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ORIGINAL ARTICLE – BREAST ONCOLOGY

Circumferential Shaving of the Cavity in Breast-Conserving Surgery: A Randomized Controlled Trial

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ABSTRACT

Background. This randomized controlled trial aimed to investigate the effects of circumferential shaving on reducing the intraoperative margin positivity rate (MPR) during breast-conserving surgery (BCS).

Methods. Eligible breast cancer patients were randomly assigned into no-shave and shave groups. In the no-shave group, the cavity margins were collected for assessment after the tumor resection, whereas in the shave group, a circumferential shaving was performed before collecting the cavity margins. The primary outcome was the intraoperative MPR by frozen section analysis.

Results. A total of 181 patients, with a median age of 49 years, were randomized. Patient characteristics at baseline were well-balanced between the two groups. The intraoperative MPRs (12.1% vs. 7.8%, $p = 0.38$), postoperative MPRs (16.5% vs. 7.8%, $p = 0.073$), intraoperative re-excision rates (26.4% vs. 23.3%, $p = 0.64$), second operation rates (4.4% vs. 1.1%, $p = 0.34$), and successful BCS rate (93.4% vs. 94.4%, $p = 0.94$) were all similar between the no-shave and the shave groups. The volume of the shaved tissues was significantly increased in patients with larger breast volume ($p < 0.01$). In patients with C–E cup breasts, the no-shave and shave groups had 16.7% and 0% ($p = 0.03$) intraoperative MPRs, and 22.0% and 0% ($p = 0.01$) postoperative MPRs, respectively. In patients with A–B cup breasts, the MPRs were similar between the two groups. The presence of the ductal carcinoma in situ component is the only determinant of margin positivity.

Conclusions. Circumferential shaving did not significantly reduce the MPR in BCS. Its benefit depends on the volume of the shaved tissues and the breast.

Trial registration This trial was registered at ClinicalTrials.gov (NCT02648802).

Local recurrence (LR) is a major concern for early-stage breast cancer patients with breast-conserving surgery (BCS). Achieving a negative surgical margin is essential to reduce the risk of LR. Currently, about 20–25% of patients with BCS receive a second operation (re-excision) due to the presence of positive margins.[1,2] Several intraoperative margin assessment techniques could reduce the risk of a second operation.[3–6] Among these techniques, frozen section analysis (FSA) and cytology were shown to have the greatest diagnostic accuracy.[7] In a systematic review, Esbona et al.[3] reported that the second operation rate was reduced to 6% when FSA was applied in BCS.

The worldwide clinical practice of margin assessment can be lumpectomy margin or cavity margin assessment, and some surgeons will perform FSA while others will

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not.[8–10] In our institution, we routinely assessed the cavity margin status using FSA, with the second operation rate standing at 3.5%.[11] About 15–20% of BCS patients received intraoperative re-excisions due to the presence of positive cavity margins[12] shown by FSA; however, routine FSA is time-consuming. If the intraoperative margin positivity rate (MPR) could be reduced to an acceptable level, e.g. $< 5\%$, FSA can be omitted for all patients. In a randomized controlled trial, Chagpar et al.[13] reported that circumferential shaving was able to decrease the MPR by 15% (from 34 to 19%) during BCS. Therefore, in a randomized controlled trial, we sought to determine the effect of circumferential shaving on reducing the intraoperative MPR during BCS. We hypothesized that circumferential shaving would significantly reduce the intraoperative MPR to $< 5\%$ so that the routine FSA could be omitted.

