Editorial Correspondence: Margo Chen, Science Editor, *Gland Surgery*. HK office: Flat/RM C 16F, Kings Wing Plaza 1, No. 3 on Kwan Street, Shatin, NT, Hong Kong. Tel: +852 3615 8769; Email: editor@glandsurgery.org.

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Aims and Scope

Gland Surgery (Gland Surg; GS, Print ISSN 2227-684X; Online ISSN 2227-8575), launched in May 2012, is an open access, peer-reviewed journal published monthly (quarterly published from 2012 to 2014 and bimonthly published from 2015~2020). GS has been indexed by PubMed/PubMed Central (PMC) and Science Citation Indexed Expanded (SCIE). Its latest impact factor (2022 citation year) is 1.8.

As a monthly published journal, it aims at providing cutting-edge findings and practical information on diagnosis, prevention, and treatment of gland diseases, such as breast, thyroid, adrenal, pancreas surgery and other related fields. Dedicated to the understanding and treatment of gland diseases, this multidisciplinary periodical publishes articles that describe basic, translational and clinical research of gland disease from a range of fields as biomarkers, imaging, pathology, biology and interventional radiology etc. Readers can expect to gain new insights into diagnosis, therapeutic approaches and prognosis of gland diseases.

The journal is proud of the quality and content, which is further enhanced by a hands-on approach by its editorial team. Its international readership is reflected in the prestigious Editorial Board supported by numerous experts worldwide. It aims to advance and improve education in surgery and to diffuse knowledge on new and improved methods of teaching and practising surgery in all its branches.

The journal features original articles, case reports, cutting-edge reviews, surgical techniques and visualized surgery, thus representing a source of valuable, novel information for clinical and basic researchers alike. The entire submission and review process are managed through OJS, an electronic system to increase efficiency and ensure that submitted papers can be published within a short turnaround period.

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HK office: Flat/RM C 16F, Kings Wing Plaza 1, No. 3 on Kwan Street, Shatin, NT, Hong Kong. Tel: +852 3615 8769;
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Original Article

Accuracy of cone-beam breast computed tomography for assessing breast cancer tumor size—comparison with breast magnetic resonance imaging

Mengran Zhao[1#], Xiangchao Song[1#], Yue Ma[1], Zhijun Li[1], Yafei Wang[1], Aidi Liu[1], Hong Lu[2], Ying Ma[3], Zhaoxiang Ye[1]

[1]Department of Radiology, Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education, Key Laboratory of Cancer Prevention and Therapy, Tianjin, China; [2]Department of Breast Imaging, Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education, Key Laboratory of Cancer Prevention and Therapy, Tianjin, China; [3]Department of Pancreatic Cancer, Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education, Key Laboratory of Cancer Prevention and Therapy, Tianjin, China

Contributions: (I) Conception and design: M Zhao, X Song; (II) Administrative support: H Lu, Z Ye; (III) Provision of study materials or patients: M Zhao, X Song; (IV) Collection and assembly of data: M Zhao, X Song, Yue Ma, Y Wang; (V) Data analysis and interpretation: M Zhao, Yue Ma, Y Wang, A Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as co-first authors.

Correspondence to: Zhaoxiang Ye, MD. Department of Radiology, Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education, Key Laboratory of Cancer Prevention and Therapy, Huan-Hu-Xi Road, Ti-Yuan-Bei, Hexi District, Tianjin 300060, China. Email: zye@tmu.edu.cn.

Background: Accurate preoperative assessment of tumor size is important in developing a surgical plan for breast cancer. The purpose of this study was to evaluate the accuracy of cone-beam breast computed tomography (CBBCT) and magnetic resonance imaging (MRI) in the assessment of tumor size and to analyze the factors influencing the discordance.

Methods: In this retrospective study, patients with breast cancer who underwent preoperative contrast-enhanced CBBCT (CE-CBBCT) and dynamic contrast-enhanced MRI (DCE-MRI) and received a complete pathologic diagnosis from August 2020 to December 2021 were included, using the pathological result as the gold standard. Two radiologists assessed the CBBCT and MRI features and measured the tumor size with a 2-week washout period. Intraclass correlation coefficient (ICC) and Bland-Altman analyses were used to assess inter-observer reproducibility and agreement based on CBBCT, MRI and pathology. Univariate analyses of differences in clinical, pathological and CBBCT/MRI features between the concordant and discordant groups was performed using the *t*-test, Mann-Whitney *U*-test, Chi-squared test and Fisher's exact test. Multivariate analyses were used to identify factors associated with discordance of CBBCT/MRI with pathology.

Results: A total of 115 female breast cancer patients (115 lesions) were included. All patients had a single malignant tumor of the unilateral breast. The reproducibility and the agreement ranged from moderate to excellent (ICC =0.607–0.983). Receiver operating characteristic (ROC) analyses showed that the cut-off values of CBBCT-pathology and MRI-pathology discordance were 2.25 and 2.65 cm, respectively. CBBCT/MRI-pathology concordance was significantly associated with the extent of pathology, lesion type, presence of calcification, human epidermal growth factor receptor 2 (HER2) status and fatty infiltration (P<0.05). In lesions containing calcification, the difference of CBBCT-pathology was significantly smaller than MRI-pathology (P=0.021). Non-mass enhancement (NME) was the main predictor of CBBCT- or MRI-pathology discordance [odds ratio (OR) =3.293–6.469, P<0.05], and HER2 positivity was a predictor of CBBCT-pathology discordance (OR =3.514, P=0.019).

Conclusions: CBBCT and MRI have comparable accuracy in measurement of tumor size, and CBBCT is advantageous in assessing the size of calcified lesions. NME and HER2 positivity are significant predictors of CBBCT-pathology discordance. This suggests that CBBCT might serve as an alternative imaging technique to assess tumor size when patients do not tolerate MRI.

Keywords: Cone-beam breast computed tomography (CBBCT); magnetic resonance imaging (MRI); tumor size; pathology

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Introduction

Surgical excision is one of the main clinical treatment modalities for breast tumors (1,2). For patients with breast cancer, radical mastectomy allows complete removal of the lesion in order to prevent recurrence of the malignant disease (3). At the same time, however, the extensive trauma of this invasive procedure can have a significant impact on the patient's quality of life and aesthetic needs after surgery. With the development of precision therapy and integrated systemic treatment, breast-conserving surgery (BCS) has been increasingly relied on by patients and surgeons in recent years (4-6). An extensive tumor is one of the main factors that can make BCS unfeasible or unsuccessful. Therefore, an accurate preoperative assessment of tumor size is important in the planning of breast cancer surgery (7,8).

Radiological techniques play a crucial role in the pretreatment assessment of breast cancer, with breast magnetic resonance imaging (MRI) considered to be the most sensitive imaging technique available (9,10). MRI has high soft tissue resolution (11) and measures tumor size more accurately than mammography or ultrasound (12). However, due to the limitations of imaging principles, MRI cannot show calcifications in a breast cancer lesion, which are often a sign of ductal carcinoma *in situ* (13). The inability of MRI to detect calcifications can lead to a false assessment of tumor size, resulting in failure of BCS and an increased rate of reoperation.

Cone-beam breast computed tomography (CBBCT) is a new breast imaging technique in which its diagnostic sensitivity is comparable to that of MRI and allows a faster acquisition speed (14,15). Enhanced imaging using an injected iodine-containing contrast agent can reveal morphological features, calcification features and hemodynamic features of lesions, making it a promising complementary imaging approach for the breast. In several previous studies, CBBCT has shown encouraging results for the diagnosis of suspicious calcifications in the breast (16), the assessment of background parenchymal enhancement (BPE) (17), and the prediction of molecular subtypes of breast cancer (18-20). Consequently, the diagnostic capabilities of CBBCT are considered comparable to those of MRI in the preoperative evaluation of breast tumors (21,22). CBBCT may be a reliable alternative for assessing the extent of lesions when patients cannot undergo MRI

Highlight box

Key findings

- Cone-beam breast computed tomography (CBBCT) and magnetic resonance imaging (MRI) have comparable accuracy in measurement of tumor size, and CBBCT is advantageous in assessing the size of calcified lesions.

What is known and what is new?

- Breast MRI is currently considered the most sensitive radiological technique in the diagnosis and preoperative evaluation of breast cancer.
- CBBCT is a new breast imaging technique of which the diagnostic sensitivity is comparable to that of MRI.

What is the implication, and what should change now?

- Our findings suggest that CBBCT- and MRI-based measurements of breast lesion size have comparable accuracy, and CBBCT is superior in assessing the size of breast lesions that contain calcification. These findings provide important insights into the utility of CBBCT in the preoperative evaluation of breast cancer, namely, that CBBCT may be an alternative to MRI for assessing tumor size when patients are intolerant to MRI.

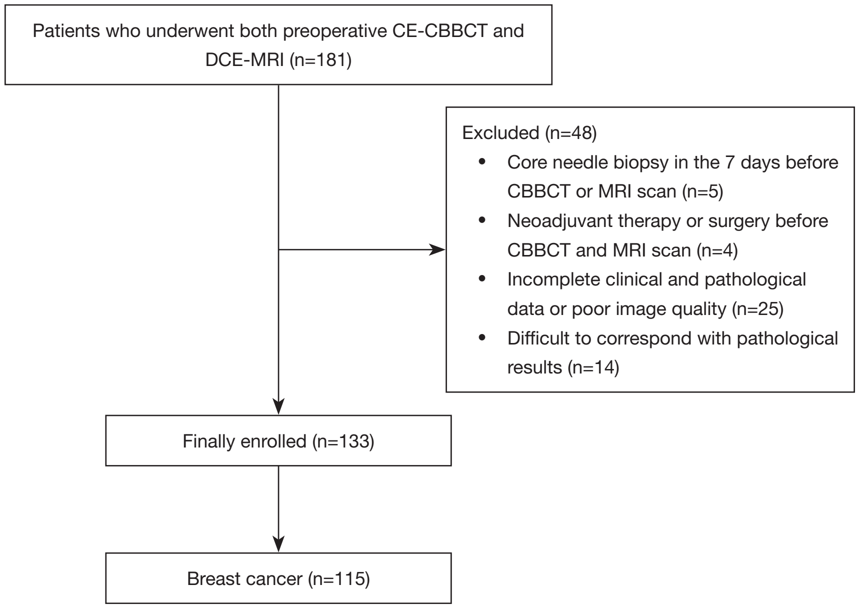

Figure 1 Flow chart of patient selection and exclusion. CE-CBBCT, contrast-enhanced CBBCT; CBBCT, cone-beam breast computed tomography; DCE-MRI, dynamic contrast-enhanced MRI; MRI, magnetic resonance imaging.

for reasons such as contraindications. However, much of the research to date has focused on the factors that lead to discordance between MRI and pathological measurements of tumor size (8,23), while little attention has been paid to the use of CBBCT for tumor size assessment.

Therefore, the main objectives of this study were to evaluate the accuracy of CBBCT and MRI for breast cancer size assessment and to analyze the influencing factors that lead to discordance between CBBCT- and MRI-pathology assessment. We present this article in accordance with the STARD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-401/rc).

Methods

Patients

This retrospective study initially included 181 patients who underwent both preoperative contrast-enhanced CBBCT (CE-CBBCT) and breast dynamic contrast-enhanced MRI (DCE-MRI), with the two examinations taking place no more than 2 weeks apart, over the period from August 2020 to December 2021. All patients were treated surgically, and a complete pathological diagnosis was obtained, in which immunohistochemical (IHC) receptor status was determined. The exclusion criteria were as follows: (I) core needle biopsy within 7 days prior to the CBBCT or MR scan; (II) a history of neoadjuvant or surgical therapy prior to the CBBCT or MR scan; (III) incomplete clinical or pathological data or insufficient image quality for analysis; and (IV) multifocal or multicentric lesions that were difficult to correlate with the pathological results (*Figure 1*). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The ethics committee of Tianjin Medical University Cancer Institute & Hospital (No. bc2016039) approved this retrospective study and waived the requirement for informed consent.

CBBCT and MRI protocols

The timing of the CBBCT and MRI examinations was not related to the menstrual cycle. The two scans were conducted more than 4 hours apart to prevent any interaction of contrast agents or increase in renal metabolic burden.

CBBCT

All CBBCT examinations were performed using a dedicated flat-panel detector breast CT system (KBCT1000, Koning Corporation, USA). During the scanning process, the patient was placed in the prone position, the breast to be examined was naturally suspended in the scanning field, and both sides of breast were scanned alternately. After an initial non-contrast-enhanced CBBCT (NCE-CBBCT) scan, a high-pressure syringe was used to inject 90 mL of a nonionic iodinated contrast agent (Iohexol, Omnipaque® 300, GE Healthcare, USA) intravenously at a rate of 2.0 or 2.5 mL/s, followed immediately by a CE-CBBCT scan. Contrast-enhanced images of the affected breast were obtained 120 s after injection of contrast agent, and images of the contralateral breast were obtained approximately 180 s after injection, depending on the time of repositioning. The specific scanning parameters were as follows: the tube voltage was constant at 49 kVp, and the tube current was automatically adjusted according to the density and size of the breast (range, 50–80 mA). Regarding doses, unilateral breast CE-CBBCT scans entailed 11.46–14.68 mGy for most women, and scans of some large and extremely dense breasts involved 18.34 mGy. The original CBBCT images were processed by the workstation to obtain an isotropic three-dimensional stereo image; the voxel size in standard mode was 0.273 mm^3.

MRI

MRI scans were performed using a 1.5 T (GE Signa HDxt, USA) system (GE Medical Systems, USA). A four-channel phased-array breast coil was used, and patients were scanned in the prone position. DCE-MRI was obtained by volume imaging for breast assessment [VIBRANT; repetition time (TR) =6.1 ms, echo time (TE) =2.9 ms; matrix size 256×128; slice thickness =1.8 mm, field of view (FOV) =26 cm × 26 cm, flip angle =15°, number of excitation (NEX) =1]. After the mask was scanned, a gadolinium contrast agent (Meglumine Gadopentetate, Magnevist, Bayer Healthcare, Germany) was injected intravenously using an MR-specific high-pressure syringe, followed by an equal volume of normal saline. The injected dose was 0.2 mL/kg, and the rate was 2 mL/s. Immediately after the injection, five phases of sagittal contrast-enhanced images were scanned continuously, with the scanning duration of each phase being approximately 90 s. Finally, axial contrast-enhanced scanning was performed.

Pathology review

All specimens were sent to the pathology department for histopathological examination and tumor size measurement. After the tumor lesions were fully exposed, each lesion specimen was cut in the plane with the maximum cross-sectional area, and both the maximum diameter line and the vertical diameter of the section were measured. In addition, IHC analyses were performed. Hormone receptor positivity was defined as estrogen receptor (ER) or progesterone receptor (PR) positivity in more than 1% of tumor cells. Human epidermal growth factor receptor 2 (HER2) positivity was defined as a staining score of 3+ or 2+ with genotype amplification by fluorescence in situ hybridization (FISH). Regarding Ki-67, specimens with staining in more than 14% of tumor cells were classified as the high-proliferation group, and those with staining in 14% of cells or fewer were classified as the low-proliferation group. Molecular subtypes of breast cancer were classified according to IHC receptor status.

Image analyses

CBBCT and MR images were transmitted to the picture archiving and communication system (PACS) for image feature evaluation. MRI and CBBCT images were independently evaluated by two radiologists with 5 and 12 years of diagnostic breast imaging experience and 3 and 10 years of diagnostic CBBCT experience, respectively, while they were blinded to the pathological findings. In the case of an inconsistent assessment, qualitative information was discussed between the radiologists until they reached a consensus, and quantitative measurements were averaged between the two radiologists to calculate the final result. The American College of Radiology (ACR) 2013 Edition of the Breast Imaging Reporting and Data System (BI-RADS) (24) was used to analyze the features of DCE-MRI. The CBBCT feature analysis was performed with reference to the mammography and MRI content in the BI-RADS atlas. The largest section of the tumor was selected by reconstructing the three-dimensional volume of the tumor by three-dimensional maximum intensity projection (3D-MIP) reconstruction of the CE-CBBCT images and DCE-MRI images of 1^{st}- and delayed-phase and the largest diameter was used for subsequent analyses. If both enhancement and calcification were present on CE-CBBCT, the overall extent was measured. Slice thicknesses of 0.273 and 1.8 mm were used for tumor size measurement on CE-CBBCT and MRI, respectively. Using the pathological result as the gold standard, CBBCT and MRI were considered concordant with pathology if the measurement difference was <±0.5 cm, while they were considered discordant with pathology if the difference was ≥±0.5 cm (23).

Table 1 The clinical characteristics of patients and lesion subtypes

Clinical and pathological characteristics	Values
Age (years)	49.63±8.26
Malignant lesions	115
Invasive ductal carcinoma	97 (84.35)
Ductal carcinoma *in situ* with microinvasion	7 (6.09)
Mucinous carcinoma	4 (3.48)
Invasive lobular carcinoma	3 (2.61)
Invasive micropapillary carcinoma	3 (2.61)
Ductal carcinoma *in situ*	1 (0.87)

Data are presented as mean ± standard deviation, n, or n (%).

Table 2 Agreement of tumor size detected between two reviewers and among CBBCT, MRI, and pathology specimens

Readers/measurement methods	ICC value (95% CI)
Reader 1 *vs.* reader 2	
CBBCT	0.983 (0.976, 0.988)
MRI	0.973 (0.983, 0.986)
CBBCT *vs.* pathology	0.673 (0.553, 0.763)
MRI *vs.* pathology	0.607 (0.453, 0.726)
CBBCT *vs.* MRI	0.956 (0.917, 0.974)
CBBCT *vs.* MRI *vs.* pathology	0.767 (0.684, 0.831)

CBBCT, cone-beam breast computed tomography; MRI, magnetic resonance imaging; ICC, intraclass correlation coefficient; CI, confidence interval.

Statistical analyses

Statistical analyses were performed using SPPS software (versions 25.0, IBM Crop). In terms of consistency analysis, the intraclass correlation coefficient (ICC) was calculated to assess the inter-observer agreement between the two reviewers and the consistency of the maximum diameter measured by CBBCT, MRI, and pathology. The ICC values were divided into three categories: poor (ICC <0.5), moderate (0.5≤ ICC <0.8) and excellent (ICC ≥0.8) (25). Bland-Altman analyses were used to assess the consistency of tumor size measurements based on CBBCT, MRI and pathology. Receiver operating characteristic (ROC) curve analyses were carried out to calculate the cut-off points where CBBCT/MRI differed from pathology. For difference analysis, the Kolmogorov-Smirnov test was used to analyze the normality of continuous variables firstly. The differences in clinical factors, pathological factors and CBBCT/MRI features between the concordant and discordant groups were statistically analyzed by Student's *t*-test, the Mann-Whitney *U* test, Chi-squared test and Fisher's exact test. Two-sided P values less than 0.05 were considered statistically significant. Factors that were statistically significant in the univariate analyses were subjected to multivariate analyses. Binary logistic regression was performed to identify factors associated with discordance of CBBCT/MRI pathology, and the odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were used to assess the strength of the association of the factors.

Results

Baseline clinical and pathological characteristics

A total of 115 breast cancer patients (115 lesions) with a mean age of 49.63±8.26 years were included in this study. The patients were all female. All patients had a single malignant tumor of the unilateral breast. *Table 1* displays the summary for the clinical characteristics of patients and breast cancer subtypes.

Interobserver reproducibility and consistency between CBBCT, MRI, and pathology

Based on ICC analyses, the agreement of tumor size measurements by the two reviewers based on both CBBCT and MRI was excellent, with ICC values of 0.983 (95% CI: 0.976, 0.988) and 0.973 (95% CI: 0.983, 0.986), respectively. The agreement between CBBCT and MRI was also excellent, with ICC values of 0.956 (95% CI: 0.917, 0.974). The ICC values of 0.673 (95% CI: 0.553, 0.763) for CBBCT-pathology and 0.607 (95% CI: 0.453, 0.726) for MRI-pathology reflected moderate levels of agreement in both cases. In addition, the agreement between CBBCT, MRI and pathology reached a moderate level with an ICC value of 0.767 (95% CI: 0.684, 0.831). The results of the ICC analyses are presented in *Table 2*. Bland-Altman analyses of the tumor size measured by CBBCT, MRI and pathology are detailed in *Figure 2*, where the mean difference between CBBCT pathology was 0.37 (95% CI: −1.97, 2.70) cm, the mean difference between MRI pathology was 0.61 (95% CI: −2.17, 3.40) cm and the mean CBBCT-MRI difference was 0.25 (95% CI: −0.78, 1.27) cm.

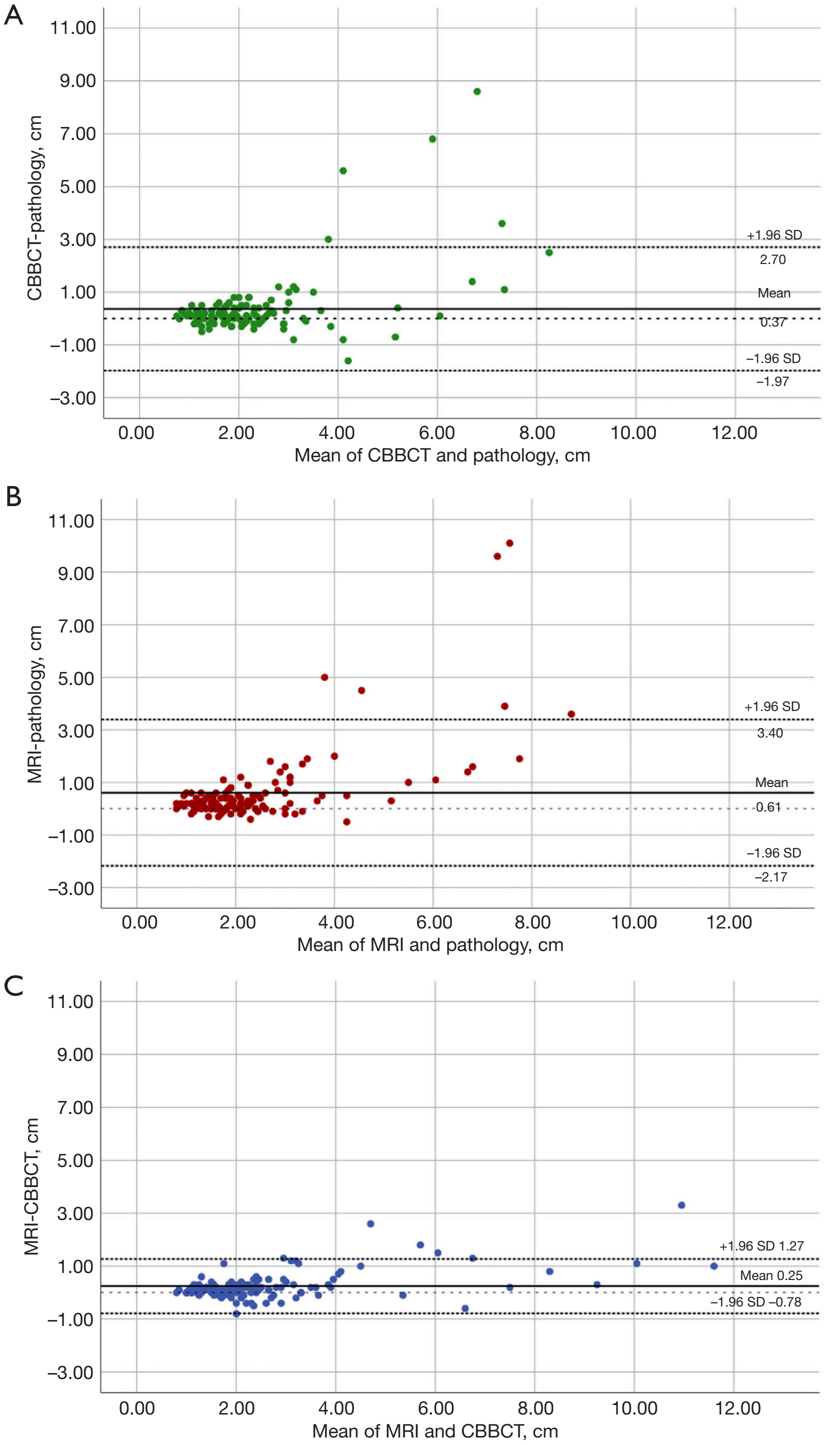

Figure 2 Bland-Altman analyses of the tumor size measured by CBBCT, MRI and pathology. Mean indicates the mean of the difference (cm), +1.96 SD and −1.96 SD indicate the 95% confidence interval of the difference (cm). CBBCT, cone-beam breast computed tomography; SD, standard deviation; MRI, magnetic resonance imaging.

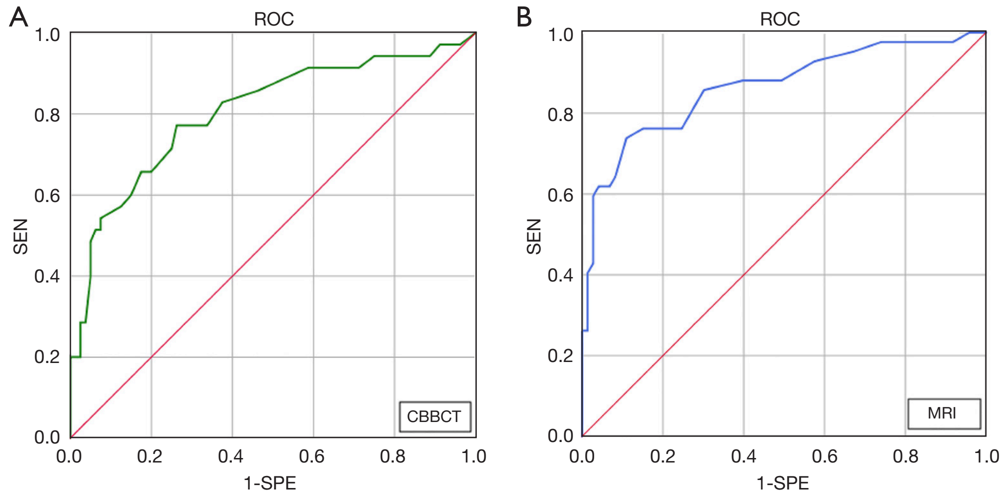

Figure 3 ROC curves based on CBBCT (A) and MRI (B) to measure the maximum diameter of the breast cancer. The results showed that the cut-off point was 2.25 cm for CBBCT-based measurements (AUC: 0.804, 95% CI: 0.710, 0.898) and 2.65 cm for MRI-based measurements (AUC: 0.864, 95% CI: 0.790, 0.939). CBBCT, cone-beam breast computed tomography; ROC, receiver operator characteristic; SPE, specificity; SEN, sensitivity; MRI, magnetic resonance imaging; AUC, area under the curve; CI, confidence interval.

Accuracy based on CBBCT and MRI measurements

Of the 115 breast cancer lesions included in this study, a total of 80 (69.6%, 80/115) were in the concordant group and 35 (30.4%, 35/115) were in the discordant group when measured by CBBCT, while a total of 73 (63.5%, 73/115) were in the concordant group and 42 (36.5%, 42/115) were in the discordant group when measured by MRI. Although CBBCT (69.6%) was slightly more accurate than MRI (63.5%), the difference was not significant (P=0.328). ROC curves were plotted with pathological tumor size as the independent variable and agreement between CBBCT- or MRI-pathology as the dependent variable (*Figure 3*). The results showed that the cut-off point was 2.25 cm for CBBCT-based measurements [area under the curve (AUC): 0.804, 95% CI: 0.710, 0.898] and 2.65 cm for MRI-based measurements (AUC: 0.864, 95% CI: 0.790, 0.939), suggesting that preoperative CBBCT and MRI assessments of tumor size tended to disagree with pathological findings when the maximum diameter was greater than 2.25 and 2.65 cm, respectively.

Factors affecting the accuracy of CBBCT/MRI-based tumor size measurement

Of the 115 breast cancers included in this study, 80 (69.6%, 80/115) were in the concordant group and 35 (30.4%, 35/115) were in the discordant group based on CBBCT measurement. Lesions in the discordant group had a greater pathological maximum diameter than those in the concordant group [2.3 (1.6, 2.9) *vs.* 1.8 (1.4, 2.2) cm, P=0.005]. HER2-positive breast cancers were more frequently found in the discordant group than in the concordant group [37.1% (13/35) *vs.* 13.8% (11/80), P=0.005]. In terms of CBBCT features, a higher proportion of lesions in the discordant group than in the concordant group exhibited non-mass enhancement (NME) [48.6% (17/35) *vs.* 13.8% (11/80), P<0.001] (*Figure 4A*), and lesions in the discordant group were also more likely to show calcifications [62.9% (22/35) *vs.* 37.5% (30/80), P=0.012] (*Figure 4B*).

Based on MRI measurements of breast cancer tumor size, a total of 73 lesions (63.5%, 73/115) were classified in the concordant group, and 42 lesions (36.5%, 42/115) were classified in the discordant group. The pathological maximum diameter of breast cancers was larger in the discordant group than in the concordant group [2.3 (1.6, 2.9) *vs.* 1.8 (1.4, 2.2) cm, P=0.002]. Fatty infiltration was more frequently observed in the concordant group than in the discordant group [84.9% (62/73) *vs.* 69.0% (29/42)]. In terms of MRI features, 50.0% (21/42) of breast cancers in the discordant group exhibited NME, whereas the vast majority of the concordant group exhibited mass-type lesions (90.4%, 66/73) (P<0.001) (*Figure 4A*).

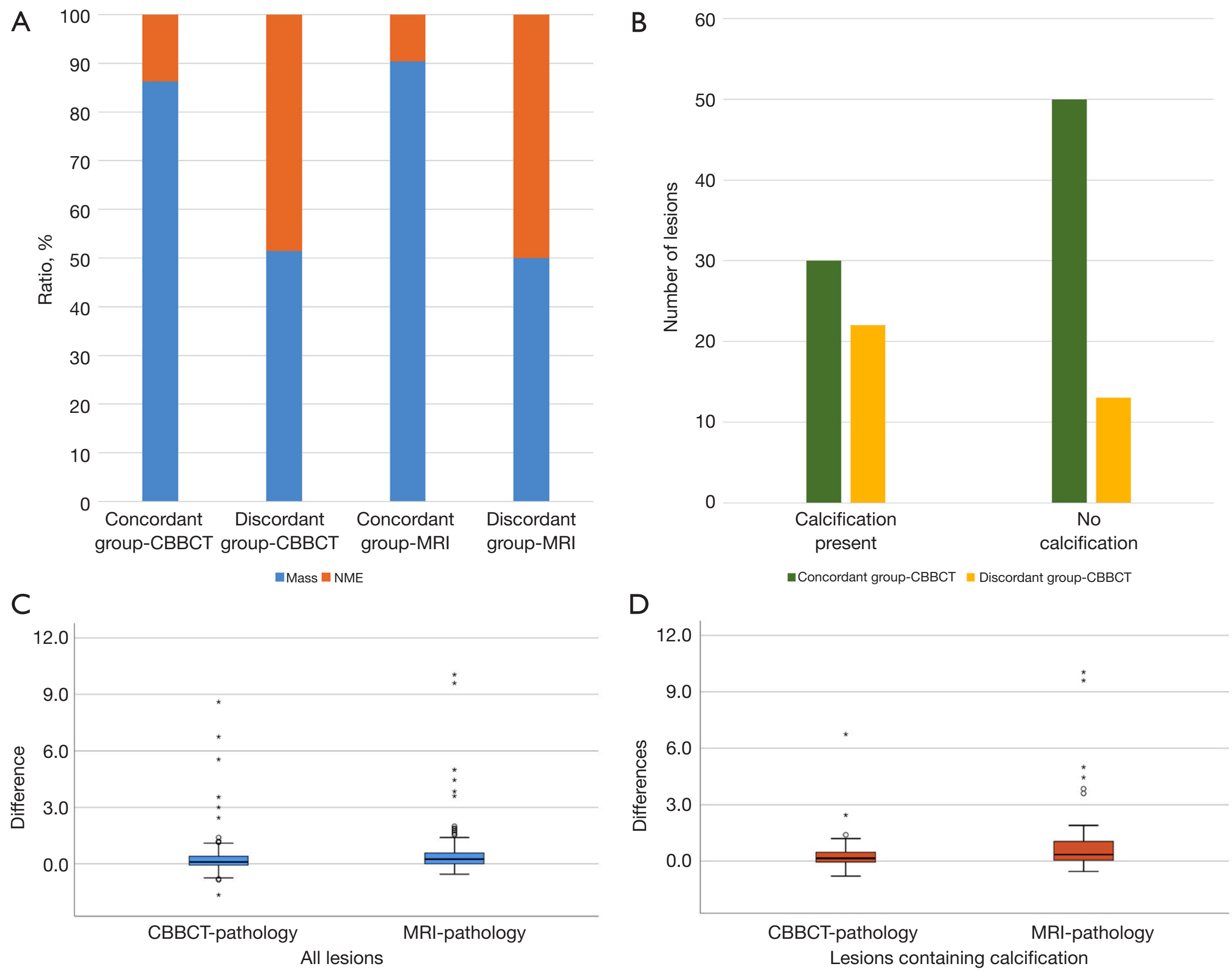

Figure 4 Representative distribution of significant clinicopathological and CBBCT/MRI features in distinguishing between concordant and discordant groups: (A) bar graph of lesion type (P<0.001); (B) bar graph of calcification in CBBCT (P=0.012); (C) boxplot of CBBCT-pathology and MRI-pathology differences in all lesions (P=0.008); (D) boxplot of CBBCT-pathology and MRI-pathology differences in lesions containing calcification (P=0.021). CBBCT, cone-beam breast computed tomography; MRI, magnetic resonance imaging; NME, non-mass enhancement.

In addition, this study compared the differences in breast cancer tumor size based on CBBCT and MRI measurements with those based on pathology specimens. Overall, the difference between CBBCT and pathology [0.1 (−0.1, 0.4) cm] was significantly smaller than that between MRI and pathology [0.3 (0.0, 0.6) cm] (P=0.008) (*Figure 4C*). In breast cancer lesions containing calcification, the difference between CBBCT and pathology was smaller than that between MRI and pathology [0.2 (−0.1, 0.5) *vs.* 0.4 (0.1, 1.0) cm, P=0.021], suggesting that CBBCT has an advantage over MRI in assessing the size of breast cancer tumors containing calcification (*Figure 4D*). *Table 3* presents the summary statistics for the univariate analyses. Example images of lesions in the concordant and discordant groups on CBBCT and MRI are shown in *Figures 5,6*.

Factors with significant differences in the univariate analyses were further subjected to multivariate analyses to identify factors contributing to inaccurate tumor size measurements. Multivariate analyses showed that NME (OR =4.289; 95% CI: 1.400, 13.140; P=0.011) and HER2 positivity (OR =3.514; 95% CI: 1.229, 10.045; P=0.019) were the main predictive factors for the difference between CBBCT and pathological assessment of tumor size, with NME having a stronger association. For MRI-based tumor size measurements, NME (OR =6.002; 95% CI: 2.058, 17.505; P=0.003) was also a significant predictor of

Table 3 Association of clinical, pathological and CBBCT/MRI features between the concordant and discordant groups in breast cancer (n=115)

CBBCT	CBBCT group				MRI group			
	Concordant (n=80)	Discordant (n=35)	$t/Z/\chi^2$	P value	Concordant (n=73)	Discordant (n=42)	$t/Z/\chi^2$	P value
Age (years)	50.09±8.71	48.57±7.14	0.905	0.368	50.51±8.68	48.10±7.32	1.516	0.192
Pathological maximum diameter (cm)	1.8 (1.4, 2.2)	2.3 (1.6, 2.9)	–2.789	0.005*	1.8 (1.4, 2.2)	2.3 (1.6, 2.9)	–3.087	0.002*
Menstrual status			1.156	0.282			1.461	0.227
Premenopausal	43 (53.8)	15 (42.9)			39 (53.4)	19 (45.2)		
Postmenopausal/premenopausal	37 (46.3)	20 (57.1)			34 (46.6)	23 (54.8)		
Histological grades/nuclear grades			0.358	0.549			0.031	0.859
Low and intermediate	55 (68.8)	26 (74.3)			51 (69.9)	30 (71.4)		
High	25 (31.3)	9 (25.7)			22 (30.1)	12 (28.6)		
Molecular subtypes			0.002	>0.999			2.103	0.147
Luminal	69 (86.3)	31 (88.6)			66 (90.4)	34 (81.0)		
Non-luminal	11 (13.8)	4 (11.4)			7 (9.6)	8 (19.0)		
DCIS component			2.166	0.141			1.446	0.229
Present	48 (60.0)	26 (74.3)			44 (60.3)	30 (71.4)		
Absent	32 (40.0)	9 (25.7)			29 (39.7)	12 (28.6)		
ER			0.002	>0.999			2.103	0.147
–	11 (13.8)	4 (11.4)			7 (9.6)	8 (19.0)		
+	69 (86.3)	31 (88.6)			66 (90.4)	34 (81.0)		
PR			0.487	0.485			1.567	0.211
–	18 (22.5)	10 (28.6)			15 (20.5)	13 (31.0)		
+	62 (77.5)	25 (71.4)			58 (79.5)	29 (69.0)		
HER2			8.068	0.005*			2.377	0.123
–	69 (86.3)	22 (62.9)			61 (83.6)	30 (71.4)		
+	11 (13.8)	13 (37.1)			12 (16.4)	12 (28.6)		
Ki-67			1.191	0.221			0.276	0.599
Low proliferation group	12 (15.0)	2 (5.7)			8 (11.0)	6 (14.3)		
High proliferation group	68 (85.0)	33 (94.3)			65 (89.0)	36 (85.7)		
Fatty infiltration			1.807	0.179			4.073	0.044*
–	14 (17.5)	10 (28.6)			11 (15.1)	13 (31.0)		
+	66 (82.5)	25 (71.4)			62 (84.9)	29 (69.0)		
Lymph vessel invasion			0.467	0.494			0.004	0.951
–	64 (80.0)	26 (74.3)			57 (78.1)	33 (78.6)		
+	16 (20.0)	9 (25.7)			16 (21.9)	9 (21.4)		

Table 3 (*continued*)

Table 3 (*continued*)

CBBCT	CBBCT group				MRI group			
	Concordant (n=80)	Discordant (n=35)	$t/Z/\chi^2$	P value	Concordant (n=73)	Discordant (n=42)	$t/Z/\chi^2$	P value
Axillary lymph node metastasis			1.739	0.187			0.070	0.892
–	57 (71.3)	29 (82.9)			54 (74.0)	32 (76.2)		
+	23 (28.8)	6 (17.1)			19 (26.0)	10 (23.8)		
Brest density			0.000	>0.999			3.948	0.054
Non-dense	8 (10.0)	3 (8.6)			10 (13.7)	1 (2.4)		
Dense	72 (90.0)	32 (91.4)			63 (86.3)	41 (97.6)		
BPE†			3.271	0.710			0.955	0.328
Low	65 (81.3)	23 (65.7)			58 (79.5)	30 (71.4)		
High	15 (18.8)	12 (34.3)			15 (20.5)	12 (28.6)		
Lesion type			16.028	<0.001*			23.637	<0.001*
Mass	69 (86.3)	18 (51.4)			66 (90.4)	21 (50.0)		
NME	11 (13.8)	17 (48.6)			7 (9.6)	21 (50.0)		
Calcification			6.320	0.012*	–	–	–	–
Absent	50 (62.5)	13 (37.1)			–	–	–	–
Present	30 (37.5)	22 (62.9)			–	–	–	–

Data are presented as n (%), mean ± standard deviation or median (interquartile range). †, lower categories (minimal and mild) were the low BPE status group and higher categories (moderate and significant) were the high BPE status group. *, P<0.05, the differences were statistically significant. CBBCT, cone-beam breast computed tomography; MRI, magnetic resonance imaging; DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; BPE, background parenchymal enhancement; NME, non-mass enhancement.

discrepancies between MRI and pathology (*Table 4*).

Discussion

Surgical excision is one of the main clinical treatments for breast cancer, and complete removal of the lesion can reduce the recurrence rate (7). Therefore, accurate assessment of breast cancer tumor size using preoperative imaging techniques is essential for the development of a rational clinical treatment plan. The results of this study showed a high level of agreement among CBBCT, MRI and pathology in measuring breast cancer tumor size, but for larger lesions, preoperative CBBCT/MRI-based measurements were prone to deviations from pathology. In addition, we found that some clinicopathological and CBBCT/MRI features of breast cancer were significantly associated with CBBCT-pathology and MRI-pathology discordance, including pathological maximum diameter, HER2 expression status, fatty infiltration, lesion type, and presence of calcification, with NME and HER2 positivity being significant predictors of CBBCT-pathology and MRI-pathology discordance in multivariate analyses.

Both enhanced CBBCT and MRI can reflect the morphological and hemodynamic characteristics of breast tumors, which makes them comparable in terms of lesion characterization and tumor size assessment (14). In this study, the inter-reader reproducibility of CBBCT and MRI for breast tumor size assessment and the agreement of CBBCT and MRI with pathology was moderate to excellent, suggesting that CBBCT may be a suitable new imaging technique for preoperative evaluation, especially in patients with contraindications to MRI.

Compared to clinical palpation and conventional mammography or ultrasound, breast MRI has superior accuracy in measuring the extent of newly diagnosed breast cancer (26-28). Previous studies have shown that

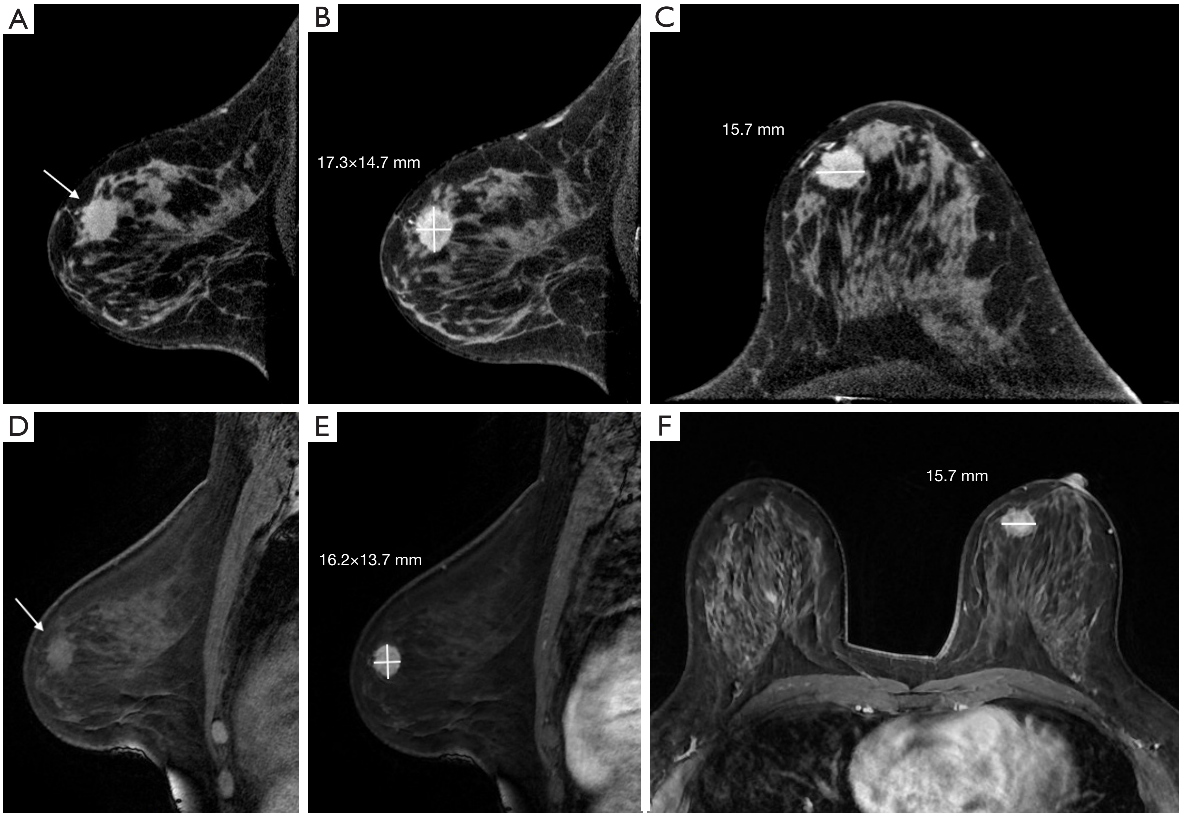

Figure 5 A 48-year-old female patient with a diagnosis of malignancy (invasive micropapillary carcinoma with invasive ductal carcinoma). The pathological maximum diameter was 1.8 cm, based on both CBBCT and MRI measurements in a concordant group. (A) A sagittal NCE-CBBCT image of a lesion presenting as a mass (arrow). A sagittal (B) and axial (C) CE-CBBCT image with a maximum lesion diameter of 1.7 cm was measured. (D) A sagittal pre-enhanced MRI image of a lesion presenting as a mass (arrow). A sagittal post-enhanced 1st phase (E) and axial delay phase (F) post-enhanced MRI image with a maximum lesion diameter of 1.6 cm was measured. CBBCT, cone-beam breast computed tomography; MRI, magnetic resonance imaging; NCE-CBBCT, non-contrast-enhanced CBBCT; CE-CBBCT, contrast-enhanced CBBCT.

the accuracy of MRI for measuring the extent of breast lesions could range from 50% (where a difference of <1 cm was classified as consistent) to 80% (where a difference of <0.5 cm was classified as consistent) (29). Discordance between MRI and pathology is often associated with larger tumor sizes, and usually MRI measurements are most accurate for tumors smaller than 2.0 cm (12,30-32). Our study showed similar results to this. Another important finding of this study is that CBBCT also had a relatively high accuracy rate (69.6%) in measuring breast tumor size, while tumors with a maximum diameter greater than 2.25 cm were prone to bias. This finding also agrees with our earlier observations (18). However, further work is required to compare the accuracy of CBBCT and MRI on a larger data set.

In addition, we found that the discrepancy between CBBCT and pathology was significantly smaller than that between MRI and pathology, and this performance may be related to the display of BPE on CE-CBBCT and DCE-MRI. Following contrast injection, enhancement of normal fibrous glandular tissue of the bilateral breast, known as BPE, may obscure the lesion or show similar enhancement, thus reducing the accuracy of tumor size assessment, particularly in breasts with moderate and marked BPE (33,34). The results of Ma *et al.* (17) confirmed that in most cases, CE-CBBCT tended to show lower BPE levels than DCE-MRI. Thus, tumor size measurement based on CE-CBBCT was less influenced by BPE than DCE-MRI, and the accuracy of measurement was higher as well.

Several previous studies have shown that NME is

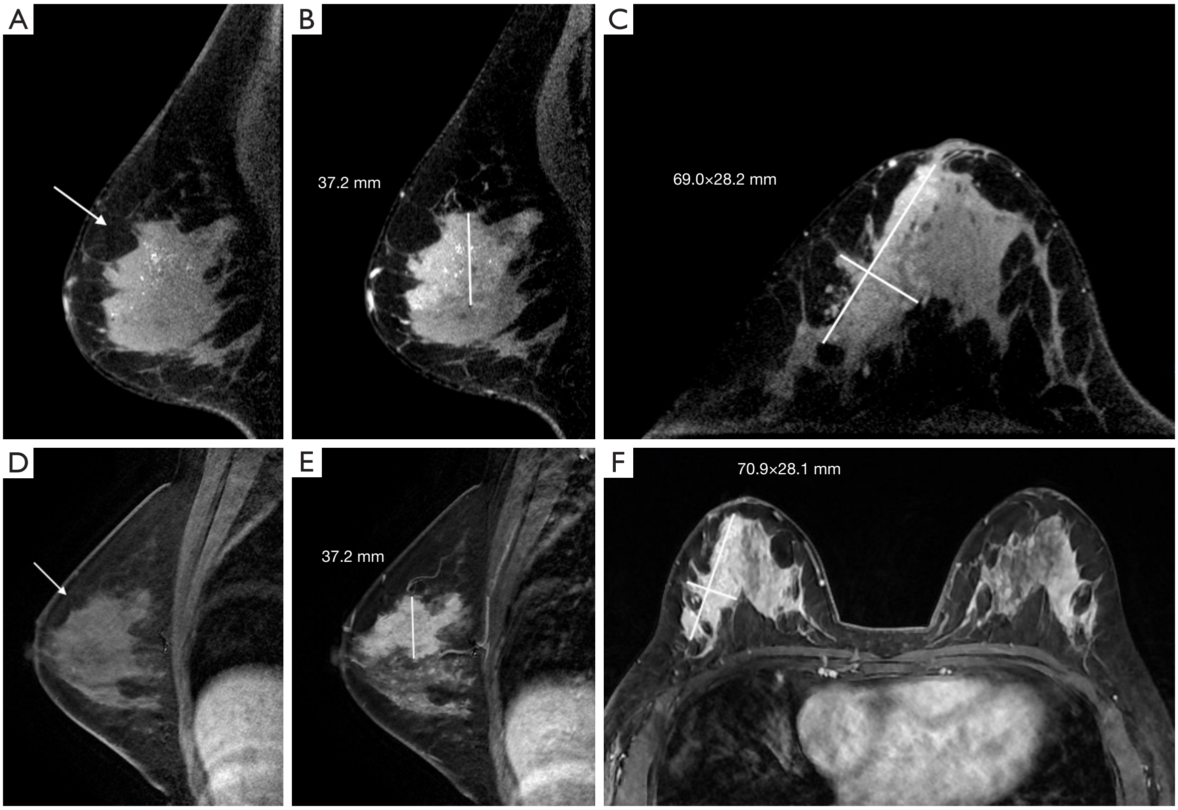

Figure 6 A 45-year-old female patient with a diagnosis of malignancy (invasive ductal carcinoma with extensive intraductal components). The pathological maximum diameter was 6.0 cm, based on both CBBCT and MRI measurements in a discordant group. (A) A sagittal NCE-CBBCT image of a lesion presenting as segmental distribution of fine polymorphic calcifications (arrow). Sagittal (B) and axial (C) CE-CBBCT images of a lesion presenting as NME, with a measured maximum diameter of 6.9 cm. (D) A sagittal pre-enhanced MRI image of a lesion that is not clearly shown (arrow). A sagittal post-enhanced 1st phase (E) and axial delay phase (F) post-enhanced MRI image of a lesion presenting as NME, with a measured maximum diameter of 7.1 cm. CBBCT, cone-beam breast computed tomography; MRI, magnetic resonance imaging; NCE-CBBCT, non-contrast-enhanced CBBCT; CE-CBBCT, contrast-enhanced CBBCT; NME, non-mass enhancement.

the most significant factor contributing to discordance between MRI and pathology measurements of tumor size (29,35-37). Similarly, our study found that NME was a significant predictor of discordance between CBBCT/MRI and pathology in multivariate analyses. Both on CBBCT/MRI and in pathological gross specimens, NME lesions often do not have clear borders, making it difficult to accurately measure tumor size (38). Preoperative assessment and clinical management of such lesions require additional care. Furthermore, a subset of breast cancers present with both mass and NME on CBBCT and MRI. There is often a non-malignant portion of such lesions, which some pathologists classify as multifocal, and usually only the clear mass portion of the lesion is measured, rather than the overall size of the tumor (35,38,39). Therefore, this part of these cases was excluded from this study.

The current study found that the presence of calcification was significantly associated with discordance between CBBCT and pathology, and that the CBBCT-pathology discrepancy of lesions with calcifications was significantly smaller than the MRI-pathology discrepancy. Breast cancers that show extensive segmental distribution of calcifications on mammography are usually seen as NME on DCE-MRI (40). In these lesions, although CE-CBBCT can show both calcification and enhancement features, the boundaries of the calcification area are difficult to determine when the lesion is large (41,42). The solid component of the tumor surrounding the calcification may not be clearly

Table 4 Multivariate analyses of factors influencing the discordance of CBBCT- and MRI-pathology measurements in breast cancer

Characteristics	CBBCT			MRI		
	OR	95% CI	P value	OR	95% CI	P value
Pathological maximum diameter	1.269	0.834, 1.932	0.266	1.543	0.955, 2.493	0.076
Lesion type						
Mass	Reference			Reference		
NME	4.289	1.400, 13.140	0.011*	6.002	2.058, 17.505	0.003*
Calcification						–
Absent	Reference			–	–	–
Present	1.290	0.488, 3.409	0.608	–	–	–
HER2						–
–	Reference			–	–	–
+	3.514	1.229, 10.045	0.019*	–	–	–
Fatty infiltration			–			
–	–	–	–	Reference		
+	–	–	–	0.887	0.282, 2.814	0.839

*, P<0.05, the differences were statistically significant. CBBCT, cone-beam breast computed tomography; MRI, magnetic resonance imaging; OR, odds ratio; CI, confidence interval; NME, non-mass enhancement; HER2, human epidermal growth factor receptor 2.

enhanced on CE-CBBCT, leading to discrepancies between CE-CBBCT and pathology (43,44).

The results of several studies have confirmed that HER2 expression status is an important factor in the accuracy of MRI assessment of tumor size (27). There is a significant correlation between HER2 positivity and tumor angiogenesis (36). For breast tumors with a high density of neovascularization, the extent of enhancement on MRI is often greater than the pathological size of the tumor (45). Although there are certain differences between CE-CBBCT and DCE-MRI in terms of image-forming principles and contrast material, CE-CBBCT has certain advantages in showing tumor angiogenesis, which can also reflect the hemodynamic characteristics of the lesion and changes in the tumor microenvironment (41). Therefore, the changes in tumor neovascularization caused by HER2 positivity would similarly affect the accuracy of CBBCT in measuring tumor size. This is supported by the finding in our study.

Despite the favorable results, a number of limitations need to be noted regarding the present study. First, our study is a retrospective analysis based on two radiologists at a single institution with a relatively small sample size. Expanding the sample size to multiple institutions would improve the reproducibility of the results of this study. Second, the measurement of non-mass type lesion size was a difficult task in both radiology and pathology. Automatic or semiautomatic measurement of NME lesion extent using artificial intelligence methods in future work will yield more accurate results. Third, the evaluation of tumor size based on 3D-MIP of CE-CBBCT or DCE-MRI may be able to improve the efficiency and accuracy of maximum tumor diameter measurement.

Conclusions

In conclusion, CBBCT- and MRI-based measurements of breast lesion size have comparable accuracy, and CBBCT is superior in assessing the size of breast lesions that contain calcification. These findings provide important insights into the utility of CBBCT in the preoperative evaluation of breast cancer, namely, that CBBCT may be an alternative to MRI for assessing tumor size when patients are intolerant to MRI. In addition, NME and HER2 positive status are significant influencing factors leading to discordance between CBBCT-based and pathology-based measurements of tumor size.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-401/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-401/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-401/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The ethics committee of Tianjin Medical University Cancer Institute & Hospital (No. bc2016039) approved this retrospective study and waived the requirement for informed consent.

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Original Article

Pre-pectoral breast reconstruction with tissue expander entirely covered by acellular dermal matrix: feasibility, safety and histological features resulting from the first 64 procedures

Marco Bernini[1], Giacomo Gigliucci[1], Dario Cassetti[1], Cinzia Tommasi[1], Ilaria Gaggelli[1], Lorenzo Arlia[1], Carlotta Becherini[2], Viola Salvestrini[2], Luca Visani[2], Jacopo Nori Cucchiari[3], Diego De Benedetto[3], Federica Di Naro[3], Giulia Bicchierai[3], Chiara Bellini[3], Simonetta Bianchi[4], Lorenzo Orzalesi[1], Lorenzo Livi[2], Icro Meattini[2]

[1]Breast Surgery Unit, Azienda Ospedaliero Universitaria Careggi - University of Florence, Florence, Italy; [2]Radiotherapy Unit, Oncology Department, Azienda Ospedaliero Universitaria Careggi, Florence, Italy; [3]Diagnostic Senology, Azienda Ospedaliero Universitaria Careggi, University of Florence, Florence, Italy; [4]Pathology Division, Azienda Ospedaliero Universitaria Careggi - University of Florence, Florence, Italy

Contributions: (I) Conception and design: M Bernini, G Gigliucci, L Arlia, I Meattini; (II) Administrative support: L Orzalesi, J Nori Cucchiari, L Livi, S Bianchi; (III) Provision of study materials or patients: M Bernini, C Tommasi, L Orzalesi, I Gaggelli, D Cassetti; (IV) Collection and assembly of data: G Gigliucci, L Arlia, D De Benedetto, G Bicchierai; (V) Data analysis and interpretation: C Bellini, L Visani, C Becherini, V. Salvestrini, F Di Naro; (VI) Manuscript writing: All authors; (VII) Final approval of the manuscript: All authors.

Correspondence to: Marco Bernini, MD, PhD. Breast Surgery Unit, Azienda Ospedaliero Universitaria Careggi - University of Florence, L.go Brambilla 3, 50134 Florence, Italy. Email: marco.bern@icloud.com.

Background: Reconstructive options that can be used following conservative mastectomy, skin-, nipple-sparing and skin-reducing mastectomies, allow a remarkable variety of safe methods to restore the natural shape and aesthetics of the breast mound. In case of two-stage breast reconstruction, tissue expanders (TEs) are usually placed in a subpectoral position. The purpose of this retrospective cohort study is to evaluate the feasibility and safety of two-step reconstruction with TE in pre-pectoral position covered by acellular dermal matrix (ADM).

Methods: Between March 2021 and May 2023, at the Azienda Ospedaliero Universitaria Careggi, University of Florence, 55 patients with BRCA 1/2 mutations or early breast cancer underwent conservative mastectomy with immediate pre-pectoral reconstruction using TE covered with ADM, followed by a second surgery with replacement of the expander with definitive prosthesis. Demographic, oncological, and histological data along with surgical complications were recorded.

Results: A total of 64 conservative mastectomies were performed. In 2 patients (3.1%) complications were found that required reintervention and, in both cases, the TE had to be removed. Two patients developed hematoma and one patient developed seroma. Two patients showed wound dehiscence, both healed after conservative treatment and without implant exposure. No case of necrosis of the skin or nipple-areola complex has been observed, neither of capsular contracture. Capsule formed around TE was populated with cells and blood vessels and showed a thin area of synovial metaplasia.

Conclusions: In selected cases it may be more cautious to perform a two-stage breast reconstruction after radical breast surgery by means of TEs. The placement of TEs in pre-pectoral position combines the excellent aesthetic and functional results of the pre-pectoral philosophy with a quite safer and more prudent two-step approach. Our experience reports optimistic results: the ADM covering the TE is seen successfully integrating during tissue expansion and becoming a vascularised new self-tissue. Complications rates are low and such ADM-assisted two-stage pre-pectoral reconstructive technique is a safe, practical, and reproducible method.

Keywords: Pre-pectoral breast reconstruction (PPBR); acellular dermal matrix (ADM); ADM-wrapped tissue expander (ADM-wrapped TE); tissue regeneration

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Introduction

Breast reconstruction is a central component of the comprehensive management of breast cancer patients, offering physical and psychological restoration for mastectomised women. Reconstructive procedures have evolved significantly over the years, providing improved outcomes and enhanced patient satisfaction (1). Optimal aesthetic outcomes with long-term functional and clinical stability are reported worldwide with pre-pectoral breast reconstruction (PPBR), turning now from innovation to new gold standard in implant-based reconstructive surgery (2,3).

Acellular dermal matrices (ADMs) have played a pivotal role in enabling pre-pectoral advancement: they allowed subcutaneous implant placement by providing a higher-quality biocompatible interface around the synthetic prosthesis which reduced incidences of capsular contracture by regeneration of subcutaneous tissue (3-8). As a matter of fact, derived from allogeneic or xenogeneic dermal tissue sources, ADMs are processed to remove cellular elements while preserving extracellular matrix (ECM) structural integrity and components (9). As a result, collagen is the major constituent of dermis-derived acellular materials, physiologically designed to provide structural support and facilitate cellular adhesion, migration, and proliferation (10,11). As such, whenever implanted within biological tissues, ADMs act as a three-dimensional scaffold that activates biological healing mechanisms involving cellular infiltration, angiogenesis, and remodelling, leading to the development of a functional neo-tissue. In other words, ADMs promote their own integration into patient's tissues, creating a coverage that minimizes implant-related foreign body reactions (4,9,12,13).

Over the past 20 years, ADMs' anti-fibrotic properties have been extensively documented in implant-based breast surgeries, with established improvements of clinical-aesthetic outcomes (14-16). The first successful pre-pectoral reconstruction with the first ADM designed to completely cover an implant, named BRAXON®, described by Berna *et al.* is one of the present-day example par excellence of the enhancement achieved thanks to these biomaterials (2,3,5,17,18).

In the wake of these results, pre-pectoral procedures are recently beginning to be performed even in two stages. Several levels of ADM coverage have been reported in this setting taking advantage of their properties by applying an ADM directly on the tissue expander (TE). Interestingly, multiple publications report favourable final outcomes, yet none report on a full wrap with xenogeneic ADM on the synthetic expander (19-22). Furthermore, studies investigating ADMs' integration in such a dynamic frame are scarce, although two-stage techniques offer the significant chance to explore the breast pocket, collecting biopsy specimens at the time of the definitive implant positioning (23,24).

The aim of this study is to share our Unit experience on two-stage pre-pectoral procedure in terms of safety and biological tissues integration using a complete ADM wrap of the TE. We report clinical and histological analyses of reconstructions performed with BRAXON®Fast, a xenogeneic dermal matrix specifically designed to completely isolate the synthetic material in the breast pocket. We present this article in accordance with

Highlight box

Key findings

- Two-stage pre-pectoral breast reconstruction (PPBR) with tissue expander (TE) entirely covered by acellular dermal matrix (ADM) is as effective as ADM-assisted direct-to-implant pre-pectoral reconstruction as concerns complications and tissue regeneration.

What is known and what is new?

- Literature data demonstrate that PPBR performed with implants entirely covered by BRAXON®Fast ADM has low complication rates with the device promoting subcutaneous tissue regeneration, hence the formation of a soft and vascularised peri-capsular tissue.
- Two-stage PPBR performed with TEs entirely covered by BRAXON®Fast shows complication rates fully in line with good clinical practice. In addition, this work proves that such ADM is compatible with the dynamic biological environment that subcutaneous tissue experiences during expansion, and matrix integration, repopulation and vascularization take place. The formed peri-capsular tissue is soft and vascularised.

What is the implication, and what should change now?

- This work enlarges the indications for BRAXON®Fast-assisted PPBR by providing insights on a variation of the technique. More patients can benefit from saving the pectoralis major muscle.

the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-432/rc).

Methods

Patients and data

A retrospective analysis was conducted on 70 patients (a total of 84 breasts) treated for breast cancer and two-stage pre-pectoral reconstruction at our Breast Unit (Azienda Ospedaliero Universitaria Careggi, University of Florence, Italy) from March 2021 to May 2023. At our Institution, the two-step procedure is offered to patients who would benefit from the sparing of the pectoralis major muscle but who are not good candidates for direct-to-implant reconstructions because of obesity, previous radiotherapy treatment, hypertension, neo-adjuvant chemotherapy, and undergoing a skin-sparing procedure (because of nipple-areola complex removal). In our work, we included these patients, plus those who had small to moderate-sized breasts (<500 g) and were wishing for a larger cup. Patients with more than two comorbidities and with TNM status >4 were not deemed suitable for such procedure. Therefore, patients who satisfied the listed criteria received a mesh/matrix-covered pre-pectoral TE breast reconstruction. no more, small to moderate-sized breasts. For the purpose of this work, in order to obtain homogeneity of the analysed population, patients who underwent two-stage pre-pectoral reconstruction with TE wrapped in ADM or meshes other than BRAXON®Fast (Decomed® S.r.l., Venice, Italy) were excluded from the analysis. Demographic data such as BMI, smoking habit, neo-adjuvant and adjuvant therapies, comorbidities, previous breast surgeries, hospital stay, and surgical details were recorded on the institutional database. Reconstructive outcomes and complications such as seroma, dehiscence, infection, hematoma, TE rupture and failure were recorded and classified as early or late depending on the timing of occurrence (before or after three months from surgery respectively).

In five cases, at second stage operation, when patients returned into the operating room for TE removal and definitive implant placement, a 1.5 cm × 1.5 cm square of peri-capsular tissue was sampled for histological investigations, consisting in haematoxylin and eosin (H&E) staining on tissue sections.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of Azienda Ospedaliero Universitaria Careggi (No. #16.069_AOUC) and individual consent for this retrospective analysis was waived.

Surgical technique

The surgical technique for two-stage ADM-assisted PPBR is similar to that of direct-to-implant (DTI) ADM-assisted PPBR. Briefly, soon after mastectomy the patient is ready for BRAXON®Fast-wrapped TE implantation. BRAXON®Fast is a pure collagen matrix devoid of preservative or cross-linking agents. It is 0.6 mm thick, and the unique three-dimensional patented design presents a dome-shaped anterior part that can easily adapt to all implants' silhouettes. The ADM preparation consists in a 5-minute hydration in room temperature sterile solution so that the matrix becomes pliable and can be easily adapted to the TE silhouette. The TE is expanded up to approximately 30-50% of the desired volume with sterile saline solution and is placed inside the ADM. The dome-shaped superior flap and the inferior flat flap of the matrix are sutured together with absorbable 3.0 Vicryl Rapide® interrupted stitches (that will dissolve in little more than 1 month) so that a snug envelope is all around the TE, quite tight in order to prevent TE malrotation but still not completely adherent to the TE itself, to allow for the first month initial expansions. The BRAXON®Fast-TE complex is then positioned in the breast pocket and fixed to the pectoralis major muscle for stability, with 2 or 3 interrupted sutures, once again absorbable even though a little more long lasting and with a 2.0 calibre. Adherence of the ADM to the mastectomy flap, to prevent the formation of dead spaces, can be adjusted by tuning the TE inflation. Nonetheless, skin flaps should always be kept quite loose in order to get an adequate blood flow and less tension on the incision edges, thus taking advantage of a two-stage reconstruction as compared to a DTI. Only one drain is placed around the TE/ADM complex. Patients are discharged with drain and wearing compressive bandages/bra. Drain is removed when the liquid volume in the output bag reaches 30 cc for 2 consecutive days. Patients are suggested to wear the compressive bra for at least one month. A variable number of TE expansions is performed until the desired final breast volume is reached. After a month the stitches of the ADM envelope are dissolved and expansion can be completed as wished, stretching entirely the matrix surface, and creating a complete adherence of TE and ADM on the inner aspect and of ADM and skin flap on the other side. At the time of TE-definite implant substitution lipofilling could be performed.

