Keystone Perforator Island Flap for Postmastectomy Defect Resurfacing in Late-stage Breast Cancer Patients

Irena Sakura Rini, MD, MARS*
Made Ananda Krisna, MD†
Jenisa Kamayana, MD‡
Kasih Rahardjo Djarot, MD†
Alberta Jesslyn Gunardi, MD*

Background: Late-stage breast cancer usually presents with locally advanced disease, with or without metastasis. The primary tumor is typically large with skin infiltration which affects quality of life. Surgical resection will result in an extensive defect which potentially deteriorates patients’ quality of life if not properly managed. Keystone perforator island flap (KPIF) is a local advancement flap based on multiple perforators which can be a reliable reconstructive method to close an extensive defect.

Methods: This is a case series of 11 patients with symptomatic late-stage breast cancers indicated for neoadjuvant chemotherapy and subsequent mastectomy at Dharmais Cancer Hospital. The postmastectomy defect was closed with KPIF and clinical evaluation included flap success rate, percentage of flap necrotic area, and quality of life. There are modifications of the KPIF consisting of the more rounded shape and additional flap movement of the flap’s distal lateral ends to the center resembling an “omega” conformation.

Results: Mean percentage of flap necrosis area was 9.7% and none of the patients needed additional surgery. The patients’ quality of life evaluated using Patient-reported Aesthetic European Organization for Research and Treatment of Cancer (EORTC) Quality of Life, Questionnaire-Core 30-questions (QLQ-C30) and Quality of Life, Questionnaire-Breast Cancer-23-questions (QLQ-BR23) was fair, with sufficiently good scores for global health status and functional scale, and minimal symptomatology burden. The lowest score was for fatigue and financial difficulties parameters from QLQ-C30 and sexual functioning and future perspective from QLQ-BR23.

Conclusion: This is a preliminary study to show that a KPIF could be considered as a method for defect-resurfacing reconstruction after mastectomy. (Plast Reconstr Surg Glob Open 2019;7:e2457; doi: 10.1097/GOX.0000000000002457; Published online 25 November 2019.)

BACKGROUND

Breast cancer is the most common type of cancer affecting women worldwide, with annual incidence reaching 25.2%. Under the 2018 Global Cancer Statistics, breast cancer accounts for the highest number of new cancer cases among women globally and is the leading cause of cancer deaths in Indonesia with 20,000 deaths annually. One possible cause of the high mortality rate is the patients were diagnosed when already in late stage.

Late-stage or advanced breast cancer (ABC) encompasses a small percentage of stage II and the entire stage III stage IV disease. Clinically, ABC is subdivided into locally advanced breast cancer, metastatic breast cancer, and the combination of both. Patients with locally advanced breast cancer typically have a large primary tumor mass with infiltration to the overlying skin, manifested as a malignant wound. Malignant wounds may also bleed easily and be malodorous which affects patients’ quality of life (QOL).

Disclosure: The authors have no financial interest to declare in relation to the content of this article.
Even after neoadjuvant chemotherapy and noteworthy improvement of tumor size and mobility, a subsequent surgical resection will result in an extensive defect that warrants plastic surgeon involvement. This reconstruction expert is not only involved during executing the surgery but also in patients’ screening, planning, and pre- and post-monitoring. There are several reconstruction techniques possible in this circumstance, such as free flap, axial flap, perforator-based local flap, and skin graft. Free flap such as free transversal rectus abdominis flap for mastectomy is time-consuming and complicated more than axial one. Meanwhile, a conventional axial flap is also time-consuming due to the need to identify and dissect the pedicle blood vessel during flap harvesting, and it is also more expensive than a perforator flap technique. Due to its disadvantage in durability and aesthetic outcome, skin graft usually works only as an aid to cover the remaining raw surface due to inadequate primary reconstruction coverage or necrosis. Therefore, we propose the keystone perforator island flap (KPIF) as an option as the first-line reconstruction method in covering extensive postmastectomy defect.

