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ORIGINAL ARTICLE

Treatment outcome in patients with breast conserving surgery after neoadjuvant therapy for breast carcinoma – a single institution experience

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Summary

Purpose: *The aim of this study was to analyze outcomes of breast conserving surgery (BCS) after neoadjuvant treatment (NAT) in comparison to radical mastectomy (RM) after NAT in terms of disease-free survival (DFS), overall survival (OS) and patients' satisfaction with the esthetic outcomes of surgery.*

Methods: *This prospective study was conducted at the National Cancer Research Center of Serbia, Belgrade, from January 1st 2011 to December 31st 2015, on breast carcinoma patients receiving NAT. Treatment outcome was assessed by MDAPI (MD Anderson Prognostic Index). Female patients (n=52) with satisfactory clinical response to NAT and MDAPI scores 0 or 1 were included into the treatment group (NAT-BCS group). The control group (NAT-RM group) consisted of patients (n=52) with poorer clinical response and MDAPI scores 2 to 4. On check-ups, local or distant relapses were noted and both groups were asked to value their satisfaction with the esthetic outcomes of surgery using the Likert scale.*

Results: *OS was 100% in both groups. DFS was 96.1% in NAT-BCS group and 100% in NAT-RM group. Local recurrences were observed in two patients from the age group ≥60 years, with initial disease stage IIIA and "clear" resection margins on frozen section study. Patients in the NAT-BCS group were more satisfied with the esthetic outcome of surgery than the control group.*

Conclusions: *BCS after NAT provides good esthetic outcome and is oncologically safe if adequate clinical response is achieved after NAT and if established criteria for patient selection are followed.*

Key words: *breast conserving surgery, neoadjuvant therapy, outcome*

Introduction

Indications for NAT in breast carcinoma have been expanding over the years [1]. Initially, NAT was only used in patients with locally advanced breast carcinoma, in order to achieve tumor and lymph node operability (downstaging). Today, NAT is also recommended in patients with operable breast carcinoma with certain molecular subtypes, with the aim of reducing the tumor size (downsizing) and enabling BCS instead of radical mastectomy (RM) [2,3].

BCS, either as the initial treatment option or applied after NAT, has two main goals that need to be achieved: curative and esthetic. These two imply clear resection (excisional) margins to avoid local

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dissemination of malignant cells, whilst preserving enough healthy breast tissue to avoid breast disfiguration. Oncoplastic approach also implies careful preoperative planning of the surgical incision with regard to tumor position and breast landmarks to avoid, if possible, poor scaring in the décolleté.

The number of patients with RM after NAT in Serbia still predominates, compared to BCS after NAT, with approximate ratio from 10:1 in our National Cancer Research Center in Belgrade, to much higher in other oncology centers in Serbia.

The aim of this study was to analyze outcomes of BCS after NAT (NAT-BCS group) in comparison to RM after NAT (NAT-RM group) in terms of DFS, OS and patients' satisfaction with the esthetic outcomes of surgery.

Methods

This prospective study was conducted at the National Cancer Research Center of Serbia, Belgrade, from January 1st 2011 to December 31st 2015 on breast carcinoma patients receiving NAT. According to the protocol, all patients with clinically suspect breast carcinoma on physical or imaging examination (ultrasound, mammography and magnetic resonance), underwent Tru-Cut biopsy to obtain histopathological confirmation of malignancy and data on tumor profile (tumor type, grade, ER/PR/Her2 status, Ki67, lymphovascular invasion). Additional diagnostics included: abdominal ultrasound, chest and bone X-ray (bone scintigraphy if indicated), complete blood and serum tests, tumor marker CA 15-3, and patient assessment by internist and anesthesiologist. Patients were staged by AJCC (American Joint Committee on Cancer) manual 2009 [4]. All patients were discussed by an expert multidisciplinary team that decided upon initial treatment based on disease stage and tumor profile. NAT included hormonotherapy and/or chemotherapy and/or targeted molecular therapy. Written informed consent was obtained from all the participants.

NAT effect (downstaging/downsizing) was monitored by physical examination and imaging methods and outcome was assessed by MDAPI, defined by experts in MD Anderson Cancer Center, Houston, Texas, USA [5]. Assigning scores were obtained for all patients of 0 (favorable) or 1 (unfavorable) for each of 4 variables: clinical N2/N3 disease, residual pathologic tumor size over 2 cm, a multifocal pattern of residual disease and lymphovascular space invasion in the specimen, overall MDAPI scores of 0, 1, 2, 3 and 4.