METHODS

We conducted a randomized controlled trial with 181 pathologically diagnosed breast cancer patients who were undergoing BCS. Subjects were (1) female patients between the age of 18 and 65 years, with an Eastern Cooperative Oncology Group (ECOG) score of ≤ 2; (2) pathologically diagnosed with breast cancer by core-needle biopsy; and (3) willing and planning to undergo BCS. Patients with any of the following factors were excluded from the trial: (1) inflammatory breast cancer; (2) plans to receive oncoplastic BCS or mastectomy; (3) preoperative systemic therapy; (4) stage IV diseases; (5) bilateral breast cancer; (5) clinical tumor size > 5 cm; and (6) multicenter/multifocal breast cancer, or with extensive suspicious microcalcification on mammography. In our institution, achieving negative surgical margins without compromising the cosmetic outcome is the major determinant to select patients appropriate for BCS. Preoperative magnetic resonance imaging (MRI) is not routinely used.

After surgeons obtained written informed consent, patients were randomly assigned, in a 1:1 ratio, to the shave and no-shave groups by NQ, a research assistant who did not participate in the management of the participants. The assignment was based on an a priori randomization list generated by a statistician (YY) using STATA MP 13 (StataCorp LLC, College Station, TX, USA). NQ was blinded to the results and the surgeons were unaware of the assignments until randomization was performed intraoperatively. Participants did not know which group they had been assigned to until 1 year after surgery. This was a block randomization with a varied and random block size (2, 4, 6).

In this trial, surgeons first performed a traditional BCS without intraoperative ultrasound guidance, and performed gross examinations of the lumpectomy margins. Intraoperative specimen radiograph was not routinely used. Resections of additional tissues where the tumors were considered to be close to the edge were allowed. Afterwards, the surgeons contacted NQ and continued the randomized trial. In the shave group, the surgeons circumferentially shaved the cavity tissues (Fig. 1). There was no standardized volume of circumferentially shaved tissues due to the varied tumor size and breast size of patients. Two principles are required for circumferential shaving: (1) the shaved tissues should encompass the entire cavity; and (2) shaving would not compromise the cosmetic outcomes based on the surgeons' experience. We assessed the cavity margin status during BCS, regardless of the lumpectomy margins. Briefly, six to eight cavity margins 1×1 cm in size (thickness 1–2 mm) were collected from the cavity walls. A positive cavity margin was defined as the presence of ductal carcinoma in situ (DCIS) and/or invasive cancer components during microscopic examinations. In the no-shave group, the cavity margins were collected after tumor excision, whereas in the shave group, the cavity margins were collected after circumferential shaving. The cavity margins were then evaluated by intraoperative FSA and postoperative formalin-fixed paraffin-embedded analysis (FFPEA) (Fig. 1). The results of FSA were then faxed back to the operating room intraoperatively. Intraoperative re-excisions were performed for patients with positive cavity margins. For those with suspicious cavity margins, whether to perform intraoperative re-excisions or not was left to the surgeons' discretion. A second operation was performed on patients who had a positive FFPEA result but did not receive intraoperative re-excisions. The pathologists were blinded to which patients participated in the trial. The data were collected by NQ and stored at the REDcap database of our institution. This trial was approved by the Ethical Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University, and was registered at ClinicalTrials.gov (NCT02648802).

The primary endpoint was the MPR by intraoperative FSA, while secondary endpoints included the MPR by postoperative FFPEA, intraoperative re-excision rate, second operation rate, and successful BCS rate. The volumes of circumferentially shaved tissues were recorded. Operation time, medical cost, cosmetic outcomes, and quality of life would be reported in a separate cost-effectiveness study. There was no planed interim analysis. We used the 'power twoproportions' code in STATA MP 13 (StataCorp LLC) to estimate that a sample of 178 patients would provide the study with 80% power to detect a difference between the anticipated intraoperative positivity rate of

