Postmastectomy radiotherapy after neoadjuvant chemotherapy in $cT_{1-2}N_{+}$ breast cancer patients: a single center experience and review of current literature

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Abstract

Purpose

Postmastectomy radiotherapy (PMRT) after NAC in breast cancer patients with initial clinical stage $cT_{1-2}N_+$, especially for those who achieved $ypT_{1-2}N_0$, is still controversial. This study was to evaluate the survival prognosis of $cT_{1-2}N_+$ 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 medical center, among whom 215 patients of $cT_{1-2}N_+$ 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) $cT_{1-2}N_+$ patients achieved $ypT_{0-2}N_0$ after NAC while 64.2% (138/215) of the patients remained nodal positive ($ypT_{0-2}N_+$). The 5-year DFS of $ypT_{0-2}N_0$ non-PMRT was 79.5% (95% confidence interval [CI] 63.4-95.6%). No statistically significant difference was observed between the $ypT_{0-2}N_0$ 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 $ypT_{0-2}N_0$ non-PMRT subgroup and $cT_{1-2}N_0$ subgroup (79.5% vs 93.3%, $p = 0.070$). By using Cox regression model in multivariate analyses of prognosis in $ypT_{0-2}N_+$ 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 ($ypT_{0-2}N_0$) indicates a sufficiently favorable prognosis, and PMRT might be omitted for $cT_{1-2}N_+$ breast cancer patients with $ypT_{0-2}N_0$ 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 T_{1-2} tumors with 1-3 positive lymph nodes remains widely controversial and is usually recommended for those $T_{1-2}N_1$ 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 $cT_{1-2}N_+$. 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 $cT_{1-2}N_+M_0$, and try to answer three relevant questions: 1) Is PMRT after NAC needed for patients presenting with $cT_{1-2}N_+$ disease who achieve $ypT_{0-2}N_0$? 2) Without PMRT, how about the prognosis of $cT_{1-2}N_+$ patients who achieve $ypT_{0-2}N_0$ compared to $cT_{1-2}N_0$ 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 $cT_{1-2}N_+$ 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), ypT_{3-4} 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 ($cT_{1\text{-}2}N_+$) 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 $cT_{1\text{-}2}N_+$ patients included were divided into two groups according to the pathological lymph nodes status of surgical specimen after NAC: $ypT_{0\text{-}2}N_+$ group or $ypT_{0\text{-}2}N_0$ 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 χ^2 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 $cT_{1\text{-}2}N_+$ 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 $cT_{1\text{-}2}N_+$ patients, 21.4% (46/215) and 78.6% (169/215) of the patients were in clinical T_1 and T_2 stages, respectively. After NAC followed by mastectomy, the primary tumor staging was ypT_0 in 18.6% (40/215), ypT_1 in 47.9% (103/215), and ypT_2 in 33.5% (72/215) of the patients. And the percentage of patients having ypN_0, ypN_1, $ypN_{2\text{-}3}$ 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 $cT_{1\text{-}2}N_+$ disease who achieve $ypT_{0\text{-}2}N_0$?

After NAC, 35.8% (77/215) $cT_{1\text{-}2}N_+$ patients achieved $ypT_{0\text{-}2}N_0$. In current clinical practice, it is still unclear whether PMRT after NAC would benefit the survival of those $cT_{1\text{-}2}N_+$ patients who achieved $ypT_{0\text{-}2}N_0$. In our study, 64.9% (50/77) of those $ypT_{0\text{-}2}N_0$ patients received PMRT while 35.1% (27/50) of whom didn't.

Most of the clinical and treatment characteristics between $ypT_{0\text{-}2}N_0$ 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 $ypT_{0\text{-}2}N_0$ PMRT subgroup and 7 (25.9%) in the non-PMRT subgroup had locoregional recurrence or distant metastasis. We further analyzed the recurrence patterns between $ypT_{0\text{-}2}N_0$ PMRT and non-PMRT subgroups, finding that the

locoregional recurrence was significantly more in $ypT_{0\text{-}2}N_0$ 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 $ypT_{0\text{-}2}N_0$ non-PMRT subgroup was 79.5% (95% confidence interval [CI] 63.4-95.6%). No statistically significant difference was observed between the $ypT_{0\text{-}2}N_0$ 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 $cT_{1\text{-}2}N_+$ patients who achieve $ypT_{0\text{-}2}N_0$ compared to $cT_{1\text{-}2}N_0$ patients?

