Postmastectomy radiotherapy after neoadjuvant chemotherapy in cT1-2N+ breast cancer patients: a single center experience and review of current literature

Meng Luo
Zhejiang University School of Medicine Second Affiliated Hospital

Huihui Chen
Zhejiang University School of Medicine Second Affiliated Hospital

Hao Deng
Zhejiang University School of Medicine Second Affiliated Hospital

Yao Jin
Zhejiang University School of Medicine Second Affiliated Hospital

Gui Wang
Lishui University

Kun Zhang
Zhejiang University School of Medicine Second Affiliated Hospital

Hong Ma
Zhejiang University School of Medicine Second Affiliated Hospital

Yiding Chen
Zhejiang University School of Medicine Second Affiliated Hospital

Suzhan Zhang
Zhejiang University School of Medicine Second Affiliated Hospital

Jiaojiao Zhou (zhoujj@zju.edu.cn)
Zhejiang University School of Medicine Second Affiliated Hospital  https://orcid.org/0000-0003-0442-6183

Research Article

Keywords: Postmastectomy radiotherapy, neoadjuvant chemotherapy, breast cancer

Posted Date: January 6th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1201823/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

Purpose

Postmastectomy radiotherapy (PMRT) after NAC in breast cancer patients with initial clinical stage cT1−2N0, especially for those who achieved ypT0-2N0, is still controversial. This study was to evaluate the survival prognosis of cT1−2N0 patients after NAC with or without PMRT, and to discuss the selection of patients who may omit PMRT.

Patients and Methods

From January 2005 to December 2017, 3055 female breast cancer patients underwent mastectomy in our center, among whom 215 patients of cT1−2N0 stage, receiving neoadjuvant chemotherapy (NAC) with or without PMRT were finally analyzed. The median follow-up duration was 72.6 months. The primary endpoint was overall survival, and the secondary endpoint was disease-free survival. Comparison was conducted between PMRT and non-PMRT subgroups.

Results

Of the 215 eligible patients, 35.8% (77/215) cT1−2N0 patients achieved ypT0-2N0 after NAC while 64.2% (138/215) of the patients remained nodal positive (ypT0-2N+). The 5-year DFS of ypT0-2N0 non-PMRT was 79.5% (95% confidence interval [CI] 63.4-95.6%). No statistically significant difference was observed between the ypT0-2N0 PMRT and non-PMRT subgroups for the 5-year DFS (78.5% vs 79.5%, p = 0.673) and OS (88.8% vs 90.8%, p = 0.721). The 5-years DFS didn't obviously differ between the ypT0-2N0 non-PMRT subgroup and cT1−2N+ subgroup (79.5% vs 93.3%, p = 0.070). By using Cox regression model in multivariate analyses of prognosis in ypT0-2N0 PMRT subgroup, HER2 overexpression and triple-negative breast cancer were significantly poor predictors of DFS and OS, while ypN stage was significant independent predictors of OS.

Conclusion

An excellent response to NAC (ypT0-2N0) indicates a sufficiently favorable prognosis, and PMRT might be omitted for cT1−2N0 breast cancer patients with ypT0-2N0 after NAC.

1. Introduction

Neoadjuvant chemotherapy (NAC) is increasingly used in breast cancer, especially for patients with locally advanced disease[1]. NAC has appealing potential benefits in facilitating surgery by converting an inoperable disease to be operable or by converting a candidate disease for mastectomy to one who can be treated with breast-conserving surgery[2]. NAC usually alters the stage, and it has been reported that NAC commonly downsizes the primary tumor in 70-80% of patients[3, 4] and downstages the axillary lymph nodes status in at least 20-40% of patients[4, 5].

Postmastectomy radiotherapy (PMRT) has been shown to reduce the risk of locoregional recurrence and benefit overall survival in breast cancer. PMRT is recommended for patients with tumors size ≥ 5cm or with at least four positive lymph nodes[6], while the role of PMRT in T1−2 tumors with 1-3 positive lymph nodes remains widely controversial and is usually recommended for those T1−2N1 patients with high-risk features. However, these principles of PMRT guidance were given in the absence of NAC, and it is unclear if we can expand the indications of these PMRT guidance for patients with NAC. Moreover, the potential downstaging of NAC also challenged the standard indications for PMRT.

PMRT indications following NAC remains widely debated, particularly in those with initial breast cancer stage of cT1−2N+. Nowadays, based on the increasing rates of breast reconstructions, this issue becomes more important as PMRT can adversely affect the complication incidence and aesthetic outcome of an immediate breast reconstructions[7]. Actually, the real debate is whether an excellent response to NAC (e.g. achieve ypT0-2N0) is a sufficiently favorable prognostic finding that PMRT can be omitted.

In this study, we aimed to evaluate the efficacy of PMRT after NAC in breast cancer patients with initial clinical stage cT1−2N0M0, and try to answer three relevant questions: 1) Is PMRT after NAC needed for patients presenting with cT1−2N0 disease who achieve ypT0-2N0? 2) Without PMRT, how about the prognosis of cT1−2N0 patients who achieve ypT0-2N0 compared to cT1−2N0 patients? 3) How about the correlations between clinical variables and prognosis in NAC patients with residual nodal disease? Moreover, we also reviewed current relevant literatures here to further interpret the indications for PMRT after NAC.

2. Methods

2.1 Patient population

From January 2005 to December 2017, 3055 female breast cancer patients diagnosed underwent mastectomy at the Second Affiliated Hospital, Zhejiang University School of Medicine, among whom 456 patients received NAC before mastectomy. Only patients with cT1−2N0 stage before NAC and underwent mastectomy were included for retrospective analysis, with a final cohort of 215 patients. Patients who had NAC less than 2 cycles (n=5), ypT3−4 stage after NAC (n=6), unknown ypT stage (n=19), unknown ypN stage (n=1), or unknown radiotherapy treatment (n=62) were excluded. This study was approved by the Ethics Committee of our hospital (Approval No: 2020-363).
The medical records of all the patients were extracted from the computerized database of the Second Affiliated Hospital, Zhejiang University School of Medicine. The follow-up information of all the patients were extracted from the follow-up records system of Cancer Institution in the Second Affiliated Hospital, Zhejiang University School of Medicine. Clinical tumor size (ct) was based on the imaging findings of ultrasound, mammography or magnetic resonance imaging (MRI). cN in this study was defined as patients with clinical diagnosed metastatic lymph nodes, including palpable lymph nodes that are fixed or matted, imaging diagnosed metastatic lymph nodes, or lymph node metastases pathologically confirmed after biopsy. And 64.2% (138/215) of the patients in final cohort (ct1-2 N0) were pathologically confirmed with lymph node metastases, either by biopsy before NAC or sentinel lymph node biopsy(SLNB)/ axillary lymph node dissection(ALND) at operation. The TNM staging was performed in accordance with American Joint Committee on Cancer (AJCC) guidance (version 8, 2017). Estrogen receptor (ER) and progesterone receptor (PR) status were evaluated by immunohistochemistry (IHC), with a cutoff value of 1% to dichotomize cases into positive and negative[8]. Human epidermal receptor 2 (HER2) status was evaluated by IHC and further determined by IHC and fluorescence in situ hybridization (FISH) when IHC was scored as 2+ which is indeterminate[9].