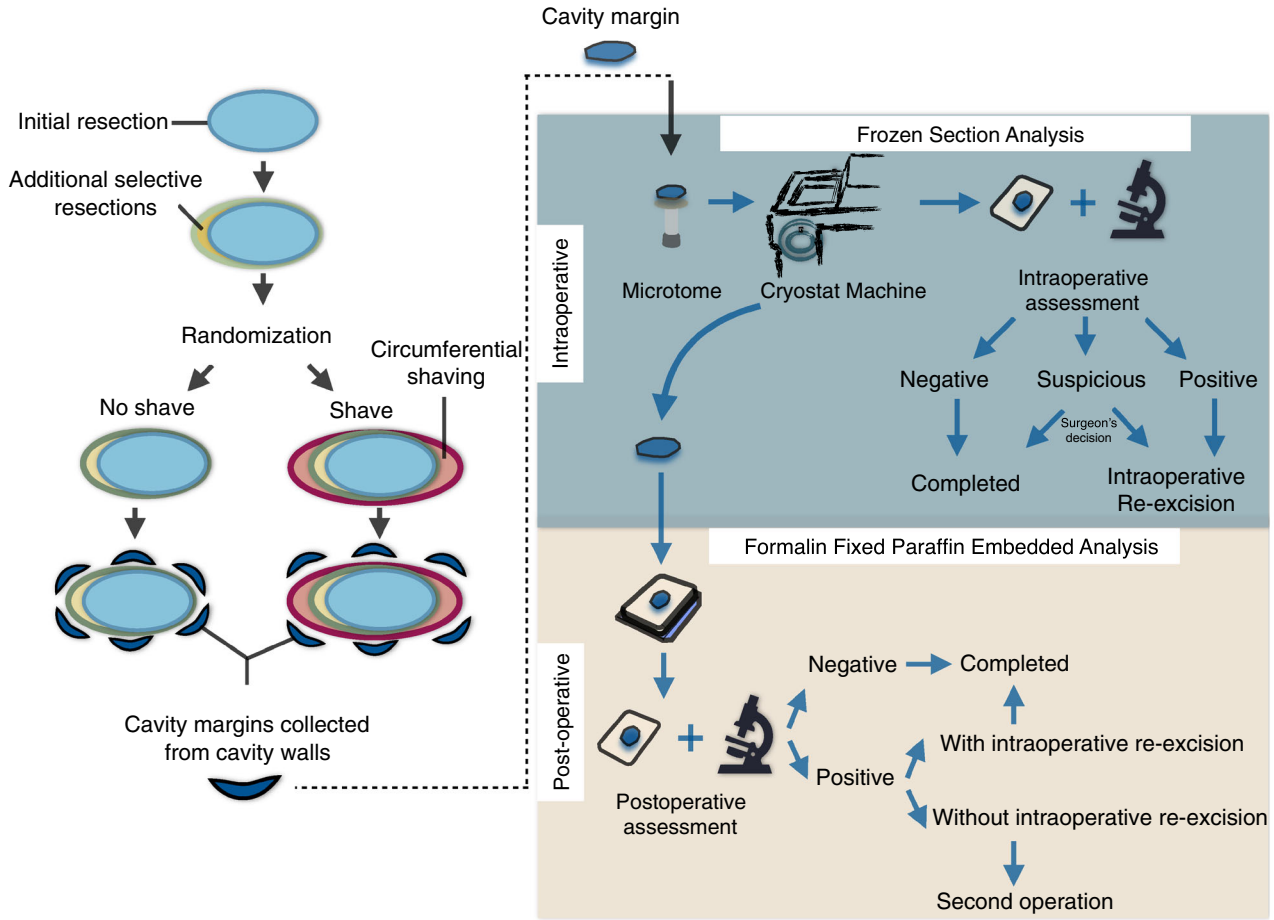

FIG. 1 Study design. After initial resection of the tumor, the surgeons were allowed for selective resection of additional tissues based on their intraoperative gross examination, before randomization. After randomization, cavity margins were collected for assessment in the no-shave group, whereas in the shave group, circumferential shaving of the cavity was performed before collecting the cavity margins. The margin tissues were sent to intraoperative FSA, as well as postoperative FFPEA. Intraoperative re-excisions were performed based on the results of the FSA. Second operations were performed in patients with positive margins shown by FFPEA but did not receive intraoperative re-excisions. *FSA* frozen section analysis, *FFPEA* formalin-fixed paraffin-embedded analysis

15% in the no-shave group and 3% in the shave group, at a one-sided significance level of 0.025. For group comparisons, we used Chi square tests (or the Fisher exact test) and Mann–Whitney *U* tests as appropriate for categorical and continuous variables, respectively. To identify the risk factors as significant determinants of MPR, we used a univariate logistic regression model. STATA MP 13 (StataCorp LLC) was used for statistical analysis.