Table 1 Demographic data and surgical details

Demographics	Values
Patients, n	55
Breasts, n	64
Follow-up (months), mean ± SD [range]	10±5.4 [1.5–28.3]
Age (years), mean ± SD [range]	50.7±10 [30–74]
BMI (kg/m^2), mean ± SD	23.1±3.8
Hospital stay (days), mean ± SD	2.4±0.9
Smoking status (per patient), n (%)	
Non smokers	39 (70.9)
Current smokers	10 (18.2)
Former smokers	6 (10.9)
Comorbidities (per patient), n (%)	
Diabetes	1 (1.8)
Autoimmune diseases	2 (3.6)
Cardio-vasculopathies	9 (16.4)
Hypothyroidism	5 (9.1)
Other comorbidities	7 (12.7)
BRCA1/2^{mut} carriers	7 (12.7)
Surgery type (per breast), n (%)	
Therapeutic	51 (79.7)
Prophilactic	13 (20.3)
Type of tumor (per breast), n (%)	
DCIS	10 (15.6)
LCIS	7 (10.9)
IDC	9 (14.1)
ILC	2 (3.1)
Mixed	1 (1.6)
Other	22 (34.4)
Mastectomy (per breast), n (%)	
Skin/nipple-sparing	32 (50.0)
Skin-sparing	30 (46.9)
Skin-reducing	2 (3.1)
Incisions (per breast), n (%)	
Italic-S	18 (28.1)
Elliptical	29 (45.3)
Wise pattern	4 (6.3)
Inframammary fold	13 (20.3)
Therapies, n (%)	
Chemotherapy (per patient)	
Neoadjuvant	7 (12.7)
Adjuvant	13 (23.6)
Radiotherapy (per breast)	
Pre-operative	3 (4.7)
Post-operative	10 (15.6)
Other details (per breast)	
Implant volume (cc), mean ± SD	380±123
Axillary lymphadenectomy, n (%)	15 (23.4)
Previous breast surgery, n (%)	11 (17.2)
Drainage (days), mean ± SD	18.5±8.0
Lipofilling, n (%)	7 (10.9)

Table 1 *(continued)*

Table 1 *(continued)*

SD, standard deviation; BMI, body mass index; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

Statistical analysis

Data are presented as a descriptive analysis of demographical and surgical data, and complications. Data are reported as number, range, mean with standard deviation, median, and percentage.

Results

From March 2021 to May 2023, a total of 55 patients (64 breasts) underwent mastectomy and two-stage ADM-assisted PPBR using BRAXON®Fast at our Institution. Data were retrieved from Institutional database for all patients. Patients were followed-up for an average of 10 months (median follow-up 8.7 months). A summary of demographic and surgical data is reported in *Table 1*.

Early complications occurred in 9.4% of the breasts (6 breasts). The most observed were dehiscence and hematoma, each occurred in 2 breasts (3.1%), followed by 1 seroma (1.6%) and 1 infection (1.6%), all conservatively treated without further complications. No skin or nipple-areola complex necrosis were observed. The only 2 (3.1%) late complications recorded were 1 wound infection with dehiscence (1.6%) and 1 expander rupture (1.6%). Both required reintervention and the TE had to be removed,

Table 2 Early and late complications

Complications	N (%)
Early complications	
Seroma	1 (1.6)
Dehiscence	2 (3.1)
Infection	1 (1.6)
Hematoma	2 (3.1)
NAC/skin necrosis	0
Total	6 (9.4)
Late complications	
Infected dehiscence	1 (1.6)
TE rupture	1 (1.6)
Capsular contracture	0
Total	2 (3.1)
Failure	2 (3.1)

NAC, nipple-areola complex; TE, tissue-expander.

Figure 1 Peri-implant capsule 8.5 months after TE pre-pectoral reconstruction and TE removal. TE, tissue expander.

thus reconstructive failure occurred in 2 breasts (3.1%). There was no evidence of capsular contracture especially for those patients with a follow-up longer than 1 and 2 years (15 patients and 3 patients, respectively). In addition, 20% of the breasts underwent radiotherapy, a known risk factor for early onset of capsular contracture. Such complication was not observed in irradiated patients. All complications are reported in *Table 2*.

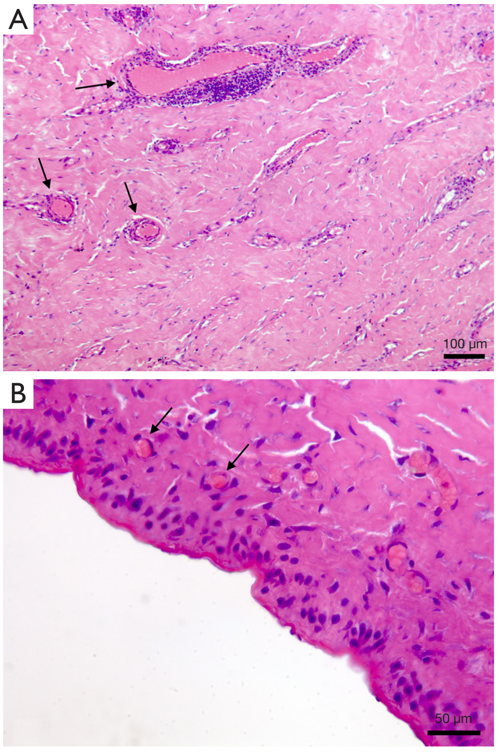

Figure 2 Haematoxylin and eosin staining of capsule samples at 8.5 months after BRAXON®Fast-wrapped TE implantation. (A) Tissue section revealing the presence of blood vessels (black arrows). (B) Breast implant capsule with synovial metaplasia (×40), capillaries are interspersed in the tissue (black arrows). TE, tissue expander.

At the time of TE-definitive implant exchange, the peri-implant capsule appeared always soft, elastic, and vascularised (*Figure 1*), indicating Braxon® successful integration into the surrounding tissues. All tissue samples analysed with H&E revealed presence of blood vessels in the newly formed tissue (*Figure 2A,2B*). Where the ADM was in contact with the expander a thin layer of synovial metaplasia had formed (*Figure 2B*).

Aesthetic results obtained with this reconstructive technique are reported in *Figure 3*, both after breast expansion (*Figure 3A*, right before implant exchange) and after definitive implant placement (*Figure 3B*).

Discussion

Recent emphasis on personalized breast reconstruction plans considers each patient's uniqueness, enhancing

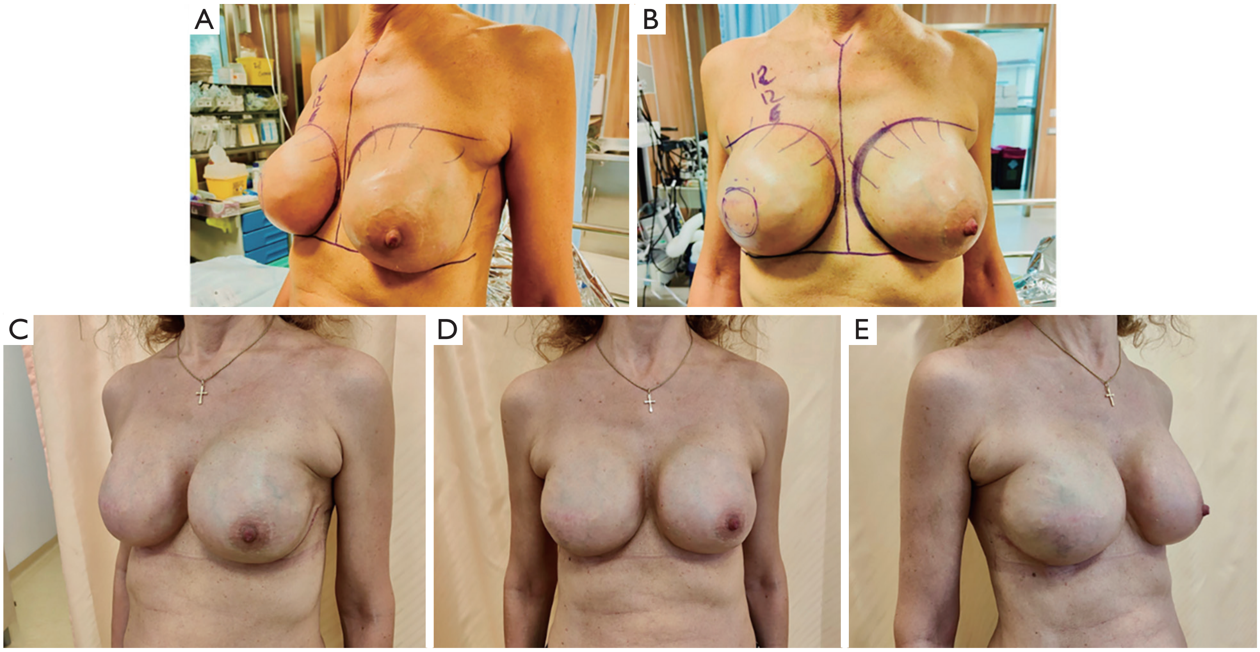

Figure 3 Aesthetic outcomes. (A,B) Pre-operative images of a patient with bilateral BRAXON®Fast-wrapped TE before implant exchange. Lateral and frontal view. (C-E) Post-operative images of bilateral breast reconstruction 2 months after TE removal and definitive implant positioning. Lateral view (left side), frontal view, and lateral view (right side). TE, tissue expander.

satisfaction and success rates with a diverse range of techniques and devices (21,25).

One prominent trend in implant-based reconstruction is ADM-assisted pre-pectoral implant placement, performed either in one-stage or two-stage modalities with established major benefits and patient satisfaction. Here we have shown the outcomes on 64 two-stage pre-pectoral reconstructions performed with BRAXON®Fast-covered TEs. The ADM used is of pig origin, it is the only one that allows complete implant coverage and that presents a three-dimensional dome shape on the anterior part which easily allocates various types and dimensions of TEs/implants without the need for time-consuming cutting and sewing required to adapt flat ADMs to curved surfaces (26). In addition, such device demonstrated adipogenic stimulation capacity, thus it is able to boost a more physiological tissue regeneration and replenishing the cells naturally present in the subcutaneous tissue (27).

Decellularized dermis materials enable subcutaneous implants, reducing inflammation and profibrotic signalling in breast capsule development (4,17,24). Based on this rationale, many clinicians have verified improved clinical-aesthetic outcomes with complete ADM wrapping of the silicone prosthesis. Masià *et al.*, for example, reported only a 2.1% capsular contracture rate on 1,450 pre-pectoral procedures, with very natural-looking aesthetic outcomes (2).

Such positive results seem to recur even in radiotherapy settings (28-30) or in obese patients (31) whenever applying a regenerative shell in pre-pectoral surgeries. TEs, like silicone implants, induce a foreign body reaction. Without a suitable bio-active coating, subcutaneous placement can lead to adverse effects (32,33). Accordingly, Chopra *et al.* reported quite frequent adverse events with plain pre-pectoral TEs, including device dystopia, with recorded rates between 32.4% and 45.9% (34). In another retrospective review of 250 nude pre-pectoral expanders, Salibian *et al.* documented grade III/IV capsular contracture in 7.6% of cases (35). Likewise, Hammond *et al.* gived evidence of 21.1% capsular contracture grade III/IV in nineteen revision surgeries following pre-pectoral conversion without ADM within a mean follow-up of 13.8 months (36).

Conversely, data on ADM-wrapped expanders generally reveal lower complication rates. Woo *et al.* describeb a 10% of adverse events when a nearly complete ADM coverage of the expander is applied, as well as Sigalove reports a total complications rate of 5.9% with expanders fully covered with one or two sheets of acellular dermis (25,29). Interestingly, when only ADM tenting is applied, post-operative clinical profile seems to shift toward slightly increased complication rates (20,37).

The extent of ADM implant coverage is still debated. In our practice, an ADM for complete prosthesis wrap was opted, as mechanical and anti-fibrotic abilities of ADMs have been extensively demonstrated and involving the entire synthetic surface could maximize their action (38,39). Several clinicians have already adopted this strategy, making use of human dermal matrices (21,22,25,38). However, allogeneic dermis is cost-prohibitive and human-derived matrices available on the market lack breast-specific indication and conformation (21,25). Disparate attempts at off-label constructs have been reported with AlloDerm® matrix to achieve easier ADM coverage for pre-pectoral placement. Whenever seeking complete coverage, only partial wrapping can often be achieved, especially when larger expanders are used (21,25).

The heterogeneity of literature data concerning two-stage ADM-assisted pre-pectoral reconstruction may reflect non-standardised implant wrapping procedures which lead to centre-to-centre variability. Our early experience with a specific standardized ADM wrapping technique for complete TE coverage reveals 12.5% total complications, and only 3.1% failure rate, fully in line with good clinical practice found in the literature so far (40,41). Our results are also in line with those reported in recent BRAXON®Fast publications (DTI procedures) (18,26,42). Within a standard patient selection, pre-pectoral TE placement with complete dermal coverage proves feasible with successful early clinical outcomes. A 0.6-mm thick and preshaped ADM easily conforms to the expander profile and histological analyses suggest a proper dynamic integration of the scaffold across the expanding process.

Understanding the cellular and molecular mechanisms behind ADM integration is crucial for improving surgical techniques and results in breast reconstruction. Our analyses confirmed matrix integration with cells and vascularization, revealing a thin cellular lining similar to the synovial membrane. Synovial metaplasia, likely stimulated by the mechanical stress of implants, is an adaptation mechanism to reduce friction between moving surfaces (23,42,43). It has been widely documented in capsules formed around silicone implants and it is indicative of a benign capsule (44). In fact, its presence is associated with Baker grade I and II capsules while its absence is typical of Baker grades III and IV capsules, possibly linking this formation with a protective effect against capsular contracture (43,45,46). Synovial metaplasia was observed to form also with other ADMs. Our histological results were similar to those reported in literature, with tissue biopsies showing blood vessels located just below the synovial metaplasia and good tissue integration overall with no signs of foreign body response (6,12). Our unit has experience with breast reconstruction performed using a titanium-coated polypropylene mesh and capsular tissue biopsies were also taken (47-49). A synovial metaplasia was observed, however, the presence of foreign body giant cells, marker of inflammation, indicates a different type of peri-implant tissue (internal data, not shown). Similarly, inflammation in such tissue was also confirmed in one previous work of ours (50). In fact, the inflammatory response initiated with the foreign body reaction can be either exacerbated or prolonged by the presence of a synthetic material, which ultimately leads to unregulated and continued stimulation of fibrosis with increased risk of capsular contracture (44,51). Hence, once again there is confirmation that, by promoting modulation of inflammation, the ADM as implant coverage creates a vascularised benign capsule integrated into the surrounding tissue that exerts a protective effect against capsular contracture (4,16).

This study is not without limitations. The retrospective and single-institution framework inevitably comes with potential surgical bias. Additionally, the small patient cohort as well as early follow-up do not allow for long-term conclusions to be drawn. Noteworthy issues such as postoperative pain and analgesic requirements, aesthetic outcomes and patient-reported outcomes were not evaluated. They will be subjects of our follow-up work, also including more extensive histopathological qualitative and quantitative analyses.

Acellular dermal matrices have revolutionized PPBR, providing surgeons with a powerful tool to enhance implant support, reduce complications, and improve overall outcomes. With this work, we have proved that a device born for DTI PPBR can be safely and effectively used in two-stage PPBR as it follows tissue expansion and successfully integrates in the surroundings. Even if this piece added to the puzzle that is Braxon body of literature, surgeons' knowledge on ADM in breast reconstruction has increased and, ultimately, patients can be offered the most appropriate reconstructive technique, tailored on their characteristics and needs. Additionally, despite the two-stage procedure is recognised as least cost-effective and there are reports of patients' lower quality of life (QoL) compared to DTI procedures (52), by placing the expander in the pre-pectoral position the functional and aesthetic benefits of the muscle-sparing technique are maintained. Cost-benefit analyses do not consider the cost of the pectoralis muscle loss and its fallout on patients' QoL. We believe two-stage pre-pectoral reconstruction to be the best alternative to submuscular breast reconstruction while being at the same time the best compromise for patients non-ideal for a pre-pectoral DTI procedure.

Despite challenges, ongoing research and refinements aim to boost ADMs benefits in breast reconstruction, solidifying their role in modern surgical approaches. Investigating ADM-host tissue interactions and considering factors like processing techniques, patient characteristics, and medical conditions will refine and expand their applications.

Conclusions

The placement of ADM-covered TEs in pre-pectoral position combines the excellent aesthetic and functional results of the pre-pectoral philosophy with a quite safer and more prudent two-step approach. Our experience is one of the first with this technique and BRAXON®Fast and has shown encouraging results: the ADM successfully integrates in the dynamic environment created during tissue expansion and becomes a vascularised new self-tissue. Complications rates are low and such ADM-assisted two-stage pre-pectoral reconstructive technique is a safe, practical, and reproducible method.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-432/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-432/dss

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-432/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-432/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of Azienda Ospedaliero Universitaria Careggi (No. #16.069_AOUC) and individual consent for this retrospective analysis was waived.

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Original Article

Clinical effectiveness of microporous polysaccharide hemospheres in mastectomy for patients with breast cancer

Yoshiaki Shinden[1,2], Yuki Nomoto[1,3], Ayako Nagata[1], Yuka Eguchi[1], Hanako Yano[1], Hazuki Saho[1], Naoki Hayashi[3], Koji Minami[1], Tadahioro Hirashima[1], Ken Sasaki[1], Heiji Yoshinaka[3], Tetsuhiro Owaki[4], Akihiro Nakajo[1], Takao Ohtsuka[1]

[1]Department of Digestive Surgery, Breast and Thyroid Surgery, Kagoshima University Graduate School of Medical and Dental Sciences, Sakuragoka, Kagoshima-City, Japan; [2]Department of Breast and Thyroid Surgery, Kagoshima University Hospital, Sakuragoka, Kagoshima-City, Japan; [3]Department of Breast Surgery, Kagoshima City Hospital, Kamiarata, Kagoshima-City, Japan; [4]Department of Community-based Medicine Education Center for Doctors in Remote Island and Rural Areas, Kagoshima University Graduate School of Medical and Dental Sciences, Sakuragoka, Kagoshima-City, Japan

Contributions: (I) Conception and design: Y Shinden, A Nakajo, T Ohtsuka; (II) Administrative support: None; (III) Provision of study materials or patients: Y Shinden, Y Nomoto, A Nagata, Y Eguchi, H Yano, H Saho, N Hayashi, K Minami, T Hirashima, K Sasaki, A Nakajo; (IV) Collection and assembly of data: Y Shinden, Y Nomoto, A Nagata, Y Eguchi, H Yano, H Saho, N Hayashi, K Minami, T Hirashima, K Sasaki; (V) Data analysis and interpretation: Y Shinden, H Yoshinaka, T Owaki, A Nakajo, T Ohtsuka; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yoshiaki Shinden, MD, PhD. Department of Digestive Surgery, Breast and Thyroid Surgery, Kagoshima University Graduate School of Medical and Dental Sciences, 8-35-1, Sakuragaoka, Kagoshima 890-8520, Japan; Department of Breast and Thyroid Surgery, Kagoshima University Hospital, Sakuragoka, Kagoshima-City, Japan. Email: yoshinden@gmail.com.

Background: Microporous polysaccharide hemospheres (MPH) are hydrophilic particles administered to reduce the incidence of seroma after mastectomy, but their clinical effectiveness remains controversial. Because a previous randomized, controlled study in a small cohort could not demonstrate the effectiveness of MPH in breast surgery, we evaluated their effectiveness in surgery for breast cancer in a larger cohort.

Methods: Medical records of 352 patients who underwent total mastectomy for breast cancer were retrospectively reviewed. Clinical data were compared between 126 patients who received MPH during surgery (MPH group) and 226 who did not (control group) according to surgical procedures. Patients were significantly older in the MPH group than in the control group because of selection bias, but other factors, such as body mass index and number of dissected lymph nodes, did not differ between groups.

Results: When analyzed by use of axillary manipulation, the drain placement period and drainage volume were significantly less in the MPH group than in the control group for patients with mastectomy and sentinel lymph node biopsy. Only drainage volume was significantly less in the MPH group for patients with mastectomy and axillary lymph node dissection. The frequency of total postoperative complications, such as seroma requiring puncture, did not differ between groups.

Conclusions: Use of MPH may decrease the postoperative drainage volume and drain placement period in mastectomy for patients with breast cancer.

Keywords: Microporous polysaccharide hemospheres (MPH); breast cancer surgery; drain placement period; drainage volume

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Introduction

Microporous polysaccharide hemospheres (MPH) are hydrophilic polysaccharide particles with a diameter of 30–100 μm that are made from 100% purified potato starch and are currently used as absorbable hemostatic agents. MPH particles extract fluid from the blood, swell to form a gelatinous matrix to concentrate serum proteins, platelets, albumin, thrombin and fibrinogen, and create a scaffold for the formation of a fibrin clot (1,2). Egeli and colleagues reported that MPH could significantly reduce the incidence of seroma after mastectomy and axillary dissection in rats (3). However, the clinical effectiveness of MPH remains controversial. Several randomized, controlled studies could not demonstrate the effectiveness of MPH in patients who underwent breast, thyroid and endoscopic sinus surgery (4-6). In contrast, the effectiveness of MPH in cardiothoracic surgery and total knee arthroplasty has been shown in several retrospective analyses (7,8). In this retrospective study, we evaluated the effectiveness of MPH in breast cancer surgery. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-297/rc).

Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of Kagoshima University Hospital (No. 220041-Epidemiology). Individual consent for this retrospective analysis was waived. Medical records of 352 consecutive patients who underwent total mastectomy for breast cancer at Kagoshima University Hospital were retrospectively reviewed. Between December 2020 and April 2023, we used MPH for all patients who underwent mastectomy with or without axillary dissection (126 patients, MPH group). As a control, we compared the clinical data of 226 patients who underwent mastectomy between January 2015 and November 2020, when we did not use MPH. Patients over 90 years of age and those who underwent breast reconstruction or skin transplantation were excluded. Surgical procedures were total mastectomy, mastectomy with sentinel lymph node biopsy (SLNB) and mastectomy with axillary lymph node dissection (ALND). Ultrasonic or microwave dissectors were used for ALND, depending on the surgeon's preference, and two drainage tubes were placed for all patients. One gram of MPH (Arista^{TM} AH, C. R. Bard, Inc. Davol, Warwick, RI, USA) was applied to the chest wall and axillary region before wound closure. The drainage tubes were removed when the daily drainage output was below 50 mL per 24 hours, or 14 days after surgery. The collected clinical data were age, height, body weight and body mass index (BMI), and outcomes such as drain placement period duration, drainage output and postoperative complications. Postoperative hemorrhage, seroma formation, wound infection and skin necrosis were recognized as postoperative complications. Postoperative hemorrhage was defined as requiring additional compression after surgery. No patient in our cohort required additional surgery for hemorrhage. Seroma was defined as requiring puncture after drain removal. Wound infection was defined as requiring drainage and/or antibiotic administration, and skin necrosis was defined as wound dehiscence and/or crust formation requiring debridement.

Highlight box

Key findings
- Use of microporous polysaccharide hemospheres (MPH) decreased the postoperative drainage volume and drain placement period in mastectomy for patients with breast cancer.

What is known and what is new?
- A previous randomized, controlled study could not demonstrate the effectiveness of MPH in breast surgery, but it was performed in a small cohort (N=50).
- Although our study was retrospective, we analyzed a larger number of patients and showed the effectiveness of MPH in mastectomy for patients with breast cancer.

What is the implication, and what should change now?
- For improving postoperative quality of life, use of MPH could be recommended in mastectomy for patients with breast cancer.

Statistical analysis

Differences between groups were evaluated with the Wilcoxon test for continuous variables and the Pearson Chi-square test for categorical variables. Statistical analysis was performed using JMP Pro, version 16.1.0 for Mac OS (SAS Institute Japan Ltd., Tokyo, Japan). P values <0.05 were considered statistically significant.

Results

Patient characteristics are shown in *Table 1*. Patients in

Table 1 Patient characteristics

Characteristics	Control (n=226)	MPH (n=126)	P value
Age (years)	64.4 [29–89]	68.9 [36–89]	0.0021
Sex, female/male	220/6	123/3	0.88
Height (cm)	153.1 [134–178]	152.4 [134–170]	0.31
Body weight (kg)	56.1 [32–93]	54.1 [35–80]	0.1
BMI (kg/m^2)	24.0 [13.5–44.2]	23.2 [16.1–34.6]	0.18
Operation method, SLNB/ALND	132/94	101/25	<0.0001

Data are presented as mean [range] or number. BMI, body mass index; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; MPH, microporous polysaccharide hemospheres.

Table 2 Patient characteristics and outcomes in patients without axillary dissection

Characteristics	Control (n=132)	MPH (n=101)	P value
Age (years)	66.7 [35–89]	69.2 [36–89]	0.14
Height (cm)	152 [134–170]	152 [139–170]	>0.99
Body weight (kg)	56.6 [32–93]	54.3 [35–80]	0.11
BMI (kg/m^2)	24.4 [13.5–44.2]	23.3 [16.1–34.6]	0.08
Intraoperative blood loss (mL)	26 [0–235]	29 [0–128]	0.43
Number of dissected lymph nodes	2.4 [0–15]	2.1 [0–11]	0.3
Drain placement period (days)	5.8 [3–14]	4.7 [3–13]	0.0003
Total drainage volume (mL)	321 [27–1,761]	254 [68–1,010]	0.03
Postoperative complications, present/absent/NA*	31/81/20	21/67/13	0.54

Data are presented as mean [range] or number. *, not available because some patients were transferred to other hospitals after surgery. BMI, body mass index; NA, not available; MPH, microporous polysaccharide hemospheres.

the MPH group were significantly older (P=0.0021), and received axillary dissection significantly less frequently (P<0.0001) than those in the control group (*Table 1*). For analysis of the clinical effectiveness of MPH, we analyzed patients with SLNB and ALND separately. For patients with SLNB, there were no significant differences in background characteristics, such as age, height, body weight, BMI, intraoperative blood loss and number of dissected lymph nodes. The drain placement period was significantly shorter and the total drainage volume was significantly smaller in the MPH group compared with the control group (*Table 2*). Analysis of the variations in the daily amount of drainage found that a significant decrease in drainage volume occurred on postoperative days 2, 3 and 4 in the MPH group compared with the control group (*Figure 1*). For patients with ALND, age was significantly higher in the MPH group than in the control group. There was no significant difference between groups in patient background characteristics, such as height, body weight, BMI, intraoperative blood loss and number of dissected lymph nodes. The drain placement period was significantly shorter in the MPH group than in the control group, but the total drainage volume did not differ between groups (*Table 3*). Analysis of the variations in the daily amount of drainage found that a significant decrease in drainage volume occurred on postoperative days 2, 3, 4 and 5 in the MPH group compared with the control group (*Figure 2*). There was no difference in the frequency of total postoperative complications between the MPH group and the control group, regardless of surgical procedure. When types of complications were analyzed, skin necrosis was significantly less frequent in the MPH group, but the incidence of other

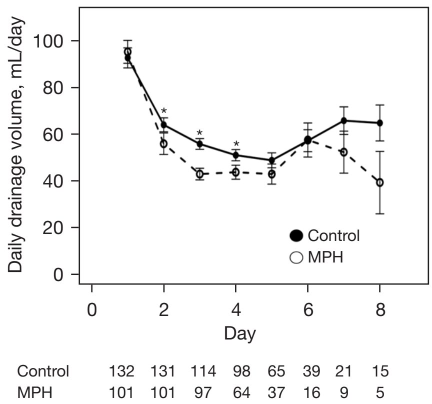

Figure 1 Daily variations in drainage volume in patients without axillary dissection. Daily drainage amounts in the control group and the MPH group. Error bars show standard deviation and asterisks show significant differences between groups. The numbers at the bottom represent the number of patients who had a drain placed on each day. MPH, microporous polysaccharide hemospheres.

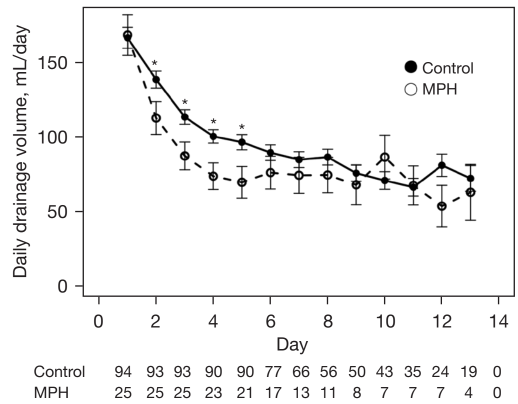

Figure 2 Daily variations in drainage volume in patients with axillary dissection. Daily drainage amounts in the control group and the MPH group. Error bars show standard deviation and asterisks show significant difference between groups. The numbers at the bottom represent the number of patients who had a drain placed on each day. MPH, microporous polysaccharide hemospheres.

Table 3 Patient characteristics and outcomes in patients with axillary dissection

Characteristics	Control (n=94)	MPH (n=25)	P value
Age (years)	61 [29–87]	68 [38–89]	0.03
Height (cm)	154 [134–178]	152 [134–166]	0.2
Body weight (kg)	55 [36–88]	53 [38–74]	0.38
BMI (kg/m^2)	23.3 [15.6–34.2]	23.0 [17.3–28.7]	0.75
Intraoperative blood loss (mL)	42 [0–244]	55 [0–176]	0.17
Number of dissected lymph nodes	17 [3–41]	14 [8–22]	0.12
Drain placement period (days)	9.8 [4–14]	8.3 [3–14]	0.038
Total drainage volume (mL)	925 [168–2,720]	709 [156–1,874]	0.064
Post operative complications, present/absent/NA*	39/43/12	8/15/2	0.28

Data are presented as mean [range] or number. *, not available because some patients were transferred to other hospitals after surgery. BMI, body mass index; NA, not available; MPH, microporous polysaccharide hemospheres.

complications did not differ between groups (*Table 4*).

Discussion

MPH is theoretically expected to reduce hemorrhage and serous exudate (1,3), while its clinical effectiveness remains controversial. Several randomized, controlled studies in various types of surgery, including breast surgery, could not establish the effectiveness of MPH (4-6), while other retrospective studies showed the effectiveness of MPH in cardiothoracic surgery and total knee arthroplasty (7,8). One reason for such a discrepancy may be the small study populations that were analyzed. Suarez-Kelly and colleagues could not show the effectiveness of MPH in mastectomy, but that study included only 50 patients who underwent various axillary manipulation techniques (4). In the current study, we analyzed a much larger population (352 patients) and showed the effectiveness of MPH in breast cancer

Table 4 Postoperative complications

Variables	SLNB			ALND		
	Control (n=132)	MPH (n=101)	P value	Control (n=94)	MPH (n=25)	P value
Any complications, present/absent/NA (n)	31/81/20	21/67/13	0.54	39/43/12	8/15/2	0.28
Hemorrhage, present/absent (n)	1/131	0/101	0.38	2/92	0/25	0.46
Infection, present/absent (n)	2/130	0/101	0.21	6/88	0/25	0.2
Skin necrosis, present/absent (n)	6/126	0/101	0.03	8/86	1/24	0.004
Seroma, present/absent/NA (n)	28/84/20	17/81/3	0.18	32/50/12	7/16/2	0.45
Number of aspiration for seroma, mean	1.9	3	0.07	2.8	2.3	0.56
Total amount of seroma (mL), mean	145	221	0.33	292	297	0.98

NA, not available; SLNB, sentinel lymph node biopsy; MPH, microporous polysaccharide hemospheres; ALND, axillary lymph node dissection.

surgery.

In our cohort, the incidence of postoperative complications was 28% (100 of 352 cases). Previous studies reported postoperative seroma incidence ranging from 0 to 35% in patients who underwent total mastectomy (4,9-11). Our outcomes are comparable with the previous data.

When we divided the patient population into two subgroups by surgical procedure (with and without ALND), MPH significantly decreased the drain placement period and the daily drainage volume in both subgroups, and the total drainage volume in the SLNB subgroup (*Tables 2,3*, *Figures 1,2*). In both the ALND and SLNB subgroups, the daily drainage volume in the MPH group reached a plateau and overlapped with that of the control group. This was attributed to the dropout of patients whose drainage output was small and whose tubes were removed. There was no difference between the MPH group and the control group in postoperative complications, except for skin necrosis. It is unclear why skin necrosis was less frequent in the MPH group. However, since the incidence of complications other than seroma was low, future studies with larger numbers of patients are needed.

Many studies have shown no effect of hemostatic agents, including MPH, fibrin glue, oxidized regenerated cellulose, polysaccharide hemostatic agents and local sclerosing agents, in breast cancer surgery (4,12-18). However, a systematic review concluded that the use of fibrin glue reduced the incidence of seroma, the postoperative drainage volume, and the duration of drainage (19). Thus, the efficacy of hemostatic agents remains controversial.

One disadvantage of using MPH is cost. One gram of MPH costs about $85 in Japan. The time required for use of MPH in surgery is less than one minute. Because the substance is derived from starch, there is no risk of allergy, and no other complications were observed in our experience.

This study has some limitations. First, it was a retrospective study, and some selection biases existed between groups. Age was higher in the MPH group than in the control group, especially in the ALND subgroup. Previous studies reported several risk factors that could contribute to drainage volume and seroma formation. Burak and colleagues reported risk factors for seroma formation after mastectomy and ALND as increased age, patient weight and other factors (20). In this study, the MPH group with elderly patients had smaller drainage volumes and a decreased incidence of seroma suggesting that the effectiveness of MPH was not affected by the selection bias of age. In addition, differences in surgeon experience and surgical equipment existed, because the timing of surgery was different in groups with and without MPH use. The detailed differences were not examined in this study. Second, the impact of MPH on number of hospitalization days was not examined, because it could be influenced by patient social background characteristics.

As a result, we showed that the use of MPH could decrease the drainage output and the number of drainage days. A disadvantage of using MPH is the increased cost of the surgical procedure, but the total cost effectiveness should be revealed with further study. For evaluation of the definitive clinical effectiveness of MPH in breast cancer surgery, a clinical trial with an appropriate number of cases is needed.

Conclusions

Use of MPH in mastectomy for patients with breast cancer was associated with decreased drainage output and fewer drainage days.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-297/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-297/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of Kagoshima University Hospital (No. 220041-Epidemiology). Individual consent for this retrospective analysis was waived.

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Original Article

Analysis of risk factors for lateral lymph node metastasis in T1 stage papillary thyroid carcinoma: a retrospective cohort study

Yuanyuan Fan[#], Xun Zheng[#], Yanhao Ran, Pengyu Li, Tianfeng Xu, Yujie Zhang, Tao Wei^

Division of Thyroid Surgery, Department of General Surgery, West China Hospital, Sichuan University, Chengdu, China

Contributions: (I) Conception and design: Y Fan, X Zheng; (II) Administrative support: T Wei; (III) Provision of study materials or patients: T Wei; (IV) Collection and assembly of data: Y Fan, X Zheng, Y Ran, P Li, T Xu, Y Zhang; (V) Data analysis and interpretation: Y Fan, X Zheng, T Wei; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as co-first authors.

Correspondence to: Tao Wei, PhD. Division of Thyroid Surgery, Department of General Surgery, West China Hospital, Sichuan University, 37 Guoxue Lane, Wuhou District, Chengdu 610041, China. Email: surgeonwei5776@163.com.

Background: The occurrence of cervical lymph node metastasis in T1 stage papillary thyroid carcinoma (PTC) is frequently observed. Notably, lateral lymph node metastasis (LLNM) emerges as a critical risk factor adversely affecting prognostic outcomes in PTC. The primary aim of this investigation was to delineate the risk factors associated with LLNM in the initial stages of PTC.

Methods: This retrospective analysis encompassed 3,332 patients diagnosed with T1 stage PTC without evident LLNM at the time of diagnosis. These individuals underwent primary surgical intervention at West China Hospital, Sichuan University between June 2017 and February 2023. The cohort was divided into two groups: patients manifesting LLNM and those without metastasis at the time of surgery. Additionally, T1 stage PTC patients were subdivided into T1a and T1b categories. Factors influencing LLNM were scrutinized through both univariate and multivariate analyses.

Results: The incidence of LLNM was observed in 6.2% of the cohort (206 out of 3,332 patients). Univariate analysis revealed significant correlations between LLNM and male gender ($P<0.001$), tumor localization in the upper lobe ($P<0.001$), maximal volume of the primary tumor ($P<0.001$), largest tumor diameter ($P<0.001$), multifocality ($P<0.001$), and bilaterality ($P<0.001$), with the exception of age ($P=0.788$) and duration of active surveillance (AS) ($P=0.978$). Multivariate logistic regression analysis identified male gender ($P<0.001$), upper lobe tumor location ($P<0.001$), maximal primary tumor volume ($P<0.001$), and multifocality ($P<0.001$) as independent predictors of LLNM. However, age categories (≤55, >55 years), maximum tumor diameter, bilaterality, and surveillance duration did not exhibit a significant impact. Comparative analyses between T1a and T1b subgroups showed congruent univariate results but revealed differences in multivariate outcomes. In the T1a subgroup, gender, tumor location, and multifocality (all $P<0.05$) were associated with elevated LLNM risk. Conversely, in the T1b subgroup, tumor location, dimensions, and multifocality (all $P<0.05$) were significant predictors of LLNM risk, whereas gender ($P=0.097$) exerted a marginal influence.

Conclusions: The investigation highlights several key risk factors for LLNM in T1 stage PTC patients, including gender, upper lobe tumor location, larger tumor size, and multifocality. Conversely, prolonged AS and younger age did not significantly elevate LLNM risk, suggesting the viability of AS as a strategic option in selected cases.

Keywords: Papillary thyroid carcinoma (PTC); lateral lymph nodes; metastasis; risk factors

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^ ORCID: 0000-0001-5413-9129.

Introduction

Background

Papillary thyroid carcinoma (PTC) constitutes the most prevalent histological variant among thyroid malignancies, accounting for approximately 89.1% of all cases. This statistic, however, shows a marginal decline between 2014 and 2018 (1). Patients diagnosed with PTC typically demonstrate favorable prognostic outcomes and low mortality rates. Nonetheless, early-stage metastasis to the cervical lymph nodes is not uncommon. Prior research (2-5) indicates that lymph node metastases are present in about 20% to 90% of PTC cases. Although central lymph node metastasis does not markedly alter the prognosis for PTC patients (6), the emergence of lateral lymph node metastasis (LLNM, N1b) often necessitates more complex and prolonged surgical procedures, potentially impacting patient prognosis adversely (7,8).

A study by Sapuppo *et al.* (7) categorized PTC patients based on their postoperative pathologic N status. Findings indicated that individuals classified at the N1b stage showed an increased incidence of structural diseases, including locoregional lymph node and/or distant metastases, compared to those in the N0 and N1a stages. At their final follow-up, N1b stage patients exhibited a higher likelihood of persistent or recurrent disease relative to those in the N1a category. Moreover, those with lateral LN metastasis demonstrated reduced disease-free and 10-year disease-related survival rates (9,10). A notable study observed a 3.0% mortality rate among N1b patients, significantly higher than that in N1a and N0 patients (11), suggesting that LLN positivity is a strong prognostic indicator for poor outcomes in PTC.

The American Thyroid Association (ATA) management guidelines for differentiated thyroid cancer (DTC) recommend central and/or lateral lymph node dissection when metastasis is clinically or radiographically evident, while cautioning against routine prophylactic dissection of lateral lymph nodes (12). The efficacy of prophylactic level VI (central) neck dissection in cN0 disease remains a topic of debate (12). Confirmed LLNMs necessitate additional lateral lymph node dissection, extending the surgery's complexity and duration. Such procedures also increase the likelihood of postoperative complications, including celiac leakage, hemorrhage, nerve injury, shoulder discomfort, and restricted mobility (13). Consequently, the development of prognostic methods for LLNM is essential in managing node metastasis and recurrence in PTC.

Despite extensive research into LLNM risk factors in PTC, findings have been inconsistent (8,14-20). Our study explored major risk factors such as patient age, gender, primary tumor location, tumor diameter, multifocality, and bilaterality. Additionally, we hypothesized that primary tumor volume and duration of active surveillance (AS) post-diagnosis could also contribute to LLNM risk. These variables were thus comprehensively integrated into our analysis.

AS involves monitoring cancer patients without immediate surgical or radiation intervention unless the disease progresses. In 1993, Dr. Akira Miyauchi proposed delayed surgical intervention as an alternative to immediate surgery for papillary thyroid microcarcinoma (PTMC, tumor diameter <1 cm) at a symposium hosted at Kuma Hospital, Japan. Subsequent trials in 2003 and 2010 corroborated the feasibility of this approach (21,22), and numerous patients in Korea have been studied (23), showcasing AS as a promising alternative for PTMC treatment. Ho *et al.*'s comprehensive study (24) found

Highlight box

Key findings

- In this retrospective study of 3,332 patients with T1 stage papillary thyroid carcinoma (PTC), we found factors (male gender, upper lobe tumor, larger volume, and multifocality) linked to lateral lymph node metastasis (LLNM) risk. Patients without these risks, particularly in T1b stage PTC, may benefit from short-term active surveillance (AS), underscoring the importance of an assertive approach in cases with increased tumor size.

What is known and what is new?

- In early-stage PTC, there is a propensity for cervical lymph node metastasis, with lateral compartment involvement correlating with an adverse prognosis for patients.
- In our study, tumor volume, not diameter, strongly correlated with LLNM risk. Notably, younger patients showed no significant increase in this risk. In T1a stage PTC, males had a closer association with LLNM, while in T1b stage PTC, tumor size played a more crucial role.

What is the implication, and what should change now?

- In clinical practice, patients with identified risk factors necessitate routine follow-up and careful consideration of the optimal timing for surgical intervention due to heightened vulnerability to lateral nodal metastasis. Nevertheless, those lacking these risks, especially younger patients, may consider short-term AS, justifying its adoption when these risk factors are absent. In T1a stage PTC, male gender prompts careful evaluation for immediate surgical intervention. In T1b stage PTC, increased tumor size emphasizes the necessity for a more assertive treatment approach.

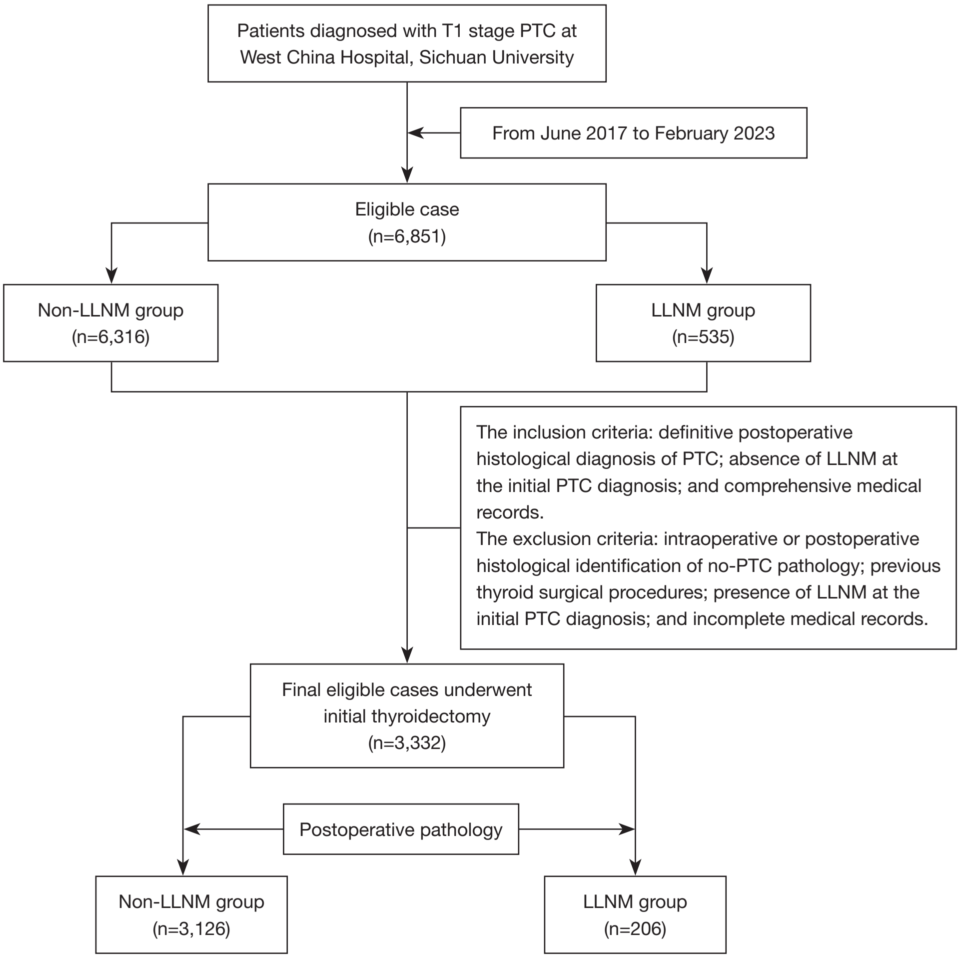

Figure 1 Flow chart of the selection of study population. PTC, papillary thyroid carcinoma; LLNM, lateral lymph node metastasis.

no significant mortality risk difference between 1.0- and 2.0-cm thyroid tumors. However, a tumor diameter of >2 cm independently correlates with an increased risk of cancer-related death. Therefore, for all T1 stage (<2 cm) tumors, AS may be a feasible alternative to immediate surgery (24,25). AS also appears as a potential therapeutic option for recurrent lymph node metastasis in DTC (26,27). During AS, most low-risk PTC patients did not develop new lymph node metastases (28-30). However, the direct link between AS and the occurrence of LLN metastasis has not been comprehensively documented.

Objective

This retrospective cohort study aims to identify risk factors for LLNM development, providing insights for the timing of surgical interventions in clinical practice and contributing to informed clinical decision-making and patient welfare. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-470/rc).

Methods

Patients

This study entailed a retrospective cohort analysis of 3,332 patients diagnosed with PTC, who underwent initial thyroidectomy at West China Hospital, Sichuan University, from June 2017 to February 2023. A detailed methodology flowchart is provided in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee of West China Hospital of Sichuan University

(2023 No. 2098). Individual consent for this retrospective analysis was waived. All participants underwent their first thyroid surgery and were confirmed to have no other histopathological types of thyroid carcinoma. The cohort was bifurcated based on the presence or absence of LLNM, as ascertained by postoperative pathological evaluation. Further, these patients were segregated into T1a (<10 mm) and T1b (>10 mm) categories, contingent on the maximum diameter of the tumor.

The inclusion criteria encompassed: definitive postoperative histological diagnosis of PTC; absence of suspicious LLNM on ultrasonography at the initial PTC diagnosis; and comprehensive medical records. The exclusion criteria included: intraoperative or postoperative histopathological identification of non-PTC pathology; previous thyroid surgical procedures; presence of LLNM on ultrasonography or distant metastasis on computed tomography/magnetic resonance imaging (CT/MRI) at the initial PTC diagnosis; and incomplete medical records.

Data collection

Clinical and pathological data were collated from electronic medical records and pathology reports.

Patient demographic information (gender and age), and the time of initial fine-needle aspiration biopsy (FNAB) confirming PTC can be retrieved from the electronic medical records. The ultrasonography report provided tumor characteristics (maximum diameter, volume, location) and clinical details (multifocality, bilaterality, and LLNM status). The tumor volume (in mm^3) was computed employing the ellipsoid volume equation: $\pi/6 \times$ length $\times$ width $\times$ height. The features of suspect malignant lymph node involvement include (with at least one of the following features): (I) microcalcifications; (II) partially cystic appearance; (III) increased peripheral or diffuse vascularity; (IV) hyperechoic tissue looking like thyroid. The characteristic of indeterminate lymph node: disappearance of lymphatic hilum and at least one of the following characteristics: round shape; increased short axis, ≥8 mm in level II and ≥5 mm in levels III and IV; absence of central vascularization (12,31,32). We conducted lymph node assessment according to those criteria. For a few indeterminate lymph nodes, after discussing with the patient, we opted for either lymph node fine-needle aspiration with thyroglobulin washout fluid testing or immediate surgery. For the LLNM group, the period of AS before surgery was demarcated as the interval from the initial FNAB confirming PTC, to the first detection of LLNM via preoperative ultrasound, subsequently corroborated by postoperative pathology. For the non-LLNM cohort, this duration was defined as the time span between the initial FNAB diagnosis of PTC and the admission for surgery. Quantitative data, including age, primary tumor's maximum diameter and volume, and waiting time for surgery, were transformed into qualitative categories based on predetermined cut-off values.

Statistical analysis

Continuous variables were converted into categorical data for analysis using SPSS version 25. The Chi-squared test was employed to compare demographic and tumor characteristics, including gender, age, tumor size, tumor location, and AS duration between the LLNM and non-LLNM groups. Multifactorial analysis was performed using binary logistic regression. A P value of less than 0.05 (two-tailed) was considered indicative of statistical significance.

Results

Patient characteristics and group analysis

Among 3,332 PTC patients meeting inclusion and exclusion criteria, 206 presented with LLNM. The clinical and pathological characteristics of all participants are delineated in *Table 1*. The average AS time of the LLNM group is 137.9±145.7 days. The LLNM group had a significantly higher proportion of males at 37.4% (77/206) compared to the non-LLNM group at 23.5% (P<0.001). The mean age in the metastasis cohort was 41.6±10.9 years, which did not significantly differ from that of the non-metastasis group (P=0.729). Tumor location was categorized as upper lobe or non-upper lobe (inclusive of middle and lower lobes and the isthmus). A higher proportion of upper lobe tumors was observed in the LLNM group (38.8%) compared to the non-LLNM group (25.0%) (P<0.001). Additionally, significant differences were noted in the maximum tumor diameter (11.5±4.1 mm in the LLNM group versus 9.0±3.5 mm in the non-LLNM group, P<0.001) and maximum tumor volume (603.1±569.4 mm^3 in the LLNM group versus 318.6±377.2 mm^3 in the non-LLNM group, P<0.001). Higher incidences of multifocal and bilateral tumors were observed in the LLNM group (29.1% and 18.0%, respectively) compared to the non-LLNM group (P<0.05 for both).

Table 1 Clinical and pathological characteristics for LLNM risk of T1 stage PTC patients by univariate analysis (n=3,332)

Category	Non-LLNM (n=3,126)	LLNM (n=206)	Total	OR (95% CI)	P value
Sex				1.945 (1.450–2.610)	<0.001
Female	2,392 (76.5)	129 (62.6)	2,521 (75.7)		
Male	734 (23.5)	77 (37.4)	811 (24.3)		
Age (years)				0.939 (0.595–1.482)	0.788
≤55	2,773 (88.7)	184 (89.3)	2,957 (88.7)		
>55	353 (11.3)	22 (10.7)	375 (11.3)		
Mean ± SD	41.3±10.8	41.6±10.9			0.729
Tumor location				0.525 (0.393–0.703)	<0.001
Upper lobe	782 (25.0)	80 (38.8)	862 (25.9)		
Non-upper lobe	2,344 (75.0)	126 (61.2)	2,470 (74.1)		
Tumor volume (mm^3)					<0.001
<319	2,149 (68.7)	78 (37.9)	2,227 (66.8)	1.000	
319–603	504 (16.1)	50 (24.3)	554 (16.6)	2.733 (1.892–3.949)	<0.001
>603	473 (15.1)	78 (37.9)	551 (16.5)	4.543 (3.269–6.315)	<0.001
Mean ± SD	318.6±377.2	603.1±569.4			<0.001
Tumor diameter (mm)				2.917 (2.167–3.927)	<0.001
≤12	2,595 (83.0)	129 (62.6)	2,724 (81.8)		
>12	531 (17.0)	77 (37.4)	608 (18.2)		
Mean ± SD	9.0±3.5	11.5±4.1			<0.001
Multifocality				2.444 (1.780–3.354)	<0.001
No	2,676 (85.6)	146 (70.9)	2,822 (84.7)		
Yes	450 (14.4)	60 (29.1)	510 (15.3)		
Bilaterality				1.907 (1.312–2.771)	0.001
No	2,804 (89.7)	169 (82.0)	2,973 (89.2)		
Yes	322 (10.3)	37 (18.0)	359 (10.8)		
AS time (months)				0.983 (0.719–1.381)	0.978
≤6	2,350 (75.2)	155 (75.2)	2,505 (75.2)		
>6	776 (24.8)	51 (24.8)	827 (24.8)		

Data are reported as n (%), unless noted otherwise. P values represent the statistically difference between the groups with and without LLNMs, unless noted otherwise. LLNM, lateral lymph node metastasis; PTC, papillary thyroid carcinoma; OR, odds ratio; CI, confidence interval; SD, standard deviation; AS, active surveillance.

Univariate and multivariate analyses

Univariate analysis (*Table 1*) revealed that male gender, primary tumor location in the upper lobe, larger tumor volume, greater tumor diameter, multifocal, and bilateral tumors were all significantly associated with LLNM (all P<0.001). The multivariate analysis was presented in *Table 2*. Male patients exhibited approximately double the risk of LLNM compared to females [odds ratio (OR) =1.782, P<0.001]. The presence of primary tumors in the upper lobes (OR =1.975, P<0.001), larger tumor volumes (319–603 mm^3, OR =2.546, P<0.001; >603 mm^3, OR =4.784,

Table 2 Multivariate analysis of the risk factors for LLNM of T1 stage PTC patients (n=3,332)

Variables	OR (95% CI)	P value
Sex		
Female	Reference	
Male	1.782 (1.315–2.417)	<0.001
Age (years)		
≤55	1.207 (0.755–1.931)	0.432
>55	Reference	
Tumor location		
Upper lobe	1.975 (1.461–2.670)	<0.001
Non-upper lobe	Reference	
Tumor volume (mm^3)		<0.001
<319	Reference	
319–603	2.546 (1.731–3.744)	<0.001
>603	4.784 (2.676–8.553)	<0.001
Tumor diameter (mm)		0.359
≤12	Reference	
>12	0.900 (0.525–1.546)	0.704
Multifocality	3.254 (1.976–5.358)	<0.001
Bilaterality	0.606 (0.337–1.089)	0.094
AS time (months)		
≤6	Reference	
>6	1.080 (0.771–1.514)	0.654

LLNM, lateral lymph node metastasis; PTC, papillary thyroid carcinoma; OR, odds ratio; CI, confidence interval; AS, active surveillance.

P<0.001), and multifocality (OR =3.254, P<0.001) were also significantly correlated with an increased risk of LLNM. Gender-specific analyses (*Table 3*) did not reveal a significant correlation between AS duration and LLNM risk.

Subgroup analysis: *T1a and T1b groups*

Supplementary material present clinical and pathological data for T1a and T1b subgroups, respectively. Univariate analysis (Tables S1,S2) indicated common LLNM risk factors: male gender, upper lobe tumor location, larger tumor size, and multifocality. Multifactorial regression analysis (*Table 4*) highlighted that gender was a significant risk factor for LLNM in the T1a group (P<0.001) but not in the T1b group (P=0.097). Furthermore, no significant differences were observed in age and AS duration between LLNM and non-LLNM groups in both subgroups (Tables S3,S4).

Discussion

In this extensive retrospective analysis of 3,332 patients, we observed a positive association between factors such as male gender, upper lobe tumor location, larger tumor volume, and multifocality with the risk of LLNM. This finding underscores the necessity of routine follow-up and careful consideration of the optimal timing for surgical intervention, particularly when these factors coexist. Conversely, factors like age, tumor diameter, bilateral tumor presence, and extended AS duration did not demonstrate a substantial correlation with lateral nodal involvement.

Aligning with Mao *et al.*'s meta-analysis (14), our study reaffirms male sex as a risk factor for LLNM in T1 stage PTC patients, highlighting a higher propensity for LLNM in men. This gender-based disparity in LLNM incidence aligns with several studies (15,33), although it remains a subject of debate in other research (34,35). Notably, the adverse prognosis associated with PTC tends to be more pronounced in men, despite its higher prevalence in women (36). This suggests the need for rigorous evaluation of immediate thyroid surgery in male patients, particularly in T1a stage PTC.

Though the traditional belief that younger age (<55 years) is a risk factor for lymph node metastasis (17,34), our study found no significant age-related differences in LLNM risk, potentially supporting the potential role of AS in specific cases.

Primary tumor location significantly affects lymph node dissemination, as supported by our findings in agreement with prior research (19,37-39). Given the complex drainage patterns and higher postoperative complication risks associated with upper thyroid tumors, accurate LLNM assessment in clinical practice is paramount.

While PTMC is generally considered low-risk for LLNM (12), our study suggests that larger tumor diameters do not necessarily predict LLNM, diverging from some previous research (40). By incorporating tumor volume in our analysis, we found a strong association between greater tumor volumes and an increased risk of LLNM. This finding is supported by research emphasizing tumor volume as a more reliable prognostic marker than diameter (41). These results highlight the importance of careful surgical

Table 3 Univariate analysis of active surveillance time of T1 stage PTC patients

AS time (months)	Non-LLNM	LLNM	Total	OR (95% CI)	P value
Female (n=2,521)					
≤6	1,789	95	1,884	1.062 (0.710–1.588)	0.770
>6	603	34	637		
≤12	2,131	119	2,250	0.686 (0.355–1.325)	0.259
>12	261	10	271		
≤24	2,325	129	2,454	–	0.100
>24	67	0	67		
Male (n=811)					
≤6	561	60	621	0.919 (0.522–1.616)	0.769
>6	173	17	190		
≤12	647	71	718	0.628 (0.265–1.489)	0.287
>12	87	6	93		
≤24	719	74	793	1.943 (0.550–6.868)	0.520
>24	15	3	18		

PTC, papillary thyroid carcinoma; AS, active surveillance; LLNM, lateral lymph node metastasis; OR, odds ratio; CI, confidence interval.

Table 4 Multivariate analysis of the risk factors for LLNM of T1a (n=2,318) and T1b (n=1,014) PTC patients

Variables	T1a (n=2,318)		T1b (n=1,014)	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex				
Female	Reference		Reference	
Male	2.253 (1.444–3.515)	<0.001	1.426 (0.937–2.169)	0.097
Age (years)				
≤55	0.712 (0.392–1.295)	0.266	2.075 (0.968–4.448)	0.061
>55	Reference		Reference	
Tumor location				
Upper lobe	2.131 (1.367–3.323)	0.001	1.951 (1.286–2.960)	0.002
Non-upper lobe	Reference		Reference	
Tumor volume (mm^3)				
≤140	Reference		Reference	
>140	1.960 (0.884–4.346)	0.098	2.072 (1.222–3.516)	0.007
Tumor diameter (mm)				
≤7	Reference		Reference	
>7	0.955 (0.432–2.111)	0.909	1.268 (0.745–2.158)	0.382
Multifocality	2.780 (1.273–6.072)	0.01	3.461 (1.747–6.857)	<0.001
Bilaterality	0.791 (0.321–1.950)	0.611	0.596 (0.268–1.326)	0.205
AS time (months)				
≤6	Reference		Reference	
>6	1.314 (0.821–2.103)	0.256	0.944 (0.578–1.541)	0.817

LLNM, lateral lymph node metastasis; PTC, papillary thyroid carcinoma; OR, odds ratio; CI, confidence interval; AS, active surveillance.

planning for patients with larger tumor volumes.

Our analysis identified multifocality as a LLNM risk factor, contrary to some studies that suggest both multifocality and bilaterality increase LLNM risk (39). Multifocality's prognostic significance, especially in tumors larger than 1 cm, is well-established (42). However, our findings do not support the hypothesis that bilaterality, an indicator of tumor invasiveness, heightens LLNM risk.

Our study delves into the potential impact of AS duration on LLNM risk. With the emerging role of AS in managing T1a and potentially T1b stage PTC (25,43), there is increasing focus on understanding the association between surveillance duration and LLNM risk. Within *Table 3*, we performed separate analyses employing surveillance duration thresholds of 6, 12, and 24 months (*Table 3*, all P values >0.05). The selection of these thresholds values was informed by clinical practice. These analyses reveal that, for those with stage T1 PTC, there were no notable differences in the distribution of time to AS between the LLNM and non-LLNM groups. In the subgroups of T1a and T1b, we encountered equivalent results. Hence, our findings suggest that short-term AS (≤24 months) may not considerably increase the risk of LLNM in T1 stage PTC patients, which is in accordance with the conclusions of previous studies (44,45). Further research, particularly focusing on long-term surveillance, is warranted to substantiate these findings.

LLNM is associated with a poor prognosis in patients (46). Nevertheless, the current indication for performing cervical lateral lymph node dissection in PTC cases remain subject to debate. According to the ATA management guidelines, patients are recommended for LLN dissection when clinical or radiographic evidence supports the presence of lymph node disease (12). Ultrasonography is the primary tool for diagnosing cN1b, but its sensitivity was found to be only 0.70 (95% CI: 0.68–0.72; I^2=96.7%) (47). Building on our earlier discussion, preoperative patients presenting with male gender, upper lobe tumor location, larger tumor dimension, and multifocality are indicative of a heightened risk of LLNM. These high-risk factors discourage AS and instead favor lateral lymph node dissection surgery. The identification of high-risk factors for predicting LLN metastasis contributes to decisions regarding total thyroidectomy and lateral lymph node dissection in PTC patients, as well as guides surgeons in evaluating and treating cervical lateral lymph nodes during postoperative follow-up. Postoperative adjuvant therapy for PTC typically comprises TSH suppression therapy and radioactive iodine treatment (48). For high-risk thyroid cancer patients, TSH levels are generally maintained below 0.1 mU/L (12). Moreover, patients with suspected or confirmed lymph node metastasis and extrathyroidal tumor extension might necessitate an increased radioactive iodine dosage to further diminish the risk of recurrence (49). Consequently, for postoperative patients meeting all the aforementioned risk factors, it seems justifiable to adopt a proactive approach in deciding on TSH suppression therapy and radioactive iodine treatment to minimize the risk of PTC recurrence after surgery.

This study, being retrospective and single-center, has its limitations, including the lack of uniformity in tumor location assessment and the absence of a separate analysis for different types of lymph node metastasis. Future multicenter, prospective studies with larger sample sizes and extended follow-up periods are necessary to address these gaps and further explore the nuances of LLNM in PTC.

Conclusions

In summary, this retrospective analysis has identified several critical risk factors for LLNM in patients with T1 stage PTC. These include male gender, tumor location in the upper third of the thyroid gland, a maximum tumor volume exceeding 603 mm^3, and the presence of multifocal tumors. In clinical practice, patients exhibiting this constellation of risk factors should give serious thought to surgical intervention due to their increased vulnerability to lateral nodal metastasis.

On the other hand, for patients not displaying these risk factors, the consideration of a short-term AS strategy may be appropriate. Our findings indicate that extended periods of AS, especially in younger patients, do not significantly escalate the risk of LLNM. This observation offers a viable justification for adopting AS in certain patient cohorts, particularly when the risk factors mentioned above are absent.

It is also noteworthy that in patients with T1a stage PTC, male gender should trigger a careful evaluation of the need for immediate surgical intervention. However, in the context of T1b stage PTC, the influence of gender appears less pronounced. Rather, an increase in tumor size emerges as a pivotal factor in elevating the risk of LLNM, underscoring the necessity for a more assertive treatment approach in these cases.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-470/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-470/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-470/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee of West China Hospital of Sichuan University (2023 No. 2098). Individual consent for this retrospective analysis was waived.

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Original Article

Tumor-derived mesenchymal progenitor cell-related genes in the regulation of breast cancer proliferation

Yizhu Chen[1,2#], Li Zhu[2#], Yiming Wang[3], Jia Hu[1,2], Hao Zhang[4], Jingjin Zhu[2,5], Wenye Gong[1,2], Xiaohan Liu[2,5], Fengjun Xiao[6], Xiru Li[2]

[1]Medical School of Chinese PLA, Beijing, China; [2]Department of General Surgery, The First Medical Center of Chinese People's Liberation Army (PLA) General Hospital, Beijing, China; [3]School of Nursing, Jilin University, Changchun, China; [4]Medical Research Institute, Hebei Yanda Hospital, Langfang, China; [5]School of Medicine, Nankai University, Tianjin, China; [6]Department of Experimental Hematology and Biochemistry, Beijing Institute of Radiation Medicine, Beijing, China

Contributions: (I) Conception and design: X Li, F Xiao, L Zhu; (II) Administrative support: X Li; (III) Provision of study materials or patients: X Li; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Xiru Li, MD. Professor, Department of General Surgery, The First Medical Center of Chinese People's Liberation Army (PLA) General Hospital, 28 Fuxing Road, Haidian District, Beijing 100853, China. Email: 2468li@sina.com; Fengjun Xiao, PhD. Professor, Department of Experimental Hematology and Biochemistry, Beijing Institute of Radiation Medicine, 27 Taiping Road, Haidian District, Beijing 100850, China. Email: xiaofjun@sina.com.

Background: Breast cancer (BC) is one of the most common malignancies worldwide, and its development is affected in various ways by the tumor microenvironment (TME). Tumor-derived mesenchymal progenitor cells (MPCs), as the most important components of the TME, participate in the proliferation and metastasis of BC in several ways. In this study, we aimed to characterize the genes associated with tumor-derived MPCs and determine their effects on BC cells.

Methods: Tumor-derived MPCs and normal breast tissue-derived mesenchymal stem cells (MSCs) were isolated from tissues specimens of patients with BC. We conducted culture and passage, phenotype identification, proliferation and migration detection, inflammatory factor release detection, and other experiments on isolated MPCs from tumors and MSCs from normal breast tissues. Three paired tumor-derived MPCs and normal breast tissue-derived MSCs were then subjected to transcriptome analysis to determine the expression profiles of the relevant genes, and quantitative real-time polymerase chain reaction (qRT-PCR) was used to further confirm gene expression. Subsequently, the overexpression plasmids were transfected into tumor-derived MPCs, and the expression of various inflammatory factors of tumor-derived MPCs and their proliferation were characterized with a cell viability test reagent (Cell Counting Kit 8). Subsequently, the transfected tumor-derived MPCs were cocultured with BC cells using a conditioned medium coculture method to clarify the role of tumor-derived MSCs in BC.

Results: Tumor-derived MPCs expressed stem cell characteristics including CD105, CD90, and CD73 and exhibited adipogenic and osteogenic differentiation in vitro. The proliferation of tumor-derived MPCs was significantly lower than that of normal breast tissue-derived MSCs, and the invasive metastatic ability was comparable; however, MPCs were found to release inflammatory factors such as interleukin 6 (IL-6) and transforming growth factor β (TGF-β). Transcriptome analysis showed that stomatin (*STOM*), collagen and calcium binding EGF domains 1 (*CCBE1*), and laminin subunit alpha 5 (*LAMA5*) were significantly upregulated in tumor-derived MPCs. Among them, *STOM* was highly expressed in tumor-derived MPCs, which mediated the slow proliferation of MPCs and promoted the proliferation of BC cells.

