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Clinical Outcomes of Breast-Conserving Surgery in Patients Using a Modified Method for Cavity Margin Assessment

Kai Chen[1], Yunjie Zeng, MD[2], Haixia Jia, MD[1,3], WeiJuan Jia, MD[1], Hua Yang, MD[1,4], Nanyan Rao, MD[1], Erwei Song, MD, PhD[1], Charles E. Cox, MD[5], and Fengxi Su, MD[1]

[1]Department of Breast Surgery, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, People's Republic of China; [2]Department of Pathology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, People's Republic of China; [3]Department of General Surgery, Second Affiliated Hospital of Guangzhou Medical School, Guangzhou, People's Republic of China; [4]Mammary Therapeutic Center, Henan Province Oncology Hospital, Zhengzhou, People's Republic of China; [5]Department of Surgery, University of South Florida College of Medicine, USF Breast Health, Tampa, FL

ABSTRACT

Background. This study describes a modified intraoperative method for cavity margin (CM) assessment in place of lumpectomy margin assessment in patients undergoing breast-conserving surgery (BCS).

Methods. This is a retrospective review of 422 breast cancer patients undergoing BCS with intraoperative CM assessment. After an initial lumpectomy with intent to obtain ≥1-cm margins, separate specimens 1 × 1 cm, 0.5-cm thick were taken from the cavity margin circumferentially. These were frozen without reference to the side of the new margin as a time-saving measure, and parallel sections of the resected surface were evaluated.

Results. After a median follow-up of 55.5 months, a cumulative 5-year locoregional recurrence-free survival rate of 95.3 %, metastasis-free survival rate of 97.8 %, disease-free survival rate of 88.3 %, and overall survival rate of 96.0 %, was achieved. The CM positivity rates were of no statistical difference when <7, 7–8, and >8 CMs were assessed. The second operation rate was 3.5 % because of the false-negative results of the frozen section analysis on CMs. Univariate and multivariate analysis revealed that a higher pN stage and cT stage as well as a lack of adjuvant chemotherapy or radiation demonstrated significantly worse clinical outcomes. Locoregional recurrences and metastasis are both correlated with worse overall survival. The number of the CMs assessed was not associated with clinical outcomes.

Conclusions. The modified CM assessment presented here is a rapid, accurate, and oncologically safe approach for margin evaluation in BCS patients. Lumpectomy margin assessment might be spared when this method is used.

C. E. Cox, MD
e-mail: coxce@hotmail.com

F. Su, MD
e-mail: fengxisu@vip.163.com

Margin clearance should be achieved during breast-conserving surgery (BCS) as recommended by the national comprehensive cancer network (NCCN) guidelines.[1] In a literature review of 34 related studies, Singletary concluded that it was unacceptable to have tumor cells at the cut edge of the excised specimen because it is associated with an increased risk of local recurrence.[2] Therefore, the methodology for margin assessment is critical for successful BCS. The traditional approach, applied in the NSABP B-06, assesses lumpectomy margins (LMs) and is further depicted in detail by Fisher et al.[3] During the past decade, surgeons began submitting cavity margins (CMs) in addition to LMs for pathological assessment with the belief that CMs may more accurately reflect the true margin status.[4–8] Studies have also revealed that the assessment of CMs reduces the second operation rate for re-excisions.[4,6,9,10]

Notably, in patients with both LMs and CMs assessed during BCS, Hewes et al. found that it was the positive CMs rather than the positive LMs that were associated with the patient's clinical outcome.[11] Thus, we hypothesize that assessing the CMs alone in BCS may be sufficient for achieving satisfactory clinical outcomes, sparing the time used to evaluate the LMs assessment. Direct comparison of these 2 strategies (LMs + CMs vs CMs alone) has not been reported to date; therefore, this study aims to validate the latter strategy of CMs alone by reviewing the clinical outcomes of patients with only CMs being assessed during BCS at our institution. In addition, we are reporting a novel method for CM assessment, which is more convenient and much more effective than the previous techniques.