KPIF is a local advancement flap based on multiple perforators, including fasciocutaneous and musculocutaneous perforators, which results in reliable and versatile vascularization. Moreover, it also has vessels linking to adjacent axial blood vessels. The location of main perforators and their linking vessels are predictable and dependable. This flap has a curvilinear shape—its width is equal to the defect’s width. Introduced in 2003, this flap is relatively used for small defect throughout the body. In 2011, keystone flap could be used for larger defect both in trunk and extremities. However, there are several modifications to cover a large defect, such as double keystone flap or deep fascia incision to allow better mobility. Another modification but commonly overlooked is the omega subtype which optimizes a part of the flap with excessive laxity during its insetting. In our center, KPIF with omega design has been utilized for 2 years to close extensive postmastectomy defects in patients with ABC. This study is a case series of ABC patients who underwent KPIF procedure and their outcomes in terms of flap success rate and QOL.

METHODS

This is a case series study in women with ABC with symptomatic primary tumor and were subsequently treated with neoadjuvant chemotherapy and mastectomy.
The mastectomy surgical technique was either radical or modified-radical mastectomy with ensuing KPIF. The data were retrieved prospectively and retrospectively, encompassing all patients admitted to Dharmais Cancer Hospital from January 2013 to December 2017. Ethical clearance from Dharmais Cancer Hospital ethics committee was obtained before data collection.

All adult breast cancer patients were screened initially with the following inclusion criteria: (1) women aged 18–60 years old; (2) stage IIB, IIIB, IIC, or IV the primary tumor status of which had infiltrated chest wall or both chest wall and skin (T4b or T4c, respectively); (3) had received or planned to receive neoadjuvant chemotherapy; (4) had or predicted to have a postmastectomy defect ≥10 cm. The 10 cm cut-off was set based on previous reports which stated that the median diameter of tumor in chest region was 10 cm and a dimension wider than this should be considered as an extensive defect requiring reconstruction.20, 21 There were 8 patients who fulfilled the eligibility criteria from January to December 2017 and asked for their consent to be included in the study. We also reviewed retrospective data starting from January 2013 to December 2016. Of 26 patients identified, there were only 14 of them whose data were adequate. Two of them were deceased and only 3 patients were contactable and gave consent to be included in the study while the rest were uncontactable. Additional data collected from eligible patients include demographic characteristics, anthropometric measurements, history of smoking, other comorbidities (cardiovascular, immune, metabolic system, etc), and consumption of substances affecting the immune system.

KPIF for defect resurfacing was performed by a single surgeon in all patients after mastectomy. To ensure the involvement of as many perforators as possible, the flap design was situated within a dermatomal segment (Fig. 1).

We made several modifications to the original design, including the more angular shape, instead of angled due to the shape of the defects which all appeared to be more rounded than elliptical (Fig. 2); in most cases, the flap’s width was narrower than the defect’s width because either the defect was very large (Fig. 2) or the abdominal skin laxity and area was limited (Fig. 5); and additional flap movement in which both flap’s corners were brought from distal ends of the defect to meet each other at the center. This modification had previously been reported as the omega variant type B of keystone flap.19 The rationale behind these modifications aside from the mentioned limitation and its subsequent adjustment was the extensive interconnection among vascular territories fed by numerous perforators in the upper abdominal and anterior thoracic region.22 Furthermore, the flap advancement into an omega shape utilizes the lateral skin pliability to facilitate movements so that the classic bilateral V-Y closure was not needed.19

After the design was drawn, measured, and documented, an incision throughout its dermal layer was made according to it, using surgical blade no. 15. Afterward, the subdermal plane was divided and dissected suprafascially using electrocautery while ensuring the overlying skin’s mobility. This mobility is also determined by the dissection area: the suprafascially dissected area needs to be sufficient enough to promote flap mobility while preserving as many perforators as possible. Approximately, up to 50% of the subdermal plane can be dissected. In this study, perforators were not specifically identified, in accordance with the suggested KPIF dissection procedure.

Along with the dissection, we inset the flap based on omega flap design: both KPIF’s edges were advanced to the center of the defect’s distal end (Fig. 4). Skin tension was evaluated to decide whether additional reconstruction adjunct such as skin graft would be needed. One to 2 draining tube(s) were placed for bodily fluid evacuation.