Conclusions: *STOM*, *CCBE1*, and *LAMA5* were highly expressed in tumor-derived MPCs, with *STOM* being found to retard the proliferation of MPCs but promote the proliferation of BC cells. There findings present new possibilities in targeted microenvironmental therapy for BC.

Keywords: Breast cancer (BC); mesenchymal stem cells (MSCs); tumor microenvironment (TME); stomatin (*STOM*)
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Introduction

Breast cancer (BC) is one of the most common malignant tumors in women. According to the survey data from the International Agency for Research on Cancer (IARC), 2.26 million new cases of BC are reported worldwide each year, and BC has replaced lung cancer as the most common cancer in the world (1). Despite numerous advances being made in BC research in recent years, the etiology of BC remains unclear, and survival rates are hampered by several challenges such as tumor metastasis and drug resistance (2). Therefore, there is an urgent need to identify new effective biomarkers to improve the prognosis and quality of life of patients with BC. The tumor microenvironment (TME) and its components play a key role in regulating tumor drug resistance, recurrence, and metastasis (3). The TME consists of all the nontumor components distributed around tumor cells, including mesenchymal progenitor cells (MPCs), fibroblasts, myeloid-derived suppressor cells (MDSCs), macrophages, lymphocytes, extracellular matrix (ECM), and interwoven vascular endothelial cells (4). Mesenchymal stem cells (MSCs) derived from bone marrow are considered common primitive cells of other stromal cells, and in tumors, MSCs tend to differentiate into tumor stromal precursor cells via the TME, thus becoming tumor-derived MPCs (5). Both MPCs and MSCs have certain stem cell properties; however, MPCs are influenced by tumor cells and the TME and have certain protumorigenic effects compared to MSCs. Research indicates that MPCs are an important component of the TME, can regulate tumor cells, and can, through multiple pathways, promote cancer formation and progression via proliferation, invasive metastasis, immune resistance, and several other malignant biological processes (6,7). Therefore, clarifying the function of MPCs and targeting MPCs can control the occurrence, progression, and metastasis of BC (8,9). RNA sequencing is commonly used to conduct differential expression analysis, ascertain the phenotypic differences between different cells, and to identify particular differential genes.

Stomatin (*STOM*) is a member of a highly conserved family of intact membrane proteins. Its encoded protein is localized in the cell membrane, where it regulates ion channels and transporter proteins (10). It has been found that *STOM* is commonly expressed in the nucleus and cytoplasm and is associated with the development of various tumors, such as oral squamous cell carcinoma (11), lung cancer (12), soft tissue sarcoma (13), and pancreatic cancer (14). In addition, the *STOM* gene is a potential therapeutic target for metastatic BC (15,16). However, few studies have focused on the role of *STOM* in the microenvironment. Previous findings suggest that the *STOM* gene is significantly upregulated in the tumor-associated macrophages (TAMs) of colorectal cancer, which may have prognostic and predictive implications for the clinical management of colorectal cancer (17). Laminin subunit alpha 5 (*LAMA5*) encodes the vertebrate laminin α-chain. It is involved in a variety of biological processes, including

Highlight box

Key findings

- We successfully extracted a specific class of mesenchymal progenitor cells (MPCs) from the cancer tumor microenvironment. We found via biological experiments and gene sequencing that MPCs can influence breast tumor development through specific gene expression. The particular relationship between the tumor microenvironment and tumor tissues was further explored.

What is known and what is new?

- Currently, breast cancer (BC) is the most common malignant tumor in the world. Various studies have investigated the mechanisms of BC development, and recently, an increasing number of researchers have begun to focus on the role of the tumor immune microenvironment, which has been found to play a key role in the development and metastasis of BC.
- We extracted a class of MPCs from the tumor microenvironment, compared their biological properties with those of common MSCs, and sequenced them to identify the differentially expressed genes. Subsequently, the role of tumor-associated mesenchymal progenitor cells differential genes in BC development was examined.

What is the implication, and what should change now?

- In this study, we conducted a preliminary exploration of MPCs and their effect in the breast tumor microenvironment. We briefly characterized the association of differential genes on the proliferation of tumor cells, but additional in-depth studies on the mechanism of these differential genes need to be conducted. Examining the tumor microenvironment can provide new ideas for microenvironment-targeted cancer therapy.

Table 1 The clinical information of patients

Patient no.	Sample type	Location	Gender	Age (years)	Pathological type	SBR stage	Pathology subtype			
							ER	PR	HER2	KI67
1	Tumor/adjacent adipose tissues	Right	Female	47	Breast invasive ductal carcinoma	III	–	–	3+	45%
2	Tumor/adjacent adipose tissues	Right	Female	46	Breast invasive ductal carcinoma	II	75%	80%	1+	60%
3	Tumor/adjacent adipose tissues	Left	Female	68	Breast invasive ductal carcinoma	II	85%	90%	2+	25%
4	Tumor/adjacent adipose tissues	Left	Female	52	Breast invasive ductal carcinoma	II	80%	85%	2+	20%
5	Tumor/adjacent adipose tissues	Left	Female	50	Breast invasive ductal carcinoma	II	80%	80%	3+	40%
6	Tumor/adjacent adipose tissues	Left	Female	51	Breast invasive ductal carcinoma	II	–	–	0	40%
7	Tumor/adjacent adipose tissues	Right	Female	44	Breast invasive ductal carcinoma	III	–	–	3+	45%
8	Tumor/adjacent adipose tissues	Right	Female	67	Breast invasive ductal carcinoma	III	90%	90%	3+	85%
9	Tumor/adjacent adipose tissues	Left	Female	49	Breast invasive ductal carcinoma	III	–	–	2+	40%
10	Tumor/adjacent adipose tissues	Left	Female	62	Breast invasive ductal carcinoma	II	80%	–	2+	35%

SBR, Scarff-Bloom-Richardson; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

cell adhesion, differentiation, migration, signaling, axonal growth, and metastasis (18). *LAMA5* is also crucially implicated in the maintenance of the ECM, which is critical for tissue development, stem cell ecological niches, cancer progression, and genetic diseases (19). Collagen and calcium-binding EGF domains 1 (*CCBE1*) is thought to play a role in ECM remodeling and migration (20). In patients with BC, *CCBE1* is frequently downregulated and its absence is associated with reduced recurrence-free survival and overall survival (21). In contrast, high expression levels of *CCBE1* in colorectal cancer are associated with high tumor aggressiveness and poor prognosis (22).

Currently, the potential of *STOM*, *CCBE1*, and *LAMA5* in the diagnosis and pathogenesis of BC microenvironment remains unexamined. Therefore, using transcriptome analysis, we investigated the expression of these genes in BC MPCs and characterize their function in the TME. We present this article in accordance with the MDAR reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-387/rc).

Methods

Patient selection and description

This study was performed in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Chinese People's Liberation Army (PLA) General Hospital (No. S2016-023-01), and informed consent was taken from all individual participants. In the Breast Surgery Department of the PLA General Hospital, samples of cancerous tissues and adjacent tissues (>5 cm from the tumor) of were obtained from patients with invasive BC who had not received neoadjuvant therapy, with the average volume of the samples being 3 g (*Table 1*). The pathology results of all samples were confirmed by three specialized pathologists. All samples were stored in saline but not for more than 2 hours so as not to affect the cellular state. The cancer and paracancer samples from the same patient were paired for subsequent experiments.

Cell lines

Cell culture of the human triple-negative BC (TNBC) cell lines MDA-MB-231 and MCF-7 were obtained from the American Typical Culture Collection (ATCC). These cell lines have been passed down from the laboratory for about 20 generations or fewer. The MDA-MB-231 and MCF-7 cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) (Gibco, Thermo Fisher Scientific, Grand Island, USA), cell cultures were supplemented with 10% fetal bovine serum (FBS) (Gibco) and 1% penicillin/streptomycin (Solarbio, Beijing, China), and cells were incubated in a 37 ℃ incubator (with a 5% CO_2 atmosphere) for later use.

Isolation and culture of MSCs and MPCs

Fresh BC tissues (n=10) and corresponding normal breast tissues (n=10) were collected from patients with BC.

Table 2 Catalog numbers of antibodies used

Antibody	Reagent brand	Catalog No.	Lot No.
CD45-FITC	BioLegend	304006	B2936670
CD14-PE cy7	BD Biosciences	557742	70811821
CD73-APC	BioLegend	344006	B293700
CD34-PE cy7	eBioscience	25-0349-42	E11311-1633
CD105-APC	BioLegend	562408	6168991
CD90-FITC	BioLegend	328108	B304448
CD146-PE	BioLegend	361006	B287407
CD11b-BV605	BD Biosciences	562721	4318545
CD31-PE	eBioscience	120319-42	E12826104

MSCs were obtained from adipose glandular tissues of the normal breast, while MPCs were obtained from BC tissues. Specimens were cut and digested with a calibrated digestion solution consisting of 0.2% collagenase I (Gibco), MSC basic medium (Chemclin Biotech, Beijing, China), and 0.25% trypsin (Biological Industries, Kibbutz Beit-Haemek, Israel) mixed at a ratio of 1:0.4:0.6 at 37 ℃ for 6 h. Cells were then washed with saline solution and resuspended in human MSC special medium (Chemclin Biotech) after centrifugation at 400 × g for 10 min. The cells were seeded in six-well plates at a concentration of 3×10^6 and incubated at 37 ℃ in a 5% CO_2 atmosphere until they reached 80% confluence. Cells were then seeded in T75 culture flasks for expansion and used for subsequent experiments.

Measurement of cell surface markers

We used third-generation cells for surface marker identification. MSCs and MPCs were seeded in six-well plates (1×10^5 cells/well), and cells were collected when the cell fusion rate reached 80% (1×10^6 cells). After the cells were washed with phosphate-buffered saline (PBS; with a PH of 7.4), the cells were incubated with 0.5 µL of fluorescein-coupled antibody or 30 min at 4 ℃ under light-proof conditions. The fluorescently labeled antibodies were CD45-FITC, CD14-PE-Cy7, CD73-APC, CD34-PE Cy7, CD105-APC, CD90-FITC, CD146-PE, CD11b-BV605, and CD31-PE (*Table 2*). Following this, cells were washed using PBS, centrifuged, and resuspended in PBS and then analyzed under a flow cytometer (FACSCelesta, BD Biosciences, San Diego, CA, USA). We adjusted the data for compensation and analyzed the data using FlowJo software (BD Biosciences).

Cell differentiation assay

After MSCs and MPCs reached 100% confluence, the MSC completion medium was replaced with MSC adipogenic or osteogenic differentiation medium (ScienCell Research Laboratories) and cultured for 20 or 15 days. Adipogenic differentiation and osteogenic differentiation were determined via staining with Oil Red O and Alizarin Red S (Solarbio, China), respectively. Thereafter, observations were made using an optical microscope (Leica, Germany). We used ImageJ software (US National Institutes of Health) for quantitative analysis of cell differentiation.

Cell proliferation assay

MSCs and MPCs grown in the logarithmic phase were washed, digested, and centrifuged, and the cell concentration was adjusted to 1×10^6 cells/0.5 mL of PBS. Subsequently, 0.5 mL of cell suspension was added with an equal volume of eFluor670 Cell Proliferation Dye (Invitrogen, CA, USA). The mixture was placed at 37 ℃ and cultured in the dark for 10 minutes, after which 5 mL of precooled complete medium was added to terminate the labeling, and the cells were incubated on ice for 5 minutes. The cells were then washed three times with a complete medium, 1×10^5 cells were resuspended in 200 µL of PBS, and a 4% paraformaldehyde solution of equal volume was added to fix the cell morphology, which was labeled as "0 h". The remaining number of 1×10^5 cells was inoculated in a six-well plate. The cells were collected at 24, 48, and

Table 3 The forward and reverse sequences of primers used for qRT-PCR

Name	Primer sequence
H-GAPDH-F	GAAGGTGAAGGTCGGAGTC
H-GAPDH-R	GAAGATGGTGATGGGATTTC
H-CCBE1-F	CGACTAAATACCCGTGTCTGAAG
H-CCBE1-R	TCGGCACAAACGTCGTAATCT
H-STOM-F	GGGAGGGACGCATAGAAGGA
H-STOM-R	GTACATTGTTGGAAAGGGAGGC
H-LAMA5-F	CCTGGAGAACGGAGAGATCG
H-LAMA5-R	CAGCGGCGAGTAGGAGAAAT
H-PPARG-F	ACCAAAGTGCAATCAAAGTGGA
H-PPARG-R	ATGAGGGAGTTGGAAGGCTCT
H-TGF-β-F	CAATTCCTGGCGATACCTCAG
H-TGF-β-R	GCACAACTCCGGTGACATCAA
H-IL6-F	CCTGAACCTTCCAAAGATGGC
H-IL6-R	TTCACCAGGCAAGTCTCCTCA
H-IL8-F	ACTGAGAGTGATTGAGAGTGGAC
H-IL8-R	AACCCTCTGCACCCAGTTTTC
H-CXCL12-F	ATTCTCAACACTCCAAACTGTGC
H-CXCL12-R	ACTTTAGCTTCGGGTCAATGC
H-IGF-F	GCTCTTCAGTTCGTGTGTGGA
H-IGF-R	GCCTCCTTAGATCACAGCTCC

qRT-PCR, quantitative real-time polymerase chain reaction.

72 h after labeling, and cell fluorescence was measured using a flow cytometer (FACSCalibur, BD Biosciences). Cell proliferation indices were analyzed using ModFit LT 5 (Verity Software House, Topsham, ME, USA).

Cell Counting Kit 8 (CCK8) cell proliferation experiment

MSCs and MPCs were washed three times and then digested and centrifuged, and the cell suspension was prepared. PBS was added to the outer circle of the 96-well plate to prevent the evaporation of the liquid in the plate, with 3,000 cells/ 100 µL per hole. MSCs and MPCs were seeded into 96-well plates and processed at 0, 48, and 72 h. CCK8 (10 µL) reagent (ScienCell, Carlsbad, CA, USA) was added to each well, and the cell was cultured again for 2 h; the absorbance was measured at 450 nm with a microplate reader, the experimental results were recorded, and a growth curve was drawn.

Scratch assay

Three horizontally spaced horizontal lines were drawn on the back of a six-well plate at equal intervals. Logarithmically grown MSCs and MPCs were collected, washed in PBS, digested, and centrifuged, and cell suspensions were prepared. After counting, the cells were seeded in a six-well plate. The next day, when the cells had fully grown, the cells were scratched with a 200 µL pipette tip in a six-well plate perpendicular to the horizontal line on the back, the original medium was discarded, PBS was applied twice to wash off the cells, and serum-free medium was added. At 0, 6, and 12 h, the cells were positioned according to the horizontal line on the back of the six-well plate and photographed to record the cell invasion.

Transcriptome sequencing of MSCs and MPCs

We selected samples from three patients to extract three sets of paired MSCs and MPCs; specifically, 1×10^6 of cells from each of the MSC and MPC samples was collected, digested, washed, and frozen in liquid nitrogen. Transcriptome analysis was performed by Annoroad Gene Technology. RNA was extracted and tested for RNA quality; then, messenger RNA (mRNA) was enriched with oligo (dT) and used as a template to synthesize complementary DNA (cDNA). Purification and amplification were applied to duplex DNA, and then cDNA fragments were selected for sequencing with a HiSeq Sequencing System (Illumina, San Diego, CA, USA).

Quantitative real-time polymerase chain reaction (qRT-PCR)

A reviewing the literature for the relevant primers, we designed and synthesized primers We used PrimerBank (https://pga.mgh.harvard.edu/primerbank) to look up the primers and evaluate their quality. Cells were removed from the incubator and washed three times with PBS to extract RNA and test for concentration. RNA was reverse transcribed into cDNA using a TransScript cDNA Synthesis Kit (Transgen, Beijing, China). The cDNA and PerfectStart Green qPCR SuperMix Kit (Transgenics) were then added to a Fluorescent Quantitative PCR Amplification Reaction System (Applied Biosystems, Thermo Fisher Scientific). All primers were obtained from Sangon Biotech, and the primer sequences are listed in *Table 3*. *GAPDH* was used as an internal control. Differential gene cycle threshold (Ct) values were calculated via the 2-ΔCt method.

Plasmid transfection

STOM (NM_004099), *CCBE1* (NM_133459), and *LAMA5* (NM_005560) overexpression plasmids and control plasmids (NewHelix Biotech, Ltd., Shanghai, China) were prepared to transfect MPCs and MSCs using a the Lipofectamine stem cell transfection reagent (Invitrogen, Thermo Fisher Scientific). Transfection was performed by inoculating 1×10^5 cells per well in 24-well plates. When the cells reached 90% confluence, the transfection mixture was added to the cells, which were then incubated at 37 ℃ for 1–2 days. Following this, the transfected cells were collected for subsequent experiments.

Coculture of BC cells

After culture, MPCs cells were transfected with the target plasmid for 24 h, the transfection efficiency was detected via qRT-PCR, and the cell supernatant was collected and centrifuged at 4 ℃. The conditioned medium (CM) was then obtained by filtrating the cell supernatant using a 0.22-μm filter, and 3,000 cells per well of BC MDA-MB-231 cells were inoculated in a 96-well plate. After cell attachment, the CM was replaced with fresh CM every 24 h. The proliferation of CCK8 cells was measured at 0, 24, 48, and 72 h.

Statistical analysis

Statistical analysis of data was performed using GraphPad Prism version 9.0 analysis software (GraphPad Software, Inc., San Diego, CA, USA). We used the *t* test to compare two different sample groups, and statistical significance was set at $P<0.05$. For transcriptome data, we screened for differential genes using |log2 fold change| >1 and $P<0.05$ and selected appropriate genes with reference to the literature.

Results

Morphology and osteogenic/adipogenic differentiation

We obtained BC specimens from ten patients and normal tissues specimens at a distance >5 cm from the tumor. MPCs and MSCs isolated from BC tissues and normal breast tissues were both adherent cell with a long spindle-shaped, and some cells were growing in a whirling pattern. There was no significant difference in morphology between MSCs and MPCs when observed microscopically (*Figure 1A*). Stem cells have the potential to differentiate into multiple cell lineages, such as osteogenic, adipogenic, and chondrogenic types. This property is considered to be an important basis for the identification of stem cells, and to confirm the differentiation potential of our extracted cells, we subjected MSCs and MPCs to differentiation culture. After induction in osteogenic and adipogenic differentiation medium, MSCs and MPCs were able to differentiate successfully. It was found that MPCs were more capable of osteogenic differentiation, while MSCs were more capable of adipogenic differentiation (*Figure 1B*). We used ImageJ software to quantify the differentiation ability, which corroborated our findings (*Figure 1B*).

Surface markers of MPCs and MSCs

Stem cells can express a fraction of nonspecific markers, and the Mesenchymal and tissues Stem Cell Committee of the International Society for Cellular Therapy recommends the phenotypic identification of MSCs expressing the CD105, CD73, and CD90 markers and not those expressing CD45, CD34, CD14, CD11b, CD79a, or CD19. To confirm the phenotype, MSCs and MPCs from different patient samples were selected. After incubation, MSCs and MPCs were found to have a phenotype of CD105+, CD73+, CD90+, CD45−, CD14−, CD31−, CD11b−, and CD34− (*Figure 1C,1D*). By flowcytometric sorting (FACS), we found that both MPCs and MSCs were consistent with stem cell characteristics.

Comparison of the proliferation ability of MSCs and MPCs

To investigate the difference in proliferation ability of MSCs and MPCs, we used CCK8 assay and eFluor670 cell proliferation assay, and the results of the eFluor670 assay showed that MSCs had stronger proliferation ability than did the MPCs (*Figure 2A,2B*). Similarly, the results of the CCK8 cell proliferation assay showed that MSCs had a stronger proliferation ability than did the MPCs at 24, 48, and 72 h (*Figure 2C*).

Migration ability of MSCs and MPCs

To investigate the difference in migration ability between

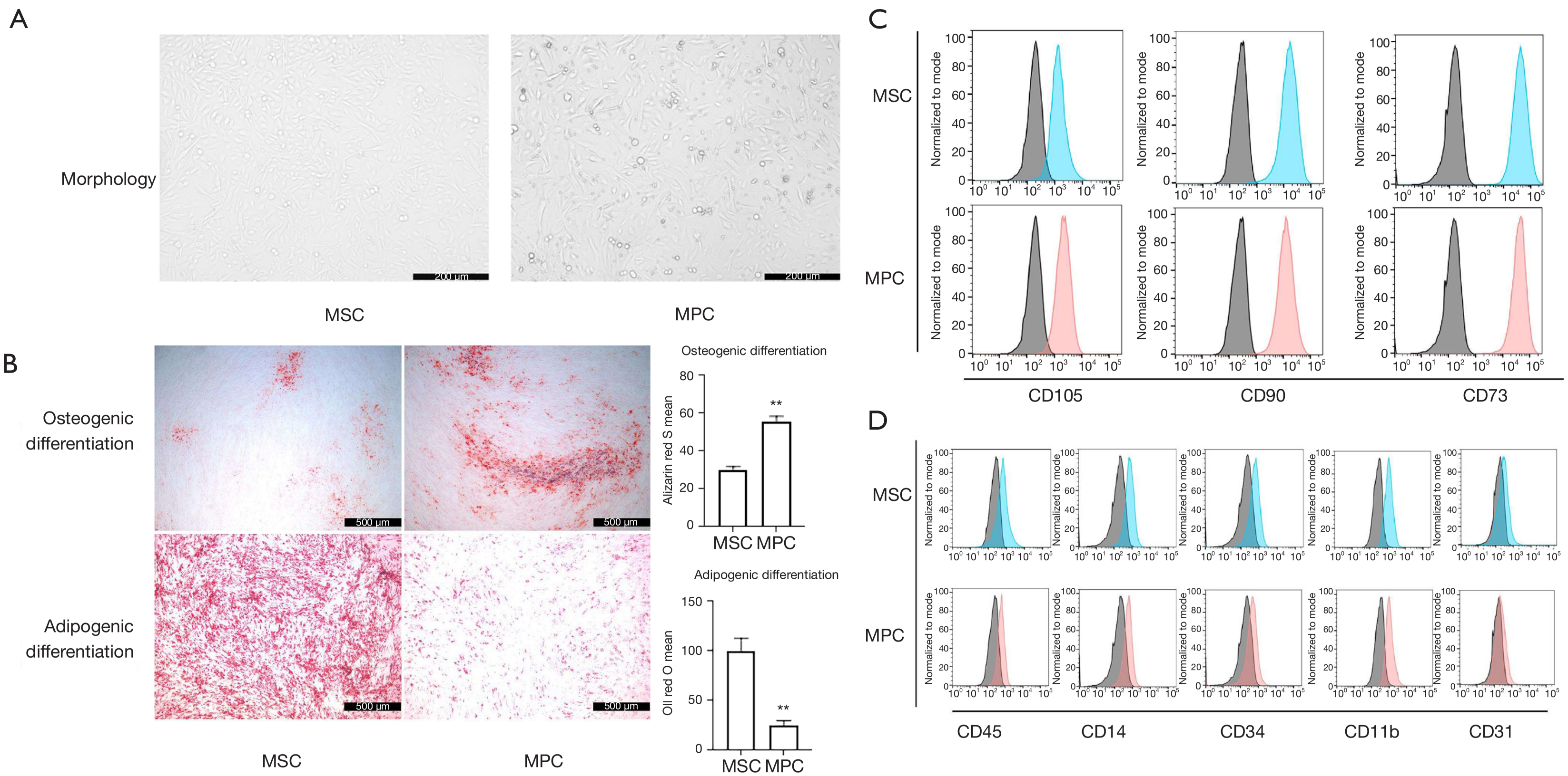

Figure 1 Comparison of MPC and MSC morphology, surface markers, and their differentiation ability. (A) Morphological characteristics of MSCs and MPCs under microscopy (10×; scale bar: 200 µm). (B) Alizarin Red staining for osteogenic differentiation and Oil Red O staining or adipogenic differentiation (4×; scale bar: 500 µm; **P<0.01). (C) Flow cytometry showing the expression of positive surface markers of MPCs and MSCs (n=3): CD90, CD105, and CD73. (D) Flow cytometry showing the expression of negative surface markers for MPCs and MSCs (n=3): CD45, CD14, CD34, CD11b, and CD31. MSC, mesenchymal stem cell; MPC, mesenchymal progenitor cell.

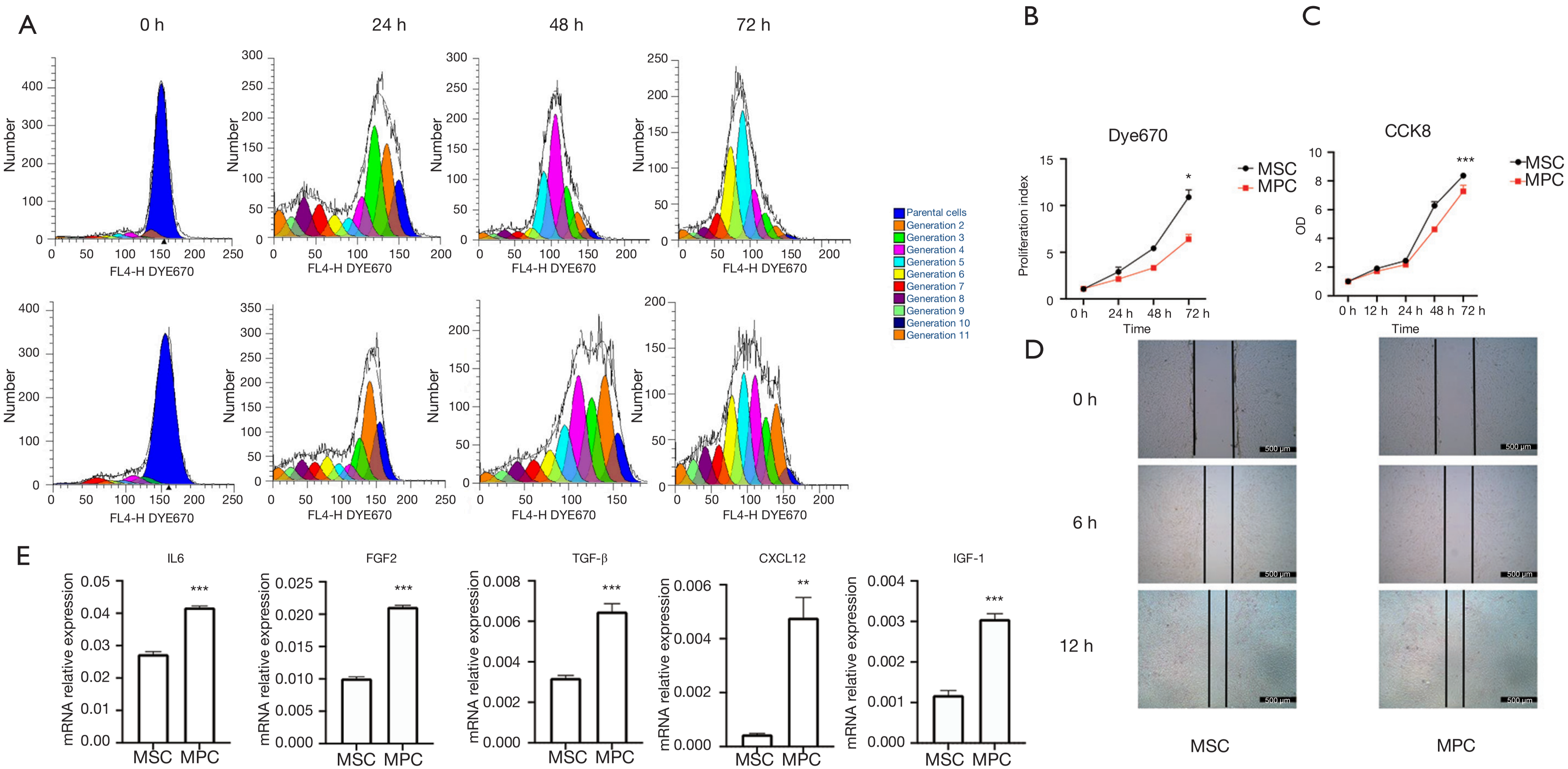

Figure 2 Comparison of cell proliferation, migration, and secretion abilities of MSCs and MPCs. (A) The cell proliferation was measured via eFluor670 dye at 0, 24, 48, and 72 hours for MSCs and MPCs. (B) MSC and MPC proliferation indices of eFluor670 dye (n=5; *P<0.05, MSC *vs.* MPC). (C) MSC and MPC proliferation indices of CCK8 assay at 0, 24, 48, and 72 hours (n=5; ***P<0.001, MSC *vs.* MPC). (D) Cell scratch assay to detect the migration ability of MPCs and MSCs (n=5). (E) Detection of cellular inflammatory factors according to qRT-PCR (n=5; **P<0.01; ***P<0.001). MSC, mesenchymal stem cell; MPC, mesenchymal progenitor cell; IL-6, interleukin 6; CXCL12, C-X-C motif chemokine ligand 12; FGF2, fibroblast growth factor 2; TGF-β, transforming growth factor β; IGF-1, insulin-like growth factor 1; CCK8, Cell Counting Kit 8; qRT-PCR, quantitative real-time polymerase chain reaction.

MSCs and MPCs, we implemented a scratch assay The experimental results showed that there was no significant difference in the migratory ability between MPCs and MSCs (*Figure 2D*).

Comparison of RNA for secreted factors in MSCs and MPCs

We verified the RNA of different secretory factors of MSCs and MPCs using qRT-PCR. MPCs were found to secrete a variety of inflammatory factors including interleukin 6 (*IL-6*), C-X-C motif chemokine ligand 12 (*CXCL12*), fibroblast growth factor 2 (*FGF2*), transforming growth factor β (*TGF*-β), insulin-like growth factor 1 (IGF-1), and other inflammatory factors (*Figure 2E*).

Comparison of the transcriptome sequencing of MSCs and MPCs

To determine the differential gene expression between MSCs and MPCs, we clarified the transcriptional changes in the genes of MSCs and MPCs in three patients with BC using transcriptome sequencing. We used transcriptome sequencing for differential expression analysis of the three data sets, and the obtained genes were quantified with an adjusted P value of <0.05 and log2 fold change (FC) >1 used as the differential gene screening threshold (*Figure 3A*). A total of 156 differential genes were identified between MPCs and MSCs, including 89 upregulated genes and 67 downregulated genes (*Figure 3B*). *CCBE1*, *LAMA5*, and *STOM* were significantly upregulated, while matrix metallopeptidase 13 (*MMP13*), *IL32*, and C-C motif chemokine ligand 11 (*CCL11*) were significantly downregulated in MPCs (*Figure 3C*). Gene ontology (GO) analysis showed that for biological process (BP), the differential genes of MPCs and MSCs were mainly enriched in cellular process, biological regulation, and regulation of BP; in molecular function (MF), the differences were mainly in binding and catalytic activity; in cell composition (CC), the differences were mainly in the cell, organelle, and membrane (*Figure 3D*). The Kyoto Encyclopedia of Genes and Genomes (KEGG) database showed that differential genes were mainly enriched in ECM receptor interactions, PI3K-AKT pathway, adhesive patch-related pathway, cytokine-cytokine receptor interactions, and Hippo pathway (*Figure 3E*).

qRT-PCR analysis of the transcriptome pairs of upregulated genes

To validate the transcriptome sequencing of genes, we used qRT-PCR to detect the expression of highly expressed genes including *CCBE1*, *STOM*, *LAMA5*, and peroxisome proliferator-activated receptor gamma (*PPARG*). At the mRNA level, these genes were upregulated in MPCs (n=3) but not in MSCs (*Figure 3F*). Because of the heterogeneity across patients, we paired the patient samples (in *Figure 3F*); for instance, MPC1 was paired with MSC1 and MPC2 was paired with MSC2.

Upregulation of inflammatory factor RNA expression after gene transfection

To confirm the effect of *STOM*, *LAMA5*, and *CCBE1*on MPCs, we transfected the *STOM*-, *LAMA5*-, and *CCBE1*-overexpression plasmid and confirmed the gene overexpression via qRT-PCR (*Figure 4A*,*4B*). The expression of *CXCL12* and *FGF2* (*Figure 4C*) was found to be upregulated in MPCs overexpressing *STOM* (*Figure 4D*), *IGF* was upregulated in MPCs overexpressing *CCBE1*, and *FGF1* (Figure4E) was upregulated in MPCs overexpressing *LAMA5*.

Effect of the overexpression of target genes on the proliferation of MPCs

To further confirm the effect of the target genes on MPCs, we examined the proliferation of MPCs after transfection with CCK8. The results showed that the *STOM* gene had an effect on cell proliferation, with overexpression of *STOM* resulting in a retarded proliferation of MPCs (*Figure 4F*); meanwhile, *CCBE1* (*Figure 4G*) and *LAMA5* (*Figure 4H*) had no obvious pro-proliferation effect on MPCs.

Effect of MPCs overexpressing the target genes on BC proliferation

We collected supernatants overexpressing the target genes and prepared them as a selective medium for the culture of BC MDA-MB-231 cells. The CCK8 results showed that there was no significant difference between the experimental group and the control group for *LAMA5* (*Figure 4I*) or *CCBE1* (*Figure 4J*), but MPCs overexpressing *STOM* could promote the proliferation of BC (*Figure 4K*). We subsequently validated the effect of *STOM* on MCF-

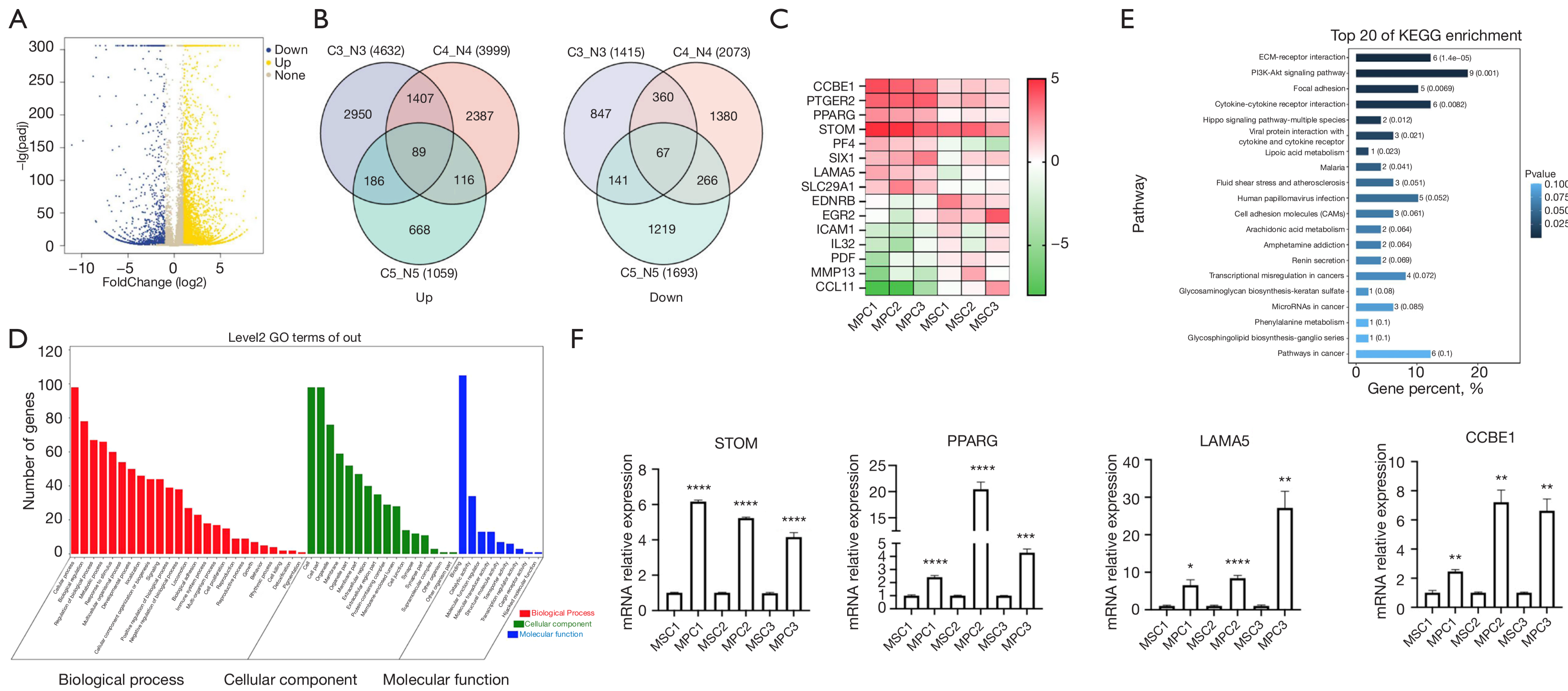

Figure 3 Transcriptome analysis of MSCs and MPCs. qRT-PCR analysis of highly expressed genes in MPCs. (A) Volcano plot analysis of differential genes. Yellow dots indicate the upregulated genes, while blue dots indicate the downregulated genes (|log2FC|>1). (B) Transcriptomic Venn diagram analysis of three samples with common up- or downregulated genes. (C) Heat map of significantly differentially up and downregulated genes. (D) GO analysis of differential genes according to three regulatory functions: BP, MF, CC. (E) KEGG enrichment analysis of differential genes. (F) Transcriptome sequencing revealed increased mRNA expression, and the expression content of *STOM*, *CCBE1*, *LAMA5*, and *PPARG* in MPC was detected using qRT-PCR (n=3; *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001; MSC *vs.* MPC). C, MPC group; N, MSC group; GO, gene ontology; BP, biological process; MF, molecular function; CC, cellular component; KEGG, Kyoto Encyclopedia of Genes and Genomes; MSC, mesenchymal stem cell; MPC, mesenchymal progenitor cell; FC, fold change. STOM, stomatin; LAMA5, laminin subunit alpha 5; CCBE1, collagen and calcium-binding EGF domains 1; PPARG, peroxisome proliferator-activated receptor gamma.

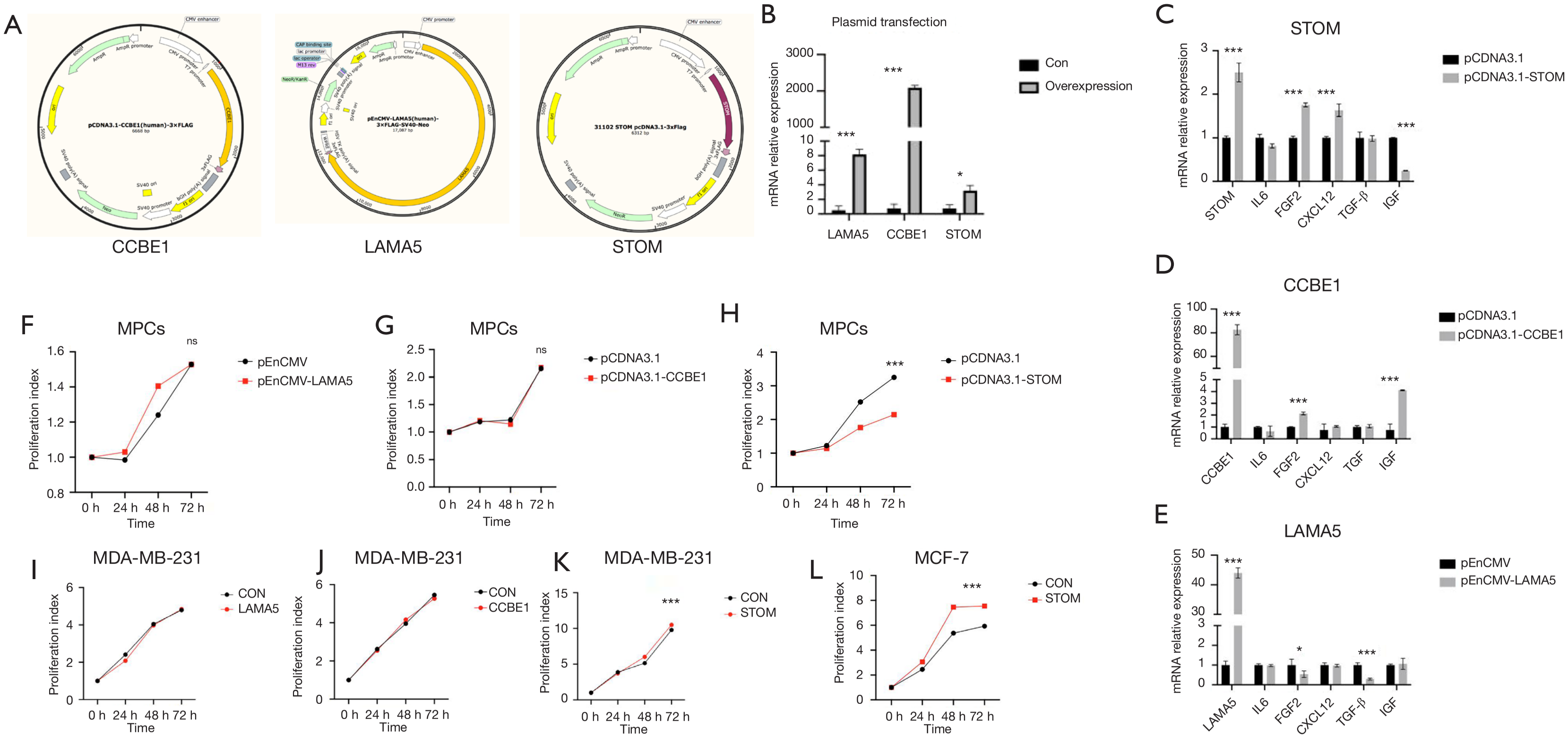

Figure 4 STOM-overexpressing MPCs secrete inflammatory factors while promoting breast cancer proliferation. (A) Plasmid constructs mapping of *LAMA5*, *CCBE1*, and *STOM*. (B) qRT-PCR mRNA expression of target genes in MPCs transfected with overexpression plasmids (n=3; *P<0.05; ***P<0.001 target group compared with the control group). (C) qRT-PCR showed upregulation of CXCL12 and FGF2 expression after upregulation of the *STOM* gene (n=5; ***P<0.001 *vs.* control). (D) qRT-PCR showed upregulation of IGF expression after upregulation of the *CCBE1* gene (n=5; ***P<0.001 *vs.* control). (E) qRT-PCR showed upregulation of FGF1 expression after upregulation of the *LAMA5* gene (n=5; ***P<0.001 *vs.* control). (F-H) CCK8 assay indicated proliferation of MPCs overexpressing *LAMA5*, *CCBE1*, and *STOM* (n=5; ***P<0.001 *vs.* control). (I-K) CCK8 assay indicated proliferation of breast cancer MDA-MB-231 cells promoted by MPCs overexpressing *STOM* after coculture, and the overexpression of *CCBE1* and *LAMA5* did not have this pro-proliferative effect (n=5; ***P<0.001 *vs.* control). (L) CCK8 assay indicated proliferation of breast cancer MCF-7 cells promoted by MPCs overexpressing *STOM* after coculture (n=3; ***P<0.001 *vs.* control). MSC, mesenchymal stem cell; MPC, mesenchymal progenitor cell; qRT-PCR, quantitative real-time polymerase chain reaction; STOM, stomatin; CCBE1, collagen and calcium binding EGF domains 1; LAMA5, laminin subunit alpha 5; CXCL12, C-X-C motif chemokine ligand 12; FGF2, fibroblast growth factor 2; FGF1, fibroblast growth factor 1; IGF, insulin-like growth factor.

7 BC cell line and found that *STOM* had the same pro-proliferative effect in noninvasive BC MCF-7 cells (*Figure 4L*).

Discussion

MPCs are critically involved in the regulation of various types of cells in the tumor and TME (23). New technologies such as single-cell sequencing and spatial transcriptomics have revealed the heterogeneity of MPCs (24,25), and the protumor proliferation and tumor drug resistance properties of MPCs have recently been identified (26-28). However, the details of the mechanisms which primarily influence MPCs to promote breast tumor development still need to be clarified. The discovery of novel targets could inform the development of targeted therapy for BC (29). This study aimed to identify several properties of MPCs and MSCs but, unfortunately, did not explore their effects on BC, and thus the relationship between MPCs and BC should be examined in future research.

In this study, we isolated and extracted MPCs from BC tumors and adjacent healthy tissues; we discovered and both normal breast tissues MSCs and tumor-derived MPCs had similar morphology, while both MSCs and MPCs expressed the same surface markers, including CD105, CD73, CD73, CD54, and CD90. In addition, MSCs and MPCs both demonstrated osteogenic and adipogenic differentiation abilities. However, tumor-derived MPCs exhibited a slower growth rate than did MSCs; consequently, we attempted to explore the biological functional properties of MPCs via transcriptome sequencing. The transcriptome results indicated that MPCs derived from tumor tissues were enriched with 89 upregulated genes and 67 downregulated genes compared to MSCs. The genes highly expressed in BC-derived MPCs included *CCBE1*, *LAMA5*, and *STOM*, which were found to be involved in cell adhesion, ECM receptor interaction, adherent patch-related pathway, and cytokine-cytokine receptor interaction pathways according GO and KEGG pathway analysis. Thus, MPCs may play a key role in the TME and serve as a link between communicating tumor cells.

STOM is a member of the mammalian stomatin-domain protein family, which is named after hereditary human hemolytic anemia (30). The increase in *STOM* expression has been observed in many cancers. In our study, MPCs overexpressing *STOM* promoted tumor proliferation to a degree. Moreover, we found that these MPCs could release inflammatory factors, such as *CXCL12* and *FGF2*, at the genetic level. *CXCL12* is also referred to as stromal cell-derived factor 1 (*SDF1*) and plays a key role in tumor development via the CXC chemokine receptor (*CXCR4*). *CXCL12* is significantly associated with invasive metastasis in BC (31), and studies have shown that high *CXCL12* expression is a poor prognostic indicator for those with BC (32,33). *FGF2*, as a member of the FGF family, can promote tumor angiogenesis by acting on FGF receptor (34) and can promote the proliferation and migration of a variety of tumors (35). Moreover, research suggests that *FGF2* can promote BC proliferation through ERK signaling (36), yet the mechanism related to the downstream pathway triggered by *STOM* remains to be explored. We found that *STOM* overexpression in MPCs slowed the growth of MPCs; in contrast, the overexpression of *STOM* in MPCs cocultured with BC cell lines resulted in accelerated BC proliferation. We speculate that this phenomenon may be caused by the secretion of pro-tumor proliferation cytokines by MPCs. Additional studies are needed to clarify the specific relationship between MPCs and BC.

CCBE1 and *LAMA5* were not found to have a significant role in MPCs. Although they were associated with the release of inflammatory factors including *IGF* and *FGF1*, the tumor proliferation effect *in vitro* was not significantly affected. Nonetheless, *CCBE1* plays an important role in lymphangiogenesis and angiogenesis (37), while both the adhesion and angiogenesis effects of *LAMA5* may be closely related to tumor metastasis (38,39), which still needs to be investigated further.

Clarifying the genomics of MPCs may help us to better understand the heterogeneity of MPCs and their role in the TME and aid in identifying therapeutic targets. In turn, this can contribute to more efficiently targeting the TME to exert an antitumor effect.

Conclusions

Our study identified certain similarities between BC-derived MPCs and normal breast tissue-derived MSCs, while differences were also observed, chiefly related to the proliferation rate and differentiation ability. Based on transcriptome analysis, we found that the *STOM* genes can regulate the proliferation of MPCs and BC, but the exact mechanisms underlying this process remain unclear. We also examined the differences between MPCs and MSCs in the TME and determined the distinct characteristics of MPCs, which may provide a reference for subsequent targeted therapies in the BC TME. However, more studies are needed to investigate the related mechanisms and isolate more specific targets within this context.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Chinese People's Liberation Army (PLA) General Hospital (No. S2016-023-01), and informed consent was taken from all individual participants.

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Original Article

Defining competencies in robotic thyroidectomy: development of a model assessing an expert operator's intraoperative performance skills and cognitive strategies

Hyejin Kim[1#], Hyeong Won Yu[2#^], Jong-hyuk Ahn[3], Tae Seon Lee[4,5], Kyu Eun Lee[6^]

[1]Department of Public Health, Graduate School, Yonsei University, Seoul, Republic of Korea; [2]Department of Surgery, Seoul National University Bundang Hospital, Seongnam, Republic of Korea; [3]Department of Surgery, Seoul National University Hospital, Seoul, Korea; [4]Department of Neurosurgery, Severance Hospital & Yonsei University College of Medicine, Seoul, Republic of Korea; [5]Center for Medical Education, Graduate School of Medicine, Nagoya University, Nagoya, Japan; [6]Department of Surgery, Seoul National University Hospital and College of Medicine, Seoul, Republic of Korea

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[#]These authors contributed equally to this work.

Correspondence to: Kyu Eun Lee, MD, PhD. Department of Surgery, Seoul National University Hospital and College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Republic of Korea. Email: kyueunlee@snu.ac.kr; Tae Seon Lee, PhD. Department of Neurosurgery, Severance Hospital & Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea; Center for Medical Education, Graduate School of Medicine, Nagoya University, Nagoya, Japan. Email: tseonlee@yonsei.ac.kr.

Background: The changing medical education environment emphasizes the need for time efficiency, increasing the demand for competency-based medical education to improve trainees' learning strategies. This study was performed to determine the competencies required for successful performance of robotic thyroidectomy (RT) and to determine the consensus of experts for performance of RT.

Methods: Data were collected through 12 semi-structured interviews with RT experts and 11 field observations. Cognitive task analysis was performed to determine the competencies required for experts to perform RT. A modified Delphi methodology was used to determine how 20 experts rated the importance of each item of RT performance on a Likert 7-point scale. The criteria for the Delphi consensus were set at a Cronbach's $\alpha \geq 0.80$ with two survey rounds.

Results: After 11 field observations and 12 semi-structured interviews, 89 items were identified within six modules. These items were grouped into sub-modules according to their theme. The modified Delphi survey, involving 21 experts, reached the consensus standard during the second round (Cronbach's α=0.954), enabling the identification of the 64 most important items within six modules related to RT performance: midline incision to isthmectomy (MID module; n=8), lateral dissection (LAT module; n=7), preservation of inferior parathyroid glands (INF module; n=16), preservation of recurrent laryngeal nerve and dissection of the ligament of Berry (BER module; n=21), dissection of the thyroid upper pole (SUP module; n=10), and specimen removal and closure (END module; n=2).

Conclusions: This mixed-method study combining qualitative and quantitative methodology identified modules of core competencies required to perform RT. These modules can be used as a standard and objective guide to train surgeons to perform RT and evaluate outcomes.

Keywords: Thyroidectomy; clinical competence; robotics; surgical procedures; reference standards

^ ORCID: Hyeong Won Yu, 0000-0001-7338-5157; Kyu Eun Lee, 0000-0002-2354-3599.

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Introduction

Recently, the educational paradigm in surgery has changed from the traditional apprenticeship model to competency-based medical education, which emphasizes the acquisition of standard technical and cognitive proficiency for performing surgery safely and effectively (1-3). To incorporate intraoperative decision-making ability into the standard surgical training curriculum, many studies have attempted to identify cognitive components associated with the success of various types of surgery, such as conventional open thyroidectomy, management of trauma patients, laparoscopic transabdominal adrenalectomy, and flexible pharyngo-laryngoscopy (3-6). Research on the techniques required for open thyroidectomy was utilized to develop high-definition video teaching modules and interactive web-based educational platforms (7,8). Although modules and platforms have been developed for open and laparoscopic surgery, surgeons are still being trained to perform robotic surgery through apprenticeship, without a standardized educational curriculum (9).

Robotic thyroidectomy (RT) is remote-access surgery and results in higher cosmetic satisfaction than conventional surgical methods (10). These advantages have increased demands for RT worldwide, increasing the number of training programs for RT. Previously, Madani and colleagues defined a model of competencies for successful open thyroidectomy performed by expert endocrine surgeons to use it as references for trainees in the context of competency-based medical education (3). RT, however, requires advanced surgical skills and utilizes different surgical instruments and approaches including behavioral and cognitive strategies compared with open thyroidectomy (11). Thus, this study was designed to organize key tasks and decision-making procedures for RT by modules and to evaluate their importance in determining the competencies of expert performance and cognitive strategies required for RT.

Highlight box

Key findings

- This study organized the key tasks and decision-making procedures for robotic thyroidectomy (RT) into modules and assessed their significance in delineating the competencies for expert performance and the cognitive strategies essential for RT.

What is known and what is new?

- While RT demands advanced surgical skills and employs various surgical instruments and approaches, including behavioral and cognitive strategies, there is a lack of research defining the competencies necessary for successful RT performance when compared to conventional thyroidectomy.
- We identified 89 items within six modules that define the competencies for RT.

What is the implication, and what should change now?

- These modules can be used as a standard and objective guide to train surgeons to perform RT and evaluate outcomes.

Methods

Setting and participants

This study recruited surgeons who perform RT with the bilateral axillo-breast approach (BABA). We defined subject matter experts (SMEs) as individuals who had conducted 40 or more BABA RT operations (11-14). Moreover, we included individuals with a minimum of 5 years of clinical experience to guarantee proficiency in BABA-RT. We used convenience sampling to enlist 12 SMEs for the qualitative cognitive task analysis (CTA) via email. Additionally, we recruited 21 surgeons through email for the modified Delphi survey. The purpose and method of the study were explained to the recruited surgeons, and they provided informed consent before participating in the study via telephone or email. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (No. H-1912-116-1090).

BABA RT

BABA RT is a surgical method in which the thyroid gland is dissected using a da Vinci robot inserted through small wounds on both sides of the axilla and breast (15). BABA RT differs from conventional open thyroidectomy, in that it

Table 1 Sample questions used for semi-structured interviews

Structure	Questions
General questions	Describe the tasks required to perform BABA RT in key steps
Questions by module	What is the purpose of this task?
	What is the sequence of actions necessary to complete this task?
	What conditions must be present before starting this task?
	What decisions have to be made during this task, including the various options and criteria to choose among options?
	What errors can occur and what tips/tricks can be used to avoid such errors during this task?
	What performance standards or quality indicators are used to ensure successful completion of this task?

BABA RT, bilateral axillo-breast approach robotic thyroidectomy.

starts with the lower pole of the thyroid gland and continues to the upper pole. BABA RT allows thyroid lobectomy, total thyroidectomy, and total thyroidectomy with modified lateral neck dissection (16,17). This study, however, was restricted to surgery involving a midline incision to remove the dissected specimen and midline closure. The RT procedures were divided into six modules, as described (15).

Qualitative study: CTA

This study was of mixed-method design, combining qualitative and quantitative methods. To collect qualitative data, one of the researchers observed the performance of RT by study participants, focusing mainly on communication with colleagues, emergency situations and coping methods, and changes in decisions during surgery. Each RT was video recorded and used as an adjunct in the subsequent semi-structured interview. The interviewee asked prescribed questions about the intent, cautions, and decision-making during each step of RT (*Table 1*) (3). The interviewer was careful not to interrupt the interviewee and to not ask close-ended questions, facilitating open and unbiased answers. Each interview was recorded, and each interview took roughly 1 hour. The recorded interviews were transcribed verbatim.

The qualitative data were analyzed by CTA, a robust method that systematically captures automated cognitive tasks performed by experts. CTA was based on naturalistic decision-making studies and has been used extensively to explore cognitive processes in medical settings (18). In this study, each surgical procedure performed by the surgeon was recorded and reviewed several times, and the cognitive factors of the task were analyzed by two task analysis experts (Ph.D. in cognitive psychology and medical education and two clinical health psychologists). To ensure the saturation of data, surgery textbooks that described the steps for open thyroidectomy and RT were reviewed to add any missing information (15,19-21).

The contents were subsequently reviewed and modified by two expert surgeons to develop a structured framework, completing it as modules in structured stages for the entire operation. This method defined the explicit and implicit knowledge and skills required, without bias, for surgical judgment and decision making.

Quantitative study: modified Delphi survey

The modified Delphi method, which is effective in drawing consensus from experts through iterative survey rounds and has been recommended for solving problems in clinical practice that lack scientific evidence (22), was utilized for quantitative analysis. Survey items were constructed from the data obtained from CTA. During the first round of the Delphi survey, participants were asked to anonymously rate the importance of each item, ranging from 1 (not at all important) to 7 (very important). During the second round, 1 week later, participants were asked to again rate the importance of each item. Rounds one and two included 21 and 20 RT experts, respectively, of various backgrounds and experience. The design of this study is shown in *Figure 1*.

Statistical analysis

To quantitatively verify the results obtained from the qualitative study, the responses to each survey round were reported as the means and variances. A consensus among

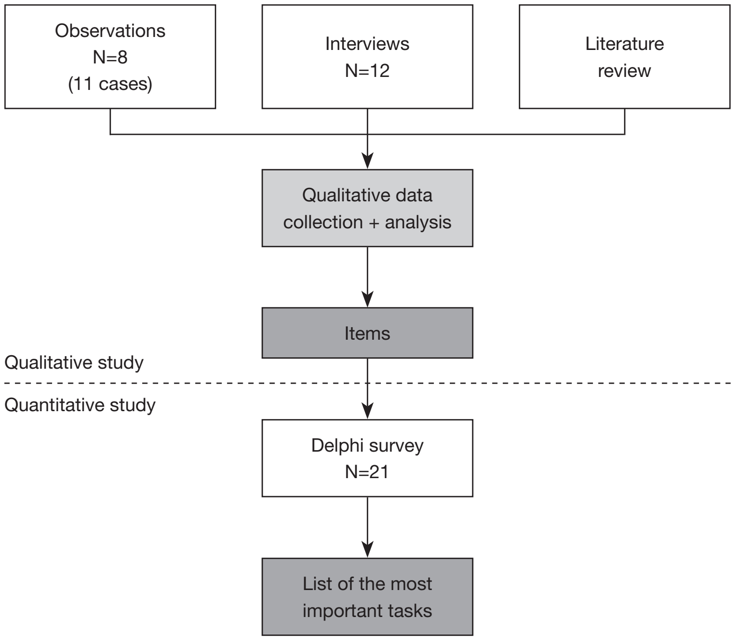

Figure 1 Flowchart of the study design.

experts was defined as a Cronbach's $\alpha \geq 0.80$ for the reliability of the participants' responses to each item. Items evaluated by over 80% of respondents as ≥5 on the Likert scale were selected as the key component in implementing RT. The results were reported as the mean (standard deviation), median (range), and N (%). All statistical analyses were performed using Microsoft Excel® software. This mixed methodology study design has been used in various studies that define key operative competencies (2,3,6).

Results

Qualitative study: CTA

CTA analysis of the data collected by the interviews and the review of video recordings of RT identified 89 meaningful items, which were divided into six modules based on the order of the tasks: midline incision to isthmectomy (MID, n=18), lateral dissection (LAT, n=16), preservation of inferior parathyroid glands (INF, n=18), preservation of recurrent laryngeal nerve (RLN) and dissection of the ligament of Berry (BER, n=22), dissection of the thyroid upper pole (SUP, n=12), and specimen removal and closure (END, n=3). The items within each module were categorized based on structural similarities and arranged as submodules (*Table 2*; for the full list, see Table S1).

Quantitative study: modified Delphi survey

In the quantitative study, the participants rated the 89 identified Delphi items by their importance. Twenty-seven RT experts, including participants in the first phase, were asked to participate in the Delphi survey, with 21 SMEs participating in the first round and 20 in the second round. The concordance of the responses among experts met the criteria for consensus set in the study, with the Cronbach's α values of 0.91 in round 1 and 0.954 in round 2.

The most important of the 89 items was determined by selecting the items (n=64) that received scores ≥5 from >80% of respondents, with these items regarded as the critical behavioral and cognitive competencies for RT. *Figure 2* shows the results of this study.

Table 3 shows the 10 most important items required for safe and efficient RT, as determined by experts. The five top-ranked items of each of the six modules are graphically shown in *Figure 3*. The order of these modules is not necessarily linear and can be altered at the discretion of the surgeon (for the full list, see Table S2).

Additional comments regarding the MID module included: (I) the need for preoperative evaluation of the possibility of isthmectomy, as cancer on the isthmus itself may alter the isthmectomy position; and (II) that care should be taken not to injure the trachea. An additional

Table 2 Items synthesized through the cognitive task analysis

MID module (n=18)	LAT module (n=16)	INF module (n=18)	BER module (n=22)	SUP module (n=12)	END module (n=3)
Identification of the midline	*Dissection of the surgical plane between the thyroid and the strap muscle*	*Identification of the RLN*	*Dissection between the medial thyroid and trachea*	*Dissection in the upward direction*	*Specimen out*
• Find the correct midline location on the strap muscles	• Separate the strap muscles and thyroid gland from cranial to caudal	• Identify the RLN between the central lymph nodes	• Separate the trachea and cricothyroid muscle from the thyroid gland	• To prevent EBSLN injury, attach as much to the thyroid as possible and simultaneously ligate the upper thyroid artery well.	• If the thyroid is too large to remove, expand the trocar tunnel site sufficiently
Retract the midline bilaterally with both graspers	• Dissect the surgical plane as close as possible to the surface of the thyroid gland	• Ensure safe distances based on the range of heat conduction to prevent thermal injury	*Dissection between the thyroid gland and fascia*	• Avoid EBSLN injury	• Use a surgical lap bag to safely remove the specimen from the operative field to prevent metastasis to other sites
• When retracting the midline with graspers on both sides, provide proper symmetrical tension and cautions to prevent muscle tearing	• Be careful when dissecting between the thyroid gland and strap muscle	• Avoid retracting the thyroid gland excessively, as it may cause mechanical injury to the RLN	• Finish the lateral dissection on the lateral side of the thyroid gland	• Map the course of the EBSLN using nerve monitoring	*Use of hemostatic dressing and anti-adhesion adjuvant*
Midline incision	• Determine whether the strap muscle is injured	• Identify the course and the location of the RLN	*Thyroid retraction—Zuckerkandl*	*Identification and preservation of the superior parathyroid glands*	• Sew the strap muscles with running sutures during midline closure (cranial to caudal)
• Follow the surgical plane well and dissect it	*Lateral retraction of the strap muscle*	*Identification of the inferior parathyroid gland*	• Retract the thyroid to enable entering the harmonic	• Avoid bleeding during the ligation of the superior thyroid artery because the operative field is narrow	*Drain insertion and midline closure*
• Identify the sternothyroid and sternohyoid muscles	• Sufficiently separate the thyroid from the strap muscle	• Recognize the typical location and shape of the parathyroid gland	• Avoid RLN injury caused by traction	• Determine which blood vessels to leave	
• Ensure sufficient incision to Delphian lymph node	• Be careful not to pull the strap muscle excessively, as it can tear and bleed	• Identify the color of the parathyroid gland	*Preservation of the RLN*	• Avoid upper parathyroid injury	
• Avoid muscle injury when making the midline incision	*Identification of the common carotid artery*	• Identify the anatomical variations in the location of the parathyroid gland	• Consider the various shapes of the RLN	*Identification and preservation of EBSLN*	
• Incise from the thyroid cartridge to the suprasternal notch (or the location at which central node dissection is possible)	• Identify the correct depth and course of the common carotid artery	• Identify the blood stream distribution and blood vessel travel of the parathyroid gland	• Continue to check the course of the RLN from view to view	• Determine whether the EBSLN is functional	
Identification of the trachea	• Avoid the blood vessels around the common carotid artery	• Determine whether to leave the parathyroid or perform auto-transplantation after removal	• Distinguish the artery from the RLN	• Determine whether the signals come from the EBSLN using nerve monitoring	
• Avoid injury to the trachea	• Determine whether the common carotid artery moves well according to the heartbeat	• If it is difficult to distinguish between the lymph nodes and parathyroid, determine whether to leave some or remove all depending on the cancer stage	• Predict RLN location and angle	• Determine whether the cricothyroid muscle twitches	
• Expose the trachea as much as possible	• Determine whether the common carotid artery is well exposed along the thyroid gland	• Avoid damage to the parathyroid gland and blood vessels leading to the parathyroid	• Determine the intensity of pulling when the Berry ligament and RLN are adjacent	*Ligation of the superior thyroid artery and vein*	
Identification of the isthmus	*Thyroid retraction—lower*	*Preservation of the blood stream of the parathyroid*	• Dissect the RLN while protecting it by covering it with a gauze ball to prevent thermal or mechanical injury	• Adjust robotic arms for better visibility	
• Avoid injury to the trachea	• Accurately locate the parathyroid gland and RLN	• Preserve blood vessels that affect the parathyroid	• Strong retraction of the thyroid may damage the RLN	• Rapidly expose and ligate the superior thyroid artery	
• Confirm the location of the isthmus carefully	• Avoid bleeding in the thyroid capsule	• Ensure safe distances considering the range of heat conduction to prevent thermal injury	• Avoid thermal injury	*Other items related to dissection of the thyroid upper pole*	
• Determine whether the isthmus was visible as soon as the midline was opened from the sternothyroid muscle	• Expose the lower pole and part of the upper part of the thyroid gland	• Identify the inferior and middle thyroidal veins	• Occasionally, a non-recurrent laryngeal nerve is present that drives directly into the vagus nerve from the upper part of the subclavian artery and enters the larynx	• Use nerve monitoring to identify the vagus nerve (located close to the carotid artery)	

Table 2 (*continued*)

Table 2 (*continued*)

MID module (n=18)	LAT module (n=16)	INF module (n=18)	BER module (n=22)	SUP module (n=12)	END module (n=3)
Isthmectomy	• Use a switching motion to support and lift the thyroid gland to check the tissue around the common carotid artery	• Preserve the parathyroid as much as possible	• Nerve monitoring determining the amplitude of the nerves when initially stimulated (whether the signal has been reduced by more than 50%)		
• Preserve the inferior thyroid vein on the non-operative side	*Other items related to lateral dissection*	• Avoid injury to the parathyroid and parathyroid feeding vessels	*Dissection of the ligament of Berry*		
• Consider the location of the isthmus	• Determine whether the central lymph nodes are removed cleanly along the thyroid gland	*Other items associated with the preservation of the inferior parathyroid glands*	• Expose Berry ligament sufficiently		
• Avoid vessel injury (such as thyroid ima)	• Determine whether the middle thyroid vein is exposed and properly ligated	• Avoid retracting the parathyroid directly to prevent damage to the parathyroid	• Determine the intensity of pulling when the Berry ligament and RLN are adjacent		
• Avoid injury to the cricoid cartilage		• If inevitable, retract tissues around the parathyroid or grab the blood vessels going to the parathyroid	• Dissect the thyroid gland below the Berry ligament		
• Determine whether the left and right sides of the thyroid are separated			• Check the cricothyroid muscle in the upper area		
Other items related to midline incision and isthmectomy			• Minimize residual thyroid tissue, as microscopic amounts of thyroid tissue may remain when the thyroid and the RLN are attached, or when the thyroid tissue covers the RLN, similar to the ears		
• Determine preoperatively whether the isthmectomy is possible (if there is cancer on the isthmus itself, the isthmectomy position might have to be changed)			• Hemostasis is difficult if bleeding occurs in the Berry ligament		
			• Determine whether the Berry ligament is well removed while protecting the RLN		
			Other items related to preservation of the RLN, dissection of the ligament of Berry		
			• Use a compression method with energy or a gauze ball for hemostasis		

MID, midline incision to isthmectomy; LAT, lateral dissection; INF, preservation of inferior parathyroid glands; BER, preservation of RLN and dissection of the ligament of Berry; SUP, dissection of the thyroid upper pole; END, specimen removal and closure; RLN, recurrent laryngeal nerve; EBSLN, external branch of superior laryngeal nerve.

