Surgery Today (2021) 51:862–871
https://doi.org/10.1007/s00595-020-02175-4

REVIEW ARTICLE

Clinical outcomes of patients after nipple-sparing mastectomy and reconstruction based on the expander/implant technique

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Received: 23 June 2020 / Accepted: 8 September 2020 / Published online: 13 November 2020

Abstract

Advances in multi-modality treatments incorporating systemic chemotherapy, endocrine therapy, and radiotherapy for the management of breast cancer have resulted in a surgical-management paradigm change toward less-aggressive surgery that combines the use of breast-conserving or -reconstruction therapy as a new standard of care with a higher emphasis on cosmesis. The implementation of skin-sparing and nipple-sparing mastectomies (SSM, NSM) has been shown to be oncologically safe, and breast reconstructive surgery is being performed increasingly for patients with breast cancer. NSM and breast reconstruction can also be performed as prophylactic or risk-reduction surgery for women with BRCA gene mutations. Compared with conventional breast construction followed by total mastectomy (TM), NSM preserving the nipple–areolar complex (NAC) with breast reconstruction provides psychosocial and aesthetic benefits, thereby improving patients' cosmetic appearance and body image. Implant-based breast reconstruction (IBBR) has been used worldwide following mastectomy as a safe and cost-effective method of breast reconstruction. We review the clinical evidence about immediate (one-stage) and delayed (two-stage) IBBR after NSM. Our results suggest that the postoperative complication rate may be higher after NSM followed by IBBR than after TM or SSM followed by IBBR.

Keywords Breast cancer · Nipple-sparing mastectomy · Implant-based breast reconstruction

Introduction

Breast cancer is the most commonly diagnosed cancer in women worldwide. In Japan alone, breast cancer was diagnosed in nearly 10,000 patients in 2016 [1, 2]. The incidence of breast cancer is also increasing significantly in line with improved detection and screening techniques. Despite this increase, the recent 5-year survival rate of patients diagnosed with breast cancer in Japan was 92.7% [3]. Because of the evolving management and treatment of breast cancer using combinations of systemic chemotherapy, endocrine therapy, and radiotherapy, the standard surgical treatment for breast cancer has undergone a paradigm shift toward less-aggressive surgery combining breast-conserving or breast-reconstruction therapy for a higher emphasis on cosmesis [4, 5]. Compared with skin-sparing mastectomy (SSM) with or without nipple reconstruction, nipple-sparing mastectomy (NSM) preserving the nipple–areolar complex (NAC) with breast reconstruction improves the cosmesis, body image and nipple sensation of patients, with psychosocial and aesthetic benefits [6–9].

Current guidelines suggest that the NSM approach should be limited to patients with early stage, non-high grade, and peripherally located small tumors, but these criteria have been challenged by the recognition of new, efficacious systemic therapies. An implant-based breast reconstruction (IBBR) method is used in approximately 80% of reconstructions performed after mastectomy [10, 11], and the number of immediate IBBRs using the direct-to-implant technique has also increased in Japan. This new surgical technique preserves the natural skin flap including the NAC, enabling the immediate reconstruction of the breast with a permanent implant, without the need for skin expansion with a tissue expander. Here, we review the risks and benefits of the various surgical techniques. We also analyze, retrospectively, the clinical results of IBBRs and compare the complication rates and outcomes of patients who underwent immediate

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(one-stage) or delayed (two-stage) IBBR following a standard total mastectomy (TM) including SSM or NSM at our hospital.

Indications for NSM followed by IBBR

Genetic panel testing is being used increasingly to identify high-risk patients with breast cancer. In Japan, risk-reducing mastectomy as prophylactic surgery to prevent contralateral breast cancer after unilateral mastectomy for patients with BRCA gene mutations was approved by the national health insurance scheme in April, 2020. The enhanced esthetics of current surgical techniques, including NSM with breast reconstruction, make these approaches an essential option for breast cancer patients at high genetic risk. Consequently, there has been a remarkable increase in oncoplastic breast surgery supported by advances in reconstructive techniques [4, 5]. Despite the lack of prospective trial data, most international guidelines recommend NSM for risk reduction [12, 13].