RESULTS

Study Participants

Between January 2016 and October 2018, we enrolled a total of 181 patients in the trial (Fig. 2). The median age of patients was 49 years (range 28–65). Overall, 113 (62.4%)

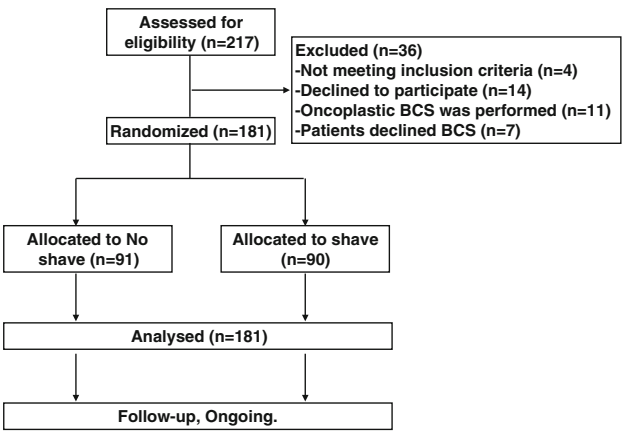

FIG. 2 Participant flow. *BCS* breast-conserving surgery

patients had A–B cup breasts, 111 (61.3%) patients had heterogeneously (50–75%) dense breasts, and 35 (19.3%) patients had extremely dense (> 75%) breasts. The median (interquartile range) sizes of the tumor and the excised specimen were 1.9 (1.4–2.3) and 5.5 (4.5–6) cm, respectively. The number of patients who were randomly assigned to the no-shave and shave groups was 91 and 90, respectively. Patient characteristics at baseline were well-balanced between the two groups (Table 1).

Endpoints

The positive predictive value (PPV) and negative predictive value (NPV) of FSA was 100% and 97.4%, respectively (electronic supplementary Table 1). After randomization, the MPRs by intraoperative FSA were 12.1% in the no-shave group and 7.8% ($p = 0.38$) in the shave group (Table 2). The MPRs by postoperative FFPEA were 16.5% and 7.8% ($p = 0.073$) for the no-shave and shave groups, respectively. The intraoperative re-excision rates (no-shave vs. shave = 26.4% vs. 23.3%, $p = 0.64$), second operation rate (no-shave vs. shave = 4.4% vs. 1.1%, $p = 0.34$), and successful BCS rates (no-shave vs. shave = 93.4% vs. 94.4%, $p = 0.94$) were comparable between the two groups.

A post hoc subgroup analysis showed that among patients with C–E cup breasts, the MPRs of the no-shave and shave groups were 16.7% and 0% ($p = 0.03$) by FSA, and 22.2% and 0% ($p = 0.01$) by FFPEA, respectively (Table 3). For patients with a DCIS component, the MPRs of the no-shave and shave groups were 28.2% and 15.4% ($p = 0.17$) by FSA, and 30.8% and 15.4% by FFPEA, respectively. The presence of a DCIS component was the only significant risk factor of margin positivity (electronic supplementary Table 2).

Volume of the Shaved Tissues

The median (IQR) volume of the shaved tissues was 12 (8–18) cm^3. The volume of the shaved tissues was correlated with tumor size (Spearman's coefficient 0.28, $p = 0.007$), as well as the size of the excised specimen (Spearman's coefficient 0.24, $p = 0.02$). The volume of the shaved tissues was significantly increased in patients with larger breast volume (Kruskal–Wallis test, $p < 0.01$) (electronic supplementary Fig. 1a). Breast density had no impact on the volume of the shaved tissues (electronic supplementary Fig. 1b).

