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Comparison of excised breast volume, re-excision rate and margin positivity in breast-conserving surgery in breast cancer patients using and not using neoadjuvant chemotherapy

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Ethics Committee Approval
Approval for this study was granted from Gaziosmanpasa Training and Research Hospital Ethics Committee for Clinical Studies in March 2021 (reg:251).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: One of the purposes of using neoadjuvant chemotherapy (NAC) is to evaluate the patients according to tumor-to-gland ratio, save them from mastectomy by reducing tumor dimension, and get more beautiful results cosmetically with less volume excision during breast-conserving surgery (BCS). Is it possible to achieve the goal of less volume excision after NAC? We aimed to compare the excised volume with BCS, margin positiveness and re-excision rates between the patients who received NAC and the ones who didn't receive NAC in patients with breast cancer and to calculate the increase in BCS performability with NAC.

Methods: Among 306 patients diagnosed with breast cancer between 2013 and 2021 at Gaziosmanpasa Training and Research Hospital, 105 patients who underwent BCS were included in this retrospective cohort study. Excised breast volume, surgical margin positiveness, re-excision and mastectomy rates were retrospectively compared in breast cancer patients underwent BCS with and without NAC. The patients who received BCS following NAC were named the primary chemotherapy (PC), and the patients whose treatment was initiated with BCS were named the primary surgery (PS) groups.

Results: BCS was performed to 105 breast cancer patients, of which 28 (26.7%) received NAC, and 77(73.7%) started the treatment with surgery. There were no significant differences between the PC and PS groups with respect to excision volume (755.86 (725.69) and 709 (637.36), P=0.822). Re-excision was more common in PS than in the PC group (39.0% vs 10.7%, P=0.008). Fourteen patients who were candidates for mastectomy at the beginning, became eligible for BCS by receiving NAC, which caused a 15.38% increase in BCS applicability. Surgical margin positivity was seen in only 3 patients, which is why a statistical comparison wasn't made.

Conclusions: Although the tumor size was higher in the PC group, the excised breast volume did not show a significant difference between the two groups. PC decreased the re-excision rates in the chemotherapy candidate group. This data shows that patients who are candidates for adjuvant chemotherapy might be considered for PC to increase BCS success with lower re-excision rates and equivalent excised breast volume.

Keywords: Breast cancer, Breast-conserving surgery, Resection volume, Re-excision rate

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Introduction

Historically, the first treatment for breast cancer has been wide excision. The radical mastectomy (RM) technique was presented by William Halsted in 1894 and this resulted with an increase in survival rates [1]. In this type of surgery, breast with is *enbloc* removed with the covering skin, pectoral muscles and the axillar lymph nodes. In the 1970s, Modified Radical Mastectomy (MRM) began to be performed in patients with a mobile smaller mass not invading the pectoral muscle, and it was shown that there was no difference between RM and MRM depending on survival rates [2]. Breast-conserving surgery (BCS) was first described in 1924 by Sir Geoffrey Keynes and developed in years, and additional radiotherapy resulted in an equivalent success as that in mastectomy [3].

BCS can be performed in both early-stage breast cancers and locally advanced tumors after neoadjuvant chemotherapy (NAC). In patients with large tumors who are candidates for chemotherapy, the tumor volume can be minimized, and BCS could be performed, while micrometastatic disease is eradicated [4].

Even though the prior aim in BCS is to obtain a tumor free margin (TFM) for reducing locoregional recurrence (LRR) and ensure cosmetically pleasing results, a surgical margin positivity for tumor (TIM) is reported at rates of 9-24.7%. These patients are treated with re-excision or mastectomy [5-7].

In locally advanced breast cancers, NAC before BCS is expected to yield cosmetically satisfying results by reducing resection volume. Is the excised breast tissue minimized after NAC, or does the surgeon remove more tissue to guarantee the result instead of sufficient tissue resection?

In our study, we aimed to compare resection volume, re-excision and margin positivity rates in breast cancer patients between the groups who received preoperative chemotherapy and started the treatment with definitive surgery, as well as evaluate the increase in BCS performability after NAC.