Female patients with satisfactory clinical response to NAT and MDAPI scores 0 or 1 were eligible for BCS, so they were included into the treatment group (NAT-BCS group). When possible, surgical incision was positioned outside the décolleté line, to avoid visible scarring. BCS consisted of tumor and tumor bed removal, with clear excisional margins that were intraoperatively verified by a pathologist on frozen section. In case of positive margins, re-excision of the tumor bed was performed immediately, with additional frozen section and standard histopathological confirmation of "clear" resection. Areola and mamila were preserved in all patients. Initially, clinically N1/N2 patients had lower and middle level axillary lymph node dissection (ALND), while clinically N0 patients were staged intraoperatively by sentinel lymph nodes (SLN) biopsy after double contrast (methylene blue dye and $Tc99^{m}$). If SLNs were positive on frozen section, lower and middle level ALND was performed. Otherwise, no additional ALND was done. Adjuvant treatment for this group included external breast radiotherapy of the remaining breast tissue based on multidisciplinary team decision for all patients within 6 weeks from surgery hormonotherapy and/or chemotherapy and/or targeted molecular therapy.

Patients with poorer clinical response and higher risk for recurrence (MDAPI 2, 3 or 4) were not subjected to BCS but to RM. Out of these patients, a control group was formed (NAT-RM group), homogeneous by number and age to the treatment group. RM implied complete breast tissue removal, with areola and mamila, and axillary node dissection. Adjuvant treatment for these patients was also adjusted to indications and treatment protocols.

Patients were followed-up for local and distant relapses three-monthly during first postoperative year, then once a year. Mammography, ultrasound and breast magnetic resonance imaging were done as adjuncts to physical examination, along with blood and biochemical tests, additional imaging diagnostics and tumor markers.

On each check-up, both groups of patients were asked to value their satisfaction with the esthetic outcome of surgery using the Likert scale. Responses included the following: very satisfied (+2), satisfied (+1), neutral (0), unsatisfied (-1), very unsatisfied (-2). These values were used to design the trend line of satisfaction with surgery for both groups of patients during the months following initial treatment.

Statistics

Data collection was closed on December 1st 2017. Statistical analyses of the data was performed by SPSS (SPSS Inc., IBM, Chicago, USA), version 23. Frequencies, percentages, mean, median, standard deviation (SD) and range were used for the description of data. Chi-square and Mann-Whitney U test were used for testing differences between treatment groups, with statistical significance level at $\alpha=0.05$. Kaplan-Meier method with log rank test and Cox proportional hazard model were used for survival analysis.

Results

Patient characteristics, tumors and disease stage are given in Table 1, while Table 2 shows pathological characteristics of tumors and differences in clinical response to NAT between treat-

Table 1. Characteristics of patients, tumors and disease stage in NAT-BCS group and the control NAT-RM group

	NAT-BCS group		*NAT-RM group*	
	n	%	*n*	%
Age group, years				
≤ 49	11	21.2	9	17.3
50 - 59	20	38.5	22	42.4
≥ 60	21	40.4	21	40.4
Menopausal status				
Premenopausal	24	46.2	15	28.8
Perimenopausal	9	17.3	6	11.5
Postmenopausal	19	36.5	31	59.6
Tumor localization				
Upper lateral quadrant	34	65.4	36	69.2
Inferior lateral quadrant	10	19.2	9	17.3
Other	8	15.4	7	13.5
Clinical stage				
IIA	8	15.4	3	5.8
IIB	27	51.9	21	40.4
IIIA	17	32.7	6	11.6
IIIB	0	0.0	22	42.2
T stage				
T1	1	1.9	4	7.7
T2	34	65.4	18	34.6
T3	17	32.7	11	21.2
T4	0	0.0	19	36.5
N stage				
N0	14	26.9	1	1.9
N1	30	57.7	17	32.7
N2	8	15.4	32	61.5
N3	0	0	2	3.7

n: number of patients, NAT: neoadjuvant therapy, BCS: breast conserving surgery, RM: radical mastectomy

ment and control group. The average age in both groups was 53.5±12.5 years. In NAT-BCS group, tumors were mostly localized in the lateral quadrants (44/52, 85%), T2 in size (34/52, 65%). Over half of the patients were staged IIB (27/52, 52%). There were no patients with T4 tumors and N3 status in the NAT-BCS compared to NAT-RM group.