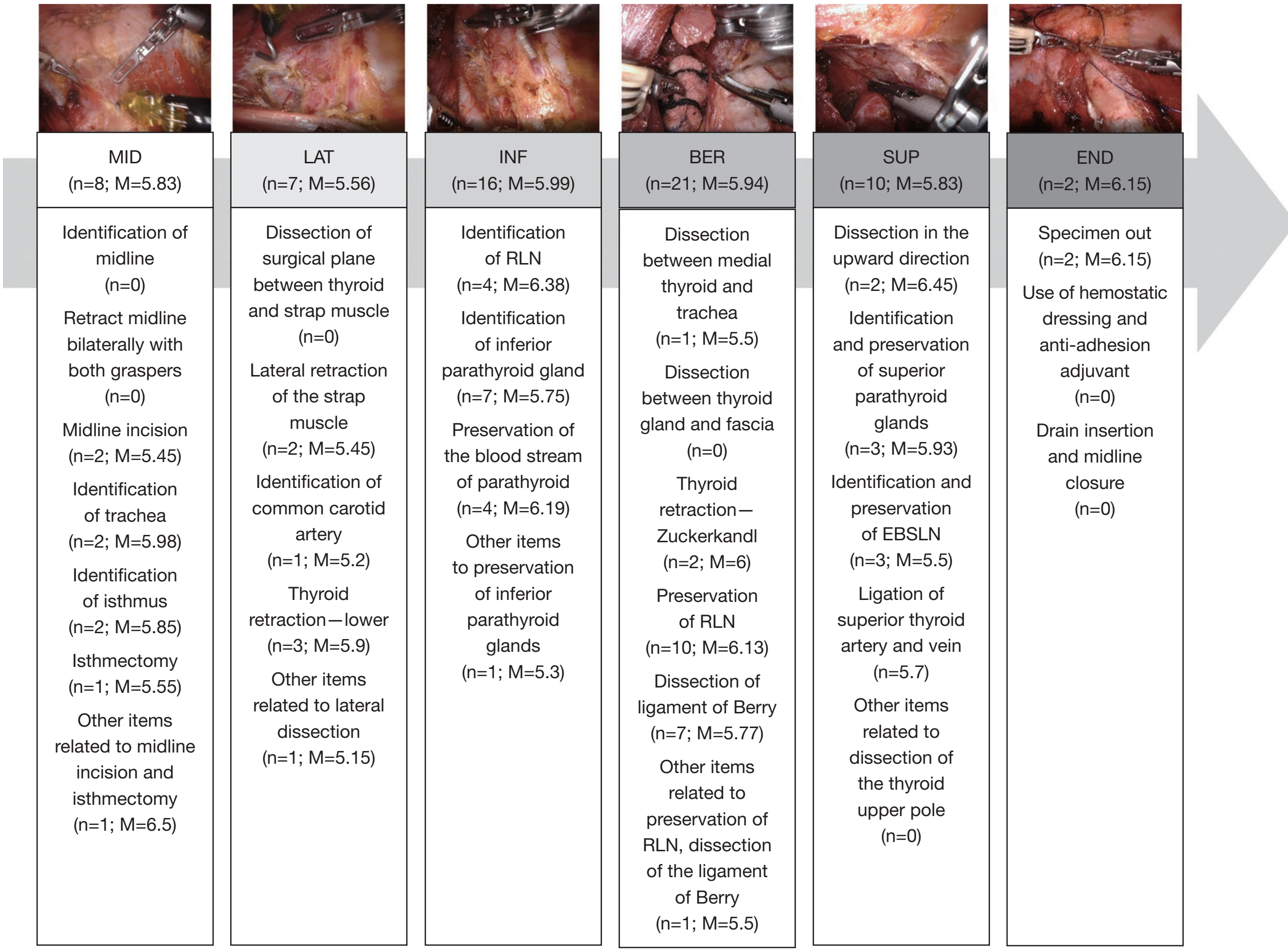

Figure 2 Modules of RT. n, the number of items; M, mean of importance scores; MID, midline incision to isthmectomy; LAT, lateral dissection; INF, preservation of inferior parathyroid glands; BER, preservation of RLN and dissection of the ligament of Berry; SUP, dissection of the thyroid upper pole; END, specimen removal and closure; RLN, recurrent laryngeal nerve; RT, robotic thyroidectomy.

comment regarding the LAT module consisted of accurate determination of the locations of the parathyroid gland and RLN, whereas additional comments regarding the INF module included (I) identifying the course and location of the RLN, (II) ensuring safe distances from the heat source based on the range of heat conduction thereby preventing thermal injury, (III) not retracting the thyroid gland excessively as it may cause mechanical injury to the RLN. Additional comments regarding the BER module included (I) checking the course of the RLN from view to view, (II) avoiding thermal injury, and (III) avoiding RLN injury caused by traction, whereas an additional comment regarding the SUP module noted that to prevent external branch of superior laryngeal nerve (EBSLN) injury, dissection should be made as close to the thyroid gland as possible while ligating the upper thyroid artery well (Table S3).

Discussion

The present study utilized CTA to identify 89 items within six modules for RT, with the modified Delphi survey identifying the 64 items finally in these six modules most important for RT performance, including 8, 7, 16, 21, 10, and 2 items in the MID, LAT, INF, BER, SUP, and END modules, respectively. The core performance skills and cognitive strategies required to perform BABA RT were determined using a mixed research method.

The list of procedural tasks and non-technical skills defined throughout this study may function as the basis

Table 3 Results of modified Delphi consensus on items required to perform robotic thyroidectomy (top 10)

Final rank	Module	Items	Round 1			Round 2	
			Mean (SD)	% rating over 5	Rank	Mean (SD)	% rating over 5
1	BER	Continue to check the course of the RLN from view to view	6.67 (0.64)	100	3	6.85 (0.65)	95
2	LAT	Accurately locate the parathyroid gland and RLN	6.76 (0.61)	100	2	6.8 (0.68)	95
2	INF	Identify the course and location of the RLN	6.81 (0.50)	100	1	6.8 (0.51)	100
4	INF	Ensure safe distances based on the range of heat conduction to prevent thermal injury	6.67 (0.56)	100	3	6.7 (0.56)	100
5	SUP	To prevent EBSLN injury, dissect as close to the thyroid as possible, and at the same time, ligate the upper thyroid artery well	6.52 (0.59)	100	6	6.55 (0.50)	100
6	MID	Determine whether isthmectomy is possible preoperatively (if there is a cancer on the isthmus itself, the isthmectomy position might be changed)	6.38 (0.79)	100	12	6.5 (0.81)	95
6	BER	Avoid thermal injury	6.52 (0.66)	100	6	6.5 (0.50)	100
8	MID	Avoid injury to the trachea when identifying the isthmus	6.43 (0.85)	100	11	6.45 (0.67)	100
8	INF	Excess retraction of the thyroid gland may cause mechanical injury to the RLN	6.19 (0.91)	90	20	6.45 (0.86)	95
8	BER	Avoid RLN injury caused by traction	6.48 (0.73)	100	10	6.45 (0.74)	100

SD, standard deviation; BER, preservation of RLN and dissection of the ligament of Berry; RLN, recurrent laryngeal nerve; LAT, lateral dissection; INF, preservation of inferior parathyroid glands; SUP, dissection of the thyroid upper pole; EBSLN, external branch of superior laryngeal nerve; MID, midline incision to isthmectomy.

for developing a standardized and valid training program, which can enhance surgeon proficiency in surgical skills and ultimately ensure patient safety. In particular, we attempted to evaluate the factors associated with competency-based medical education, including knowledge, skills, values, and attitudes, which could be reflected in both the behavioral tasks and cognitive schema of RT (4,23). The skills learned in the operative field are based on both situational and practice-based learning, both of which could affect the development of professional identity throughout the proper training and evaluation as a thyroid surgeon.

Previous studies have attempted to define the competencies required for each targeted medical treatment, including open thyroidectomy, radiation protection, advanced care planning, endoscopic submucosal dissection, and laparoscopic transabdominal adrenalectomy (2-4,24-26). In some of these studies, when the researchers developed the items for the Delphi consensus, they only used literature review or task analyses of their own performances (24-26). In addition, two of these studies analyzed the performance of multiple SMEs, but did not apply modified Delphi methodology for validation (2,4). This study adopted a mixed-method approach, differentiating this study from previous research, enabling the collection of as much unbiased information as possible and determining the most important competencies for RT, as assessed by various experts, thereby improving its validity (3).

This study, however, did not assess pre-operative steps, such as adjusting the settings on the robot. Although intraoperative patient care includes pre-operative preparation and post-operative management, this study assessed operative skills and techniques with the surgical robot. Pre-operative preparation for RT may include steps associated with the ease of tool usage, as settings for the surgical robot before the operative procedure can be important factors. Another consideration is that our study is demographically homogeneous. Since BABA RT is a surgical method that originated in Korea, this initial

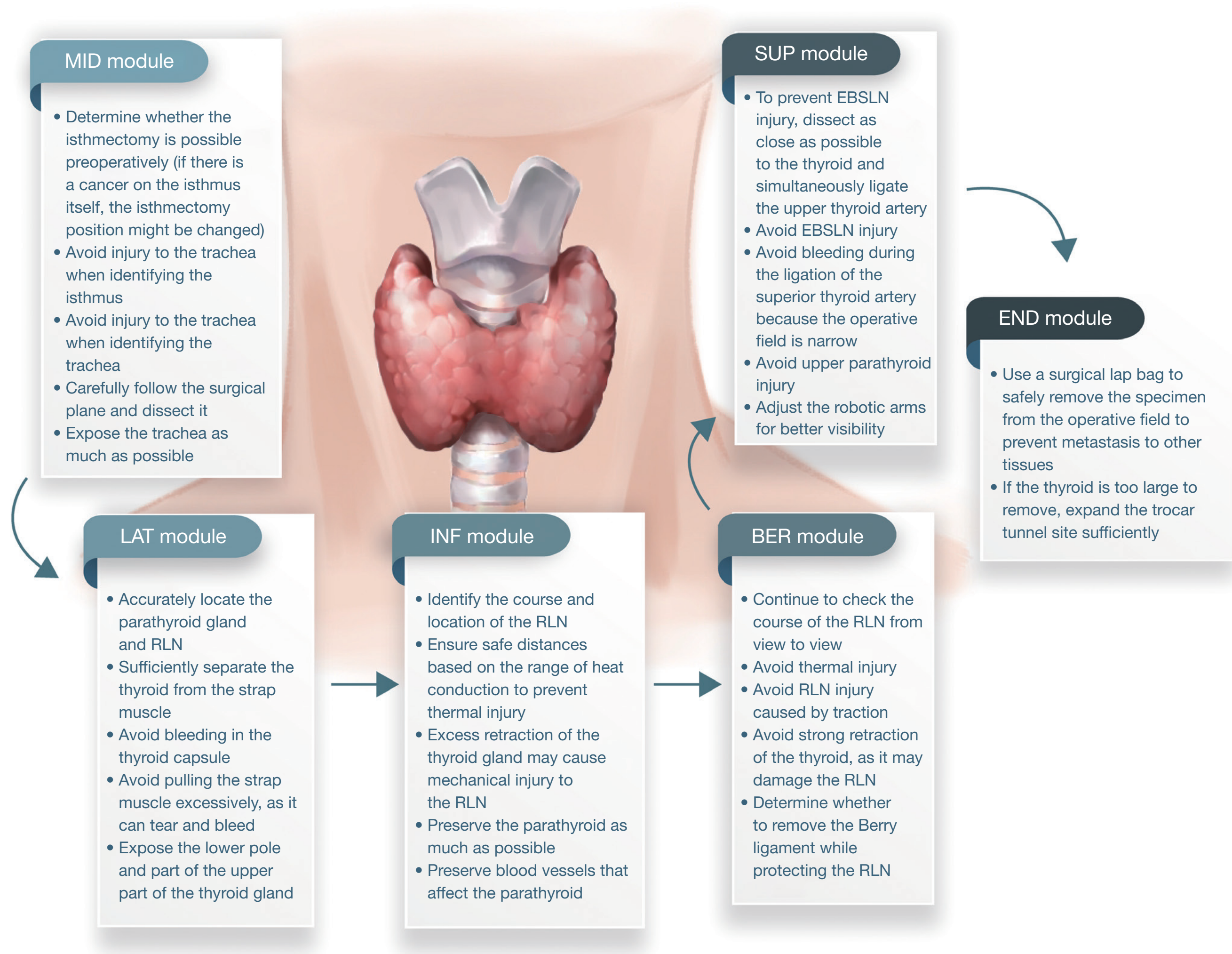

Figure 3 Top 5 items of each modules. MID, midline incision to isthmectomy; LAT, lateral dissection; INF, preservation of inferior parathyroid glands; BER, preservation of RLN and dissection of the ligament of Berry; SUP, dissection of the thyroid upper pole; END, specimen removal and closure; RLN, recurrent laryngeal nerve; EBSLN, external branch of superior laryngeal nerve.

Delphi study had to focus on expert surgeons in Korea. However, presently, the same surgery is being conducted on individuals of different races in various countries worldwide. With the insights gained from this study, it will be possible to develop surgical guidelines from a global perspective in the future. Nevertheless, this study focused on the surgical process and analyzed the surgeon's cognitive behavior when performing RT, resulting in meaningful results, regarded as offsetting the preoperative process. The unique features of RT that is distinct from open thyroidectomy identified in the present study were the proficient use of robotic instruments and the method of securing the operative field visually. These characteristics may be regarded as results associated with differences in surgical tools.

Surgeons should be mindful that, despite their proficiency in the surgical skills we provide, complications may arise in rare cases. A recent analysis of a large-scale robotic surgery study revealed rare complications in 60 out of 5,011 patients. These rare complications comprised hematoma in 4 cases (0.44%), chyle leakage in 15 cases (0.3%), flap injury in 4 cases (0.08%), RLN injury in 7 cases (0.14%), open conversion in 8 cases (0.16%), and pneumothorax in 4 cases (0.08%) (27).

Conclusions

Because of the lack, to date, of step-by-step surgical procedure guidelines for BABA-RT, the results of this study may be used to develop standardized educational criteria for training novice surgeons sufficiently to perform operations independently. These systematic and evidence-based procedures for RT could reduce the quality gap in accordance with training settings, and may contribute to the long-term narrowing of medical gaps among communities and surgeons. It might also help RT trainees to form accurate mental representations of successful performance and improve their surgical skills based on more detailed feedback.

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Footnote

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-467/dss

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-467/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-467/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (No. H-1912-116-1090) and informed consent was taken from all the participants.

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Original Article

Normative electromyography data and influencing factors in intraoperative neuromonitoring using adhesive skin electrodes during thyroid surgery

Sung-Chan Shin[1,2]^, Yong-Il Cheon[1,2]^, Minhyung Lee[1,3]^, Eui-Suk Sung[1,3]^, Jin-Choon Lee[1,3]^, Mijin Kim[2,4]^, Bo Hyun Kim[2,4]^, Byung-Joo Lee[1,2]^

[1]Department of Otorhinolaryngology-Head and Neck Surgery, College of Medicine, Pusan National University, Busan, Republic of Korea; [2]Biomedical Research Institute, Pusan National University Hospital, Busan, Republic of Korea; [3]Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, Gyeongsangnam-do, Republic of Korea; [4]Division of Endocrinology and Metabolism, Department of Internal Medicine, Pusan National University College of Medicine, Pusan National University Hospital, Busan, Republic of Korea

Contributions: (I) Conception and design: BJ Lee; (II) Administrative support: None; (III) Provision of study materials or patients: YI Cheon, SC Shin; (IV) Collection and assembly of data: YI Cheon, M Kim, BH Kim; (V) Data analysis and interpretation: BJ Lee, SC Shin; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Byung-Joo Lee, MD, PhD. Department of Otorhinolaryngology-Head and Neck Surgery, College of Medicine, Pusan National University, 179, Gudeok-ro, Seo-gu, Busan 49241, Republic of Korea; Biomedical Research Institute, Pusan National University Hospital, Busan, Republic of Korea. Email: voiceleebj@gmail.com.

Background: Skin electrodes have been reported to be a useful alternative recording method for intraoperative neuromonitoring (IONM) and show typical electromyography (EMG) waveforms while overcoming the shortcomings of the EMG endotracheal tube. However, the skin electrodes showed relatively lower evoked amplitudes than other recording methods. In this study, we analyzed normative EMG data using skin electrodes and factors that affect the evoked amplitude of thyroid IONM.

Methods: In total, 167 patients [242 nerves at risk (NAR)] who underwent thyroidectomy under IONM with adhesive skin electrodes were analyzed. A pair of skin electrodes was attached to the lateral border of the lamina of the thyroid cartilage. Evoked EMG data, including mean amplitude and latency, obtained after stimulation of the recurrent laryngeal nerve (RLN) and vagus nerve (VN), were collected and analyzed.

Results: The mean amplitudes of RLN and VN recorded via skin electrodes were 255.48±96.53 and 236.15±69.72 µV, respectively. The mean latency of the right and left RLN was 3.22±0.03 and 3.49±0.08 mS, respectively. The mean latency of the right and left VN was 5.37±0.80 and 7.57±0.10 mS, respectively. The mean amplitude was significantly lower in the obesity, male, and total thyroidectomy (TT) groups. As body mass index (BMI) and age increased, the amplitude of EMG tended to decrease significantly.

Conclusions: The evoked amplitude recorded with the skin electrodes was relatively low. A larger surgical extent, obesity, male sex, and age >55 years showed significantly lower evoked amplitudes.

Keywords: Neuromuscular monitoring; thyroid gland; recurrent laryngeal nerve (RLN); vagus nerve (VN); electrodes

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^ ORCID: Sung-Chan Shin, 0000-0003-2329-0648; Yong-Il Cheon, 0000-0003-0288-0542; Minhyung Lee, 0000-0002-4038-1667; Eui-Suk Sung, 0000-0001-8752-3426; Jin-Choon Lee, 0000-0002-5629-4277; Mijin Kim, 0000-0002-1538-8859; Bo Hyun Kim, 0000-0001-9632-9457; Byung-Joo Lee, 0000-0001-7091-6688.

Introduction

Intraoperative neuromonitoring (IONM) has been reported to help identify the nerve early, safely dissect the nerve, and predict postoperative vocal cord movements in thyroid surgery (1). Currently, the most popular electromyography (EMG) signal recording method for thyroid IONM is to use an endotracheal tube with surface electrodes (EMG tube), which has been the best established to date and is easy to use if the equipment is ready (1). However, the EMG tube has the disadvantage of false-positive loss of signal (LOS) due to poor contact between the EMG tube and vocal folds (2). IONM using needle or skin electrodes has been proposed as an alternative method (3-8). Among them, the skin electrode is the most noninvasive and free of false-positive LOS due to tube malposition and has an economic advantage compared to the EMG tube (6-8). However, skin electrodes have the disadvantage that the evoked amplitude value is relatively low and an appropriate standard value has not yet been established.

In this study, we analyzed normative thyroid IONM data recorded via skin electrodes and factors, such as age, sex, side and extent of surgery, and body mass index (BMI), which could affect the evoked amplitude of thyroid IONM. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-428/rc).

Methods

Patients

This retrospective study reviewed the medical records of 167 consecutive patients with 242 nerves at risk (NAR) who underwent conventional thyroid lobectomy or total thyroidectomy (TT) with IONM using skin electrodes between May, 2020 and June, 2021. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of Pusan National University Hospital approved this study (No. 1910-042-084) and waived the requirement for informed consent. All enrolled patients showed normal glottic function on preoperative laryngoscopic examination. Clinicopathological characteristics, such as age, sex, BMI, surgical extent, tumor size, and tumor pathology, were analyzed (*Table 1*).

Table 1 Clinicopathological characteristics

Clinicopathologic characteristics	Value
Number of patients	167
NAR, n	242
Type of surgery, n (hemithyroidectomy/total thyroidectomy)	92/75
Age (mean ± SD, years)	51.92±12.53
Sex (M:F), n	22:145
Body mass index (mean ± SD, kg/m^2)	24.38±3.09
Tumor size (mean ± SD, cm)	0.86±0.64
Pathology, n	
Papillary thyroid carcinoma	137
Follicular neoplasm	16
Benign thyroid disease	14

NAR, nerves at risk; SD, standard deviation; M, male; F, female.

Highlight box

Key findings
- A larger surgical extent, obesity, male sex, and age >55 years showed significantly lower evoked amplitudes in thyroid intraoperative neuromonitoring using skin electrodes.

What is known and what is new?
- Skin electrodes have been reported to be a useful alternative recording method for intraoperative neuromonitoring.
- The evoked amplitude recorded with the skin electrodes was relatively low. A larger surgical extent, obesity, male sex, and age >55 years showed significantly lower evoked amplitudes.

What is the implication, and what should change now?
- Surgeons should think various clinical factors when interpreting electromyographic data in thyroid intraoperative neuromonitoring using skin electrodes.

General anesthesia and monitor setup

After standard general anesthesia, anesthesia was maintained with sevoflurane, and neuromuscular blockade was not administered during surgery. All patients were placed in the Rose position and a pair of skin electrodes (DSE3125, Medtronic Xomed Inc., Jacksonville, FL, USA) was attached to the lateral border of the thyroid cartilage lamina (*Figure 1A*). The NIM-Neuro 3.0 system (Medtronic Xomed Inc.) was used for IONM analysis. The duration of stimulation was set at 100 μS, with a frequency of 4 Hz. Recurrent laryngeal nerve (RLN) and vagus nerve (VN) stimulation was performed after extraction of the thyroid specimen, and evoked EMG data, including mean amplitude

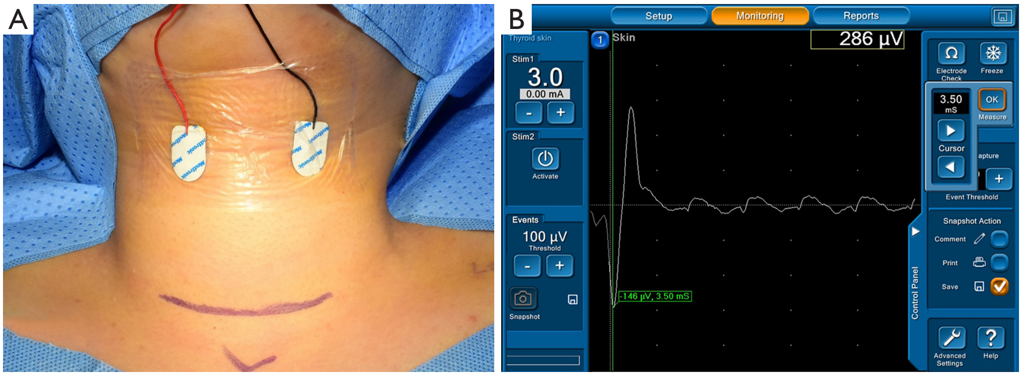

Figure 1 A representative photo of thyroid IONM using adhesive skin electrodes. (A) Patient; (B) IONM data. IONM, intraoperative neuromonitoring.

and latency, were recorded (*Figure 1B*). Furthermore, the recorded EMG values were compared according to clinical factors, such as age, sex, side and extent of surgery, and BMI.

Statistical analysis

The collected EMG data were expressed as mean ± standard error and compared for each variable using a paired *t*-test and one-way analysis of variance. Multiple regression analysis was performed to assess the effects of age and BMI on EMG data. Statistical significance was set at P<0.05. Statistical analyses were performed using the Statistical Package for the Social Sciences version 27 for Windows (IBM Corp., Armonk, NY, USA).

Results

A total of 167 patients with 242 NARs were included in the study. The ratio of hemithyroidectomy (HT) to TT was 92:75. The mean age of the patients was 51.92±12.53 years (range, 24–78 years). Among the 167 patients, 137 had papillary thyroid carcinoma, 16 had follicular neoplasm, and 14 had benign thyroid disease. The mean tumor size was 0.86±0.64 cm. The mean BMI was 24.38±3.09 kg/m^2.

The mean amplitude of both RLN and VN recorded via skin electrodes was 264.37±101.49 and 243.71±77.82 µV, respectively. The mean latency of the right and left VN was 5.37±0.08 and 7.57±0.10 mS, respectively. There were no cases of LOS in the current study.

Comparison of EMG data according to surgical side

Of the 242 NARs, 132 were left and 110 were right. The mean amplitude of the left and right VN was 241.95±79.45 and 249.97±76.83 µV, respectively. The mean latency of the left and right VN was 7.57±0.10 and 5.37±0.08 mS, respectively. The mean amplitude of the left and right RLN was 270.45±104.87 and 262.31±98.96 µV, respectively. The mean latency of the left and right RLN was 3.49±0.08 and 3.22±0.03 mS, respectively. There was no statistical difference in the amplitude value according to the surgical side but a statistical difference in the VN latency according to the surgical side (P<0.01) (*Table 2*).

Comparison of EMG data according to sex

Of the 242 NARs, 38 were from men, and 204 were from women. The mean amplitude values of VN according to sex were as follows: men, 200.50±57.12 µV and women, 254.35±79.18 µV (P<0.05). The mean latency values of the VN according to sex were as follows: men, 6.44±0.10 mS and women, 6.39±0.13 mS. The mean amplitude of RLN for men and women was 196.05±77.68 and 280.44±101.49 µV, respectively. The mean latency of RLN for men and women was 3.73±0.13 and 3.58±0.09 mS, respectively. There were no significant differences in latency according to sex in RLN and VN. Otherwise, there was a statistically significant difference in the amplitude value according to the surgical side in the RLN and VN (P<0.001) (*Table 2*).

Comparison of EMG data according to surgical extent

Of the 242 NARs, 92 were in the HT group and 150 in the TT group. The mean amplitude values of both VN and RLN according to the surgical extent were the following: the VN HT group, 261.89±88.49 µV; VN TT group,

Table 2 Analysis of electromyography data according to clinical parameters

Parameters	Nerve	Subtypes	NAR (n)	Amplitude (mean ± SD, μV)	P value	Latency (mean ± SD, mS)
Side	VN	Left	132	241.95±79.45	0.84	7.57±0.10
		Right	110	249.97±76.83		5.37±0.08**
	RLN	Left	132	270.45±104.87	0.76	3.49±0.08
		Right	110	262.31±98.96		3.22±0.03
Sex	VN	Male	38	200.50±57.12***	<0.001	6.44±0.10
		Female	204	254.35±79.18		6.39±0.13
	RLN	Male	38	196.05±77.68***	<0.001	3.73±0.13
		Female	204	280.44±101.49		3.58±0.09
Surgical extent	VN	HT	92	261.89±88.49	0.01	6.68±1.54
		TT	150	236.15±69.72*		6.62±1.44
	RLN	HT	92	285.57±108.82	0.02	3.42±0.65
		TT	150	255.48±96.53*		3.25±0.50
Age (years)	VN	<55	113	266.44±89.69	<0.001	6.25±1.49
		≥55	129	226.44±60.39***		6.35±1.55
	RLN	<55	113	291.39±110.67	<0.001	3.32±0.72
		≥55	129	244.44±88.37***		3.35±0.48

Statistical difference: *, P<0.05; **, P<0.01; ***, P<0.001. NAR, nerves at risk; SD, standard deviation; VN, vagus nerve; RLN, recurrent laryngeal nerve; HT, hemithyroidectomy; TT, total thyroidectomy.

236.15±69.72 μV; RLN HT group, 285.57±108.82 μV; and RLN TT group, 255.48±96.53 μV. The mean latency values of both VN and RLN according to the surgical extent were as follows: the VN HT group, 6.68±1.54 mS; VN TT group, 6.62±1.44 mS; RLN HT group, 3.42±0.65 mS; and RLN TT group, 3.25±0.50 mS. There were no significant differences in latency according to BMI in both RLN and VN. However, the mean amplitude value of the TT group was significantly lower than that of the HT group for the VN and RLN (P<0.05) (*Table 2*).

Comparison of EMG data according to BMI

We classified the patient group according to the Asia-Pacific BMI classification (normal, <18.5 kg/m^2; overweight, 18.5–22.9 kg/m^2; and obesity, ≥23 kg/m^2). Of the 242 NARs, 93 were in the normal group, 59 in the overweight group, and 90 in the obesity group. The mean amplitude values of both VN and RLN according to BMI were as the following: the VN normal group, 261.58±68.57 μV; VN overweight group, 240.85±90.62 μV; VN obesity group, 226.89±75.44 μV; RLN normal group, 288.86±95.36 μV; RLN overweight group, 272.56±116.87 μV; and RLN obesity group, 233.97±90.50 μV. The three groups showed significant differences in mean amplitude values. The mean amplitude values of VN (P<0.05) and RLN (P<0.01) in the obese group were significantly lower than those of the normal group (*Table 3*). In multiple regression analyses, as BMI increased, the RLN amplitude tended to decrease significantly (P<0.01) (*Table 4*). Similarly, the VN amplitude tended to decrease with increasing BMI, but no statistical significance was observed (*Table 5*).

Comparison of EMG data according to age

According to the American Joint Committee on Cancer staging system, patients were classified according to the age of 55 years. Of the 242 NARs, 113 were aged <55 years and 129 were aged ≥55 years. The mean amplitude values of both VN and RLN according to the age group were as follows: the VN aged <55 group, 266.44±89.69 μV; VN aged ≥55 group, 226.44±60.39 μV; RLN aged <55 group, 291.39±110.67 μV; and RLN aged ≥55 group, 244.44±88.37 μV. The patients aged ≥55 years showed significantly lower amplitude values

Table 3 Analysis of electromyography data according to BMI classification

Nerve	BMI group[†]	NAR	Amplitude (mean ± SD, µV)	*F*	P value	Scheffe
VN	Normal (a)	93	261.58±68.57	4.161	0.017*	a<c
	Overweight (b)	59	240.85±90.62			
	Obesity (c)	90	226.89±75.44			
RLN	Normal (a)	93	288.86±95.36	6.403	0.002**	a<c
	Overweight (b)	59	272.56±116.87			
	Obesity (c)	90	233.97±90.50			

[†], categories are based on Asia-Pacific BMI classification: normal, <18.5 kg/m^2; overweight, 18.5–22.9 kg/m^2; obesity, ≥23 kg/m^2. Statistical difference: *, P<0.05; **, P<0.01. BMI, body mass index; NAR, nerves at risk; SD, standard deviation; VN, vagus nerve; RLN, recurrent laryngeal nerve; *F*, *F*-static.

Table 4 Multiple regression analysis of the effects of BMI and age on evoked amplitude (recurrent laryngeal nerve)

Variables	Unstandardized coefficients		Standardized coefficients (β)	*T* (P value)	Collinearity statistics	
	B	SE			Tolerance	VIF
(Constant)	479.475	63.171		7.590 (<0.001)***		
BMI	−6.180	2.227	−0.188	−2.775 (0.006)**	0.997	1.003
Age	−1.236	0.551	−0.152	−2.246 (0.026)*	0.997	1.003
Adjusted R square			0.046			
Durbin-Watson			1.986			

Statistical difference: *, P<0.05; **, P<0.01; ***, P<0.001. BMI, body mass index; B, beta; SE, standard error; *T*, *t*-static; VIF, variance inflation factor.

Table 5 Multiple regression analysis of the effects of BMI and age on evoked amplitude (vagus nerve)

Variables	Unstandardized coefficients		Standardized coefficients (β)	*T* (P value)	Collinearity statistics	
	B	SE			Tolerance	VIF
(Constant)	353.674	49.189		7.190 (<0.001)***		
BMI	−0.724	0.429	−0.116	−1.689 (0.093)	0.997	1.003
Age	−2.962	1.734	−0.118	−1.708 (0.089)	0.997	1.003
Adjusted R square			0.016			
Durbin-Watson			1.847			

Statistical difference: ***, P<0.001. BMI, body mass index; B, beta; SE, standard error; *T*, *t*-static; VIF, variance inflation factor.

than those aged <55 years (P<0.001) (*Table 2*). In multiple regression analyses, as age increased, the RLN amplitude tended to decrease significantly (P<0.05) (*Table 4*). The VN amplitude decreased with age, but the difference was not statistically significant (*Table 5*).

Discussion

Wu *et al.* reported for the first time the results of thyroid IONM using adhesive skin electrodes (8). Using porcine models, although the evoked amplitude value of the adhesive skin electrode was lower than that of the EMG tube, IONM could be successfully performed without false positives, and the stress injury of the RLN could be evaluated identically to that of the EMG tube. Furthermore, unlike the EMG tube, which showed a false LOS when there was a trachea displacement, the adhesive skin electrode showed a stable signal (8). Lee *et al.* successfully performed thyroid IONM in human patients using adhesive skin electrodes. In their study, some NARs showed amplitudes of ≤100 μV, but all showed biphasic waveforms (6). Liddy *et al.* performed thyroid IONM using an anterior laryngeal electrode attached to the thyroid cartilage; their study showed that the amplitude was relatively lower (up to 83%) than the EMG tube, but there were no differences in latency (9). Previously, we compared the EMG data recorded using the EMG tube and the skin electrode simultaneously in the same patient (7). The amplitude of the skin electrode was approximately one-third of the EMG tube.

Previous studies have shown that skin electrodes have several advantages: (I) they are noninvasive; (II) they are free from false-positive LOS due to tube malposition; and (III) they are economical (6-8). Unfortunately, the adhesive skin electrode does not have as many previous research results as the EMG tube, so the normative value ranges and event threshold have not yet been established.

In this study, the normative values of thyroid IONM using adhesive skin electrodes and factors that could affect the amplitude values were analyzed. IONM data were obtained for all NARs without a false LOS during the study period. The mean amplitude of both RLN and VN recorded via skin electrodes was 264.37±101.49 and 243.71±77.82 μV, respectively. These values correspond to approximately 32–35% of the amplitude of the EMG tube (7,10). Furthermore, the mean latency of the right VN was 5.37±0.80 mS and the left VN was 7.57±1.02 mS. These values correspond to approximately 137% of the latency of the EMG tube (7,10). The normative value of the current study was only one-third of the EMG tube amplitude value compared to previous reports (7,10,11). This assumes that the distance between the vocal cord muscle where the EMG signal is generated and the skin electrode that records the EMG signal is relatively far compared to the EMG tube; thus, signal attenuation occurs due to barriers, such as cartilage, muscle, and fat, that could increase resistance.

Factors affecting the values of the EMG data, such as surgical side, surgical extent, sex, BMI, and correlations were analyzed. The amplitude tended to decrease significantly with greater surgical extent, male sex, obesity, and age ≥55 years. These clinical factors may have confounding factors each other. However, the reason for this tendency is assumed to be that the thickness of the neck tends to increase in men and obese people, and as a result, the distance between the adhesive skin electrode and the vocal cord muscles increases, resulting in EMG signal attenuation. Furthermore, the amplitude was significantly lower in the TT group than in the HT group, which is believed to be related to the flap elevation range. The resistance between the adhesive skin electrode and vocal cord muscles increased as the flap elevation range increased, causing signal attenuation.

This study has the limitations such as retrospective, non-comparative design, insufficient number of cases. And although skin electrodes are useful, the standard IONM method so far is the EMG tube.

Conclusions

In conclusion, the mean amplitude of both RLN and VN recorded via skin electrodes was 264.37±101.49 and 243.71±77.82 μV, respectively, which corresponded to approximately one-third of the EMG tube. The factors influencing the amplitude values were sex, surgical extent, BMI, and age. Male sex, larger surgical extent, obesity, and age ≥55 years showed significantly lower amplitude values.

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Footnote

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Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-428/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-428/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of Pusan National University Hospital approved this study (No. 1910-042-084) and waived the requirement for informed consent.

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Original Article

Oncoplastic breast-conserving surgery (OBCS) *vs.* mastectomy with reconstruction: a comparison of outcomes in an underserved population

Angela Foley[1]^, Adrian Choppa[1], Fardeen Bhimani[2], Thoran Gundala[3], Meredith Shamamian[1], Samantha LaFontaine[4], David Tran[5], Kelly Johnson[6], Katie Weichman[7], Sheldon Feldman[2], Maureen P. McEvoy[2]

[1]Albert Einstein College of Medicine, Bronx, NY, USA; [2]Breast Surgery Division, Department of Surgery, Montefiore Medical Center, Montefiore Einstein Comprehensive Cancer Center, Bronx, NY, USA; [3]Department of Obstetrics and Gynecology, Northwell - Long Island Jewish Medical Center/North Shore University Hospital, Manhasset, NY, USA; [4]Department of Surgery, NYU Langone Hospital, Mineola, NY, USA; [5]Department of Surgery, Montefiore Medical Center, Bronx, NY, USA; [6]New York Breast Health, Great Neck, NY, USA; [7]Hansjorg Wyss Department of Plastic Surgery, NYU Grossman School of Medicine, Manhattan, NY, USA

Contributions: (I) Conception and design: A Foley, A Choppa, MP McEvoy; (II) Administrative support: K Johnson, K Weichman, S Feldman, MP McEvoy; (III) Provision of study materials or patients: K Johnson, K Weichman, S Feldman, MP McEvoy; (IV) Collection and assembly of data: A Foley, A Choppa, M Shamamian, S LaFontaine, D Tran; (V) Data analysis and interpretation: A Foley, F Bhimani, T Gundala, MP McEvoy; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Angela Foley, BA. Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10461, USA.
Email: angela.foley@einsteinmed.edu.

Background: Oncoplastic breast-conserving surgery (OBCS) has demonstrated superior cosmetic outcomes to traditional breast-conserving surgery (BCS) while maintaining oncologic safety. While prior studies have compared OBCS to mastectomy, there is a scarcity of literature on the impact of social determinants of health on outcomes. Furthermore, although traditionally tumors larger than 5 cm and multifocal disease were treated with mastectomy, the literature has now shown OBCS to be safe in treating such disease. As a result, patients with large or multifocal tumors could be eligible for both mastectomy and OBCS, which prompts the need for comparison between the two. Thus, the aim of our study was to compare OBCS and mastectomy with reconstruction using BREAST-Q and oncologic outcome measures, as well as stratify these outcomes based on race, ethnicity, and body mass index (BMI).

Methods: A retrospective chart review was performed for 57 patients treated with OBCS and 204 patients treated with mastectomy with reconstruction from 2015 to 2021. Variables including age, race, ethnicity, BMI, insurance status, surgery type, pathology, recurrence, and complications were recorded. Patient-reported outcomes (PROs) were recorded using BREAST-Q pre- and post-operatively.

Results: Despite having a higher BMI ($P<0.001$), OBCS yielded higher "satisfaction with breast" and "satisfaction with outcome" than mastectomy ($P=0.02$ and $P=0.02$, respectively). When stratified by race, there were no statistical differences in the PROs between the two surgeries for Hispanic nor African American patients. OBCS had a significantly lower rate of infection and fewer additional surgeries than mastectomy ($P=0.004$ and $P<0.001$, respectively). There were no differences in positive margin rate or recurrence rate between the groups.

Conclusions: In our study, OBCS yielded better PROs than mastectomy while maintaining oncologic safety and resulting in fewer surgeries and complications. These excellent outcomes in a majority non-Caucasian cohort support the utilization of OBCS for underserved, minority populations. Larger studies evaluating PROs in diverse and uninsured groups are needed to reinforce these conclusions.

^ ORCID: 0000-0001-7478-6585.

Keywords: Oncoplastic breast-conserving surgery (OBCS); mastectomy; BREAST-Q; patient-reported outcomes (PROs); social determinants of health

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Introduction

Background

Breast cancer is the most common newly diagnosed malignancy among women across the United States (1). Breast cancer incidence increases by about 0.5% per year; approximately 290,560 patients will be diagnosed with breast cancer in 2022 (1,2). For many years, mastectomy was perceived as the only treatment option; however, as the number of cases has grown, so has the advancement of treatment options, leading to a transition from radical mastectomy to simple mastectomy, and then to breast-conserving surgery (BCS). In terms of oncological outcomes, BCS followed by adjuvant radiotherapy has been shown to be as effective as mastectomy (3-5). With the evolution of new surgical techniques and improved survival rates, the demand for better cosmetic outcomes has become paramount. Oncoplastic BCS (OBCS) has demonstrated promising cosmetic outcomes and thus has become a popular choice of treatment amongst patients and providers (6-8). OBCS combines BCS with a plastic surgery procedure, such as breast reduction, mastopexy, or mammoplasty, and has shown to have equal, if not superior, oncologic safety as compared to standard BCS (6,8-10).

A caveat for performing BCS has been proven to be patient dissatisfaction. Prior literature demonstrates that 30–40% of breast cancer patients who undergo BCS suffer from poor cosmetic outcomes (6,9,11-13). Patient dissatisfaction after BCS is multifactorial, with higher body mass index (BMI), adjuvant treatment, tumor location, and adverse effects of BCS surgery all contributing significantly to patients' dissatisfaction and poor cosmesis (6,8,14,15). Furthermore, the degree of dissatisfaction is proportional to the amount of breast tissue excised (6,8,14,16). OBCS, on the other hand, results in a better patient experience because it allows for large tissue excision without compromising cosmesis (6-8). Additionally, compared to BCS, OBCS has been shown to have lower positive margin, re-excision, and local recurrence rates (6,8,9).

Highlight box

Key findings

- In our majority non-Caucasian cohort, oncoplastic breast-conserving surgery (OBCS) yielded better patient-reported outcomes (PROs) than mastectomy while maintaining oncologic safety and resulting in fewer surgeries and complications.

What is known and what is new?

- In small studies comparing OBCS to mastectomy, OBCS had better PROs, but these analyses did not include race, ethnicity, body mass index (BMI), or socioeconomic status.
- We compared OBCS to mastectomy in an underserved, majority non-Caucasian Bronx population with relatively large breast tumors and a high prevalence of multifocal disease.
- Despite a higher BMI in the OBCS group, patient satisfaction after OBCS was significantly higher than after mastectomy.

What is the implication, and what should change now?

- Although traditionally large and multifocal tumors were treated with mastectomy, OBCS has been shown to be equally as safe and effective.
- This study confirms the safety and improved satisfaction of OBCS even in an underserved population with such tumors.

Rationale, knowledge gap, and objective

Traditionally, tumors larger than 5 cm and multifocal disease were treated with mastectomy (17,18). However, one study analyzing outcomes of OBCS in patients with multifocal, multicentric, and locally advanced tumors >5 cm found positive margin rates similar to that of BCS as well as relatively low conversion-to-mastectomy and local recurrence rates (19). Similarly, another study compared long-term oncologic outcomes of OBCS to those of mastectomy for patients with primary multicentric and multifocal tumors and did not find any difference in overall survival, disease-free survival, or local and distant recurrence rates (20). Therefore, patients with large or multifocal tumors could be eligible for both mastectomy and OBCS, which prompts the need for comparison between the two.

Moreover, the current OBCS literature focuses on technique, safety, cosmesis, and patient satisfaction associated with this procedure, often in comparison to BCS; however, there is a paucity of literature comparing OBCS and mastectomy on these same variables. Several small retrospective studies have shown that OBCS supersedes both mastectomy and BCS in terms of patient-reported outcomes (PROs), cosmesis, and overall quality of life (QOL) improvement (21-24). However, none of these studies stratified outcomes based on race, ethnicity, or BMI nor analyzed these data in relation to surgical outcomes such as complications or need for additional procedures. Including data on race, ethnicity, and socioeconomic status is crucial in research overall considering the significant effects that social determinants of health have on health outcomes. In cancer screening in particular, health literacy and access to care can significantly affect patients' screenings and thus cancer detection as well as their ability to undergo treatment. Furthermore, PROs, specifically those relating to one's sexuality and satisfaction with appearance, are heavily influenced by cultural norms and societal standards. Patients from different backgrounds have different perceptions of what beauty is and what an "ideal" female form looks like. Thus, it is crucial to study the effect of different operations on PROs in a wide range of patient demographics, as the impact of fully removing breasts via mastectomy may vary significantly based on the patient's background and expectations. Therefore, the aim of our study was to compare OBCS and mastectomy with reconstruction on a range of different variables, including PROs and measures of oncologic safety, as well as stratify these outcomes based on race, ethnicity, and BMI in order to help give all patients, including those minorities underrepresented in medical research, evidence-based recommendations in pre-operative planning. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-403/rc).

Methods

Data collection

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Albert Einstein College of Medicine (No. FWA #00023382) and individual consent for this retrospective analysis was waived. A retrospective chart review was performed for breast cancer patients treated with either OBCS or mastectomy with reconstruction from 2015 to 2021 at Montefiore Einstein Comprehensive Cancer Center, Albert Einstein College of Medicine in the Bronx. Demographic information such as age, race, ethnicity, BMI, language, and insurance status in addition to clinical information such as date of diagnosis, type of surgery, pathology, treatment (including chemotherapy and radiation), recurrence, complications (including wound healing issues), and the need for additional surgery were all recorded. PROs were measured using BREAST-Q, specifically its reduction/mastopexy and mastectomy with reconstruction modules.

Statistical analysis

A chi-square test was performed for categorical variables. For numerical variables, normality was first assessed for each variable using a combination of visual assessment using Q-Q plots and mathematical interpretation using a Shapiro-Wilk test. If the data was normally distributed, an unpaired two-tail *t*-test was performed. If a numerical data was not normally distributed (as was often the case), a non-parametric equivalent of the *t*-test called the Mann-Whitney test was used. For the correlations, a Pearson correlation (parametric) was performed on normally distributed data and a Spearman correlation (nonparametric equivalent) was performed on non-normal distributions. Patients with missing data in any given variable were excluded from that analysis, and the n values for each were reported accordingly.

PROs

BREAST-Q is a clinically validated tool used for collection of PROs following various types of breast surgery. Patient-reported data from BREAST-Q surveys are converted to a score between 0 and 100 with the higher scores indicating more favorable outcomes (25-27). In our study, PROs were recorded using BREAST-Q pre-operatively as well as post-operatively. The post-operative time point used was the one furthest away from the surgery, ranging between 6 months and 5 years after.

Results

Demographics

A total of 261 patients' data were evaluated, of which 204 patients underwent mastectomy and 57 patients underwent OBCS. In total, 89% of the OBCS group and 79% of the mastectomy group identified as Hispanic and/or non-Caucasian. When compared to the mastectomy group, patients in the OBCS group were older (P=0.02) and had higher BMIs (P<0.001) (*Table 1*). However, there was no correlation between BMI and PROs (*Table 2*).

Disease and management

Between the two groups, there was no significant difference in the prevalence of multifocal disease (P=0.27); however, OBCS patients had a lower clinical stage of disease than mastectomy patients (P=0.04). In the OBCS group, 15/57 (26.3%) patients had stage 0 disease, 22/57 (38.6%) had stage 1, 14/57 (24.6%) had stage 2, 3/57 (5.3%) had stage 3, no patients were stage 4, and in 3/57 (5.3%) the stage was unknown. Contrastingly, among mastectomy patients, 31/204 (15.2%) had stage 0 disease, 63/204 (30.9%) had stage 1, 70/204 (34.3%) had stage 2, 32/204 (15.7%) had stage 3, 4/204 (2.0%) had stage 4, and in 4/204 (2.0%) the stage was unknown. There was no difference in tumor size between the two groups, with a median size of 22.5 mm among OBCS patients (range, 0.5–120 mm) compared to 20 mm among mastectomy patients (range, 0–140 mm) (P=0.59). More mastectomy patients had nodal-positive

Table 1 Comparison of OBCS *vs.* mastectomy demographics

Variables	OBCS	Mastectomy + reconstruction	P value
Total number of patients	57	204	
Age (years)[†]	55 [39–77]	52 [26–82]	0.018*
Race			
White	5 (8.8)	24 (11.8)	0.525
Black/African-American	26 (45.6)	62 (30.4)	0.032*
Asian	1 (1.8)	4 (2.0)	0.920
Other	20 (35.1)	88 (43.1)	0.275
Unavailable	5 (8.8)	26 (12.7)	0.412
Ethnicity			
Non-Hispanic	28 (49.1)	95 (46.6)	0.732
Hispanic	21 (36.8)	80 (39.2)	0.745
Unavailable	8 (14.0)	29 (14.2)	0.972
Medicaid/no insurance	24 (42.0)	83 (40.7)	0.847
BMI (kg/m^2)	32.4 [27.7–38.1]	29.0 [17.3–49.7]	<0.001*
Multifocal disease	27 (47.4)	80 (39.2)	0.269
Clinical stage			0.038*
0	15 (26.3)	31 (15.2)	
1	22 (38.6)	63 (30.9)	
2	14 (24.6)	70 (34.3)	
3	3 (5.3)	32 (15.7)	
4	0 (0.0)	4 (2.0)	
Unknown	3 (5.3)	4 (2.0)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	OBCS	Mastectomy + reconstruction	P value
Procedure type	Oncoplastic reduction + symmetrizing reduction: 53 (93.0)	Nipple sparing: 55 (27.0)	
	Oncoplastic mastopexy + symmetrizing mastopexy: 2 (3.5)	Skin sparing: 149 (73.0)	
	Oncoplastic mastopexy: 1 (1.8)	Bilateral: 60 (29.4)	
	Bilateral oncoplastic reduction: 1 (1.8)	Immediate TE: 138 (67.6)	
	Wise incision pattern: 50 (87.7)	Implant after TE: 81/138 (58.3)	
	Vertical incision pattern: 7 (12.3)	Autologous recon after TE: 33/138 (23.9)	
	Periareolar incision pattern: 1 (1.8)	TE removal 2/2 infection: 8/138 (5.8)	
		TE & awaiting further recon: 9/138 (6.5)	
		TE then lost-to-follow-up/ deceased: 7/138 (5.1)	
		Immediate autologous recon: 54 (26.5)	
		Immediate implant recon: 12 (5.9)	
Weights (g)	Lumpectomy: 157 [37–722]	Mastectomy: 660 [59–2,378]	<0.001*
	Ipsilateral reduction: 180.5 [10–1,754]	Mastectomy: 660 [59–2,378]	<0.001*
	Contralateral reduction: 438 [87–1,726]	Mastectomy: 660 [59–2,378]	<0.001*
Positive margins	4 (7.0)	10 (4.9)	0.525
Pathology			
IDC	33 (57.9)	120 (58.8)	0.900
ILC	5 (8.8)	22 (10.8)	0.659
DCIS	15 (26.3)	29 (14.2)	0.031*
Pathology (mixed)	4 (7.0)	33 (16.2)	
Hormone receptor status			
Estrogen receptor (+)	46 (80.7)	150 (73.5)	0.268
Triple negative	9 (15.8)	36 (17.6)	0.743
HER2 (+)	4 (7.0)	32 (15.7)	0.093
Tumor size (mm)	22.5 [0.5–120]	20 [0–140]	0.585
Patients with positive lymph nodes			
0	31(54.4)	125 (61.3)	0.348
≥1	17 (29.8)	65 (31.9)	
1–4	14 (24.6)	42 (20.6)	0.518
5–9	2 (3.5)	14 (6.9)	0.351
≥10	1 (1.8)	9 (4.4)	0.355
No sentinel lymph node biopsy	9 (15.8)	14 (6.9)	0.036*
Neoadjuvant chemotherapy	11 (19.3)	64 (31.4)	0.075

Table 1 (*continued*)

Table 1 (*continued*)

Variables	OBCS	Mastectomy + reconstruction	P value
Neoadjuvant endocrine therapy	9 (15.8)	14 (6.9)	0.036*
Adjuvant chemotherapy	17 (29.8)	87 (42.6)	0.080
Adjuvant endocrine therapy	39 (68.4) (compliance rate =68.9%)	134 (65.7) (compliance rate =64%)	0.699
Adjuvant radiation therapy	45 (78.9)	75 (36.8)	<0.001*
Radiation toxicity (≥ grade 2)	2 (3.5)	6 (2.9)	0.826
Any additional surgery	8 (14.0)	172 (84.3)	<0.001*
Unplanned additional surgery	8 (14.0)	113 (55.4)	<0.001*
Number of total surgeries	1	3	<0.001*
Complications			
Infection	3 (5.3)	45 (22.1)	0.004*
Wound healing problems	19 (33.3)	90 (44.1)	0.144
Mastectomy skin flap necrosis	–	52 (25.5)	–
Overall	19 (33.3)	97 (47.5)	0.056
Length of follow-up (months)	24.6	29.9	0.037*
Total recurrences	3 (5.3)	16 (7.8)	0.507
Local recurrences	1 (1.8)	2 (1.0)	0.628
Distant recurrences	2 (3.5)	14 (6.9)	0.351

Data are presented as number, median [range], n (%), n/total (%), or median. †, indicates a numerical variable that was normally distributed. *, P<0.05. OBCS, oncoplastic breast-conserving surgery; BMI, body mass index; TE, tissue expander; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; DCIS, ductal carcinoma in situ; HER2, human epidermal growth factor receptor 2.

Table 2 PROs correlations

Correlation	OBCS	Mastectomy + reconstruction
Number of surgeries *vs.* post-op breast satisfaction	r=−0.070	r=0.088
Number of surgeries *vs.* outcome satisfaction	r=−0.086	r=0.087
Any complications *vs.* post-op breast satisfaction	r=−0.07	r=−0.21
Any complications *vs.* outcome satisfaction	r=0.10	r=0.17
Infection *vs.* post-op breast satisfaction	r=0.329	r=−0.236
Infection *vs.* satisfaction with outcome	r=0.273	r=0.0854
BMI *vs.* post-op satisfaction with breasts	r=−0.0332	r=−0.138
BMI *vs.* satisfaction with outcome	r=0.163	r=−0.116

PROs, patient-reported outcomes; OBCS, oncoplastic breast-conserving surgery; post-op, post-operative; r, correlation coefficient; BMI, body mass index.

disease than OBCS patients (31.9% *vs.* 29.8%) and when positive they tended to have more nodes involved; however, these differences were not statistically significant. Patients in the OBCS group had a median follow-up of 24.6 months compared to 29.9 months in the mastectomy group (P=0.04) (see *Table 1*).

In terms of additional treatment, significantly more OBCS patients received neoadjuvant endocrine therapy and adjuvant radiation therapy than mastectomy patients, but there were no statistical differences between rates of neoadjuvant chemotherapy, adjuvant chemotherapy, or adjuvant endocrine therapy. Nine of 57 (15.8%) OBCS patients received neoadjuvant endocrine therapy, compared to 14/204 (6.9%) mastectomy patients (P=0.04). Forty-five of 57 (78.9%) OBCS patients had adjuvant radiation therapy compared to 75/204 (36.8%) mastectomy patients (P<0.001). Of note, it could not be confirmed if the remaining 12 OBCS patients received adjuvant radiation therapy despite it being the standard of care, as they were lost to follow-up or transitioned their care to an outside hospital with inaccessible records. Contrastingly, although more mastectomy patients had neoadjuvant chemotherapy than OBCS patients (31.4% *vs.* 19.3%), this difference was not statistically significant (P=0.08). Similarly, more mastectomy patients underwent adjuvant chemotherapy than OBCS patients (42.6% *vs.* 29.8%), but this difference also was not statistically significant (P=0.08). Comparable proportions of patients from both groups had adjuvant endocrine therapy (68.4% of OBCS *vs.* 65.7% of mastectomy, P=0.70) with similar compliance rates (68.9% for OBCS *vs.* 64% for mastectomy) (see *Table 1*).

Type of surgery

The majority of the OBCS patients underwent an oncoplastic reduction with a contralateral symmetrizing reduction (53/57, 93.0%) using a wise incision pattern (50/57, 87.7%). Two patients (3.5%) had an oncoplastic mastopexy with a contralateral symmetrizing mastopexy, 1 patient (1.8%) had a bilateral oncoplastic reduction, and 1 patient (1.8%) had an oncoplastic mastopexy without an operation on the contralateral breast (see *Table 1*).

Most mastectomy patients had a skin-sparing mastectomy (149/204, 73.0%), with the remainder having nipple-sparing (55/204, 27.0%), and 29.4% of them were bilateral (60/204). All mastectomy patients underwent immediate reconstruction: 67.6% via tissue expander (TE) placement (138/204), 26.5% via autologous reconstruction with flaps (54/204), and 5.9% via implant-based reconstruction (12/204). Of those patients with an immediate TE, 81/138 (58.3%) had a delayed implant placement, 33/138 (23.9%) patients had delayed autologous reconstruction, 8/138 (5.8%) had the TE removed due to infection, 9/138 (6.5%) were awaiting the second stage of reconstruction at the time of this study, and 7/138 (5.1%) were lost-to-follow-up (see *Table 1*).

PROs

BREAST-Q questionnaires were completed post-operatively by 18 of the 57 patients in the OBCS group (31.6%) and 77 of the 204 patients (37.7%) in the mastectomy group (P=0.39). Twelve of the 57 patients (21.1%) in the OBCS group and 77 of the 204 patients (37.7%) in the mastectomy group completed both pre- and post-operative BREAST-Q (P=0.02) (see *Table 3*). Of the OBCS patients who filled out BREAST-Q, 7/18 identified as African-American, 3/18 as White, 5/18 as other, 2/18 declined, and 1/18 as Asian. In terms of ethnicity, 7/18 identified as Hispanic, 8 identified as non-Hispanic, and the rest declined. Of the mastectomy patients who filled out BREAST-Q, 26/77 identify as African-American, 37/77 as other, 4/77 as white, 2/77 as Asian, 1/77 as Indian, and 7/77 declined. In terms of ethnicity, 33/77 identified as Hispanic, 36/77 as non-Hispanic, and the rest declined.

In two of the four categories analyzed, "satisfaction with breasts" and "satisfaction with outcome", OBCS yielded better post-operative PROs than mastectomy. The median post-operative "satisfaction with breast" was 71.5/100 for OBCS and 58/100 for mastectomy (P=0.02). Similarly, the median "satisfaction with outcome" was 100/100 for OBCS and 75/100 for mastectomy (P=0.02). Of note, mastectomy patients had significantly lower "satisfaction with outcome" and "satisfaction with breast" than OBCS patients, regardless of whether they had adjuvant radiation or not. In the other two categories, "psychosocial well-being" and "sexual well-being", the difference in post-operative scores was not statistically significant (P=0.42 and P=0.78, respectively) (see *Table 3*).

In stratifying PROs by type of mastectomy, there was no difference in post-operative "satisfaction with breast", "satisfaction with outcome", "psychosocial well-being", or "sexual well-being" between nipple-sparing and skin-sparing mastectomies (P=0.99, P=0.88, P=0.85, P=0.40, respectively) (*Table 4*). Furthermore, when comparing OBCS to nipple-sparing mastectomies only, OBCS patients still reported

Table 3 Comparison of OBCS *vs.* mastectomy PROs

Variables	OBCS	Mastectomy + reconstruction	P value
Patients who filled out BREAST-Q	18 (31.6)	77 (37.7)	0.392
Patients who filled out BREAST-Q & received radiation	–	27 (13.2)	–
Patients who filled out BREAST-Q & did not receive radiation	–	45 (22.1)	–
Patients who filled out BREAST-Q pre-op and post-op	12 (21.1)	77 (37.7)	0.0188*
Last post-op survey time point			
1 month	4/18 (22.2)	0/77 (0.0)	
3 months	1/18 (5.6)	8/77 (10.4)	
6 months	2/18 (11.1)	14/77 (18.2)	
Last post-op survey time point			
1 year	4/18 (22.2)	30/77 (39.0)	
2 years	0/18 (0.0)	14/77 (18.2)	
3 years	2/18 (11.1)	6/77 (7.8)	
4 years	3/18 (16.7)	5/77 (6.5)	
5 years	2/18 (11.1)	0/77 (0.0)	
PRO: pre-op sexual well-being	49/100	54/100	0.836
PRO: pre-op psychosocial well-being	62/100	63/100	0.911
PRO: pre-op satisfaction with breasts	49/100	58/100	0.276
PRO: post-op sexual well-being			
All	52/100 [18]	53/100 [77]	0.783
With radiation	52/100 [18]	52/100 [27]	0.924
Without radiation	52/100 [18]	54/100 [45]	0.660
PRO: post-op psychosocial well-being			
All	72.5/100 [18]	68.5/100 [77]	0.415
With radiation	72.5/100 [18]	68/100 [27]	0.332
Without radiation	72.5/100 [18]	65/100 [45]	0.464
PRO: post-op satisfaction with breasts			
All	71.5/100 [18]	58/100 [77]	0.0165*
With radiation	71.5/100 [18]	55/100 [27]	0.0443*
Without radiation	71.5/100 [18]	59/100 [45]	0.0192*
PRO: satisfaction with outcome			
All	100/100 [11]	75/100 [77]	0.0197*
With radiation	100/100 [11]	75/100 [27]	0.0182*
Without radiation	100/100 [11]	71/100 [45]	0.0461*
Black post-op satisfaction with breasts†	84/100	56.5/100	0.199
Black satisfaction with outcome†	88.5/100	67/100	0.108
Hispanic post-op satisfaction with breasts†	59/100	58/100	0.533
Hispanic satisfaction with outcome	100/100	75/100	0.421

Data are presented as n (%), n/total (%), or median score out of 100 possible points [n]. †, indicates a numerical variable that was normally distributed. *, P<0.05. OBCS, oncoplastic breast-conserving surgery; PROs, patient-reported outcomes; pre-op, pre-operative; post-op, post-operative.

Table 4 PROs based on type of mastectomy

Variables	Skin-sparing mastectomies	Nipple-sparing mastectomies	P value
Number of patients who filled out BREAST-Q	63	14	
Post-op satisfaction with breasts	58/100	58/100	0.994
Satisfaction with outcome	75/100	67/100	0.882
Post-op psychosocial well-being	66/100	77.5/100	0.848
Post-op sexual well-being	53/100	65/100	0.398

Data are presented as number or median score out of 100 possible points. PROs, patient-reported outcomes; post-op, post-operative.

Table 5 OBCS *vs.* nipple-sparing mastectomy PROs

Variables	OBCS	Only nipple-sparing mastectomies	P value
Number of patients who filled out BREAST-Q	18	14	
Post-op satisfaction with breasts	71.5/100	58/100	0.077
Satisfaction with outcome	100/100	67/100	0.055
Post-op psychosocial well-being	72.5/100	77.5/100	0.755
Post-op sexual well-being	52/100	65/100	0.427

Data are presented as number or median score out of 100 possible points. OBCS, oncoplastic breast-conserving surgery; PROs, patient-reported outcomes; post-op, post-operative.

Table 6 PROs and outcomes based on type of reconstruction

Variables	Mastectomy + flap	Mastectomy + implant	P value
Number of patients	94	93	
Number of patients who underwent unplanned surgeries	62 (66.0)	41 (44.1)	0.002*
Number of patients who experienced a complication	52 (55.3)	40 (43.0)	0.0192*
Number of patients who filled out BREAST-Q	42	32	0.059
Post-op satisfaction with breasts	59/100	58.5/100	0.598
Satisfaction with outcome	75/100	71/100	0.996
Post-op psychosocial well-being	76/100	63/100	0.140
Post-op sexual well-being	60/100	53/100	0.638

Data are presented as number, n (%), or median score out of 100 possible points. *, P<0.05. PROs, patient-reported outcomes; post-op, post-operative.

higher post-operative "satisfaction with breasts" (71.5/100 *vs.* 58/100) and "satisfaction with outcome" (100/100 *vs.* 67/100), although these differences were not statistically significant (P=0.08 and P=0.06, respectively) (*Table 5*). Lastly, mastectomy patients who received autologous reconstruction with flaps *vs.* those who received implant-based reconstruction (whether immediately or delayed) did not report any statistically significant difference in satisfaction in any of the four categories analyzed (P=0.60, P>0.99, P=0.14, P=0.64, respectively) (*Table 6*).

Additionally, African American patients who underwent OBCS reported better "satisfaction with breast" compared to those who received a mastectomy (84/100 *vs.* 56.5/100), but this difference was not statistically significant (P=0.20). Hispanic patients, on the other hand, did not demonstrate any significant difference in "satisfaction with breast"

Table 7 Comparison of OBCS PROs before and after surgery

PRO category	Pre-operative	Post-operative	P value
Number	12	12	
Sexual well-being	49/100	84/100	0.721
Psychosocial well-being	62/100	85/100	0.518
Satisfaction with breasts	49/100	86/100	0.0588

Data are presented as number or median score out of 100 possible points. OBCS, oncoplastic breast-conserving surgery; PROs, patient-reported outcomes.

Table 8 Comparison of mastectomy PROs before and after surgery

PRO category	Pre-operative	Post-operative	P value
Sexual well-being	54/100	53/100	0.605
Psychosocial well-being	63/100	68.5/100	0.987
Satisfaction with breasts	58/100	58/100	0.974

Data are presented as median score out of 100 possible points. PROs, patient-reported outcomes.

between the two surgeries (59/100 for OBCS *vs.* 58/100 for mastectomy, P=0.53). Additionally, both African American and Hispanic patients reported better "satisfaction with outcome" post-OBCS than post-mastectomy, but these differences were not statistically significant (African Americans: 88.5/100 *vs.* 67/100, P=0.11; Hispanics: 100/100 *vs.* 75/100, P=0.42) (*Table 3*).

Furthermore, in comparing the pre- and post-operative PROs, "sexual well-being", "psychosocial wellbeing", and "satisfaction with breast" were higher post-OBCS than pre-OBCS, although none of these differences were statistically significant (P=0.72, P=0.52, and P=0.06, respectively) (*Table 7*); whereas these same three PROs were unchanged pre- and post-mastectomy (P=0.61, P=0.99, and P=0.97, respectively) (*Table 8*).

Oncologic safety

Positive margins after surgery were identified in four of 57 patients (7.1%) in the OBCS group compared to ten of 204 (4.9%) patients in the mastectomy group (P=0.53) (*Table 1*). These patients underwent different treatment modalities based on their preference and pathology report. All four patients in the OBCS group with positive margins underwent mastectomy (two nipple-sparing and two radical modified mastectomies) (7.0%) with reconstruction and of those, two received post-mastectomy radiation. Furthermore, of the ten out of 204 (4.9%) patients in the mastectomy group who had positive margins, seven received post-mastectomy radiation for local control, five received adjuvant chemotherapy, two underwent re-excision, and one underwent axillary lymph node biopsy.