Materials and methods

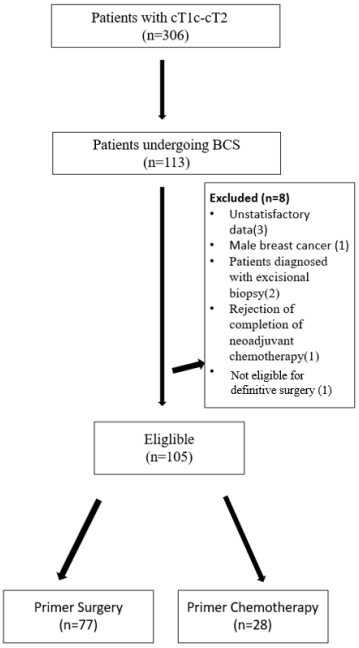
Data collections

The ethics committee approval (approval number: 251 and date: 31/03/2021) was obtained from Gaziosmanpasa Training and Research Hospital Ethics Committee, with which our hospital is affiliated. Informed consent forms from the patients were not required due to the retrospective use of anonymous administrative data.

This retrospective cohort study included 105 patients who underwent BCS, among 360 patients who received a diagnosis of stage cT1c-cT2 non-metastatic invasive breast cancer in Gaziosmanpasa Training and Research Hospital between 2013 and 2021. Patients diagnosed with excisional biopsy (n=2), those who rejected completing neoadjuvant treatment (n=1), patients not eligible for definitive surgery (n=1), those whose data cannot be reached (n=3), and males (n=1) were excluded. The data flow diagram was shown in Figure 1. Demographic, clinical, and pathological data were retrospectively collected from the medical records. Pathological data involved CNB, excision material, re-excision after BCS and mastectomy reports.

The study population was divided into two, as the primary surgery (PS) and preoperative chemotherapy (PC) groups and compared. The patients who received BCS after NAC were named the primary chemotherapy (PC) group, and the patients whose treatment was initiated with BCS were named the primary surgery (PS) groups. All patients in the PC group received 4 AC+ T (doxorubicin plus cyclophosphamide followed by paclitaxel) as the NAC regimen, trastuzumab was added to Her-2 positive patients and these patients' treatment lasted 1 year after the surgery. After NAC treatment, all patients in the PC group received definitive surgery within 3-4 weeks. The total number of patients who received BCS was low. The reasons include the patients requesting to get completely free of tumor, not accepting radiotherapy and surgeons' preferences.

Figure 1: Flow diagram of the study



Histopathological evaluation

The pathology reports of breast resection materials were examined depending on the volume of breast tissue, the biggest tumor diameter, histopathological diagnosis, histological grade, surgical margin, estrogen receptor (ER), progesterone receptor (PR), Ki-67 and Her-2 neu status. The Bloom-Richardson system, Nottingham modification was used for histological rating identification. The tumor stage was clarified in accordance with the 2017 AJCC breast cancer staging guidelines, the 8th Edition, and 2019 CAP guidelines [8, 9].

ER and PR scoring: A nuclear reaction below %1 was considered negative, and that over %1 was considered positive.

Her-2 scoring: Score 0: No reaction in tumor cells or incomplete reactions ≤ 10% of tumor cells, Score 1: 10% of tumor cells have pale, unclear incomplete membranous reactions, Score 2: > 10% of tumor cells have incomplete weak/moderate stage membranous reactions or ≤ 10% of tumor cells have complete strong membranous reactions, Score 3: > 10% of tumor cells have uniform strong membranous reactions. Score 0 and 1 were considered negative, score 2 was weakly positive and score 3 was considered positive. Score 2 patients were then evaluated with fluorescent in situ hybridization (FISH).

Clinicopathological definitions of breast cancer subtypes were made as follows [10]:

Luminal A like: ER positive, PR positive (>20%), Ki-67 low, Her-2 negative

Luminal B like: ER positive, PR low (<20%), or ER positive, Her-2 positive (3 + on IHC/amplified on FISH), any PR. Ki-67 values or low PR may be used to distinguish between Luminal A-like and Luminal B-like.

Her-2neu positive (non-luminal): ER and PR negative, Her-2 positive (3+ on IHC or amplified on FISH (for 2+ IHC results).

Triple negative (TNBC): ER, PR and Her-2neu negative

Neoadjuvant chemotherapy response was evaluated with the Miller Payne staging system [11]. According to this staging system, Grade 1 indicated no reduction in overall cellularity, Grade 2 indicated a minor loss of tumor cells (up to 30% loss), Grade 3 indicated an estimated reduction between 30% and 90% in tumor cells, Grade 4 indicated the marked disappearance of tumor cells (more than 90% loss), and Grade 5 indicated no identifiable malignant cells, although ductal carcinoma in situ may be present.

Margin status

Absence of tumor cells in the free surgical margin inked lines was defined as "no ink on the tumor''. A close margin indicated the presence of tumor cells closer to the border than 1mm [12]. Also, DCIS was present on the margin.