2.2 Treatment

All the ct1-2 N0 patients included were divided into two groups according to the pathological lymph nodes status of surgical specimen after NAC: ypT0-N0 group or ypT0-N2 group, which were further divided into two groups respectively based on whether they received PMRT or not. (Figure 1) In this study, axillary lymph node dissection was performed in 97.2% of the patients. All the hormonal receptor (HR)-positive patients received adjuvant endocrine therapy. In cases of HER2-positive breast cancer, 47 cases (49.5%) were treated with Trastuzumab.

For patients received PMRT, radiation was delivered to chest wall and/or the regional lymph nodes (supraclavicular/infraclavicular and/or internal mammary lymph node region), with a prescription dose of 50 Gy (range: 45-60 Gy) in 25 fractions (range: 24-28 Gy). 3D conformal radiation therapy was applied in 13.56% of patients, while intensity-modulated radiation therapy in 86.44% of patients.

2.2 Study endpoints

The last update date of following-up was on September 16th, 2021. The median follow-up time of this study was 72.6 months (5.96 yrs). The primary endpoint is overall survival (OS), defined as the time from the date of diagnosis (before NAC) to the time of death due to any cause or the last follow-up. The secondary endpoint is disease free survival (DFS), defined as the time from the date of diagnosis to the time of first locoregional recurrence (LR), distant metastasis (DM), death, or the last follow-up. LR included clinical, radiographic, or pathological evidence of recurrence in ipsilateral chest wall and/or regional lymph nodes, while DM were recurrences at other sites except LR (i.e. contralateral breast, bone, lung, liver, brain metastasis).

2.3 Statistical analysis

The clinical and pathological characteristics between each groups of patients were compared using the Pearson’s χ² test or Fisher’s exact test as appropriate. Continuous variables were tested by a t-test. Survival analysis including DFS and OS was carried out with Kaplan-Meier method and differences were tested by log-rank test. For NAC patients with residual nodal disease, univariate and multivariate analyses for survival associated factors were performed using a Cox proportional hazards model with crude hazard ratio. All the tests were two-sided, and p values < 0.05 was considered statistically significant. SPSS version 20.0 software (IBM Institute, Chicago, IL, USA) and Graphpad Prism version 8 (GRAPH PAD software Inc, California, USA) were used for all statistical analyses.

3. Results

3.1 Patient and tumor characteristics

A total of 215 ct1-2 N0 patients were analyzed in this study. And the clinical characteristics of the patients were illustrated in Table 1. The median age of the patients at diagnosis was 51.2 years (range: 25–75 years). About 87.44% (188/215) of all the breast cancer patients were invasive ductal carcinomas. Among the enrolled ct1-2 N0 patients, 21.4% (46/215) and 78.6% (169/215) of the patients were in clinical T1 and T2 stages, respectively. After NAC followed by mastectomy, the primary tumor staging was ypT0 in 18.6% (40/215), ypT1 in 47.9% (103/215), and ypT2 in 33.5% (72/215) of the patients. The percentage of patients having ypN0, ypN1, ypN2 lymph node stages was 35.8% (77/215), 30.2% (65/215) and 34.0% (73/215), respectively. A total of 32 (14.9%) triple negative breast cancer (TNBC) patients was enrolled. ER was positive in 60.5% of patients, and all the ER-positive patients received endocrine therapy. HER2 was positive in 37.7% of patients, while trastuzumab was received by 49.5% of these HER2+ patients. For the chemotherapy regimens, 91.2% of the patients received anthracycline-containing chemotherapy regimens, 79.1% of the patients received taxane-containing chemotherapy regimens, and a total of 70.2% of the patients received anthracycline and taxane combined chemotherapy regimens. A total of 46.3% of 177 patients received PMRT to the chest wall and/or the regional lymph nodes (supraclavicular/infraclavicular and/or internal mammary lymph node region).

3.2 Is PMRT after NAC needed for patients presenting with ct1-2 N0 disease who achieve ypT0-N0?

After NAC, 35.8% (77/215) ct1-2 N0 patients achieved ypT0-N0. In current clinical practice, it is still unclear whether PMRT after NAC would benefit the survival of those ct1-2 N0 patients who achieved ypT0-N0. In our study, 64.9% (50/77) of those ypT0-N0 patients received PMRT while 35.1% (27/50) of whom didn't. Most of the clinical and treatment characteristics between ypT0-N0 PMRT and non-PMRT were with no significant difference, except the pathological complete response (pCR) ratio (42% vs 14.8%, p=0.021) and therapeutic ratio of trastuzumab for HER2+ patients (72.0% vs 18.2%, p=0.009). (Table 2)

With the median follow-up duration of 66.5 months, a total of 11 (22%) patients in the ypT0-N0 PMRT subgroup and 7 (25.9%) in the non-PMRT subgroup had locoregional recurrence or distant metastasis. We further analyzed the recurrence patterns between ypT0-N0 PMRT and non-PMRT subgroups, finding that the
locoregional recurrence was significantly more in ypT1−2N1 non-PMRT subgroup (2% vs 14.8%, p=0.048) while the distant metastasis was with no difference between these two subgroups. (Table 3)

The 5-year DFS of ypT0−2N0 non-PMRT subgroup was 79.5% (95% confidence interval [CI] 63.4–95.6%). No statistically significant difference was observed between the ypT0−2N0 PMRT and non-PMRT subgroups for the 5-year DFS interval (78.5% vs 79.5%, p = 0.673). (Figure 2A) Consistently, no OS difference was observed with the use of PMRT in ypT0−2N0 patients, with an observed 5-year OS of 88.8% (95% CI 79.6–98.0%) for PMRT and 90.8% (95% CI 78.6–103%) without (p = 0.721). (Figure 2B)