Among the 15 patients with DCIS who underwent OBCS, only one had positive margins (6.7%) treated with a mastectomy and none of them experienced a local or distant recurrence. Of the 11 OBCS patients (19.3%) had neoadjuvant chemotherapy, one had positive margins (9.1%) treated with a mastectomy and another one had a local recurrence in the lumpectomy site treated with a mastectomy and is now in remission.

Furthermore, the recurrence rate in the OBCS group was 5.3% while it was 7.8% in the mastectomy group (P=0.51). Of note, there was one local recurrence in the OBCS group and two local recurrences in the mastectomy group, making the local recurrence rates 1.8% and 1.0% respectively (P=0.63). There were two distant recurrences in the OBCS group and fourteen distant recurrences in the mastectomy group, making the distant recurrence rates 3.5% and 6.9% respectively (P=0.35) (*Table 1*).

Finally, patients with positive margins after surgery underwent different treatment modalities based on their preference and pathology report. All four patients in the OBCS group with positive margins underwent mastectomy (7.1%) and of those, two received post-mastectomy radiation. Furthermore, of the 10 out of 204 (4.9%) patients in the mastectomy group who had positive margins, seven received post-mastectomy radiation for local control, five received adjuvant chemotherapy, two underwent re-excision, and one underwent axillary lymph node biopsy.

Complications

Complications were defined as the presence of infection, difficulty in wound healing, and/or mastectomy skin flap necrosis. OBCS patients had a significantly lower rate of infection as compared to mastectomy patients (5.3% *vs.* 22.1%, P=0.004) as well as a lower rate of overall complications, although the difference was not statistically significant (33.3% *vs.* 47.5%, P=0.06) (*Table 1*). There were no correlations between overall complications and post-operative "satisfaction with breast" (OBCS: r=−0.07; mastectomy: r=−0.21) or "satisfaction with outcome" (OBCS: r=0.10; mastectomy: r=0.17) in either group. Similarly, there were no correlations between infection and post-operative "satisfaction with breast" (OBCS: r=0.33; mastectomy: r=−0.24) or "satisfaction with outcome" (OBCS: r=0.27; mastectomy: r=0.09) in either group (*Table 2*).

Moreover, OBCS patients underwent fewer additional surgeries as compared to mastectomy patients (14.0% *vs.* 84.3%, P<0.001). The median number of total surgeries was one for the OBCS group and three for the mastectomy group (P<0.001). Furthermore, mastectomy patients had significantly more unplanned surgeries compared to OBCS (P<0.001). There were 280 total unplanned surgeries in the mastectomy group, with a median of 2 (range, 1–8) unplanned operations per patient, and thirteen total unplanned surgeries in the OBCS group, with a median of 1 (range, 1–4) unplanned operation per patient (*Table 1*). There were no correlations between number of surgeries and "satisfaction with breast" or "satisfaction with outcome" in either group (*Table 2*). In addition, patients undergoing autologous reconstruction had more unplanned surgeries compared to implant-based reconstruction (66.0% *vs.* 44.1% respectively, P=0.002) and a higher rate of complications (55.3% *vs.* 43.0% respectively, P=0.02) (*Table 6*).

Discussion

Women's psychosocial well-being is significantly impacted by the diagnosis and treatment of breast cancer. In addition to fears about their health and survival, cancer patients' perceptions of their bodies, sexuality, and self-esteem have been shown to be negatively impacted by oncologic resection of their disease, which in turn affects their marriage, family and social life (28). However, these fears can be alleviated not only by encouraging the patient to participate in the decision-making process, but also by assisting them in achieving balance on all fronts—physical, emotional, spiritual, and social (29). To achieve this balance, it is imperative to focus on patients' QOL while also aiming for better cosmetic outcomes, since psychological recovery has been linked to cosmetic perception (30). OBCS, a non-inferior surgical management, helps to bridge a few of these concerns by providing better cosmesis and overall improved patient satisfaction and QOL (6-8,21-24).

In our study, we used BREAST-Q, a validated PRO questionnaire that includes multiple patient satisfaction and health-related QOL domains, to assess patient perception of results following breast surgery (26). This questionnaire encompasses four independent modules for breast surgery: breast reduction, augmentation, reconstruction, and mastectomy (26,31,32). Thus, when used in clinical practice, it can provide evidence-based data on QOL and patient satisfaction (33).

Multiple studies have been conducted comparing OBCS and mastectomy using this validated BREAST-Q instrument; however, there is a lack of literature highlighting the potential impact of race, ethnicity, BMI, and socioeconomic status on both surgical and PROs of OBCS. To the best of our knowledge, most OBCS studies thus far have not reported the race or ethnicity of their patients, nor taken those factors into account in analyzing the results [one exception is found in a recent study which compared PROs of OBCS to those of BCS and included race and BMI (34)]. Thus, in our study we analyzed these variables in conjunction with pre- and post-operative PROs and surgical outcomes to compare OBCS and mastectomy with reconstruction.

Prior literature has demonstrated that patients with higher BMIs have poor patient satisfaction after BCS and an increased rate of complications after OBCS requiring additional surgeries (14,15,35). Contrastingly, in our study the median BMIs in the OBCS and mastectomy group were 32.4 and 29 kg/m^2 respectively, and despite significantly higher BMI in the OBCS group than in the mastectomy group (P<0.001), OBCS patients were still more satisfied and experienced fewer unplanned surgeries. Moreover, 42% of the patients in OBCS group and 40.7% patients in mastectomy group were uninsured or on Medicaid, demonstrating the low socioeconomic status of our patient population. Of note, when stratified by race, either by

Hispanic patients or African American patients, there was no longer statistically significant differences between the OBCS and mastectomy groups in terms of PROs. This result is most likely a result of our relatively small sample size of patients with BREAST-Q forms overall, making the numbers of patients in these subgroups too small. Our findings and prior study (22) found that patients undergoing OBCS had better patient satisfaction and lower complication rates, but also had earlier clinical stages of disease than mastectomy patients. However, Bazzarelli *et al.* (21) found that OBCS patients still had better PROs than mastectomy patients despite having more advanced stages of disease.

Although our study had a shorter duration of follow-up in the OBCS group as compared to the mastectomy group (24.6 *vs.* 29.9 months, P=0.04), prior literature shows that even with long-term follow-up, no significant difference between OBCS and mastectomy recurrence rates emerges (20). In addition, the oncologic outcomes of the OBCS group in our study were comparable to those reported in previous literature (although this end point was significantly limited by our small cohort size and relatively short follow-up period). A large meta-analysis of over 8,000 patients comparing OBCS to traditional BCT found a positive margin rate of 12% after OBCS, a conversion-to-mastectomy rate of 6.5%, and a local recurrence rate of 4% over 37 months of follow-up with an average tumor size of 2.7 cm (36). Our data showed a positive margin rate of 7.1%, a conversion-to-mastectomy rate of 7.0%, and a local recurrence rate of 1.8% over 24.6 months with a median tumor size of 2.3 cm.

In focusing on OBCS patients with DCIS and those who received neoadjuvant chemotherapy, two less common subgroups in the OBCS literature, their recurrence and positive margin rates were similar to those of the cohort overall. The DCIS subgroup had a 6.7% positive margin rate and a 0% recurrence rate. The neoadjuvant chemotherapy group had a positive margin rate of 9.1% and a recurrence rate of 9.1%.

The clinical utility of BREAST-Q in our patient population yielded better results for OBCS than mastectomy, with patients scoring higher in terms of "satisfaction with breasts" and "satisfaction with outcome", but similar scores were observed for post-operative "psychosocial well-being" and "sexual well-being". Multiple studies have found similarly high levels of patient satisfaction after OBCS, but in different domains (21-23). However, none of these studies determined pre-operative satisfaction and well-being; whereas in our study, we first determined that there were no differences in any of the PRO measures between the two groups pre-operatively. As a result, we were able to demonstrate that the difference in post-operative outcomes between OBCS and mastectomy was not due to mastectomy decreasing breast satisfaction, but rather to OBCS improving patients' satisfaction with their breasts.

Additionally, a presumed contributor to patient dissatisfaction following mastectomy is the loss of the nipple (37-39). Our data potentially supports this hypothesis. On one hand, when comparing only nipple-sparing mastectomies to OBCS, there is no longer any statistically significant difference between post-operative satisfaction with breasts nor satisfaction with outcome between the groups (see *Table 5*). However, this could be due to the relatively small sample size of patients who underwent nipple-sparing mastectomies and filled out BREAST-Q (n=14) considering that the type of mastectomy procedure had no impact on PROs in our cohort; those who had non-nipple-sparing procedures reported the same levels of satisfaction as those who had nipple-sparing surgeries in all four PRO domains (see *Table 4*). This outcome is contrary to most studies which found nipple-sparing mastectomies to result in higher patient satisfaction than non-nipple-sparing procedures (40-46). Similarly, Char *et al.* (46) and Yueh *et al.* (47) found that autologous/flap-based reconstruction resulted in significantly higher satisfaction than implant-based reconstruction, and yet we found there no be no differences in PROs based on the type of reconstruction.

Our study demonstrates that mastectomy patients experienced significantly higher rates of infection as well as significantly more surgeries. Even when controlling for the fact that many mastectomy patients had a planned 2-stage reconstruction with a TE and subsequent implant exchange or autologous reconstruction, these patients underwent more unplanned surgical procedures than OBCS patients did, primarily to address the plethora of complications they experienced such as infection, wound healing problems, and mastectomy skin flap necrosis. Brown *et al.* (35) also evaluated the need for secondary surgeries following OBCS and found that 21% of patients in their cohort required unplanned returns to the operating room. Chand *et al.* (23) found that 29.3% of OBCS patients (mammaplasty specifically) underwent additional surgeries. These rates are slightly higher than in our study where 14% of OBCS patients had unplanned surgeries following the initial procedure. Chand *et al.* (23) also found that 34.8% of mastectomy with reconstruction patients (latissimus dorsi miniflap) underwent additional surgical procedures, significantly lower than our group in which 55.4% underwent unplanned additional surgeries.

Although prior literature has shown that patient satisfaction is negatively impacted by surgical complications (48), we did not find any correlations between complications and PROs in our study. However, higher rates of infection and more surgery in the mastectomy group could explain their worse PROs. In comparison to the existing literature, our study had much higher overall complication rates for both OBCS and mastectomy with reconstruction patients. Prior literature showed complication rates of 8.9% for OBCS (49) and 10–35% for mastectomy (with and without reconstruction) (50,51), as opposed to 33.3% and 47.5% in our study, respectively. This disparity between our study and established complication rates could be attributed to our high BMI, high rate of comorbidities (particularly diabetes and smoking), and possibly compliance due to lower socioeconomic status.

Our study has several limitations. Firstly, the relatively small number of patients studied overall, in addition to the even smaller amount who filled out all the BREAST-Q questionnaires (31.6% and 37.7% for OBCS and mastectomy with reconstruction, respectively), reduced the power of our conclusions. If we had been able to collect more surveys, we also could have also stratified the results by stage of disease. The coronavirus disease 2019 (COVID-19) pandemic was a significant contributor to difficulty acquiring these surveys, as it increased loss to follow-up and resulted in more virtual visits, during which BREAST-Q forms were not collected. Furthermore, comparing surveys filled out at different time points post-operatively may have influenced PROs, as patients may have a better perception further away from the operation itself. If we had been able to collect more surveys, we could have stratified comparisons by different time points. Secondly, there were many significant differences between the groups at baseline, namely different ages, BMIs, and clinical stages of disease, that were not controlled for in our analyses. In particular, the higher average BMI in the OBCS group compromised the strength of our conclusions as higher BMIs can directly impact patient satisfaction with a breast reduction. The difference in age is also significant, as the patients in the mastectomy group were younger and younger patients can have higher aesthetic standards, potentially resulting in worse PROs post-operatively. Lastly, the relatively short follow-up of both groups made it difficult to draw dramatic conclusions about recurrence rates. Thus, we plan on following this group longitudinally to collect more data and report on it in the future in order to bolster our findings. By following more patients for longer, such research would confirm the oncologic safety of OBCS in patients belonging to ethnic and racial minority groups and further strengthen our knowledge of how certain drawbacks to both OBCS and mastectomy affect these patients' QOL.

Conclusions

In our study, OBCS yielded better PROs than mastectomy while maintaining oncologic safety and resulting in fewer surgeries and complications. These excellent outcomes in a majority non-Caucasian cohort support the utilization of OBCS for patients of color. However, larger studies evaluating PROs in diverse and underserved populations are needed to reinforce these conclusions.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-403/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-403/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Albert Einstein College of Medicine (No. FWA #00023382) and individual consent for this retrospective analysis was waived.

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Original Article

Short-term efficacy and safety of neoadjuvant pyrotinib plus taxanes for early HER2-positive breast cancer: a single-arm exploratory phase II trial

Guolin Ye[1#], Peixian Chen[1#], Xiangwei Liu[1#], Tiancheng He[1#], Xavier Pivot[2], Ruilin Pan[1], Dan Zhou[1], Lewei Zhu[1], Kun Zhang[1], Wei Li[1], Shuqing Yang[1], Jiawei Lin[1], Gengxi Cai[1], Huiqi Huang[1]

[1]Department of Breast Surgery, The First People's Hospital of Foshan, Foshan, China; [2]Medical Oncology Department, Institute of Cancerology Strasbourg Europe (ICANS), Strasbourg, France

Contributions: (I) Conception and design: G Ye; (II) Administrative support: G Ye; (III) Provision of study materials or patients: X Liu, R Pan, D Zhou, L Zhu; (IV) Collection and assembly of data: P Chen, T He, K Zhang, W Li, S Yang, J Lin, G Cai, H Huang; (V) Data analysis and interpretation: P Chen, T He; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Guolin Ye, MD. Department of Breast Surgery, The First People's Hospital of Foshan, 81 Lingnan Avenue North, Foshan 528000, China. Email: yglin@fsyyy.com.

Background: The effectiveness and safety of pyrotinib have been substantiated in human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer (BC). However, the role of pyrotinib as a single HER2 blockade in neoadjuvant setting among BC patients has not been studied. The objective of this study was to evaluate the efficacy and tolerability of pyrotinib plus taxanes as a novel neoadjuvant regimen in patients with HER2-positive early or locally advanced BC.

Methods: In this single-arm exploratory phase II trial, patients with treatment-naïve HER2-positive BC (stage IIA–IIIC) received pyrotinib 400 mg once daily and taxanes [docetaxel 75 mg/m^2 or nanoparticle albumin-bound (nab)-paclitaxel 260 mg/m^2 every 3 weeks, or paclitaxel 80 mg/m^2 weekly] for a total of four 21-day cycles before surgery. Efficacy assessment was based on pathological and clinical measurements. The primary endpoint of this study was the total pathological complete response (tpCR) rate. The secondary endpoints included breast pCR (bpCR) rate, investigator-assessed objective response rate (ORR) and adverse events (AEs) profiles.

Results: From 1 September 2021 to 30 December 2022, a total of 31 patients were enrolled. One patient was withdrawn due to unbearable skin rash after the second cycle of neoadjuvant therapy. The majority of the intention-to-treat (ITT) population was premenopausal (54.8%), had large tumors (90.3%) and metastatic nodes (58.1%) at diagnosis and hormone-receptor positive tumors (64.5%). Most participants used nab-paclitaxel (74.2%) and received mastectomy (67.7%) after neoadjuvant treatment. The tpCR and bpCR rates were 48.4% [95% confidence interval (CI): 30.8–66%] and 51.6% (95% CI: 34–69.2%), respectively. Grade ≥3 treatment-related AEs were observed in 16.1% (5/31) of the ITT population, including diarrhea (n=2, 6.5%), hand and foot numbness (n=1, 3.2%), loss of appetite (n=1, 3.2%), and skin rash (n=1, 3.2%). AE related dose reduction or pyrotinib interruption was not required.

Conclusions: In female patients with HER2-positive non-metastatic BC, neoadjuvant pyrotinib monotherapy plus taxanes appears to show promising clinical benefit and controllable AEs [Chinese Clinical Trial Registry (ChiCTR2100050870)]. The long-term efficacy and safety of this regime warrant further verification.

Keywords: Pyrotinib; chemotherapy; neoadjuvant therapy; human epidermal growth factor receptor 2 (HER2); breast cancer (BC)

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Introduction

Overexpression and/or amplification of human epidermal growth factor receptor 2 (HER2) is present in around 22% of early breast cancers (BC), and is associated with aggressive disease and poor prognosis (1,2). According to the National Comprehensive Cancer Network (NCCN) (3) and Chinese Society of Clinical Oncology (CSCO) (4) guidelines, neoadjuvant therapy is recommended for patients with staged II–III HER2-positive (HER2$^+$) early or locally advanced BC (5,6). In HER2-positive breast tumors, pathological complete response (pCR) achieved by neoadjuvant regimen has been found to be correlated with improved survival outcomes, suggesting that it may serve as an early surrogate marker of clinical benefit (7-9).

HER2-targeted therapy has dramatically improved outcomes in patients with HER2$^+$ BC and therefore constituted a standard of care. Trastuzumab (Herceptin; Roche, Basel, Switzerland), a recombinant humanized monoclonal antibody, was the first HER2 blocker and remains the cornerstone of therapy for all HER2$^+$ BCs. Despite the efficacy of trastuzumab, drug resistance and recurrence/metastasis may occur in some patients, enhancing the need for new regimens. Small-molecule tyrosine kinase inhibitors (TKIs) have been found to suppress the growth of HER2$^+$ BC cells through different signaling pathways, therefore representing a promising HER2 blockade overcoming drug resistance.

Pyrotinib is a new irreversible inhibitor of epidermal growth factor receptor (EGFR), HER2, and HER4. In the metastatic setting, a recent meta-analysis revealed that pyrotinib-containing regimens demonstrated considerable tumor response, survival outcome and manageable toxicity in any line of treatment for HER2$^+$ metastatic BC (10,11). Recently, the final analysis of the phase II PANDORA trial (12) suggested that pyrotinib monotherapy plus docetaxel given in the first-line treatment was highly active with an objective response rate (ORR) of 79.7% [95% confidence interval (CI): 70.8–88.6%] among patients with HER2$^+$ advanced BC. In a neoadjuvant setting, different pyrotinib-based chemotherapeutic regimes, mostly involving a taxane and pyrotinib plus trastuzumab, have been evaluated in some phase 2 studies which yielded high response rates (13-15). In addition, the phase 3 PHEDRA trial (16) demonstrated that neoadjuvant pyrotinib, trastuzumab, and docetaxel significantly improved the pCR rate compared with placebo, trastuzumab, and docetaxel, supporting the accelerated approval of pyrotinib for HER2$^+$ BC in the neoadjuvant setting by China Food and Drug Administration. Nonetheless, the effect of combination of pyrotinib plus a taxane was assessed alongside with trastuzumab in the abovementioned studies. For patients with contraindications to trastuzumab or developing countries where macro-molecule monoclonal antibodies are inaccessible, evidence supporting the use of pyrotinib monotherapy plus taxanes as neoadjuvant treatment is lacking. This preliminary study aimed to explore the efficacy and safety of pyrotinib as a single HER2 blocker plus taxanes as preoperative systemic treatment for patients with early or locally advanced HER2$^+$ BC. We present this article in accordance with the TREND reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-38/rc).

Highlight box

Key findings

- Neoadjuvant pyrotinib monotherapy plus chemotherapy shows promising clinical benefit in patients with human epidermal growth factor receptor 2-positive (HER2$^+$) non-metastatic breast cancer (BC).

What is known and what is new?

- Pyrotinib-based therapy is effective for HER2$^+$ BC at all stages.
- This study supports the use of this new neoadjuvant regimen for early or locally advanced HER2$^+$ BC.

What is the implication, and what should change now?

- Our regime might be an alternative option for patients who have contraindications for large-molecule monoclonal antibodies or when these drugs are not available. The efficacy of pyrotinib-based neoadjuvant therapy and the optimal combination require further verification.

Methods

Study design

This single-arm, open-label phase 2 trial was implemented at The First People's Hospital of Foshan in Guangdong, China during 1 September 2021 to 30 December 2022. The sample size of this trial was determined by the willingness of patients with early or locally advanced HER2-positive BC at The First People's Hospital of Foshan during the study period. The trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (as revised in 2013). The Ethics Committee at The First People's Hospital of Foshan approved the protocol (approval number: 2021[113-1]), and all participants provided written informed consent. This study is registered in the Chinese Clinical Trial Registry under ChiCTR2100050870.

Participants

The key inclusion criteria were as follows: (I) patients' age between 18 and 70 years at initial treatment; (II) patients with clinically staged II–III BC based on the criteria of the American Joint Committee on Cancer (AJCC); (III) HER2 immunohistochemical staining of 3+ and/or amplification of *HER2* gene copy number by fluorescence *in situ* hybridization; (IV) Eastern Cooperative Oncology Group (ECOG) score of 0–1; (V) 1 or more measurable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (17); (VI) adequate bone marrow, hepatic, renal, and cardiac functions (left ventricular ejection fraction ≥55%).

The key exclusion criteria were as follows: (I) bilateral BC; (II) those with advanced BC (stage IV); (III) prior systemic therapy or radiotherapy for any malignant tumor (except for cured cervical carcinoma *in situ* and basal cell carcinoma); (IV) prior anticancer therapy in other clinical trials or pregnancy or lactation.

Interventions

Oral pyrotinib was administered at a dose of 400 mg once daily beginning on day 1 of taxanes and continuing through until day 28 from the final cycle of taxanes. A total of 4 cycles of docetaxel (75 mg/m^2, escalating, if well tolerated, to 100 mg/m^2) or nanoparticle albumin-bound (nab)-paclitaxel (260 mg/m^2) were given intravenously every 3 weeks or 4 cycles of paclitaxel (80 mg/m^2) given on days 1, 8, and 15 of a 21-day cycle. The choice of taxanes was determined by the treating physician and the patient. In total, patients received 4 cycles of neoadjuvant therapy of taxanes plus pyrotinib before surgery. After completion of neoadjuvant treatment, eligible patients underwent surgery and adjuvant fluorouracil/epirubicin/cyclophosphamide (FEC) therapy (3 cycles of fluorouracil 600 mg/m^2 intravenously, epirubicin 90 mg/m^2 intravenously, and cyclophosphamide 600 mg/m^2 intravenously every 3 weeks). Thereafter, adjuvant trastuzumab was administered every 3 weeks for 1 year. Radiotherapy and standard hormone treatment for patients with positive estrogen receptor (ER) were prescribed if necessary.

Adjustment of pyrotinib dosage was adverse events (AEs)-oriented, which corresponded to a gradient of 400, 320, and 240 mg. To guarantee the drug intensity of the treatment, the maximal cumulative interruption time of pyrotinib allowed in each cycle was 14 days. Since diarrhea was expected with pyrotinib, primary prophylaxis with loperamide (4 mg) was given at the beginning of the first dose of therapy, and supplemented with 2 mg after each loose stool thereafter.

Tumor response (clinical breast examination) was assessed at every cycle. Patients underwent physical examination and ultrasound every cycle for efficacy evaluation before breast surgery. Magnetic resonance imaging (MRI) was performed at baseline and before surgery. Surgical breast specimens were assessed for pCR by the pathological department and no central review were planned.

Study endpoints and assessments

Efficacy assessment was based on pathological and clinical measurements. The primary endpoint was the total pCR (tpCR) rate, defined as absence of microscopic invasive cancer cells in both the breast and axillary lymph nodes, whereas ductal carcinoma *in situ* was allowed (ypT0/Tis ypN0). The secondary endpoints included: the breast pCR (bpCR) response rate defined as absence of microscopic invasive cancer cells in the breast (ypT0/Tis); the Miller-Payne (MP) system (18) was applied for analysis of histological response to study treatment; the investigator-assessed ORR which referred to the proportion of patients with complete response (CR) or partial response (PR) defined by The RECIST 1.1 criteria after completion of the neoadjuvant therapy; survival outcomes. The safety profiles were reported based on AEs graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae_4_with_lay_terms.pdf). A sensitivity analysis was planned for efficacy in the per protocol set.

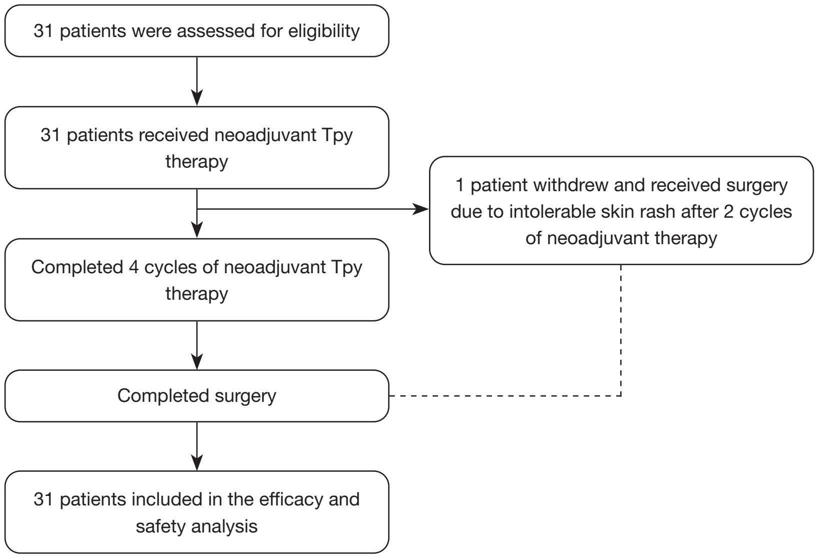

Figure 1 Study flowchart. Tpy, taxanes plus pyrotinib.

Statistical analysis

The analysis population of this study consisted of participants in the intention-to-treat (ITT) population including all patients who received at least one dose of the study treatment. A sensitivity analysis was planned for efficacy in the per protocol set. The results of this study were analyzed using descriptive statistical methods. The continuous data were presented as means ± standard deviation or medians [range], and the categorical data were presented as frequency, percentage, and 95% CIs. The software SPSS 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. The two-sided P value <0.05 was considered statistically significant.

Results

Patient characteristics

From 1 September 2021 to 30 December 2022, a total of 31 patients were enrolled (*Figure 1*); 30 patients completed the entire neoadjuvant therapy. After 2 cycles of neoadjuvant therapy, one patient withdrew from the trial due to intolerable skin rash, and discontinued the drugs in cycle 3. After surgery, the patient received a pertuzumab-trastuzumab containing regimen.

The baseline characteristics of the ITT population are shown in *Table 1*. The median age was 53 years (range, 38–65 years) with predominantly premenopausal patients (n=17, 54.8%). The proportion of patients with T2–T4 disease was 90.3% (28/31) and the proportion of patients with N1–N3 disease was 58.1% (18/31). Of the 31 cases, 20 (64.5%) showed positive ER and/or progesterone receptor (PR).

Most participants used nab-paclitaxel (23/31, 74.2%) in the neoadjuvant setting and had a mastectomy (21/31, 67.7%) after preoperative systemic treatment. No patient was given a weekly paclitaxel regimen.

Efficacy

The tpCR rate after 4-cycle neoadjuvant therapy was 48.4% (95% CI: 30.8–66%) (15/31) (*Table 2*). Among them 8 of 20 (40.0%; 95% CI: 18.5–61.5%) tumors had positive hormone receptor (HR) and 7 of 11 (63.6%; 95% CI: 35.2–92%) tumors had negative HR (P>0.99). Postoperative pathological measurement showed that 51.6% (95% CI: 34–69.2%) (16/31) achieved bpCR. There were 2 (6.5%) and 12 (38.7%) cases with MP G1–2 and G3–4, respectively. The patient who dropped out of the trial after 2 cycles of preoperative therapy received breast conserving surgery and the pathological evaluation was MP G3. Pathological response assessment was failed in one non-pCR case because the patient underwent biopsy in another hospital.

Regarding clinical response to neoadjuvant therapy based on MRI, 23 of 31 patients (74.2%) had complete imaging results at baseline and 4 cycles (*Table 2*). There were 4 patients (17.4%) who presented with stable disease (SD) and no tumor progression occurred.

All 31 patients (100%) experienced treatment-related

Table 1 Clinical and pathological characteristics of the ITT patients at baseline

Characteristics	ITT population (n=31)
Age (years), median [range]	53 [38–65]
Menopausal status, n (%)	
Premenopausal	17 (54.8)
Postmenopausal	14 (45.2)
Clinical tumor stage, n (%)	
T1	3 (9.7)
T2	20 (64.5)
T3	5 (16.1)
T4	3 (9.7)
Clinical lymph node status, n (%)	
N0	10 (32.3)
N1	14 (45.2)
N2	0
N3	4 (12.9)
Nx	3 (9.7)
Clinical stage, n (%)	
II	20 (64.5)
III	11 (35.5)
ECOG performance status, n (%)	
0	31 (100.0)
Hormone receptor status, n (%)	
ER and/or PR positive	20 (64.5)
ER and PR negative	11 (35.5)
Histological grading, n (%)	
I	1 (3.2)
II	22 (71.0)
III	7 (22.6)
Unknown	1 (3.2)
Ki-67 level, n (%)	
<20%	9 (29.0)
≥20%	21 (67.7)
Unknown	1 (3.2)
Neoadjuvant regimen, n (%)	
Docetaxel plus pyrotinib	8 (25.8)
Nab-paclitaxel plus pyrotinib	23 (74.2)
Surgery, n (%)	
Mastectomy	21 (67.7)
Breast conserving surgery	10 (32.3)

ITT, intention-to-treat; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor; nab-paclitaxel, nanoparticle albumin-bound paclitaxel.

AEs, the majority of which were grade 1–2. A large number of AEs were due to the taxane. AEs with an incidence of ≥10% are listed in *Table 3*. The most frequent AEs were diarrhea (100%), fatigue (64.5%), loss of appetite (61.3%), abdominal pain (54.8%), and hand and foot numbness (54.8%). Grade ≥3 AEs included diarrhea (n=2, 6.5%), hand and foot numbness (n=1, 3.2%), loss of appetite (n=1, 3.2%), and skin rash (n=1, 3.2%). All patients with grade 3 AEs recovered to grade 2 or below before the following cycle of therapy; no dose adjustment or treatment delayed was required. Only one patient experienced uncontrollable skin rash and left the trial after completion of the second cycle of neoadjuvant therapy.

Discussion

This study investigated the efficacy and safety of neoadjuvant pyrotinib monotherapy plus taxanes in patients early or locally advanced HER2+ BC. The data showed encouraging tpCR and bpCR rates of 48.4% (95% CI: 30.8–66%) and 51.6% (95% CI: 34–69.2%) (16/31), respectively.

The HER2-targeted drugs are composed of large-molecule monoclonal antibodies (including trastuzumab and pertuzumab) and small-molecule TKIs (such as lapatinib, neratinib and pyrotinib). In some randomized controlled trials (NeoALTTO, Neosphere, PEONY, and PHEDRA), neoadjuvant trastuzumab monotherapy plus taxanes exhibited a tpCR rate of 21.5–27.6% (19-22). In the subgroup of patients receiving pertuzumab plus docetaxel in the Neosphere trial (20), the tpCR rate was 29%.

In contrast to anti-HER2 monoclonal antibodies, TKIs compete with tyrosine kinase coupling with the HER2 intracellular kinase domain and block downstream signaling pathways. TKIs have the advantages of blocking multiple targets, oral administration, and decreased cardiac toxicity (23). The NeoALTTO trial (19) showed that the pCR rate of lapatinib monotherapy arm was 24.7% (95% CI: 18.1–32.3%). In the NSABP FB-7 trial, the numerical pCR rate in the single-targeted therapy with neratinib arm was 33% (24). In studies assessing lapatinib/neratinib-containing neoadjuvant therapies, the pCR rates of the TKI groups were 24–53.2% (19,25,26). In these studies, the pCR rates were comparable between the lapatinib/neratinib group and the trastuzumab group. Furthermore, addition of a TKI into a trastuzumab-based regime in a neoadjuvant setting has resulted in a favorable pCR rate of 51–62% with tolerable toxicity (24,27,28).

Table 2 Pathological and clinical response in the ITT population, and by HR status at baseline

Variables	ITT (n=31)		HR positive (n=20)		HR negative (n=11)	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
tpCR	15	48.4 (30.8–66.0)	8	40.0 (18.5–61.5)	7	63.6 (35.2–92.0)
bpCR	16	51.6 (34.0–69.2)	8	40.0 (18.5–61.5)	8	72.7 (46.4–99.0)
MP grading[#]						
1 or 2	2	6.5 (–2.2 to 15.2)	2	10.0 (–3.1 to 23.1)	0	–
3 or 4	12	38.7 (21.6–55.8)	9	45.0 (23.2–66.8)	3	27.3 (0.97–53.6)
ORR[&]	19	82.6 (81.9–83.3)	–	–	–	–
CR[&]	5	21.7 (21.0–22.4)	–	–	–	–
PR[&]	14	60.9 (41.0–80.8)	–	–	–	–

[#], MP grading was not given in one HR positive patient due to absence of biopsied sample for assessment; [&], ORR, CR and PR rates were based on 23 patients who had complete MRI data for assessment. ITT, intention-to-treat; HR, hormone receptor; CI, confidence interval; tpCR, total pathological complete response; bpCR, breast pathological complete response; MP, Miller-Payne; ORR, objective remission rate; CR, complete remission; PR, partial remission; MRI, magnetic resonance imaging.

Table 3 Treatment-related adverse events occurred in patients who received neoadjuvant therapy

Adverse event	Patients (n=31), n (%)		
	Any grade	Grade 3	Grade 4
Diarrhea	31 (100.0)	2 (6.5)	0
Neutrophil count decreased	11 (35.5)	0	0
WBC count decreased	11 (35.5)	0	0
Hand and foot numbness	17 (54.8)	1 (3.2)	0
Fatigue	20 (64.5)	0	0
Vomiting	11 (35.5)	0	0
Nausea	15 (48.4)	0	0
Oral mucositis	10 (32.3)	0	0
Loss of appetite	19 (61.3)	1 (3.2)	0
Increased transaminase	8 (25.8)	0	0
Skin rash	9 (29.0)	0	1 (3.2)
Abdominal pain	17 (54.8)	0	0
Cardia dysfunction	0	0	0
Death related to treatment	0	0	0

WBC, white blood cell.

In this present exploratory study, the tpCR and bpCR rates of pyrotinib plus taxanes were encouraging with 48.4% (95% CI: 30.8–66%) and 51.6% (95% CI: 34.0–69.2%), respectively. Anti-tumor activity appeared to be among the highest observed activity among the abovementioned mono-targeted anti-HER2 regimen.

Regardless of the different clinical settings between the studies, the role of pyrotinib as a component of neoadjuvant therapy for HER2-positive BC deserves further research. Recently, various combinations of pyrotinib plus chemotherapy for HER2$^+$ BC in the neoadjuvant setting have been increasingly explored. Several phase II trials showed that dual-target therapy with trastuzumab and pyrotinib plus neoadjuvant chemotherapy (NAC) exhibited pCR rates between 51.6% and 73.7% (13,15,29,30). A real-world analysis found that the tpCR rate of pyrotinib-containing neoadjuvant therapy was 48.5%, respectively (28). An observational study comparing pyrotinib or pertuzumab plus trastuzumab in combination with NAC revealed that the tpCR and bpCR rates were 64.5% *vs.* 54.0% and 76.2% *vs.* 58.0%, albeit insignificantly (31). Incorporating the results of the present prospective study, pyrotinib-based neoadjuvant treatment shows a promising effectiveness for patients with early or locally advanced HER2$^+$ BC.

As expected, pyrotinib-related diarrhea was the most frequent AE, whereas the overall safety profile in the present study was acceptable. The incidence of grade ≥3 diarrhea in this study was much lower than that of previously reported pyrotinib-containing neoadjuvant therapy (6.5% *vs.* 18.2–64.5%) (13-15,29). The use of a single HER2-targeted agent and a single chemo-drug in the neoadjuvant setting might have contributed to the low incidence of severe diarrhea. Moreover, primary prophylaxis with loperamide may also be helpful. No evidence showed that pyrotinib is correlated with cardiotoxicity. Definitively, the overall tolerability profile of pyrotinib regimen remained favorable allowing further development.

There were some limitations in this study that should be mentioned. Firstly, the sample size was limited and prolonged follow-up is required to verify the clinical benefit. The absence of a control group limits the level of evidence. Moreover, differences in defining pCR as well as in the chemotherapeutic regimes adopted in each trial may result in variations regarding pCR rates. Nevertheless, we aimed to provide supplementary data on pyrotinib-containing neoadjuvant therapy in HER2$^+$ breast cancer.

Conclusions

In conclusion, our study suggested that the association pyrotinib plus taxanes is a promising neoadjuvant regimen in patients with early or locally advanced HER2$^+$ BC. Pyrotinib should be considered in the treatment of early breast cancer. This combination in our study might provide an alternative option for patients who cannot receive large-molecule monoclonal antibody treatment or when these drugs are not available. However, the reported efficacy of pyrotinib-based neoadjuvant therapy should trigger further assessments. The investigation of the optimal chemo-partner, the activity of a doublet regimen combining pyrotinib and trastuzumab worth further trials.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-24-38/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-38/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-38/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (as revised in 2013). The Ethics Committee at The First People's Hospital of Foshan approved the protocol (approval number: 2021[113-1]), and all participants provided written informed consent.

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Original Article

A WeChat-based nursing intervention program improves the postoperative rehabilitation of breast cancer patients: results from a randomized controlled trial

Li-Ping Wang[1#], Li-Hua Yao[2#], Dan Wang[1#], Geok Hoon Lim[3,4], Mohammed Yahia Almaghrabi[5], Hua Shen[6], Xiao Yuan[6], Shan-Shan Liang[7]

[1]Department of Breast Surgery/Plastic Surgery, Xinhua Hospital Affiliated with Shanghai Jiaotong University School of Medicine, Shanghai, China; [2]Department of General Wards, Huashan Hospital, Fudan University Red Cross Society of China, Shanghai, China; [3]Breast Department, KK Women's and Children's Hospital, Singapore, Singapore; [4]Duke-NUS Medical School, Singapore, Singapore; [5]Radiation Oncology Department, King Abdullah Medical City, Makkah Al-Mokarramah, Kingdom of Saudi Arabia; [6]Department of Special Clinic, Changhai Hospital Affiliated to Naval Medical University, Shanghai, China; [7]Department of Breast Surgery/Plastic Surgery, Chongming Hospital Affiliated to Shanghai University of Medicine and Health Sciences, Shanghai, China

Contributions: (I) Conception and design: SS Liang; (II) Administrative support: SS Liang; (III) Provision of study materials or patients: LP Wang, LH Yao; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Shan-Shan Liang, MD. Department of Breast Surgery/Plastic Surgery, Chongming Hospital Affiliated to Shanghai University of Medicine and Health Sciences, No. 25 Nanmen Road, Chengqiao Town, Shanghai 200082, China. Email: lisan999@126.com; Hua Shen, MB; Xiao Yuan, MB. Department of Special Clinic, Changhai Hospital Affiliated to Naval Medical University, 168 Changhai Road, Shanghai 200433, China. Email: 357690660@qq.com; 18251837874@163.com.

Background: In postoperative setting, breast cancer (BC) patients can experience adverse effects, including fatigue, sleep disorders, and pain, which substantially affect their health-related quality of life (HRQoL). This study sought to assess the effectiveness of a WeChat-based multimodal nursing program (WCBMNP) that was specifically designed for the rehabilitation of women following BC surgery.

Methods: BC patients were randomly, single-blinded allocated to either the intervention (n=62) or control (n=63) cohorts. Over a period of 6 months (24 weeks), the intervention cohort received a WCBMNP in addition to routine nursing care, while the control cohort received routine nursing care only. To evaluate patients' fear of cancer recurrence (FCR), their overall fear score was assessed using the Japanese version of the Concerns About Recurrence Scale (CARS-J) for primary outcome. The initial outcome (HRQoL) and secondary results, such as fatigue, sleep, and pain, were examined using the Functional Assessment of Cancer Therapy-Breast (FACT-B, version 4.0) and Nursing Rating Scale (NRS), respectively.

Results: Two hundred and ten participants, 85 participants were excluded. Compared to the controls (n=63), the intervention cohort (n=62) showed statistically significant improvements in their CARS-J scores. The intervention cohort aggregate scores on the FACT-B improved significantly but were affected by the compounding influences of cohort dynamics, temporal progression, and their interaction. Similar improvements were observed in the social/family and functional well-being domains. Emotional well-being was improved based on the effects of time and group-time interaction. In the intervention cohort, the "BC-specific subscale for additional concerns" was affected by group and time, whereas physical well-being was only affected by time. Conversely, there were no statistically significant changes in the variables of fatigue, sleep, and pain.

Conclusions: The WCBMNP reduced FCR and significantly increased the HRQoL of female patients with BC postoperatively. The WCBMNP could be implemented as a postoperative rehabilitation intervention in this patient population to improve outcomes.

Trial Registration: Chinese Clinical Trial Registry (ChiCTR2400081557).

Keywords: Breast cancer (BC); fear of cancer recurrence (FCR); health-related quality of life (HRQoL); pain; sleep

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Introduction

Breast cancer (BC) is the most prevalent malignancy among women worldwide, and the second leading cause of cancer mortality in women (1), The primary approach for early-stage BC involves surgery with additional therapies, such as endocrine therapy, radiotherapy, and chemotherapy (2-4). Unfortunately, these treatments have adverse effects, including pain, fatigue, and sleep disturbances (5), which significantly affect the health-related quality of life (HRQoL) of patients postoperatively (6).

BC survivors commonly experience uncertainty, anxiety, and the fear of cancer recurrence (FCR) (7-9). Psychological issues, particularly the FCR, are important unmet needs among ambulatory BC patients, affecting over half of BC patients (10). The FCR is prevalent among BC patients and has been shown to be correlated with diminished HRQoL (11-13).

Numerous initiatives to improve physical health, psychological state, and spiritual well-being, etc. have been implemented to improve the HRQoL of women with BC (14-16). Despite achieving some satisfactory results, there is a lack of programs that adopt a holistic methodology that integrates physical, psychological, and social rehabilitation in the postoperative phase (17-20). Leveraging on the extensive accessibility of the mobile internet and the widespread adoption of WeChat, a no-cost communication platform widely embraced by Chinese adults (21), a WeChat-based multimodal nursing program (WCBMNP) has emerged as an appropriative intervention to improve nursing care and to serve a larger population despite geographical restrictions (22). This trial sought to examine the potential advantages of a WCBMNP in women with BC postoperatively. We present this article in accordance with the CONSORT reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-40/rc).

Highlight box

Key findings

- This study found that a WeChat-based multimodal nursing program (WCBMNP) reduced the fear of cancer recurrence (FCR) and significantly increased the health-related quality of life (HRQoL) of women with breast cancer (BC) postoperatively.

What is known, and what is new?

- WeChat use had been previously reported to be useful for healthcare intervention, whereby it could complement regional nursing resources and serve a larger population despite geographical restrictions.
- Our study showed the effectiveness of a WCBMNP in decreasing FCR and increasing the HRQoL of BC patients postoperatively.

What is the implication, and what should change now?

- The WCBMNP has potential advantages for BC women. It could be implemented as part of these patients' postoperative protocol to improve their care.

Methods

Participants

BC patients were recruited using the method of convenience sampling. This randomized clinical trial was conducted at the Xinhua Hospital Affiliated with Shanghai Jiaotong University School of Medicine, and the participants provided informed consent. To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) patient with primary diagnosis of histologically confirmed BC; (II) age ≥18 but <55 years; (III) patient received breast surgery within the last 12 months; (IV) patients are in remission; and (V) patient who are able to complete an electronic patient-reported outcome measure via WeChat. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had other active, severe physical illness, and/or a current or prior history of cancers other than BC; (II) were unable to comprehend Chinese; and/or (III) were engaged in ongoing follow-up, or were being treated by psychiatrists, or other mental health professionals. Post-surgery, all the patients received patient-controlled analgesia. This is a two-parallel study, and allocation ratio is about 1:1. The study protocol was approved by the Institutional Review Board of the Xinhua Hospital Affiliated with Shanghai Jiaotong University School of Medicine (No. XHEC-D-2023-203). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Intervention cohort

Patients in the intervention cohort received the WCBMNP in addition to routine nursing care (23) (details of the intervention are shown in *Table 1*). The intervention was administered throughout the hospitalization period and up to 6 months post-surgery. Rigorous measures were implemented to prevent inter-cohort contamination. Patients were physically segregated in distinct sections of the BC department, and any form of interaction between the cohorts was strictly prohibited. Patients in each cohort were also cared for by designated staff, with no overlap of the staff for each cohort.

Control cohort

The patients allocated to the control cohort received a standard nursing intervention, which included standard health education protocols, vital sign monitoring, postoperative complication surveillance, and postoperative drainage-tube management.

Evaluation metrics

The patients were assessed at 2, 8, and 24 weeks post-surgery in the study period (weeks 0–24). Our primary endpoint was Japanese version of the Concerns About Recurrence Scale (CARS-J) and secondary endpoint was FACT-B. FCR was assessed using the fear scores of the CARS-J (24). Fear scores ranged from 4 to 24, with a higher score indicating an increased FCR. This scale was also used as a screening tool to evaluate FCR.

The Chinese Functional Assessment of Cancer Therapy-Breast (FACT-B, version 4.0), which has been verified previously among BC patients in mainland China (25), was used to gather HRQoL information. The evaluation covered social/family, functional, emotional, and physical well-being, and included a "BC-specific subscale for additional concerns". The FACT-B comprises 36 items, and the patients were asked to rate each item on a five-point Likert scale, on which 0= not at all, 1= a little bit, 2= somewhat, 3= quite a bit, and 4= very much. Potential total scores ranged from 0 to 144, and a higher score indicated improved HRQoL (26); Cronbach's α in this study was 0.82.

The Nursing Rating Scale (NRS) is a succinct numerical adaptation of the visual analog scale, wherein individuals evaluate the intensity of a particular sensation on a continuum ranging from 0 to 10 (27). Widely used as a straightforward tool for evaluating feelings in clinical nursing settings (28), the NRS was employed in this study to evaluate patients' fatigue, sleep, and pain; 0 represented no pain/fatigue, or high sleep quality, while 10 represented severe pain/fatigue, or bad sleep quality.

Statistical analysis

The data were examined using SPSS software (version 23.1, IBM Corp., Armonk, NY, USA). To assess the baseline characteristic differences between the cohorts, multiple statistical tests (e.g., Fisher's exact test, the chi-square test, and the independent *t*-test) were performed. A P value ≤0.05 was considered statistically significant.

Sample size

We calculated that group sample sizes of 110 patients (55 in group 1; 55 in group 2) would provide 80% power to reject the null hypothesis of equal means when the mean difference is 7 [108–101] with standard deviations of 13 for group 1 and 13 for group 2 at a two-sided alpha of 0.05. Given an anticipated dropout rate of 12%, total sample size required is 125 (62 in intervention group 1; 63 in control group 2).

Randomization and implementation

Director of this trial and surgeon were used computer randomize sheet to reroll patients into two cohorts. Trials were using single blind mechanism for patients after assignment to interventions.

Results

Study design

From June 2021 to July 2022, 210 participants were assessed for eligibility. All the participants were women. Of these patients, 85 participants were excluded (*Figure 1*). The remaining 125 patients were randomly allocated to either the intervention or the control cohort.

Table 1 WeChat-based multimodal nursing program

Stages	Physical rehabilitation	Psychological rehabilitation	Social rehabilitation	Implementation in WeChat platform
Stage I: from hospital admission to the time of surgery	Provision of individualized information[†,‡]: illness condition; planned surgery and adjuvant therapy; diet, rest, and activity	Relaxation training[†,‡]: e.g., muscle relaxation, music listening, meditation (face-to-face and video frequency)	Adaptation to patient role[†,‡]: cooperating with the treatment; doing self-care activities under permission	Web-MNP group:
	Surgical side upper limb exercise training[†,‡]: finger → wrist → elbow → shoulder → upper limb (face-to-face and video frequency)	Feeling expression (face-to-face): writing (e.g., diary); communicating with relatives, significant others, or peers	Social training[†,‡]: keeping original social relationship; avoiding self-isolation; establishing good relationship with professional staff and peers	Establishing WeChat platform
Stage II: 0–24 weeks following surgery	Provide individualized information[†,‡]: post-surgery complications; adverse effects of adjuvant therapy; complications regarding peripherally inserted central catheter or implantable venous access port	Performing need-oriented psychological counseling	Role transformation[†,‡]: progressively completing the role transformation from patient to the original family/social role; performing original family/social role well	Recruiting the patient with permission
	Self-surveillance and recurrence prevention after hospital discharge[†,‡]	Family/spouse (guided by professional staff face-to-face): understanding feelings and meeting demands of the patient; accompanying the patient as much as possible		From hospital admission to 6 months following surgery, continuously
	Developing and updating patient-oriented plan of diet, rest, and activity[†,‡]	Peers (guided by professional staff face-to-face): sharing negative psychological state coping experiences		Professional staff:
	Coping with fatigue and poor sleep[†,‡]: keeping physical activity under permission, relaxation training (e.g., muscle relaxation, listening to music, meditation)			Daily delivery of the BC rehabilitation information (5 p.m.–7 p.m.)
	Pain relieving[†,‡]: medication and non-medication (e.g., muscle relaxation training, listening to music)			Assessing and responding to the rehabilitation problems submitted by the patients as soon as possible
				Patients:
				Submitting rehabilitation problems
				Sharing rehabilitation experiences

[†], dissemination of pertinent information (e.g., employing textual content, images, audio, or video formats) on the WeChat platform aligned with the face-to-face intervention; [‡], need-oriented patient-professional staff or patient-peer communication in WeChat platform during the intervention period based on face-to-face intervention. BC, breast cancer.

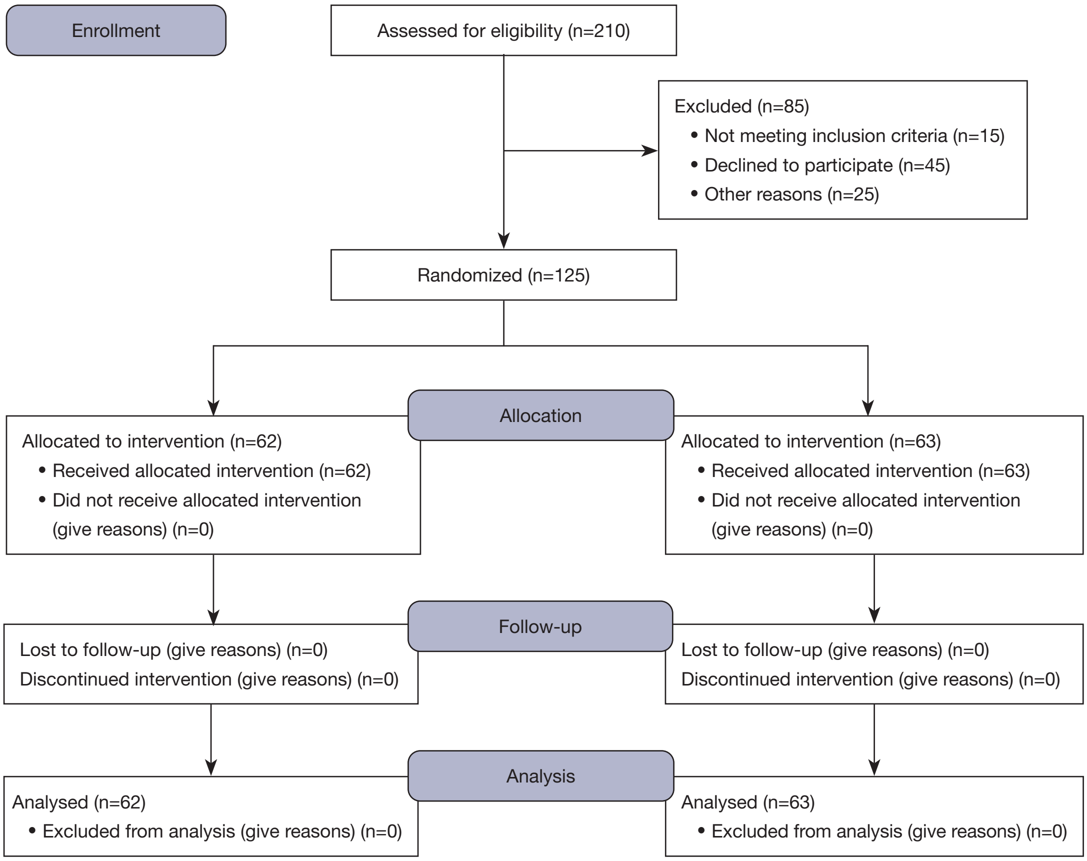

Figure 1 Flowchart of the study.

Mean age of the intervention cohort was 41 [27–53] years old, and mean age of the control cohort was 43 [25–54] years old. There were no statistically significant differences between the two cohorts in terms of their demographics and pathological characteristics (*Table 2*).

The WCBMNP improved the HRQoL of BC patients postoperatively

Analysis of the scores using FACT-B showed the dynamic evolution of physical well-being with a pronounced effect over time ($P<0.05$) (*Table 3*). Social/family and functional well-being demonstrated the interplay of time, cohort, and cohort-time interaction effects. Emotional well-being manifested time effects ($P<0.05$) and cohort-time interaction effects ($P<0.05$). The “BC-specific subscale for additional concerns” reflected the influence of cohort effects ($P<0.05$) and time ($P<0.05$) effects. The overall FACT-B scores were affected by cohort ($P<0.05$), time ($P<0.05$), and the interaction of cohort-time ($P<0.05$). These suggested that WCBMNP improved the HRQoL of BC patients postoperatively.

Conversely, pain, fatigue, and sleep, evaluated using the NRS did not exhibit any significant cohort effects ($P>0.05$). Both pain and fatigue displayed time effects ($P<0.05$), while only pain showed a cohort-time interaction effect ($P<0.05$) (*Table 4*).

The WCBMNP reduced the FCR of BC patients postoperatively

Regarding FCR, the patients in the intervention cohort exhibited a statistically significant improvement in their CARS-J scores at 8 and 24 weeks, compared to the control cohort (*Table 5*, *Figure 2*). This hence demonstrated that WCBMNP reduced the FCR of BC patients postoperatively. However, within the intervention cohort, there were no significant differences in the outcomes observed at 8 and 24 weeks in terms of the CARS-J (see *Figure 2* and *Table 6*).

Table 2 Patients' baseline characteristics

Variables	Intervention cohort (n=62)	Control cohort (n=63)	P value
Age (years)			0.126
≤45	32	30	
>45	30	33	
Educated			0.848
Junior middle school and below	5	7	
Senior middle school	32	37	
Undergraduate	25	19	
Marital status			0.884
Married	19	16	
Never married/separated/divorced/widowed	43	47	
Employment			0.584
Unemployed	21	18	
Employed	41	45	
Tumor stage			0.312
<III	32	27	
≥III	30	36	
Income (RMB/month)			0.551
<3,000	12	9	
3,000–7,000	25	28	
>7,000	25	26	
Breast surgery			0.843
Modified radical mastectomy	19	23	
Total mastectomy	12	17	
Breast conserving surgery	31	23	
Axillary surgery type			0.525
Sentinel lymph node biopsy	23	28	
Axillary lymph node dissection	39	35	
Radiotherapy			0.486
Yes	17	19	
No	45	44	
Neo-adjuvant chemotherapy			0.814
Yes	23	20	
No	39	43	
Adjuvant chemotherapy			0.709
Yes	32	30	
No	30	33	

Table 3 Alterations in each cohort and differences between the cohorts in the FACT-B scores: examination via a linear mixed model analysis

Cohort	Baseline	2 weeks after surgery		8 weeks after surgery		24 weeks after surgery	
	Score	Score	Change from baseline (95% CI)	Score	Change from baseline (95% CI)	Score	Change from baseline (95% CI)
PWB†							
Intervention	24.90±2.73	22.05±1.26	−2.77 (−4.23, −1.54)	21.93±0.69	−3.73 (−8.56, −3.55)	22.37±2.17	−1.28 (−8.73, −0.12)
Control	24.39±2.79	21.57±2.57	−2.44 (−5.63, −2.13)	22.47±0.46	−4.89 (−7.34, −2.98)	23.77±1.02	−1.68 (−2.68, −0.78)
MD (95% CI)	−0.71 (−1.83, 0.56)	0.55 (−0.83, 2.13)		0.71 (−2.03, 3.51)		−0.87 (−1.99, 1.59)	
SWB‡							
Intervention	22.08±2.34	21.87±1.23	−2.47 (−5.45, −2.19)	20.29±0.62	−2.96 (−7.43, −0.84)	22.89±2.64	0.15 (−0.14, 3.24)
Control	21.83±3.41	19.08±2.46	−1.21 (−3.57, −0.44)	18.98±0.14	−2.82 (−9.34, −0.73)	19.11±1.34	−2.71 (−7.62, −0.63)
MD (95% CI)	1.55 (0.45, 3.61)	1.89 (1.03, 3.92)				6.11 (2.81, 10.33)	
EWB§							
Intervention	15.89±4.51	17.36±2.31	2.58 (1.22, 6.16)	21.75±2.75	5.97 (1.56, 8.16)	20.86±2.52	4.15 (2.53, 7.34)
Control	16.73±4.72	18.05±1.98	1.82 (0.59, 5.51)	19.67±0.62	2.79 (1.15, 9.72)	19.94±1.62	2.93 (0.35, 9.18)
MD (95% CI)	−1.97 (−3.11, 0.09)	−1.16 (−2.85, 0.53)		1.76 (1.23, 5.17)		1.71 (−1.04, 5.91)	
FWB¶							
Intervention	21.06±2.52	17.84±1.61	−3.69 (−6.23, −1.98)	23.36±2.94	−1.97 (−6.56, −0.57)	22.57±2.52	2.91 (0.96, 3.72)
Control	20.14±1.23	12.25±2.81	−3.57 (−7.23, −1.41)	18.32±1.53	−2.93 (−5.23, −1.99)	17.03±1.34	−1.72 (−2.51, 0.15)
MD (95% CI)	1.85 (−0.11, 4.01)	3.72 (2.85, 8.66)		2.73 (1.65, 6.31)		3.74 (2.01, 19.05)	
BCSǀ							
Intervention	32.21±0.65	29.57±2.69	−2.69 (−5.23, −2.23)	28.12±0.92	−4.39 (−8.45, −2.31)	29.31±2.85	−3.24 (−7.38, −1.12)
Control	32.78±0.54	22.33±2.43	−2.28 (−6.31, −1.46)	26.44±2.47	−3.02 (−7.35, −1.78)	26.82±2.79	−2.83 (−5.3, −1.19)
MD (95% CI)	1.67 (−0.32, 3.69)	2.42 (0.89, 6.91)		6.91 (2.52, 14.64)		9.22 (7.09, 12.06)	
Total score#							
Intervention	116.14±12.01	108.69±13.58	−12.6 (−16.36, −2.08)	115.45±13.77	−3.34 (−7.45, 0.58)	118.00±10.55	4.82 (−3.33, 8.38)
Control	115.87±13.21	93.28±13.01	−11.67 (−19.42, −2.57)	105.88±12.06	−15.34 (−19.42, −1.63)	106.67±12.4	−6.84 (−12.05, 0.94)
MD (95% CI)	2.57 (−2.18, 5.92)	9.42 (5.09, 16.74)		8.83 (3.62, 16.65)		12.51 (6.83, 19.62)	

Data are presented as mean ± SD, unless otherwise stated. †, PWB model: (cohort) F=1.03; P=0.563; (time) F=6.15, P<0.001; (cohort × time interaction) F=1.03, P=0.342; ‡, SWB model: (cohort) F=10.09; P< 0.001; (time) F=11.82, P<0.001; (cohort × time interaction) F=5.49, P=0.015; §, EWB model: (cohort) F=0.82; P=0.632; (time) F=9.99, P<0.001; (cohort × time interaction) F=5.46, P=0.001; ¶, FWB model: (cohort) F=5.32; P<0.001; (time) F=9.62, P<0.001; (cohort × time interaction) F=11.78, P=0.006; ǀ, BCS model: (cohort) F=5.66; P<0.001; (time) F=9.65, P<0.001; (cohort × time interaction) F=0.83, P=0.283; #, total score model: (cohort) F=6.35; P<0.001; (time) F=6.66, P<0.001; (cohort × time interaction) F=8.88, P=0.007. A linear mixed model was used to analyze the in-cohort variations and between-cohort variations of FACT-B scores. Baseline measurements of the FACT-B total and five subscales' scores were incorporated as covariates, with cohort, time, and cohort × time interaction as fixed effects, and patients as random effects. FACT-B, Functional Assessment of Cancer Therapy-Breast; CI, confidence interval; PWB, physical well-being; MD, mean difference; SWB, social/family well-being; EWB, emotional well-being; FWB, functional well-being; BCS, BC-specific subscale for additional concerns; BC, breast cancer; SD, standard deviation.

Table 4 In-cohort changes and comparisons between the cohorts in terms of pain, fatigue, and sleep scores: linear mixed model analysis

Cohort	Baseline	2 weeks after surgery		8 weeks after surgery		24 weeks after surgery	
	Score	Score	Change from baseline (95% CI)	Score	Change from baseline (95% CI)	Score	Change from baseline (95% CI)
Pain†							
Intervention	1.88±1.91	1.72±1.76	−0.02 (−1.05, 0.85)	1.87±1.85	−0.12 (−1.06, 1.24)	1.81±1.78	−0.56 (−1.75, 0.89)
Control	1.33±1.56	2.86±2.12	1.69 (0.89, 3.19)	2.97±1.31	1.78 (0.24, 2.35)	2.37±1.85	1.23 (0.15, 1.97)
MD (95% CI)	0.53 (−0.35, 1.78)	−0.92 (−1.77, −0.02)		−0.67 (−1.71, −0.19)		−0.89 (−1.92, 0.34)	
Fatigue‡							
Intervention	1.56±1.55	2.36±1.46	0.93 (−0.08, 1.92)	2.39±1.57	0.69 (−1.42, 1.92)	2.19±1.31	0.84 (−0.32, 2.33)
Control	1.75±1.76	1.97±2.39	−0.15 (−0.89, 0.92)	2.48±1.77	0.97 (−0.15, 1.74)	2.81±1.94	0.91 (0.18, 2.15)
MD (95% CI)	−0.34 (−1.67, 0.87)	0.67 (−0.22, 1.97)		−0.23 (−1.84, 0.93)		−0.78 (−1.93, 0.68)	
Sleep§							
Intervention	3.76±1.47	2.99±2.32	−0.78 (−1.83, 0.93)	2.78±2.67	−0.83 (−1.52, 0.58)	2.46±2.69	−0.93 (−1.72, 0.73)
Control	3.82±1.59	3.96±2.29	0.67 (−0.92, 1.95)	3.93±2.65	0.13 (−0.90, 0.74)	2.75±2.52	−0.56 (−1.84, 0.94)
MD (95% CI)	−0.01 (−2.32, 0.87)	−0.55 (−1.92, 0.94)		−0.85 (−3.01, 0.91)		−0.75 (−1.62, 0.86)	

Data are presented as mean ± SD, unless otherwise stated. †, pain model: (cohort) F=4.69, P=0.05; (time) F=3.02, P=0.01; (cohort time interaction) F=4.19, P=0.005; ‡, fatigue model: (cohort) F=0.03, P=0.67; (time) F=4.78, P=0.03; (cohort × time interaction) F=1.03, P=0.64; §, sleep model: (cohort) F=1.67, P=0.35; (time) F=1.73, P=0.43; (cohort × time interaction) F=0.68, P=0.85. A linear mixed model was employed to examine changes in the cohorts and make comparisons between the cohorts in terms of their pain, fatigue, and sleep scores measured using the NRS. Baseline measurements of pain, fatigue, and sleep scores were used as covariates, with cohort, time, and cohort × time interplay as fixed effects, while the subject was treated as a random effect. CI, confidence interval; MD, mean difference; SD, standard deviation; NRS, Nursing Rating Scale.

Table 5 CARS-J in intervention/control cohort

Variables	Intervention cohort *vs.* control cohort		
	Adjusted difference	95% CI	P
CARS-J: 2 weeks	−0.87	−1.58 to 0.59	0.463
CARS-J: 8 weeks	−0.73	−1.25 to −0.34	<0.01
CARS-J: 24 weeks	−0.99	−2.14 to −0.51	<0.01

CARS-J, Japanese version of the Concerns About Recurrence Scale; CI, confidence interval.

Discussion

This study showed the benefits of a WCBMNP on women with BC postoperatively, notably resulting in an increase in HRQoL and a decrease in FCR. Hence, WCBMNP could be implemented as a potential tool to improve the care for the post-surgery rehabilitation of BC patients.

Patients in both the intervention and control cohorts showed significant decreases in their FACT-B total scores 2 weeks post-surgery compared to the baseline, which indicated a substantial decrease in HRQoL in the immediate postoperative phase. This finding was also concordant with the findings in earlier studies (29-31). However, patients in the intervention cohort had notably increased FACT-B total scores in comparison to those in the control cohort at various study time intervals, which suggested that the WCBMNP could have a positive effect of increasing patients' HRQoL. At the 8- and 24-week follow-up periods, the intervention cohort's average FACT-B scores became similar to that at the baseline, which indicated that the patients exhibited a swift return to their preoperative health status as early as 8 weeks post-surgery. Conversely, the control cohort's average FACT-B scores consistently lagged significantly behind both the control cohort's baseline score and the intervention cohort's score during the later period of 24 weeks follow-up. The control cohort's health status only resembled their status at the baseline at the 6-month post-surgery mark; however, the control cohort's total FACT-B score remained significantly lower than that of the intervention cohort at the same juncture. This affirmed our hypothesis regarding the positive effect of the WCBMNP on patients' HRQoL at the three assessed time points, underscoring its effectiveness in enhancing HRQoL for BC patients postoperatively.

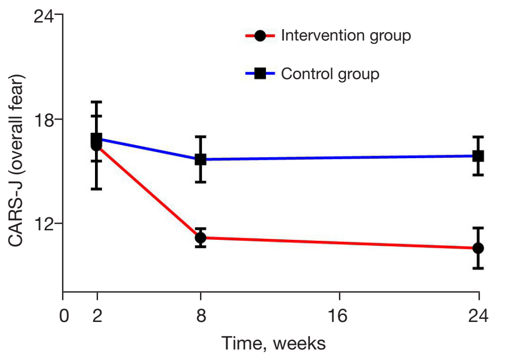

Figure 2 Changes in the baseline fear scores on the CARS-J. Scores for overall fear ranged from 2 to 24; a higher score indicated an increased FCR. CARS-J, Japanese version of the Concerns About Recurrence Scale; FCR, fear of cancer recurrence.

