Neoadjuvant chemotherapy or surgery: which is the optimal initial option for T3 breast cancer (> 5 cm) —a real world research from Chinese society of clinical oncology breast cancer database

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Abstract

Background: The objectives were to explore the real world treatment of T3 breast cancer (maximum diameter of tumor bigger than 5 centimeters). **Materials and Methods:** We selected T3 breast cases diagnosed from 2011 to 2017 in the CSCO BC database. These cases were categorized into two groups: non-NAC group and NAC group. Adjusted hazard ratios for known predictors of event free survival (EFS) using Kaplan-Meier and Cox proportional hazards regression. **Results:** The study included 868 patients: 49.0%(425/868) of patients chose NAC after diagnosis, 51.0%(443/868) chose surgery as their initial therapeutic strategy(non-NAC group). Compared with non-NAC group, patients in NAC group were correlated with clinical positive lymph nodes, hormonal receptor(HR) negative and human epidermal receptor growth factor 2(HER2) positive. For non-NAC group, only 87.1%(386/443) of patients were pathologic T3 after surgery, the overestimation of clinical examination of tumor lesion was 12.9% (57/443). In addition, there was no significance of EFS between the NAC group and non-NAC group(HR=0.82, 95%CI: 0.64-1.05). However, for T3 breast cancer patients with positive lymph nodes, HR negative and HER2 positive tumors, the NAC group had a better survival than the non-NAC group. Cox proportional analysis showed that lymph node negative, HER2 negative status and neoadjuvant chemotherapy were associated with a longer survival time. **Conclusion:** As the initial option for T3 breast cancer patients with positive lymph nodes, HR negative and HER2 positive tumors, neoadjuvant chemotherapy is the first therapy.

1. Introduction

Neoadjuvant chemotherapy (NAC) was initially aimed to downstage locally advanced or make inoperable breast cancer operable. It was then extended to early breast cancer to get breast conserving surgery. Now it has been widely accepted in aggressive subtypes like stage II or III, HER2 positive or triple-negative breast cancer, particularly for large tumor lesions [1].

NAC has provided one more therapy option for T3 patients, even though there is no evidence to prove whether initially NAC is better than initially surgery or not. For one thing, early eradication of large tumor lesion might be conducive to lighten tumor load and to decrease the risk of metastatic spread for T3 patients. For another, NAC might also provide useful information about the drug sensitivity to different regimens, helping to guide subsequent therapy selection. Thus, we are in urgent need of clinical evidence in this type of breast cancer patients.

Recently, the American Food and Drug Administration (FDA) has regard evidence from real world study (RWS) and from randomized clinical trial (RCT) as complementary. FDA is now working hard to collect data from electronic health records, billing data and so on[2]. In the last past two years, we have been committed to establishing the Chinese breast cancer database founded by Chinese society of clinical oncology of breast cancer (CSCO BC). Afterwards,we used these real world data to explore the disparities of trastuzumab use in resource-limited or resource-abundant regions and its survival benefit on HER2 positive breast cancer in China (CSCO BC RWS 15001)[3]. Hence, we were going to use these data to

explore the real world treatment of T3 patients, and to evaluate whether NAC is better than surgery as the initial option for T3 breast cancer. (CSCO BC RWS 17001)

2. Materials And Methods

Patients and population

From December 2015, we started to establish the first multicenter database funded by Chinese society of clinical oncology of breast cancer (CSCO BC database). Until November 2017, there were more than 17,000 patient cases in CSCO BC database. These data were collected from more than 11 hospitals in 9 provinces across east of China. To be eligible, studies had to meet these inclusion criteria: early stage invasive breast cancer (EBC) diagnosed from 2011 to 2017; maximum diameter of tumor bigger than 5 centimeters (T3) no matter what kind of clinical examination; clearly clinical or pathological axillary nodes staging; receiving either NAC or breast cancer surgery as their initial therapeutic strategies.