METHODS

Patients

This retrospective review was approved by the Institutional Review Board (IRB) at Sun Yat-sen Memorial Hospital. Patients who had only CMs assessed during BCS between 1999 and 2007 were identified. Patients were excluded from this review for: prior neoadjuvant chemotherapy, conversion to mastectomy intraoperatively or postoperatively, incomplete clinical data, if a quadrantectomy was used for breast conservation, and finally patients with evidence of distant metastasis before BCS. Adjuvant endocrine therapy and chemotherapy were performed when
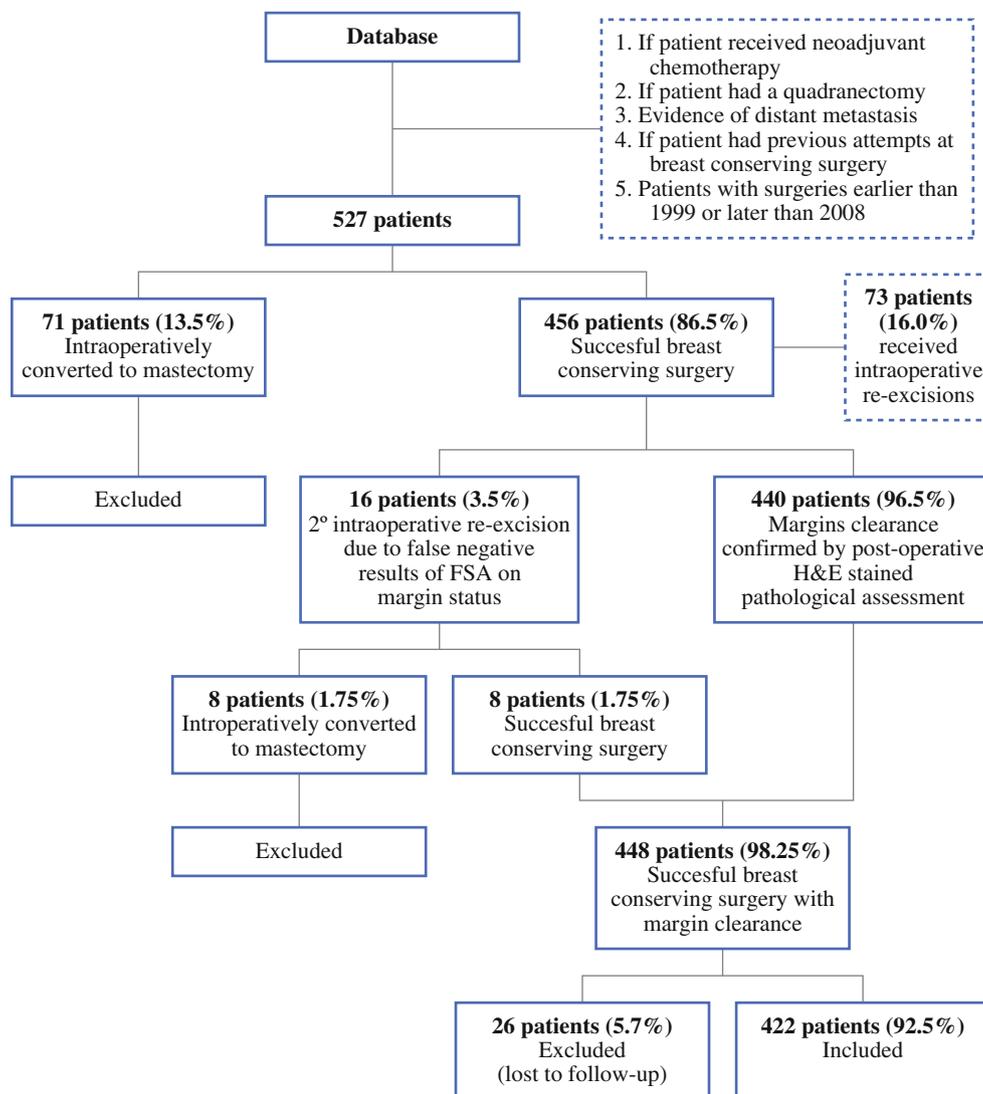
FIG. 1 Inclusion and exclusion criteria for patients in our study

appropriate for tumor stage and size as defined in the NCCN guidelines (Fig. 1).