In relation to the FACT-B subscales, the changes in the social/family and functional well-being domains mirrored those of the overall score, which suggested that the WCBMNP facilitated substantial improvements during the postoperative follow-up period. In comparison to the baseline, both cohorts exhibited significantly reduced scores for the "BC-specific subscale for additional concerns" at the 6-month follow-up, which suggested that the persistent BC-specific concerns may be attributable to the adverse effects of the adjuvant therapies or the relatively brief follow-up duration. The intervention cohort exhibited a markedly elevated score on this subscale compared to that of the control cohort.

In contrast, no cohort effects were evident in terms of patients' physical and emotional well-being. Nonetheless, the intervention cohort exhibited a discernible upward trajectory in these two subscales during the follow-up period, suggesting that the WCBMNP conferred a potential advantage in these two aspects. Despite this positive trend, the post-surgical physical well-being score of the intervention cohort remained significantly lower than the baseline score, mirroring the observations in the "BC-specific subscale for additional concerns" at the 6-month post-surgery juncture. This emphasized the need to pay increased attention to patients' physical health during the early stages of rehabilitation. Future investigations should consider a prolonged intervention and follow-up period, such as 12 months, so that a more comprehensive understanding can be gained.

Contrary to our secondary hypothesis, our findings failed to substantiate the proposition that the WCBMNP could alleviate sleep disorders, pain, and fatigue at the three-time points. The intervention cohort had lower sleep, pain, and fatigue scores than the control cohort at the 6-month post-surgery mark; however, these score disparities, in both the intervention cohort and between the intervention and control cohorts, were not statistically significant. This

Table 6 CARS-J alterations from weeks 2 to 24 in the intervention cohort

Variables	Differences in least square		
	Adjusted difference	95% CI	P
CARS-J: 2 *vs.* 8 weeks	−0.79	−1.31 to −0.27	<0.01
CARS-J: 8 *vs.* 24 weeks	−0.94	−1.04 to 0.291	0.532
CARS-J: 2 *vs.* 24 weeks	−0.82	−1.83 to −0.28	<0.01

CARS-J, Japanese version of the Concerns About Recurrence Scale; CI, confidence interval.

implies that, in the initial 6-month period post-surgery, the WCBMNP did not have a notable effect in mitigating sleep disorders, pain, and fatigue. Notably, patients in the control cohort exhibited significantly elevated pain and fatigue scores at 6 months post-surgery compared to the baseline, which shows the inadequacy of routine nursing care in ameliorating these adverse effects. Consequently, the effects of the WCBMNP on pain and fatigue warrant further exploration in future research with an extended follow-up period.

The present study showed the effectiveness of the WCBMNP in mitigating the FCR in BC survivors. Our findings revealed a statistically significant increase in the CARS-J scores of the patients in the intervention cohort at week 8 in comparison to the control cohort. However, one limitation of this study was that the potential effects of the WCBMNP on depression, as well as patients' unmet psychological needs was not studied. Given that depression and unmet psychological needs frequently contribute to psychological distress in cancer patients, future research needs to be conducted to examine the effectiveness of smartphone-based psychological therapies in addressing various facets of distress.

Conclusions

In summary, our study showed the effectiveness of the WCBMNP in reducing FCR and significantly enhancing HRQoL in BC patients postoperatively. This intervention may be applied in the early stages of patients' rehabilitation journeys.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-24-40/rc

Trial Protocol: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-40/tp

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-40/dss

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-40/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-40/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the Institutional Review Board of the Xinhua Hospital Affiliated with Shanghai Jiaotong University School of Medicine (No. XHEC-D-2023-203). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The participants provided informed consent.

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Review Article

Use of artificial intelligence in breast surgery: a narrative review

Ishith Seth[1,2]^, Bryan Lim[1,2], Konrad Joseph[3], Dylan Gracias[4], Yi Xie[1], Richard J. Ross[1,2], Warren M. Rozen[1,2]

[1]Department of Plastic Surgery, Peninsula Health, Melbourne, Victoria, Australia; [2]Central Clinical School at Monash University, The Alfred Centre, Melbourne, Victoria, Australia; [3]Department of Surgery, Port Macquarie Base Hospital, New South Wales, Australia; [4]Department of Surgery, Townsville Hospital, Queensland, Australia

Contributions: (I) Conception and design: I Seth, B Lim, K Joseph, D Gracias, Y Xie; (II) Administrative support: RJ Ross, WM Rozen; (III) Provision of study materials or patients: I Seth, B Lim, K Joseph, D Gracias, Y Xie; (IV) Collection and assembly of data: I Seth, B Lim, K Joseph, D Gracias, Y Xie; (V) Data analysis and interpretation: I Seth, B Lim, K Joseph, D Gracias, Y Xie; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Ishith Seth, BSc, BBiomed(Hons), MD, MS. Central Clinical School at Monash University, The Alfred Centre, 99 Commercial Rd, Melbourne, Victoria, 3004, Australia; Department of Plastic Surgery, Peninsula Health, Melbourne, Victoria, Australia. Email: ishithseth1@gmail.com.

Background and Objective: We have witnessed tremendous advances in artificial intelligence (AI) technologies. Breast surgery, a subspecialty of general surgery, has notably benefited from AI technologies. This review aims to evaluate how AI has been integrated into breast surgery practices, to assess its effectiveness in improving surgical outcomes and operational efficiency, and to identify potential areas for future research and application.

Methods: Two authors independently conducted a comprehensive search of PubMed, Google Scholar, EMBASE, and Cochrane CENTRAL databases from January 1, 1950, to September 4, 2023, employing keywords pertinent to AI in conjunction with breast surgery or cancer. The search focused on English language publications, where relevance was determined through meticulous screening of titles, abstracts, and full-texts, followed by an additional review of references within these articles. The review covered a range of studies illustrating the applications of AI in breast surgery encompassing lesion diagnosis to postoperative follow-up. Publications focusing specifically on breast reconstruction were excluded.

Key Content and Findings: AI models have preoperative, intraoperative, and postoperative applications in the field of breast surgery. Using breast imaging scans and patient data, AI models have been designed to predict the risk of breast cancer and determine the need for breast cancer surgery. In addition, using breast imaging scans and histopathological slides, models were used for detecting, classifying, segmenting, grading, and staging breast tumors. Preoperative applications included patient education and the display of expected aesthetic outcomes. Models were also designed to provide intraoperative assistance for precise tumor resection and margin status assessment. As well, AI was used to predict postoperative complications, survival, and cancer recurrence.

Conclusions: Extra research is required to move AI models from the experimental stage to actual implementation in healthcare. With the rapid evolution of AI, further applications are expected in the coming years including direct performance of breast surgery. Breast surgeons should be updated with the advances in AI applications in breast surgery to provide the best care for their patients.

Keywords: Artificial intelligence (AI); breast surgery; breast imaging

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^ ORCID: 0000-0001-5444-8925.

Introduction

Background

The first concept of computer systems as an imitator of human intelligence was conceived by Turing in 1950 (1). Artificial intelligence (AI) is a particular computer system or machine that can solve problems that usually require human intelligence. Early generations performed a simple algorithm of 'if, then' rules, but subsequent developments in technology and coding have resulted in complex systems that can operate similarly to human intelligence, including the ability to learn from past errors and cross-check results (1-3). Such capacity, coupled with fast processing times and no requirement for rest has created a formidable tool at the heart of the fourth industrial revolution.

Machine learning (ML) is a subset of AI in which the algorithm improves its performance (mode of analysis and patterns) by learning from new datasets without being explicitly re-programmed. The data used for learning may exist in the form of imported features (e.g., breast lesion density) or the form of raw data (e.g., radiological images). Deep learning (DL) is a subset of ML that involves the stacking of multiple algorithmic components into layers, each feeding into the next, operating on raw data and self-learn high-level features. DL models include convolutional, recurrent, and artificial neural networks (CNN, RNN, and ANN), generative adversarial networks (GAN), deep belief nets, and autoencoders (4-9). CNN are designed specifically to analyze and find features from images as seen in *Figure 1* (10). Large language models (LLMs) are another type of AI that utilizes natural language processing methods to synthesize user inputs and generate human-like speech (11-13). They have been used to aid diagnosis, medical research, and improve hospital workflow (14-20).

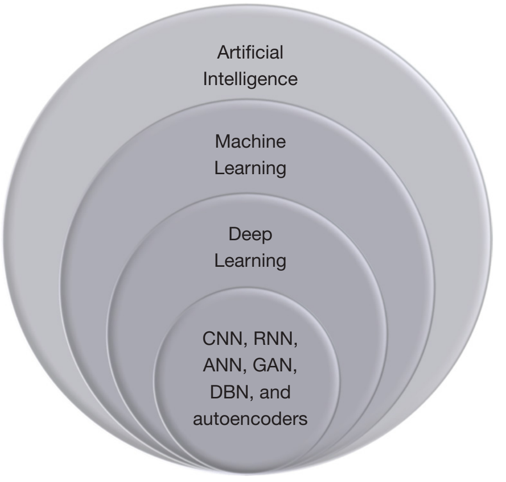

Figure 1 Subsets of artificial intelligence. CNN, convolutional neural networks; RNN, recurrent neural networks; ANN, artificial neural networks; GAN, generative adversarial networks; DBN, deep belief network.

Rationale and knowledge gap

AI models are rapidly evolving and present one of the most significant developments in information processing and problem solving in health care the past 50 years (21). As widespread health data collection creates enormous volumes of information, this data must be processed by consequently more complex systems. AI models are currently applied to optimize different aspects of patients' care including disease risk prediction, diagnosis, treatment decision-making, predicting treatment response, and predicting survival (2,4,5,22-24). By being able to operate on large volumes of data with high precision, AI models offer distinct advantages over unassisted human performance. A recent publication has successfully elucidated the applications of AI technologies within breast reconstructive procedures, where the authors highlight the promising role of AI in advancing breast reconstruction techniques (25). However, authors state refinement of AI algorithm with cross-disciplinary partnerships for prioritizing their dataset. The scope of breast surgery is much greater than reconstruction alone and further research is needed to characterize the current and prospective implementation of AI in the field.

Objective

Breast cancer is increasing in prevalence and is the leading cause of cancer death among women (26-29). Breast surgery can be used as a prototypical example for the application of AI in healthcare. It is a field comprising population health, risk prediction, diagnostic tests, medical and surgical treatments and integrated health systems and economics, all of which can directly benefit from various mechanisms of AI (30,31). We performed this review aiming to summarize the current literature findings on the application of AI in diagnosing breast lesions as well as preoperative, intraoperative, and postoperative applications of AI in breast surgery. We present this article in accordance with the Narrative Review reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-414/rc).

Table 1 Search strategy for this review

Item	Specification
Date of search	13/9/2023
Databases searched	PubMed, Google Scholar, EMBASE, Cochrane CENTRAL
Search terms used	#1 (“artificial intelligence” [Mesh] OR “machine learning” [Mesh] OR “deep learning” [Mesh]))
	#2 (“breast surgery” [Mesh] OR “breast neoplasm” [Mesh]) #1 AND #2
Timeframe	1/1/1950 to 4/9/2023
Inclusion and exclusion criteria	Studies that discussed any application of artificial intelligence in breast surgery were included in this review
	Studies reported in a language other than English were excluded
Selection process	I.S., B.L., K.J., D.G. and Y.X. conducted the selection, searched and discussed which studies were relevant until consensus was reached

Methods

PubMed, Google Scholar, EMBASE, and Cochrane CENTRAL databases were searched by two authors for relevant studies using the keywords: (“artificial intelligence” [Mesh] OR “machine learning” [Mesh] OR “deep learning” [Mesh]) AND (“breast surgery” [Mesh] OR “breast cancer” [Mesh]) from January 1st, 1950 to 4th of September, 2023. Relevant English publications were included in our review without publication time constraints. Publication relevance was determined by title and abstract screening followed by a full-text screening. In addition, the reference lists of the included publications were screened for inclusion of further relevant studies. We included studies that discussed the applications of AI in different aspects of breast surgery from breast lesion diagnosis to postoperative follow-up (*Table 1*). Publications focusing specifically on breast reconstructions were excluded from this review.

Results

AI applications in breast lesion diagnosis

Recent advances in CNN-based computer vision algorithms and growing training datasets has allowed AI to be used in medical imaging and histopathology for breast pathologies (32-35). Such systems can not only create streamlined workflows for reporting clinicians but may also improve diagnostic accuracy. This is especially true in large population breast screening programs (6,7,33,34). Modern feedforward ANN utilize multilayered perceptron to analyze images by classifying them to different color channels, processing the pixel-level images using nonlinear functions, and outputting probability distributions (36). As such, these algorithms have the promise to detect lesions not easily visible to human observers.

Digital mammography (DM)

DM is a breast imaging technique that produces 2-dimensional radiographic images. This imaging modality is used for breast cancer screening because of its feasibility and efficacy in detecting asymmetries, distorted architecture, and abnormal calcifications in breast lesions. Nevertheless, DM image interpretation is difficult and needs extensive experience (37). Smaller lesions can be missed due to obscuration by the overlying breast tissue. This is encountered mostly in younger females who have high breast tissue densities due to higher concentrations of fibroglandular tissue. Therefore, DM images are taken in a mediolateral oblique view and a craniocaudal view (38).

The application of AI in DM image interpretation was introduced in the 1990s and has since evolved with the advances of DL (39-42). DL-based models such as CNNs autonomously learn to identify specific imaging features to differentiate benign breast lesions from malignant ones (43-45). Several studies have been conducted to evaluate the efficacy of AI-based systems on detecting and classifying breast lesions on DM images and have found that AI-based DM image evaluation is noninferior and may be superior to radiologists (39,40,42,46-49). A study conducted by Romero-Martín *et al.* evaluated the performance of DL-based systems in DM image assessment. Their findings suggest that DL-based systems have an equivalent sensitivity in detecting and classifying breast lesions when compared to the best standard (radiologists). In addition, DL methods have been shown to decrease over-investigation by decreasing breast imaging recall rates (subsequent images for evaluating a suspicious lesion) (48). Another study by Burhenne *et al.* detected the missed findings in 77% of false-negative mammographic images by subsequent applications of AI (50). Thus, AI applications in mammography can improve breast cancer screening programs' efficiency with reduced need for human efforts (51,52). Moreover, AI-based models have been proven efficacious in predicting the risk of developing breast cancer in the future by utilizing data collected from DM images (53,54).

Digital breast tomosynthesis (DBT)

DBT is an X-ray-based imaging modality that takes images from different angles to create a partial tomographic 3-dimensional (3D) image, minimizing the problem of tissue superposition (55). However, the complexities associated with DBT result in difficult image interpretation, and longer reading times when compared to DM (56). This has represented another area for AI models to improve efficiency and accuracy.

When evaluated versus the best available standard (radiologists), AI-based DBT image assessment models show non-inferior efficacy in detecting and classifying breast lesions with reduced false-negative rates (39,46-48,57). AI-based DBT interpretation systems are cost-effective, as they improve radiologists' performance and reduce DBT reading time (58,59). However, in contrast to in DM evaluation, AI-based DBT image evaluation models can result in higher recall rates for further evaluation (48). This may be because DL models can pick up trivial microcalcifications in breast tissue (60).

There exist differences in the utility of different AI models when it comes to DBT analysis. DL models that use multiple images as an input to compare DBT images show better performance in detecting and classifying breast masses when compared to those their single-view counterparts (42,61-64). This benefit extends to techniques that uses multiple views of the ipsilateral breast as the aforementioned input (64). In 2023, Ren *et al.* proposed a framework for a multi-view detection framework to adaptively refine single view detection scores by matching lesions between two ipsilateral screening views of each breast (65). Their framework, developed from 8,034 DBT cases, improved screening performance without significantly increasing analysis run-time. Another subset of DL, GAN, can generate new images from an input set of images. This was successfully applied in breast imaging to generate DM images from already existing DBT images. Hence, more patient data is acquired without additional radiation exposure (66).

Images imported to AI-based diagnostic models are suspected to include lesions. These images are usually extracted by hand from entire DM or DBT scans (43). AI models can be used to support radiologists in their work by preselecting suspicious lesions for subsequent assessment by radiologists (51,52). These models can even calculate the regional probability of cancers from the DM or DBT scan (38). Accordingly, complete DM and DBT scans can be used as input to DL image assessment models (67-69). In 2017, Kooi *et al.* trained a CNN on a dataset of 45,000 mammographic images and found it non-inferior to radiologists at triaging images, and superior to a computer aided detection model that relied on human input (43).

Ultrasound (US)

US of the breast is an imaging modality that depends on sending sound waves through the breast tissue and simultaneously detecting the backscattered waves to construct the image. Thus, US carries no risk of ionizing radiation. It is, however, an operator-dependent imaging modality that can be difficult to read. The images are displayed as they are generated, and breast US should therefore be performed by an expert for direct interpretation (69). Yet, resource constraints often prevent a radiologist's expertise from being available at the time of imaging. This represents another opportunity for AI to reduce burden on healthcare systems.

DL was initially used in conjunction with US for classifying breast lesions into benign or malignant (68-72). Studies on breast lesion detection and classification using DL from US images have concluded a high accuracy in detecting and classifying lesions when the input is full US images, and a much higher accuracy when the input consists of US images of suspicious lesions (71,73-76). To classify US images of breast lesions, radiologists use the Breast Imaging Reporting and Data System (BI-RADS) that incorporates the probability of lesion malignancy and the recommended management (77). However, inter-observer variability can be high, and misclassification can result. DL models have been applied to effectively assist radiologists in choosing the appropriate BI-RADS class (78,79). DL systems have also been implemented for image segmentation of breast lesions (detecting the lesion size and extent) (80-82). Moreover, DL applications with US have broadened to include predicting the molecular subtype of malignant breast lesions. This was investigated for predicting triple negative, HER2 (+), and HR (+) subtypes and showed high efficacy (1,78).

AI models increase radiologists' classification specificity in cases where the radiologist has already detected a lesion (83-85). Some lesions in the breast could, however, be missed by the radiologist (86). Another proposed method is the application of an AI system integrated into the US device where, when the US is performed, the system directly analyzes the constructed image and provides timely detection of breast lesions (87).

Another application of DL in breast US imaging is in the assessment axillary lymph nodes for malignant lesion metastases. DL models have superior accuracy when compared to radiologists in detecting suspicious axillary lymph nodes for biopsy (88). DL models have also been used to predict axillary lymph node metastasis using the features of the breast lesion without the need for axillary US images (89). It does so by aiding in extracting relevant information by retaining only the intermediate lesion position in the images (89). It also utilizes random horizontal flipping, elastic transformation, and random cropping to simulate various scenarios (89). When compared to radiologists, DL models display comparable sensitivity and specificity (90). Such models could be further improved and implemented in US imaging to reduce the time needed for axillary lymph node imaging.

Another model was designed to predict response to neoadjuvant chemotherapy (NAC) using only the initial lesion US image (91). GAN have been applied in US imaging for reconstructing high-resolution images using low-resolution ones, for reducing the required time for 3D image acquisition, and for generating US images of the breast with and without lesions for educational purposes (for radiologists and DL models) (92,93).

Magnetic resonance imaging (MRI)

MRI of the breast depends on exciting water molecules using a heavy magnetic field and short-pulsed radio waves. When water molecules fall back to their ground form, radio waves are transmitted. These radio waves are detected to create the MR image (3D image). When an intravenous contrast is administered, a 4D image is created, with time captured as a fourth dimension. It is worth mentioning that MRI is the most sensitive breast cancer imaging modality (94).

Several AI models have been applied to breast MRI for breast lesion detection, classification, and segmentation. Here, AI models also show a superior specificity and a comparable sensitivity when compared to the best standard (radiologists) (95-98). Models have also been designed and successfully applied to predict the molecular subtype of breast cancer based on MRI image data (99-103). In 2021, Liu *et al.* evaluated the ability of a novel CNN architecture to predict 5-year cancer recurrence after MRI imaging of breast lesions. The AI was able to identify image features relevant to prognostic outcomes and increased the accuracy of tumour classification (103).

Like their integrations with US technology, DL models have been designed for detecting axillary lymph node metastasis using MRI scans. These models have shown superior accuracy in detecting pathological axillary lymph nodes when compared to radiologists (104-106). AI models have also been used to predict the NAC treatment response of breast cancer. Some models use the pre- and post MRI scans whereas others use only the initial MRI scans (107-110). GAN have been applied in breast MRI to normalize the variations in MRI intensity and noise distribution between different brands of MRI machines (111). They have also been applied to minimize issues that arise from heterogeneous fat suppression (112).

Positron emission tomography (PET)

PET and scintigraphy scans are nuclear medicine imaging modalities that use radionuclide-attached metabolites circulating in the body. When radionuclides decay, photons are emitted, the detection of which can be used to construct 3D PET and 2D scintigraphy images. Thus, nuclear medicine scans represent the metabolic activity of tissues rather than anatomical structure alone (112).

In breast cancer, PET scans are used for cancer staging. DL has been used to assist radiologists in detecting axillary lymph node metastasis on PET scans (113). In 2021, Li *et al.* found that AI assistance considerably improved the diagnostic accuracies of clinicians in a retrospective trial involving 414 pre-procedure PET scans of the axilla from patients with biopsy-proven breast cancer (113). The sensitivity of the radiologists was improved but their specificity remained unaffected. CNN have been similarly applied to detect distant breast cancer metastases from scintigraphy scans, displaying high accuracy (114). Another use of DL in conjunction with PET scans is the evaluation of the tumor burden on the whole body as measured by the metabolic tumor volume. However, DL models have not achieved satisfying sensitivity in this application (115). In 2020, Choi *et al.* have investigated the applicability of DL in predicting tumor response to NAC using PET scans as input. Their results showed improved performance in comparison with the conventional predictors (116).

Thermal imaging

AI was also applied in other proposed imaging modalities including thermal imaging. On digital infrared imaging, thermal activity is increased in the breast tissues surrounding the malignant tumor. DL models have demonstrated high accuracy in detecting breast tumours from digital infrared images (117). The benefit of DL integration with thermal imaging extends to forecast modelling, where DL has been successfully applied to predict personal breast cancer risk (118).

Pathology

The gold standard for diagnosing breast cancer is biopsy evaluation by pathology (119). This allows for classifying and grading breast cancer as well as detecting lymph node metastasis, planning for treatment, evaluating resection margins status, and predicting patients' prognosis (120-122). However, pathological evaluation of microscopic biopsies carries the risk of inter-observer variability.

Applying AI models in analyzing microscopic images can assist pathologists in achieving faster, more precise, and reproducible breast cancer diagnosis (123,124). By reducing the workload on pathologists, AI integration can help compensate for resource strain within healthcare systems (12,125,126). In 2022, Cheng *et al.* applied CNN and RNN models in pathological classifications of breast fibroepithelial lesions into benign fibroadenomas and phylloid tumors. These models could accurately differentiate between and classify lesion types using images of the whole slide (127). AI-based models have also exhibited promising performance in applications to assess the risk of breast ductal carcinoma in situ (DCIS) invasion (128-130).

Preoperative applications of AI in breast surgery

Decision-making in cancer treatments is complex as it involves a diversity of data that need to be considered (131). Moreover, with the advances in medicine, new therapeutic options are proposed. Given the large amount of data for consideration and the rapid updates in the field, AI assistance in treatment decision-making would reduce the burden on clinicians and help them revise their treatment decisions (132,133). Bouaud *et al.* designed a decision support system that is based on guidelines to provide a complete patient care plan. In their study, they investigated the performance of this system in making treatment decisions for breast cancer patients. Clinicians changed their treatment decisions after reviewing the decision support system recommendations in 17% of the cases. The changed decisions were beneficial in 75% of these cases (134). In 2019, Xu *et al.* have also compared the decisions of their designed decision support system to the decisions of oncologists. The compared decisions were not concordant in 45% of the assessed cases. This nonconcordance was caused by variations in the clinical judgment in 21% of the cases, greater oncologists' adherence to the guidelines in 15%, and inaccessibility to the suggested treatment by the system in 5% (135). Another decision-making support system evaluation was conducted by Xu *et al.* in 2020 for breast cancer patients. Their support system resulted in treatment decision change by the physician in 5% of the patients and thus higher concordance with breast cancer treatment guidelines. In 63% of these cases, physicians changed their decisions because of considering the treatment option recommended by the system. Other reasons for treatment decision changes included highlighting certain patient factors by the system in 23% of the cases, and the system logic for decision making in 13% of the cases (136). Applying ML in decision making would allow surgeons with low operational volume to take decisions similar to the most experienced surgeons, as ML models learn and gain experience with each input (137).

The preferred management option for early-stage breast cancer is conservative breast surgery with sentinel lymph node biopsy and subsequent radiotherapy (138-140). However, some patients experience complete cure from neoadjuvant systemic treatment (NAST). For such patients, it may be reasonable to adopt a "watch-and-wait" approach before starting therapeutic surgery (138). For that reason, precise detection of the patient's response to NAST is necessary to avoid subjecting the patient to unnecessary surgery. At the same time, precise detection is crucial to eliminate the risk of missing residual malignant foci. AI-models have been successfully applied in this area to detect responses to NAST using MRI images and pathological specimens. Thereafter, AI models were designed to evaluate patients' responses to NAST by combining patients' imaging and biopsy findings with patient data. These models showed high accuracy in excluding residual malignant foci in the breast and axilla following NAST and determining eligibility for breast surgery (141-145).

An extra application of AI models is for educating breast cancer patients before breast surgery. A randomized control trial aimed at evaluating the ability of an AI model to educate women about the expected aesthetic outcomes following locoregional breast cancer surgery is currently being carried out. The model is expected to improve women's satisfaction with breast surgery, raise their psychological status, and reduce the need for subsequent plastic surgeries (146). A ML model was also applied in predicting the financial burden of breast cancer surgery. The investigated model showed high prediction accuracy (147).

Intraoperative applications of AI in breast surgery

In breast-conserving surgery, ensuring clear margins is crucial to prevent the recurrence of breast cancer. Malignant foci in the resection margins necessitate subsequent re-excision surgery (148). Hence, intraoperative evaluation of resection margins is of significant value (149,150). Laser Raman spectroscopy (LRS) is an optical imaging technique that generates a biochemical tissue signature by detecting the vibration in the molecular bonds. Thus, microcalcifications as well as immortalized and transformed cancer tissues can be detected (151-156). In 2021, Kothari *et al.* developed a ML model that was integrated with LRS to evaluate resection margins intraoperatively in vivo. This model could rapidly generate multiple models of tissue classification and directly calculate the probability of malignancy in the margins (157). Applying this type of system in breast conservative therapy could improve resection margin precision and reduce the need for re-excision surgeries.

Postoperative applications of AI in breast surgery

Lymphedema is a devastating condition that can occur immediately following axillary procedures, such as mastectomy with axillary clearance, or up to 20 years thereafter. This condition can present with a variety of symptoms (158). In 2018, Fu *et al.* designed ML models that assesses the occurrence of lymphedema following breast surgery based on symptoms reported by the patients. The designed model was tested and proved high accuracy (159). LLMs, like ChatGPT, are currently the most discussed AI tool to utilize in medicine, including breast surgery. Lukac *et al.* concluded that while it has potential, its current version is incapable of providing suitable recommendations for patients with primary breast cancer (160). Another possible devastating complication from axillary clearances is injury to the long thoracic, thoracodorsal, or intercostobrachial nerve, which sometimes must be sacrificed (161-163). AI could potentially be used to determine certain characteristics of breast tumors and axillary lymphadenopathy, making it safer to encroach more delicate structures like neurovascular bundles. They could also theoretically be employed to further study patient anatomy from pre-operative scans, which can be used to help predict the risk of nerve injury intra-operatively. During the writing of this manuscript however, the authors were unable to find dedicated studies to this topic.

Applications of AI in predicting breast surgery outcomes

van Egdom *et al.* designed an ML model that uses patient data and breast cancer characteristics to predict patient-reported outcomes postoperatively. However, when investigated, the model could not find a relationship between the input variables for predicting postoperative patient-reported outcomes (164). ML has, however, been used to effectively predict complications in the abdominal flap donor site following autologous breast surgery. Using these predictions, surgeons can tailor their operative techniques to achieve better outcomes and minimize the burden postoperatively (165).

About 15% of women with breast cancer experience severe pain postoperatively, which can last for years (166,167). Early identification of women's susceptibility to developing postoperative pain would allow for early initiation of medical and psychological treatment for those in need and avoidance of unnecessary interventions for those less susceptible (168,169). Using ML technology, Lötsch *et al.* designed and evaluated a system for predicting persistent pain following breast surgery. The model showed high accuracy in predicting postoperative persistent pain and a much higher negative predictive value (170). Another ML predictive model designed by Sipilä *et al.* showed high negative predictive value but low accuracy (171). In 2020, Juwara *et al.* designed an ML-derived model for predicting neuropathic pain following breast surgery. The model was superior to the traditional prediction model in predicting postoperative neuropathic pain (172).

Identifying women with high risk for recurrence would aid in providing the necessary follow-up and preventing potentially deadly disease progression. Lou *et al.* designed an ML-derived model that could accurately predict the risk of breast cancer recurrence within ten years following breast surgery (173). Other prediction models can provide high accuracy in predicting breast cancer recurrence after three and five years of breast surgery (174,175).

AI has been applied in predicting survival and mortality following breast cancer surgery as well. Huang *et al.* designed and evaluated an ANN model to predict the five-year mortality following surgery for breast cancer. The designed model showed greater accuracy when compared to conventional prediction methods such as the Nottingham prognostic index and breast cancer-specific survival (176-178). An additional ML model was developed by Moncada-Torres in 2021 to predict women's survival after undergoing breast cancer surgery. The model was similarly accurate as conventional prediction methods, if not superior (179).

Discussion

AI technologies are rapidly evolving and gaining interest, and their applications in healthcare are broadening to improve patients' outcomes (180). Models based on AI have the feature of learning from data, and hence, their performance gets improved. Breast surgery for benign or malignant breast lesions has markedly benefited from the advances in AI (4,5,12,13). These systems can rapidly process vast amounts of data and update the saved data, as well as their ability to logically operate with complex rules and decision trees. Thus, AI outperforms human cognitive functions and could assist healthcare providers in a diversity of tasks related to breast surgery from breast lesions detection and diagnosis to postoperative detection of breast surgery complications. As well, AI models assisted in predicting patient's response to therapy and postoperative breast appearance, cancer recurrence, and patient's survival (11,132,133,181,182). Most AI models currently approved by the Food and Drug Administration are designed to assist in breast lesion diagnosis through imaging and histopathological evaluation. Various models have been designed to assist in detecting and classifying breast lesions, describing breast tumor microenvironment and molecular subtype, predicting the risk of breast cancer, as well as predicting and evaluating treatment response. An AI-based model has been applied in US breast imaging to predict malignant lesion response to NAC using features of the lesion US before versus after one or two courses of NAC. In addition, some AI models have the capacity for reconstructing or even generating breast images (4,5,13,14). Our search revealed AI applications aimed at supporting oncologists in treatment decision-making and predicting postoperative outcomes (162,172,173,176,183).

Despite the notable breakthrough of AI technologies, some limitations are encountered. Highlighting these drawbacks is essential for making improvements in the models. As AI models' performance improves when more data are imported, the size of datasets used for learning matters. For some models, large datasets are not available (as for breast US imaging). Thus, these models are not trained enough and subsequently do not achieve a satisfactory performance. To overcome this shortcoming, data could be shared across medical centers. This solution cannot always be pursued because of patients' privacy policies, privatized health systems like the USA, and ethical laws regarding the transfer of sensitive patient information (184). Alternative solutions including federated learning and transfer learning are proposed. Federated learning implies sharing the algorithm after learning from data, but patients' data remains within the medical center. Transfer learning refers to learning from different datasets (e.g., US models can learn from DM images) (35,185). Special care must always be taken when data are imported to train AI models. Poor datasets could lead to inaccuracies (e.g., including wrong diagnosis of tumor and inter-observer variability) and various biases could lead to patient population underrepresentation. For these reasons, large multi-central multi-reader datasets are preferred for training AI models (186). Prediction models that provide clinicians with justification for their prediction provide more comprehensive assistance (187,188). However, it was evident from the results of our search that not all AI models are effective in establishing relationships between variables and predicting outcomes. As computing powers and data availability increase, prediction AI models are recommended to incorporate multi-dimensional predictors for stronger prediction evidence. When patients' physical examination and lab data are incorporated with their disease characteristics, the model can get a holistic picture and thus improve its performance. When an AI decision support model was compared to oncologists in terms of adherence to breast cancer treatment guidelines, oncologists showed better adherence. However, this was owing to the multiple input and factors driving the algorithm. The investigated algorithm was designed to take decisions not only based on breast cancer treatment guidelines, but also on some selected literature and information from textbooks (134). Finally, medicolegal dilemmas surround the application of AI in medical practice. Whether final decisions could be made by AI models and who would take the responsibility for wrong decisions are questions yet to be answered. This endorses the need for a regulatory body for AI applications in medicine. As well, if AI is proposed to replace humans, ethical issues of job losses would be encountered. It should be noted that articles with the specific focus of breast reconstruction, an important part of the recuperation process post-mastectomy, were not included in this review. The applications of AI in this domain have been elucidated in prior research. This theme was therefore excluded to maintain our objective of addressing current knowledge gaps.

Further improvements in AI are anticipated and AI models are desired to move from the experimental phase to actual implementation in healthcare. In breast lesion biopsy, future applications of AI might allow for identifying a few deformed cells within normal breast tissue. Regarding breast surgery, AI's possible preoperative applications involve surgical planning. The models could be used in anatomical data analysis for recommending individualized optimal approaches for breast surgeries. Moreover, future intraoperative applications of AI might include assistance in timely image analysis for precise tumor resection and intraoperative decision-making. AI-integrated robotic models, akin to the DaVinci system, that directly perform breast surgery or assist surgeons could also be introduced in the future (3,189,190). Postoperatively, AI could be applied in patient monitoring and follow-up for early detection of breast surgery complications or breast cancer recurrence. As uptake of these technologies increases within healthcare systems, the implications for training new clinicians involved in the surgical management of breast lesions must be considered. Healthcare education in the era of increasing AI integration will be a major topic for research in the coming years. Breast surgeons should be updated with the recent advances and applications of AI in their field to provide the best care for their patients (191,192).

Conclusions

AI algorithms are increasingly applied in all aspects of breast surgery. Different AI models were designed and evaluated to assist in breast tumor detection, classification, segmentation, staging, and grading. Preoperatively, AI models were applied in determining the need for breast cancer surgery and educating women. Intraoperatively, they enhanced surgical precision in tumor resection. Postoperatively, AI was able to predict breast surgery complications, survival, and cancer recurrence. However, more research is required to move AI from the experimental phase to widespread implementation in healthcare. Improved, novel applications of AI are already in development, and breast surgeons should stay updated to provide the best care for their patients.

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Review Article

Evolution of breast conserving surgery—current implementation of oncoplastic techniques in breast conserving surgery: a literature review

Inés Torras[#]^, Isaac Cebrecos[#]^, Helena Castillo, Eduard Mension^

Department of Obstetrics and Gynecology, Hospital Clínic of Barcelona, Barcelona, Spain

Contributions: (I) Conception and design: E Mension, I Torras, I Cebrecos; (II) Administrative support: H Castillo; (III) Provision of study materials or patients: I Torras, H Castillo; (IV) Collection and assembly of data: I Torras, I Cebrecos; (V) Data analysis and interpretation: I Torras, I Cebrecos; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as co-first authors.

Correspondence to: Inés Torras, MD. Department of Obstetrics and Gynecology, Hospital Clínic of Barcelona, Calle Villarroel, 170, 08036 Barcelona, Spain. Email: itorras@clinic.cat.

Background and Objective: De-escalation in breast cancer surgery has been a natural evolution since breast conserving surgery (BCS) was introduced in the early 1980s. From Halsted mastectomies to wide local excisions, we are facing nowadays the next trend in form of oncoplastic breast surgery. Oncoplastic breast surgery combines oncological principles with plastic surgery techniques to preserve the breast shape and appearance. The aim of this work is to review recent oncological and quality of live outcomes derived from oncoplastic techniques as well as offer a perspective about its implementation in breast cancer units.

Methods: A literature review was conducted to explore the landscape of oncoplastic breast surgery. Key terms related to oncoplastic techniques and breast cancer were used in searches across databases such as PubMed, Embase and Cochrane Library. Inclusion criteria focused on recent articles discussing oncological and quality of life (QoL) outcomes, as well as perspectives on the role of oncoplastic surgery.

Key Content and Findings: The research aims to contribute valuable insights into the efficacy and impact of oncoplastic surgery in the context of breast cancer treatment. In this new era of precision medicine, it is more than just healing patients; it is about improving their well-being. We ought to consider specific oncoplasty role in leading this paradigm shift. It is also relevant to define whether these new technical-demanding surgical options can be applied to all patients and if professional training performs adequately to current demands of personalized treatments.

Conclusions: The global adoption of oncoplastic BCS is recommended due to its oncological safety and improvement in QoL compared to standard procedures. Emphasizing the need for skilled surgeons in complex cases, collaboration between breast surgeons and scientific societies is urged to certify ongoing educational training in oncoplastic techniques.

Keywords: Surgery; breast cancer; oncoplastic

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^ ORCID: Ines Torras, 0000-0001-5961-2843; Isaac Cebrecos, 0000-0002-9333-3642; Eduard Mension, 0000-0002-1227-1137.

Introduction

Breast cancer is the most common cancer among women worldwide, with one out of seven women suffering a breast cancer in their lifetime (1). Breast conserving surgery (BCS) was adopted three decades backward, as trials like NSABP B-06, EORTC and the Milan trials demonstrated similar survival and recurrence rates for BCS compared to simple mastectomy and Halsted mastectomy procedures in early breast cancer (2-4). Even some authors suggest recently better survival outcomes comparing BCS versus mastectomies irrespective of reconstruction techniques (5). Additionally, it's become clear that, if possible, BCS should be performed, since better quality of life (QoL), psychological well-being and aesthetic outcomes have been reported comparing to mastectomy (6,7).

At a similar onset of the standard BCS (S-BCS), the term oncoplastic BCS (O-BCS) was firstly used, at the "Santa Fe Symposium on Breast Surgery and Body Contouring" in 1993 (8), but was not until 2006 in the Milan conference when the aims of the oncoplastic were defined, being these the complete excision of the tumor with free margins, minimal aesthetic compromise and simultaneity of the breast tissue reshaping if needed. Since then, interest in oncoplastic surgery within the scientific community has grown exponentially, leading to a "change of paradigm" in breast surgery in 2014 (9). This shift is reflected in recent international guidelines, such as National Comprehensive Cancer Network (NCCN) recommendations (10). This represents a fundamental change in how this type of surgery is approached and conducted, involving a departure from traditional practices, approaches or perceptions. We reference the advancement of techniques, comprehension of outcomes, and the integration of oncoplastic surgery into the broader context of breast cancer treatment. This transformation could result from technological progress, emerging scientific evidence and an approach centered on patients' well-being and QoL. Despite this increasing interest, oncoplastic techniques are not fully implemented in many breast cancer units world-wide yet.

The review aimed to provide a comprehensive overview of recent findings and perspectives in the field, highlighting the benefits and risks that O-BCS may offer. This contributes to the ongoing debate on the role and implementation of oncoplastic surgery in breast cancer units. We present this article in accordance with the Narrative Review reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-454/rc).

Methods

A literature review was conducted to identify articles related to oncoplastic surgery in breast cancer published in English up to March 2023 (*Table 1*). The focus was on publications that provided insights into the application, oncological and QoL outcomes, and challenges of oncoplastic surgery in the context of breast cancer treatment.

Oncologic outcomes

Local recurrence (LR), disease-free survival (DFS) and overall survival (OS)

In the context of O-BCS achieving good outcomes in terms of LR, DFS, and OS is essential. Reducing the risk of LR while maintaining a patient's OS and DFS are indicative of successful breast cancer management. The latest Cochrane review (11) published in 2021, which includes 78 non-randomized cohort studies evaluating 178,813 women, indicates that when comparing O-BCS to S-BCS, there may be little or no difference in terms of LR [hazard ratio (HR) 0.90, 95% confidence interval (CI): 0.61–1.34] and DFS (HR 1.06, 95% CI: 0.89–1.26). In comparison to mastectomy alone, O-BCS may lead to an increase in LR-free survival (HR 0.55, 95% CI: 0.34–0.91).

When compared to mastectomy with reconstruction, O-BCS may show little or no difference in LR-free survival (HR 1.37, 95% CI: 0.72–2.62) or DFS (HR 0.45, 95% CI: 0.09–2.22).

Despite oncoplastic procedures seems to offer comparable oncological results, it should be highlighted that most studies in oncoplasty are retrospective in nature, and there is still a lack of prospective randomized multicenter clinical trials in the literature. In addition, it should be considered that O-BCS comprises many techniques and each individual breast cancer patient does not have a unique surgical solution, thus there is great heterogeneity in oncoplastic techniques among studies when evaluating oncoplastic safety, since both reduction mammoplasties and volume replacement with local flaps are usually included in their analysis. It is challenging to conduct a randomized controlled trial (RCT) comparing O-BCS to mastectomy or S-BCS, given ethical considerations, patient preferences, clinical variability, and changing contexts in medical practice. Also, it is plausible that patients opting for reconstruction may have smaller and less aggressive tumors compared to mastectomy without reconstruction, influencing the outcomes and making them more similar to

Table 1 The search strategy summary

Items	Specification
Date of search	April 20th, 2023
Databases and other sources searched	PubMed-MEDLINE, Embase and Cochrane Database
Search terms used	"Oncoplastic surgery", "breast conservative surgery"
Timeframe	January 1985 to March 2023
Inclusion criteria	Reviews, systematic reviews, prospective and retrospective studies, case reports published in English
Selection process	Selection was independently carried out by the authors

those achieved with O-BCS.

Summarizing, the evidence is very uncertain regarding oncological outcomes following O-BCS, although has not been shown to be inferior.

Hence, current data supports the use of O-BCS in patients with breast cancer but better designed studies are needed to provide more robust data on its safety.

Margin status, lesion localization and tumor bed

In BCS, achieving clear margins is a critical aspect of the surgical procedure. S-BCS aims to remove the tumor with a margin of healthy tissue but may be more conservative in terms of breast tissue removal. O-BCS involves the simultaneous removal of the tumor while reshaping the breast. It often allows for a more extensive resection while preserving a satisfactory cosmetic outcome. The ability to achieve clear margins in O-BCS may be influenced by the surgeon's expertise in breast reshaping techniques. In most cases, the risk of positive margins can be lower due to the wider resections and the flexibility provided by these techniques. Losken *et al.* (12) showed a lower incidence of positive margins in oncoplastic surgery compared to S-BCS (12.2% versus 20.6%). Positive margin rate reported in oncoplastic studies ranges from 10.9% to 18.9% (13-15). In a systematic review (11), it was concluded that O-BCS may reduce the rate of re-excisions needed for oncological resection [risk ratio (RR) 0.76, 95% CI: 0.69–0.85], but the evidence is very uncertain.

The pre-surgical localization of lesions is a crucial point, and if necessary, employing multiple techniques or multiple markers to delineate the area for resection. Wire-guided localization (WGL) is the most common used localization method, and it is considered the standard localization method of non-palpable breast lesions. Notwithstanding, newer technologies have emerged that enable the localization of lesions with a similar detection rate and clear margins, enhancing the experiences for both the surgeon and the patient. These include radio-guided occult lesions localization (ROLL), intraoperative ultrasound (IOUS), seeds [Radioactive Seed, MagSeed® (Endomagnetics Inc., Cambridge, UK), SAVI Scout® (Merit Medical, South Jordan UT, previously Cianna Medical, Aliso Viejo, CA, USA)], among others.

In this context, the ongoing EUBREAST MELODY study aims to assess different imaging-guided localization methods in terms of oncological safety, patient-reported outcomes, and satisfaction levels among surgeons and radiologists. The target accrual is 7,416 patients, with enrollment starting in January 2023. The study will be conducted across 20 countries (16).

When facing O-BCS accurate localization of tumor bed, detailed specimen orientation and clear marking of lumpectomy cavity are important factors not only for surgery success, but also for guiding further procedures such as margin re-excision when needed and radiotherapy planning (17). In order to reduce positive margins rates during oncoplastic procedures some groups propose several options to assess intraoperatively margin status, such as routine margin shaving or intraoperative specimen radiography and gross pathological evaluation to guide the need for further tissue resection during index surgery (18-20). The most well-established methods for margin assessment include gross inspection, frozen section analysis (FSA), and imprint cytology (IC). According to one systematic review, FSA and IC could reduce reoperation rates from 35% to 10% and 11%, respectively (21).

Radiological methods have shown promising results, with numerous studies unanimously demonstrating the excellence of IOUS in achieving negative margins, reducing resection tissue volume, and improving overall aesthetic results and patient satisfaction (22).

Regarding the use of mammography, the reported sensitivity of specimen mammography for intraoperative margin assessment ranged from 20.6% to 45.45% (23). According to the authors, mammography would be highly useful in cases that radiologically present as microcalcifications.

An emerging trend involves the participation of artificial intelligence (AI) during image identification. Novel techniques provide alternative approaches to evaluating margins during surgery and include radiofrequency spectroscopy, bio-impedance spectroscopy, and optical coherence tomography (OCT). There are also preliminary studies involving the use of drugs to modify and make lesions visible, such as studies including EC17 and trastuzumab, or 18F-fluorodeoxyglucose (^{18}F-FDG) used for specimen positron emission tomography-computed tomography (PET-CT).

Nevertheless, BCS for ductal carcinoma in situ (DCIS) and BCS after neo-adjuvant chemotherapy pose significant challenges in achieving negative margins.

“Negative margins” is currently considered as no ink on the tumor when we are referring to infiltrating breast carcinoma, as indicated by the NCCN guidelines (10). However, distinctions arise in cases of DCIS, where margins of at least 2 mm are linked to a decreased risk of ipsilateral breast tumor recurrence (24). While oncoplastic level II resections in high-risk breast cancer patients enhance margin width, they do not correlate with lower rates of LR. Interestingly, the use of oncoplastic level II techniques significantly reduces the number of re-excisions attributed to R1 (25).

In De la Cruz’s systematic review (26), the rate of positive margins in oncoplastic surgery varied widely (0–39.7%), given that the assessment of positive margins is highly heterogeneous. Eleven studies reported specific margins for 1,455 patients. Among these patients, 143 (9.8%) were classified as having positive margins, of which 113 (7.8%) had ink on the tumor.

The problem lies in cases of oncoplastic surgery with involved margins and the oncological safety of margin re-excision. According to the authors, we believe that margin re-excision is feasible even if there has been glandular mobilization. To achieve this, it’s important to mark both the tumor bed and the surgical field with clips, ensure good communication between the pathologist and the surgeon, and ensure concordance between imaging results and pathological findings. It won’t be the same a margin in focal contact as it would be for several involved margins or multifocal/multicentric lesions. If possible, it is advisable that the same surgeon performs both surgeries. One must be realistic when considering the possibility of margin re-excision to avoid false reassurance.

In some cases, patients with positive margins after O-BCS will proceed to mastectomy. Nevertheless, there is a great discrepancy in mastectomy conversion rates after upfront O-BCS in the literature for involved margins, ranging from 12.5% to 100% (15,27-31). Despite this fact, mastectomy is not always necessary when managing a positive margin after O-BCS. In a retrospective study where 649 patients underwent oncoplastic Wise pattern reduction, 95% were successfully managed with margin re-excision while maintaining breast-conserving therapy. There was only one in-breast recurrence in this case series (32). The use of magnetic resonance imaging (MRI), which enhances lesion detection sensitivity, could potentially increase the mastectomy rate. Additionally, it has not been demonstrated that the use of MRI increases the risk of involved margins.

In summary, despite great volume displacement resulting during oncoplastic procedures, re-excision for margin clearance is possible as long as margin involvement is focal in pathological specimen. Otherwise, when facing multiple margins affection ensuring new clear margins would be challenging and a mastectomy should be offered.

Mastectomy reduction rate: extreme oncoplasty [neoadjuvant chemotherapy (NAC) and DCIS]

Oncoplastic surgery is extending the role of BCS to an increasing number of patients who are candidates for mastectomy. This new approach includes patients with locally advanced breast cancer tumors larger than 5 cm at presentation, multifocal and multicentric disease and intraductal carcinoma with extensive involvement. Silverstein *et al.* was the first to introduce the term extreme oncoplastic (EO) to describe breast cancer patient candidates for BCS for which most physicians would performs a mastectomy (33). Trying to get a more adjusted definition of EO-BCS, we must push Clough *et al.*’s classification beyond level 2, were breast volume excision greater than 50% or skin replacement would be needed to achieve free margins tumor excision (34). In these cases, we should consider volume displacement techniques to reconstruct partial breast defect using mammoplasty techniques including local glandular tissue advancement flaps, mastopexy, and reduction mammoplasty or volume replacement procedures, including autologous flaps designed to reconstruct a new breast after resection, such as chest wall perforator flaps (CWPFs), among which are the lateral intercostal artery perforator (LICAP), lateral thoracic artery perforator (LTAP), a combined flap, and anterior intercostal artery perforator/medial intercostal artery perforator (AICAP)/(MICAP).

These extreme procedures should also be considered even in the neoadjuvant setting for tumors that did not shrink optimally after NAC or in the presence of extensive intraductal disease. NAC was initially introduced for patients with large breast cancer to downsize the tumor in an attempt to allow breast conservation for patients who would have been treated by mastectomy. Van la Parra *et al.* (35), showed that EO-BCS can further extend the indications for breast conservation after NAC, providing equal local control to those tumors that did respond optimally and underwent S-BCS, and similar to smaller cancers that did not undergo NAC.

Because of the great amount of breast resection carried out during EO procedures, immediate or delayed breast symmetrization should be offered when considering patients for O-BCS, especially in EO procedures definition. The ideal timing for symmetrization is not clear and remains controversial. Some authors argue that it should occur after index breast surgery and the administration of adjuvant radiotherapy, as longitudinal changes due to radiotherapy can affect the final outcome. However, predicting these changes can be challenging (36).

Other authors (37,38) believe that contralateral symmetrization could be performed at the time of O-BCS in carefully selected patients without significantly increasing the risk of complications or delaying adjuvant radiation therapy. Also delayed symmetrization in BCS resulted in an additional cost when compared with immediate bilateral mammoplasty. In this context, it is relevant to address the availability of operating theaters, as this surgical intervention aims to achieve aesthetic symmetry. In some countries, there is a significant limitation in terms of access to operating theaters and adequately trained medical staff, which can prevent or hinder the execution of contralateral symmetrization procedures.

EO is an excellent alternative to mastectomy since locally advanced tumors are most of breast cancer candidates for oncoplastic procedures requiring radiation therapy anyway. Radiotherapy after conservative surgery will offer kinder results than mastectomy with implant reconstruction followed by mastectomy chest wall irradiation in term of QoL, cosmetic results and healthcare costs (39,40).

Complications

The Clavien Dindo Classification assesses the severity grade of postoperative complications in breast surgery on a scale from 1 to 5. Grades 1–2 represent minor complications (requiring no treatment or only pharmacological treatment), Grades 3–4 signify major morbidity (requiring surgical treatment and involving life-threatening complications), and Grade 5 is associated with postoperative death (41).

Complication rates for oncoplastic procedures reported in most studies are relatively high (range, 16–30%) (14,20,29,42) although there are also a few studies in large populations reporting lower complications rates (8–10%) (13,15). O-BCS and EO inherently involve greater technical complexity and are associated with glandular tissue mobilization that may entail a higher risk of fat necrosis and complications compared to S-BCS (43). According to Nizet *et al.*, size resection was the only factor associated with postoperative complications, confirming that complexity of O-BCS is linked to postoperative complications risk (44).

Fat necrosis and wound dehiscence, ranging from 0.9% to 6% (45,46), are uncommon yet challenging complications of oncoplastic procedures. It is important to emphasize that while these issues are indeed associated with technical flaws, patient-related risk factors have been identified as significant influences on wound healing, underscoring the necessity for careful patient selection. This consideration aligns with findings demonstrating that high-volume oncoplastic BCS is an independent risk factor for delayed wound healing (47,48).

Extreme fine dissection of glandular flaps and excessive suture tension in wound predispose to their appearance. Thus, adjuvant treatments administrations will be delayed until wound closure is settled, which may result in prognosis impairment. On the other hand, although fat necrosis is usually asymptomatic it is and evolving complication enhanced by radiation therapy (45,46).

Cosmetic sequelae (CS) should also be considered when analyzing oncoplastic results, since it usually arises during the first 5 years after surgery and affect up to 17% of oncoplastic procedures. Acea-Nebril *et al.* proved in a multivariate analysis that CS were significant related to complexity of oncoplastic procedure [odds ratio (OR) 2.605; 95% CI: 1.623–4.181; P<0.01] and clinical postoperative complications (OR 4.626; 95% CI: 2.719–7.868; P<0.01), especially fat necrosis and hematoma (49).

Finally, increase in postoperative complication rate derived from oncoplastic procedures is an issue of great concern, because it may cause delay in adjuvant treatments administration. The Cochrane review by Nanda *et al.* suggests that the time to adjuvant therapy may be increased, specifically in the case of adjuvant radiotherapy, when utilizing O-BCS as opposed to S-BCS. This potential extension in time could be attributed to delays arising from complications. The delay in adjuvant radiotherapy is estimated to range between 7.21 and 12.1 days, which could hold clinical significance (11).

Skilled and trained surgeons in oncoplastic techniques are needed in present and future breast cancer units in order to reduce technical failures. Accurate selection of both, patients who are candidate for O-BCS and selective mammoplasty techniques adapted to each individual situation is essential to improve oncoplastic complications rate (34).

QoL outcomes

QoL is a multidimensional concept with challenging evaluating issues. QoL usually includes traditional outcomes such as survival, efficacy, and safety, but they do not provide a complete picture, thus assessing well-being emotional perception component, patients' preferences, goals, and personal satisfaction are also crucial. These aspects are related to different aspects of life, such as physical and mental health, social relationships, and economic status.

O-BCS is often considered to have a positive impact on patient's QoL outcomes, as it can provide better cosmetic results and a lower risk of sequelae compared to mastectomy (50). However, the specific impact can vary for each individual and may depend on various factors such as tumor size and location, patient's overall health, and type of treatment received after surgery. Evidence is required to assess whether high-volume O-BCS, which entails a heightened risk of complications but potentially a lower rate of re-excisions, may impact QoL.

Patient-reported outcome measures (PROMs) are assessments of health status, function, or symptoms directly reported by patients, rather than observed or recorded by clinicians. These measures provide valuable information on patient's perspective and can complement traditional clinical measures. PROMs have become increasingly important in breast surgery evaluation, as they allow patients to provide feedback on their outcomes and help to identify areas for improvement in care delivery. One of the most widely used tools to evaluated QoL is BREAST-Q (51), a validated and specific test, translated into many languages, which includes physical, psychosocial, sexual and satisfaction questions. BREAST-Q has become the gold standard PROMs instrument for breast surgery.

There are other PROMs used to assess outcomes in breast surgery, including European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, the EORTC QLQ-BR23 and QLQ-BR45 questionnaires, The Functional Assessment of Cancer Therapy-Breast (FACT-B) or MD Anderson Symptom Inventory module specific to breast cancer (MDASI-Br) (52-55).

Currently, the COSMAM study is being conducted at a single-center in the Netherlands. This prospective study aims to evaluate the QoL and cosmetic outcomes in patients undergoing standard lumpectomy versus level I or II O-BCS (56).

Aesthetic results

Achieving good cosmetic result is one of the factors which is proportional and directly linked to QoL (57). Evaluation of aesthetic results can be subjective, based mainly on patient's self-assessment or evaluation by a single or panel of observers. It can also be objective, using tools like Breast Symmetry Index (BSI) or Breast Cancer Conservation Treatment cosmetic results software (BCCT.core) which measure symmetry and proportion in postoperative photographs (58,59).

Three-dimensional surface imaging (3D-SI) is being marketed as a tool in aesthetic breast surgery, and it has recently also been studied in the objective evaluation of cosmetic outcome of oncological procedures and have the potential to assist in pre-operative planning (60,61). Efforts are ongoing to develop objective measures for this subjective concept.

When comparing O-BCS to standard breast surgical techniques, O-BCS volume displacement procedures had significantly better aesthetic outcomes than conventional BCS, either if objective methods (breast retraction assessment) and subjective methods (panel assessment) are used in evaluation, as well as when body image questionnaires are available (62).

It is crucial to note that tumor size and location play a significant role. For larger primary tumors in cosmetically sensitive zones of the breast, O-BCS is likely to result in significantly improved aesthetic outcomes when compared to S-BCS.

In two studies including over 120 patients with unilateral O-BCS, BREAST-Q "Satisfaction with their breast" median score was reported between 65–74/100, and factors associated with a score below median value were axillary clearance (OR 2.46, 95% CI: 1.09–5.56), NAC (OR 3.26, 95% CI: 1.15–9.24), and low breast density (OR 2.32, 95% CI: 1.02–5.29). It is remarkable that only 11% of these patients were interested in contralateral surgery (63,64). Similar results regarding breast symmetry where reported by de Oliveira-Junior *et al.* in a series where contralateral surgery for symmetrization was not associated with high patient satisfaction (65).

When compared with mastectomy, a literature review showed significantly higher scores in BREAST-Q questionnaire in O-BCS, regardless of the type of the reconstruction performed after mastectomy (66).

When analyzing QoL results according to oncoplastic technique used, volume displacement techniques reported significantly higher scores for "physical well-being of the chest" than patients who underwent volume replacement. Also, patients without complications had significantly higher scores in "satisfaction with the breast" and "satisfaction with information about the surgery" domains compared to patients with complications (64).

Sexual well-being

Breast cancer survivors have the highest rates of lost disability-adjusted life years (DALYs) among all types of cancer and often experience high rates of sexual dysfunction (SD) as well, which can persist for years and significantly impact their QoL (67). SD rates among breast cancer survivors can range from 60–90% (68-72). It is a multifactorial entity severely influenced by the secondary effects of treatments and the psychological impact of presenting the disease itself. Breast cancer survivors often report various symptoms of SD, including difficulties with arousal or excitation, decreased sexual desire, insufficient lubrication, and penetration pain. These symptoms can have a profound impact on sexual function.

Surgery causes a direct disruption in body image. This alteration is magnified by the fact that breasts, apart from being one of the key erogenous parts of the female body, are considered to be symbols of sexuality and sexual identity. The section on sexual well-being in the BREAST-Q questionnaire has been reported to receive lower scores compared to other sections in many studies.

Some studies suggest that BCS with radiotherapy can lead to clinically meaningful improvements in psychosocial and sexual well-being for women with early breast cancer, compared to those who underwent mastectomy with reconstruction (73).

A systematic review found that women who underwent O-BCS had better sexual well-being and residual skin sensitivity compared to those who underwent mastectomy, despite the type of reconstruction (74). These findings suggest that preserving the breast tissue and improving breast appearance through oncoplastic techniques can have a positive impact on sexual well-being for breast cancer survivors (75). However, it is important to note that individual experiences may vary and additional support may still be needed.

Psychological well-being

There are two components as main cornerstones of psychological well-being: the cognitive component, which refers to global judgments about life satisfaction; and the affective component, which refers to feelings about life experiences and the roles a person holds. Both components are important for overall psychological well-being and contribute to successful social functioning (76).

Patient's perception of preoperative information and the opportunity to participate in decision-making are crucial factors in determining satisfaction with diagnostic-therapeutic process. Patients who feel involved and well-informed during the process are more likely to have positive outcomes and be satisfied with the results. This is why it is essential for healthcare providers to settle effective and clear communicative pathways with their patients, listen to their concerns and preferences, and involve them in the decision-making process as much as possible (77).

Surgical removal of gross part of breast tissue can result in visible scars, deformities, or asymmetry, which can have a negative impact on mental health, including anxiety, depression, body image issues, and difficulties with sexual intimacy. Postoperative recovery and its sequelae are involved in QoL, however other subjective factors such as the aesthetic result and changes in physical appearance play an important role for a large part of the patients. Also, undergoing multiple interventions for cancer treatment may have a significant impact on a person's daily life and overall health perception. It can lead to chronic distress and make it difficult for them to return to their normal routine (78).

Research in the field of literature indicates that patients tend to experience improved physical and psychological health when oncoplastic surgery techniques are employed, as opposed to undergoing mastectomy with or without reconstruction (79). Additionally, the average psychosocial well-being score in the BREAST-Q questionnaire is notably higher in patients who undergo O-BCS when compared to those who opt for simple S-BCS alone (41.94±5.78 versus 38.02±7.21; with a statistically significant P value of <0.0001) (80).

Current implementation of oncoplasty

Standardization and evaluation of oncoplastic techniques

Several O-BCS classifications have been proposed to create homogeneity, decrease complexity, and form a basic lexicon for patients, surgeons, trainees, and educators for worldwide standardization. Currently, the most used classification divides the techniques into two groups: volume displacement procedures and volume replacement interventions.

Clough *et al.* (34) classified oncoplastic surgical techniques based on the breast volume to be resected and the quadrant of the tumor located serving to standardize O-BCS to adopt in routine clinical practice. They included only volume displacement techniques denoted up to 20% of the breast volume to be resected as level I and 20–50% of the volume to be resected as level II techniques.

In 2019, the American Society of Breast Surgeons (ASBrS) performed a comprehensive literature search and created a consensus definition and classification based on 30 articles defining oncoplastic surgery (81), using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (*Figure 1*).

When considering cancer surgery outcomes, case-adjusted improvements in long-term survival probably represent the best measure of performance. But today, demand in breast surgery has increased, being essential the aesthetic results and QoL outcomes.

Future of quality improvement and standardization is only possible by conceptualization of value through quality indicators (82). It is currently recommended to carry out systematically questionnaires that can serve as tools to assess QoL and cosmetic results, as well as a registry of morbidity, complications and post-surgical sequelae in prospective trials. It is also essential to take images before surgery and during follow-up to acquire scientific evidence and evaluate aesthetic results of oncoplastic procedures. Photographic documentation of patients before and after surgery is an important standard for clinical routine practice, as recommended by the panel in the first international consensus conference on standardization of oncoplastic surgery in 2017 (83).

Aesthetic results in breast surgery are dynamics, influenced by physical changes such as weight change or aging, as well as others factors derived from treatments, such as radiotherapy. Times and periodicity for iconography acquisition and storage should be standardized, requiring a baseline image, before radiotherapy, 1 year after radiotherapy and 5 and 10 years after surgery (84). Unfortunately, the major issue about O-BCS outcomes is the absence of standardized quantitative evaluation measures to permit comparative research and to access high level of evidence which is a must to create applicable guidelines.

A review published in 2021 by a panel of experts utilized the GRADE system to analyze published data. Despite certain areas of controversy, approximately one-third (36%) of the panel members strongly recommended O-BCS (85).

Patient expectations play a crucial role in the overall success and satisfaction with any medical procedure, particularly in the field of breast surgery. In the absence of clear communication and alignment of expectations between patients and surgeons, there is a growing challenge leading to increased rates of litigation related to breast surgery in various countries. Addressing and managing patient expectations should be considered a key component in the comprehensive evaluation and standardization of oncoplastic techniques to ensure not only medical success but also patient contentment and reduced legal repercussions.

Learning curve in oncoplastic techniques and training

Historically, breast surgery was quite simple, all women were treated with mastectomy and axillary clearance without reconstruction, and it was performed by gynecologist and general surgeons who had finished their residency training programs with mixed contents. Modern breast surgery is now highly complex and such limited training is not adequate for actual standard of care.

When learning a new procedure, performance tends to improve with experience, and graphically plotting performance against experience produces a learning curve. The origins of this concept derive from aviation and industry, but it has been transferred to different areas of medical practice (86).

Trainees have to explore their learning process. The use of simulation and virtual reality can offer several

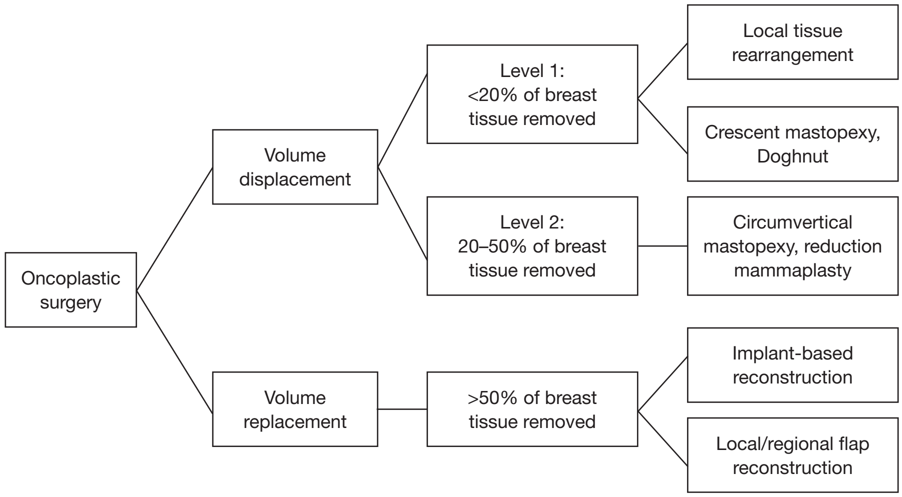

Figure 1 Oncoplastic surgery classification by the American Society of Breast Surgeons, 2019. Adapted from Chatterjee *et al.* 2019 (81) with permission.

advantages, such as providing a safe and controlled environment for surgeons to practice and refine their skills. These simulations can help train and educate medical professionals without exposing patients to unnecessary risks. It's essential for researchers and practitioners in the field of breast surgery to consider and incorporate these innovative training tools and methodologies into their practice to enhance surgical skills and patient safety.

The advantage of having an organized breast unit with trained professionals and in training in oncological and reconstructive surgery techniques made possible to develop these procedures and obtain good results. The role of the breast surgeon mainly consists in proposing the optimal surgical treatment without compromising further adjuvant treatments. Plastic surgeons may be unavailable or not involved in breast cancer management, so it is mandatory that breast surgeons be trained and skilled in O-BCS techniques to provide the optimal quality of care (87).

It is important to point out that in all new surgical techniques the key relies on the cases needed to learn how to do the procedure and how it will be evaluated. Defining a number of procedures that are needed to reach a certain level of safety can be helpful for educational purposes. During surgical training, new skills and competences need to be acquired safely without compromising patient safety. Once the procedure is successfully performed then it is necessary to identify quality measures that evaluate outcomes and opportunities to improve the technique with appropriate feedback. The constant maintenance of the learning curve is necessary, especially in oncoplastic techniques of level 2 and 3 which represent a higher level of complexity.

