old, with histologically confirmed invasive BC, receipt of neoadjuvant therapy (chemotherapy, targeted therapy, or a combination), and subsequent mastectomy with a pCR on the surgical specimen. Bilateral mammography and breast ultrasound were routinely performed at the time of diagnosis, regardless of the reason leading to diagnosis, which could be part of the screening program or after symptoms onset. All patients enrolled had a histological diagnosis of invasive BC performed by an ultrasound-guided core needle biopsy, a stereotaxis-guided core needle biopsy, or a vacuum-assisted core needle biopsy, depending on tumor presentation, that is nodular or not, size, and site. Biological factors were routinely assessed. In order to complete the diagnostic process, a contrasted-enhanced bilateral magnetic resonance imaging (MRI) or contrasted-enhanced mammography were performed by highly qualified breast radiologists. In addition, a complete blood test routine, including a complete blood count, renal and liver function tests, and the CA 15-3 tumor marker, was performed. Regarding systemic staging, a chest X-ray, and a complete abdominal ultrasound were usually considered sufficient. Exceptions were made for patients with negative prognostic factors at the time of diagnosis. If one or more risk factors were present, patients underwent a total body computed tomography (CT) scan and bone scintigraphy. A fluorodeoxyglucose positron emission tomography (FDG-PET) or FDG-PET/CT was considered a II-level exam when further confirmations were required. Chemotherapy response was assessed both clinically and radiologically, repeating mammography, breast ultrasound, and magnetic resonance after the end of neoadjuvant therapy. FDG-PET was repeated if performed at the time of diagnosis. Patients received a mastectomy either because of residual microcalcifications or the absence of pre-chemotherapy proper tumor localization, through positioning of an amagnetic clip. Patients with incomplete data, previous BC treatment, and known high oncological risk status at the time of diagnosis, including the presence of oncogenic mutations or metastatic disease at presentation, were excluded from the study. Patient demographics, clinical characteristics, neoadjuvant treatment regimens, surgical details, and adequate follow-up information were collected from electronic medical records. Key variables included age, menopausal status, tumor stage and focality, hormone receptor status (estrogen receptor, progesterone receptor), human epidermal growth factor receptor 2 (HER2) status, neoadjuvant treatment regimen, duration of NAC, nodal status at all stages, surgical approach, and pCR status. Moreover, variables such as time from diagnosis to surgery, the delta of the dimension before and after chemotherapy, and the type of adjuvant therapy applied were considered.

The histopathological assessment was conducted on post-mastectomy specimens by experienced pathologists following standardized protocols. The presence or absence of invasive cancer cells in the breast and axillary lymph nodes was evaluated to determine pCR status. Patients were grouped into two subgroups for comparison: The subgroup with residual DCIS (ypTis) and the subgroup with the absence of invasive and *in situ* disease (ypT0). In our hospital, the pathological response to NAC was evaluated using the criteria proposed by Pinder et al. (18). It is important to consider that more than one definition exists. First, it is important to determine the absence of invasive disease in the surgical specimen obtained after NAC. Still, there is no consensus on whether pCR should be considered only in the mammary tissue or also in the lymph nodal tissue (19). Several systems are used to determine pCR. The standard assessment of response to solid tumors is based on the Response Evaluation Criteria in Solid Tumors (RECIST) (20). This system considers the complete response as the disappearance of all tumoral lesions and the regression of any pathological lymph nodes to <10 mm, but it is related to a clinical and radiological evaluation. From a histopathologic standpoint, several classifications have been proposed. The American Joint Committee on Cancer considers the pCR both in the breast and the regional lymph nodes as the absence of invasive carcinoma; DCIS still present

after treatment constitutes a pCR (21). Although using other specific criteria for the response assessment, the Residual Cancer Burden (RCB) system and the Sataloff classification for NAC evaluation categorize DCIS as a pCR (22, 23). Differently, the Chevallier Method and the National Surgical Adjuvant Breast and Bowel Project categorize the residual DCIS after NAC as a separate response class from a true pCR (24). Since pCR has a prognostic value, reaching a consensus about the most accurate definition and understanding of the pathological and prognostic meaning of a residual DCIS in the breast tissue after NAC is salient. For this reason, the aim of our study was to enhance the meaning of the different possible outcomes depending on the pattern of pCR, with a particular focus on distinguishing between complete response with or without a ductal *in situ* component. The Humanitas University Research Committee and Institutional Board approved this retrospective study (approval no.: EC04-06-CT34-NAC, date: 27.05.2024).