DISCUSSION

It is important to achieve negative surgical margin during BCS. Both lumpectomy margin and cavity margin are applicable for margin assessment. Hewes et al.[14] showed that cavity margin status was more significant in predicting clinical outcomes than lumpectomy margin status. The oncological safety of assessing cavity margin status during BCS in the Chinese population was shown in our previous study.[11] Thus, we routinely assessed cavity margin status rather than lumpectomy margin status after BCS. In addition, the use of FSA significantly reduced the second operation rate (e.g. < 5% in our study), and thus facilitated the implementation of BCS. The average BCS rate is < 15% in most institutions in China;[15,16] however, in our institution, the BCS rate is 52%,[17] with a second operation rate of < 5%. FSA for intraoperative margin assessment was recommended by the American Society of Breast Surgeons consensus conference (CALLER conference).[18] In our study, we confirmed the efficacy of FSA and reported that its PPV and NPV were 100% and 97.4%, respectively, for margin assessment. Although the use of FSA led to prolonged operative time (our trial vs. the trial by Chagpar et al.: 130–140 min vs. 66–77 min), the second operation rate was only 2.7%, which is consistent with our previous study (3.5%).[11] It is possible that FSA is more appropriate to Chinese patients with more dense breast tissues. In Western countries, where patients had more fatty breast tissues, pathologists may have some concern about the difficulty of sectioning fatty tissue during FSA; however, the techniques to deal with this difficulty have been reported.[19] Furthermore, the feasibility and efficacy of FSA has been reported by a large number of studies since 1994.[7,20,21] Thus, we recommend FSA for intraoperative cavity margin assessment during BCS.

However, routine FSA is time-consuming, especially for patients with positive margins that need intraoperative re-excisions. To reduce the intraoperative MPRs helps to shorten the operation time and reduce medical costs. Specimen imaging using an in-theater intraoperative specimen radiography (IOSR) system reduced specimen weights,[22] MPRs, and subsequent undesired mastectomies.[23] In a multicenter randomized controlled trial (COBALT trial) that randomly assigned eligible patients into palpation-guided versus ultrasound-guided BCS, the MPRs were 27% vs. 11%, respectively. The use of ultrasound-guided BCS was also associated with smaller resected specimens. Intraoperative handheld devices, such as the MarginProbe™ device[24] and optical coherence tomography system,[6] were applicable for immediate assessment of margin status. However, all of the above-mentioned approaches need additional devices and have thus not been widely adapted. Chagpar et al.[13] reported that circumferential shaving of the cavity after standard BCS significantly reduced the MPR by 15%. Since this approach is convenient and easy to implement, we hypothesize that circumferential shaving could reduce intraoperative MPRs