3.3 Without PMRT, how about the prognosis of cT1−2N1+ patients who achieve ypT0−2N0 compared to cT1−2N0 patients?

Considering the non-inferior prognosis of ypT0−2N0 patients without PMRT, we further compared the survival of these ypT0−2N0 non-PMRT patients to those of cT1−2N0 stage before NAC. The clinical and treatment characteristics between these two groups were with no significant difference. (Supplementary table 1) The 5-years DFS didn't obviously differ between the ypT0−2N0 non-PMRT group and cT1−2N0 group (79.5% vs 93.3%, p = 0.070). (Figure 3A) By the date of the last follow-up, no patient died in cT1−2N0 group. And the 5-years OS between ypT0−2N0 non-PMRT group and cT1−2N0 group were with no significant difference (p = 0.063). (Figure 3B)

3.4 Correlations between clinical variables and prognosis in NAC patients with residual nodal disease

As the consensus statement suggested by National Cancer Institute[10], most of NAC patients with residual nodal disease in our study (PMRT in ypT0−2N1+ 128/138) received PMRT. We further analyzed the correlations between clinical variables and prognosis in these NAC patients with residual nodal disease who received PMRT. Various prognostic factors correlated to DFS and OS were listed in Table 4. In univariate analysis, factors including ypN stage, estrogen receptor status, molecular subtypes including HER2 overexpression and triple-negative breast cancer were significantly associated with both DFS and OS. Distant recurrence rate and all-cause mortality of patients with ypN1−2 was 1.98 and 4.19 times higher than that of ypN0 patients, respectively. Above variables including molecular subtypes and ypN stage were involved in advanced multivariate analysis, which shows that HER2 overexpression and triple-negative breast cancer were significantly poor predictors of DFS and OS, while ypN stage was significant independent predictors of OS in ypT0−2N+ PMRT group. (Table 5)

3.5 Indications for PMRT after NAC: current literature review

To further examine the benefits or lack for PMRT in the setting of NAC, we systematically reviewed current literatures and compared our results with these published studies. The PubMed literature search resulted in 184 articles related to PMRT after NAC (from 1993 Mar to 2021 Nov), by using search terms “postmastectomy radiation therapy” “neoadjuvant chemotherapy” and “breast cancer” in all their forms. After reviewing the abstracts and full texts of all these published studies. The PubMed literature search resulted in 184 articles related to PMRT after NAC (from 1993 Mar to 2021 Nov), by using search terms “postmastectomy radiation therapy” “neoadjuvant chemotherapy” and “breast cancer” in all their forms. After reviewing the abstracts and full texts of all these studies. To further examine the benefits or lack for PMRT in the setting of NAC, we systematically reviewed current literatures and compared our results with these published studies. The PubMed literature search resulted in 184 articles related to PMRT after NAC (from 1993 Mar to 2021 Nov), by using search terms “postmastectomy radiation therapy” “neoadjuvant chemotherapy” and “breast cancer” in all their forms. After reviewing the abstracts and full texts of all these studies.

4. Discussion

Current prospective and retrospective data has provided evidence for recommending PMRT after NAC for breast cancer patients with cT3−4, cN2−3 or residual lymph node disease, as well as suggested omitting PMRT for cT1−2N0−1 patients who develop a pathologic complete response[20]. However, the efficacy of PMRT after NAC in breast cancer patients with initial clinical stage cT1−2N+, especially for those who achieved ypT1−2N0, is still largely unknown. In this study, we conducted a retrospective analysis of postmastectomy radiation therapy after neoadjuvant chemotherapy in cT1−2N+, breast cancer patients in our medical center. And our findings suggested that PMRT might not be necessary for cT1−2N+, patients with ypT0−2N0 after NAC.

In our study, most of the clinical and treatment characteristics between ypT0−2N0 PMRT and non-PMRT were with no difference, only except pCR and therapeutic ratio of trastuzumab for HER2+ patients. Patients in ypT0−2N0 non-PMRT group had lower pCR ratio, which may due to the lower percentage of patients who had completed the neoadjuvant chemotherapy regimens (33.3% vs 64%, p = 0.010) (Supplementary table 2). However, when included the adjuvant chemotherapy after operation into analysis, we found that percentage of patients who completed the whole chemotherapy (neoadjuvant and adjuvant) regimens between ypT0−2N0 PMRT and non-PMRT group is with no significant difference (96% vs 92.6%, p = 0.609) (Supplementary table 2). We believe that completion rate of the whole chemotherapy regimens is more related to the prognosis of the patients. Therapeutic ratio of trastuzumab for HER2+ patients in total ypT0−2N0 group was 55.6%, which probably due to the absence of local medical insurance policy for trastuzumab until Sep. 2017. Therapeutic ratio of trastuzumab for HER2+ patients were lower in ypT0−2N0 non-PMRT than those in PMRT group, which resulted in inadequate treatment in that such patients. However, under all these circumstances, no statistically significant difference of 5-year DFS and OS was still observed between ypT0−2N0 PMRT and non-PMRT group. And this result makes us more believe the favorable prognosis of ypT0−2N0 even without PMRT.

Moreover, it is interesting that the survival between cT1−2N0 patients who achieved ypT0−2N0 without PMRT and those of cT1−2N0 before NAC were with no significant difference. Although there were concerns that the lymph node status of cT1−2N0 might be downstaged, all the cT1−2N0 patients remained ypT1−2N0 after NAC. Patients of T1−2N0 stage without NAC didn’t need PMRT according to current acknowledged PMRT guideline[6]. In our study, none of patients with cT1−2N0 received PMRT after NAC and the 5-years DFS and OS were quite favorable of these patients. Therefore, considering the comparable survival between
cT_{1-2}N_{0} patients who achieved ypT_{0-2}N_{0} without PMRT and those of cT_{1-2}N_{0}, we speculate that patients of cT_{1-2}N_{0} who achieved ypT_{0-2}N_{0} can still have favorable survival even without PMRT.

Until now, there are two ongoing prospective trials that address the PMRT value for cT_{1-2}N_{0} patients who have nodal pCR after NAC. The NSABP51 trial is a randomized phase III clinical trial evaluating PMRT in cT_{1-2}N_{0} patients (pathologically proven) who convert to pN_{0} after NAC (www.nsabp.pitt.edu/B-51.asp). The RAPCHEM trial is prospective observational study, aiming to evaluate the 5-years LRR in cT_{1-2}N_{0-1} patients after NAC, breast surgery and radiotherapy that is protocolized based on the ypTNM stage (https://clinicaltrials.gov/ct2/show/study/NCT01279304). As RAPCHEM’s protocol demonstrated, patients with ypN_{0} will be stratified to low risk group and won’t have PMRT.