### Statistical Analysis

Descriptive statistics were calculated to summarize patient demographics and clinical characteristics. The association between categorical variables was examined using the chi-square test or Fisher's exact test, as appropriate. Survival outcomes, including DFS and overall survival (OS), were estimated using a Kaplan-Meier graph, and differences between survival curves were assessed using Cox or log-rank tests, as appropriate. Subgroup analyses were performed to explore the impact of specific factors, such as hormone receptor status or HER2 status, on pCR rates and survival outcomes. All statistical analyses were performed using StataCorp STATA (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC). A $p$-value <0.05 was considered statistically significant.

## Results

### Demographic and Tumor Characteristics

During the period considered in this retrospective study, 681 patients were treated with NAC. Among these, 175 patients achieved a pCR on the surgical specimen, considering both ypT0 and ypTis. Out of these, 60 patients (34.3%) were treated with mastectomy. Only 3 (5.0%) had a confirmed DCIS component at the diagnostic core biopsy. However, after NAC, 24 patients (40.0%) had residual DCIS in the surgical specimen (ypTis), while 36 patients (60.0%) had a pCR without residual tumor (ypT0). The median (range) age for the entire cohort was 50 (31–75) years. Among the ypT0 group, the median age was 50 (31–75) years, while in the ypTis group, it was 51 (32–71) years, with no significant difference between the groups ($p$ = 0.188). The ypTis group had a significantly higher rate of multifocal disease (62.5%) compared to the ypT0 group (27.8%) ($p$ = 0.006). Monofocal disease was observed in 72.2% of the ypT0 group and 37.5% of the ypTis group. Menopausal status distribution was not significantly different between the groups, with 53.3% premenopausal in the entire cohort. In the ypT0 group, 47.2% were premenopausal, compared to 62.5% in the ypTis group ($p$ = 0.245). Six patients (10.0%) overall presented with microcalcifications in pre-treatment imaging assessment. At diagnosis, 65.0% of patients had positive lymph node status (cN+), which was 63.9% in the ypT0 group and 66.7% in the ypTis group ($p$ = 0.825). After NAC, 26.7% remained lymph node positive, with 33.3% in the ypT0 group and 16.7% in the ypTis group ($p$ = 0.225). Disease stage was higher in the ypTis group, with 33.3% at stage III compared to 11.1% in the ypT0 group ($p$ = 0.046). There was a significant difference in the distribution of biological factors between the two groups ($p$ = 0.005). In the ypT0 group, 55.6% had triple-negative breast cancer (TNBC) compared to 20.8% in the ypTis group. The median reduction in tumor size (delta dimension) was 32 (12-100) mm overall, with 31 (15-100) mm in the ypT0 group and 33 (12-100) mm in the ypTis group. The median time from diagnosis to surgery was 8 (5-14) months for the entire cohort. The demographic and tumor characteristics are detailed in Table 1.

### Adjuvant Therapies and Long-Term Oncological Outcomes

Table 2 shows the adjuvant therapy distribution, demonstrating homogeneous values comparing the two groups. Radiotherapy was administered to 43.3% of the total cohort, with 44.4% in the

**Table 1.** Demographic and tumor characteristics distribution in the general population and in the two subgroups, ypT0 and ypTis

| | All patients ($n$ = 60) | % | ypT0 ($n$ = 36) | % | ypTis ($n$ = 24) | % | $p$-value |
|---|---|---|---|---|---|---|---|
| **Age: median (range)** | 50 (31–75) | | 50 (31–75) | | 51 (32–71) | | 0.188 |
| **Focality** | | | | | | | |
| Unifocal | 35 | 58.3% | 26 | 72.2% | 9 | 37.5% | 0.006 |
| Multifocal | 25 | 41.7% | 10 | 27.8% | 15 | 62.5% | |
| **Menopausal status** | | | | | | | |
| No | 32 | 53.3% | 17 | 47.2% | 15 | 62.5% | 0.245 |
| Yes | 28 | 46.7% | 19 | 52.8% | 9 | 37.5% | |
| **Nodal status pre NAC** | | | | | | | |
| N0 | 21 | 35.0% | 13 | 36.1% | 8 | 33.3% | 0.825 |
| N+ | 39 | 65.0% | 23 | 63.9% | 16 | 66.7% | |
| **Nodal status after NAC** | | | | | | | |
| N0 | 44 | 73.3% | 24 | 66.7% | 20 | 83.3% | 0.225 |
| N+ | 16 | 26.7% | 12 | 33.3% | 4 | 16.7% | |