Considering the non-inferior prognosis of $ypT_{0\text{-}2}N_0$ patients without PMRT, we further compared the survival of these $ypT_{0\text{-}2}N_0$ non-PMRT patients to those of $cT_{1\text{-}2}N_0$ 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 $ypT_{0\text{-}2}N_0$ non-PMRT group and $cT_{1\text{-}2}N_0$ group (79.5% vs 93.3%, p = 0.070). **(Figure 3A)** By the date of the last follow-up, no patient died in $cT_{1\text{-}2}N_0$ group. And the 5-years OS between $ypT_{0\text{-}2}N_0$ non-PMRT group and $cT_{1\text{-}2}N_0$ 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 $ypT_{0\text{-}2}N_+$: 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 $ypN_{2\text{-}3}$ was 1.98 and 4.19 times higher than that of ypN_1 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 $ypT_{0\text{-}2}N_+$ 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 systemically 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 literatures, nine studies[11-19] were found to report results comparable to our study. The summary of the literature search and a comparison of the nine studies to our results are presented in **Table 6**. Five out of nine studies presented with OS analysis, within which three study[13, 14, 18] found that PMRT didn't improve OS in cN_+ who achieving ypN_0 after NAC, while another two[12, 15] found that PMRT significantly improved OS in cN_+ patients after NAC, whatever achieving ypN_0 or still remaining ypN_+ patients. Besides the primary endpoint of OS, other endpoints (e.g. LRR, LRFS, DMFS, RFS) varies among the nine studies.

4. Discussion

Current prospective and retrospective data has provided evidence for recommending PMRT after NAC for breast cancer patients with $cT_{3\text{-}4}$, $cN_{2\text{-}3}$ or residual lymph node disease, as well as suggested omitting PMRT for $cT_{1\text{-}2}N_{0\text{-}1}$ patients who develop a pathologic complete response[20]. However, the efficacy of PMRT after NAC in breast cancer patients with initial clinical stage $cT_{1\text{-}2}N_+$, especially for those who achieved $ypT_{1\text{-}2}N_0$, is still largely unknown. In this study, we conducted a retrospective analysis of postmastectomy radiation therapy after neoadjuvant chemotherapy in $cT_{1\text{-}2}N_+$ breast cancer patients in our medical center. And our findings suggested that PMRT might not be necessary for $cT_{1\text{-}2}N_+$ patients with $ypT_{0\text{-}2}N_0$ after NAC.

In our study, most of the clinical and treatment characteristics between $ypT_{0\text{-}2}N_0$ PMRT and non-PMRT were with no difference, only except pCR and therapeutic ratio of trastuzumab for HER2+ patients. Patients in $ypT_{0\text{-}2}N_0$ 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 $ypT_{0\text{-}2}N_0$ 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 regimen is more related to the prognosis of the patients. Therapeutic ratio of trastuzumab for HER2+ patients in total $ypT_{0\text{-}2}N_0$ 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 $ypT_{0\text{-}2}N_0$ 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 $ypT_{0\text{-}2}N_0$ PMRT and non-PMRT group. And this result makes us more believe the favorable prognosis of $ypT_{0\text{-}2}N_0$ even without PMRT.