In this study, we reviewed current relevant literatures and compared our results with these published studies (Table 6). All these relevant literatures are retrospective. In Huang’s study (2004)[11] of 676 locally advanced breast cancer treated with NAC and mastectomy, which included 145 cases of cT_{1-2} stage, PMRT didn't decrease LRR and didn't improved 10-years cause-specific survival (CSS) in cT_{1-2} patients after NAC. In their study, ypN_{0} after NAC only accounted for 29.7% of the patients. PMRT still didn't benefit survival although 68.9% of the patients had residual nodal disease after NAC. In McGuire’s study (2007)[12] of 106 cT_{1-2}N_{0} breast cancer patients who achieved pCR after NAC, PMRT didn’t improve 10-yr LRR in clinical stage II patients with pCR after NAC, but significantly improve 10-yr LRR, DMFS and OS in those of clinical stage III patients. It indicated that PMRT may be more likely to benefit survival in cases of more advanced stages. Both of Le Scordan’s (2012)[13] and Shim’s (2014)[14] studies demonstrated that PMRT didn’t improve 10-yr LRFS and OS in clinical stage II-III patients with pN0 after NAC. In Rusthoven’s study (2016)[15], which had a large study population of 10283 cN_{0} patients, they found that PMRT significantly improved 5-years OS in cT1-3N1 patients after NAC, whatever achieving ypN_{0} or still remaining ypN_{0} patients. However, they had 40.1% of cT3 patients at diagnosis, which can definitely have survival benefits from PMRT, and PMRT after NAC for clinical stage III breast cancer (i.e. T3N1) has been a consensus clinically[10]. It is still unclear if PMRT is needed for cT_{1-2}N_{0} patients who develop ypN_{0} after NAC. Caoa et al[16] analyzed a small population of 88 cT_{1-2}N_{0} cases. They found that PMRT significantly improved 5-years LRFS in cT_{1-2}N_{0} patients after NAC, but didn’t affect DMFS and DFS. However, 39.8% of the cases remained ypN_{1}, which can gain survival benefits from PMRT. Therefore, the effect of PMRT for cT_{1-2}N_{0} patients who achieve ypN_{0} after NAC is still not clarified in Caoa’s study. Interestingly, in Wang’s study (2018)[17] of 217 cT_{1-2}N_{0-1} patients, they demonstrated that PMRT didn’t decrease 5-years LRR in cT_{1-2}N_{0-1} patients with low risk, but significantly decrease LRR in those with high risk. Risk factors in their study included ypN stage, histologic grade and lymphatic vessel invasion (LVI). We speculate that cT_{1-2}N_{0} patients with ypN_{0} after NAC in our study may be more comparable to the cT_{1-2}N_{0-1} population with low risk in Wang’s study, in which PMRT didn’t decrease the 5-years LRR. The study by Wang (2020)[18] was most comparable to our study. They analyzed 142 cT_{1-2}N_{0} breast cancer patients and found that PMRT didn’t improve OS in cT_{1-2}N_{0} who achieving ypT_{1-2}N_{0} after NAC, which is consistent with the findings of our study. However, they found that PMRT significantly improved RFS but not LRFS. It is needed to point out that, in their study, the locoregional recurrence or distant metastasis rate was with no difference between PMRT and non-PMRT group. The latest study by Zhang (2021)[19] of 554 clinical stage II-III patients, demonstrated that PMRT significantly reduced 5-years LRR in clinical stage II-III patients after NAC, however those with ypN_{0} derived no local control or survival benefit from PMRT.

Our study has some limitations. This is a retrospective study that selection bias between PMRT and non-PMRT group is the inherent shortcoming. The sample size of the study is limited. Therapeutic ratio of trastuzumab for HER2+ patients is low, resulting in inadequate treatment. A small proportion of initial axillary lymph node status (16.3%) was not determined by pathology.

In conclusion, in this study, no difference was observed when PMRT was omitted in cT_{1-2}N_{0} breast cancer patients who achieve ypT_{0-2}N_{0} after NAC. However, the necessity of PMRT for these patients needs further assessment in more prospective studies with larger sample size.

**Abbreviations**

PMRT postmastectomy radiotherapy, NAC neoadjuvant chemotherapy, cT clinical tumor size, cN clinical lymph node, ypT pathologic tumor size after neoadjuvant therapy, ypN pathologic lymph node after neoadjuvant therapy, DFS disease-free survival, OS overall survival, CI confidence interval, MRI magnetic resonance imaging, SLNB sentinel lymph node biopsy, ALND axillary lymph node dissection, AJCC American Joint Committee on Cancer, ER estrogen receptor, PR progesterone receptor, IHC immunohistochemistry, HER2 human epidermal receptor 2, FISH fluorescence in situ hybridization, HR hormonal receptor, LR locoregional recurrence, DM distant metastasis, TNBC triple negative breast cancer, pCR pathological complete response, LRR local regional recurrence, LRFS local recurrence free survival, DMFS distant metastases-free survival, RFS recurrence-free survival, CSS cause-specific survival, LVI lymphatic vessel invasion.

**Declarations**

**Data availability**

In this study, all the patients’ data were from the Second Affiliated Hospital, Zhejiang University School of Medicine, which are not publicly available in order to protect patient privacy, but can be accessed from the corresponding author, Dr. Jiaojiao Zhou (e-mail: zhoujj@zju.edu.cn), on reasonable request.

**Conflict of Interests**

The authors declare that there is no conflict of interest regarding the publication of this paper.
Ethical approval

This study was approved by the Ethics Committee of our hospital (Approval No: 2020-363) with waiver of informed consent.

Consent for publication

Given for all authors.

Authors’ contributions

JJ Zhou, YD Chen and SZ Zhang planned and designed this study. JJ Zhou, YD Chen drew the outline of this study. JJ Zhou, M Luo and HH Chen wrote the manuscript. M Luo, HH Chen, HDeng and Y Jin collected the all the clinical data. M Luo and HH Chen performed the data analysis. HDeng, Y Jin, K Zhang and HM did the follow-up of patients. M Luo, HH Chen and G Wang participated in searching relevant literatures. All authors have read and approved the final manuscript.

Acknowledgments

We gratefully thank Wenhong Xu for her valuable assistance in radiation therapy related data collection and analysis.

