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Level-2 Oncoplastic Surgical Techniques for Breast Cancer: A Preliminary Vietnamese Report

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ABSTRACT

Background: Breast cancer is the most common malignancy and remains the first cause of death related to cancer among Vietnamese women, with an incidence of 21,555 cases in 2020. Most breast cancer patients present with invasive disease and relatively large tumor sizes. While oncoplastic surgery (OPS) are commonly applied in Western countries, data on Asian population remains relatively limited. **Objective:** This study aims to assess the outcomes of level-2 oncoplastic techniques in breast-conserving surgeries at the Vietnam National Cancer Hospital. **Methods:** From January 2017 to June 2021, a cohort of 257 breast cancer patients who underwent breast-conserving surgery with OPS techniques were examined. Surgical complications, cosmetic outcome, recurrence and survival rates were assessed. **Results:** The mean age was 47.6±9.4 years, most patients had breast cup sizes B and C. The mean tumor size upon pathological examination was 2.00 ± 0.74 cm. Only 7 cases required reoperation, resulting in a mastectomy rate of 1.17%. The overall complication rate was low at 11.46%, with 9 cases (3.56%) experiencing delayed complications. Cosmetic results were rated as "excellent" in 20.6% and "good" in 60.5%, with a statistically significant difference. The rates of local recurrence, regional recurrence, and distant metastasis at five years were 2.78%, 1.19%, and 2.36%, respectively. **Conclusion:** The level 2 oncoplastic techniques had low complication rates, favorable oncological outcomes, and cosmetically satisfying results.

Keywords: Breast cancer, breast-conserving surgery, Oncoplastic surgery, complication, local recurrence, survival..

1. BACKGROUND

Breast cancer is the most common malignancy and remains the first cause of death related to cancer among Vietnamese women, with an incidence of 21,555 cases in 2020 (1). Most breast cancer patients present with invasive disease and relatively large tumor sizes (2). Furthermore, the average breast volume in Vietnamese women is approximately 399ml, smaller than that of Western women (3), posing challenges for breast-conserving surgery and emphasizing the importance of level 2 OPS techniques. Various clinical trials have demonstrated that breast-conserving surgery combined with radiotherapy resulted in equivalent disease-free survival and an overall survival rates to that of total mastectomy in early-stage breast cancer (4-6) while brought better quality of life (7, 8). In Western countries, the high rate of successful breast conservation has made it the standard treatment for early-stage breast cancer patients. Initially indicated for tumors under 2 cm, subsequent research expanded the eligibility criteria for breast-conserving surgery to include larger tumors, even up to 5 cm, provided clear margins are ensured. Nevertheless, wide tumor excision followed by radiotherapy may lead to suboptimal cosmetic results in about 20-30% of cases (9, 10). Reconstruction of such post-treatment cosmetic deformities is difficult, particularly when addressing irradiated fibrotic tissues.

The term "Oncoplastic Surgery" (OPS) was first introduced by Audretsch during the 1990s, encompassing a variety of techniques to secure clear surgical margins and high cosmetic results, especially in cases involving larger tumor volume relative to breast size (11). According to Clough's classification (12), OPS is divided into different levels depending on the percentage of

the removed tumor volume. For small tumors, involving less than 20% of breast volume excision level 1 OPS with a direct wound closure and immediate in-situ glandular tissue filling. For a 20%-50% volume excision of the breast with or without partial skin excision, level 2 OPS needs the use of an in situ glandular flap to fill the excised area. Various level 2 OPS techniques tailored to tumor location and individual breast characteristics have been recognized for their minimal invasion, assured safety, and high cosmetic and oncological outcomes.

2. OBJECTIVE

This study aimed to assess the outcomes of level-2 oncoplastic techniques in breast-conserving surgeries at the Vietnam National Cancer Hospital.