**Table 1.** Continued

| | All patients (*n* = 60) | % | ypT0 (*n* = 36) | % | ypTis (*n* = 24) | % | *p*-value |
|---|---|---|---|---|---|---|---|
| **Stage** | | | | | | | |
| I | 3 | 5.0% | 3 | 8.3% | 0 | 0% | 0.046 |
| II | 44 | 73.3% | 29 | 80.6% | 15 | 62.5% | |
| III | 12 | 20.0% | 4 | 11.1% | 8 | 33.3% | |
| **Biological factor status** | | | | | | | |
| HR+/HER2+ | 11 | 18.3% | 2 | 5.6% | 9 | 37.5% | 0.005 |
| HR-/HER2+ | 16 | 26.7% | 9 | 25.0% | 7 | 29.2% | |
| HR+/HER2- | 8 | 13.3% | 5 | 13.9% | 3 | 12.5% | |
| TNBC | 25 | 41.7% | 20 | 55.6% | 5 | 20.8% | |
| **Ki67 (*n* = 57)** | | | | | | | |
| ≤20% | 8 | 13.3% | 5 | 13.9% | 3 | 12.5% | 1.000 |
| >20% | 49 | 81.7% | 28 | 77.8% | 21 | 87.5% | |
| **Delta dim (mm) pre/post NAC: median (range)** | 32 (12–100) | | 31 (15–100) | | 33 (12–100) | | |
| **Time to surgery: median (range)** | 8 (5–14) | | 8 (6–14) | | 8 (5–10) | | |

NAC: Neoadjuvant chemotherapy; HR+: Hormonal receptor positive; HR-: Hormonal receptor negative; HER2+: Human epidermal growth factor receptor 2 positive; HER2-: Human epidermal growth factor receptor 2 negative; TNBC: Triple negative breast cancer; Dim: Dimension

**Table 2.** Adjuvant therapies and long-term oncological outcomes in the general population and in the two subgroups, ypT0 and ypTis

| | All patients (*n* = 60) | % | ypT0 (*n* = 36) | % | ypTis (*n* = 24) | % | *p*-value |
|---|---|---|---|---|---|---|---|
| Radiotherapy | 26 | 43.3% | 16 | 44.4% | 10 | 41.7% | 0.832 |
| Hormonal therapy | 17 | 28.3% | 7 | 19.4% | 10 | 41.7% | |
| **Recurrence** | | | | | | | 0.061 |
| Local | 2 | 3.3% | 1 | 2.8% | 1 | 4.2% | 1.000 |
| Distant | 7 | 11.7% | 4 | 11.1% | 3 | 12.5% | |
| Local + distant | 2 | 3.3% | 2 | 5.6% | 0 | 0% | |
| **Death** | | | | | | | |
| For BC | 2 | 90.0% | 1 | 2.8% | 1 | 4.2% | 1.000 |
| For other causes | 3 | 13.3% | 2 | 5.6% | 1 | 4.2% | |

BC: Breast cancer

ypT0 group and 41.7% in the ypTis group ($p$ = 0.832). Hormonal therapy was given to 28.3% of the patients, with a higher percentage in the ypTis group (41.7%) compared to the ypT0 group (19.4%), approaching statistical significance ($p$ = 0.061). Long-term oncological outcomes are also shown in Table 2. During a mean follow-up of 47 months, 11 patients experienced recurrence. In the ypT0 group, 7 patients (19.4%) had a recurrence, compared to 4 patients (16.7%) in the ypTis group ($p$>0.05). Recurrences included local (3.3% total, 2.8% ypT0, 4.2% ypTis), distant (11.7% total, 11.1% ypT0, 12.5% ypTis), and combined local and distant (3.3% total, 5.6% ypT0, 0% ypTis). There were two BC-related deaths (3.3% total, 2.8% ypT0, 4.2% ypTis) and three deaths from other causes (5.6% total, 5.6% ypT0, 4.2% ypTis), with no significant difference between the groups ($p$>0.05). No statistical difference was observed in analyzing both DFS ($p$ = 0.781) and OS ($p$ = 0.963) between the two groups, as shown in Figures 1 and 2, respectively.