We started with suturing areas with the highest tension using 3.0 polypropylene thread (Prolene; Ethicon,

![Fig. 2. The patients’ defects were more rounded than elliptical. A, Patient number 2. B, Patient number 3. The dotted line represents the approximated flap base area. The circumventing area is dissected suprafascially.](image-url)
Subsequently, we made intradermal sutures using 2.0 Polysorb (Polysorb; Covidien, Mansfield, Massachusetts, USA) between the previous dermal stitches, and continue completing the dermal stitches until the flap was completely attached to the defect. Bleeding was controlled with direct pressure and electrocautery.

The first 6 hours, check every 2 hours. The next 6 hours, check every 4 hours. And the last 12 hours, check every 6 hours. Wound care and wound drainage measurement was done daily with the following principles: raw surface caused by either flap necrosis or wound dehiscence and lacerated skin adjacent to the wound was treated with a hyaluronic acid–containing cream; antibacterial gauze dressing was applied as primary dressing; an additional alginate dressing was utilized for wounds with excessive exudation; dry sterile gauze was used as the secondary dressing. After the patients were discharged, we evaluate the flap twice a week in the first 2 weeks, once a week for the next 4–6 weeks, and once/twice a month for the next 2 months after the procedure.

Once the wound had reached its remodeling phase with complete epithelization, we instructed the patients to visit only when there is a complaint regarding the surgical wound (eg, hypertrophic scarring, keloid, wound contracture, pain, presence of new wound, etc).

There are several main outcomes evaluated in this study: flap success rate, percentage of necrotic area of the flap, and QOL. Flap success rate was defined as the number of cases without reoperation after the initial KPIF reconstruction. The percentage area of necrosis was measured through digital photography method using Adobe Photoshop CC 2018 software (Fig. 5). The medical photography processed was at least taken at 1 month up to 2 months after the surgery. The need for reoperation was regarded as a nominal variable.

Other than clinical evaluation of flap success and necrotic area, the EORTC QOL questionnaire was used to assess the QOL score quantitatively. The questionnaire comprises of 2 parts: the EORTC QLQ-C30 and BR23 which was intended for QOL evaluation for patients with cancer in general and breast cancer patient, respectively. The patients filled these questionnaires directly under the supervision of the researcher at least 1 month up to 2 years after operation and their final scores were measured in accordance with EORTC QLQ-C30 Scoring Manual.23

RESULTS AND DISCUSSION

Table 1 delineated the baseline clinical characteristics of each patient.

All patients had KPIF reconstruction as planned. There was minor modification in some patients: 2 patients had double KPIF reconstruction (Fig. 6). The skin on the cranial side of the defect was also designed as a KPIF because of the limited soft tissue coverage provided by the KPIF harvested from caudal (abdominal) area.

One patient from retrospective data was reconstructed with KPIF to manage a compromised transversal rectus abdominis flap. The secondary defect was closed using skin graft.

All patients from the prospective group were followed up according to the plan with great compliance. There was a variability in follow-up frequency for patients whose data were collected retrospectively. However, in the first 4 weeks after hospital discharge, patients had at least attended weekly follow-up visit.

The results of each patient in this case series are shown in Tables 2 and 3. There was 1 missing data on QOL score and accordingly the mean score of each scales was generated only from the patients who completed the entire questionnaire.

As a part of the evaluated outcomes, we discovered flap necrosis in 2 of 8 patients in the prospective group (Table 2). In our series, flap necrosis and wound dehiscence always happened concurrently. None of the patients showed signs and symptoms of infection during the follow-up period. No other adverse event related to reconstructive surgical procedure was noted. Most patients showed good tolerability to reconstructive surgical procedure.
Postsurgical pain was adequately managed by nonsteroidal anti-inflammatory analgesics. However, 2 patients had prolonged stays at high-care unit postoperatively due to low hemoglobin level in 1 patient and respiratory distress in another. To reach the minimum target of hemoglobin is paramount for the flap viability. Meanwhile, the respiratory distress in the other patient was attributable to previously known lung metastasis.