Grant support

This study was supported by the National Natural Science Foundation of China (Grant No. 82172344, 81702866), the funding of the Key Program of the Natural Science Foundation of Zhejiang Province (Grant No. L216H160002), the funding of Medical Science and Technology Project of Zhejiang Province (Grant No. 2022RC174), the Fundamental Research Funds for the Central Universities (Grant No. 2021FZZX002-09)

References

1. Ikeda T, Jinno H, Matsu A, et al (2002) The role of neoadjuvant chemotherapy for breast cancer treatment. Breast Cancer 9. https://doi.org/10.1007/BF02967540

2. Hayes DF, Schott AF (2015) Neoadjuvant Chemotherapy: What Are the Benefits for the Patient and for the Investigator? J Natl Cancer Inst Monogr 2015:36-39. https://doi.org/10.1093/jncimonographs/lgv004

3. Group EBCTC (2018) Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol 19:27-39. https://doi.org/10.1016/S1470-2045(17)30777-5

4. Fisher B, Brown A, Mamounas E, et al (1997) Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol 15:2483-2493. https://doi.org/10.1200/JCO.1997.15.7.2483

5. Kuerer HM, Sahin AA, Hunt KK, et al (1999) Incidence and impact of documented eradication of breast cancer axillary lymph node metastases before surgery in patients treated with neoadjuvant chemotherapy. Ann Surg 230:72-78. https://doi.org/10.1097/00000658-199907000-00011

6. Taylor ME, Haffty BG, Rabinovitch R, et al (2009) ACR appropriateness criteria on postmastectomy radiotherapy expert panel on radiation oncology-breast. Int J Radiat Oncol Biol Phys 73. https://doi.org/10.1016/j.ijrobp.2008.10.080

7. Kronowitz SJ, Robb GL (2004) Breast reconstruction with postmastectomy radiation therapy: current issues. Plast Reconstr Surg 114:950-960. https://doi.org/10.1097/01prs.0000133200.99826.7f

8. Hammond MEH, Hayes DF, Wolff AC, et al (2010) American society of clinical oncology/college of american pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Oncol Pract 6:195-197. https://doi.org/10.1200/JOP.2009.00777003

9. Wolff AC, Hammond MEH, Allison KH, et al (2018) Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol 36:2105-2122. https://doi.org/10.1200/JCO.2018.77.8738

10. Buchholz TA, Lehman CD, Harris JR, et al (2008) Statement of the science concerning locoregional treatments after preoperative chemotherapy for breast cancer: a National Cancer Institute conference. J Clin Oncol 26:791-797. https://doi.org/10.1200/JCO.2007.15.0326

11. Huang EH, Tucker SL, Strom EA, et al (2004) Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. J Clin Oncol 22:4691-4699. https://doi.org/10.1200/JCO.2004.11.129

12. McGuire SE, Gonzalez-Angulo AM, Huang EH, et al (2007) Postmastectomy radiation improves the outcome of patients with locally advanced breast cancer who achieve a pathologic complete response to neoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys 68:1004-1009. https://doi.org/10.1016/j.ijrobp.2007.01.023
13. Le Scodan R, Selz J, Stevens D, et al (2012) Radiotherapy for stage II and stage III breast cancer patients with negative lymph nodes after preoperative chemotherapy and mastectomy. Int J Radiat Oncol Biol Phys 82:e1-e7. https://doi.org/10.1016/j.ijrobp.2010.12.054

14. Shim SJ, Park W, Huh SJ, et al (2014) The role of postmastectomy radiation therapy after neoadjuvant chemotherapy in clinical stage II-III breast cancer patients with pN0: a multicenter, retrospective study (KROG 12-05). Int J Radiat Oncol Biol Phys 88:65-72. https://doi.org/10.1016/j.ijrobp.2013.09.021

15. Rusthoven CG, Rabinovitch RA, Jones BL, et al (2016) The impact of postmastectomy and regional nodal radiation after neoadjuvant chemotherapy for clinically lymph node-positive breast cancer: a National Cancer Database (NCDB) analysis. Ann Oncol 27:818-827. https://doi.org/10.1093/annonc/mdw046

16. Cao L, Ou D, Shen KW, et al (2018) Outcome of postmastectomy radiotherapy after primary systemic treatment in patients with clinical T1-2N1 breast cancer. Cancer Radiother 22:38-44. https://doi.org/10.1016/j.canrad.2017.07.051

17. Wang X, Xu L, Yin Z, et al (2018) Locoregional recurrence-associated factors and risk-adapted postmastectomy radiotherapy for breast cancer staged in cT1-2N0-1 after neoadjuvant chemotherapy. Cancer Manag Res 10:4105-4112. https://doi.org/10.2147/CMAR.S173628

18. Wang Q, Zhao J, Han X, et al (2020) Is There a Role for Post-Mastectomy Radiotherapy for T1-2N1 Breast Cancers With Node-Positive Pathology After Patients Become Node-Negative Pathology Following Neoadjuvant Chemotherapy? Front Oncol 10:892. https://doi.org/10.3389/fonc.2020.00892

19. Zhang Y, Zhang Y, Liu Z, et al (2021) Impact of Postmastectomy Radiotherapy on Locoregional Control and Disease-Free Survival in Patients with Breast Cancer Treated with Neoadjuvant Chemotherapy. J Oncol 2021:6632635. https://doi.org/10.1155/2021/6632635

20. Kishan AU, McCloskey SA (2016) Postmastectomy radiation therapy after neoadjuvant chemotherapy: review and interpretation of available data. Ther Adv Med Oncol 8:85-97. https://doi.org/10.1177/1758834015617459

Tables
| Variable                          | N=215   | %  |
|----------------------------------|---------|----|
| Age                              |         |    |
| Mean                             | 51.3    |    |
| Range                            | 25-75   |    |
| <40                              | 20      | 9.3|
| ≥40                              | 195     | 90.7|
| Clinical T stage                 |         |    |
| 1                                | 46      | 21.4|
| 2                                | 169     | 78.6|
| ypT stage                        |         |    |
| 0-is                             | 40      | 18.6|
| 1                                | 103     | 47.9|
| 2                                | 72      | 33.5|
| ypN stage                        |         |    |
| 0                                | 77      | 35.8|
| 1                                | 65      | 30.2|
| 2-3                              | 73      | 34.0|
| Estrogen receptor status         |         |    |
| Positive                         | 130     | 60.5|
| Negative                         | 77      | 35.8|
| Unknown                          | 8       | 3.7 |
| HER2 status                      |         |    |
| Positive                         | 81      | 37.7|
| Negative                         | 115     | 53.5|
| Unknown                          | 19      | 8.8 |
| TNBC                             |         |    |
| Yes                              | 32      | 14.9|
| No                               | 174     | 80.9|
| Unknown                          | 9       | 4.2 |
| Molecular subtype                |         |    |
| Luminal A                        | 39      | 18.1|
| Luminal B                        | 79      | 36.7|
| HER2 overexpression              | 43      | 20.0|
| Triple-negative                  | 32      | 14.9|
| Unknown                          | 22      | 10.2|
| pCR                              |         |    |
| Yes                              | 25      | 11.6|
| No                               | 190     | 88.4|
| Preoperative chemotherapy regimes|         |    |
| Anthracycline containing         | 196     | 91.2|
| Taxane containing                | 170     | 79.1|
| Anthracycline and taxane containing| 151    | 70.2|
| Hormone therapy/Estrogen receptor status | 130/130 | 100.0 |
|-----------------------------------------|--------|-------|
| HER2-targeted therapy/HER2 status       | 44/81  | 54.3  |
| PMRT                                    |        |       |
| Yes                                     | 178    | 82.8  |
| No                                      | 37     | 17.2  |