## Discussion and Conclusion

The current study focused on patients undergoing a mastectomy after NAC to analyze a more complete pathological picture of the entire breast tissue. Radiological and clinical evaluation plays a critical role at diagnosis and post-therapy assessment, despite known limitations. For example, contrast-enhanced MRI with significant background parenchymal enhancement may have limited accuracy, especially for non-mass enhancement and small-size tumors (25). Moreover, due to the increased application of BCS, post-NAC residual DCIS could be missed if not present in the surgical specimen. By assessing the whole glandular tissue after mastectomy, we ensured a complete pathological evaluation.

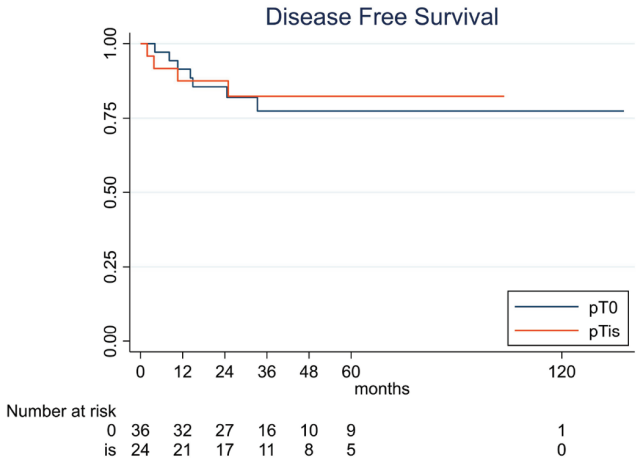


**Figure 1.** This figure represents the disease-free survival curves for the two groups, ypT0 and ypTis, showing no statistical difference ($p = 0.781$)

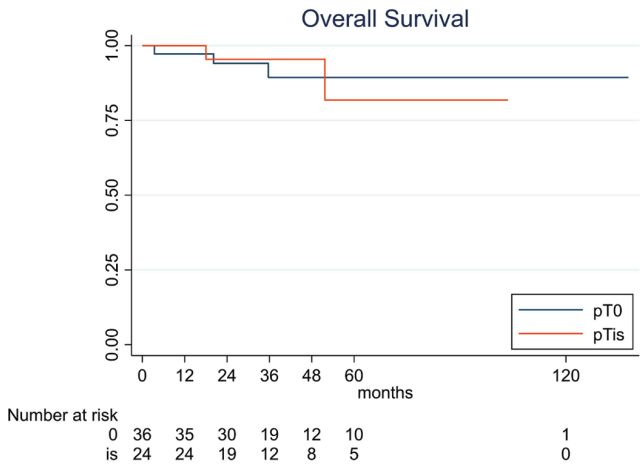


**Figure 2.** This figure represents the overall survival curves for the two groups, ypT0 and ypTis, showing no statistical difference ($p = 0.963$)

The reasons for performing a mastectomy were not related to the purpose of this study; data were collected retrospectively without influencing the surgical approach. Our analysis revealed that only a small percentage of patients had a DCIS component at the time of diagnosis on the core biopsy. However, a higher percentage of patients had residual DCIS in the surgical specimen. The presence of DCIS was not consistently associated with microcalcifications at diagnosis or after chemotherapy, indicating a low correlation between the two phenomena. Goldberg et al. (26) illustrated that NAC might completely eradicate DCIS while associated microcalcifications persist. A recent systematic review and meta-analysis conducted by Conforti et al. (27), found that pCR should not be used as a primary endpoint in regulatory neoadjuvant trials of BC due to weak association between pCR and long-term clinical outcomes at the trial level. This demonstrates the need for further studies to better understand the true clinical meaning of pCR without confounding factors, such as adjuvant therapies, which might alter survival outcomes (28, 29).