Currently we do not have enough evidence about learning curve of O-BCS, but it has been studied in other surgical techniques of breast surgery that can guide us about the process. In a prospective study where learning curve of IOUS in BCS was evaluated, it was concluded that 11 cases were sufficient to acquire skills to perform the technique (88). Krekel *et al.* establish that the learning curve for this type of surgery would be two cases to obtain the basic concepts and skills and eight procedures to perform autonomously (89). A systematic review that included 29 studies focused on the learning curve of plastic surgery (including mastectomy, non-free flap and free flap reconstruction) did not allow pooling of the data because of heterogeneity, but improvement was demonstrated in operation time, success and complication rate with surgeon experience, and the plateau of the learning curve was reached after 45 to 100 cases (90). About endoscopic total mastectomy, it is described a plateau at 30 to 50 endoscopic total mastectomy procedures (91). Other authors reported learning curves in time, which are more prolonged, such as 8–12 years of experience on mammoplasty (92,93).

Despite these publications, the medical community has been moving away from using the number of repetitions or cases as the sole benchmark for proficiency and competence. Instead, there is a growing emphasis on establishing objective, expert-derived benchmarks that are based on a deeper understanding of the skills and competencies required in a particular medical procedure.

In USA breast surgery is a subspecialty with available fellowships. However, in Europe O-BCS techniques are performed by gynecologists, general or plastic surgeons who became breast surgeons after adequate training and experience, but at present is not a recognized subspecialty. To overcome this regulation difficulty, the European Breast Surgical Oncology (BRESO) initiated a pan-European curriculum for completely trained breast surgeons and proposes that all surgeons practicing in Europe should be certified, by means of undertaking high level training either within their residency (if available) or by means of approved specialist fellowships, which includes O-BCS (94). The Association of Breast Surgery (2) in the UK is a professional organization dedicated to promoting the highest standards in breast surgery. They provide education, training, and support for healthcare professionals involved in breast surgery.

Limitations

The literature included diverse study designs, ranging from case reports to prospective studies, leading to variability in the level of evidence and potential biases. Several studies had relatively small sample sizes, which may limit the generalizability of findings and the ability to detect significant differences or trends. The absence of RCTs in some areas of oncoplastic surgery limits the ability to establish causal relationships and ascertain the true effectiveness of specific interventions.

Future research should prioritize prospective studies with extended follow-up periods to better understand the long-term oncological and cosmetic outcomes of oncoplastic surgery. Research should aim for standardized reporting of outcomes and methodologies, facilitating more robust meta-analyses and systematic reviews.

Conclusions

O-BCS should be offered as a possible therapeutic option in every breast cancer unit world-wide, since evidence support its oncological safety and reports better QoL and well-being compared to S-BCS and mastectomy. In order to improve surgical results and avoid complications derived from increasingly complex oncoplastic procedures, only skilled and trained surgeons should be allowed to perform type 2 or 3 O-BCS. Simultaneously, it is breast surgeons' responsibility to deal with scientific societies to finally certify continuing educational training in oncoplastic techniques.

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Footnote

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Case Series

Radiofrequency ablation as a novel modality in Ecuador for treating toxic thyroid nodules: a case series

Cristhian García[1], Paola Solis-Pazmino[1,2,3]^, Eduardo Pilatuna[1], Ana Perez[1], Luis A. Figueroa[1,4]

[1]Institute of Thyroid and Head and Neck Diseases (ITECC), Quito, Ecuador; [2]Head and Neck Surgery Department, Surgery Group of Los Angeles, Los Angeles, CA, USA; [3]General Surgery Department, Santa Casa de Misericordia, Porto Alegre, Brazil; [4]Facultad de Ciencias Médicas, Universidad Central del Ecuador, Quito, Ecuador

Contributions: (I) Conception and design: C García, P Solis-Pazmino; (II) Administrative support: C García; (III) Provision of study materials or patients: C García, P Solis-Pazmino; (IV) Collection and assembly of data: E Pilatuna, A Perez; (V) Data analysis and interpretation: LA Figueroa, P Solis-Pazmino; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Paola Solis-Pazmino, MD. Institute of Thyroid and Head and Neck Diseases (ITECC), Quito, Ecuador; Head and Neck Surgery Department, Surgery Group of Los Angeles, 8635 West 3rd Street, Suite 880W, Los Angeles, CA 90048, USA; General Surgery Department, Santa Casa de Misericordia, Duque de Caxias 1667, Porto Alegre, Brazil. Email: paosolpaz18@gmail.com.

Background: Treating hyperthyroidism induced by autonomously functioning thyroid nodules (AFTNs) through radioactive iodine and surgery often results in undesirable hypothyroidism. Radiofrequency ablation (RFA) has arisen as a favorable option. European guidelines recommend RFA for small AFTN in young patients, aiming to restore normal thyroid function and avoid irradiation. The procedure, costing between 500 and 1,000 euros, is conducted in outpatient clinics and takes 15 to 40 minutes. We aimed to describe the clinical outcomes of AFTN patients treated with RFA in Ecuador.

Case Description: We included eight patients with toxic thyroid nodules suppressed thyroid-stimulating hormone (TSH), with symptomatic hyperthyroidism. The mean age was 41.63 years [standard deviation (SD): 14.97 years]. The median follow-up time was 8 months. Nodules were solid (37.5%) or predominantly solid (62.5%). The mean volume pre-RFA was 5.27 mL [interquartile range (IQR), 0.70–9.66 mL]. After ablation, the median volumes at 1, 3, and 6 months were [2.25 (SD: 1.67; P<0.12), 1.28 (SD: 1.1; P=0.013), and 1.37 (SD: 1; P=0.23) mL], respectively. The volume reduction (VR) was 45.8%, 75.1%, and 69.7% at 1-, 3-, and 6-month follow-up, respectively.

Conclusions: RFA holds promise as a potential therapeutic approach for managing AFTNs. The success and the feasibility of RFA in this series are consistent with other studies as a treatment option in young patients with small AFTN. However, more research is needed to establish comprehensive guidelines and protocols to maximize the benefits of RFA in AFTNs.

Keywords: Case series; toxic thyroid nodule; radiofrequency ablation (RFA); hyperthyroidism

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Introduction

An autonomously functioning thyroid nodule (AFTN) is typically benign and makes up roughly 5% of all thyroid nodules. It presents with a wide range of clinical features, with the potential to progress from normal thyroid function to hyperthyroidism. Antithyroid drugs (ATDs) may be employed to restore a euthyroid state. The primary treatments for AFTN include surgery and radioiodine (RAI), according to the initial approach. However, some patients may opt out of these options or face contraindications.

^ ORCID: 0000-0003-1725-232X.

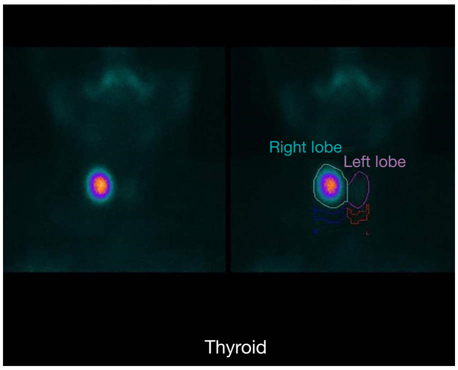

Figure 1 Thyroid scintigraphy.

Minimally invasive techniques like radiofrequency ablation (RFA) have shown volume reduction (VR) and euthyroid restoration in treating AFTN (1).

RFA is widely acknowledged as an effective treatment for non-functioning benign thyroid nodules, primarily aimed at alleviating compressive symptoms (2). European guidelines advocate for RFA in young patients with small AFTN, emphasizing a higher likelihood of restoring normal thyroid function and avoiding irradiation. Furthermore, an international consensus suggests that RFA is most suitable for patients with small nodules (≤3 cm) and contraindications to RAI or surgery (3). In Europe, an RFA applicator costs between 500 and 1,000 euros, and the procedure is typically performed in an outpatient setting, taking 15 to 40 minutes (4). While RFA has recently been introduced in the U.S. and Latin American countries, Ecuador began using it in 2019 for patients with AFTN and papillary thyroid carcinoma (PTC).

Our study aims to describe the demographic characteristics and clinical outcomes following the first cohort of patients with AFTN who underwent RFA in Ecuador. We present this article in accordance with the PROCESS reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-425/rc) (5).

Highlight box

Key findings
- Radiofrequency ablation (RFA) was a feasible and safe alternative for treating autonomously functioning thyroid nodules (AFTNs).
- The nodular volume reduced significantly after RFA treatment over time (P<0.001).
- The thyroid-stimulating hormone normalized after RFA and they did not use hyperthyroid medications.

What is known and what is new?
- The euthyroid restorage at 12 months after a single session of RFA.
- After a single RFA session, the volume reduction at 6 months was 70% (standard deviation: 6.79; P=0.016).

What is the implication, and what should change now?
- RFA may be more helpful in single AFTN than toxic multinodular goiter.
- Small nodules (<12 mL) responded better to RFA than medium-sized nodules (>12 mL).

Methods

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients to publish this case series and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Participants

This case series occurred at the Institute of Thyroid and Head and Neck Diseases (ITECC), a private referral center for individuals with thyroid nodules in Quito, Ecuador. From July 2022 to May 2023, the study included eight patients who underwent RFA for AFTN under the care of a head and neck surgeon (C.G.).

Pre-ablation assessment

Before treatment, comprehensive assessments were conducted, encompassing blood tests, thyroid function tests, coagulation tests, and imaging evaluations. Ultrasound scans provided detailed information on nodule characteristics such as size, location, margin, shape, echogenicity, calcification, and vascularity. Thyroid scintigraphy was performed for all patients to visually depict functional thyroid tissue based on the selective uptake of radionuclides (*Figure 1*). Nodule volume was determined using the American Thyroid Association (ATA) formula (6). Nodules were categorized as solid, predominantly solid, predominantly cystic, or cystic based on their cystic-to-solid ratio (7), with mixed nodules defined as having a solid component between 30% and 70%.

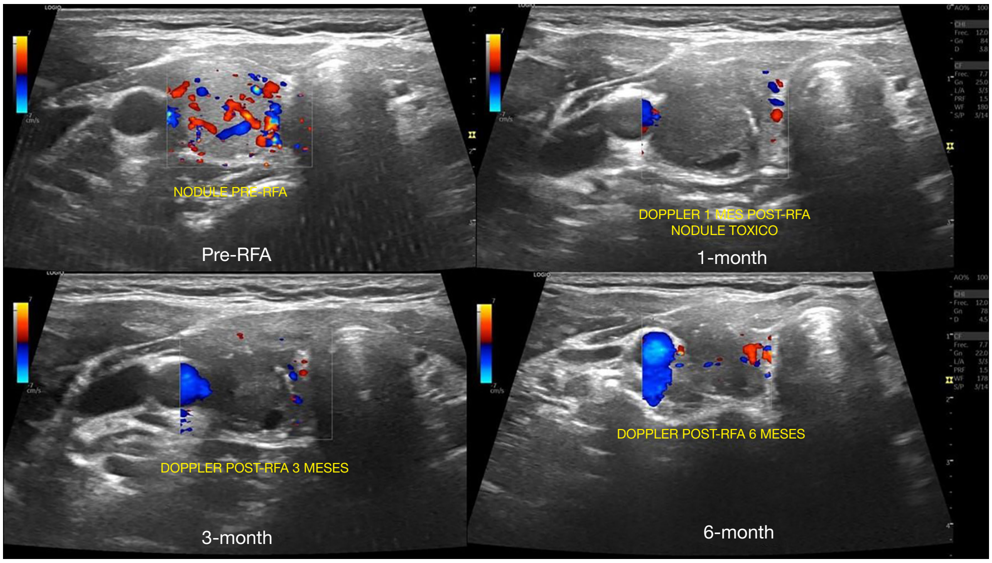

Figure 2 Follow-up at 1-, 3-, and 6-month post-RFA. RFA, radiofrequency ablation.

Ablation technique

RFA, administered by a head and neck surgeon with 3 years of RFA experience, was carried out using local anesthesia (2% lidocaine without epinephrine) as an outpatient procedure. After cleansing with povidone-iodine, a needle with an 18-gauge, 7-mm active tip size electrode was positioned within the nodule using a long-axis trans-isthmic approach. Nodules were then subjected to ablation using the moving-shot technique.

Follow-up evaluation

Patients were monitored at 1, 3, and 6 months post-RFA (*Figure 2*). The evaluation included an assessment of hyperthyroid symptoms and the use of antithyroid medication. Ultrasound neck scans and laboratory tests were mandatory at each follow-up visit. The ATA volume calculator determined the treated nodules' VR.

Analysis and statistics

Statistical analysis utilized the R program. Distribution normality was assessed visually and through the Shapiro-Wilks test. For continuous variables, the medians and interquartile ranges (IQRs) were calculated. Categorical variables were presented by frequency (percentage). The pre- and post-RFA VR changes, thyroid-stimulating hormone (TSH), and free thyroxine (fT4) laboratory values were assessed using a paired *t*-test. Cohen's d value was employed to gauge the magnitude of mean differences as small, medium, or large.

Case presentation

Demographic characteristics

Table 1 shows the clinical characteristics of the patients with AFTNs who underwent RFA. All the patients were females (n=8). The mean age was 41.63 years [standard deviation (SD): 14.97 years]. Five patients who had symptomatic hyperthyroidism (tachycardia, high blood pressure, or weight loss) were treated with hyperthyroid drugs in addition to RFA. Also, three patients had subclinical hyperthyroidism. All the patients had a thyroid scintigraphy pre-RFA (*Figure 1*).

The median follow-up time was 10 months (IQR, 7–12 months). All the patients required one session of RFA, and most AFTNs were located on the right side (62.5%). Nodules were solid (37.5%) or predominantly solid (62.5%).

VR

Table 2 shows that the overall median baseline volume of the AFTNs before RFA was 5.27 mL (IQR, 0.70–9.66 mL). After ablation, the 1-, 3-, and 6-month median volumes were 2.25 (SD: 1.67; P<0.12), 1.28 (SD: 1.1; P=0.013), and 1.37 (SD: 1; P=0.23) mL, respectively. Moreover, the

Table 1 Baseline characteristics

Variables	Value
Sex, n (%)	
Female	8 (100.0)
Age at diagnosis (years), mean (SD)	41.63 (14.97)
Residence, n (%)	
Coast	3 (37.5)
Highland	5 (62.5)
Employment, n (%)	
Domestic chores	1 (12.5)
Student	–
Labor	7 (87.5)
Education level, n (%)	
High school	1 (12.5)
University	7 (87.5)
BMI (kg/m^2)	
Mean (SD)	25.13 (4.34)
Normal, n (%)	3 (37.5)
Overweight, n (%)	4 (50.0)
Obesity, n (%)	1 (12.5)
Nodule composition, n (%)	
Solid	3 (37.5)
Predominantly solid	5 (62.5)
Laterality, n (%)	
Right lobe	5 (62.5)
Left lobe	3 (37.5)
Isthmus	–
Methods of detection, n (%)	
Hyperthyroidism	5 (62.5)
Subclinical hyperthyroid	3 (37.5)
Hyperthyroid drugs before RFA, n (%)	
None	3 (37.5)
Propylthiouracil	4 (50.0)
Propylthiouracil + beta-blocker	1 (12.5)
Methimazole	0 (0.0)
Radioactive iodine	0 (0.0)

SD, standard deviation; BMI, body mass index; RFA, radiofrequency ablation.

results showed that the overall nodular volume reduced significantly after RFA treatment over time (P<0.001) (*Figure 3*).

Patients undergoing RFA experienced a large and statistically significant difference in the percentage of toxic nodule reduction (%) over time. *Figure 4* shows that in the first month, percentage reduction data was reported for five patients (mean =45.8%; 19.2–83.0%). In the third month of follow-ups, data from six patients were reported (mean =75.1%; 54.4–92.5%; SD: 13.1; P=0.029), and in the sixth month, two patients were reported (mean =69.7%; 64.9–74.5%; SD: 6.79; P=0.016).

The active ablation time, power, and energy delivered by the procedure were 6 minutes 59 seconds (SD: 5 minutes 7 seconds), 38.57 W (SD: 6.48 W; range, 35–60 W), and 9.28 kJ (SD: 7.03 kJ), respectively.

TSH reduction

Figure 5 shows that patients who underwent RFA experienced a small but not statistically significant difference in the increase in TSH levels (mIU/mL) after 1, 3, and 6 months post-RFA (mean =3,312 mIU/mL; SD: 3,001 mIU/mL).

We did not have complications after the RFA. After RFA, patients reported improved hyperthyroidism symptoms and quality of life. Also, they did not need more RFA sessions, which made them happy.

Discussion

This study found that all isolated AFTNs were ablated in a single session, and all patients had significant reductions in the volume of nodules, improved hyperthyroidism symptoms, and reduced use of ATD medication.

The European, AHNS international, NASOIE, and ATA guidelines all state that RFA is an option for AFTN—with the European guidelines being the most conservative. Moreover, the Korean RFA guidelines advocate using RFA for AFTNs following a biopsy (6). This recommendation extends to patients with cosmetic concerns or hyperthyroid symptoms, irrespective of the nodule's size. In contrast, a German consensus discourages using RFA for AFTNs with volumes exceeding 12 to 15 mL (7). We followed Korean guidelines to include the patient for RFA. The inclusion criteria of our patients agree with a recent statement of the ATA, citing that a unique skill set, and environment

Table 2 Nodule volume and thyroid function before and after RFA

Variables	Baseline	1 month	3 months	6 months
Longest tumor diameter				
Mean [SD] (mm)	30.38 [12.22]	25 [8.86]	19.5 [5.54]	14.3 [4.04]
N	8	5	6	3
Tumor volume				
Mean [SD] (mL)	5.27 [3.64]	2.25 [1.67]	1.28 [1.1]	1.37 [1]
N	8	5	6	2
P	–	<0.12	0.013	0.23
VR				
Mean [SD] (%)	–	45.8 [28.89]	75.1 [13.1]	69.7 [6.8]
N	–	5	6	2
TSH	1.22	2.86	1.76	1.88

RFA, radiofrequency ablation; SD, standard deviation; VR, volume reduction; TSH, thyroid-stimulating hormone.

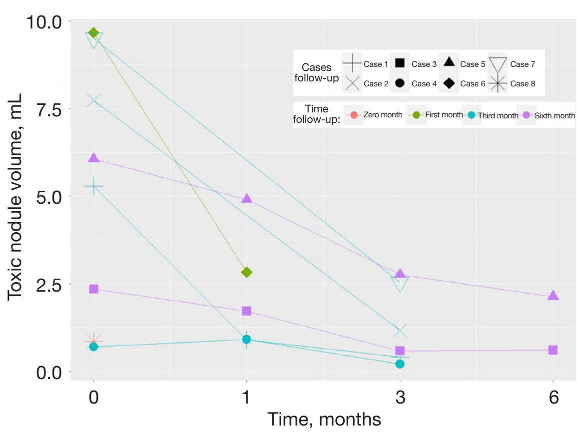

Figure 3 Toxic nodules volume (mL) after RFA. The follow-up of eight individual cases who underwent RFA therapy for toxic nodule treatment was plotted according to toxic nodule volume (mL) over time, showing that at the beginning of the study eight patients started (mean =5.27 mL; 0.70–9.66 mL), in the first-month data of five patients (mean =2.25 mL; 0.90–4.90 mL), at the third month of follow-ups data from six patients were reported (mean =1.28 mL; 0.21–2.76 mL), at the sixth month two patients were reported (mean =1.37 mL; 0.60–2.13 mL). RFA, radiofrequency ablation.

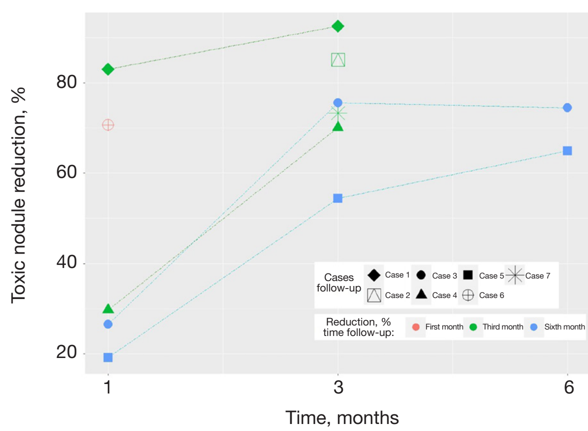

Figure 4 Toxic nodules reduction (%) in the time (months) after RFA. The percentage reduction of the toxic nodule was only reported in seven of eight cases that underwent RFA therapy for toxic nodule treatment. It was graphed according to the percentage of reduction of the toxic nodule (%) over time, showing that in the first month, percentage reduction data was reported for five patients (mean =45.8%; 19.2–83.0%). In the third month of follow-ups, data from 6 patients were reported (mean =75.1%; 54.4–92.5%), and in the sixth month, two patients were reported (mean =69.7%; 64.9–74.5%). RFA, radiofrequency ablation.

are needed for optimal, safe performance and consistent outcomes (8).

RFA is a new alternative to treat patients with AFTN. The European guideline shows that RFA proves effective in treating thyroid nodules, with a mean VR of 69–78% at 12 months in randomized controlled trials, and long-term clinical efficacy is demonstrated in a 5-year retrospective study, showing a median VR of 67% (4). Regarding the

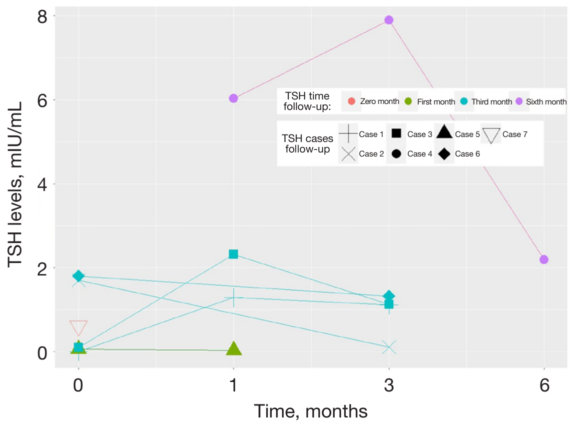

Figure 5 TSH changes after RFA. TSH, thyroid-stimulating hormone; RFA, radiofrequency ablation.

AFTN, the VR and reduction of hyperthyroidism symptoms are used to evaluate the efficacy. In a retrospective study of 20 AFTN, Wang *et al.* reported a median VR of 88.3% (78.3–96.2%) with a euthyroid restoration rate of 75.0% at 12 months after a single session of RFA (9). Cappelli *et al.* reported a VR of 72.9% and thyroid function normalization of 94.1% in 17 patients with toxic nodules at 12 months after a single session of RFA (10). One recent meta-analysis that included 10 AFTN studies showed a pooled VR of 76.5% and a normalization of thyroid function rate of 61.7% for RFA approaching toxic AFTN, with sample sizes ranging from 9 to 44 and follow-up periods varying from 6 to 24 months (11). Our results align with previous studies with a VR at 6 months of 70% (SD: 6.79; P=0.016) after a single RFA session.

Cesareo *et al.*, in a prospective study of 24 AFTNs, found that small nodules (<12 mL) responded better to RFA than medium-sized nodules (>12 mL) (12). All our AFTNs had a volume of less than 12 mL.

Moreover, RFA may be more helpful in single AFTN than TMG. van der Meeren, in a retrospective study of 36 patients with isolated AFTN and 12 TMGs with 1-year follow-up post-RFA, showed a cure rate of 72% *vs.* 25% in TMG (P=0.004) (13). This study reported that the severity of hyperthyroidism [higher baseline TSH and a lower free triiodothyronine (fT3)] and kJ/mL delivered during RFA (>2.1 kJ/mL) predicts a cure. Moreover, this study demonstrated that the efficacy of RFA was nearly three times higher in solitary toxic adenoma than in TMG. Our study was focused on solitary AFTN.

This study has several limitations. The sample size needs to be increased to have significant results. Furthermore, we could only provide information about the outcomes for a short follow-up since the RFA started recently in our country. Despite these limitations, the strength of this study is that the RFA has allowed treating patients with AFTN who are contraindicated to other therapies.

Conclusions

In this first report from Ecuador, we found that RFA was a feasible and safe alternative for treating AFTNs. Long-term data are needed to evaluate the prediction of treatment success with the association between energy delivered per mL, the severity of hyperthyroidism, and thyroid volume before RFA.

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Footnote

Reporting Checklist: The authors have completed the PROCESS reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-425/rc

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-425/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-425/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for the publication of this case series and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Case Report

The effect of hypotonic pharmacologic lipodissolution on abdominal free flap perfusion: a case report

Junggyo Seo^, Joseph Kyu-hyung Park[#]^, Chan Yeong Heo[#]^

Department of Plastic and Reconstructive Surgery, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam-si, South Korea

Contributions: (I) Conception and design: JK Park; (II) Administrative support: CY Heo; (III) Provision of study materials or patients: CY Heo; (IV) Collection and assembly of data: J Seo; (V) Data analysis and interpretation: JK Park, J Seo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work as co-corresponding authors.

Correspondence to: Chan Yeong Heo, MD, PhD; Joseph Kyu-hyung Park, MD, PhD. Department of Plastic and Reconstructive Surgery, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam-si, South Korea; 82, Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam-si 13620, South Korea. Email: lionheo@gmail.com; josephpark85@gmail.com.

Background: Hypotonic pharmacologic lipodissolution (HPL) has gained popularity as a treatment for abdominal fat reduction, especially among Asian individuals. However, research on the effect of HPL on abdominal vascularity and abdominal autologous tissue flap are limited.

Case Description: This case report describes a patient who underwent HPL treatment in November 2022 and subsequently underwent nipple-sparing mastectomy with free transverse rectus abdominis musculocutaneous (TRAM) flap reconstruction on April 4, 2023. The preoperative evaluation included computed tomography (CT) angiography to assess the viability of abdominal perforators and vasculature for TRAM flap reconstruction. Intraoperatively, indocyanine green (ICG) fluoroscopy was performed after TRAM flap elevation to evaluate flap perfusion. The findings revealed compromised skin-side perfusion but satisfactory deep layer perfusion, with subdermal plexus perfusion observed during de-epithelialization.

Conclusions: These findings suggest that in nipple sparing mastectomy cases with minimal skin flap preservation requirements, a history of HPL may have less negative impact on TRAM flap reconstruction. However, in skin sparing mastectomy cases with extensive skin flap preservation needs, careful assessment, including preoperative CT angiography and intraoperative ICG imaging, is essential to minimize the risk of partial flap necrosis.

Keywords: Transverse rectus abdominis musculocutaneous flap (TRAM flap); hypotonic pharmacologic lipodissolution (HPL); indocyanine green (ICG); case report

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Introduction

Since its introduction by Hoefflin in 1999, hypotonic pharmacologic lipodissolution (HPL) has been gradually expanding and gaining popularity (1). HPL is a commonly utilized treatment for abdominal fat reduction, particularly among Asian individuals. In addition to that, various ingredients such as phosphatidylcholine, deoxycholate, L-carnitine, aminophylline, collagenase, among others, are being used in injection lipolysis for body sculpting in areas such as the abdomen, flanks, and thighs (2). Despite the increasing popularity of body contouring through injection procedures, there is a lack of sufficient research

^ ORCID: Junggyo Seo, 0000-0001-7478-7051; Joseph Kyu-hyung Park, 0000-0002-0812-6228; Chan Yeong Heo, 0000-0001-9003-7365.

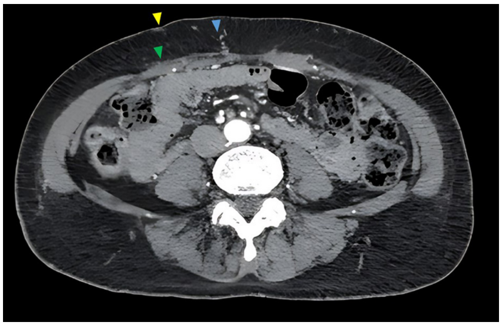

Figure 1 Pre-operative CT angiography with the skin irregularity characterized by visible contour abnormalities (yellow arrowhead), Scarpa's fascia scarring (green arrowhead), and the kinking of perforators accompanied by surrounding scarring (blue arrowhead). CT, computed tomography.

on transverse rectus abdominis musculocutaneous (TRAM) flap reconstruction following injection treatments. While studies on the safety and complications of TRAM flap reconstruction after liposuction exist (3-6), there is inadequate research specifically focusing on TRAM flap reconstruction after injection procedures. Also, research on the combination of HPL and TRAM flap elevation, specifically in the context of nipple sparing mastectomy (NSM), remains limited. This case report presents a patient who underwent NSM with free TRAM flap reconstruction, emphasizing the need for thorough evaluation and caution in TRAM flap reconstruction in patients with a history of HPL. We present this case in accordance with the CARE reporting checklist (7) (available at https://gs.amegroups.com/article/view/10.21037/gs-23-445/rc).

Highlight box

Key findings

- In a patient who underwent transverse rectus abdominis musculocutaneous (TRAM) flap surgery after hypotonic pharmacologic lipodissolution (HPL), intraoperative indocyanine green (ICG) imaging showed compromised skin-side perfusion, but deep layer perfusion was stable.

What is known and what is new?

- While studies on the safety and complications of TRAM flap reconstruction after liposuction exist, there is inadequate research specifically focusing on TRAM flap reconstruction after injection procedures.
- In nipple sparing mastectomy cases where minimal skin flap preservation is necessary, a history of HPL may have limited impact on TRAM flap reconstruction. However, in skin sparing mastectomy cases with substantial skin flap preservation needs, meticulous evaluation through techniques like preoperative computed tomography angiography and intraoperative ICG imaging is crucial to minimize the risk of fat necrosis.

What is the implication, and what should change now?

- During preoperative consultations, it would be beneficial to thoroughly investigate not only liposuction and previous abdominal operation history but also procedures that patients consider "simple" in order to enhance flap survivability and patient satisfaction.

Case presentation

A 54-year-old woman with a history of HPL treatment in November 2022 presented with a diagnosis of right breast cancer, necessitating NSM for oncologic management. In the case of this patient, although her breast size was not substantial, considering the high likelihood of postoperative radiation therapy, complications such as capsular contracture associated with implant insertion were anticipated. Therefore, during the decision-making process, both direct-to-implant insertion and autologous tissue-based reconstruction were considered, and the patient opted for autologous tissue-based reconstruction. In the preoperative computed tomography (CT) angiography, perforators were visualized, but there were partial findings of depression, scar tissue, and abnormal subcutaneous perforator kinking (*Figure 1*). Considering the possibility of compromised vascularity, the decision was made to proceed with TRAM flap instead of deep inferior epigastric perforator (DIEP) flap reconstruction. The patient was adequately informed about the possibility of flap necrosis and provided informed consent before undergoing autologous tissue-based reconstruction.

On April 4, 2023, the patient underwent NSM with immediate breast reconstruction using a free TRAM flap. Intraoperative indocyanine green (ICG) fluoroscopy was performed after TRAM flap elevation to assess flap perfusion. Scar tissue was observed in the subcutaneous fat during flap elevation (*Figure 2*). The ICG images showed a speckled pattern of perfusion on the skin side of the flap, which has not been previously observed by the senior author with experience in over 500 TRAM flap elevations (*Figure 3A*). For patients with no prior abdominal procedures, ICG fluoroscopy during TRAM flap elevation confirms well-established skin perfusion on the flap's medial side, similar to the illustration in the figure (*Figure 3B*). Moreover, the speckled pattern similar to the patient's case is exceptionally rare. Fortunately, ICG imaging of the underside and the

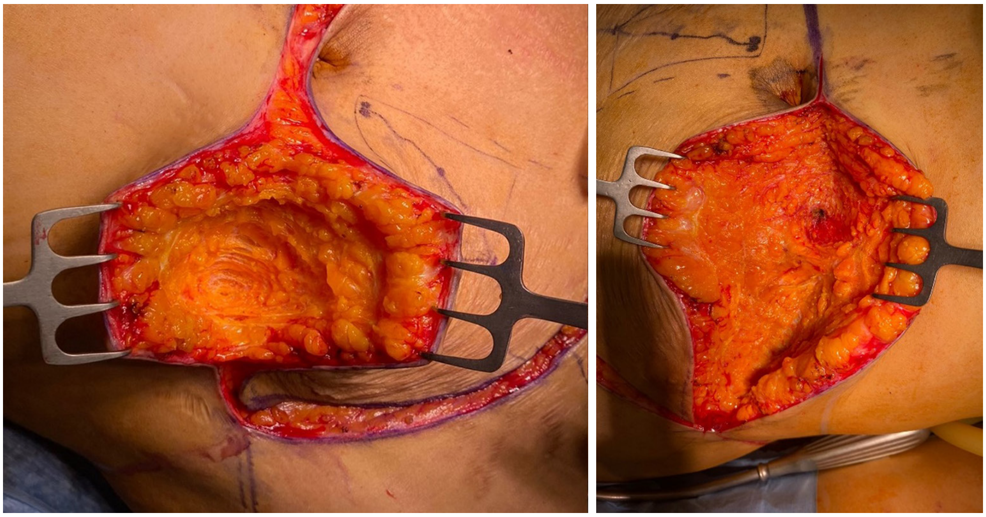

Figure 2 Visible scarring both superficial to and deep to the Scarpa's fascia.

lateral sides of the flap (*Figure 3C*) did not exhibit decreased perfusion. Flap perfusion was checked again after de-epithelialization, where sufficient dermal bleeding was observed along with well perfused deep dermis on the ICG, indicating the presence of subdermal plexus perfusion (*Figure 4*). This observation provided further evidence of adequate blood flow within the subdermal plexus, which is critical for ensuring proper healing and viability of the flap.

The patient was discharged on postoperative day 7 without any complications requiring emergency surgery, such as hematoma or flap necrosis. At our institution, a protocol is in place to conduct ultrasound examinations immediately in the outpatient setting for nodules that are palpable and exceed 1 cm in size. Following surgery, evaluations for fat necrosis involve physical examinations at regular intervals, specifically at 2 weeks, 4 weeks, 8 weeks, and 3 months, in the outpatient setting. During the first 3 months of follow-up, no palpable lesions suggestive of fat necrosis were detected in the patient's breast, and additional investigations such as ultrasound were not performed.

The study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB #B-2308-846-701). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

In the field of abdominal fat contouring, procedures such as abdominoplasty and liposuction have been widely used. However, in recent years, various methods such as injection lipolysis, cryolipolysis, and radiofrequency-assisted contouring have gained popularity. Particularly, lipolysis injections have been extensively used in Asian countries for fat reduction in various body areas. While FDA-approved Kybella has clearly disclosed its ingredients, numerous clinics employ different products with undisclosed substances for abdominal fat reduction. Research on the impact of these products on abdominal subcutaneous perfusion is limited. The patient, being well aware that hypotonic pharmacologic dissolution had been performed, led to the meticulous review of a preoperative CT angiography to identify the most suitable perforators for TRAM flap elevation.

Due to the lack of detailed information regarding the prior hyponotic pharmacologic dissolution, including the specific composition of drugs, injection location, and depth, it is challenging to precisely evaluate the impact of the injection. However, based on CT angiography and intraoperative observations, we observed skin retraction, scarring, deterioration of Scarpa's fascia, and kinking of some perforators. Fortunately, in our case, utilizing the TRAM technique with multiple perforators and continuous flap monitoring throughout the procedure, we did not encounter any acute complications related to flap perfusion.

Additionally, intraoperatively, multiple ICG scans were performed to identify areas of decreased perfusion within

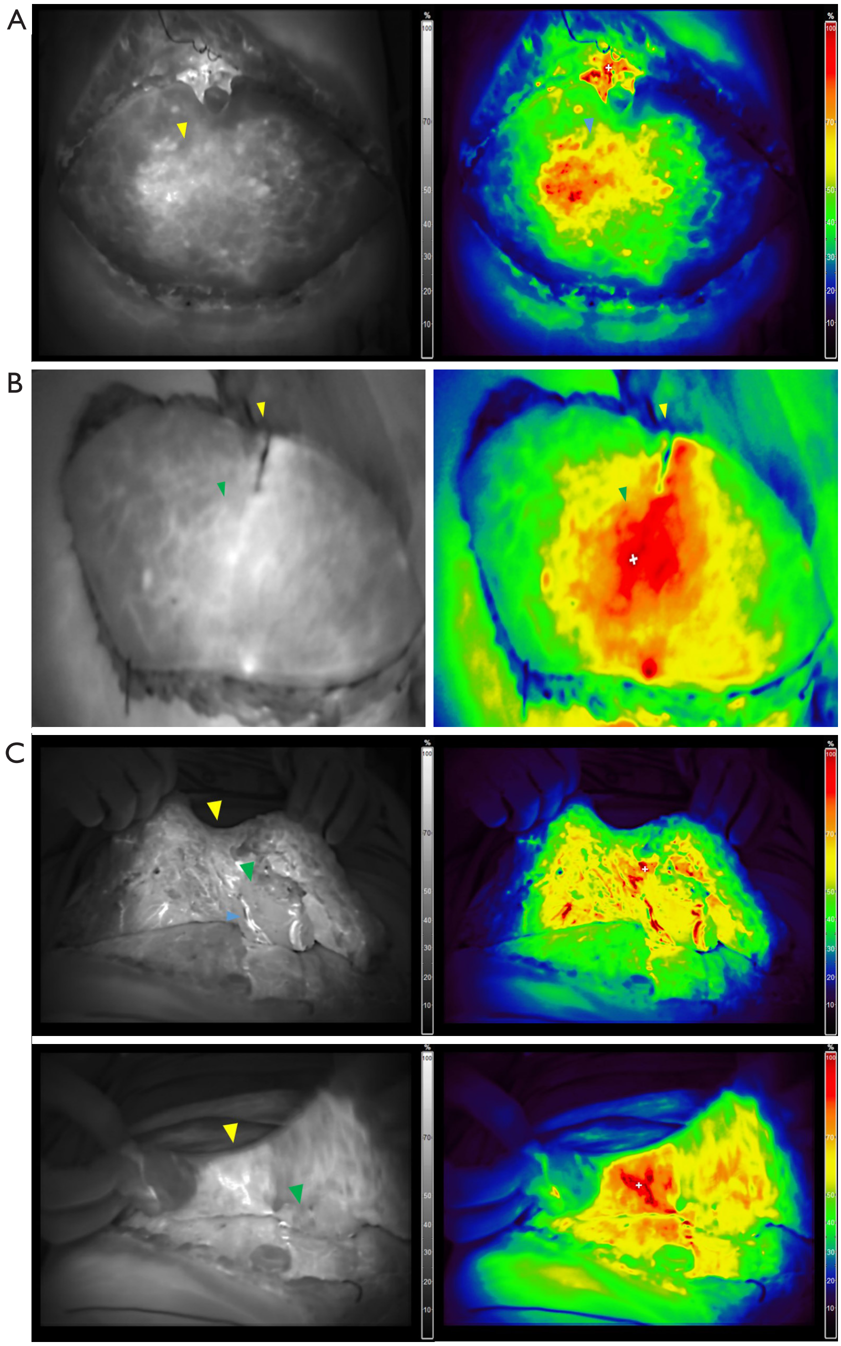

Figure 3 Intraoperative ICG fluoroscopy findings for the case patient and the patient without previous abdominal procedures. (A) The left image demonstrates ICG fluoroscopy, where brighter shades indicate better perfusion and darker shades indicate decreased perfusion. The right image, based on the left image, shows a gradient of colors from red indicating good perfusion to blue indicating compromised perfusion. Compared to a normal TRAM flap, the skin side exhibits decreased perfusion even in the vicinity of the main perforator (yellow arrowhead, blue arrowhead). (B) In patients without previous abdominal procedures, ICG fluoroscopy demonstrates successful skin perfusion on the medial side of the TRAM flap during elevation, as shown in the figure (yellow arrowhead: umbilicus; green arrowhead: main perforator). (C) ICG fluoroscopy images demonstrating satisfactory deep layer perfusion, including the subdermal plexus, within the TRAM flap (yellow arrowhead: umbilicus; green arrowhead: rectus muscle; blue arrowhead: pedicle). ICG, indocyanine green; TRAM, transverse rectus abdominis musculocutaneous.

Figure 4 Flap image after de-epithelialization, demonstrating dermal bleeding and confirming the presence of subdermal plexus perfusion.

the flap. Adequate perfusion was confirmed following de-epithelialization, and the flap was completely inset. Although this case did not require skin due to nipple sparing mastectomy, in cases of skin sparing mastectomy where skin is needed, decreased skin perfusion may increase the risk of complications, such as skin necrosis and wound dehiscence. When considering the detergent effect of phosphatidylcholine, which can cause non-specific cell lysis, it is important to note that it can induce more scarring and be slightly more destructive compared to HPL using osmotic pressure. Taking these factors into account, it is recommended that a more detailed preoperative evaluation is conducted for injection lipolysis procedures other than HPL (8).

The findings from this case report emphasize the importance of individualized assessment and careful evaluation of flap perfusion in patients with a history of HPL undergoing TRAM flap reconstruction. In NSM cases where minimal skin flap preservation is necessary, a history of HPL may have limited impact on TRAM flap reconstruction. However, in skin-sparing mastectomy cases with substantial skin flap preservation needs, meticulous evaluation through techniques like preoperative CT angiography and intraoperative ICG imaging is crucial to minimize the risk of fat necrosis. Unlike nipple-sparing mastectomy, in the skin-sparing mastectomy performed at our institution, there are instances where more than 10×10 cm of skin is resected, necessitating a sufficient abdominal skin envelope to match the size of the contralateral breast.

Accordingly, during preoperative consultations, it would be beneficial to thoroughly investigate not only liposuction and previous abdominal operation history but also procedures that patients consider "simple" in order to enhance flap survivability and patient satisfaction.

Conclusions

This case report highlights the successful NSM with free TRAM flap reconstruction in a patient with a history of HPL. The compromised skin-side perfusion observed in the ICG fluoroscopic images necessitates cautious evaluation and consideration of alternative surgical approaches in cases with significant skin flap preservation requirements. The confirmation of satisfactory deep layer perfusion and subdermal plexus perfusion during de-epithelialization supports the feasibility of TRAM flap reconstruction in cases with minimal skin flap preservation needs.

Further research is needed to explore the implications of HPL on TRAM flap viability and optimize surgical outcomes in patients with a history of HPL undergoing TRAM flap reconstruction.

In the current landscape of increasing options for minimally invasive treatments for abdominal body contouring, there is a need for thorough preoperative evaluations in these areas. This case is considered significant as it demonstrates the potential impact of various procedures, including HPL and lipolysis injections, on abdominal vascularity, emphasizing the importance of detailed preoperative assessment.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-445/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-445/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB #B-2308-846-701). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Case Report

Mucoepidermoid carcinoma—a rare salivary gland-type tumor of the breast: are we dealing with primary or secondary?—a case report and literature review

Janice S. Zhang[1]^, Fardeen Bhimani[2], Sonali Lanjewar[3], Sheldon Feldman[2], Maureen McEvoy[2], Jessica Pastoriza[2], Anjuli Gupta[2]

[1]Albert Einstein College of Medicine, Bronx, NY, USA; [2]Breast Surgery Division, Department of Surgery, Montefiore Medical Center, Montefiore Einstein Center for Cancer Care, Bronx, NY, USA; [3]Department of Pathology, Montefiore Medical Center, Bronx, NY, USA

Contributions: (I) Conception and design: A Gupta, S Feldman, S Lanjewar, JS Zhang; (II) Administrative support: JS Zhang, F Bhimani; (III) Provision of study materials or patients: A Gupta, S Feldman; (IV) Collection and assembly of data: JS Zhang, S Lanjewar, A Gupta; (V) Data analysis and interpretation: JS Zhang, F Bhimani, S Lanjewar, A Gupta; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Anjuli Gupta, MD. Breast Surgery Division, Department of Surgery, Montefiore Medical Center, Montefiore Einstein Center for Cancer Care, 1250 Waters Place, 7th Floor, Tower 1, Bronx, NY, USA. Email: anjuligupt@montefiore.org.

Background: Salivary gland-like tumors are extremely unusual in the breast, and their histology is very similar to primary salivary gland neoplasms. Mucoepidermoid carcinoma (MEC), a common salivary gland tumor, displays an infrequent occurrence in the breast, accounting for a mere 0.2–0.3% incidence. Given its rarity, it is critical to accurately distinguish it from metastatic cases before diagnosing it as a primary breast MEC for appropriate treatment. Currently, there is no consensus on the treatment of MEC, and there is a paucity of literature highlighting the ideal treatment modality, especially for estrogen receptor (ER)-positive cancers. Therefore, the aim of our case report was to underscore the diagnostic process, surgical and adjunctive treatments for our patient with ER-positive, progesterone receptor (PR)-negative and human epidermal growth factor receptor 2 (HER2)-negative MEC while also conducting a literature review to contribute to the limited existing data.

Case Description: A 67-year-old African American woman presented with a lobulated 3.1-cm left breast mass on mammography, for which she underwent ultrasound-guided core needle biopsy that revealed invasive carcinoma with squamous differentiation. The carcinoma was ER-positive, PR-negative and HER2-negative. Subsequently, she underwent a lumpectomy with sentinel lymph node biopsy. Her final pathology revealed an intermediate-grade MEC with negative lymph nodes. She had a past medical history of benign salivary gland tumor, as well as a family history of BReast CAncer gene 1 (*BRCA1*)-associated breast cancer in her daughter.

Conclusions: MEC of the breast is a rare tumor with a relatively favorable overall prognosis. The early and precise diagnosis of this condition plays a pivotal role in formulating effective treatment strategies and ensuring positive survival rates. Nonetheless, future studies are recommended to further explore the role of surgical approaches and adjuvant therapy to improve treatment outcomes.

Keywords: Breast cancer; mucoepidermoid carcinoma (MEC); pathologic morphology; case report

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^ ORCID: 0000-0003-3759-9689.

Introduction

Mucoepidermoid carcinoma (MEC) is an invasive tumor of the breast that histologically resembles its salivary gland counterpart (1). Since its initial documentation in 1979, approximately 47 cases have been reported in the English literature to date (2,3). The estimated incidence of MEC accounts for 0.2–0.3% of all breast tumors; however, some authors believe that the true incidence may be higher due to the potential misclassification of cases as carcinomas with squamous differentiation (4,5). Furthermore, despite being most frequently detected in the salivary gland, MEC has been reported to occur in a variety of organs, including the lungs, bronchus, esophagus, and thyroid (6). Regardless of location, the morphology of this tumor is characterized by a mixture of mucinous, squamous, and intermediate neoplastic cells arranged in solid and cystic patterns (1,6). Based on the tumor's histomorphology, MEC can be categorized into low, intermediate, or high grades (7). Regardless of the grade, the cell composition is similar. Low-grade MEC tend to be more cystic, while high-grade MEC is more solid with a high nuclear grade, necrosis, and brisk mitotic figures (8,9). To identify these aforementioned cell types observed in MEC, several immunohistochemical stains are utilized. CK14 stains basaloid cells, p63 stains epidermoid cells, and CK7 delineates mucous cells (9). Moreover, using GATA3 and mammaglobin expression, these stains help distinguish MEC of the breast from MEC of the salivary, where the former will be expressed in breast MEC and negative in the latter (3).

While most documented cases in the literature emphasize MEC as a prevalent form of triple-negative breast cancer, these cases generally exhibit low invasiveness and a favorable prognosis (10). In fact, tumor grade has been identified as the most important predictor of long-term prognosis in MEC patients. Currently, there is no consensus or standard therapeutic guideline for the treatment of MEC. Prior studies have suggested that high-grade MEC is typically managed through mastectomy and axillary lymph node dissection, while breast conservation and sentinel node biopsy may be options for tumors of low and intermediate grade. However, a significant portion of these studies did not account for the hormone receptor status of patients, and those that did reported a prevalence of triple-negative breast cancer phenotypes. Consequently, there exists a scarcity of literature that examines the role of hormone receptor status on treatment outcomes (3,11). Thus, our case report aimed to underscore the diagnostic process, surgical and adjunctive treatments for our patient with estrogen receptor (ER)-positive, progesterone receptor (PR)-negative, human epidermal growth factor receptor 2 (HER2)-negative MEC, while also conducting a literature review to contribute to the limited existing data. We present this case in accordance with the CARE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-372/rc).

Highlight box

Key findings

- We report a rare case of estrogen-receptor positive mucoepidermoid carcinoma (MEC) of the breast in a patient with salivary gland tumor history.

What is known and what is new?

- MEC is a tumor most commonly occurring in the salivary glands. MEC of the breast is a rare, predominantly triple-negative breast cancer with a relatively favorable prognosis but little consensus on ideal treatment modality.
- No other cases of MEC of the breast in a patient with salivary gland tumor history have been reported. The current report highlights the importance of accurate diagnosis and appropriate surgical and adjuvant treatments.

What is the implication, and what should change now?

- The early and precise diagnosis of MEC of the breast, including evaluation of possible associated tumors, is crucial to formulating effective treatment strategies and ensuring positive survival rates.

Case presentation

A 67-year-old postmenopausal African American woman presented with a lobulated 3 cm left breast mass on screening mammogram. She denied any nipple inversion, nipple discharge or skin changes. Diagnostic mammogram and ultrasound demonstrated a 3.1 cm mass at 2:00 o'clock 9 cm from the nipple and an abnormal left axillary node with a thickened cortex. Subsequently, an ultrasound-guided core biopsy revealed carcinoma with squamous differentiation, ER-positive (51–60%), PR-negative, and HER2-negative by fluorescence in situ hybridization (FISH). Biopsy of the left axillary lymph node was benign. A follow-up magnetic resonance imaging (MRI) confirmed the tumor at 2:00 o'clock about 6.7 cm from the nipple measuring 2.1 cm × 2.9 cm × 2.8 cm with biopsy clip and no additional sites of disease. She had a past medical history significant for a 10-year history of a slowly enlarging right parotid mass, for which she underwent right deep lobe parotidectomy with

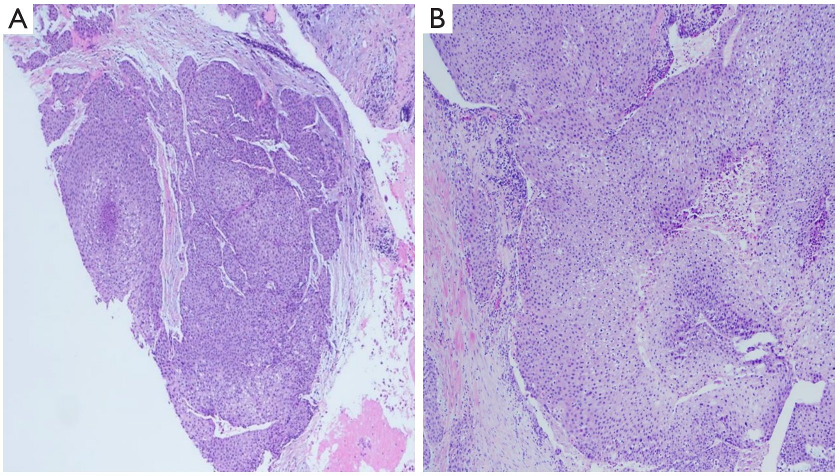

Figure 1 Histopathologic features of MEC of the breast. (A) 4× magnification of H&E-stained tumor showing a polypoid and solid growth with papillary configuration; (B) 10× magnification of H&E-stained section of eosinophilic cells with epidermoid appearance. H&E, hematoxylin and eosin; MEC, mucoepidermoid carcinoma.

facial nerve dissection and preservation at age 51. Pathology report of the excised mass revealed a 2.3-cm pleomorphic adenoma, with no features suggestive of malignant transformation. One intraparotid and two right neck lymph nodes were also negative. Her family history included breast cancer in her daughter, who was diagnosed in her late thirties and was found to have a pathogenic BReast CAncer gene 1 (*BRCA1*) variant. However, the patient's genetic testing results were negative.

The patient was presented at our institutional multidisciplinary tumor board with recommendations to undergo left breast lumpectomy and left sentinel lymph node biopsy.

A left breast lumpectomy with margin assessment and sentinel lymph node biopsy was performed. The patient had four sentinel lymph nodes sent for final pathology. The surgery was successful, and the patient tolerated the procedure well. There were no intraoperative or postoperative complications. After an uneventful recovery, she was discharged the same day. Final pathology revealed the presence of 33 mm × 30 mm × 25 mm, grade-2 (as per salivary grading system) stage IIA MEC without angiolymphatic or perineural invasion that had been fully removed with clear margins. The tumor tested positive for ER but negative for PR and HER-2. Histologically, the tumor comprised of irregular nests of intermediate tumor cells with squamous differentiation (*Figure 1*) and mucous cells (*Figures 2,3*). It stained positive for GATA3 (diffuse, weak) (*Figure 4*) and ER. Additionally, as part of her adjuvant treatment, the patient was referred to medical oncology and radiation oncology for adjuvant treatment recommendations. She underwent 15 fractions of external beam radiation (48 Gy) and was stated on adjuvant aromatase inhibitor.

On follow-up, the patient was noted to have an enlarging neck mass for which she underwent a positron emission tomography (PET) scan and subsequent fine needle aspiration. While the PET scan showed increased focal uptake in the left inferior thyroid lobe, cytological test demonstrated numerous lymphoid cells and scattered oncocytic cells, negative for malignancy.

The total length of post-operative follow-up was 7 months. The patient's is alive with no evidence of disease. No recurrence or metastasis were reported during the follow-up period.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Primary MEC of the breast is a rare, atypical tumor, accounting for only 0.2–0.3% of all primary breast tumors (4).

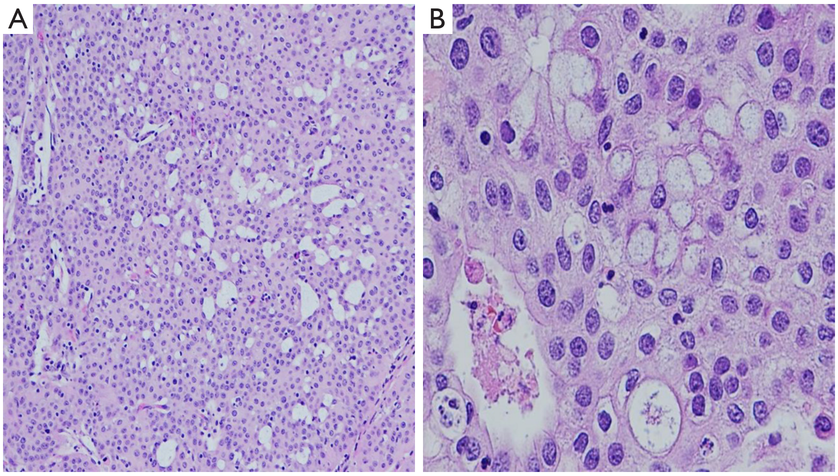

Figure 2 Histopathologic features of mucin-filled glandular cells of MEC of the breast. (A) Cystic spaces indicate mucin-filled glandular structures at 10× magnification stained with H&E; (B) 20× magnification of corresponding section (H&E). H&E, hematoxylin and eosin; MEC, mucoepidermoid carcinoma.

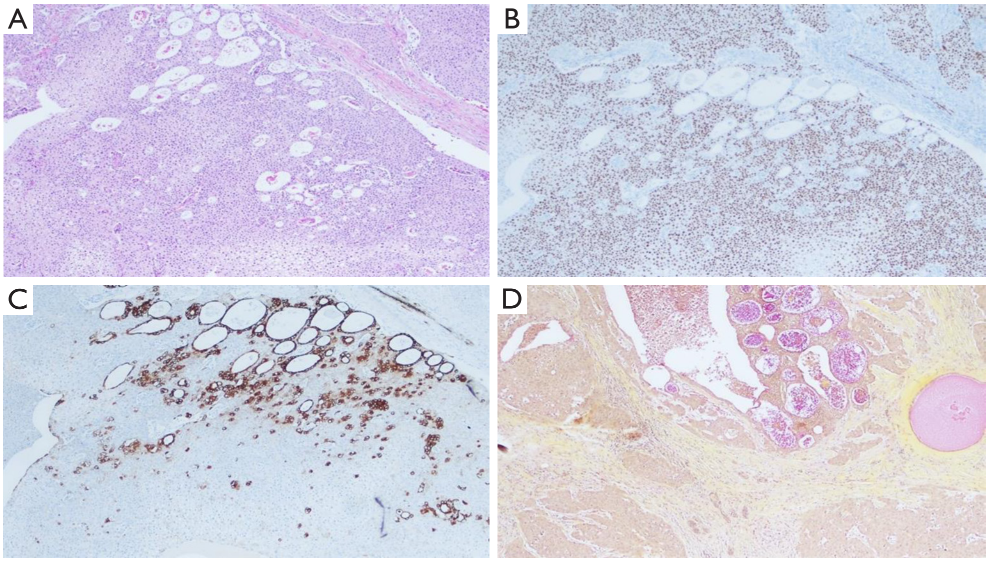

Figure 3 Immunohistochemistry of MEC of the breast. (A) H&E staining showing solid growth of eosinophilic epidermoid appearing cells merging with cystic spaces lined by mucous cells at 4× magnification; (B) IHC staining for P63 showing epidermoid cells at 4× magnification; (C) IHC staining for CK7 showing mucous cells at 4× magnification; (D) IHC staining for mucicarmine showing mucin in the cystic spaces at 4× magnification. MEC, mucoepidermoid carcinoma; IHC, immunohistochemical; H&E, hematoxylin and eosin.

The first cases were reported in 1979 by Patchefsky *et al.* (2) and since then 47 cases have been reported (2,7). MEC morphology can be heterogenous. Therefore, it is often confused with other benign and malignant neoplasms (6). All 47 reported cases have occurred in adult women with a wide age range of 29 to 80 years and a mean age of 55.7. None of the previously reported cases reported presence of BRCA gene positivity, but of note, our patient reported a family history of *BRCA1* positivity in her daughter, who was diagnosed with breast cancer in her late thirties. Furthermore, our patient had a history of pleomorphic adenoma removal at age 51. The significance of this benign salivary gland tumor history is unclear. Given MEC is a common salivary tumor with varying potential for aggressive behavior, there was suspicion to whether the patient's MEC tumor of the breast was a primary or secondary tumor (12,13). Since pleomorphic adenomas harbor a small risk of malignant transformation, it was determined the patient's MEC of the breast was likely a primary tumor.

Although the majority of MEC cases have been documented in the United States (11 cases) (2,4-6,14), followed by Italy (6 cases) (15,16), China (6 cases) (9,11,17), and Turkey (3 cases) (18-20), none have provided insights into the racial or ethnic backgrounds of their patients. To the best our knowledge, we report the first case of MEC in an African American patient. Multiple studies have demonstrated that breast MEC presents as a triple-negative cancer (7,9). Contrastingly, our patient showed positivity for ER (60%) and absence of PR and HER2. Moreover, in terms of receptor status, 12 studies were triple-negative (4,7,9,14,19,21-25). Six were ER^-, PR^-, and HER2 unspecified (26-30). In cases not classified as triple negative, three were ER^+, PR^-, and $HER2^-$ including our case (8,11); two were ER^+, PR^+, $HER2^-$. This has been further illustrated in *Figure 5*. Recent cases have shown an increasing incidence of non-triple negative breast cancers (6,8,21). The hypothesis that hormone receptor plays a role in prognosis was corroborated by Sherwell-Cabello *et al.* (21), who found favorable outcomes associated with lower hormone receptor expression. This finding suggests a potential hormone dependency of the disease and raises the possibility of considering endocrine therapy as a viable option.

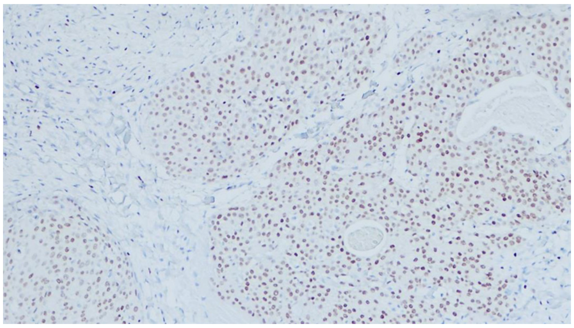

Figure 4 GATA3 staining weakly positive at 10× magnification (immunohistochemistry).

Histological grade is an important prognostic factor in MEC of the breast (23). This type of tumor is graded using either the salivary gland grading system or the breast grading system, both yielding comparable outcomes. Among these grading frameworks, the Elston Ellis scoring system takes prominence. This system effectively categorizes tumors into low, intermediate, and high grades, factoring in components like cystic proportion, nerve invasion, necrosis, as well as the count of mitoses per 10 high-power fields (9,31). Patients diagnosed with high-grade MEC face a less favorable prognosis, often experiencing the development of distant metastases (9). Of the reported cases with low and intermediate grade, no deaths were reported which

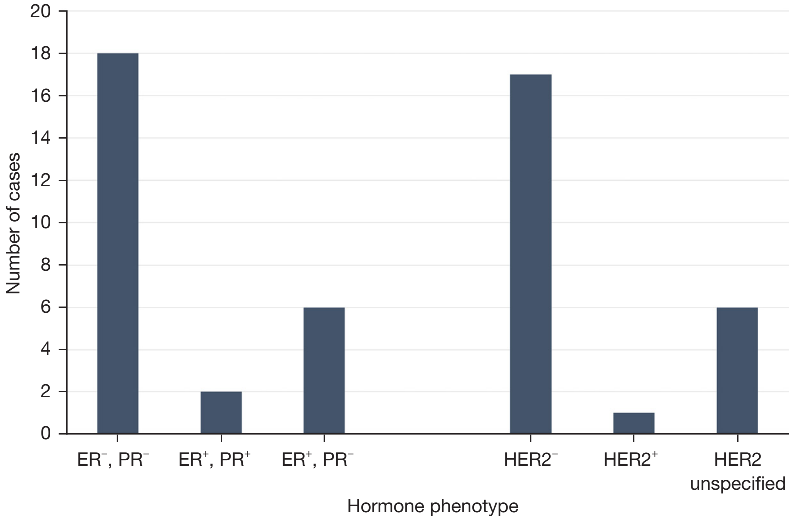

Figure 5 Hormone immunophenotype in reported cases of MEC of the breast. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; MEC, mucoepidermoid carcinoma.

supported the hypothesis that low and intermediate grade MEC had a favorable clinical outcome (11,32). Low-grade MEC is non-aggressive, whereas high-grade MEC is aggressive, frequently leading to metastasis in axillary lymph nodes and distant organs (9,14,15).

To better understand the pathogenesis of MEC in salivary versus extra-salivary origins, researchers have compared the molecular profile of primary breast MECs with salivary and extra-salivary MECs (33). Primary MEC in the salivary gland and lung have been found to be associated with MAML2 fusion (34,35), however, the pathogenesis of primary thyroid MEC seems to be MAML2-independent (36). Among the reported cases of breast MEC that have been investigated for presence of MAML2 rearrangements, three have presented with the feature, suggesting a need for the classification of more tumors (1,14).

In the present literature, the standard surgical approach for MEC of the breast has not been well established because of its low incidence. Our patient underwent a lumpectomy for an intermediate-grade tumor measuring 2.9 cm. In cases documented prior to 2000, most patients underwent mastectomy or modified radical mastectomy (14 cases), regardless of tumor size or grade, while only three cases mentioned breast-conserving procedures such as quadrantectomy, lumpectomy, or wide local excision. Post-2000, the majority of reported cases involved mastectomies or modified radical mastectomies (18 cases), with six cases reporting lumpectomies or local excisions, and three cases involving quadrantectomies (*Table 1*). This trend indicates a growing number of surgeons opting for breast-conserving surgery for removing breast MEC tumors, although mastectomies continue to be the preferred treatment option.

Lastly, there are no established guidelines for adjuvant therapy for treatment of MEC. Prior studies have documented a range of approaches, including chemotherapy, radiation, hormonal therapy, different combinations of these methods, or no additional treatment. Except for one patient who did not receive any adjuvant therapy and died due to unrelated causes, all patients who received adjuvant therapy survived until the end of the follow-up period. As noted earlier, the prognosis of breast MEC remains dependent on the pathological grade of the tumor, and the role of adjuvant therapy remains unclear. Therefore, future studies with a larger sample size are needed to explore the role of adjuvant therapy in MEC. Furthermore, additional studies are also required to better understand the significance of hormone receptor status in the context of MEC.

Table 1 Summary of treatment approaches in all cases

Case No.	Author (ref.)	Year	Surgical approach	Adjuvant therapy	Follow-up (mo.)	Status
Present case	Zhang *et al.*	2023	Lumpectomy + SLD	Radiation, hormonal	6	Alive
1	Gupta *et al.* (7)	2023	MRM	None	NA	Alive
2	Bak *et al.* (8)	2022	Lumpectomy + SLD	Chemotherapy, radiation, hormonal	37	Alive
3	Chen *et al.* (17)	2022	Excision	NA	6	Alive
4	Bui *et al.* (6)	2022	Lumpectomy + SLD	Radiation, hormonal	NA	Alive
5	Ye *et al.* (9)	2020	MRM	Chemotherapy	12	Alive
6	Yan *et al.* (14)	2020	Lumpectomy	NA	60	Alive
7	Burghel *et al.* (10)	2018	NA	None	NA	NA
8	Sherwell-Cabello *et al.* (21)	2017	MRM	None	3	Alive
9	Cheng *et al.* (11)	2017	MRM	NA	156	Alive
10			MRM	NA	41	Alive
11			Mastectomy + SLD	NA	9	Alive
12			Mastectomy + SLD	NA	4	Alive
13	Arun Kumar *et al.* (22)	2016	MRM	Chemotherapy, radiation, hormonal	24	Alive
14	Fujino *et al.* (23)	2016	Mastectomy + SLD	NA	NA	NA

Table 1 (*continued*)

Table 1 (*continued*)

Case No.	Author (ref.)	Year	Surgical approach	Adjuvant therapy	Follow-up (mo.)	Status
15	Palermo *et al.* (24)	2013	NA	NA	NA	NA
16	Turk *et al.* (18)	2013	MRM	NA	5	Alive
17	Basbug *et al.* (19)	2011	MRM	Chemotherapy, radiation	12	Alive
18	Camelo-Piragua *et al.* (4)	2009	MRM	Chemotherapy	8	Alive
19	Hornychová *et al.* (25)	2007	SM + LND	Chemotherapy, radiation	18	Alive
20			MRM	Chemotherapy, radiation	60	Alive
21	Horii *et al.* (32)	2006	Mastectomy + LND	Hormonal	36	Alive
22	Gómez-Aracil *et al.* (37)	2006	MRM + LND	NA	54	Alive
23	Di Tommaso *et al.* (15)	2004	Excision	NA	5	Alive
24			Excision	NA	90	Alive
25			Quadrantectomy + LND	NA	13	Alive
26			Quadrantectomy + LND	NA	3	Alive
27			Quadrantectomy + LND	NA	18	Alive
28	Terzi *et al.* (20)	2004	MRM	NA	NA	NA
29	Tjalma *et al.* (30)	2002	RM	None	156	Alive
30	Berry *et al.* (38)	1998	Mastectomy + LND	NA	NA	NA
31	Markopoulos *et al.* (29)	1998	Wide local excision + LND	Chemotherapy, radiation, hormonal	60	Alive
32	Chang *et al.* (26)	1998	MRM	Chemotherapy	48	Alive
33	Lüchtrath and Moll (39)	1989	RM	NA	30	DOD
34	Pettinato *et al.* (16)	1989	MRM	NA	10	DOD
35	Hanna and Kahn (27)	1985	MRM	NA	8	Alive
36			MRM	NA	14	Alive
37	Hastrup and Sehested (28)	1985	RM	NA	25	DOD
38	Leong and Williams (40)	1985	SM	NA	7	DOD
39	Ratanarapee *et al.* (41)	1983	NA	NA	14	DOD
40	Fisher *et al.* (5)	1983	Lumpectomy	NA	60	Alive
41			MRM	NA	48	Alive
42			MRM	NA	120	Alive
43			RM	NA	108	Alive
44			SM	NA	48	Alive
45	Kovi *et al.* (42)	1981	MRM	NA	NA	NA
46	Patchefsky *et al.* (2)	1979	RM	None	94	DOR
47			Quadrantectomy	None	10	Alive

SLD, sentinel lymph node; MRM, modified radical mastectomy; NA, not applicable; SM, simple mastectomy; LND, lymph node dissection; RM, radical mastectomy; DOD, died of disease; DOR, died of other reasons.