Calculation of the volume

To calculate excision volume (lumpectomy volume) in the surgical specimen, the ellipsoid formula, a.k.a., 4/3π (length x width x height), was used [13].

Re-excision

Re-excision was defined as any additional surgical therapy following BCS for margin positiveness, close margin, or positive palpation findings.

Statistical analysis

Normality control of continuous variables was evaluated with the Shapiro Wilk test. The continuous variables between the primary surgery and primary chemotherapy groups were compared with the Mann Whitney U test. In the analysis of categorical data, Chi-square's test and Fisher Exact tests were used. Multiple Logistic Regression analysis was used between the groups with the variables thought to be effective in the multiple models. The data were analyzed in the IBM SPSS 21.0 program. A *P*-value of <0.05 indicated statistical significance.

Results

Of the 105 patients included in the study, 28 (26.7%) were in the PC group and 77 (73.3%) were in the PS group. Patients in the PC group were younger than the patients in the PS group (*P*>0.05). The tumors of the patients in the PC group were larger (27.61 (15.42) mm, vs 17.83 (6.7) mm, respectively, *P*<0.001). Although the excised lumpectomy volume did not significantly differ, it was slightly higher in the PC group (755.86 (725.69) and 709 (637.36), respectively (*P*>0.05)). The distribution of histopathological subtypes, tumor grade and Her-2 neu status differed between the groups *(P*<0.05*).* The demographic and histopathological data of the patients and the evaluation of the surgical margin are summarized in Table 1.

Table 1: The demographic and histopathological data of the patients and the evaluation of the surgical margin

	Primer Surgery (n=77) Mean (SD)		Primer Chemotherapy (n=28) Mean (SD)		Total (n=105) Mean (SD)		*P*-value [1]
Age (year)	54 (11.07)		50.25 (8.53)		53 (10.54)		0.093
Tumor size (mm)	17.83 (6.7)		27.61 (15.42)		20.44 (10.65)		<0.001**
Lumpectomy volume (cm^3)	709 (637.36)		755.86 (725.69)		721.49 (658.8)		0.822
	n	%	n	%	n	%	*P*-value [2]
Histopathological type							
Invasive ductal	68	88.3	28	100.0	96	91.4	0.167
Invasive lobular	2	2.6	0	0.0	2	1.9	
Other	7	9.1	0	0.0	7	6.7	
Histopathological subtype							
Luminal A	53	68.8**	9	32.1	62	59.0	0.006**
Luminal B	19	24.7	16	57.1**	35	33.3	
Her2 enriched	2	2.6	2	7.1	4	3.8	
TNBC	3	3.9	1	3.6	4	3.8	
ER							
Negative	5	6.5	3	10.7	8	7.6	0.437*
Positive	72	93.5	25	89.3	97	92.4	
PR							
Negative	6	7.8	4	14.3	10	9.5	0.451*
Positive	71	92.2	24	85.7	95	90.5	
Her-2 neu status							
Negative	65	84.4**	15	53.6	80	76.2	0.001**
Positive	12	15.6	13	46.4**	25	23.8	
Margin for invasive cancer							
Tumor free margin	50	64.9	24	85.7	74	70.5	
Close margin ≤1 mm	24	31.2	2	7.1	26	24.8	0.083
DCIS involved margin	1	1.3	1	3.6	2	1.9	
Tumor involved margin	2	2.6	1	3.6	3	2.9	
Grade							
Low	9	11.7	0	0.0	9	8.6	0.010**
Moderate	58	75.3	18	64.3	76	72.4	
High	10	13.0	10	35.7**	20	19.0	

[1]: Mann Whitney U test, [2]: Chi-Square test *Fisher Exact test **: statistically significant (*P*<0.05), Tumor size: Before surgery or chemotherapy according to the clinical and radiological findings, TNBC: Triple negative breast cancer, ER: Estrogen receptor, PR: Progesterone receptor, Her-2: Human epidermal growth factor receptor 2, DCIS: Ductal carcinoma in situ.

The rates of additional surgery differed between the PC and PS groups, and re-excision was more common in the PS group (10.7% vs 39.0%, respectively, *P*<0.05).

In the PS group, re-excision was performed 30 patients. One patient in the PS group underwent mastectomy because the surgical margin was positive, one patient underwent re-excision in a second operation due to margin positivity in the final pathology examination, and one patient, due to margin positivity in the final pathological examination. Re-excision was performed in 21 patients because of the near-margin tumors, and in 6 patients, re-excision was needed due to suspicious palpation findings although the pathology report was negative, and tumor was observed in the re-excision material in these patients.