Currently, there is no single definition of pCR, with various classifications considering different aspects. This lack of a uniform definition creates challenges in reporting and interpreting data from neoadjuvant trials (30, 31). Some studies have shown different prognostic values for ypT0 and ypTis (32). Symmans et al. (23) calculated the RCB as a continuous index combining pathologic measurements of the primary tumor (size and cellularity) and nodal status, using corrective coefficients such as the presence of residual DCIS. The RCB was found to be a significant predictor of distant relapse-free survival (33). To address this, the Food and Drug Administration established the Collaborative Trials in Neoadjuvant Breast Cancer working group (30), which analysed data from nearly 13,000 patients enrolled in large-scale international neoadjuvant trials. They compared the three most commonly used definitions of pCR [pT0/Tis (absence of invasive cancer in the breast), pT0/Tis pN0 (absence of invasive cancer in the breast and axillary nodes), and pT0 pN0 (absence of invasive and *in situ* cancer in the breast and axillary nodes)] and their relationship to long-term patient outcome. After a pooled analysis, they recognized either pT0/Tis pN0 or pT0 pN0 for the purposes of designing trials. However, this dual definition remains an open question in BC research, which the present article sought to address.

We compared the survival outcomes between the pCR ypT0 and the pCR ypTis group to determine if a prognostic difference exists. In a meta-analysis by Broglio et al. (34), pCR in HER2+ BC was significantly associated with improved DFS and OS compared to those with residual disease. Specifically, patients achieving pCR had a hazard ratio of 0.37 for DFS and 0.34 for OS, indicating a substantially lower risk of recurrence and death. This association was more pronounced in hormone receptor-negative patients. In a retrospective study by Yoshioka et al. (35), it was found that achieving a pCR after NAC significantly improved DFS and OS in BC patients, particularly in those with high Ki67 expression. The study demonstrated that patients with TNBC, estrogen receptor-negative/HER2+, and luminal B tumors who achieved pCR had a significantly better prognosis compared to those with residual disease. However, this benefit was not observed in patients with luminal A or estrogen receptor-positive/HER2+ subtypes. However, in our study we found no differences in DFS and OS. Only a few tumor-related characteristics were statistically associated with a specific pathological response after NAC, such as TNBC, unifocal disease, and a lower stage at presentation related to a ypT0 response. Currently, no consensus has been reached concerning the prognostic value of residual DCIS after NAC. Our study demonstrated a correlation between tumor focality and stage with a ypTis response, showing that a multifocal and higher stage disease constitute a specific risk factor for residual DCIS. From a biological standpoint, luminal-like BC is mostly related to a ypTis response after NAC. These factors should be considered while planning neoadjuvant therapy for a more accurate prediction of the pathological response.

If residual DCIS after NAC does not change the prognosis, as demonstrated in this study, this knowledge should be considered during the surgical planning phase. Specifically, if only microcalcifications are present after NAC, although diffuse, a BCS could still be considered, potentially increasing the aesthetic and psychological outcomes (26). Adjuvant therapy planning could be affected by no longer considering DCIS as a residual disease to be targeted, reducing patients' exposure to unnecessary therapies in the de-escalation setting. A refined estimate of an individual's risk of recurrence, based on their subtype and RCB, might be useful for informing decisions on adjuvant treatment selection, even though the presence or absence of residual disease is already being used to guide adjuvant decisions following NAC (36-38). Another important factor is that neoadjuvant and

adjuvant therapies themselves might mitigate differences between the two groups, reducing adverse events homogeneously. Moreover, newly diagnosed DCIS lesions are a heterogeneous group in morphology, genetics, cellular biology, and clinical behavior. Approximately half of all DCIS lesions progress to an invasive status with an unknown underlying mechanism (39).

This study has several limitations. First, the retrospective design introduces inherent bias and limitations associated with data collection and potential confounding variables. Second, the small sample size may affect the statistical power to detect significant associations between the pathological response and the occurrence of adverse events. In addition, the study was conducted at a single institution, which may limit the generalizability of the findings. Moreover, the extended enrollment period from 2010 to 2021 could introduce a time-based bias, with potential prognostic changes over time due to improvements in therapeutic regimes. Another significant limitation is the lack of data on patient preferences in surgical planning. Understanding patient preferences could provide valuable insights into the decision-making process and improve personalized treatment approaches. Lastly, long-term follow-up data beyond the scope of this study were not available, precluding the evaluation of late recurrences and/or cancer-related mortality.