3. PATIENTS AND METHODS

Patients and data collection

This is an ambispective cohort study on a total of 257 breast cancer patients who underwent breast-conserving surgery and received level 2 OPS techniques at the Vietnam National Cancer Hospital from January 2017 to June 2021. We included female patients of ≥18 years of age, with a confirmed histological diagnosis of stage 0-2 breast cancer, regardless of immunohistochemistry subtype. Candidates for level 2 Oncoplastic Surgery included large tumor relative to breast size, multifocal tumors, tumors in challenging locations (upper inner quadrant, lower quadrant), extensive superior skin involvement and hypertrophic/ptosis breast. Patients with significant coexisting malignancies or severe co-morbidities, or those who demonstrated non-compliance with the prescribed treatment regimen were excluded. This study was approved by Hanoi Medical University Institutional Ethical Review Board (Approval No. 132/GCN-HDDD-NCYSH-DHYHN), informed consent from all patients involved was obtained.

We collected information about patients' demographic data, comorbidities, characteristics of tumor (size, location, multifocality) and breast (volume, degree of ptosis), disease stage, immunohistochemical subtype, as well as treatment data, including surgical approach, operative duration, hospital stay, removed specimen volume, margin status, early complications. Long term endpoints included cosmetic results, recurrence, survival, and breast satisfaction based on BREAST-Q Score (13).

Surgical techniques

Nonpalpable lesions were marked preoperatively using mammographic-guided needle localization. In cases with calcification, radiography of the specimen was performed to precisely determine the extent of the surgical intervention. The surgical incision was planned prior to the operation, with the patient positioned upright. The selection of techniques was based on tumor location and breast characteristics (Figure 1). For tumors located in the upper outer quadrant, lateral mammoplasty was employed. Tumors in the lower outer quadrant were approached using the J mammoplasty technique, while those in the lower inner quadrant were addressed with the V mamoplasty. The round block technique was reserved for sagging tumors in the upper half of the breast. In cases of significant ptosis and hypertrophy, inverse T techniques were utilized, with an inferior pedicle flap for upper pole tumors and a superior pedicle flap for lower pole tumors. Following breast-conserving surgery, if asymmetry was anticipated between the breasts, recommendations for contralateral breast adjustment would be provided to the patient. This adjustment might be undertaken either immediately or postponed until post-treatment stability was achieved.

The excised tumor was resected extensively through the full thickness, from the skin down to the pectoralis major muscle. Margins surrounding the surgical cavity were additionally excised and promptly submitted for frozen section evaluation during surgery. If there was residual cancer, immediate additional resection would be conducted. Five clips were placed around the tumor bed to aid in subsequent radiotherapy. Axillary dissection was performed either through the same incision or via a separate incision, depending on the chosen technique. The removed specimen was meticulously marked and subsequently analyzed. The volume of the removed specimen was obtained by multiplying the three dimensions of the specimen size in the pathology report. Systemic treatment comprising chemotherapy, targeted therapy, and endocrine therapy were administered as per current guidelines. All patients received adjuvant radiotherapy with a total dose of 50 Gy with 2 Gy/day fractionation, and a booster dose of 10 Gy on the tumor bed.

Follow-up and cosmetic outcome assessment

Patients underwent regular follow-up appointments at three-month intervals during the initial two years, followed by semiannual appointments thereafter. These evaluations encompassed clinical examinations, breast ultrasounds, annual mammograms, abdominal ultrasounds, chest X-rays, and MRI scans of the breasts as required. All complications were recorded, with early