In the PC group, re-excision was performed in 1 patient due to close margin, in 1 patient, due to marginal tumor, and in 1 patient, because of borderline DCIS. None of the patients in the PC group required a second operation. Surgical outcomes of the patients are shown in Table 2.

Because TIM was seen in only 3 patients, no statistical comparison could be made between the factors affecting margin positivity, and the findings are summarized in Table 3.

According to the multivariate analysis, the tumor size (mm) was 1.114 times higher in the PC group, while re-excision was observed 0.181 times less (*P*<0.05). Multiple logistic regression analysis results are summarized in Table 4.

BCS was initially planned for 91 of 306 patients, with a rate of 29.74%. In the PC group, 14 patients who were initially ineligible for BCS became eligible, increasing the rate to 34.31%. The absolute increase in the mean was 4.58%.

Table 2: Surgical outcomes of patients

	Primer Surgery (n=77)		Primer Chemotherapy (n=28)		Total (n=105)		
	n	%	n	%	n	%	*P*-value
Additional surgical therapy							
No	47	61.0	25	89.3**	72	68.6	0.008[a]*
Yes	30	39.0**	3	10.7	33	31.4	
Type of additional surgical therapy							
Re-excision	27	90.0	3	100.0	30	90.9	0.102
Mastectomy after re-excision	1	3.3	0	0.0	1	3.0	
Second Mastectomy	1	3.3	0	0.0	1	3.0	
Second re-excision	1	3.3	0	0.0	1	3.0	
Additional tumor in re-excision specimen							
Tumor free	25	83.3	3	100.0	28	84.4	0.745
DCIS involved	4	13.3	0	0.0	4	12.5	
Tumor involved	1	3.3	0	0.0	1	3.1	

Chi-Square test, [a] Fisher Exact test, *: statistically significant ($P<0.05$), DCIS: Ductal carcinoma in situ

Table 3: Surgical margin status

	Tumor Free Margin (102) Mean (SD)		Tumor Involved Margin (3) Mean (SD)	
Age (year)	52.86 (10.49)		57.66 (13.79)	
Tumor size (mm)	20.42 (10.77)		21.00 (6.04)	
Lumpectomy volume (cm3)	724.20 (667.40)		629.38 (248.02)	
	n	%	n	%
Histopathological Type				
Invasive ductal	93	91.2	3	100.0
Invasive lobular	2	1.9	0	0.0
Other	7	6.9	0	0.0
Subtype				
Luminal A	59	57.8	3	100.0
Luminal B	35	34.3	0	0.0
Her-2 enriched	4	3.9	0	0.0
TNBC	4	3.9	0	0.0
ER				
Negative	8	7.8	0	0.0
Positive	94	92.2	3	100.0
PR				
Negative	10	9.8	0	0.0
Positive	92	90.2	3	100.0
Her-2 neu status				
Negative	78	76.5	3	100.0
Positive	24	23.5	0	0.0
NAC response (n=28)	n=27	%	n=1	%
Miller-Payne 1	4	14.8	0	0.0
Miller-Payne 2	2	7.5	0	0.0
Miller-Payne 3	3	11.1	1	100.0
Miller-Payne 4	6	22.2	0	0.0
Miller-Payne 5	12	44.4	0	0.0

TNBC: Triple negative breast cancer, ER: Estrogen receptor, PR: Progesterone receptor, Her-2: Human epidermal growth factor receptor 2, NAC: Neoadjuvant chemotherapy

Table 4: Multiple logistic regression analysis

	Odds Ratio	95% CI for Odds Ratio		*P*-value
		Lower	Upper	
Age	0.966	0.917	1.018	0.199
Tumor size (mm)	1.114	1.044	1.189	0.001*
Lumpectomy volume	1.000	0.999	1.001	0.348
Re-excision (yes)	0.181	0.038	0.857	0.031*
Tumor involved (yes)	12.393	0.470	327.028	0.132
Constant	0.401			0.541

*: statistically significant ($P<0.05$)

Discussion

NAC is successfully administered in patients who are candidates for systemic chemotherapy, showing equal overall and disease-free survival rates to adjuvant chemotherapy. One of its advantages is that it reduces tumor size and makes patients with large tumors requiring mastectomy eligible for BCS [4].

Studies report that there is an increase in the performability of BCS after NAC. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18, one of the pioneering studies in this regard, it has been reported that BCS rates increased from 60% to 68%, although modest pathological complete response (PCR) was observed in patients with breast cancer after NAC [14].

Especially in TNBC and Her-2 enriched subgroups, an increase in PCR rate up to 50-70% after NAC and an increase in BCS rate were demonstrated [15, 16].