The current study demonstrated that residual DCIS after NAC (ypTis) does not significantly impact DFS or OS compared to complete pathologic response without residual tumor (ypT0). The findings suggest that residual DCIS should be considered in surgical planning, potentially allowing for BCS in suitable cases, and may inform decisions on adjuvant therapy de-escalation. The study highlights the need for a standardized definition of pCR and further research to refine treatment approaches for better patient outcomes.

---

**Ethics Committee Approval:** The Humanitas University Research Committee and Institutional Board approved this retrospective study (approval no.: EC04-06-CT34-NAC, date: 27.05.2024).

**Informed Consent:** Retrospective study.

**Authorship Contributions:** Surgical and Medical Practices: C.T., S.S.D., E.B., A.S., V.V., D.G.; Concept: C.T., S.S.D., E.B., A.S., V.V., D.G.; Design: C.T., S.S.D., E.B., A.S., V.V., D.G.; Data Collection and/or Processing: C.T., S.S.D., A.S., V.V., D.G.; Analysis and/or Interpretation: C.T., S.S.D., E.B., D.G.; Literature Search: C.T., S.S.D., D.G.; Writing: C.T., S.S.D., E.B., V.V., D.G.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

## References

1. Hortobagyi GN, Ames FC, Buzdar AU, Kau SW, McNeese MD, Paulus D, et al. Management of stage III primary breast cancer with primary chemotherapy, surgery, and radiation therapy. Cancer. 1988; 62: 2507-2516. (PMID: 3056604) [Crossref]
2. Sacchini V, Norton L. Escalating de-escalation in breast cancer treatment. Breast Cancer Res Treat. 2022; 195: 85-90. (PMID: 35902432) [Crossref]
3. Schiavone A, Ventimiglia F, Zarba Meli E, Taffurelli M, Caruso F, Gentilini OD, et al. Third national surgical consensus conference of the Italian Association of Breast Surgeons (ANISC) on management after neoadjuvant chemotherapy: The difficulty in reaching a consensus. Eur J Surg Oncol. 2024; 50: 108351. (PMID: 38701582) [Crossref]
4. Barbieri E, Gentile D, Bottini A, Sagona A, Gatzemeier W, Losurdo A, et al. Neo-Adjuvant Chemotherapy in Luminal, Node Positive Breast Cancer: Characteristics, Treatment and Oncological Outcomes: A Single Center's Experience. Eur J Breast Health. 2021; 17: 356-362. (PMID: 34651115) [Crossref]
5. Cortazar P, Geyer CE. Pathological Complete Response in Neoadjuvant Treatment of Breast Cancer. Ann Surg Oncol. 2015; 22: 1441-1446. (PMID: 25727556) 10.1245/s10434-015-4404-8
6. Kong X, Moran MS, Zhang N, Haffty B, Yang Q. Meta-analysis confirms achieving pathological complete response after neoadjuvant chemotherapy predicts favourable prognosis for breast cancer patients. Eur J Cancer. 2011; 47: 2084-2090. (PMID: 21737257) [Crossref]