A limitation of this case study is its short length of follow-up (6 months). Additionally, to our knowledge, this is the first and only case of MEC of the breast reported at our institution. Therefore, we are unable to comment on whether breast-conserving surgery and adjuvant therapy is the best approach to treatment. Nevertheless, MEC of the breast has relatively good prognosis, as none of the intermediate grade lesions, similar to the present study, led to distant metastasis or death (4,8,23).

Conclusions

MEC of the breast is a rare tumor with a relatively favorable overall prognosis. The early and precise diagnosis of this condition plays a pivotal role in formulating effective treatment strategies and ensuring positive survival rates. Nonetheless, future studies are recommended to further explore the role of surgical approaches and adjuvant therapy to improve treatment outcomes.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Editorial Commentary

A plastic surgery perspective on the choice between breast conserving surgery with radiotherapy versus mastectomy and reconstruction

Max L. Silverstein, Arash Momeni^

Division of Plastic and Reconstructive Surgery, Stanford University School of Medicine, Palo Alto, CA, USA

Correspondence to: Arash Momeni, MD, FACS. Division of Plastic and Reconstructive Surgery, Stanford University School of Medicine, 770 Welch Road, Suite 400, Palo Alto, CA 94304, USA. Email: amomeni@stanford.edu.

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We congratulate Dr. Diao and colleagues on their excellent article comparing patient-reported quality of life (QOL) outcomes following breast conserving surgery with radiotherapy (BCS + RT) versus mastectomy and reconstruction (Mast + Recon) (1). Their study is impressively powered with long-term follow-up and sound, detailed methodology. Their findings, that the two treatments were similar in terms of satisfaction with breasts, physical well-being, and upper extremity function, while Mast + Recon was associated with worse sexual well-being but better physical function, align with the previous literature as well as our clinical experiences. In this commentary, we hope to complement the thoughts of the radiation oncologists who authored the paper by providing another perspective on this multidisciplinary topic.

As reconstructive plastic surgeons, we counsel patients on the decision between BCS + RT and Mast + Recon on a near-daily basis. While surgically involved in only the latter strategy, we frequently discuss the advantages and disadvantages of each treatment given their oncologic equivalency. In these conversations, we are asked to describe the most likely aesthetic outcomes of each option, the risks for complications, and discuss patient-specific factors that might influence patient and surgeon towards one procedure or the other. Studies like this one can help to better inform these conversations and, ultimately, lead to more satisfied patients.

Both BCS + RT and breast reconstruction were developed to alleviate the negative effects of mastectomy. Despite this common objective, the two approaches are not equally appropriate for every woman with early-stage breast cancer. In our experience, several specific factors serve as relative indications or contraindications for each procedure and influence our discussions with patients. For example, women with large breasts or pre-existing asymmetry (with a larger affected side) may not suffer a major aesthetic deformity with a relatively small BCS excision. Patients with very large breasts may even benefit from oncoplastic reduction, in which BCS + RT is combined with simultaneous bilateral breast reduction (2,3). Conversely, patients with small or medium-sized breasts are more likely to notice the asymmetry rendered by lumpectomy and RT, both of which reduce the treated breast.

Moreover, Diao *et al.*'s finding, of an association between BCS + RT and worse upper extremity function, alludes to a well-known effect of radiation-induced fibrosis of the chest and upper arm tissues and must be emphasized in conversations with women who are physically active (4,5).

^ ORCID: 0000-0002-6452-751X.

It is noteworthy, however, that radiotherapy for breast cancer has undergone substantial changes over the past 20 years. Hence, patients who have undergone radiotherapy may, in fact, represent a rather heterogeneous cohort, with treatment modalities ranging from whole breast radiation to intensity-modulated protocols and partial breast radiation. A complete discussion of radiotherapy modalities, however, is beyond the scope of this commentary. On the other hand, the negative connection between Mast + Recon and sexual function is predictable given the nipple denervation inherent in mastectomy and is disclosed to every patient in our breast reconstruction clinic (6,7). Patients who undergo implant-based reconstruction will have a prosthesis interposed between the breast skin and underlying tissues making some level of breast skin and nipple numbness inevitable. These examples highlight just a few of the many variables that direct our recommendations to patients considering BCS + RT versus Mast + Recon on a case-by-case basis.

The structure of Diao *et al.*'s study, therefore, while experimentally sound, serves to answer a question that rarely presents itself, in our experience. That is, we see few women who are truly agnostic about the choice between BCS + RT versus Mast + Recon or who clearly self-select into one treatment group or the other. Instead, the fact that BCS + RT and Mast + Recon were found to be largely equivalent in terms of QOL outcomes in Diao *et al.* emphasizes the importance of focusing on specific, often subjective, patient factors when making treatment recommendations. The significant differences in baseline characteristics between the two groups (in terms of age, ethnicity, smoking status, body mass index, bra cup size, household income, tumor size, and rate of bilateral breast cancer) further complicate interpretations of the survey data and allude to the many variables that influence patient preferences and post-operative QOL. Numerous prior studies on the topic of breast reconstruction have demonstrated the complex relationships between specific baseline patient characteristics, treatment preferences, and levels of satisfaction. For example, the national trend mentioned by Diao *et al.*, toward increasing rates of contralateral prophylactic mastectomy, was recently shown to be driven by younger patients seeking implant-based, immediate breast reconstruction (8). Until similar associations are fully understood, conclusions from studies like this one should inform, but not direct, the decision-making processes of patients and surgeons.

One point from the article that we, as reconstructive microsurgeons, must comment on is the superiority of autologous reconstruction. In the study, satisfaction with breasts and physical well-being scores were significantly higher for autologous reconstruction compared to either implant-based reconstruction or BCS + RT. Autologous reconstruction was also not found to have the negative effect on sexual well-being associated with implant-based reconstruction. These findings echo decades of plastic surgery research showing that autologous breast reconstruction is superior to implants in terms of QOL, aesthetics, complication rates, durability, and functional outcomes (9,10). A landmark study in this regard was the Mastectomy Reconstruction Outcomes Consortium (MROC) study. Among other questions, the MROC study investigated patient-reported outcomes 1 year after immediate breast reconstruction and demonstrated that patients who had undergo autologous reconstruction had greater satisfaction with their breasts and had greater psychosocial and sexual well-being than those who underwent who underwent implant-based reconstruction (11).

At present, the only common legitimate reasons to avoid autologous reconstruction are operative duration and surgeon unfamiliarity with alternative donor sites when abdominal tissue is unavailable or insufficient. While the length of autologous reconstruction surgery may result in increased upfront costs, the reduction in complications and elimination of required implant maintenance (i.e., routine imaging, replacement in the case of rupture) may nullify this concern (12,13). In combination with nipple-sparing mastectomy, microsurgical breast reconstruction is safe and replicates the original appearance and quality of the breast better than any other treatment strategy. Given these proven advantages, it is incumbent on plastic surgeons to continue to improve microsurgical techniques, accelerate post-operative recovery, and increase the availability of our gold standard operation among women with breast cancer.

Diao *et al.*'s conclusion that their data "*demonstrating similar clinically meaningful long-term QOL outcomes between BCS + RT and Mast + Recon*" suggest a relative equivalency between strategies that favors BCS + RT in most cases due to reduced surgical complexity. Our takeaway is different: the absence of clear QOL contraindications to either procedure underscores the importance of accounting for specific patient characteristics and priorities when discussing surgical options with women who have breast cancer. Every woman faced with the dilemma between BCS + RT and Mast + Recon cares about their aesthetic and functional results and deserves to make an individualized, informed decision that includes consultation with a board-certified plastic surgeon.

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Editorial Commentary

Long-term quality of life after breast surgery—are breast conserving surgery and mastectomy comparable?

Hans-Christian Kolberg[1]^, **Rachel Würstlein**[2]

[1]Department of Gynecology and Obstetrics, Marienhospital Bottrop, Bottrop, Germany; [2]Breast Cancer Center, Department of Gynecology and Obstetrics, Ludwig-Maximilian-University Hospital, Munich, Germany

Correspondence to: Hans-Christian Kolberg, MD, PhD. Department of Gynecology and Obstetrics, Marienhospital Bottrop, Josef-Albers-Str. 70, 46236 Bottrop, Germany. Email: hans-christian.kolberg@mhb-bottrop.de.

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Keywords: Breast cancer; mastectomy; breast conserving surgery; quality of life; patient-reported outcome (PRO)

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In a population-based study of long-term quality of life among breast cancer survivors, Diao *et al.* demonstrated an association of mastectomy and reconstruction with worse sexual well-being compared to breast conserving surgery and radiotherapy. Patients older than 65 who received breast conserving surgery and radiotherapy and young patients who received mastectomy and autologous reconstruction reported the highest quality of life scores. Of the 1,215 included patients with breast cancer stage 0–II and a median follow up of 9 years, 631 had received breast conserving surgery and radiotherapy and 584 had been treated by mastectomy and reconstruction. All patients answered paper surveys using BREAQST-Q and Patient-Reported Outcome Measurement Information System (PROMIS). Of the items investigated, including psychosocial well-being, physical function and well-being, upper extremity function, satisfaction with breasts and sexual well-being, only sexual well-being showed a statistically significant difference between the two groups as mentioned above. No difference in overall survival could be demonstrated. However, the use of chemotherapy had a negative impact (1).

With a median follow up of 9 years the authors focused on long term quality of life. This is a very important aspect of the analysis, because it is known that quality of life changes over time. Short-term analyses demonstrate a better quality of life in patients after breast conserving surgery compared to mastectomy (2). In a recently published study from Germany, patients after mastectomy had an impairment of quality of life shortly after surgery whereas after 24 months it had improved substantially and was even better than in patients after breast conserving surgery (3). Satisfaction after reconstructive surgery also changes over time. While the satisfaction with the body image improves after breast conserving surgery and simple mastectomy, the opposite has been demonstrated for mastectomy and immediate reconstruction (4). These findings underscore the importance of long-term approaches as chosen in the study conducted by Diao *et al.* The main goal of breast surgery for early breast cancer—survival—is always a long-term endpoint. But other endpoints like quality of life and body image also have to be investigated with an adequate follow up, because in a situation with curative intent the next 10 to 20 years do matter.

Age plays an important role in the deterioration of quality of life after breast cancer surgery. While this has been demonstrated for all surgical approaches, the effect is more pronounced after mastectomy (5). In another

^ ORCID: 0000-0003-0221-3272.

recently published analysis young age was associated with poorer social and sexual function, as well as poorer sexual enjoyment and lower expectations of the future (6). These data demonstrate the importance to include the factor age in all analyses regarding quality of life after breast cancer surgery. The new aspect in the work discussed here is that there is a difference between women younger than 50 and women older than 65 in the long-term quality of life depending on the type of surgery, with younger women being more satisfied with mastectomy and autologous (but not implant) reconstruction and older women with breast conserving surgery and radiation. This result can add a very important aspect in the situation of preoperative counseling.

However, many factors have an impact on the quality of life and this is not always associated with the type of surgery. Thus the interpretation of dichotome results as in the paper of Diao *et al.* always warrants caution.

Some caveats and limitations of the analysis have to be mentioned. The approach of a long-term follow up resulted in a response rate of only 25% and that may have an impact on the results and furthermore as always in long-term observations included patients with techniques of surgery and radiation as well as systemic regimens that are no longer state of the art. Also adding to the possibility of a selection bias is the fact that the indications for mastectomy are not discussed. Maybe the decision for a mastectomy in a situation where it is not clearly indicated represents an attitude towards life that is also mirrored in long-term quality of life?

The authors only included patients after breast conserving surgery and radiation and after mastectomy and reconstruction. In consequence their analysis allow no conclusions regarding simple mastectomy and mastectomy and post-mastectomy-radiation. This has to be taken into account when using the data for preoperative counseling. Furthermore the statistically significant preference for mastectomy in women younger than 50 occurred only after autologous reconstruction and not after implant based reconstruction.

Despite these limitations the publication of Diao and colleagues from the MD Anderson Cancer Center delivered important information regarding the quality of life after breast cancer surgery. Sexual well-being is better in younger women after mastectomy and autologous reconstruction and in older women after breast conserving surgery and radiation. Although these findings are far from leading to a recommendation they can be of use when discussing surgery with patients who are struggling to find out what their preference is.

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Editorial Commentary

Immediate lymphatic reconstruction for breast cancer-related lymphedema: current status and challenges

Yuki Otsuki, Takashi Nuri, Koichi Ueda

Department of Plastic and Reconstructive Surgery, Osaka Medical and Pharmaceutical University, Takatsuki City, Osaka, Japan

Correspondence to: Yuki Otsuki, MD, PhD. Department of Plastic and Reconstructive Surgery, Osaka Medical and Pharmaceutical University, 2-7 Daigakucho, Takatsuki City, Osaka 569-8686, Japan. Email: yuuki.ootsuki@ompu.ac.jp.

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Breast cancer-related lymphedema (BCRL) after axillary lymph node dissection (ALND) has reportedly reduced patients' quality of life (1,2). In recent years, immediate lymphatic reconstruction (ILR) has been reported as a prophylactic surgical treatment for BCRL, in which lymphatic vessels are identified immediately after ALND and anastomosed to a nearby vein. In 2009, Boccardo *et al.* reported the concept of ILR as the lymphedema microsurgical prevention healing approach (LYMPHA) and showed positive results with postoperative lymphoscintigraphy (3). Some retrospective studies of the effectiveness of ILR have recently been published (4,5). In a recent report with a relatively large number of cases, Le *et al.* reported that in 252 patients treated with ILR, BCRL occurred in 4.8% of patients, compared with 24.1% in 29 patients not treated with ILR, indicating that ILR was effective in preventing BCRL (6). Hill *et al.* also conducted a systematic review and meta-analysis of the efficacy of ILR for BCRL. The systematic review analyzed 11 articles and found that 24 of 417 patients (5.7%) who underwent ILR developed BCRL. Furthermore, a meta-analysis showed that 6 of 90 patients (6.7%) in the ILR group developed BCRL, whereas 17 of 50 patients (34%) in the control group developed it, for a risk ratio of 0.22 in the ILR group (7). However, Levy *et al.* found that, in a retrospective study of 90 patients with more than 4 years of follow-up after ILR, the incidence of BCRL was 31.1% in the ILR group and 33.3% in the non-ILR group, with no significant difference (8). In their discussion, they noted that the definition and diagnosis of lymphedema varied greatly among studies, and no consensus has been reached on the diagnostic criteria for lymphedema.

In addition, for ILR to develop into a widely used treatment throughout the world, one must not only ensure its efficacy and safety, but also solve the issue of insurance coverage for ILR. La-Anyane *et al.* reported that more than half of the main insurance companies in the United States that have a public coverage statement deny ILR coverage (9). Furthermore, Rochlin *et al.* indicated that the current relative value unit (RVU) allocation undervalues ILR, introducing inefficiency into breast cancer operations when combined with ILR. The RVUs assigned to ILR should be re-evaluated to protect patient access to this procedure (10). Thus, from these perspectives, more studies with high-quality evidence, such as randomized controlled trials (RCTs) of the efficacy and safety of ILR are desirable.

Coriddi *et al.* conducted an RCT to evaluate the efficacy of ILR (11). They randomized 152 breast cancer patients who had undergone ALND 1:1 to two groups: ILR or non-ILR. They calculated the relative volume change (RVC) by measuring arm circumference from the wrist to axilla at 4-cm intervals in patients enrolled in this RCT, and they defined BCRL as a case in which the value changed by 10% or more between preoperative and postoperative periods of

12, 18, and 24 months. Bioimpedance, indocyanine green (ICG) lymphangiography, and 4 patient-reported outcome measures (PROMs) were also used as secondary outcomes. They used the Lymphedema Quality of Life (LYMQOL) and the Upper Limb Lyphedema-27 (ULL-27) to quantify subjective symptoms of BCRL, and the Center for Epidemiologic Studies Depression Scale-Revised (CESD-R) and the Beck Anxiety Inventory (BAI) to measure depression and anxiety. The cumulative incidence of BCRL was significantly lower in the ILR group than in the control group. In the ILR group, the cumulative incidence of BCRL was 2.0% [95% confidence interval (CI): 0.16–9.3%] at 12 months, 9.5% (95% CI: 3.0–21%) at 18 months, and 9.5% (95% CI: 3.0–21%) at 24 months, compared to 18% (95% CI: 9.0–30%) at 12 months, 24% (95% CI: 12–37%) at 18 months, and 32% (95% CI: 17–47%) at 24 months in the control group. In the secondary outcomes, the average change in bioimpedance values from baseline was also smaller in the ILR group than in the control group, but this difference was not statistically significant. ICG lymphangiography-based lymphedema stage at 12 and 24 months was compared between the ILR and control groups using the Fisher exact test. It showed substantially and significantly fewer cases of dermal back flow in the ILR group at 12 months postoperatively. Patient-reported lymphedema symptoms assessed using lymphedema-specific PROMs did not differ significantly between the ILR and control groups over time, but there was a trend toward a better function score in the ILR group. ULL-27 physical domain scores and LYMQOL function domain scores worsened in both groups over time, although the ILR group showed less changes from baseline scores than the control group. This report is beneficial by providing meaningful objective and subjective data, however it is limited in that it is not blinded, as the operative details were recorded in the operative report and made available to the patients.

Another issue that was not discussed in this RCT was whether ILR increases lymph node metastasis and distant metastasis. Although a few publications regarding the oncological safety of ILR have been published (12,13), they were all retrospective studies, and obtaining high-level evidence about not only the efficacy of ILR, but also its oncological safety is required.

In conclusion, the study undertaken by Coriddi *et al.* (11) is a rare randomized controlled study in this field and makes a substantial contribution to evaluating the efficacy of ILR. Further high-quality studies are expected in the near future to determine whether ILR is an effective intervention.

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The value of CA19-9 dynamics in decision making for treatment of locally advanced pancreatic cancer

Ingmar F. Rompen, Joseph R. Habib, Elisabetta Sereni, Ammar A. Javed

Department of Surgery, The NYU Grossman School of Medicine and NYU Langone Health, New York, NY, USA

Correspondence to: Ammar A. Javed, MD. Department of Surgery, The NYU Grossman School of Medicine and NYU Langone Health, 550 1st Ave., New York, NY 10016, USA. Email: Ammar.Javed@nyulangone.org.

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Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies with a dismal 5-year overall survival of only 12% across all stages of disease (1). Poor survival is primarily driven by its asymptomatic nature and early propensity of systemic spread of disease (1,2). Even in patients with localized disease who undergo resection, treatment failure occurs in approximately two out of three patients in the form of local or systemic progression of disease (3,4). In combination with improved local and systemic control via multiagent chemotherapy regimens, recent advances in surgical techniques such as improvements in vascular reconstructions and arterial divestment have increased surgical candidacy in patients with locally advanced pancreatic cancer (LAPC) (5-9). The current treatment approach for patients with LAPC now entails induction chemotherapy followed by surgical resection if deemed appropriate (10). However, there remains considerable variability in adherence to these guidelines (11-15). Determining surgical candidacy such that a patient derives maximal benefit from resection remains a challenge (16). This is primarily due to lack of reliable biomarkers to assess treatment response early on during induction therapy to guide treatment decision making.

Carbohydrate antigen 19-9 (CA19-9) is the most frequently used prognostic and monitoring biomarker for assessment of disease in pancreatic cancer. Except in CA19-9 non-producers (approximately 15–20% of the patients), CA19-9 levels at diagnosis and their dynamic changes are often used to inform treatment decisions (17). In this noteworthy nationwide effort, Seelen *et al.* define a minimal (≥40%) and optimal (≥60%) percent decrease in CA19-9 survival cut-off after 2 months of induction therapy (13). The authors demonstrate that these cut-offs are robust predictors of patient prognostication. Moreover, CA19-9 response may serve as a surrogate biomarker for favorable tumor biology and treatment response, hence informing optimal candidacy for surgical selection. Indeed, they demonstrate that in CA19-9 producers, this cut-off was associated with survival, in addition to surgical resection, SBRT, and duration of induction therapy. Similarly, in a study on LAPC after induction treatment with FOLFIRINOX, at the Heidelberg University Hospital, a 60% reduction in CA19-9 was identified as the optimal cut-off and yielded a positive predictive value for resectability of 83% (18). Furthermore, a post-treatment level of <91.8 U/mL was predictive of resectability and survival. Interestingly, patients above the cut-off did not benefit from resection compared to exploration only in terms of overall survival (18).

While a sufficient decrease and low post-induction treatment levels seem convincing in informing treatment decisions, the role of pre-treatment CA19-9 remains controversial. While having an important prognostic value, pretreatment CA19-9 levels do not necessarily predict resectability in LAPC (9,18). Seelen *et al.* address this important clinical question via a sub-analysis of patients with pre-treatment levels of >500 and <500 U/mL with significantly worse outcomes in inadequate responders with high pre-treatment levels. The optimal decrease of CA19-9 was only independently associated with an improved survival in patients with <500 U/mL pre-treatment levels and therefore questions the applicability of this threshold in patients with higher baseline levels. Further research, such as creating a composite score combining these values, may be necessary to increase applicability to patients with high pretreatment levels. Second, further research is necessary to inform treatment decisions in patients that fail to meet these cut-offs for optimal treatment response. Alva-Ruiz *et al.* have shown promising results for change in regimen in patients with unsuccessful induction treatment (19). However, high-level evidence for the decision on prolonging treatment with the same regimen versus switching the regimen versus surgery, to date, is lacking (20,21). Third, it is unlikely that CA19-9 as a sole biomarker can predict surgical candidacy with high accuracy. Currently, large efforts are being undertaken in employing liquid biopsies to harness ctDNA and circulating tumor cells as biomarkers of systemic disease and treatment response (22). Multianalyte tests could help determine the presence and extent of systemic disease and therefore define optimal surgical candidates for surgery as the most effective local treatment.

To date, evidence suggests that using CA19-9 dynamics with a cut-off of ≥60% reduction is the best data we have for treatment decision making after 2 months of induction chemotherapy in clinical practice. We would like to congratulate the authors on conducting a robust nationwide analysis to address this important question in the management of LAPC. This study adds to the growing evidence that CA19-9 dynamics can add value in patient prognostication and determining surgical candidacy in LAPC and hence improve survival.

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Editorial Commentary

Pitfalls in the preoperative and postoperative workup of patients with primary aldosteronism

Marta Araujo-Castro[1,2]^, Iñigo García Sanz[3,4]

[1]Endocrinology & Nutrition Department, Hospital Universitario Ramón y Cajal, Madrid, Spain; [2]Instituto de Investigación Biomédica Ramón y Cajal (IRYCIS), Madrid, Spain; [3]General & Digestive Surgery Department, Hospital Universitario de La Princesa, Madrid, Spain; [4]Instituto de Investigación Sanitaria Princesa (IIS-IP), Universidad Autónoma de Madrid (UAM), Madrid, Spain

Correspondence to: Marta Araujo-Castro, PhD. Instituto de Investigación Biomédica Ramón y Cajal (IRYCIS), Ctra. Colmenar Viejo, Fuencarral-El Pardo, 28034 Madrid, Spain; Endocrinology & Nutrition Department, Hospital Universitario Ramón y Cajal, Madrid, Spain. Email: marta.araujo@salud.madrid.org.

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We were highly interested in the findings of Vignaud *et al.*'s study (1), which showed that preoperative workup was consistent with guidelines for only 40% of the patients with primary aldosteronism (PA). In addition, they found that complete biological success was not sufficiently assessed after surgery, and no differences in surgical outcomes were observed between patients operated based on the results of adrenal computed tomography (CT) scanning or adrenal venous sampling (AVS).

It is known that PA is the most frequent cause of endocrine arterial hypertension and it is associated with a higher cardiometabolic risk than primary hypertension (2,3). However, despite its importance, PA remains highly underdiagnosed (4), and the PA management guidelines are poorly applied for its detection and management (2,3). At the moment, the real-life situation is that only 1.9% of the expected cases of PA are diagnosed and as a consequence, just 1% of the expected adrenalectomies are performed (4). In addition, discrepant recommendations were identified at all management steps (screening, confirmation, classification, treatment and follow-up) among 12 guidelines for the diagnosis and treatment of PA, published between 2006 and 2016 (5).

In terms of the preoperative work-up, no consensus exists about which aldosterone to renin ratio should be used for PA screening, nor what confirmatory test is the most reliable to confirm autonomous aldosterone secretion (2,3). Nevertheless, as Vignaud *et al.* (1) highlighted, the most challenging diagnostic step is the subtyping of PA since CT and magnetic resonance imaging (MRI) are considered unreliable procedures to differentiate between unilateral and bilateral PA, with a reported discordance between these techniques and AVS of 38% (6). Thus, the last guidelines recommend that when surgical treatment is desired by the patient, an experienced radiologist should use an AVS to make the distinction between unilateral and bilateral disease (3). The exceptions proposed by the guidelines for performing AVS are to suspect an adrenocortical carcinoma, cortisol co-secretion or an age <35 years old and clear unilateral adrenal nodule in CT/MRI (2,3). However, there is a gap between clinical guidelines recommendations and current clinical practice. In this regard, as it has been reported by Vignaud *et al.* (1), only 31% of the patients with PA underwent AVS before surgery and preoperative AVS was "adequately" performed in just 40% of the cases (2,3). These results are in agreement with the described in the SPAIN-ALDO study, where only 35% of the patients had

^ ORCID: 0000-0002-0519-0072.

an available AVS (7). The criteria for using AVS are quite heterogeneous across centers. For example, in the Vignaud series (1), some centers hardly ever used the procedure, others limited AVS use to specific situations such as bilateral lesions on imaging, small lesions on imaging or large number of preoperative antihypertensive treatments, and others followed strictly the French recommendations. Nonetheless, in this study, there was no correlation between complete clinical success and the completeness of preoperative workup. These results are in line with the described in the unique prospective randomized study published comparing CT-based and AVS-based management (8). However, we have to take into account that SPARTACUS study has several limitations, including that they selected the most severe group of patients with PA; the four cases in whom AVS failed were included in the CT cohort; the difficulties in reconciling CT diagnoses between cooperating institutions and the study was not generated to evaluate secondary endpoints (hypertension cure and biochemical cure) (8).

Other factors that may justify the existence of a heterogenous use of AVS is the lack of consensus about which is the best approach in the AVS: (I) some authors defend the use of adrenocorticotropic hormone (ACTH) stimulation during AVS since its use results in a higher proportion of successful samples, while other authors found that its use may lead to an inversion of the lateralization index (LI) to the wrong side (9); (II) adrenal venous samples might be obtained simultaneously or sequentially; but, although with simultaneous sampling thought to potentially avoid problems related with ACTH fluctuation, simultaneous sampling increased technical difficulty of the AVS; (III) discontinuing renin angiotensin-system-interfering medications is not always feasible, so some authors have proposed the possibility of continuing some of these medications such as mineralocorticoid receptors antagonist during the procedure as long as renin levels remained unsuppressed (10). Furthermore, the interpretation of the results is not easy nor is it standardized, varying the cutoff values of the selectivity index (SI), LI and contralateral suppression index between centers. Theoretically, the AVS, despite correct implementation and interpretation, can fail in certain situations: (I) abnormal adrenal venous drainage (accessory hepatic vein, double veins or cannulation of veins not draining the aldosterone producing adenoma); (II) bilateral PA with asymmetrical production of aldosterone or cortisol; (III) connshing syndrome may lead to a higher rate of misclassified AVS; (IV) stress reaction starting the procedure may alter the LI. All these factors may contribute to the quite low use of the AVS in the subtyping diagnosis of PA. This finding challenges the current recommendation to perform AVS in all patients with PA. On the other hand, NP59 scintigraphy or positron emission tomography (PET)-metomidate could be considered in certain clinical situations, especially when the AVS is unsuccessful or the results are indeterminate (11).

Finally, although there is plenty of evidence about the positive effect of adrenalectomy for PA on cardiometabolic outcomes, the reported rates of complete clinical cure are as low as 30–40% in most of the series (3,12), even though it has been reported that some patients classified as cured may developed hypertension after a relative short-term follow-up. For example, in the Vignaud study (1), 16% of the patients considered as cured at the first follow up (median 43 days) had contradictory results at the second follow-up visit (median 377 days) due to the resumption of antihypertensive drugs. The criteria to classify outcomes of adrenalectomy for unilateral PA are quite heterogenous. Thus, it is essential to standardize the way of publishing the outcomes (*Table 1*) (13), which implies hormonal determination once the patient has undergone surgery, as well as a minimum follow-up time. The outcomes after adrenalectomy for unilateral primary aldosteronism (PASO criteria) are the most widely used (*Table 1*) (13). Based on them, complete clinical success is defined by normal blood pressure without antihypertensive medication after surgery. At the last follow-up, it was achieved in 31% of patients in the series of Vignaud (1). These results are in accordance with the reported in our Spanish registry, of 38% (14). Nevertheless, it should be noted that even biochemical cure without hypertension cure is associated with an improvement in the cardiometabolic risk and a major increase in health-related quality of life (HRQoL) after surgery. In this way, it has been recently described that correction of hypokalemia and control of diastolic blood pressure are essential factors contributing to the improvement in the HRQoL in patients with PA (15).

The ideal situation will be to predict before surgery which PA patients are going to have hypertension cure. In this regard, several prognostic models have been proposed to predict outcome after adrenalectomy. In agreement with the results of the Eurocrine Study Group (1), the SPAIN-ALDO score includes female sex, use of two or fewer antihypertensive medications, hypertension grade 1, no type 2 diabetes and non-obesity as the predictive variables of hypertension cure. The chance of hypertension cure was

Table 1 Outcomes after adrenalectomy for unilateral primary aldosteronism (PASO criteria) (13)

Outcome	Clinical	Biochemical
Complete success (remission)	Normal BP without antihypertensive medication	1. Hypokalemia correction (if present before operation)
		and
		2. Normalization of ARR
		or
		3. Aldosterone suppressed during confirmatory testing if ARR increased postoperatively
Partial success (improvement)	Stable BP with less antihypertensive medication or lower BP with an equal or a smaller number of antihypertensive drugs	1. Correction of hypokalemia (if present before surgery) and increased postoperative ARR
		And at least one of the following (compared with presurgical):
		2. Decreased ≥50% in basal aldosterone levels
		or
		3. Abnormal but improved postoperative aldosterone during confirmatory testing
Absence of success (persistence)	Unchanged or higher BP with equal or greater n° of antihypertensive drugs	1. Persistent hypokalemia (if present before operation)
		or
		2. Persistent increase in ARR after surgery
		and
		3. Failure to suppress aldosterone secretion during confirmatory testing

BP, blood pressure; ARR, aldosterone-to renin ratio.

80.4% if all these variables were present before surgery (14). Nevertheless, in the Vignaud *et al.* (1) study, body mass index, duration of hypertension, and number of antihypertensive drugs were the important predictive variables of hypertension cure identified on the multivariate analysis.

In conclusion, there are still several pitfalls and limitations in the diagnosis of PA, including case detection, confirmatory and subtyping diagnosis. The rates of complete clinical cure are still quite low, probably related to the selection of surgical patients. AVS is the best lateralization test at present, although it has several limitations, including that it is not universally available, it is not a standardized test, neither the technique nor the interpretation of the results and has a modest correct catheterization rate in multiple studies and therefore not easily reproducible. The available evidence should act as a wake-up call to improve the way we select patients' candidates for surgical treatment.

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Letter to the Editor

Papillary thyroid carcinoma of isthmus: total thyroidectomy or isthmusectomy?

Yunlong Dai[1], **Qingbo Feng**[2]

[1]Department of Hepatobiliary Surgery, Wenjiang District People's Hospital of Chengdu, Chengdu, China; [2]Department of General Surgery, Digestive Disease Hospital, Affiliated Hospital of Zunyi Medical University, Zunyi, China

Correspondence to: Yunlong Dai, MD. Department of Hepatobiliary Surgery, Wenjiang District People's Hospital of Chengdu, 86 Taikang Rd., Wenjiang District, Chengdu 611130, China. Email: 393680291@qq.com.

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Papillary thyroid carcinoma (PTC) is the most common malignant tumor originated from thyroid follicular epithelial cells. PTC is mostly located in the thyroid gland lobe. According to relevant literature, the incidence rate of thyroid isthmus papillary carcinoma is 2.5–12.3% (1). Compared to those located in the glandular lobe, papillary carcinoma of the isthmus of the thyroid has a higher probability of extraglandular infiltration, multifocal tumor, and lymph node metastasis due to different anatomical locations (2). The treatment plan for papillary carcinoma of the isthmus of the thyroid is still controversial, with the core of the controversy being the scope of surgical resection of the thyroid and whether preventive central lymph node dissection should be performed. Some scholars advocate for simple isthmus resection, preserving bilateral glands without the need for preventive lymph node dissection; some scholars advocate for total thyroidectomy and preventive central lymph node dissection.

Recently, Gong and his colleagues performed a meta-analysis to compare the recurrence rate and incidence of complications between total thyroidectomy and subtotal thyroidectomy for PTC of isthmus (PTCI) (3), which has been published in *Gland Surgery*. Gong *et al.*'s research found no significant difference between the two surgical methods. After careful reading, we found that some issues may have an impact on the conclusion.

Firstly, the inclusion criteria proposed in the article are that both the control group and the experimental group have more than ten people. In *Tab. 1*, we found that reference 23 (4) only has six people in the control group, which does not meet the inclusion criteria specified in the article.

Secondly, reference 23 (4) was published in 1993, and the inclusion criteria proposed in the article require case selection to meet the criteria of the 2015 American Thyroid Association (ATA) guidelines for indications for surgical treatment of differentiated thyroid cancer; this poses a conflict in terms of timing.

Thirdly, the inclusion criteria proposed in the article state that studies with a follow-up period of more than 2 years are required to be included. However, the original reference 22 (5) mentioned a follow-up period of 2–54 months, indicating that some patients did not meet the criteria for a follow-up period of more than 2 years. If reference 22 (5) needs to be included, it is recommended to remove the inclusion criterion of follow-up period of 2 years or more.

At present, a consensus has been reached on performing total thyroidectomy combined with central lymph node dissection for patients with preoperative detection of central lymph node metastasis. However, there is still controversy over whether prophylactic central lymph node dissection should be performed for papillary carcinoma of the isthmus without lymph node metastasis in preoperative imaging examinations. One drawback of this meta-analysis is the lack of subgroup analysis on whether total or partial thyroidectomy is combined with neck lymph node dissection.

In conclusion, Gong *et al.* performed an excellent study to explore the therapeutic effects of total thyroidectomy and partial thyroidectomy on PTCI. The authors' contribution to this study is appreciated. In our opinion, additional high-quality studies are needed to further confirm the conclusions.

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Revisiting meta-analysis: surgical approaches for papillary thyroid carcinoma of isthmus

Hao Gong#, Yuhan Jiang#, Anping Su

Division of Thyroid & Parathyroid Surgery, Department of General Surgery, West China Hospital Sichuan University, Chengdu, China
#These authors contributed equally to this work as co-first authors.
Correspondence to: Anping Su, MD, PhD. Division of Thyroid & Parathyroid Surgery, Department of General Surgery, West China Hospital Sichuan University, No. 37 Guoxue Xiang, Chengdu 610041, China. Email: suanping15652@163.com.
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First, we are very grateful to Dr. Dai and Dr. Feng for their questions and suggestions, which were helpful to our study (1). When we set up a topic of this study, we set up the inclusion and exclusion criteria (2). There is no doubt that strict inclusion and exclusion criteria are important for meta-analysis, and the quality of the included studies determines the rigor of the meta-analysis. However, due to the small amount of original literature having published on surgical modality selection for papillary thyroid carcinoma of isthmus (PTCI), we included all of the retrieved study in our data analysis, which led to the questions about our article raised by Dr. Dai and Dr. Feng.

Therefore, according to the suggestions made by Dai *et al.*, references [22] and [23] did not meet the inclusion criteria that we established when we set up the study, which was our overlook. We re-searched for articles on papillary carcinoma of the thyroid isthmus and found a new study published by Dr. Dan and colleagues in August 2023 (3). After careful review, we found that this study met our inclusion criteria. Therefore, we hereby include this study in our analysis with updated findings as follows.

Meta-analysis for tumor recurrence rate

The results of the study after the inclusion of Dan *et al.* 2023 showed that the overall tumor recurrence rate was the same as that obtained in the previous studies, i.e., there was no statistically significant difference in tumor recurrence rate between the two groups (3). A total of 781 individuals were included, with 19 tumor recurrences in the less than total thyroidectomy group and 14 tumor recurrences in the total thyroidectomy group [OR =1.10 (95% CI: 0.45, 2.69); P=0.35, and I^2=10%], which showed a low degree of heterogeneity (*Figure 1*). It was imported into Stata 17, Influence Analysis, metan-based (metaninf) board, and the random effects model, M-H method was selected to analyze the OR values, and the results were validated by deleting one article at a time, as shown in *Figure 2*, which showed that the 95% CI crossed the null line after deleting any article.

Incidence rate

Regarding the incidence of postoperative complications between the two groups, Dan *et al.*'s study (3) proposed that the difference in the incidence of temporary postoperative hypocalcemia between the two groups was statistically significant (P=0.032), but the difference in the incidence of permanent postoperative hypocalcemia, hoarseness, and choking on drinking water was not statistically significant. The studies describing the presence of postoperative complications included a total of 488 people, 49 cases of postoperative complications in the less-than-total thyroidectomy group and 114 cases in the total thyroidectomy group. The results of the meta-analysis of the overall complication rate showed that there was no statistically significant difference in the overall postoperative complication rate between the two groups, with OR =0.29 (95% CI: 0.03, 2.46), P=0.26, and I^2=95%, which was highly heterogeneous (*Figure 3*). There was significant

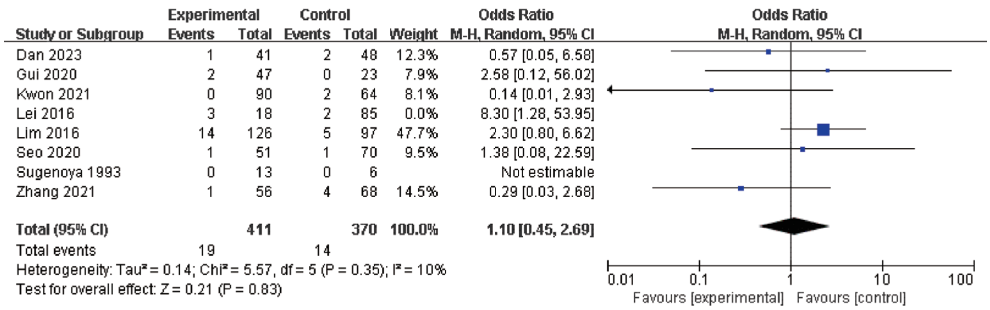

Figure 1 Meta-analysis of tumor recurrence rate. The figure was adapted from Gong *et al.* (2). CI, confidence interval.

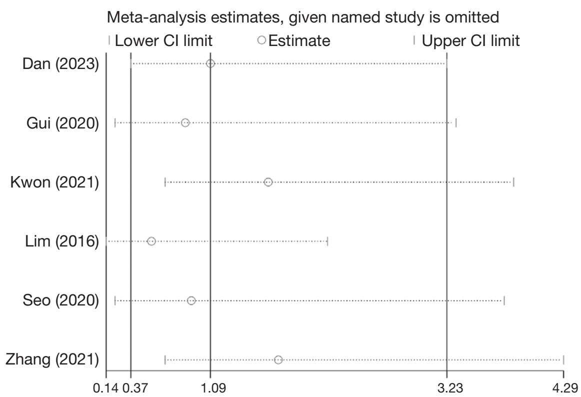

Figure 2 Sensitivity analysis of tumor recurrence rate. The figure was adapted from Gong *et al.* (2). CI, confidence interval.

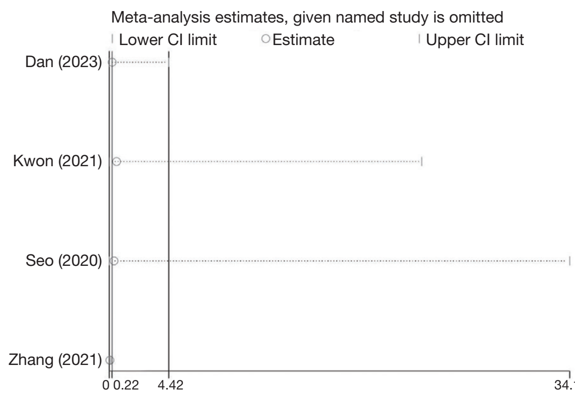

Figure 4 Sensitivity analysis of postoperative complications. The figure was adapted from Gong *et al.* (2). CI, confidence interval.

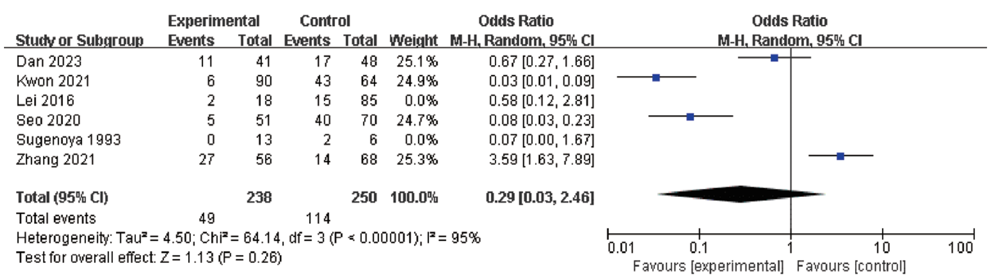

Figure 3 Meta-analysis of overall postoperative complication rate. The figure was adapted from Gong *et al.* (2). CI, confidence interval.

heterogeneity in the studies (P<0.00001, I^2=95%). The results of the sensitivity analysis showed that none of the included studies affected the overall results, so the overall results can be considered stable and reliable (*Figure 4*).

There is a controversy about whether prophylactic central lymph node dissection should be performed for papillary carcinoma of the thyroid isthmus without preoperative lymph node metastasis, and the studies we included did not describe the lymph node dissection of the two groups in detail, and thus relevant subgroup analyses could not be performed. In the future, we expect more high-quality randomized controlled trials to supplement the evidence and thus guide the surgical treatment strategy for papillary carcinoma of the thyroid isthmus and bring better prognosis to patients.

Finally, thanks again to Dr. Dai and Dr. Feng for their questions, which have undoubtedly promoted greater rigor in our research.

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Supplementary

Table S1 Clinical and pathological characteristics for LLNM risk of T1a PTC patients by univariate analysis (n=2,318)

Category	Non-LLNM (n=2,228)	LLNM (n=90)	Total	OR (95% CI)	P value
Sex				2.287 (1.479–3.535)	<0.001
Female	1,743 (78.2)	55 (61.1)	1,798 (77.6)		
Male	485 (21.8)	35 (38.9)	520 (22.4)		
Age (years)				1.512 (0.842–2.715)	0.164
≤55	1,986 (89.1)	76 (84.4)	2,062 (89.0)		
>55	242 (10.9)	14 (15.6)	256 (11.0)		
Mean ± SD	41.5±10.5	42.7±11.3			0.386
Tumor location				0.513 (0.332–0.792)	0.002
Upper lobe	548 (24.6)	35 (38.9)	583 (25.2)		
Non-upper lobe	1,680 (75.4)	55 (61.1)	1,735 (74.8)		
Tumor volume (mm^3)				1.944 (1.270–2.975)	0.002
≤140	1,332 (59.8)	39 (43.3)	1,371 (59.1)		
>140	896 (40.2)	51 (56.7)	947 (40.9)		
Mean ± SD	140.4±99.0	181.4±114.8			<0.001
Tumor diameter (mm)				1.725 (1.129–2.633)	0.011
≤7	1,316 (59.1)	41 (45.6)	1,357 (58.5)		
>7	912 (40.9)	49 (54.4)	961 (41.5)		
Mean ± SD	7.1±1.7	7.7±1.6			0.003
Multifocality				2.407 (1.494–3.877)	<0.001
No	1,921 (86.2)	65 (72.2)	1,986 (85.7)		
Yes	307 (13.8)	25 (27.8)	332 (14.3)		
Bilaterality				2.014 (1.152–3.520)	0.012
No	2,012 (90.3)	74 (82.2)	2,086 (90.0)		
Yes	216 (9.7)	16 (17.8)	232 (10.0)		
AS time (months)				1.244 (0.785–1.972)	0.353
≤6	1,657 (74.4)	63 (70.0)	1,720 (74.2)		
>6	571 (25.6)	27 (30.0)	598 (25.8)		

Data are reported as n (%), unless noted otherwise. P values represent the statistically difference between the groups with and without LLNM, unless noted otherwise. LLNM, lateral lymph node metastasis; PTC, papillary thyroid carcinoma; OR, odds ratio; CI, confidence interval; AS, active surveillances.

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Table S2 Clinical and pathological characteristics for LLNM risk of T1b PTC patients by univariate analysis (n=1,014)

Category	Non-LLNM (n=898)	LLNM (n=116)	Total	OR (95% CI)	P value
Sex				1.479 (0.986–2.220)	0.057
Female	649 (72.3)	74 (63.8)	723 (71.3)		
Male	249 (27.7)	42 (36.2)	291 (28.7)		
Age (years)				0.525 (0.249–1.106)	0.085
≤55	787 (87.6)	108 (93.1)	895 (88.3)		
>55	111 (12.4)	8 (6.9)	119 (11.7)		
Mean ± SD	40.8±11.5	40.8±10.5			0.963
Tumor location				0.556 (0.372–0.831)	0.004
Upper lobe	234 (26.1)	45 (38.8)	279 (27.5)		
Non-upper lobe	664 (73.9)	71 (61.2)	735 (72.5)		
Tumor volume (mm^3)				2.191 (1.483–3.238)	<0.001
≤760	575 (64.0)	52 (44.8)	627 (61.8)		
>760	323 (36.0)	64 (55.2)	387 (38.2)		
Mean ± SD	760.4±443.9	930.2±566.3			<0.001
Tumor diameter (mm)				1.817 (1.229–2.685)	0.002
≤14	607 (67.6)	62 (53.4)	669 (66.0)		
>14	291 (32.4)	54 (46.6)	345 (34.0)		
Mean ± SD	13.7±2.4	14.5±2.7			<0.001
Multifocality				2.281 (1.477–3.524)	<0.001
No	755 (84.1)	81 (69.8)	836 (82.4)		
Yes	143 (15.9)	35 (30.2)	178 (17.6)		
Bilaterality				1.652 (0.988–2.762)	0.054
No	792 (88.2)	95 (81.9)	887 (87.5)		
Yes	106 (11.8)	21 (18.1)	127 (12.5)		
AS time (months)				0.882 (0.548–1.419)	0.604
≤6	693 (77.2)	92 (79.3)	785 (77.4)		
>6	205 (22.8)	24 (20.7)	229 (22.6)		

Data are reported as n (%), unless noted otherwise. P values represent the statistically difference between the groups with and without LLNMs, unless noted otherwise. LLNM, lateral lymph node metastasis; PTC, papillary thyroid carcinoma; OR, odds ratio; CI, confidence interval; AS, active surveillance.

Table S3 Univariate analysis of AS time of T1a PTC patients (n=2,318)

Gender	AS time (months)	Non-LLNM	LLNM	Total	OR (95% CI)	P value
Female (n=1,798)	≤6	1,292	37	1,329	1.394 (0.786–2.473)	0.254
	>6	451	18	469		
Male (n=520)	≤6	365	26	391	1.053 (0.480–2.310)	0.898
	>6	120	9	129		
Female (n=1,798)	≤12	1,557	48	1,605	1.221 (0.544–2.737)	0.628
	>12	186	7	193		
Male (n=520)	≤12	428	33	461	0.455 (0.106–1.947)	0.417
	>12	57	2	59		
Female (n=1,798)	≤24	1,694	55	1,749	0.969 (0.960–0.977)	0.401
	>24	49	0	49		
Male (n=520)	≤24	476	34	510	1.556 (0.191–12.641)	>0.99
	>24	9	1	10		

AS, active surveillance; PTC, papillary thyroid carcinoma; LLNM, lateral lymph node metastasis; OR, odds ratio; CI, confidence interval.

Table S4 Univariate analysis of AS time of T1b PTC patients (n=1,014)

Gender	AS time (months)	Non-LLNM	LLNM	Total	OR (95% CI)	P value
Female (n=723)	≤6	497	58	555	0.902 (0.504–1.615)	0.728
	>6	152	16	168		
Male (n=291)	≤6	196	34	230	0.870 (0.380–1.991)	0.742
	>6	53	8	61		
Female (n=723)	≤12	574	71	645	0.323 (0.099–1.052)	0.049
	>12	75	3	78		
Male (n=291)	≤12	219	38	257	0.768 (0.256–2.305)	0.638
	>12	30	4	34		
Female (n=723)	≤24	631	74	705	–	0.290
	>24	18	0	18		
Male (n=291)	≤24	243	40	283	2.025 (0.395–10.386)	0.725
	>24	6	2	8		

AS, active surveillance; PTC, papillary thyroid carcinoma; LLNM, lateral lymph node metastasis; OR, odds ratio; CI, confidence interval.

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Supplementary

Table S1 Full items synthesized through the cognitive task analysis (full list)

Section	CTA items
MID phase	*Identification of midline*
	Find the correct midline position in the strap muscles
	Retract midline bilaterally with both graspers
	When retracting the midline with graspers on both sides, give proper symmetrical tension and cautions for muscle tearing
	Midline incision
	Follow the surgical plane well and dissect it
	Identify the sternothyroid muscle and sternohyoid muscle
	Ensure sufficient incision to Delphian lymph node
	Caution of muscle injury when midline incision is made
	Incision from the thyroid cartridge to the suprasternal notch (or the location where central node dissection is possible)
	Identification of trachea
	Beware trachea injury
	Implement trachea exposure as much as possible
	Identification of isthmus
	Beware trachea injury
	Find isthmus well
	Whether you see the isthmus as soon as you open the midline from the sternohyoid muscle
	Isthmectomy
	Preserve the inferior thyroid vein on the non-operative side
	Consider the location of isthmus
	Beware vessel injury (such as thyroid ima)
	Beware cricoid cartilage injury
	Whether the left and right sides of the thyroid is separated
	Other items related to midline incision and isthmectomy
	Whether the isthmectomy is possible preoperatively (if there is a cancer on the isthmus itself, the isthmectomy position might be changed)
LAT phase	*Dissection of surgical plane between thyroid and strap muscle*
	Separate strap muscles and thyroid gland from cranial to caudal
	Dissect the surgical plane as close as possible to the surface of thyroid gland
	Be careful between thyroid gland and strap muscle
	Whether the strap muscle is injured
	Lateral retraction of the strap muscle
	Sufficiently separate the thyroid from the strap muscle
	Be careful if you pull the strap muscle excessively, it can tear and bleed

Table S1 (*continued*)

Table S1 (*continued*)

Section	CTA items
	Identification of common carotid artery
	Identify the correct depth and course of the common carotid artery
	Leave the blood vessels around common carotid artery
	Whether the common carotid artery moves well according to the heartbeat
	Whether the common carotid artery is well exposed along the thyroid gland
	Thyroid retraction—lower
	Accurately locate parathyroid gland and RLN
	Beware of bleeding in thyroid capsule
	Expose the lower pole and part of the upper part of the thyroid gland
	Switching motion to support and lift the thyroid gland to check the tissue around the common carotid artery
	Other items related to lateral dissection
	Whether the central lymph nodes is removed cleanly along the thyroid gland
	Whether the middle thyroid vein is exposed and ligated certainly
INF phase	*Identification of RLN*
	Identify RLN between central lymph nodes
	Ensure safe distances considering the range of heat conduction in order to prevent thermal injury
	Retracting the thyroid gland excessively may cause mechanical injury of RLN
	Identify the course and the location of RLN
	Identification of inferior parathyroid gland
	Recognize the typical location and shape of parathyroid gland
	Identify the color of parathyroid gland
	Identify the anatomical mutations in the location of parathyroid gland
	Identify the blood stream distribution and blood vessel travel of parathyroid gland
	Determine whether to leave parathyroid or auto-transplantation after removal
	When the distinction between lymph nodes and parathyroid is difficult, determine whether to leave some or remove all depending on the cancer stage
	Beware of damage to parathyroid gland and the blood vessels leading to the parathyroid
	Preservation of the blood stream of parathyroid
	Preserve blood vessels that affect parathyroid
	Ensure safe distances considering the range of heat conduction to prevent thermal injury
	Identify inferior thyroidal vein and middle thyroidal vein
	Preserve parathyroid as much as possible
	Beware injury to parathyroid and parathyroid feeding vessels

Table S1 (*continued*)

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Table S1 (*continued*)

Section	CTA items
	Other items to preservation of inferior parathyroid glands
	Avoid retracting the parathyroid directly to prevent damage to the parathyroid
	If inevitable, retract tissues around the parathyroid or grab the blood vessels going to the parathyroid
BER phase	*Dissection between medial thyroid and trachea*
	Separate trachea and cricothyroid muscle from the thyroid gland
	Dissection between thyroid gland and fascia
	Finish the lateral dissection on the lateral side of the thyroid gland
	Thyroid retraction—Zuckerkandl
	Retract the thyroid in favor of entering the harmonic
	Beware of RLN injury caused by traction
	Preservation of RLN
	Consider various shapes of RLN
	Continue to check RLN's course from view to view
	Distinguish artery from RLN
	Predict RLN location and angle
	When Berry ligament and RLN are placed together, which intensity will you pull to?
	Dissect RLN while protect it by covering it with gauze ball to prevent thermal or mechanical injury
	Strong retraction on the thyroid may damage the RLN
	Beware of thermal injury
	Occasionally non-recurrent laryngeal nerve exists that drives directly into the vagus nerve from the upper part of the subclavian artery and enters the larynx
	Nerve monitoring allows you to see the amplitude of the nerve when initially stimulated (whether the signal has been reduced by more than 50%)
	Dissection of ligament of Berry
	Expose Berry ligament sufficiently
	When Berry ligament and RLN are placed together, which intensity will you pull to?
	Dissect thyroid gland below Berry ligament
	Check the cricothyroid muscle in the upper area
	Minimize residual thyroid tissue: may leave microscopic amounts of thyroid tissue when the thyroid and the RLN are attached, or when the thyroid tissue is covering the RLN like ears
	Hemostasis is difficult if bleeding occurs in Berry ligament
	Whether you remove Berry ligament well while protecting RLN
	Other items related to preservation of RLN, dissection of the ligament of Berry
	Use compression method with energy or gauze ball in some cases for hemostasis

Table S1 (*continued*)

 https://dx.doi.org/10.21037/gs-23-467

Table S1 (*continued*)

Section	CTA items
SUP phase	*Dissection in the upward direction*
	To prevent EBSLN injury, proceed dissection as close to the thyroid as possible and at the same time ligate the upper thyroid artery well
	Beware of EBSLN injury
	Mapping the course of EBSLN using nerve monitoring
	Identification and preservation of superior parathyroid glands
	Be careful of bleeding during the ligation of superior thyroid artery because the op field is narrow
	Determine which blood vessels to leave
	Beware of upper parathyroid injury
	Identification and preservation of EBSLN
	Whether EBSLN functions
	Whether the signals come from the EBSLN while using nerve monitoring
	Whether the cricothyroid muscle has twitching
	Ligation of superior thyroid artery and vein
	Adjust robotic arms for better visibility
	Expose the superior thyroid artery well at once and ligate it at once
	Other items related to dissection of the thyroid upper pole
	Use nerve monitoring to identify vagus nerve (located close to carotid artery)
END phase	*Specimen out*
	If the thyroid is too large to remove, expand the Troca tunner site sufficiently
	Use a surgical lap bag to safely discharge specimen out of the op field to prevent the metastasize to other tissues
	Use of hemostatic dressing and anti-adhesion adjuvant
	Sewing strap muscles with running sutures during midline closure (cranial to caudal)
	Drain insertion and midline closure

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Table S2 Results of modified Delphi consensus on items required to perform robotic thyroidectomy (full list)

Final rank	Phase	Items	Round 1			Round 2	
			Mean (SD)	% rating over 5	Rank	Mean (SD)	% rating over 5
1	BER	Continue to check RLN's course from view to view	6.67 (0.64)	100	3	6.85 (0.65)	95
2	LAT	Accurately locate parathyroid gland and RLN	6.76 (0.61)	100	2	6.8 (0.68)	95
2	INF	Identify the course and the location of RLN	6.81 (0.50)	100	1	6.8 (0.51)	100
4	INF	Ensure safe distances considering the range of heat conduction in order to prevent thermal injury	6.67 (0.56)	100	3	6.7 (0.56)	100
5	SUP	To prevent EBSLN injury, proceed dissection as close to the thyroid as possible and at the same time ligate the upper thyroid artery well	6.52 (0.59)	100	6	6.55 (0.50)	100
6	MID	Whether the isthmectomy is possible preoperatively (if there is a cancer on the isthmus itself, the isthmectomy position might be changed)	6.38 (0.79)	100	12	6.5 (0.81)	95
6	BER	Beware of thermal injury	6.52 (0.66)	100	6	6.5 (0.50)	100
8	MID	Beware trachea injury	6.43 (0.85)	100	11	6.45 (0.67)	100
8	INF	Retracting the thyroid gland excessively may cause mechanical injury of RLN	6.19 (0.91)	90	20	6.45 (0.86)	95
8	BER	Beware of RLN injury caused by traction	6.48 (0.73)	100	10	6.45 (0.74)	100
11	BER	Strong retraction on the thyroid may damage the RLN	6.24 (0.87)	95	15	6.4 (0.66)	100
12	MID	Beware trachea injury	6.52 (0.85)	95	6	6.35 (0.57)	100
12	INF	Preserve parathyroid as much as possible	6.57 (0.49)	100	5	6.35 (0.85)	95
12	BER	Whether you remove Berry ligament well while protecting RLN	6.24 (1.11)	90	15	6.35 (0.57)	100
12	SUP	Beware of EBSLN injury	6.29 (0.82)	95	13	6.35 (0.79)	95
12	END	Use a surgical lap bag to safely discharge specimen out of the op field to prevent the metastasize to other tissues	6.52 (0.73)	95	6	6.35 (0.79)	95
17	BER	Consider various shapes of RLN	6.24 (1.11)	86	15	6.3 (0.71)	95
18	BER	Distinguish artery from RLN	6.00 (1.15)	90	27	6.25 (0.77)	100
18	SUP	Be careful of bleeding during the ligation of superior thyroid artery because the op field is narrow	6.19 (0.91)	95	20	6.25 (0.77)	95
20	INF	Preserve blood vessels that affect parathyroid	6.24 (0.68)	100	15	6.2 (0.75)	100
21	INF	Ensure safe distances considering the range of heat conduction to prevent thermal injury	6.00 (0.69)	100	27	6.15 (0.73)	100
22	BER	When Berry ligament and RLN are placed together, which intensity will you pull to?	6.00 (0.93)	95	27	6.1 (0.62)	100
23	INF	Beware of damage to parathyroid gland and the blood vessels leading to the parathyroid	6.05 (1.05)	90	26	6.05 (0.80)	95

Table S2 (*continued*)

Table S2 (*continued*)

Final rank	Phase	Items	Round 1			Round 2	
			Mean (SD)	% rating over 5	Rank	Mean (SD)	% rating over 5
23	INF	Beware injury to parathyroid and parathyroid feeding vessels	6.29 (0.76)	100	13	6.05 (0.80)	95
23	SUP	Beware of upper parathyroid injury	6.24 (0.92)	95	15	6.05 (0.80)	95
26	BER	When Berry ligament and RLN are placed together, which intensity will you pull to?	5.90 (0.92)	95	33	6 (0.55)	100
27	INF	Identify the blood stream distribution and blood vessel travel of parathyroid gland	6.14 (1.17)	86	22	5.95 (0.97)	95
27	BER	Predict RLN location and angle	5.90 (1.02)	90	33	5.95 (0.74)	100
27	BER	Dissect RLN while protect it by covering it with gauze ball to prevent thermal or mechanical injury	6.00 (1.11)	86	27	5.95 (0.97)	90
27	END	If the thyroid is too large to remove, expand the Troca tunner site sufficiently	6.00 (0.87)	100	27	5.95 (0.59)	100
31	INF	Identify the color of parathyroid gland	6.10 (0.97)	90	24	5.9 (0.70)	95
31	BER	Expose Berry ligament sufficiently	5.95 (0.95)	90	32	5.9 (0.70)	95
33	INF	Recognize the typical location and shape of parathyroid gland	6.14 (0.99)	90	22	5.85 (0.73)	95
34	SUP	Adjust robotic arms for better visibility	6.10 (0.97)	90	24	5.8 (0.81)	90
35	INF	Determine whether to leave parathyroid or auto-transplantation after removal	5.90 (0.97)	90	33	5.7 (0.71)	95
35	SUP	Whether the cricothyroid muscle has twitching	5.86 (1.39)	90	37	5.7 (1.27)	95
37	BER	Minimize residual thyroid tissue: may leave microscopic amounts of thyroid tissue when the thyroid and the RLN are attached, or when the thyroid tissue is covering the RLN like ears	5.71 (0.98)	86	43	5.65 (0.73)	90
37	SUP	Whether EBSLN functions	5.76 (1.41)	90	38	5.65 (1.39)	90
39	MID	Follow the surgical plane well and dissect it	5.67 (1.32)	81	49	5.6 (0.80)	90
39	MID	Implement trachea exposure as much as possible	5.57 (1.09)	76	53	5.6 (0.66)	95
39	BER	Occasionally non-recurrent laryngeal nerve exists that drives directly into the vagus nerve from the upper part of the subclavian artery and enters the larynx	5.76 (1.11)	81	38	5.6 (0.73)	90
39	BER	Hemostasis is difficult if bleeding occurs in Berry ligament	5.57 (1.18)	76	53	5.6 (0.73)	90
39	SUP	Expose the superior thyroid artery well at once and ligate it at once	5.71 (1.12)	81	43	5.6 (0.86)	90
44	MID	Beware cricoid cartilage injury	5.67 (1.21)	86	49	5.55 (0.92)	85
44	LAT	Sufficiently separate the thyroid from the strap muscle	5.62 (0.79)	90	52	5.55 (0.59)	95

Table S2 (*continued*)

Table S2 (*continued*)

Final rank	Phase	Items	Round 1			Round 2	
			Mean (SD)	% rating over 5	Rank	Mean (SD)	% rating over 5
44	LAT	Beware of bleeding in thyroid capsule	5.67 (0.89)	95	49	5.55 (0.80)	95
44	INF	Identify RLN between central lymph nodes	5.90 (1.19)	90	33	5.55 (0.92)	90
44	BER	Retract the thyroid in favor of entering the Harmonic	5.76 (0.92)	90	38	5.55 (0.80)	90
49	BER	Separate trachea and cricothyroid muscle from the thyroid gland	5.76 (1.06)	86	38	5.5 (0.67)	95
49	BER	Nerve monitoring allows you to see the amplitude of the nerve when initially stimulated (whether the signal has been reduced by more than 50%)	5.43 (1.43)	76	57	5.5 (1.28)	90
49	BER	Use compression method with energy or gauze ball in some cases for hemostasis	5.71 (0.93)	90	43	5.5 (0.81)	85
49	SUP	Determine which blood vessels to leave	5.48 (1.05)	81	55	5.5 (0.81)	90
53	BER	Check the cricothyroid muscle in the upper area	5.71 (1.03)	81	43	5.45 (0.86)	90
54	INF	Identify the anatomical mutations in the location of parathyroid gland	5.71 (1.08)	86	43	5.4 (0.92)	80
54	INF	When the distinction between lymph nodes and parathyroid is difficult, determine whether to leave some or remove all depending on the cancer stage	5.71 (0.98)	86	43	5.4 (0.80)	85
56	LAT	Be careful if you pull the strap muscle excessively, it can tear and bleed	5.14 (0.89)	76	64	5.35 (0.65)	90
56	LAT	Expose the lower pole and part of the upper part of the thyroid gland	5.29 (0.88)	81	62	5.35 (0.73)	90
56	BER	Dissect thyroid gland below Berry ligament	5.76 (0.97)	86	38	5.35 (0.85)	80
59	MID	Incision from the thyroid cartridge to the suprasternal notch (or the location where central node dissection is possible)	5.43 (1.18)	81	57	5.3 (0.78)	85
59	INF	If inevitable, retract tissues around the parathyroid or grab the blood vessels going to the parathyroid	5.24 (1.19)	67	63	5.3 (0.71)	85
61	MID	Find isthmus well	5.38 (0.84)	90	59	5.25 (0.70)	85
62	LAT	Identify the correct depth and course of the common carotid artery	5.48 (1.26)	81	55	5.2 (0.93)	85
63	LAT	Whether the middle thyroid vein is exposed and ligated certainly	5.38 (1.17)	86	59	5.15 (0.96)	80
63	SUP	Whether the signals come from the EBSLN while using nerve monitoring	5.38 (1.43)	81	59	5.15 (1.49)	80

Table S3 Additional comments

Phase	Comments
MID	If only lobectomy is operated, the lateral approach could be considered
LAT	During the LAT phase, the direction of dissection is recommended to be cranial
BER	I think it is necessary to discuss whether continuous nerve monitoring should be applied to all patients
SUP	Try to identify EBSLN as possible
END	“Simple interrupted suture is recommended for midline closure because when there is op bed bleeding, you can secure golden time” and “Interrupted inverted suture is recommended because it can buy time by becoming window during bleeding”

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