Surgical and Pathological Considerations

For the lumpectomy, 1 cm of macroscopically normal tissue was removed to ensure that the margins of the tumor-containing lumpectomy specimen would be tumor free. Needle localization was used to facilitate the resection of nonpalpable tumors. Radiographically detected microcalcifications were excised and sent for examination. Standard excision of the tumor-containing specimen extended anteriorly to the subdermal plane of the skin and posteriorly to the pectoralis major fascia. CM assessment included rectangular-shaped CMs [length × width × thickness: (5–10 mm) × (5–10 mm) × (5 mm)] that were systematically harvested by shaving along the circumference of the lumpectomy cavity in a clockwise direction, as reported by Povoski et al.,[12] after the tumor-containing specimen was removed. A surgical blade was used for resecting the CMs to render the thickness of the CMs as thin as possible. After the resection of each CM, silk was stitched to mark its location within the lumpectomy cavity. These silks were all removed before closing, if no more re-excisions were needed. We used 1 forcep to clamp the silk corresponding to the superior part of the cavity and designated this as 12 o'clock CM. The numeration of the other CMs starts from the 12 o'clock CM in a clockwise direction (Fig. 2). All of the CMs were handled and fixed like an "en face" margin. No

inking or other procedures were required for distinguishing the inner and outer surface. They were then frozen and cut parallel to the largest surface area, but not perpendicularly to that area (Fig. 2). CMs were defined as positive when in situ or invasive carcinoma was found microscopically. A technique known as frozen-section analysis (FSA) was performed intraoperatively and re-excisions were made on the corresponding sites where the CMs were positive, until negative CMs were ultimately obtained. Patients were converted to mastectomy intraoperatively if more than half of the CMs were positive at the time of first collection or no negative CMs were achieved after 3 intraoperative re-excisions. Postoperative paraffin-embedded hematoxylin and eosin (H&E) staining was performed to confirm the pathology diagnosis in all specimens and CMs.

A sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND) was performed at the time of the BCS for all necessary patients as per NCCN guidelines. All BCS and pathological assessments were performed by F. Su and Y. Zeng, respectively.

Statistical Analysis

The 5-year cumulative locoregional-free survival, metastasis-free survival, disease-free survival, and overall survival were calculated using Kaplan-Meier survival analysis. Comparison of clinicopathological features and positivity rates of CMs among patients with different numbers of CMs assessed were determined using the

A modified method for Cavity margin assessment
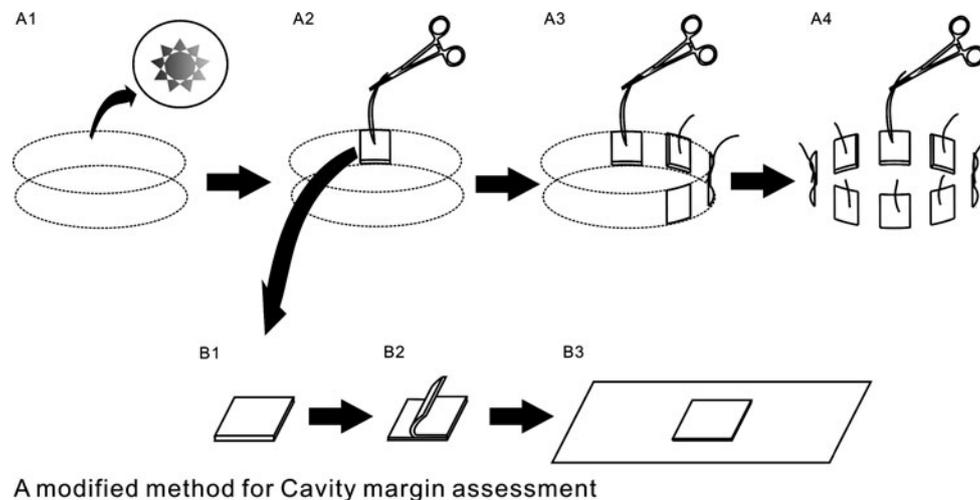
FIG. 2 Our modified method for cavity margin assessment. **A1** Tumor-containing specimen was removed. **A2** The first CM was usually harvested at the superior part of the cavity. After resection of the CM, a silk suture was used to mark its location within the lumpectomy cavity. A forcep was used to clamp this silk; its corresponding CM was designated as 12 o'clock CM. **A3** The numeration of the other CMs starts from the 12 o'clock CM in a clockwise direction. Silk sutures were used, but no more forceps were needed. **A4** If FSA revealed any of the CMs was positive, intraoperative re-excisions were made at its location marked by the silk. All of the silks were removed before closing if all of the CMs were negative. **B1, B2** CMs were cut in an "en face" pattern: parallel to the biggest surface without distinguishing the outer or inner one. **B3** Pathological evaluation was performed through frozen section and permanent H&E staining, intraoperatively and postoperatively, respectively