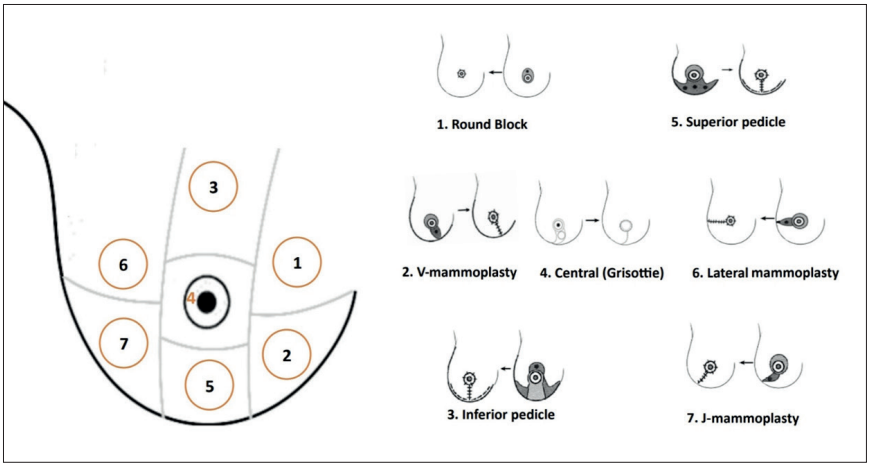

Figure 1: Level 2 OPS techniques tailored to tumor location

Characteristics	n (N=257)	%
Age (years old)		
Mean ± SD	47.56 ±9.39	
Median (Range)	47 (23-73)	
Menstrual status		
Premenopause	166	64.59
Menopause	91	35.41
BMI		
Mean ± SD	23.68 (2.77)	
Median (Range)	23 (16.60-42.00)	
Comorbidities		
Diabetes	10	3.89
No	247	96.11
Tumor size		
Tumor size from MRI results		
Mean ± SD	2.1 ± 0.61	
Median (IQR)	2 (1-5)	
Tumor–Nipple distance		
Mean ± SD	3.94 ± 1.60	
Median (IQR)	4 (0-10)	
Tumor size on pathology		
Mean ± SD	2.00 ± 0.74	
Median (IQR)	2 (0.8-5)	
Specimen volume (cm^3)		
Mean ± SD	204.83 ± 252.61	
Median (IQR)	126.00 (18-2100)	
Focality		
Unifocal	251	97.67
Multifocal	6	2.33
Oncology indication		
Tumor size	170	66.15
Poor tumor location	101	39.30
Multifocality	6	2.33
Skin retraction	8	3.11
Cosmetic	15	5.84
Contralateral reduction		
No	224	87.2
Yes	33	12.8
Pathological tissue type		
Invasive ductal	212	82.49
Invasive lobular	10	3.89
In situ	13	5.06
Mucinous	22	8.56
Histological grade		
I	27	10.51
II	156	60.70
III	74	28.79
Histologic subtype (invasive)		
Luminal A	78	31.97
Luminal B Her2 negative	76	31.15
Luminal B Her2 positive	34	13.93
Her2 positive	24	9.84
Triple negative	32	13.11
Pathological T stage		
pTis	13	5.06
pT1b	24	9.34
pT1c	140	54.47
pT2	80	31.13
Nodal status		
N0	194	75.48
N1	63	24.52
Disease stage		
0	13	5.06
I	126	49,03
IIA	93	36.19
IIB	25	9.73
Adjuvant therapy		
Chemotherapy + Radiation	55	21.65
Chemotherapy + Radiation + Hormone	144	56.69
Radiation + Hormone	54	21.26
Radiation	1	0.39
Total	254	100

Table 1. Characteristics of participants (N=257)

complications including bleeding, seroma formation, infection, delayed wound healing, skin necrosis, and nipple-areolar complex complications. Late complications primarily involved fat necrosis. In terms of severity, complications were classified as "minor" when managed conservatively and "major" when intervention and surgical correction were necessitated (14). These complications could impede the initiation of adjuvant therapies (chemotherapy or radiation therapy) if their commencement was delayed beyond six weeks.

Cosmetic and patient satisfaction evaluations were conducted postoperatively and after two years. The Lowery-Carlson scale (15) was employed for aesthetic evaluation, comprising four parameters: breast volume, breast contour, breast mound positioning, and nipple-areolar complex appearance. These parameters were rated on a scale ranging from "excellent," "good," and "fair" to "poor". Patient satisfaction levels were gauged using the BREAST-Q scale (Module Postoperative Version 2.0 - Satisfaction with Breast), consisting of 11 questions, each assessed on a four-level satisfaction scale. The questions were translated into the Vietnamese language with appropriate permissions and consent from the relevant governing body. A physician in surgeons team and a nurse assessed these parameters from patient.