Moreover, it is interesting that the survival between $cT_{1\text{-}2}N_+$ patients who achieved $ypT_{0\text{-}2}N_0$ without PMRT and those of $cT_{1\text{-}2}N_0$ before NAC were with no significant difference. Although there were concerns that the lymph node status of $cT_{1\text{-}2}N_0$ might be downstaged, all the $cT_{1\text{-}2}N_0$ patients remained $ypT_{1\text{-}2}N_0$ after NAC. Patients of $T_{1\text{-}2}N_0$ stage without NAC didn't need PMRT according to current acknowledged PMRT guideline[6]. In our study, none of patients with $cT_{1\text{-}2}N_0$ received PMRT after NAC and the 5-years DFS and OS were quite favorable of these patients. Therefore, considering the comparable survival between

$cT_{1-2}N_+$ patients who achieved $ypT_{0-2}N_0$ without PMRT and those of $cT_{1-2}N_0$, we speculate that patients of $cT_{1-2}N_+$ 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 $cT_{1-2}N_+$ patients who have nodal pCR after NAC. The NSABP51 trial is a randomized phase III clinical trial evaluating PMRT in $cT_{1-3}N_1$ 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 $cT_{1-4}N_+$ breast cancer patients who achieved pCR after NAC, PMRT didn't improve 10-yr LRR in clinical stage I-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 Scodan's (2012)[13] and Shim's (2014)[14] studies demonstrated that PMRT didn't improved 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_+ patients, they found that PMRT significantly improved 5-years OS in cT1-3N1 patients after NAC, whatever achieving ypN_0 or still remaining ypN_+ patients. However, they had 40.1% of cT_3 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 $cT_{1-2}N_+$ patients who develop ypN_0 after NAC. Caoa et al[16] analyzed a small population of 88 $cT_{1-2}N_1$ cases. They found that PMRT significantly improved 5-years LRFS in $cT_{1-2}N_1$ 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 $cT_{1-2}N_+$ 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 $cT_{1-2}N_+$ 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 $cT_{1-2}N_1$ breast cancer patients and found that PMRT didn't improve OS in $cT_{1-2}N_1$ 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 $cT_{1-2}N_+$ breast cancer who achieve $ypT_{0-2}N_0$ after NAC. And without PMRT, the prognosis of $cT_{1-2}N_+$ patients who achieve $ypT_{0-2}N_0$ after NAC wasn't significantly different from that of $cT_{1-2}N_0$ patients. Therefore, PMRT might not be necessary for $cT_{1-2}N_+$ breast cancer patients with $ypT_{0-2}N_0$ 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, H Deng and Y Jin collected the all the clinical data. M Luo and HH Chen performed the data analysis. H Deng, Y Jin, K Zhang and H Ma 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.

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Tables

Table 1 Clinical characteristics of all the patients

	All patients ($cT_{1-2}N_+M0$)	
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 $ypT_{0-2}N_0$ PMRT and non-PMRT subgroups

	$ypT_{0-2}N_+$					$ypT_{0-2}N_0$				
	PMRT		non-PMRT		*P* value	PMRT		non-PMRT		*P* value
Variable	n=128	%	n=10	%		n=50	%	n=27	%	
Age										
Mean	51.3		53.1			51.4		50.4		
Range	30-75		39-69		1.000	25-73		33-65		0.996
<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					-					-
	92/92	100.0	6/6	100.0		20/20	100.0	10/10	100.0	
HER2-targeted therapy/HER2 status					1.000					**0.009**
	21/40	50.0	3/5	60.0		18/25	72.0	2/11	18.2	

ypT pathologic tumor size after neoadjuvant therapy, ypN pathologic lymph node after neoadjuvant therapy, PMRT postmastectomy radiotherapy, HER2 human epidermal receptor 2, TNBC triple negative breast cancer, pCR pathological complete response.

Table 3 Recurrence patterns between $ypT_{0\text{-}2}N_0$ PMRT and non-PMRT subgroups

	$ypT_{0\text{-}2}N_0M_0$		
Initial recurrent sites	PMRT	non-PMRT	*P value*
	(n=50)	(n=27)	
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.