Patients received NAC as their initial therapy were required to receive at least 2 cycles of chemotherapy. Either breast conserving surgery or mastectomy should be performed by these received no NAC. Patients with borderline, unknown, or missing information for treatment were excluded.

Outcome measures

The demographic and clinical characteristics were summarized and compared between the two groups, defined by NAC (non-NAC group, or NAC group). The primary endpoint of this study is event free survival (EFS). We calculated EFS as the interval from randomization to the earliest occurrence of disease progression resulting in inoperability, loco regional recurrence (after NAC), distant metastasis, or death from any cause. Patients alive without an event as of the analysis cutoff date were censored at last study follow-up date. The second endpoint is the surgery methods especially the breast conserving rates in two groups.

Statistical analysis

In this real world study, we compared the characteristic differences between the two groups using Person's test. We also used Kaplan-Meier and Cox proportional hazards regression to estimate hazard ratio (HR) and 95% confidence interval (CI) for the relationship between different initial therapeutic strategies and EFS. P values ≤ 0.05 was considered statistically significant; all tests were two-sided. Statistical analysis was carried out using SPSS 20.0.

3. Results

Demographic Characteristics

We collected 868 cases diagnosed as clinical T3 breast cancer from CSCO BC database according to the inclusion and exclusion criteria (Figure 1). Table 1 showed clinical and demographic characteristics of

patients. Only 49.0% (425/868) of patients chose NAC after diagnosis, the other part (51.0%) chose surgery as their initial therapeutic strategy (non-NAC group). Patients in NAC group had more clinical positive lymph nodes (82.1% vs. 55.1%, $p=0.001$), more HER2-positive tumors (54.1% vs. 44.0%, $p=0.05$) and hormonal receptor (HR) negative tumors (23.8% vs. 16.3%, $p=0.05$) compared with non-NAC group. (Table 1).

Treatment

There was no difference in surgery category between two groups. Most patients in two groups chose mastectomy and axillary lymph node dissection (ALND). Less than 5% of patients chose breast conserving surgery in both groups. In addition, 168(39.5%) patients in NAC group and 343(77.4%) in non-NAC group underwent adjuvant chemotherapy. Overall, 70 out of 425 patients (16.5%) achieved breast pCR (Table 2).

Overestimation and underestimation of tumor lesion

We investigated the accuracy rate between iconography and histopathology. To avoid the influence from chemotherapy, we just included these patients in non-NAC group as they all received surgery at first. For these patients, actually there were 573 patients diagnosed as T3 clinically or pathologically or both. However, 77.3% (443/573) of patients were diagnosed as clinical T3. 130 patients were diagnosed as pathologically T3 but not be clinical T3. The underestimation of clinical examination was as high as 22.7% (85/573). For these 443 patients, only 87.1% (386/443) of patients were pathologic T3 after surgery, the overestimation of clinical examination was 12.9% (57/443).

Survival estimates

We analyzed the difference of survival in these two groups. We recorded 257 events among these patients. For these who had NAC first, the median time for EFS was 55 months, while in non-NAC group, the median time was 43 months, with no significance between the two groups (HR=0.82, 95% CI: 0.64-1.05) (Figure 2A). Besides, we found for these clinical lymph nodes negative or HR positive or HER2 negative patients, they had a prior survival than the other (Figure 2B, C and D)

However, is it the similar for all T3 breast cancer people to choose neoadjuvant chemotherapy or surgery as the initial option for prognosis? Then we analyzed the EFS of different subgroups. Specifically, we found in positive lymph nodes group, the NAC group had a better survival than the non-NAC group (Figure 3B). However, in negative lymph nodes group, the difference in EFS was not significant in NAC and non-NAC group (Figure 3A). In addition, in HR negative and Her2 positive group, the EFS curve showed an advantage with the NAC group than non-NAC group (Figure 3C and 3F). However, in negative lymph nodes group, the difference in EFS was not significant in NAC and non-NAC group (Figure 3D and 3E).