The flap success rate was 100%. The mean percentage area of flap necrosis was 9.7%, ranging from 0% to 27.3%. Flap necrosis was found distal area with a healthy granulation tissue underneath the necrotic skin (Fig. 5). The necrotic area was originally the most lateral part on the each side of the flap and brought together toward the center. Predictably, this area would receive less vascularization from the base of the flap while the interconnecting vessels might have not yet dilated to provide an adequate perfusion. Wound healing through secondary intention was expected, with the help from the hyaluronic acid.

Fig. 4. Flap insetting procedure. A, After incision and dissection completion. B, Flap insetting.

Fig. 5. Digital image processing to calculate % of area of flap necrosis. A, Area of flap necrosis in pixels. B, Total area of flap.
| Patient | Age* | Stage, Uni/ Bilateral, Recurrent | Defect Size (cm²) | Metastasis | NACT Type | Radiotherapy | Biopsy | Immunohistochemistry |
|---------|------|---------------------------------|-------------------|------------|------------|--------------|--------|---------------------|
| Prospective data | | | | | | | | |
| 1 | 47 | IV, bilateral, recurrent | 1,400 (total) | Yes (vertebrae, costae, clavicle, humerus) | FAC, docetaxel, carboplatin | Yes, postsurgery | Invasive lobular carcinoma | + + − + |
| 2 | 59 | IIIB, bilateral, recurrent | 625 and 357 | None | Herceptin, FEC | None | Invasive breast carcinoma NST grade III | − − + ? |
| 3 | 50 | IIIB, bilateral, recurrent | 885 (total) | None | Herceptin, FAC | None | Tubular carcinoma grade I | + + + + |
| 4 | 57 | IIIB, unilateral, nonrecurrent | 348 | None | FAC | None | Invasive breast carcinoma NST grade II | + + + + |
| 5 | 44 | IV, unilateral, nonrecurrent | 560 | Yes (brain, vertebral, sacroiliac, sacral, costae) | Herceptin, FAC, bondromat | Yes, presurgery (for metastatic lesion) | Invasive lobular carcinoma grade II + DCIS grade III | + + + + |
| 6 | 53 | IIIB, unilateral, nonrecurrent | 805 | None | Docetaxel | None | Invasive breast carcinoma NST grade III | − − − + |
| 7 | 42 | IIIB, unilateral, recurrent | 756 (total) | Yes, liver | FAC | None | Invasive breast carcinoma NST grade II | + + + + |
| 8 | 47 | IIIB (+Paget disease), unilateral, nonrecurrent | 717 | None | FAC | None | Invasive breast carcinoma NST grade III | − − − + |
| Retrospective data | | | | | | | | |
| 1 | 54 | IIIC, unilateral, recurrent | 875 | Costae invasion | Docetaxel, cyclophosphamide | Yes, postsurgery | Invasive carcinoma NST grade III | + + − + |
| 2 | 29 | IIIB, unilateral, recurrent | N/A | None | FAC | Yes, postsurgery | Invasive carcinoma NST grade II | − − − + |
| 3 | 35 | IIIB, unilateral, recurrent | 750 | None | Docetaxel, cyclophosphamide | Yes, postsurgery | Invasive carcinoma NST grade II | + + − + |

FAC regimen: doxorubicin, 5-fluourouracil, cyclophosphamide; FEC regimen: epirubicin, 5-fluorouracil, cyclophosphamide.

ER, estrogen receptor; FAC, Fluorouracil, Doxorubicin and Cyclophosphamide; HER2, human epidermal growth factor receptor 2; Ki67, proliferation marker Ki67; NACT, neoadjuvant chemotherapy; NST, nonspecific type; PR, progesterone Receptor.
acid–containing silver sulphadiazine cream which promoted faster and gentler necrotic skin sloughing.

Compared with previous studies, our series discovered similar results. The most recent study assessing KPIF for cutaneous defect showed no flap loss among 30 patients. The size of their defects ranged from 1.44 to 225 cm², but 75% of the defects were located on lower extremity.24 Khouri et al25 reported KPIF for defect reconstruction in 28 patients with a mean defect area of 250.5 cm². There was 4% partial flap loss and 3% of total flap loss needing reoperation for defect closure. Similar result was described by Findlay et al26 who found 2.5% of flap loss requiring surgical management and 3.5% of flap loss managed with wound care protocol. No study has reported the mean percentage area of necrosis in KPIF.