Data analysis

Data was entered and processed using SPSS 25.0 software. Data distribution was presented as mean ± standard deviation (SD) or n (%). The Kaplan-Meier survival estimates were utilized to evaluate disease-free survival (DFS) and overall survival (OS). OS was calculated from the date of surgery to the date of death from any causes. DFS was determined from the date of surgery to the first relapse, including ipsilateral or contralateral breast recurrence, regional lymph node recurrence, or distant metastasis, or death from any causes. An author who did not involve in surgery analyzed the data.

4. RESULTS

Patients and surgical treatment characteristics

Tumor location	Surgical technique	n	%
Upper outer quadrant	Lateral Mammoplasty	131	50.97
Upper inner quadrant	Round block	53	20.62
Lower inner quadrant	V mammoplasty	6	2.33
Upper pole	Inferior pedicle	29	11.28
Lower pole	Superior pedicle	12	4.67
Central subareolar	Central	10	3.89
Lower outer quadrant	J mammoplasty	16	6.23
Total		257	100%

Table 2. Tumor location and surgical techniques

Margin status	Overall	Invasive ductal	Invasive Lobular	In situ	Mucinous
Clear	224 (100%)	184 (82.14%)	9 (4.02%)	11 (4.91%)	20 (8.93%)
Involved	33 (100%)	28 (84.85%)	1 (3.03%)	2 (6.06%)	2 (6.06%)
Total	257 (100%)	212 (82.49%)	10 (3.89%)	13 (5.06%)	22 (8.56%)

Table 3. Immediate Margin status by the histology

Techniques	n	Mean (SD)	Median (IQR)
Lateral Mammoplasty	122	60.5 (11.0)	59 (57-59)
Round block	51	73.6 (15.4)	65 (59-88)
Superior pedicle	12	71.5 (17.3)	63 (59-88)
Inferior pedicle	28	73.7 (15.5)	67 (59-88)
Central	10	64.7 (13.4)	59 (59-59)
J mammoplasty	16	57.1 (6.5)	59 (55-59)
V mammoplasty	6	63.8 (20.8)	60 (51-72)
Total	245	65.3 (14.4)	59 (59-67)

Table 4. Surgical complications

A total of 257 patients who underwent breast-conserving surgery using Level 2 OPS techniques were eligible and enrolled in this study. The mean age was 47.56±9.4 years, 64.6% of the patients were premenopausal. The majority of patients had moderate breast volume (Cup B and Cup C, accounting for 92.22%). The mean postoperative tumor size was 2.00 ± 0.74 cm. The mean BMI was 23.7 ± 2.8. The mean distance from the tumor margin to the nipple-areolar complex was 3.94 ±1.60 cm. The disease stages and immunohistochemistry characteristics are clearly summarized in Table 1.

Indications for oncoplastic surgery included tumor size (66.15%), tumor location (39.30%), multifocality (2.33%), Skin retraction (3.11%), and aesthetic consideration (5.84%). Lateral mammoplasty for tumors in the upper outer quadrants (50.97%) was the most common OPS technique, followed by round block technique (20.62%), and inverse T techniques (superior pedicle flap: 4.67%, inferior pedicle flap: 11.28%) (Table 2).

Surgical margin and complications

Frozen section margin evaluation was performed for all patients, revealing that 33 patients (12.8%) required immediate additional resection to achieve adequate surgical margins (Table 3). Following tumor excision, both the tumor specimens and surgical margins were meticulously examined using routine histopathology. In which, 15 patients (4.84%) exhibited insufficient surgical margins, prompting 7 patients (2.72%) to undergo reoperations for additional resection. Moreover, 3 patients (1.17%) who declined breast conservation opted for mastectomy.