chi-squared test or Fisher exact test when appropriate. Univariate and multivariate analysis for determining predictors of clinical outcomes were performed with Cox regression survival model. The reported P values were 2-sided and considered statistically significant at ≤ 0.05. All data analyses were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

A total of 456 patients underwent BCS. Among those 456 patients, 73 patients (16 %) received intraoperative re-excisions ultimately resulting in a successful BCS. Additionally, 16 patients (3.5 %) underwent a second operation because of the false negative results of FSA for margin assessment. Of those 16 patients, 8 patients (1.75 %) were converted to a mastectomy and excluded from the review and 8 patients (1.75 %) had successful BCS, therefore remaining in the study. In conclusion, 448 patients (98.25 %) received successful BCS with margin clearance, but 26 patients (5.8 %) were lost to follow-up, resulting in 422 patients evaluated in this study (Fig. 1).

The clinicopathological features are shown in Table 1. The median age of the patients at diagnosis was 46.0 years (range 24–89 years). Nearly 90% of the included patients had early-stage diseases (stage I and II). Approximately a quarter of our patients (23.5 %) received an excisional biopsy to obtain diagnosis before the BCS. The average pathological tumor size was 1.9 cm (excluding patients who received excisional biopsy prior to surgery or unknown tumor size). The average diameter for the tumor-containing specimen was estimated to be 3.9 cm. At a median follow-up of 55.5 months (range 12–130 months), the cumulative 5-year locoregional recurrence-free survival rate, metastasis-free survival rate, disease-free survival rate, and overall survival rate of the entire cohort of 422 patients was 95.3, 97.8, 88.3, and 96.0 %, respectively. Among the total patients currently enrolled in the study, 90.5 % of patients are alive and disease-free (Table 2). Risk factors for clinical outcomes were analyzed and are summarized in Table 3. Univariate and multivariate analysis revealed that higher pN stage (>pN0 vs pN0, $P < 0.05$, HR = 3.67) and lack of adjuvant radiation therapy ($P < 0.01$, HR = 9.25) significantly predicted locoregional recurrence. Higher pN stage (pN >0 vs pN0) also increased the risk of metastasis ($P < 0.01$, HR = 4.07) as well as predicted a poor disease-free survival ($P < 0.01$, HR = 3.36). Lack of adjuvant radiation therapy was also independently associated with lower disease-free survival ($P < 0.01$, HR = 6.50). Higher cT stage (cT >1 vs cT1, $P = 0.017$, HR = 5.39), lack of chemotherapy ($P < 0.01$, HR = 6.96), locoregional recurrence ($P < 0.01$, HR = 10.62), and metastasis ($P < 0.01$,

TABLE 1 Clinicopathological features of the patients

Features	No.	%
Age		
>35	369	87.4
≤35	53	12.6
Stage		
I	213	50.5
II	166	39.3
III	30	7.1
Unknown	13	3.1
cT stage[a]		
T1	241	57.1
T2	152	36.0
T3	3	0.7
T4	0	0.0
Tx	26	6.2
pT stage[a]		
T1	246	58.3
T2	90	21.3
T3	9	2.1
T4	0	0.0
Tx	77	18.3
pN stage		
N0	296	70.1
N1	96	22.8
N2	23	5.5
N3	7	1.7
Excisional biopsy prior to lumpectomy		
No	323	76.5
Yes	99	23.5
Initial margin status		
Negative	360	85.3
Positive	62	14.7
Lymphovascular invasion		
Negative	397	94.1
Positive	25	5.9
Histology		
IDC	297	70.4
Presence of DCIS	56	13.3
Others	69	16.4
Number of cavity margins at primary lumpectomy		
≤6	131	31.0
7–8	158	37.4
≥9	133	31.5
ER status		
Negative	117	27.7
Positive	305	72.3
PR status		
Negative	114	27.0
Positive	308	73.0