As a result of preoperative planning of the position of the surgical incision in relation to the tumor localization and breast landmarks, 44/52 (85%) patients in the NAT-BCS group had a scar outside the décolleté line, while in the remaining 8/52 (15%), it was in the décolleté due to poor tumor localization.

During the operation, intraoperative pathological verification of the resection margins confirmed clear margins in 48/52 (92.3%) patients of the NAT-BCS group. In the remaining 4/52 (7.7%) patients, due to insufficient margins, one-time re-excision of the tumor bed was performed and clear margins were additionally confirmed, both on frozen section and standard pathology study. Table 3 shows the extent of axillary lymph node dissection and the pathological findings of the axillary lymph nodes in both groups. SLN biopsy was performed in 14/52 (27%) of clinically N0 patients of the NAT-BCS group, with extension to ALND in 13/14 (93%) who had metastases in the examined SLNs. On the other hand, ALND was immediately performed in 38/52 patients that were initially staged as N1/N2, which makes a total of 51/52 (98%) patients with ALNDs in the NAT-BCS group. All patients in the NAT-RM group were immediately treated with ALND. The average number of positive axillary lymph nodes was higher in the NAT/RM group (8.2 vs. 5.0). In the postoperative course, 5 cases of seroma and 2 of hematoma were observed in the treatment group (7/52, 13.5%), all treated conservatively. The NAT-RM group had more patients with complications like seroma (8 patients) and hematoma (4 patients), in total 12/52 (23.1%).

Table 2. Pathological characteristics of tumors and tumor response to neoadjuvant therapy in NAT-BCS group and the control NAT-RM group

	NAT-BCS group		*NAT-RM group*	
	n	%	*n*	%
Tumor type				
Lobular invasive carcinoma	19	36.5	23	44.2
Ductal invasive carcinoma	33	63.5	29	55.8
Tumor grade				
I	2	3.8	2	3.8
II	43	82.7	46	88.5
III	7	13.5	4	7.7
Estrogen receptor (ER)				
Positive	31	59.6	28	53.8
Negative	21	40.4	24	46.2
Progesterone receptor (PR)				
Positive	31	59.6	28	53.8
Negative	21	40.4	24	46.2
Her2 receptor				
Positive	20	38.5	22	42.3
Negative	32	61.5	30	57.7
Ki67				
High	34	65.4	36	69.2
Low	18	34.6	16	30.8
Lymphovascular invasion				
Yes	11	21.2	27	51.9
No	41	78.8	25	48.1
Molecular tumor subtype				
Luminal A	16	30.8	3	5.8
Luminal B	20	38.5	33	63.4
Her2	9	17.3	13	25
Triple negative	7	13.5	3	5.8
Clinical response to neoadjuvant therapy				
Complete response	9	17.3	3	5.8
Partial response	42	80.8	34	65.4
Stable disease	1	1.9	9	17.3
Disease progression	0	0	6	11.5

n: number of patients, NAT: neoadjuvant therapy, BCS: breast conserving surgery, RM: radical mastectomy

Table 3. Extent of axillary lymph node dissection and pathological findings on axillary lymph nodes in the NAT-BCS group and the control NAT-RM group

	NAT-BCS group		*NAT-RM group*	
	n	%	*n*	%
Sentinel lymph node biopsy	14	26.9	0	0.0
Negative*	1	7.1		
Positive*	13	92.9		
Axillary lymph node dissection	51	98.1	52	100.0
Negative	27	52.9	24	46.2
Positive	24	47.1	28	53.8
Dissected lymph nodes				
Mean number per patient (range)	16.2 (10-34)		19.2 (13-35)	
Positive lymph nodes				
Mean number per patient (range)	5.0 (1-21)		8.2 (3-30)	

* on frozen section and standard pathology analysis; n: number of patients, NAT: neoadjuvant therapy, BCS: breast conserving surgery, RM: radical mastectomy

Patients were followed-up (until closure of the database) for an average of 42 months (range 23-82), with no lethal outcomes observed in both groups (OS 100%). None of the patients had local recurrence in first 2 years of follow-up. Only 2 patients in the NAT-BCS group (3.9%) had local recurrences in breast tissue at 33 and 34 months assessment. Both patients were in the ≥ 60 years age group, with initial stage IIIA and clear resection margins on frozen section. There were no local recurrences in the control group (Table 4). Statistical significance between patients' and tumor characteristics in relation to local recurrences was not shown. However, the number of patients with local recurrence was too small for adequate analysis, as well as the total number of patients in each group. Patients with local recurrence were re-operated and in both cases simple mastectomy was performed.