Table 4 Univariate analysis of DFS and OS in $ypT_{0\text{-}2}N_{+}$ PMRT subgroup

		DFS		OS	
Variable	No. of patients	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age			0.973		0.739
<40	13	ref.		ref.	
≥40	115	1.020 (0.313-3.33)		1.410 (0.187-10.62)	
Clinical T stage			0.380		0.125
1	32	ref.		ref.	
2	96	1.420 (0.649-3.108)		3.160 (0.726-13.756)	
ypT stage			0.174		0.168
0-is	14	ref.		ref.	
1	68	0.666 (0.348-1.272)		0.681 (0.288-1.608)	
2	46	1.550 (0.905-2.655)		2.001 (0.918-4.36)	
ypN stage			**0.043**		**0.011**
1	62	ref.		ref.	
2-3	66	1.981 (1.023-3.837)		4.189 (1.387-12.648)	
Estrogen receptor status			**0.001**		**0.010**
Positive	92	ref.		ref.	
Negative	31	3.037 (1.572-5.867)		3.329 (1.337-8.29)	
HER2 status			0.166		0.194
Positive	40	ref.		ref.	
Negative	72	0.613 (0.307-1.224)		0.532 (0.205-1.379)	
TNBC			**0.024**		**0.041**
Yes	12	ref.		ref.	
No	112	0.387 (0.17-0.882)		0.313 (0.103-0.955)	
Molecular subtype			**0.020**		**0.030**
Luminal A	28	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					
			0.238		0.078
Anthracycline containing	118	ref.		ref.	
Without anthracycline	11	1.780 (0.683-4.642)		2.797 (0.892-8.771)	
			0.582		0.807
Taxane containing	99	ref.		ref.	
Without Taxane	30	0.816 (0.395-1.684)		1.148 (0.379-3.477)	
			0.23		0.371
Anthracycline and Taxane containing	89	ref. (0.346-1.291)		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 $ypT_{0\text{-}2}N_{+}$ PMRT subgroup

		DFS		OS	
Variable	No. of patients	HR (95% CI)	*P* value	HR (95% CI)	*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	Huang EH, et al[11]	McGuire SE, et al[12]	Le Scodan R, et al[13]	Shim SJ, et al[14]	Rusthoven CG, et al[15]	Cao L, et al[16]	Wang X, et al[17]	Wang Q, et al[18]
(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	cT_{1-2} (100%)	cT_{1-2} (21.4%) cT_{3-4} (78.6%)	cT_{1-2} (33%) cT_{3-4} (67%)	cT_{1-2} (50.7%) cT_{3-4} (49.3%)	cT_{1-2} (49.0%) cT_{3-4} (51.0%)	cT_{1-2} (59.9%) cT_3 (40.1%)	cT_{1-2} (100%)	cT_{1-2} (100%)	cT_{1-2} (100%)
Clinical N stage	cN_+ (100%)	cN_+ (79.4%)	cN_+(71.7%)	cN_+(47.8%)	cN_+(84.8%)	cN_+ (100%)	cN_+ (100%)	cN_+ (75.6%)	cN_+(100%)
ypT stage	ypT_{0-2}(100%)	ypT_{0-2} (86.1%) ypT_{3-4} (12.6%)	ypT_0 (100%)	NA	ypT_{0-1} (62.9%) ypT_{2-4} (37.1%)	NA	ypT_{0-2} (93.2%) ypT_{3-4} (2.2%)	ypT_{0-2} (92.2%) ypT_{3-4} (7.8%)	ypT_{1-2} (100%)
ypN stage	ypN_0 (34.9%) ypN_+ (64.3%)	ypN_0 (29.7%) ypN_+ (68.9%)	ypN_0 (100%)	ypN_0 (100%)	ypN_0 (100%)	ypN_0 (29.6%) ypN_+ (70.4%)	ypN_0 (60.2%) ypN_+ (39.8%)	ypN_0 (26.7%) ypN_+(73.3%)	ypN_0 (100%)
pCR	pCR：10.4%；	pCR ：12.7%；	pCR：100%；	pCR ：17.9%；	NA	pCR：16.3%；	pCR：27.3%；	NA	pCR：33.8%；
PMRT	PMRT：82.8%；	PMRT ：80.2%；	PMRT ：67.9%；	PMRT ：58.2%；	PMRT ：69.5%；	PMRT ：71.8%；	PMRT ：85.2%；	PMRT ：59.0%；	PMRT ：77.5%；
NAC regimens	A containing(91.2%) T containing(79.1%； A and T containing (70.2%；	NA	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%；	NA	A-based (25%) T-based (30.7%； A and T (5.7%；	NA	A-based (2.1%) T-based (15.5%； A and T (82.4%；
LRR/LRFS	NA	10-yr LRR： PMRT vs non-PMRT in cT_1: 8 % vs 0 % （*P*： 0.050); in cT_2: 10 % vs 7 % （*P*： 0.050)	10-yr LRR： PMRT vs non-PMRT in clinical stage I or II: 0 % vs 0 % （*P*：0.050); in stage III: 7.3 % vs 33.3 % （***P*=0.04**)	10-yr LRFS： PMRT vs non-PMRT: 96.2 % vs 86.8 % （*P*：0.050)	10-yr LRFS： PMRT vs non-PMRT: 98.1 % vs 92.3 % （*P*：0.050)	NA	5-yr LRFS： PMRT vs non-PMRT: 96.9 % vs 78.6 % （***P*=0.020**)	5-yr LRR: PMRT vs non-PMRT in low-risk group: 3.3% vs 1.7% （*P*：0.050); in high-risk group: 21.8% vs 42.2% (***P*=0.031**)	5-yr LRFS： PMRT vs non-PMRT: 94.5 % vs 90.1 % （*P*：0.050)
DFS/RFS/PFS /DM/DMFS	5-yr DFS： PMRT vs non-PMRT in $ypT_{0-2}N_0$: 74.7 % vs 73.3 % （*P*：0.050)	NA	10-yr DMFS： PMRT vs non-PMRT in stage III: 40.7 % vs 87.9 % （***P*=0.01**)	NA	10-yr DFS： PMRT vs non-PMRT: 91.2 % vs 83 % (*P*：0.050)	NA	5-yr DMFS： PMRT vs non-PMRT: 92.9 % vs 81.5 % （*P*：0.050) 5-yr DFS： PMRT vs non-PMRT: 92.9 % vs 72.9 % （*P*：0.050)	NA	5-yr RFS： PMRT vs non-PMRT: 88.7 % vs 72.4 % （***P*=0.028**)
OS/CSS	5-yr OS：	10-yr	10-yr OS：	10-yr OS：	10-yr OS：	5-yr OS：	NA	NA	5-yr OS：