A total of 29 patients (11.46%) experienced postoperative complications. These detailed complications rates were presented in Table 4. The mean time for initiating adjuvant therapy was 3.02 ± 1.25 weeks. Eight patients (3.11%) commenced adjuvant therapy after six weeks due to 1 seroma formation, 1 nipple necrosis, 1 delayed wound healing, 2 fat necrosis, and 2 reoperations. After surgery, 78.34% of the patients received adjuvant chemotherapy and/or targeted therapy, while 54 patients (21.26%) with luminal A subtype were treated with adjuvant radiotherapy and endocrine therapy.

Cosmetic results and patient satisfaction.

Tumors at challenging location such as lower inner quadrant (V mammoplasty) and lower outer quadrant (J mammoplasty) resulted in poorer cosmetic outcomes (see details in Figure 2).

The Figure 3 illustrate the examples of cosmetic outcomes of the participants. Quality of life after surgerywas presented in Table 5.

Recurrence and survival

During an average follow-up duration of 44.9 months, 10 recurrences (3.89%) were recorded, including seven recurrences within the breast, three cases involved regional lymph nodes (including ipsilateral axillary and supraclavicular nodes), and 6 cases of distant metastasis. The DFS rates at one year, two years, three years, and four years were 100%, 98.4%, 96.1%, and 95.3%, respectively while the OS rates were 100%, 99.2%, 99.2%, and 98.3%, respectively. The Kaplan Meier curves for overall survival and recurrences are presented in Figure 4 and Figure 5, respectively.

Techniques	n	Mean (SD)	Median (IQR)
Lateral Mammoplasty	122	60.5 (11.0)	59 (57-59)
Round block	51	73.6 (15.4)	65 (59-88)
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Table 5. Quality of life according to Breast Q score (N=245) * *Missing data in 9 patients

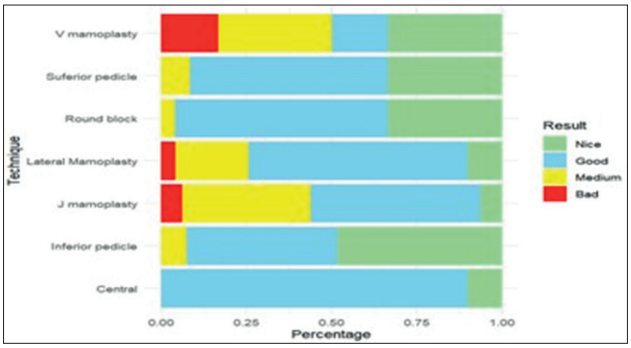

Figure 2. Cosmetic outcomes by surgical techniques

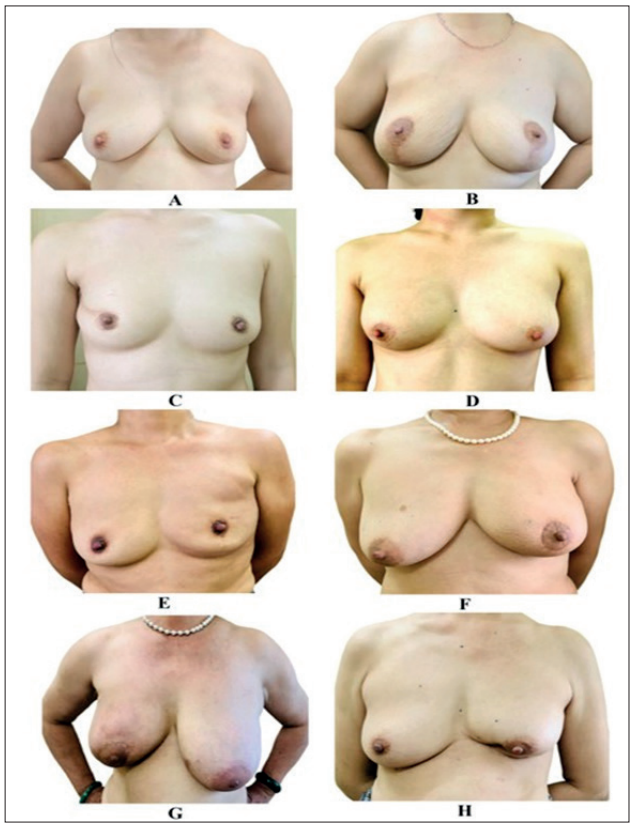

Figure 3. Aesthetic outcomes: (A & B) excellent, (C & D) good, (E & F) Fair, (G & H) poor