Cox proportional models were used to assess the clinicopathological factors related to prognosis (Table 3). Lymph node metastasis, Her2 status and neoadjuvant chemotherapy were found to be an independent poor prognostic factor of survival in the T3 breast cancer patients. Specifically, Lymph node

negative, HER2 negative status and neoadjuvant chemotherapy were associated with a longer survival time.

In other words, for T3 breast cancer patient who had positive lymph nodes and her2 positive tumors, these patients should choose neoadjuvant chemotherapy. However, for T3 breast cancer patient who had negative lymph node and her2 negative tumors, these patients either should choose neoadjuvant chemotherapy or surgery as the optimal initial therapy.

4. Discussion

There have been several studies about the large operable or locally T3 breast cancer and its survival [4]. However, we have little literature on comparison of survival between NAC and non-NAC groups in T3 patients. In this real world research, we found for clinical T3 patients there were more patients taking surgery as their initial therapy other than neo-adjuvant chemotherapy. The major operation is modified radical mastectomy even if they have had neoadjuvant chemotherapy. The inconsistency rate between imaging examination and histopathologic analysis has affected the following therapies. Moreover, patients with aggressive subtypes (lymph node positive, HER2 positive, HR negative) showed inferior outcome in DFS compared with these mild ones. We can witness the improvements in patients received neoadjuvant chemotherapy as there were more aggressive subtypes in NAC group.

Many researches have tried to explore whether imaging modalities such as magnetic resonance imaging, sonography, and mammography are as accurate at predicting breast tumor size as histopathologic analysis of resected tumors[5]. However, we paid less attention to the impact of medical resources on breast cancer. Although the number of primary health-care professionals is increasing recently in China, the regional distribution of health-care doctors and medical equipment is still uneven [6]. For example, only a small part of patients received all the imaging examinations to evaluate the dimension of tumor lesions. Most of patients would receive biopsy or surgery after a routine ultrasound examination, let alone a simple physical examination. There is no doubt that different imagings have their own characteristics and all these have been recommended by Chinese guideline [7]. The irrational use of imagings contributed to the high proportion of overestimation and underestimation.

In this study, we found less than 5% of patients choose breast conserving surgery neither received NAC or not, at odds with other literature[8]. For these in non-NAC group, the low proportion of BCS is appropriate as the high burden of tumor lesion. Nevertheless, for these received NAC, it deserves further discussion as the main rationale for NAC is to down-staging the cancer. This down-staging was initially to convert inoperable patients to operable and later to increase rates of breast conservation in patients initially deemed mastectomy only candidates[9]. However, we did not find such changes in this study. In some cases, such proportion may be appropriate, because patients with poor financial status must save precious resources to continue their costly and lasting therapies especially for these T3 breast cancer patients[3]. Although it has been proved that breast conserving surgery plus radiotherapy is as effective as mastectomy, sometimes better[10], the additional high price of radiotherapy, the old fashioned

aesthetic concept and the complex breast conserving technology in China all contributed to the low rate of BCS. Besides, there is no rigorous randomized clinical trials (RCT) to prove the survival benefit of BCS at present.

Although the latest guideline of American society of clinical oncology indicated no SLNB should be performed in large or locally advanced invasive breast cancers[11], we can also find more than 10% of patients underwent SLN, not to mention some were clinical lymph nodes positive patients. Some trials has explored the feasibility of SLNB after NAC with T0-4, N1-2, M0 patients, and has found an acceptable false negative rate (9.8%) when combined normal axillary ultrasound with more than two SLNs removed or some other methods[12, 13], it is not widely accepted by experts in China. Under such circumstance, radical lymph node dissection is deemed necessary when lymph nodes are clinically positive after NAC. However, when lymph nodes are clinically negative after NAC, although SLNB appears a reasonable compromise between axillary lymph node dissection and no surgery at all, we still encouraged more clinical trials due to the little evidence of survival to SLN alone[14].