TABLE 1 continued

Features	No.	%
cerbB-2 status		
Negative	309	73.8
Intermediate	44	10.5
Positive	66	15.8
Date of surgery		
Before 2004	127	30.1
2005–2006	128	30.3
After 2007	167	39.6
Adjuvant chemotherapy		
Yes	379	89.8
No	43	10.2
Adjuvant radiation therapy		
Yes	390	92.4
No	26	6.2
Unknown	6	1.4
Adjuvant endocrine therapy		
Yes	341	80.8
No	81	19.2

[a] Patients who received an excisional biopsy without available record of the pathological tumor size were classified as Tx

TABLE 2 Recurrences, metastasis, and other events

Events	No.	%
Local recurrence	12	2.8
Regional recurrence	5	1.2
Metastasis	19	4.5
Second cancer (included contralateral breast cancer)	2	0.5
Death without evidence of breast cancer	2	0.5
Total deaths	14	3.3
Alive, event-free	382	90.5
Total patients	422	

HR = 37.06) independently correlated with overall survival. The cumulative 5-year metastasis-free survival rate of patients with and without locoregional recurrence were 84.4 and 95.5 % ($P = 0.135$), respectively. The overall survival rate of patients with locoregional recurrence was 80.2 % and without locoregional recurrence was 96.7 % ($P < 0.01$), and the overall survival rate for patients with metastasis was 59.2 % and without metastasis was 98.1 % ($P < 0.01$).

A total of 3220 margin tissues were collected from all of the patients, and 87 (2.7 %) were found to be positive for carcinoma at the primary intraoperative excision. The positivity rate at the margin level was similar even when different numbers of cavity margin were collected (Table 4). In patients without history of an excisional biopsy, positivity rates at the patient level [(no. of patients with at least 1 positive margins)/(total no. of patients)] were increased when more cavity margins were collected, with marginal significant difference (Table 4, $P = 0.051$). It should be noted that the number of the margins (≤ 6, 7–8, ≥ 9) collected for assessment did not alter the clinical outcomes in our study because in the end all margins were found to be negative. The distribution of the clinicopathological features among these 3 groups were similar (Supplemental Table 1).

DISCUSSION

Breast-conserving surgery has been validated as a standard surgical treatment for breast cancer around the world. Margin clearance is warranted for successful local control.[2] The method of LM assessment in NSABP B-06 is widely used.[3] During the past decade, surgeons have started to submit CMs (separate or continuous) in addition to LMs for assessment during BCS. Studies have shown that assessing the CMs may spare approximately 50 % of patients with positive LMs from re-excision.[4–11] However, it is still unknown whether the assessment of CMs alone, without evaluation of LMs, guarantees oncological safety and acceptable clinical outcomes. Because China's breast conservation rate was an astonishingly low 10 % in 2008, it is critical to introduce a convenient, reliable, and effective method for margin assessment.[13] This study retrospectively reviewed the clinical outcomes of 422 patients with only CMs assessed during their BCS. Margin clearance was achieved in all of our CMs through intraoperative or postoperative re-excisions. Our results revealed that assessing CMs alone is oncologically sound as well as time and cost efficient because it is no longer necessary to review LMs.

The complete list of advantages of our approach is shown in Table 5. The inking procedure was omitted because it was not necessary to distinguish the outer surface from the inner surface of the CMs, nor did we have to measure the distance between the tumor cells and the surfaces (See the "Methods" section). Therefore, our method may substantially reduce the amount of time and workload the pathologists spend on each case. It is theoretically plausible that without marking the true margin of the CM tissue, pathologists may have a 50 % chance of not assessing the real margins. However, it had been estimated that for a complete examination of the surface of a lumpectomy specimen measuring 2 cm in diameter, approximately 10,000 sections are needed.[14,15] Thus, such a thorough evaluation of the margin status of the excised specimen is impossible for clinical practice. The reliable index to justify an approach should be the clinical outcome, which is attributed to various factors in the era of multidisciplinary teamwork. Our approach