5. DISCUSSION

In our series, the follow-up of the patient has shown a rate of locoregional recurrence similar to those observed in the literature. Moreover, a large part of our patients has shown a high rate of satisfaction of their aesthetic result after the surgery even after the adjuvant treatment.

Breast-conserving surgery (BCS) has become the standard treatment for early-stage breast cancer patients in many countries. In the United States and Europe, the utilization of breast-conserving surgery is notably high, accounting for about 70% cases (16, 17). In developed Asian countries like Japan and Singapore, the rate of BCS was approximately 40% for early-stage breast cancer patients (18).

Insufficient knowledge about the disease and the fear of economic burdens often makes many patients lean towards total mastectomy as the primary surgical approach. The absence of a national-level screening program also contributes to a significant proportion of patients being diagnosed at advanced stages with considerably large tumor volume (19). Furthermore, breast sizes among Vietnamese and Asian women are smaller than their European and American counterparts (3, 20). These factors contribute to the challenges in achieving higher breast-conservation rate in Vietnam. Despite the lack of a thorough statistical database on breast-conservation rates, it is noteworthy that at the Vietnam National Cancer Hospital, a major referral cancer center of the country, the breast-conservation rate remains modest, below 20%. In cases involving tumors of relatively large size compared to the breast volume, implementing OPS techniques plays a pivotal role in ensuring a clear excision and high cosmetic outcomes. At the MD Anderson Cancer Center in 2014, OPS accounted for 33% of all breast-conserving surgeries conducted (21). Despite their numerous advantages, the application of OPS techniques also encounters challenges such as extended operation time, higher cost, and the requirement for comprehensive and specialized training of surgeons. Given these complexities, the available reports and data on OPS in Asian countries, particularly developing ones, remains limited. The focus of global breast cancer surgery management has shifted from survival metrics to the post-treatment quality of life.

Similar to other studies on OPS, the indication of oncoplastic surgery was predominantly associated with tumor size in our study. The mean tumor size was 2 cm, while the average volume of removed specimens was 204.8 cm^3, relatively smaller compared to Fitoussi's study (2.91 cm) (22) and Clough's study (2.6 cm and 331 cm^3) (23). Given that the majority of breast sizes fell within intermediate range (Cup B and Cup C accounting for 92.22%), the implementation of OPS became imperative to ensure both oncologic safety and cosmetic results.