	PMRT vs non-PMRT in $ypT_{0-2}N_0$: 85.5 % vs 90.8 % (*P*=0.050)	CSS： PMRT vs non-PMRT in cT_1: 92 % vs 80 % (*P*=0.050)； in cT_2: 66 % vs 56 % (*P*=0.050)	PMRT vs non-PMRT in stage III: 77.3 % vs 33.3 % (*P*=0.01)	PMRT vs non-PMRT: 77.2 % vs 87.7 % (*P*=0.050)	PMRT vs non-PMRT: 93.3 % vs 89.9 % (*P*=0.050)	PMRT vs non-PMRT in ypN_0: 88.3% vs 84.8% (*P*=0.019); in ypN_+: 74.1% vs 70.9% (*P* < 0.010)			PMRT vs non-PMRT: 96.1 % vs 95 % (*P*=0.050)
Conclusion	PMRT didn't improve 5-yr DFS and 5-yr OS in $cT_{1-2}N_+$ breast cancer patients with $ypT_{0-2}N_0$ after NAC.	PMRT didn't decrease 10-yr LRR and didn't improve 10-yr CSS in cT_{1-2} patients after NAC.	PMRT didn't improve 10-yr LRR in clinical stage I-II patients with pCR 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 and OS in clinical stage II-III patients with pN0 after NAC.	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 OS in $cT_{1-3}N_1$ patients after NAC, whatever achieving ypN0 or still remaining ypN+ patients.	PMRT significantly improved 5-yr LRFS in $cT_{1-2}N_1$ patients after NAC, but didn't affect 5-yr DMFS and DFS. OS is not evaluated.	PMRT didin't decrease 5-yr LRR in $cT_{1-2}N_{0-1}$ patients with low risk, but significantly decrease 5-yr LRR in those with high risk (risk factors including ypN stage, histologic grade and LVI).	PMRT significantly improved 5-yr RFS in $cT_{1-2}N_1$ patients who achieving $ypT_{1-2}N_0$ after NAC, but didn't improve 5-yr LRFS and OS.