Several factors should be evaluated preoperatively and intraoperatively when treating cancer in candidates for NSM, to assess the potential risk of tumor involvement of the nipple, including the tumor distance from the nipple, tumor size, and nodal status [14–16]. A positive association between tumor size and the likelihood of pathologic nipple involvement has been observed. For example, nipple involvement rates were significantly lower for smaller tumors (< 2–2.5 cm) [14, 17], and a patient with tumor distance < 1–2 cm from the nipple was approximately three times more likely to have pathologic nipple involvement [18, 19]. Thus, the practice guidelines initially suggested that patients with favorable characteristics including non-high-grade, small (< 2–2.5 cm), node-negative, and peripheral tumors ≥ 2 cm from the nipple on imaging may be suitable candidates for NSM [20]. On the other hand, SSM, which is characterized by minimal skin excision, is preferred for patients undergoing immediate IBBR. In the SSM approach, the NAC is removed, and mastectomy is performed through a small skin incision, but the flaps are preserved with overlying breast skin for the reconstruction. Therefore, if NAC involvement is found intraoperatively to be positive for malignancy on histologic examination of the nipple margins, NSM should be converted immediately to SSM [21, 22].

These criteria have been challenged by recent advances in multi-modality treatments that incorporate systemic chemotherapy, endocrine therapy, and radiotherapy, to prevent local and distant recurrences from primary breast cancer. Although there is no long-term evidence of the risk of local recurrence when the NSM approach is used, its oncologic safety is promising, with local recurrence rates comparable to those of conventional TM at 5 years [6–8, 23, 24]. Current guidelines, including those issued by the Japanese Breast Cancer Society (JBCS) and the U.S. National Comprehensive Cancer Network (NCCN), recommend simply that experienced multidisciplinary teams may consider NAC-sparing procedures for carefully selected patients with breast cancer [13]. Nevertheless, the gradually broadening indications for NSM have led to its being reconsidered for some patients who have undergone prior breast surgery and/or radiotherapy and patients with large breast tumors, ptosis, or obesity; initially considered to be contraindicated for NSM, because these factors can increase complication rates [25–29] and diminish aesthetic outcomes [30–32]. In general, the contraindications for NSM include T4 or inflammatory breast cancer, Paget's disease, and tumors with clinical or imaging findings suggestive of extension into the NAC or patients with pathologic nipple discharge. Relative contraindications are severe and life-threatening medical comorbidities, massive obesity, and long-standing cigarette smoking [12, 13] (Table 1). Clinical studies have also shown that performing immediate IBBR based on an implant after mastectomy, including NSM, has little impact on postoperative recurrence, survival, or delayed diagnosis of recurrence [33, 34].

Since the surgical procedure of NSM + IBBR is technically challenging, the candidates for immediate IBBR after an NSM are healthy, young non-smokers with small- or

Table 1 Contraindications for implant-based breast reconstruction (IBBR) followed by nipple-sparing mastectomy (NSM)

Contraindications	T4 or inflammatory breast cancer
	Paget's disease
	Tumors within 1 cm of the nipple or with clinical or radiologic extension into the nipple–areolar complex (NAC)
	Tumors with pathologic nipple discharge
Relative contraindications	Large breast tumors
	Ptosis
	Massive obesity
	Severe life-threatening medical comorbidity
	Long-standing cigarette smoking

intermediate-sized and well defined breasts (B to C cup) without large ptosis, and those with biologically favorable, small, peripheral, node-negative tumors without nipple involvement [26, 34]. Other candidates include women who are undergoing prophylactic mastectomy. Bilateral reconstruction using a similar implant for the contralateral breast can also provide better symmetry and higher satisfaction [34, 35]. In addition to appropriate patient selection, to ensure the success of immediate IBBR after an NSM, radical surgery of the primary breast cancer should be prioritized for oncologic purposes over aesthetic desire.

Surgical procedure of the NSM before IBBR

Nipple- or areolar-sparing mastectomy (NSM) should be performed by a breast surgeon, and the most common incisions used are peri- or circum-areolar, lateral, or inframammary [12, 30, 36, 37]. Incisions around or through the NAC have been reported to increase the risk of nipple necrosis and are not recommended [5, 38, 39] and radical or periareolar incisions leave visible scars on the anterior surface of the breast. Thus, lateral or inframammary skin incisions are more desirable than peri- or circum-areolar incisions for preserving blood supply to the NAC, but the choice of incision line usually depends on the breast size and the distance from the inframammary fold to the clavicle level.