Neoadjuvant chemotherapy, compared to conventional adjuvant therapy, does not seem to improve the overall survival of patients with breast cancer. Indeed, several RCTs have demonstrated similar outcomes, in terms of DFS and overall survival, between NAC and adjuvant chemotherapy in patients with breast cancer[15]. A recent meta-analysis[16] found NAC to be associated with a higher frequency of local recurrence than was the same chemotherapy started after surgery due to the increased BCS rates. Reassuringly, the increase in local recurrence was not associated with any significant increase in distant recurrence or breast cancer mortality, which indirectly supported the low rate of BCS in real world. As the RCTs have indicated the scientific evidence about the safety and efficacy of NAC for T3 breast cancer, we used real world evidence to investigate the survival benefit of NAC to T3 patients[2]. In our study, there were little survival benefit gained from NAC, comparable to those in the pivotal randomized controlled trials[17]. However, patients received NAC were more likely to have lymph node positive with aggressive subtypes (HER2-positive or hormonal receptor negative). These subtypes are the major recurrence risks for patients[18].

From this prospective, NACT does moderately reduce distant recurrence compared with the same chemotherapy given postoperatively. Although for all T3 breast cancer, there was no difference of EFS in NAC group and surgery group. In this study, we find in T3 breast cancer patient who had lymph node positive, HE R2 positive or HR negative tumors, NAC can also improve the survival. In multivariate analysis, Lymph node metastasis, Her2 status and neoadjuvant chemotherapy were found to be an independent poor prognostic factor of survival in the T3 breast cancer patient. As the pathological and molecular features of the primary tumor are getting more and more importance in the decision-making process, once we find T3 breast cancer patients with these risks, like lymph node positive, HER2 positive or HR negative, we will recommend neoadjuvant chemotherapy rather than surgery first.

There were several limitations in this study. First, we selected these data from 17,000 patient cases in CSCO BC database. However, this database has expanded to more than 34,000 cases now (until Jan 1,

2018). The allure of analyzing existing data may lead to flawed conclusions, and the survival benefit might be improved if data expended. Second, the regimens and courses of neoadjuvant or adjuvant therapy were not taken into consideration, which would be obscure the association between NAC and survival if different regimens were necessary to meaningfully affect long-term outcomes. Third, the incomplete data of pathologic complete remission set measures to our further exploration. The number of patients in this group were too small to draw conclusions.

The importance of NAC should be taken seriously. In next step, we will set a randomized clinical trial to compare NAC with adjuvant chemotherapy. In real world study, we will also explore the survival benefit in different molecular subtypes. Neither RCT nor RWS could be overlooked. We will combine these two methods to explore the optimal scheme to breast cancer patients.

5. Conclusion

As the initial option for T3 breast cancer patients with positive lymph nodes, HR negative and Her2 positive tumors, neoadjuvant chemotherapy is the first therapy. For T3 breast cancer patient who had negative lymph node and her2 negative tumors, these patients either should choose neoadjuvant chemotherapy or surgery as the optimal initial therapy.

Declarations

Authors' contribution

Zefei Jiang contributed to design the manuscript.: Haibo Wang, Jianbin Li ,Jianguo Zhang, Zhenzhen Liu, Cuizhi Geng, Feng Jin, Peifen Fu, Yongmei Yin, Zhimin Fan, Haiqing Zhang, Zefei Jiang contributed to the provision of study material or patients. Haibo Wang, Jianbin Li ,Gang Nie contributed to the collection and/or assembly of data. Jianbin Li, Meng Lv, Yan Mao contributed to the data analysis and interpretation. Haibo Wang, Jianbin Li contributed to the manuscript writing. Haibo Wang, Zefei Jiang contributed to the final approval of manuscript.

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Availability of data and materials

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the affiliated hospital of Qingdao University. Informed consent was obtained from all individual participants included in the study.