PMRT postmastectomy radiotherapy, NAC neoadjuvant chemotherapy, NA not applicable, cT clinical tumor size, cN clinical lymph node, ypT pathologic tumo neoadjuvant therapy, ypN pathologic lymph node after neoadjuvant therapy, pCR pathological complete response, A anthracycline, T Taxane, 5-yr 5-year, 10-y local regional recurrence, LRFS local recurrence free survival, DFS disease-free survival, DMFS distant metastases-free survival, RFS recurrence-free survival, C survival, CSS cause-specific survival.

Figures

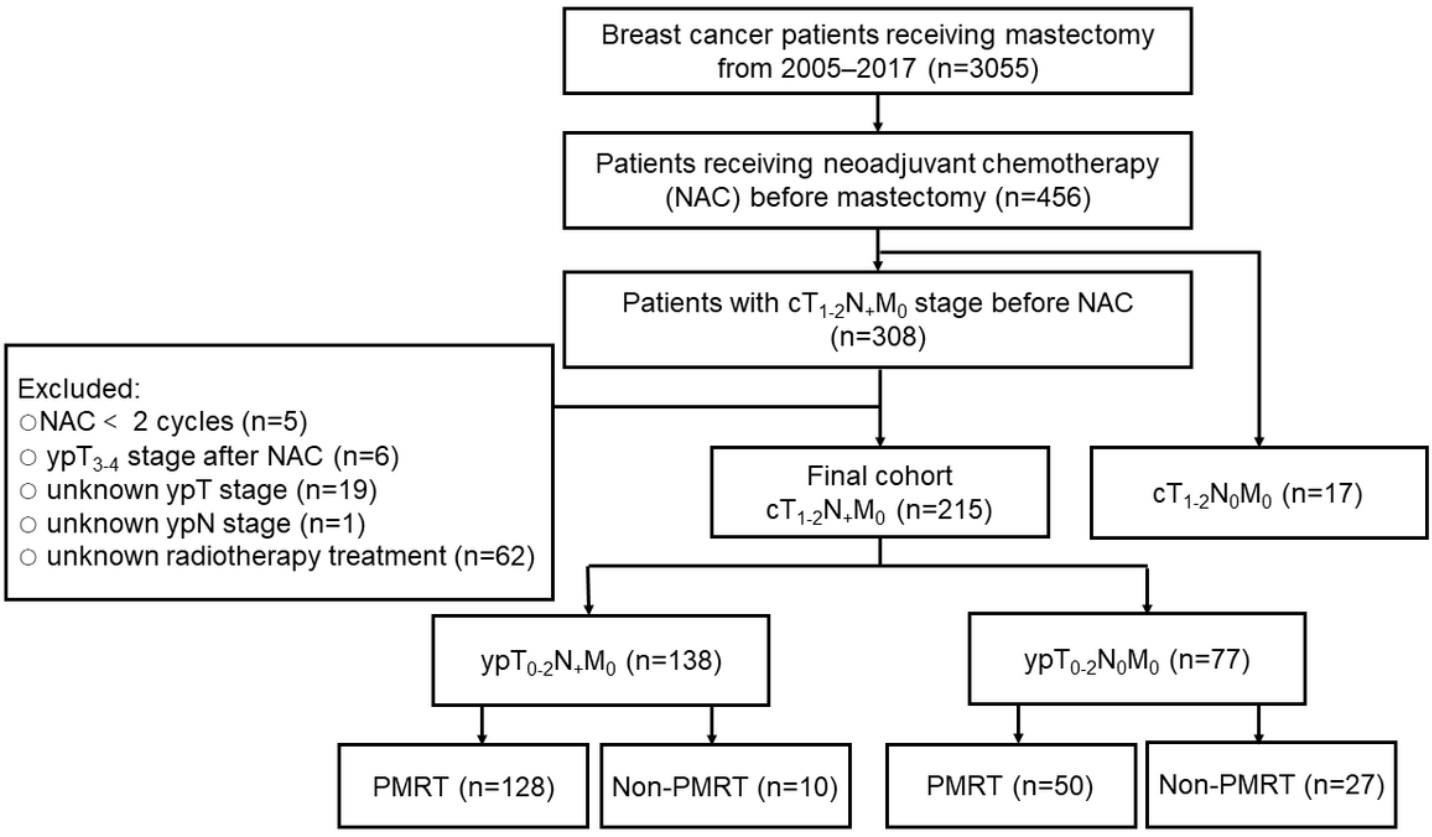

Figure 1