TABLE 3 Univariate and multivariate analysis of risks factors for clinical outcomes

Features	Univariate analysis P value	Multivariate analysis		
		HR	95% CI	P value
Locoregional recurrence				
cT >1/cT1	<0.05	–	–	NS
pN >0/pN0	<0.05	3.7	1.3–10.0	<0.05
Adjuvant radiation therapy ±	<0.01	9.3	3.2–27.1	<0.01
Adjuvant endocrine therapy ±	<0.05	–	–	NS
Metastasis recurrence				
Stage				
II/I	NS	–	–	NS
III/I	<0.01	–	–	NS
pN >0/pN0	<0.01	4.1	1.6–10.5	<0.01
Locoregional recurrence ±	NS	–	–	NS
Disease-free survival				
Stage				
II/I	<0.01	–	–	NS
III/I	<0.05	–	–	NS
>cT1/cT1	<0.01	–	–	NS
>pN0/pN0	<0.01	3.4	1.8–6.3	<0.01
Adjuvant radiation therapy ±	<0.01	6.5	2.9–12.9	<0.01
Overall survival				
Stage				
II/I	<0.01	–	–	NS
III/I	<0.01	–	–	NS
>cT1/cT1	<0.01	5.4	1.4–21.5	<0.05
>pN0/pN0	<0.01	–	–	NS
PR ±	<0.01	–	–	NS
Date of surgery				
2005–2006/before 2004	<0.05	–	–	NS
After 2007/before 2004	NS	–	–	NS
Adjuvant radiation therapy ±	<0.01	–	–	NS
Adjuvant chemotherapy ±	<0.01	7.0	2.1–23.2	<0.01
Locoregional recurrence ±	<0.01	10.62	2.5–45.2	<0.01
Metastasis ±	<0.01	37.06	10.9–126.5	<0.011

Risk factors predicting clinical outcomes were analyzed by univariate and multivariate analysis. Age, LVI, pathology, cT stage, pN stage, history of excisional biopsy, initial margin numbers, initial margin status, lack of radiation or chemotherapy, ER, PR, and Her2 status were all included in these evaluations

HR hazard ratios, *CI* confidential interval, *NS* nonsignificant, *RT* radiation therapy, *PR* progesterone receptor

yielded satisfactory clinical outcomes when adjuvant therapies were administered, even if only a minority of HER2-positive patients were able to receive the standard trastuzumab (Herceptin) treatment because trastuzumab is not covered by medical insurance in China. The clinical outcomes might have been more favorable if those patients had received a year-long trastuzumab treatment.

When inking is used during traditional LM assessment, unwanted artifacts may also be present in the specimen including ink seepage, natural tissue retraction, distortion during radiologic examination, and potential loss of fat

issue near the margins, all of which may have an impact on margin measurement. In addition, there is a sustained debate regarding the definition of the optimal surgical margin width in BCS. Surveys sent to surgeons revealed significant variation in the definition of an acceptable surgical margin.[16,17] For some institutions where cavity margins were assessed, similar inking procedures and perpendicular sectioning were applied. Without the use of an inking procedure, our method avoided the potential altering of the specimen as well as the controversial issue of optimal width of surgical margin.

TABLE 4 Association between the number of margins being assessed and the positivity rate

Features		No. of patients	No. of collected margins	No. of positive margins (margin level) No. (%)	P value	No. of patients with at least one positive margin (patient level) No. (%)	P value
Excisional biopsy	No. of margins collected						
No	≤6	102	513	11 (2.1)	NS	8 (7.8)	0.051
	7–8	116	887	22 (2.5)		20 (17.2)	
	≥9	105	1062	35 (3.3)		20 (19.1)	
Yes	≤6	29	151	4 (2.7)	NS	3 (10.3)	NS
	7–8	42	324	10 (3.1)		7 (16.7)	
	≥9	28	283	5 (1.8)		4 (14.3)	

NS nonsignificant

TABLE 5 Our modified cavity margin assessment will be more time and cost saving when compared with lumpectomy margin assessment