cT clinical tumor size, cN clinical lymph node, ypT pathologic tumor size after neoadjuvant therapy, ypN pathologic lymph node after neoadjuvant therapy, HER2 human epidermal receptor 2, TNBC triple negative breast cancer, pCR pathological complete response, PMRT postmastectomy radiotherapy.
### Table 2: Patient characteristics and comparison between ypT0-2N0 PMRT and non-PMRT subgroups

| Variable                  | ypT0-2N0 PMRT | non-PMRT | P value | ypT0-2N0 PMRT | non-PMRT | P value |
|---------------------------|---------------|----------|---------|---------------|----------|---------|
|                          | n=128 %       | n=10 %   |         | n=50 %        | n=27 %   |         |
| Age                       |               |          |         |               |          |         |
| Mean                      | 51.3          | 53.1     | 1.000   | 51.4          | 50.4     | 0.996   |
| Range                     | 30-75         | 39-69    |         | 25-73         | 33-65    |         |
| <40                       | 13 10.2       | 1 10.0   |         | 7 14.0        | 3 11.1   |         |
| ≥40                       | 115 89.8      | 9 90.0   |         | 43 86.0       | 24 88.9  |         |
| Clinical T stage          |               |          | 0.157   |               |          | 0.383   |
| 1                         | 32 25.0       | 0 0.0    |         | 11 22.0       | 3 11.1   |         |
| 2                         | 96 75.0       | 10 100.0 |         | 39 78.0       | 24 88.9  |         |
| ypT stage                 |               |          | 0.061   |               |          | 0.052   |
| 0-is                      | 14 10.9       | 1 10.0   |         | 21 42.0       | 4 14.8   |         |
| 1                         | 68 53.1       | 2 20.0   |         | 18 36.0       | 14 51.9  |         |
| 2                         | 46 35.9       | 7 70.0   |         | 11 22.0       | 9 33.3   |         |
| ypN stage                 |               |          | 0.426   |               |          |         |
| 0                         | 0 0.0         | 0 0.0    |         | 50 100.0      | 27 100.0 |         |
| 1                         | 62 48.4       | 3 30.0   |         | 0 0.0         | 0 0.0    |         |
| 2-3                       | 66 51.6       | 7 70.0   |         | 0 0.0         | 0 0.0    |         |
| Estrogen receptor status  |               |          | 0.627   |               |          | 0.550   |
| Positive                  | 92 71.9       | 6 60.0   |         | 20 40.0       | 10 37.0  |         |
| Negative                  | 31 24.2       | 4 40.0   |         | 28 56.0       | 14 51.9  |         |
| Unknown                   | 5 3.9         | 0 0.0    |         | 2 4.0         | 3 11.1   |         |
| HER2 status               |               |          | 0.889   |               |          | 0.158   |
| Positive                  | 40 31.3       | 4 40.0   |         | 25 50.0       | 11 40.7  |         |
| Negative                  | 72 56.3       | 5 50.0   |         | 25 50.0       | 14 51.9  |         |
| Unknown                   | 14 10.9       | 1 10.0   |         | 0 0.0         | 2 7.4    |         |
| TNBC                      |               |          | 0.704   |               |          | 0.267   |
| Yes                       | 12 9.4        | 0 0.0    |         | 13 26.0       | 7 25.9   |         |
| No                        | 112 87.5      | 10 100.0 |         | 36 72.0       | 17 63.0  |         |
| Unknown                   | 4 3.1         | 0 0.0    |         | 1 2.0         | 3 11.1   |         |
| Molecular subtype         |               |          | 0.364   |               |          | 0.518   |
| Luminal A                 | 29 22.7       | 2 20.0   |         | 4 8.0         | 4 14.8   |         |
| Luminal B                 | 56 43.8       | 3 30.0   |         | 15 30.0       | 5 18.5   |         |
| HER2 overexpression       | 22 17.2       | 3 30.0   |         | 15 30.0       | 7 25.9   |         |
| Triple-negative           | 12 9.4        | 0 0.0    |         | 13 26.0       | 7 25.9   |         |
| Unknown                   | 9 7.0         | 2 20.0   |         | 3 6.0         | 4 14.8   |         |
| pCR                       |               |          |         |               |          | 0.021   |
| Yes                       | 0 0.0         | 0 0.0    |         | 21 42.0       | 4 14.8   |         |
| No                        | 128 100.0     | 10 100.0 |         | 29 58.0       | 23 85.2  |         |
| Preoperative chemotherapy regimes |               |          | 0.964   |               |          | 0.172   |
| Anthracycline containing  | 118 92.2      | 10 100.0 |         | 41 82.0       | 27 100.0 |         |
| Taxane containing         | 99 77.3       | 7 70.0   |         | 48 96.0       | 16 59.3  |         |
Anthracycline and taxane containing 89 69.5 7 70.0 39 78.0 16 59.3

Hormone therapy/Estrogen receptor status - - - - - - -

|                | PMRT       | non-PMRT   | P value |
|----------------|------------|------------|---------|
| **Locoregional** | 1 (2%)     | 4 (14.8%)  | **0.048** |
| **Distant metastasis** | 10 (20%)   | 3 (11.1%)  | 0.500   |