7. Tinterri C, Barbieri E, Sagona A, Bottini A, Canavese G, Gentile D. De-Escalation Surgery in cT3-4 Breast Cancer Patients after Neoadjuvant Therapy: Predictors of Breast Conservation and Comparison of Long-Term Oncological Outcomes with Mastectomy. Cancers (Basel). 2024; 16: 1169. (PMID: 38539504) [Crossref]
8. Kerr AJ, Dodwell D, McGale P, Holt F, Duane F, Mannu G, et al. Adjuvant and neoadjuvant breast cancer treatments: A systematic review of their effects on mortality. Cancer Treat Rev. 2022; 105: 102375. (PMID: 35367784) [Crossref]
9. Gentile D, Sagona A, De Carlo C, Fernandes B, Barbieri E, Di Maria Grimaldi S, et al. Pathologic response and residual tumor cellularity after neo-adjuvant chemotherapy predict prognosis in breast cancer patients. Breast. 2023; 69: 323-329. (PMID: 37001289) [Crossref]
10. Takada M, Toi M. Neoadjuvant treatment for HER2-positive breast cancer. Chin Clin Oncol. 2020; 9: 32. (PMID: 32527117) [Crossref]
11. Kuerer HM, Smith BD, Krishnamurthy S, Yang WT, Valero V, Shen Y, et al. Eliminating breast surgery for invasive breast cancer in exceptional responders to neoadjuvant systemic therapy: a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2022; 23: 1517-1524. (PMID: 36306810) [Crossref]
12. Clough KB, Acosta-Marín V, Nos C, Alran S, Rouanet P, Garbay JR, et al. Rates of Neoadjuvant Chemotherapy and Oncoplastic Surgery for Breast Cancer Surgery: A French National Survey. Ann Surg Oncol. 2015; 22: 3504-3511. (PMID: 25665949) [Crossref]
13. Vugts G, Maaskant-Braat AJG, Nieuwenhuijzen GAP, Roumen RMH, Luiten EJT, Voogd AC. Patterns of care in the administration of neo-adjuvant chemotherapy for breast cancer. A population-based study. Breast J. 2016; 22: 316-321. (PMID: 26945566) [Crossref]
14. Golshan M, Cirrincione CT, Sikov WM, Berry DA, Jasinski S, Weisberg TF, et al. Impact of neoadjuvant chemotherapy in stage II-III triple negative breast cancer on eligibility for breast-conserving surgery and breast conservation rates: Surgical results from CALGB 40603 (Alliance). Ann Surg. 2015; 262: 434-439; discussion 438-439. (PMID: 26222764) [Crossref]
15. Galimberti V, Vicini E, Corso G, Morigi C, Fontana S, Sacchini V, et al. Nipple-sparing and skin-sparing mastectomy: Review of aims, oncological safety and contraindications. Breast. 2017; 34: S82-S84. (PMID: 28673535) [Crossref]
16. Zarba Meli E, De Santis A, Cortese G, Manna E, Mastropietro T, La Pinta M, et al. Nipple-Sparing Mastectomy After Neoadjuvant Chemotherapy: Definitive Results with a Long-Term Follow-Up Evaluation. Ann Surg Oncol. 2023; 30: 2163-2172. (PMID: 36598627) [Crossref]
17. Scardina L, Di Leone A, Biondi E, Carnassale B, Sanchez AM, D'Archi S, et al. Prepectoral vs. Submuscular Immediate Breast Reconstruction in Patients Undergoing Mastectomy after Neoadjuvant Chemotherapy: Our Early Experience. J Pers Med. 2022; 12: 1533. (PMID: 36143318) [Crossref]