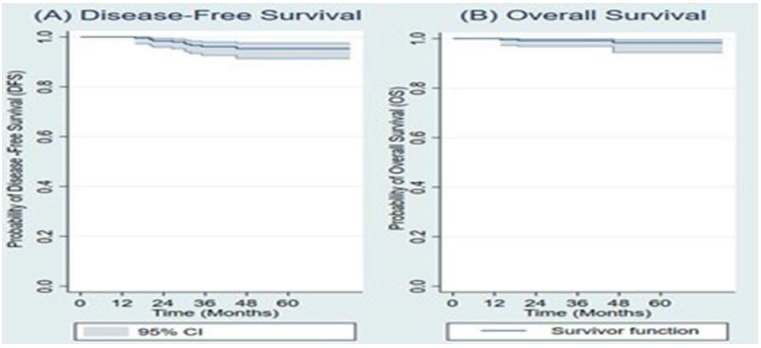

Figure 4. Disease free survival (A) and overall survival (B) of the patients

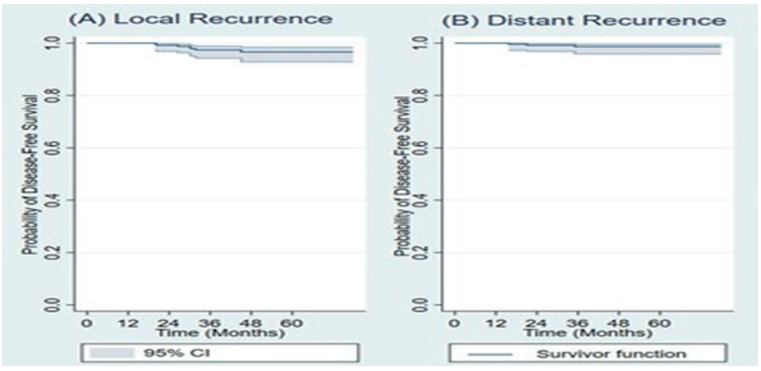

Figure 5. Kaplan Meier curve for local recurrence(A) and distant recurrence (B)

Among the patient cohort, 139 cases (54.09%) had a tumor ≥ 2 cm in size, up to 5 cm in some cases - significantly larger than previous studies within the country, in which the mean tumor size was around 1 cm. The

lateral mammaplasty technique was the most frequently employed in our study. This technique was applied to tumors in the outer quadrant which has higher cancer incidence due to the densest breast tissue concentration (24). This was the first OPS technique we implemented thanks to its simplicity, safety, reduced operation time, and the possibility of immediate access to the axilla for lymph node dissection. Another widely utilized technique within our study was the round block technique, applied to tumors occupying the upper half with mild to moderate ptosis breast. This technique employed a discreet incision around the areola, yielding high patient cosmetic satisfaction. Following breast-conserving surgery, the discrepancies in size, nipple-areolar complex position, and varying ptosis degrees might result in breast asymmetry. It is suggested that resection surpassing 200 cc mandates contralateral breast adjustment, which can be done immediately or after adjuvant therapy. The surgical method chosen depends on the amount of tissue and the OPS technique used. Our study recorded 33 cases (12.99%) undergoing contralateral breast adjustment, a comparatively low rate due to patient preference. Fitoussi et al documented a higher contralateral breast adjustment rate of 46.1%, with the majority of cases involving immediate reconstruction (22).

The status of surgical margins significantly influences the local recurrence risk and treatment outcomes. However, extensive excision to ensure clear margins could potentially lead to compromised cosmetic results. Over time, a consensus has emerged, defining clear margins as the absence of tumors on ink for invasive cancer cases (25) and margins greater than 2mm for intraductal breast cancer cases (26). Previous studies on OPS showed a substantial rate of 15-30% cases with positive margin, requiring reoperation (22, 23, 27). Reoperation can lead to delayed adjuvant therapy, higher complication rates, and compromised cosmetic results, contributing to patient and family distress, patient discomfort, and increased healthcare costs. To mitigate the need for multiple reoperations, our study adopted a comprehensive approach, in which all patients underwent a wide excision of more than 1cm and had frozen section evaluation of margin status. Among these cases, 33 cases (12.84%) exhibited insufficient margin, prompting an immediate additional resection. Only 7 cases (2.27%) necessitated reoperation, and 3 patients (1.17%) needed a mastectomy. Various studies have highlighted the efficacy of frozen section assessment of margin, achieving sensitivity and specificity of 98-100% (28, 29). However, this procedure might extend the operation time by approximately 20-30 minutes.