Lumpectomy margin assessment	Cavity margin assessment
Tumor-containing specimen sent to the pathologist for inking	No inking procedure for tumor-containing specimen and the cavity margins
Lumpectomy margins were collected by the pathologist from the tumor-containing specimen as depicted by Fisher et al.[3]	Pathologist can directly deal with the cavity margins submitted by the surgeon
Distance between the tumor cells and the inked margins was measured by pathologist	No distances were measured or calculated

The positivity rate of CMs at the tissue level and the patient level were 2.7 and 14.7 %, respectively. We performed intraoperative re-excisions to achieve final margin clearance in these patients. Only 3.5 % of patients received a postoperative re-excision as a result of the discordant results between the intraoperative and postoperative pathological evaluation. This is an eminent observation because it has been reported that second operation rates are as high as 40% for the assessment of lumpectomy margins.[18] In the United States, FSA is not widely accepted for margin assessment. However, there is a large amount of evidence supporting the feasibility, reliability, and safety of using FSA in margin assessment.[19–26] Additional time for FSA in our study was 30–50 min, which is acceptable. In studies conducted by Olson et al. and Cendan et al.[21,23] the FSA time for margin assessment was 25 and 13 minutes, respectively. Despite the additional time, using FSA is worthwhile. In current studies, the combination of FSA and our margin assessment method yielded a much lower second operation rate, which in turn greatly decreases the cost compared with the traditional approach.

Our univariate and multivariate analysis did not reveal any association between initial margin status and the patient's clinical outcome. Patients with negative margins obtained through multiple re-excisions had a similar prognosis to those patients with negative margins initially. These results are consistent with those reported by O'Sullivan,[27] in which 2770 patients undergoing BCS over 25 years were analyzed.

A study conducted by Huston et al.[28] suggests that 4–6 CMs for assessment was superior to 1–3 CMs. We also looked at how many CMs should be submitted for evaluation in our modified method. We divided the patients into 3 subgroups based on the number of the CMs collected (GI: ≤6; GII: 7–8; GIII: ≥9). Clinicopathological features of these patients were similar (Supplemental Table 1). Patients with fewer margins collected (GI: ≤6) had lower margin positivity rates. The optimal number of CMs for assessment may be 7–8 (GII), as submitting more margins (GIII: ≥9) would not significantly increase the positivity rate (Table 4). It is interesting to observe that the clinical outcomes were similar among these 3 groups. Therefore, the optimal number of CMs for pathological assessment is still unclear. Until more substantial evidence emerges, we still suggest 7–8 CMs for assessment as fewer CMs (≤6) may lead to inadequate positivity rates, whereas more margins (≥9) may compromise the cosmetic appearance without more benefits.

It should be mentioned that breast size, depth, and parenchymal density of the Chinese patients may vary from populations in North America, making this methodology uniquely effective in this population. In Asian women with comparatively smaller breasts, the less tissue we resect, the better cosmetic outcomes we would have. The average resection volume of the specimen in our study was only 64.8 cm.[3] The general size of each CM was approximately (5–10 mm) by (5–10 mm) by (5 mm), and the average volume of each CM may range from 125 to 500 mm^2,

which was much lower than those reported by Povoski et al.[12] Hence, the thinness of the CMs was essential in our technique to have satisfactory cosmetic outcomes. From the perspective of oncological safety, only when the CMs were adequately thin (less than 5 mm) could we ignore the distinction between the inner and outer surface of the CM tissues. For CMs with a thickness greater than 5 mm, we suggest that the inking procedure is mandatory to mark the outer surface.[4,5,9–11,29] Thus, the unique features of the Chinese patients might bring potential bias and possibly limits the efficacy of our method in patients with more fat tissue. However, the method is fast, effective, and oncologically safe at least in Chinese patients, indicating its potential value for other Asian populations with similar features of the breast. Additionally, cost analysis is needed in the future.

Our results showed that assessing the CMs alone does lead to satisfactory clinical outcomes. We also introduced a modified method for CM assessment that did not require inking procedures or distance measurement. With only 3.5% of the patients requiring a second operation to yield negative margins, this translates into a significant time and cost savings for the health care system. Thus, our approach is likely to be more time and cost effective. With standard adjuvant chemotherapy and radiation, our method gave rise to acceptable clinical outcomes. In the future, a prospective, well-designed, randomized-controlled study comparing our method and the conventional assessment of LMs should be conducted.

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