On each check-up, both groups of patients were asked to value their satisfaction with the esthetic outcomes of surgery using the Likert scale. Responses included the following: very satisfied (+2), satisfied (+1), neutral (0), unsatisfied (-1), very unsatisfied (-2). The average values of patients' satisfaction with esthetic outcomes of surgery, obtained by Likert scale in pre-determined time frames following initial treatment were used to design the trend line of patient satisfaction for both groups. As shown in Figure 1, all patients in NAT-BCS group were satisfied (+1) to very satisfied (+2) with the esthetic outcome of the surgery, with lowest value observed one year after treatment and positive trend later on. The patients' answers were more often positive if the surgical scar was positioned outside the décolleté line, compared to the scars that were visible in the décolleté, which is schematically shown in Figure 2. On the other hand, patients in the NAT-RM group had a lower level of satisfaction regarding the esthetic results of their surgery and they never achieved the level of satisfaction of patients in the NAT-BCS group (Figure 1). They were initially satisfied with the esthetic outcome of surgery, with negative trend

Table 4. Overall survival and disease-free survival in the NAT-BCS and the control NAT-RM group

	NAT-BCS group		*NAT-RM group*	
	n	%	*n*	%
Overall survival	52	100	52	100
Disease-free survival	50	96.1	52	100

n: number of patients, NAT: neoadjuvant therapy, BCS: breast conserving surgery, RM: radical mastectomy

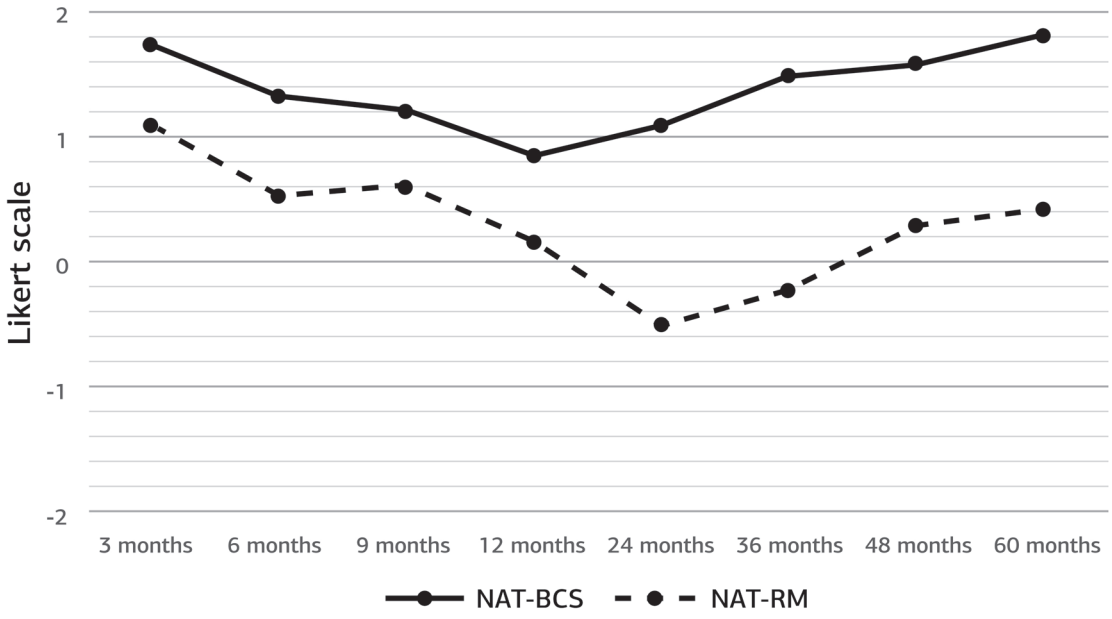

Figure 1. Trend line of patients' satisfaction with the esthetic outcome of surgery in the NAT-BCS group and the control NAT-RM group, obtained by Likert scale in pre-determined time frames following initial treatment. BCS: breast conserving surgery; RM: radical mastectomy; Likert scale: +2 very satisfied, +1 satisfied, 0 neutral, -1 unsatisfied, -2 very unsatisfied.