In our study, a total of 29 patients encountered complications, accounting for 11.46%. There was merely one case of partial nipple necrosis. Fat necrosis emerged as the predominant delayed complication (3.56%), 11 patients (4.28%) required corrective surgical interventions. OPS techniques are characterized by expansive tumor excision, flap dissection, and breast tissue mobilization. Longer incisions inherent to these techniques may elevate the likelihood of tissue ischemia. Nevertheless, most studies comparing OPS to conventional breast-conserving surgery report negligible differences in complication rates between the two groups (30, 31). Carter et al. compared complication rates among 9,861 patients undergoing conventional breast-conserving surgery, OPS, mastectomy, and immediate breast reconstruction, which revealed that OPS showed a lower seroma rate (13%) than standard breast-conserving surgery but had a higher wound-related complication rate (4.8%). Furthermore, OPS had a significantly lower complication rate compared to both breast-conserving surgery and immediate breast reconstruction (21). The range of complication rates associated with OPS varies from 7.5% to 30% (23, 32, 33). Factors contributing to complication risk includes the removed specimen volume (34), high BMI history (35), and concurrent comorbidities such as diabetes and smoking (36). Special attention must be given to the impact on adjuvant therapy for patients. In our study, the average time for postoperative adjuvant therapy was 3.02 weeks. Eight patients experienced delayed adjuvant therapy (over six weeks), attributable to the surgical complications. Level-2 OPS techniques require meticulous surgeon training to minimize complication rates and their potential impacts on patient treatment.

Effective control of local recurrence remains pivotal in the context of breast cancer-conserving surgery. In the study by Chakravorty et al. with an average follow-up of 28 months, the OPS group exhibited larger tumor sizes, higher histologic grades, and a higher frequency of prior adjuvant chemotherapy. However, no significant differences were observed in local recurrence rates or distant metastasis rates (37). In a more comprehensive study by Carter et al. on 9,861 patients with an average follow-up of 3.4 years, no notable differences emerged between the two groups regarding three-year disease-free survival or overall survival (38). It is important to note that the OPS group had a higher proportion of younger patients, larger tumor sizes, later-stage disease, increased lymph node involvement, higher histologic grades, and multifocality. Multiple studies investigating OPS techniques have consistently demonstrated low local recurrence rates over extended follow-up periods. Clough et al evaluated 350 patients undergoing OPS with a 55-month follow-up and reported a local recurrence rate of 2.2% (23). Fitoussi et al., examining 540 patients over a 49-month follow-up period, recorded a local recurrence rate of 6.8% (33). In our study, with an average follow-up duration of 44.9 months, 2.78%, 1.19%, and 2.36% were observed for local recurrence, regional recurrence, and distant metastasis rates, respectively, which are relatively low compared to previous studies, which can likely be due to the selection of early-stage patients (stage 0-2).

In terms of cosmetic results, the assessment involves a wide range of tools, and there is yet to be a standardized evaluation timeline. However, an evaluation conducted two years post-surgery is commonly chosen, as it allows for determining the long-term effects of radiation therapy. Across various studies, OPS consistently yields commendable cosmetic results in 80-90% of cases (39). In our study with 7 OPS techniques, the round block and bilateral inverse T techniques achieved the highest cosmetic results. Regarding quality of life, our study employed the BREAST-Q BCT module with questions about post-surgical breast satisfaction for interviews and evaluations. The average "Satisfaction with Breast" score was 65.3 out of 100. Among the different techniques examined, the round block and bilateral inverse

T techniques attained the highest scores, indicating the highest levels of patient satisfaction.

Limitations of the study

A notable limitation of this study is the relatively short follow-up duration. Given the early-stage patient cohort, a more extended observation period will help to capture a more comprehensive long-term outcome. Ongoing monitoring of the patient group is intended to further assess treatment outcomes, particularly concerning recurrence rates and overall survival.

6. CONCLUSION

Level-2 OPS techniques displayed good surgical outcome and low recurrence rates in early-stage Vietnamese breast cancer patients. With numerous advantages including enhanced conservation rates for larger tumor sizes, the assurance of safe surgical margins, and superior cosmetic results, these procedures should be widely applied in clinical practice.

- **Author's contribution**: Hoang Anh Dung gave a substantial contribution in acquisition, analysis, and data interpretation. Hoang Anh Dung prepared, drafted, and revised manuscript critically for important intellectual content. Each author gave the final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved..
- **Conflicts of interest**: There are no conflicts of interest.
- **Financial support and sponsorship**: None.

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