The global health status from EORTC QLQC-30 delineates the overall QOL as perceived by the patients: the higher the score, the better the QOL. In this series, the mean global health status reached 70.8 (41.7–91.7). To date, there has not been any report on QOL in patients who underwent KPIF reconstruction. A previous study by De Gournay et al27 reviewed QOL in breast cancer patients reconstructed with latissimus dorsi myocutaneous flap and found a similar global health status with a mean score of 65.9 (16.7–100).

Each parameter’s mean score of the functional scales was similar to one another, with the lowest and highest score of 62.7 and 78.3 attributable to physical and cognitive functioning, respectively. This was expected as the primary tumor resection method included axillary node dissection. Axillary node dissection has been linked to limitation in arm range of movement and even lymphedema, causing further impediment in physical functioning of arm.28 However, lymphedema was not reported in any of our patients.

Symptom scales were used to evaluate systemic symptoms related to all breast cancer treatments and financial difficulties. With the mean score of 46.7, financial difficulties were the most troublesome element of symptom scale as all patients but 1 in this series used national healthcare insurance. The Indonesian National Health Insurance covered all the cost for the surgery including the defect-resurfacing reconstructive surgery utilizing KPIF and consequently the patients who scored high in financial difficulties scales felt it was mostly due to expenditure on transportation and accommodation fee. The most bothersome symptom was fatigue with a mean score of 38.3. The fatigue was said to have occurred even during the time when the patients were diagnosed to have an ABC. The magnitude of the fatigue they experienced increased during the period when neoadjuvant chemotherapy was administered and a few days after the mastectomy and KPIF surgery. There were several factors linked to postmastectomy fatigue, such as degree of preoperative fatigue and lower preoperative functioning.29 Presence of chronic fatigue, current psychological disorder, physical discomfort, and high body mass index are predictors for postmastectomy fatigue.30 The fatigue can also be cancer related and its causes are multifactorial, several of which include genetic polymorphism, serotonin dysregulation, hypothalamus-pituitary-axis disturbance, dysfunctional circadian rhythm, defective adenosine triphosphate (ATP) generation in skeletal muscle, induction of vagosomatic

Table 2. Flap Necrosis, Reoperation Rate, and Quality of Life QLQ-C30 in Advanced Breast Cancer Patients Undergoing Postmastectomy Keystone Flap Reconstruction

| Patient No. | Area of Flap Necrosis (%) | Reoperation | Time to Complete Healing (d) | Time from Operation to Death (mo) |
|-------------|---------------------------|-------------|-----------------------------|---------------------------------|
| Prospective data |
| 1 | 8 | None | 120 | 9 |
| 2 | 1.8 | None | 60 | N/A* |
| 3 | 10 | None | 75 | N/A† |
| 4 | 0 | None | 45 | 2 |
| 5 | 0 | None | N/A‡ | 1 |
| 6 | 27.3 | None | N/A‡ | 1 |
| 7 | 20.7 | None | N/A§ | 3 |
| 8 | 8 | None | N/A§ | N/A† |
| Retrospective data |
| 1 | N/A¶ | Yes || N/A¶ | N/A† |
| 2 | N/A¶ | None | N/A¶ | N/A¶ |
| 3 | N/A¶ | None | N/A¶ | N/A¶ |
| Mean | 9.7 | — | — | — |

*Noncontactable. †Still alive. ‡Died before complete healing occurred. §Still in follow-up period, wound has not healed completely. ¶No medical photography records. ||Previously operated using transversal rectus abdominis flap. Keystone flap was not reoperated. N/A, not available.
inhibitory reflex, and excessive production of proinflammatory cytokines.31,32

The breast cancer module of QLQ-BR23 comprises of functional and symptom scales. Among the functional scales parameters, body image (BI) score was the highest, reaching 84.2. Several patients in this series gave an explanation of their positive attitude toward their BI. For the most part, they had accepted the presence of the postsurgical scar because it is part of the treatment which made them healthy (cancer-free). Health was their primary concern and they realized that having a postsurgical scar was the consequence they had been willing to take since they gave their consent for surgery. There is no previous study with a similar result to our finding of considerably high BI score. A study by Slowik found that the mean score of BI parameter was 64.7, almost 20 points lower than the score we obtained.33