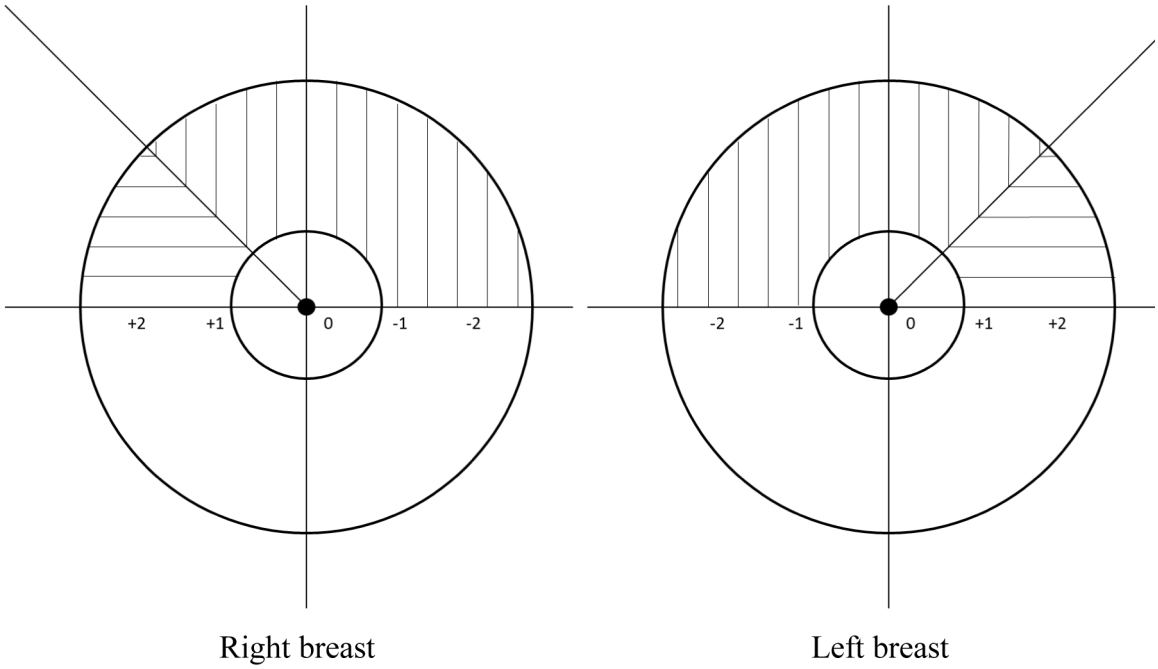

Figure 2. Schematic diagram on how the position of surgical scars in relation to the décolleté line influenced patients' satisfaction with the esthetic outcome of surgery in the treatment group (NAT-BCS). Likert scale: +2 very satisfied, +1 satisfied, 0 neutral, -1 unsatisfied, -2 very unsatisfied.

towards two years after treatment, when they felt mostly unsatisfied. This is probably due to the fact that they initially thought of their well-being and not the cosmetic results, while after the treatment completion they did not think of the esthetic results.

Discussion

The use of NAT before mastectomy was once reserved only for inoperable disease as introduction to radical surgery, but more recently has become a common approach for stage II and III with an aim of increasing surgical options [6,7]. Depending on the breast carcinoma subtype, NAT can include cytotoxic chemotherapy, and/or hormonal therapy and/or targeted molecular agents such as trastuzumab and pertuzumab [1].