In a study of stage 2-3 TNBC patients, 42% of patients who were initially ineligible for BCS became eligible for BCS after the treatment. The results of the study show a 14% absolute increase in BCS performability [17]. Again, Golshan et al. [18] showed an increase in the rate of BCS after NAC from 41% to 64% in both positive subgroups.

In our study, 14 patients who were not suitable for BCS before NAC became eligible after treatment and this increased by 15.38% in the group of patients who received BCS. However, in our study, contrary to the literature, most patients who became suitable for BCS after PC and developed PCR were in the luminal A subgroup. This was thought to be because the patients in the TNBC and Her-2 enriched groups had smaller tumor diameters at baseline and were suitable for BCS.

By considering the volume removed, studies focused more on patients' cosmetic satisfaction, and it was reported that as the volume of the removed tissue increases, so does dissatisfaction [19, 20].

In our study, we investigated whether there was a difference in the excised breast volume between the groups that did and did not receive NAC, based on the hypothesis that the tumoral mass in the breast would shrink and less volume excision would be sufficient after NAC. The tumor size was significantly higher in the PC group, while the excised volume was not. When we evaluated according to the pathological response, the increase in PCR did not cause a change in the excised volume. Since the tumor could not be palpated in patients who received PCR, it did not cause an increase in the resection volume, although the resection margins were blindly determined by marking earlier.

When Valejo et al. [21] compared the excision volumes of the groups that did not receive NAC over 267 breast cancer patients, they showed that the resection volume was higher in patients who received NAC, regardless of tumor size, and they stated that the cause of this was the thought that the tumor did not shrink concentrically and that there might be a residual microscopic foci around the palpable mass.

Similarly, Komenaka et al. [22] found the excision volume higher in the NAC group. However, unlike these studies, Karanlik et al. [23] showed that the resection volume was lower in the patient group receiving primary chemotherapy.

There is a wide margin for post-NAC re-excision rates and TIM. In one review, the TIM rate was between 5-39.8% and 13.1-46% for patients receiving NAC and undergoing primary surgery, respectively. Accordingly, re-excision rates range from 0-45.4% to 0-76.5%, respectively [24]. In another study by Volders et al. [25], re-excision rates were 24.3% in the group operated after TIM NAC, and 10.2% in the group undergoing primary surgery. In the same study, the close margin rate after NAC was 17.7%. The re-excision rates were higher in the patients receiving NAC than in the primary surgery group (9.1% and 5.3%, respectively), and 4.9% of re-excisions in the group receiving NAC resulted in mastectomy.

Correspondingly, Devane et al. [26] showed re-excision rates of 32% in patients who received NAC, while it was 17% in the primary surgery group. Re-excision is more common, especially in patients with lobular cancer and ER+ tumor.

By examining national cancer data, Spronk et al. [27] found a TIM rate after NAC of 6.7% and a re-excision rate of

6.6%, and the margin positivity in cT3 tumors was lower than in the primary surgery group, while it was higher in cT1 tumors.

In the study of Woeste et al. [28] including 162 patients, the TIM and re-excision rates were lower in patients who received NAC than in the group who underwent primary surgery.

Christy et al. [29] also showed that re-excision rates after NAC in tumors sized 2-4 cm were lower than in the primary surgery group.

When Clement et al. [7] examined 416 patients, they found TIM or close margin in 9% of the patients and determined that 48.78% of these patients underwent re-excision, 46.34% underwent mastectomy, and 4.87% underwent both re-excision + mastectomy.

In our study, we found that 31.4% of the patients underwent re-excision due to TIM or close margin. Re-excision was performed in more patients in the PS group, its rates were 39.0% in the PS group and 10.7% in the PC group.

The limitations of our study include the small number of patients and the inability to evaluate cosmetic results because patients were lost to follow-up. In addition, since the TIM rate is low, statistical comparisons between the factors affecting margin positivity could not made. Another limitation of our study is that breast surgery in our hospital was performed not only by a team specialized in this field but by all surgical specialists in the past, affecting the surgical technique.

Conclusion

The primary goal of BCS after NAC is achieving a lower resection volume and negative surgical margins. This 8-year retrospective cohort study showed that PC significantly reduces the rate of re-excision in patients undergoing BCS without increasing the excision volume. In addition, larger tumors can be shrunk and successfully removed as well as increasing the feasibility of BCS with PC. We believe that in patients with cT1-T2 breast cancer who are candidates for adjuvant therapy, PC can be safely performed oncologically without any surgical disadvantage.

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