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 $ypT_{0\text{-}2}N_0$ PMRT and non-PMRT subgroups. Abbreviations: PMRT postmastectomy radiotherapy

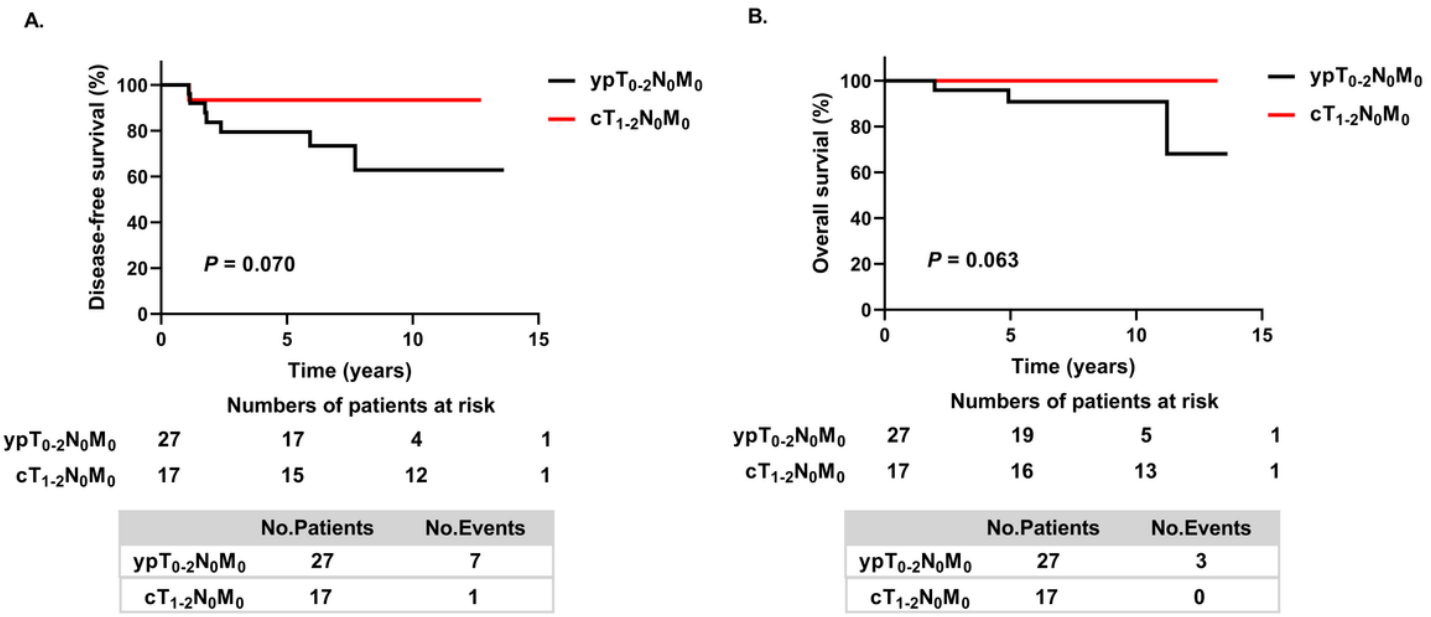

Figure 3

Kaplan-Meier survival analysis of (A) Disease-free survival and (B) Overall survival in $cT_{1\text{-}2}N_+$ patients who achieve $ypT_{0\text{-}2}N_0$ but without PMRT and $cT_{1\text{-}2}N_0$ 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

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- Supplementarytable1.docx
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