Experts from MD Anderson Cancer Center reported back in 2004 [8] a 5- and a 10-year DFS of 95% and 90%, respectively, in stages I to III, showing that NAT-BCS patients have acceptably low rates of locoregional recurrences, even though 72% of them initially had disease stage IIB/III. Attention was paid to the group with favorable response to NAT, since patients with T3/T4 tumors had a very low risk of recurrence if the tumor shrank to a solitary lesion or showed pathological complete response, while the recurrence rate was 20% if residual tumor had a multifocal pattern [8]. These results helped define four factors that are directly associated with BC recurrence: clinical N2/N3 at diagnosis, residual tumor larger than 2 cm, multifocal residual disease and lymphovascular invasion. Based on these criteria, further research [5] distinguished 3 risk groups in NAT patients: a low-risk group (MDAPI score 0 or 1), an intermediate-risk group (MDAPI score 2) and a high-risk group (MDAPI score 3 or 4), with 5-year DFS of 94, 83, and 58%, respectively. Other studies supported this risk stratification [9,10]. Namely, the low-risk group of patients had excellent results, both with BCS as well as RM, while the high-risk group had a statistically significant benefit from RM with adjuvant radiotherapy, compared with BCS. Similar to these results, 5-year DFS rates were improved by RM instead BCS in the high-risk group [10].

Following these recommendations and risk stratification, patients were selected for the NAT-BCS group only if MDAPI score was 0 or 1, regardless the initial tumor size. The local recurrence rate of 3.9% in our patients with NAT-BCS treatment suggests good selection of patients and these results are in accordance with other available data on NAT-BCS approach [11-16].

Although MDAPI criteria [5,8] do not include initial tumor size, one of the ongoing debates refers to whether downsizing of a large primary tumor with a subsequent smaller tissue resection in comparison to the initial tumor volume would leave residual disease and increase the probability of local recurrence [7]. This can be supported by

the pattern of tumor reduction that is not strictly concentric and leaves room for microscopic residual disease. The risk for microscopic residual disease is higher in multifocal residual disease than in patients with concentric tumor reduction and initially smaller tumor diameter [12]. Frozen section of the specimen's excisional margins should help preventing inadequate tissue resection.

Although the 2015 St. Gallen Consensus Conference on early breast cancer states by 89% support that the entire area of the primary tumor downsized by NAT does not need to be excised [17], we have performed larger excisional margins in patients with initially larger tumors, removing greater volume of the breast tissue in these patients. However, the cosmetic result of the BCS does not necessarily have to be compromised, not even in larger tissue excisions, since the remaining glandular tissue can be transposed to the former tumor bed to close the tissue defect and achieve excellent esthetic results [18]. Other authors also underline the significance of safe wider excisional margins to achieve better oncological control, whilst preserving good esthetic results [19,20].

In the postoperative course, less percents of complications were observed in NAT-BCS compared to NAT-RM group (13.5 vs 23.1%). Patients in the NAT-BCS group were very satisfied with the esthetic outcome of their treatment, with positive trend of the curve one year and more after treatment completion. As expected, patients in the NAT-RM group had a lower level of satisfaction regarding the esthetic results of their operation and they never achieved the level of satisfaction of patients in the NAT-BCS group. Besides the shape and volume of the breast in BCS, patients are generally most concerned about scars, even those with RM. Due to favorable tumor localization in NAT-BCS group (85% were positioned in lateral breast quadrants), the majority of our patients had a scar outside the décolleté line (not visible in décolleté), which improved their impressions about the esthetic results of surgery.

Kosovac et al. [21] showed that postoperative complications in breast reconstructions occur in half of the patients with T2 tumors and N1 stage, observed independently. Here, in NAT-BCS group, 65% of the patients had T2 tumors and 73% were staged as N1. As a result, NAT-BCS patients were not offered subcutaneous mastectomy with breast reconstruction, instead of BCS, neither were they offered delayed breast reconstruction, since literature data [21] suggest that there is a higher percentage of complications in patients with adjuvant radiotherapy, which was delivered to the whole NAT-BCS group.

To date, literature data suggest that BCS after NAT can be oncologically safe if adequate clinical response is achieved after NAT and if established criteria for patient selection are followed [7]. Our results show a DFS of 96.1% in patients who were treated with BCS after NAT. Additionally, patients' satisfaction with the esthetic outcome is significantly higher in patients that are subjected to BCS after NAT than in those with RM. Therefore, NAT should always be considered for patients who desire BCS, but who initially present with a large primary tumor or unfavorable tumor-to-breast size ratio. These results might be encouraging for surgeons in Serbia to embark on NAT-BCS approach more often than they used to, and reduce the number of radical procedures, if these are not strictly indicated.

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Conflict of interests

The authors declare no conflict of interests.

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