On the other hand, sexual functioning mean score was the lowest. Almost all patients did not have any interest in sex nor were they sexually active. Breast cancer surgery had been known to cause problems in sexual activity, such as disturbance in arousal, lubrication, orgasm, and sexual pleasure.34

Future perspective was also considerably low. This parameter evaluated whether the patient was worried about their health in the future. Consistently, this could be partly explained by the high tendency of postsurgery breast cancer patients to have significant anxiety and depression based on Hospital Anxiety and Depression Scale scores, as shown by previous study.35

There had not been any previous report on QLQ-BR23 in breast cancer patients managed with KPIF. The most similar one was a study by Min et al36 in breast cancer patients managed with latissimus dorsi myocutaneous flap. The sexual functioning score was also the lowest, and the highest score was for BI parameter reaching 64.9, which was still lower than the score in our study. The reason for the discrepancy was beyond the scope of this study, although it is imperative to say that the multifactorial nature of QOL might have explained it.

Based on QLQ-BR23 measurement, symptoms related to systemic therapy side effects were most complained, with the mean score of 29. There were 7 symptoms related to systemic therapy side effects and the ones which were more chronic contributed more to the total score. These chronic symptoms include the persistence of hair loss, feeling unwell, and headaches. The previous study had reported scalp alopecia as a persisting side effect of fluorouracil/epirubicin/cyclophosphamide chemotherapy regimen.37 Feeling unwell and headaches could possibly be interrelated if their presence is linked to chronic fatigue syndrome after breast surgery.38 However, headache can be a manifestation of underlying hormonal imbalance caused by ovarian dysfunction following cyclophosphamide or even an early sign of brain metastasis.39,40

In our series, all the patients were diagnosed as locally advanced or ABC, the overall survival rate of which was only 45% and 15%, respectively.41,42 In area with low-resource setting, the survival rate of locally ABC even dropped to 1%–30%.43 Accordingly, the major concern when mastectomy had been decided for locoregional
control was the defect closure technique as the patient might not tolerate prolonged surgery such as the ones requiring delicate pedicle dissection and/or micro-anastomosis. On the other hand, the defect was large. From the perspective of breast reconstructive surgery, we hope that a simpler defect-resurfacing technique with reliable vascularization such as KPIF will overcome the challenges. Socioeconomically, this method of defect-resurfacing reconstruction was covered by the National Health Insurance and it is hoped that this coverage would persist. The QOL score evaluated in this study depicted the overall psychological state of patients with ABC who underwent chemotherapy and surgery. Psychologist and/or psychiatrist department involvement should be encouraged in managing patients with ABC from the time of the first visit/diagnosis.

This case series applied a clear, well-formulated inclusion and exclusion criteria which helped in deciding whether or not the result of the study can be applied when facing a patient with ABC. The completeness of follow-up was adequate with only 1 incomplete data on QOL. However, as this is a case series, there was not any attempt to control the confounding factors. Possible biases included selection bias due to the consecutive sampling method, observer bias in delivering explanation about the QOL questionnaire, and information bias for patients in the retrospective group. This study is descriptive in nature, and consequently, the result of the QOL parameter as one of the evaluated outcomes of the surgery might not have been unique to KPIF property and cannot conclude KPIF superiority as a reconstruction method to close postmastectomy defect.

CONCLUSION

Late-stage breast cancer can affect patients’ QOL due to the malignant wound. There is no known best method for defect-resurfacing reconstructive surgery postmastectomy procedure. This is a preliminary study to show that a KPIF could be considered as a method for defect-resurfacing reconstruction after mastectomy. Further study, such as a well-designed prospective cohort study with better control in possible confounding factors, is needed.

Irena Sukara Rini, MD, MARS
Department of Plastic Surgery
Dharmais Cancer Hospital
Jalan Letjen Jend. S. Parman No. 84–86
West Jakarta, DKI Jakarta 11420 Indonesia
E-mail: irena_s_rini@yahoo.com

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