TABLE 1 Patient characteristics at baseline

	No shave	Shave
Age, years [median (range)]	49 (29–65)	48 (29–65)
Breast density, grandular		
< 25% (almost entirely fat)	6 (6.6)	3 (3.3)
20–50% (scattered fibrograndular tissue)	14 (15.4)	12 (13.3)
50–75% (heterogeneously dense)	56 (61.5)	55 (61.1)
> 75% (extremely dense)	15 (16.5)	20 (22.2)
Breast volume, cup size		
A	12 (13.2)	11 (12.2)
B	43 (47.3)	47 (52.2)
C	32 (35.2)	25 (27.8)
D	3 (3.3)	6 (6.7)
E	1 (1.1)	1 (1.1)
Palpable		
No	8 (8.8)	5 (5.60)
Yes	83 (91.2)	85 (94.40)
Histology		
Ductal	81 (89.01)	83 (92.2)
Lobular	3 (3.30)	4 (4.4)
Others	7 (7.69)	3 (3.3)
Percentage of DCIS component		
0 (none)	54 (59.34)	53 (58.89)
1–25	18 (19.78)	19 (21.11)
≥ 25	19 (20.88)	18 (20.00)
Estrogen receptor		
Negative	12 (13.2)	13 (14.4)
Positive	79 (86.8)	77 (85.6)
Progesterone receptor		
Negative	24 (26.4)	23 (25.6)
Positive	67 (73.6)	67 (74.4)
HER2 status		
Negative	64 (70.3)	68 (75.6)
Borderline	1 (1.1)	2 (2.2)
Positive	18 (19.8)	13 (14.4)
Not available	8 (8.8)	7 (7.8)
Ki67 status (20% cut-off)		
Negative	46 (50.5)	47 (52.2)
Positive	45 (49.5)	43 (47.8)
pT-stage		
Tis	2 (2.20)	3 (3.3)
T1	59 (64.84)	63 (68.9)
T2	30 (32.97)	24 (26.7)
pN-stage		
N0	66 (72.5)	63 (70.0)
N1	15 (16.5)	19 (21.1)
N2	8 (8.8)	4 (4.4)
N3	2 (2.2)	4 (4.4)
AJCC stage		
0	2 (2.20)	3 (3.3)
I	45 (49.45)	44 (48.9)
II	34 (37.36)	35 (38.9)
III	10 (10.99)	8 (8.9)
Size of the excised specimen, cm [median (range)]	5 (3–10)	6 (3–10)
Tumor size, cm [median (range)]	2 (1–4)	2(1–7)

Data are expressed as *n* (%) unless otherwise specified

DCIS ductal carcinoma in situ, *HER2* human epidermal growth factor receptor 2, *AJCC* American Joint Committee on Cancer

to an acceptable level (e.g. < 5%), and FSA can be safely omitted, which will significantly change our clinical practice.

However, the current trial showed a 4.3% reduction in the intraoperative MPR, which is not statistically significant. This result is different from that reported in the trial by Chagpar et al., in which circumferential shaving achieved a 15% reduction in MPR. One of the reasons for this could be the small volume of shaved tissues in our trial (median 12 cm^3), which was significantly lower than that reported in the trial by Chagpar et al. (median 36.1 cm^3).[13] In this trial, we did not specify the volume of the shaved tissues, and the surgeons were instructed to circumferentially shave the cavity as much as possible, as long as shaving would not compromise the cosmetic results based on the surgeons' judgments. We speculated that the small volume of shaved tissues was caused by the small breast volume of Chinese female patients, since 62.4% of participants had A–B cup breasts. This is supported by the significant correlation between the volume of circumferentially shaved tissues and patients' breast volume. Furthermore, subgroup analysis showed that circumferential shaving significantly reduced the MPRs in patients with C–E cup breasts. As breast volumes are generally different between Eastern and Western female populations,[25] whether circumferential shaving in Eastern countries would be valid in reducing MPRs requires further investigation.

The MPR of the no-shave group was 34% in the trial by Chagpar et al.[13] and 12.1% (FSA) to 16.5% (FFPEA) in our trial. A possible explanation of the difference was that the proportion of patients with a DCIS component was higher in the trial by Chagpar et al.[13] than in our trial (70–75% vs. 43%). Moreover, the presence of a DCIS component was a significant determinant of positive margins in both studies. Hence, we speculate that the benefit of circumferential shaving is more prominent in populations with high MPRs. Moreover, for patients with a DCIS component, the MPR in the current trial was numerically, although not

TABLE 2 Study endpoints

	No-shave group	Shave group	*p* Value
MPRs by intraoperative FSA, %	12.1	7.8	0.38[a]
MPRs by postoperative FFPEA, %	16.5	7.8	0.073[a]
Intraoperative re-excision rate, %	26.4	23.3	0.64[a]
Second operation rate, %	4.4	1.1	0.34[b]
Successful BCS rate	93.4	94.4	0.94[a]