Consent for publication

Informed consent for publication was obtained.

Competing interests

The authors declare that they have no competing interests

Acknowledgements

Not applicable.

Data Availability

All research data are available and will be provided on request to the corresponding author.

Conflicts of Interest

The authors have stated that they have no conflict of interest.

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Tables

Table 1 Clinical characteristics of two groups

Variable	NAC n (%)	Surgery n (%)	Total n (%)	P
No. of patients	425(49.0)	443(51.0)	868(100)	
Age at diagnosis of the primary tumor (years old)				0.445
≤ 45	128(30.1)	123(27.8)	251(28.9)	
> 45	297(69.9)	320(72.2)	617(71.1)	
Menopause				0.590
Premenopause	161(37.9)	160(36.1)	321(37.0)	
Postmenopause	264(62.1)	283(63.9)	547(63.0)	
Lymph node				0.000
Negative	76(17.8)	199(44.9)	275(31.7)	
Positive	349(82.1)	244(55.1)	593(68.3)	
HR status				0.006
Negative	101(23.8)	72(16.3)	173(19.9)	
Positive	319(75.1)	363(81.9)	682(78.6)	
Unknown	5(1.2)	8(1.8)	13(1.5)	
Her 2 status				0.007
Negative	171(40.2)	213(48.1)	384(44.2)	
Positive	230(54.1)	195(44.0)	425(50.0)	
Unknown	24(5.7)	35(7.9)	59(5.8)	

Table 2 Treatment of two groups

Variable	NAC n (%)	Surgery n (%)	Total n (%)	P
No. of patients	425(49.0)	443(51.0)	868(100)	
Surgery category				0.665
Mastectomy	376(88.5)	413(93.2)	789(89.1)	
Breast conserving surgery	14(3.3)	18(4.1)	32(3.7)	
Unknown	35(8.2)	12(2.7)	47(5.4)	
Axillary lymph node surgery				0.080
SLNB	105(24.7)	89(2.0)	194(22.3)	
ALND	311(73.2)	351(79.2)	662(76.3)	
Unknown	9(2.1)	3(0.7)	12(1.4)	
PCR status				
Yes	70(16.5)	/	/	
No	336(79.1)	/	/	
Unknown	19(4.5)	/	/	
Adjuvant Chemotherapy				0.000
Yes	168(39.5)	343(77.4)	512(59.0)	
No	257(60.5)	100(22.6)	357(41.0)	

Table 3 Multivariate analysis of EFS in T3 breast cancer cases

Factor	HR	p	95%
Lymph node			
Negative	0.575	0.001	0.417-0.791
Positive	Referent		
HR			
Negative	1.143	0.364	0.857-1.525
Positive	Referent		
Her 2 status			
Negative	0.553	0.000	0.420-0.729
Positive	Referent		
Neoadjuvant Chemotherapy			
No	1.516	0.002	1.168-1.969
Yes	Referent		

Figures

Figure 1

Cohort selection diagram. The pathologically confirmed invasive breast cancer diagnosed between 2011 and 2017 were identified from the CSCO BC database and categorized into the following two groups: NAC and non-NAC group.

Figure 3

Survival for T3 patients in real world. (A): EFS in NAC and surgery group ;(B): EFS in LN(-) and LN(+) group; (C) EFS in HR(-) and HR(+) group; (D) EFS in Her2(-) and Her2(+) group. Abbreviations: CI, confidence interval; EFS, event-free survival. LN(-), lymph node negative; LN(+), lymph node positive.

Figure 5

Survival for T3 patients of different subgroup in real world. (A, B): EFS of NAC and surgery group in T3 patients with lymph node negative (LN(-)) and lymph node positive (LN(+)) (C,D): EFS of NAC and surgery group in T3 patients with HR negative (HR-) and positive (HR+) tumors. (E, F) EFS of NAC and surgery group in T3 patients with Her2 negative (Her2-) and positive (Her2+) tumors.