*Represents the patient who had chest wall, supraclavicular, or axillary LN recurrence. PMRT, postmastectomy radiotherapy, ypT pathologic tumor size after neoadjuvant therapy, ypN pathologic lymph node after neoadjuvant therapy.
| Variable                          | DFS No. of patients | DFS HR (95% CI) | DFS P value | OS No. of patients | OS HR (95% CI) | OS P value |
|----------------------------------|---------------------|-----------------|-------------|-------------------|----------------|------------|
| **Age**                          |                     |                 |             |                   |                 |            |
| <40                              | 13                  | ref.            | 0.973       |                   | ref.           | 0.739      |
| ≥40                              | 115                 | 1.020 (0.313-3.33) | 1.410 (0.187-10.62) |            |                  |            |
| **Clinical T stage**             |                     |                 |             |                   |                 |            |
| 1                                | 32                  | ref.            | 0.380       |                   | ref.           | 0.125      |
| 2                                | 96                  | 1.420 (0.649-3.108) | 3.160 (0.726-13.756) |            |                  |            |
| **ypT stage**                    |                     |                 |             |                   |                 |            |
| 0-1                              | 14                  | ref.            | ref.        |                   | ref.           | ref.       |
| 2                                | 68                  | 0.666 (0.348-1.272) | 0.681 (0.288-1.608) |            |                  |            |
| 3                                | 46                  | 1.550 (0.905-2.655) | 2.001 (0.918-4.36) |            |                  |            |
| **ypN stage**                    |                     |                 |             |                   |                 |            |
| 1                                | 62                  | ref.            | ref.        |                   | ref.           | ref.       |
| 2-3                              | 66                  | 1.981 (1.023-3.837) | 4.189 (1.387-12.648) |            |                  |            |
| **Estrogen receptor status**     |                     |                 |             |                   |                 |            |
| Positive                         | 92                  | ref.            | ref.        |                   | ref.           | ref.       |
| Negative                         | 31                  | 3.037 (1.572-5.867) | 3.329 (1.337-8.29) |            |                  |            |
| **HER2 status**                  |                     |                 |             |                   |                 |            |
| Positive                         | 40                  | ref.            | ref.        |                   | ref.           | ref.       |
| Negative                         | 72                  | 0.613 (0.307-1.224) | 0.532 (0.205-1.379) |            |                  |            |
| **TNBC**                         |                     |                 |             |                   |                 |            |
| Yes                              | 12                  | ref.            | ref.        |                   | ref.           | ref.       |
| No                               | 112                 | 0.387 (0.17-0.882) | 0.313 (0.103-0.955) |            |                  |            |
| **Molecular subtype**            |                     |                 |             |                   |                 |            |
| Luminal A                        | 28                  | ref.            | ref.        |                   | ref.           | ref.       |
| Luminal B                        | 55                  | 2.114 (0.706-6.324) | 4.865 (0.613-38.639) |            |                  |            |
| HER2 overexpression              | 10                  | 4.944 (1.486-16.451) | 10.077 (1.114-91.159) |            |                  |            |
| Triple-negative                  | 17                  | 4.648 (1.310-16.486) | 12.693 (1.412-114.062) |            |                  |            |
| **Preoperative chemotherapy regimes** |                 |                 |             |                   |                 |            |
| Anthracycline containing         | 118                 | ref.            | ref.        |                   | ref.           | ref.       |
| Without anthracycline            | 11                  | 1.780 (0.683-4.642) | 2.797 (0.892-8.771) |            |                  |            |
| Taxane containing                | 99                  | ref.            | ref.        |                   | ref.           | ref.       |
| Without Taxane                   | 30                  | 0.816 (0.395-1.684) | 1.148 (0.379-3.477) |            |                  |            |
| Anthracycline and Taxane containing | 89              | ref. (0.346-1.291) | ref.        |                   | ref.           | ref.       |
| Without both anthracycline and Taxane | 40              | 0.668           | 0.653 (0.257-1.660) |            |                  |            |

ypT pathologic tumor size after neoadjuvant therapy, ypN pathologic lymph node after neoadjuvant therapy, PMRT postmastectomy radiotherapy, DFS disease-free survival, OS overall survival, HR hazard ratio, CI confidence interval, ref reference, HER2 human epidermal receptor 2, TNBC triple negative breast cancer, pCR pathological complete response.
Table 5 Multivariate analysis of DFS and OS in ypT0-2N+ PMRT subgroup

| Variable                  | No. of patients | DFS HR (95% CI)       | DFS P value | OS HR (95% CI)    | OS P value |
|---------------------------|-----------------|-----------------------|-------------|-------------------|------------|
| ypN stage                 | 0.222           |                       |             | 0.024             |            |
| 1                         | 55              | ref.                  |             | ref.              |            |
| 2-3                       | 60              | 1.549 (0.767-3.127)   | 3.687 (1.184-11.480) |            |            |
| Molecular subtype         | 0.022           |                       | 0.039       |                   |            |
| Luminal A                 | 29              | ref.                  |             | ref.              |            |
| Luminal B                 | 56              | 2.021 (0.674-6.060)   | 4.512 (0.566-35.982) |            |            |
| HER2 overexpression       | 12              | 4.167 (1.162-14.947)  | 9.709 (1.066-88.391) |            |            |
| Triple-negative           | 18              | 5.138 (1.541-17.130)  | 11.402 (1.255-103.612) |            |            |

DFS disease-free survival, OS overall survival, PMRT postmastectomy radiotherapy, HR hazard ratio, CI confidence interval, ypT pathologic tumor size after neoadjuvant therapy, ypN pathologic lymph node after neoadjuvant therapy, HER2 human epidermal receptor 2.
### Table 6: Current literature review for PMRT after NAC

| Study | Luo M, et al | McGuire SE, et al | Le Scodan R, et al | Shim SJ, et al | Rusthoven CG, et al | Cao L, et al | Wang X, et al | Wang Q, et al |
|-------|--------------|-------------------|-------------------|---------------|-----------------|-------------|-------------|-------------|
| (year) | (2021) | (2004) | (2007) | (2012) | (2014) | (2016) | (2017) | (2018) | (2020) |
| Follow-up (years) | 6.0 | 5.8 | 5.2 | 7.6 | 4.9 | 3.25 | 5.6 | 5.1 | 6.0 |
| No. of cases | 215 | 676 | 106 | 134 | 151 | 10283 | 88 | 217 | 142 |
| Mean ages (years) | 51.2 | 48-49 | NA | 50 | 47 | NA | 48 | 50 | 49 |

**Clinical T stage**
- cT₁₂ (100%)
- cT₂₋₄ (21.4%)
- cT₃₋₄ (57.5%)
- cT₃₋₄ (49.0%)
- cT₄₋₄ (50.1%)
- cT₁₋₂ (59.9%)
- cT₃₋₄ (40.1%)
- cT₁₋₂ (100%)
- cT₁₋₂ (100%)