FFPEA formalin-fixed paraffin-embedded analysis, *FSA* frozen section analysis, *MPRs* margin positivity rates, *BCS* breast-conserving surgery

[a]Chi-square test

[b]Fisher exact test

TABLE 3 Subgroup analysis

	N	Intraoperative MPRs by FSA		Postoperative MPRs by FFPEA	
		No-shave vs. shave group (%)	*p* Value	No-shave vs. shave group (%)	*p* Value
Density, %					
< 50	35	10 vs. 6.7	0.73[b]	20.0 vs. 6.7	0.37[b]
> 50	146	12.7 vs. 8.0	0.35[a]	15.5 vs. 8.0	0.16[a]
Breast volume, cup size					
A–B	113	9.1 vs. 12.1	0.61[a]	12.7 vs. 12.1	0.92[a]
C–E	68	16.7 vs. 0	0.03[b]	22.2 vs. 0	0.01[b]
Size of the excised specimen, cm					
≤ 5	78	12.2 vs. 10.3	1.00[b]	18.4 vs. 10.3	0.37[b]
> 5	103	11.9 vs. 5.9	0.46[b]	14.3 vs. 5.9	0.29[b]
Presence of DCIS component					
Absence	103	0 vs. 2.0	0.50[b]	5.8 vs. 2.0	0.62[b]
Presence	78	28.2 vs. 15.4	0.17[a]	30.8 vs. 15.4	0.11[a]

FFPEA formalin-fixed paraffin-embedded analysis, *FSA* frozen section analysis, *MPRs* margin positivity rates, *DCIS* ductal carcinoma in situ

[a]Chi-square test

[b]Fisher exact test

statistically, lower in the shave group (15.4%) than in the no-shave group (28.2–30.8%). For patients without a DCIS component, the MPR was similar between the two groups (shave vs. no-shave: 2.0% vs. 0–5.8%). Additionally, 90% of participants in our trial had palpable tumors, compared with 22% in the trial by Chagpar et al. Whether the MPR was higher for patients with non-palpable tumor is still unclear. However, in the COBALT trial, all participants had palpable breast cancer, and the MPR of the controlled group was still as high as 27%,[4] whereas in a prospective cohort study of non-palpable breast cancer patients, the MPR was only 7%.[26] Therefore, other factors, such as breast volume, breast density, and surgical experience might all be potential determinants of MPR.

Several limitations should be addressed. First, whether circumferential shaving could significantly decrease the MPR of patients after neoadjuvant chemotherapy (NAC) is still unclear. Both the trial by Chagpar et al. and our trial did not address this issue. Although NAC could downstage the tumor and decrease the MPR,[27,28] a radiology study showed that different patterns of shrinkage of the tumor, e.g. concentric and non-concentric, occurred after NAC.[29] It is still unclear whether circumferential shaving would benefit patients with non-concentric (mosaic/honeycomb) tumor shrinkage after NAC. Second, oncoplastic BCS allows for wide resections with acceptable oncological outcomes,[30] and has been widely adapted as a standard-of-care treatment in many institutions. De La Cruz et al.[31] reported that the MPR of patients with oncoplastic BCS was 10.8%, which is significantly lower than that with traditional BCS (35%).[3] In an era where more and more oncoplastic BCS are adapted, the value of shaving approach needs to be reconsidered. Third, the majority of patients had palpable tumors in this trial, indicating that the generalizability of our results requires further validation in a screen-detected breast cancer patient cohort.

CONCLUSIONS

FSA for cavity margin assessment helps to facilitate BCS with a low second operation rate. Circumferential shaving did not significantly reduce the MPR during BCS. The benefit of circumferential shaving is dependent on the volume of the shaved tissues and the breast. Patients with smaller breast volume are less likely to benefit from circumferential shaving.

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