18. Pinder SE, Provenzano E, Earl H, Ellis IO. Laboratory handling and histology reporting of breast specimens from patients who have received neoadjuvant chemotherapy. Histopathology. 2007; 50: 409-417. (PMID: 17448015) [Crossref]
19. Provenzano E. Neoadjuvant Chemotherapy for Breast Cancer: Moving Beyond Pathological Complete Response in the Molecular Age. Acta Med Acad. 2021; 50: 88-109. (PMID: 34075766) [Crossref]
20. Schwartz LH, Litière S, De Vries E, Ford R, Gwyther S, Mandrekar S, et al. RECIST 1.1 - Update and clarification: From the RECIST committee. Eur J Cancer. 2016; 62: 132-137. (PMID: 27189322) [Crossref]
21. Giuliano AE, Edge SB, Hortobagyi GN. Eighth Edition of the AJCC Cancer Staging Manual: Breast Cancer. Ann Surg Oncol. 2018; 25: 1783-1785. (PMID: 29671136) [Crossref]
22. Sataloff DM, Mason BA, Prestipino AJ, Seinige UL, Lieber CP, Baloch Z. Pathologic response to induction chemotherapy in locally advanced carcinoma of the breast: A determinant of outcome. J Am Coll Surg. 1995; 180: 297-304. (PMID: 7874340) [Crossref]
23. Symmans WF, Peintinger F, Hatzis C, Rajan R, Kuerer H, Valero V, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol. 2007; 25: 4414-4422. (PMID: 17785706) [Crossref]
24. Litton JK, Regan MM, Pusztai L, Rugo HS, Tolaney SM, Garrett-Mayer E, et al. Standardized Definitions for Efficacy End Points in Neoadjuvant Breast Cancer Clinical Trials: NeoSTEEP. J Clin Oncol. 2023; 41: 4433-4442. (PMID: 37433103) [Crossref]
25. Marinovich ML, Macaskill P, Irwig L, Sardanelli F, von Minckwitz G, Mamounas E, et al. Meta-analysis of agreement between MRI and pathologic breast tumour size after neoadjuvant chemotherapy. Br J Cancer 2013; 109: 1528-1536. (PMID: 23963140) [Crossref]
26. Goldberg H, Zandbank J, Kent V, Leonov-Polak M, Livoff A, Chernihovsky A, et al. Chemotherapy may eradicate ductal carcinoma in situ (DCIS) but not the associated microcalcifications. Eur J Surg Oncol. 2017; 43: 1415-1420. (PMID: 28526187) [Crossref]
27. Conforti F, Pala L, Sala I, Oriecuia C, De Pas T, Specchia C, et al. Evaluation of pathological complete response as surrogate endpoint in neoadjuvant randomised clinical trials of early stage breast cancer: Systematic review and meta-analysis. BMJ. 2021; 375: e066381. (PMID: 34933868) [Crossref]
28. Burstein HJ. Systemic Therapy for Estrogen Receptor–Positive, HER2-Negative Breast Cancer. Longo DL, editor. N Engl J Med. 2020; 383: 2557-2570. (PMID: 33369357) [Crossref]
29. Castaneda SA, Strasser J. Updates in the Treatment of Breast Cancer with Radiotherapy. Surg Oncol Clin N Am. 2017; 26: 371-382. (PMID: 28576177) [Crossref]
30. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. Lancet. 2014; 384: 164-172. (PMID: 24529560) [Crossref]
31. von Minckwitz G, Rezai M, Loibl S, Fasching PA, Huober J, Tesch H, et al. Capecitabine in Addition to Anthracycline- and Taxane-Based Neoadjuvant Treatment in Patients With Primary Breast Cancer: Phase III GeparQuattro Study. J Clin Oncol. 2010; 28: 2015-2023. (PMID: 20308671) [Crossref]
32. von Minckwitz G, Untch M, J Blohmer U, Costa SD, Eidtmann H, Fasching PA, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol. 2012; 30: 1796-1804. (PMID: 22508812) [Crossref]
33. Symmans WF, Wei C, Gould R, Yu X, Zhang Y, Liu M, et al. Long-Term Prognostic Risk After Neoadjuvant Chemotherapy Associated With Residual Cancer Burden and Breast Cancer Subtype. J Clin Oncol. 2017; 35: 1049-1060. (PMID: 28135148) [Crossref]
34. Broglio KR, Quintana M, Foster M, Olinger M, McGlothlin A, Berry SM, et al. Association of pathologic complete response to neoadjuvant therapy in HER2- positive breast cancer with long-term outcomes ameta-analysis. JAMA Oncol. 2016; 2: 751-760. (PMID: 26914222) [Crossref]
35. Yoshioka T, Hosoda M, Yamamoto M, Taguchi K, Hatanaka KC, Takakuwa E, et al. Prognostic significance of pathologic complete response and Ki67 expression after neoadjuvant chemotherapy in breast cancer. Breast Cancer. 2015; 22: 185-191. (PMID: 23645542) [Crossref]
36. Yau C, Osdoit M, van der Noordaa M, Shad S, Wei J, de Croze D, et al. Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients. Lancet Oncol. 2022; 23: 149-160. (PMID: 34902335) [Crossref]
37. 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: 2147-2159. (PMID: 28564564) [Crossref]
38. von Minckwitz G, Huang C-S, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019; 380: 617-628. (PMID: 30516102) [Crossref]
39. Hophan SL, Odnokoz O, Liu H, Luo Y, Khan S, Gradishar W, et al. Ductal Carcinoma In Situ of Breast: From Molecular Etiology to Therapeutic Management. Endocrinology. 2022; 163. (PMID: 35245349) [Crossref]