**Clinical N stage**
- cN₀ (100%)
- cN₁ (79.4%)
- cN₁₋₂ (71.7%)
- cN₁₋₂ (47.8%)
- cN₂ (84.8%)
- cN₃ (100%)
- cN₄ (100%)
- cN₄ (75.6%)
- cN₄ (100%)

**ypT stage**
- ypT₀₋₂ (100%)
- ypT₀ (100%)
- ypT₀₋₁ (62.9%)
- ypT₀₋₁ (37.1%)
- ypT₀₋₂ (93.2%)
- ypT₀₋₂ (92.2%)
- ypT₀₋₂ (7.8%)
- ypT₁₋₂ (100%)

**ypN stage**
- ypN₀ (34.9%)
- ypN₀ (64.3%)
- ypN₁ (29.7%)
- ypN₁ (68.9%)
- ypN₁ (100%)
- ypN₁ (100%)
- ypN₁ (29.6%)
- ypN₁ (39.8%)
- ypN₂ (26.7%)
- ypN₂ (73.3%)

**pCR**
- pCR₁₀.₄ (100%)
- pCR₁₀.₄ (12.7%)
- pCR₁₀.₄ (100%)
- pCR₁₀.₄ (17.9%)
- pCR₁₀.₄ (100%)
- pCR₁₀.₄ (16.3%)
- pCR₁₀.₄ (27.3%)
- pCR₁₀.₄ (33.8%)

**PMRT**
- PMRT₈₂.₈ (82.8%)
- PMRT₆₇.₉ (80.2%)
- PMRT₆₉.₅ (82.6%)
- PMRT₆₉.₅ (69.5%)
- PMRT₭₁.₈ (71.8%)
- PMRT₮₇₆.₉ (85.2%)
- PMRT₮₉.₀ (59.0%)
- PMRT₮₇₇.₅ (77.5%)

**NAC regimens**
- A containing (91.2%)
- T containing (79.1%)
- A and T containing (70.2%)
- A containing (92%)
- T containing (38%)
- A-based (90.3%)
- T-based (9.7%)
- A-based (36.4%)
- T-based (6%)
- A and T (55.6%)
- A-based (25%)
- T-based (30.7%)
- A and T (5.7%)
- A-based (2.1%)
- T-based (15.5%)
- A and T (82.4%)

**LRR/LRFS**
- NA
- 10-yr LRR: PMRT vs non-PMRT in clinical stage I or II: 96.2% vs 87.7% (P=0.050)
- 10-yr LRR: PMRT vs non-PMRT in clinical stage III: 93.1% vs 83.9% (P=0.050)
- 5-yr LRR: PMRT vs non-PMRT: 96.9% vs 78.6% (P=0.020)
- 5-yr LRR: PMRT vs non-PMRT in high-risk group: 3.3% vs 1.7% (P=0.050)
- 5-yr LRR: PMRT vs non-PMRT in high-risk group: 21.8% vs 42.2% (P=0.031)

**DFS/RFS/PFS/DM/DMFS**
- 5-yr DFS: PMRT vs non-PMRT in ypT₀₋₂ N₀: 74.7% vs 73.3% (P=0.050)
- 5-yr DFS: PMRT vs non-PMRT in ypT₀₋₂ N₀: 87.9% vs 88.7% (P=0.028)
- 5-yr DFS: PMRT vs non-PMRT in ypT₀₋₂ N₀: 82.8% vs 84.1% (P=0.050)
- 5-yr DMFS: PMRT vs non-PMRT: 59.2% vs 81.5% (P=0.050)
- 5-yr DFS: PMRT vs non-PMRT: 92.9% vs 72.9% (P=0.050)
- 5-yr DFS: PMRT vs non-PMRT: 88.7% vs 72.4% (P=0.028)

**OS/CSS**
- 5-yr OS: 10-yr OS: 10-yr CSS: 10-yr OS: 5-yr OS: NA: NA: 5-yr OS:
| PMRT vs non-PMRT | PMRT vs non-PMRT | PMRT vs non-PMRT | PMRT vs non-PMRT | PMRT vs non-PMRT |
|------------------|------------------|------------------|------------------|------------------|
| **CSS** in cT1: | **CSS** in cT1: | **CSS** in cT1: | **CSS** in cT1: | **CSS** in cT1: |
| 85.5% vs 90.8% | 77.3% vs 87.7% | 93.3% vs 89.9% | 88.3% vs 84.8% | 96.1% vs 95% |
| **P < 0.010** | **P < 0.050** | **P < 0.019** | **P < 0.050** | **P < 0.010** |

**Conclusion**

PMRT didn't improve 5-yr DFS and 5-yr OS in cT1-2N+ breast cancer patients with ypT0-2N0 after NAC.

PMRT didn't decrease 10-yr LRR and didn't improve 10-yr CSS in cT1-2 patients after NAC.

PMRT didn't improve 10-yr LRFS and OS in clinical stage III patients after NAC, but significantly improve 10-yr LRR, DMFS, and OS in those of clinical stage III patients.

PMRT didn't improve 10-yr LRFS, DFS and OS in clinical stage II-III breast cancer patients with pN0 after NAC.

PMRT significantly improved 5-yr LRFS in cT1-2N1 patients who achieving ypT1-2N0 after NAC, but didn't improve 10-yr OS.

**Figures**

![Breast cancer patients receiving mastectomy from 2005–2017 (n=3055)](image)

Patients receiving neoadjuvant chemotherapy (NAC) before mastectomy (n=456)

Patients with cT1-2N,M0 stage before NAC (n=308)

Excluded:

1. NAC < 2 cycles (n=5)
2. ypT3-4 stage after NAC (n=6)
3. ypN + stage after NAC (n=10)

Final cohort
Study design. Abbreviations: NAC neoadjuvant chemotherapy, PMRT postmastectomy radiotherapy, cT clinical tumor size, cN clinical lymph node, ypT pathologic tumor size after neoadjuvant therapy, ypN pathologic lymph node after neoadjuvant therapy.

Figure 2
Kaplan-Meier survival analysis of (A) Disease-free survival and (B) Overall survival in ypT_{0-2}N_{0} PMRT and non-PMRT subgroups. Abbreviations: PMRT postmastectomy radiotherapy.

Figure 3
Kaplan-Meier survival analysis of (A) Disease-free survival and (B) Overall survival in cT_{1-2}N_{0} patients who achieve ypT_{0-2}N_{0} but without PMRT and cT_{1-2}N_{0} non-PMRT patients. Abbreviations: ypT pathologic tumor size after neoadjuvant therapy, ypN pathologic lymph node after neoadjuvant therapy, cT clinical tumor size, cN clinical lymph node.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarytable1.docx
- Supplementarytable2.docx