Although the approach using a lateral inframammary fold (LMF) incision can make it difficult to access the upper quadrants of the breast to perform an NSM [40, 41], this is the preferred approach at our hospital, as it not only provides cosmetic exposure without leaving visible scars on the anterior surface of the breast (Fig. 1a, b), but it also allows us to perform NSM and axillary lymph node surgery through the same incision. This is important, because TM or NSM combined with sentinel node biopsy and/or axillary lymph node dissection is the standard procedure for breast cancer surgery (Fig. 2b). The LMF incision is made along the curvilinear skin crease, starting from the lateral site, around the 3 o'clock position for the left breast or the 9 o'clock position for the right breast, and extending inferiorly to near the 6 o'clock position (Fig. 2a, b).

NSM should leave the dermis and epidermis of the NAC at the level of the subcutaneous fat layer to preserve an NAC flap that is ≥ 3 mm thick. It should also remove the major ducts using intraoperative frozen sections to identify the

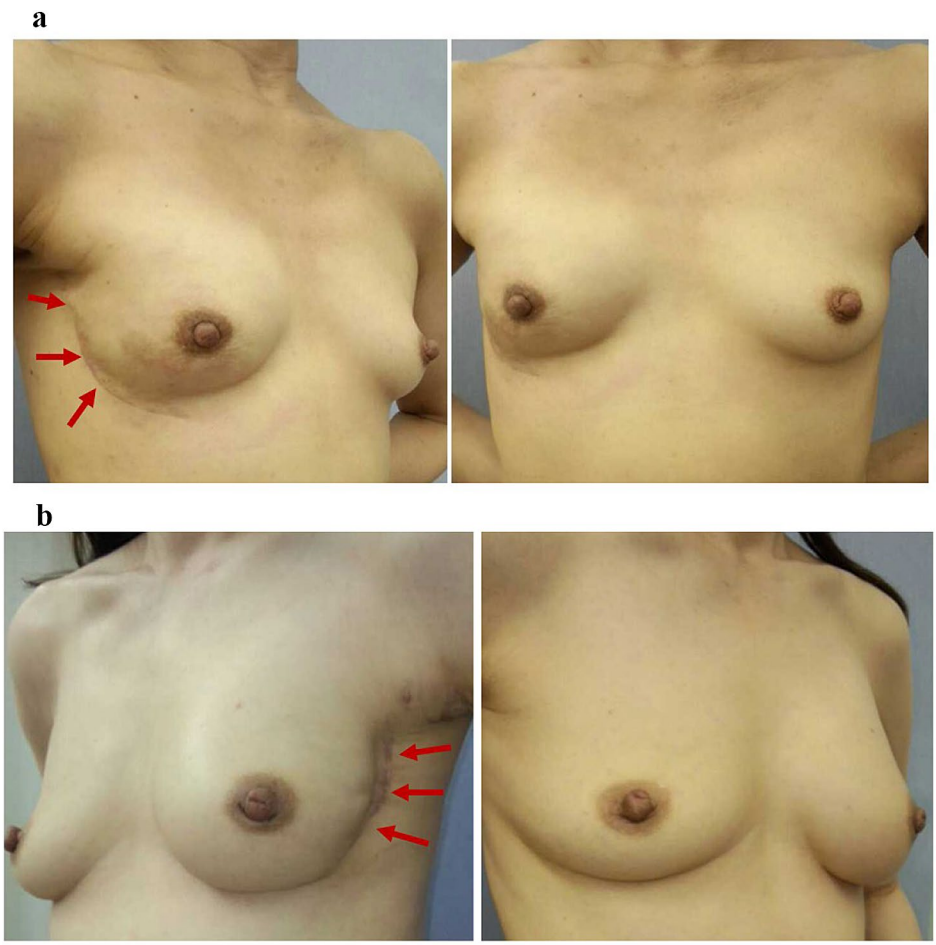

Fig. 1 Scars (*red arrows*) of a lateral inframammary fold (IMF) incision after nipple-sparing mastectomy (NSM) followed by one-stage or two-stage implant-based breast reconstruction (IBBR). **a** One-stage IBBR. Immediate direct-to-implant reconstruction following a right NSM. **b** Two-stage IBBR. Delay in the implant reconstruction following a left NSM

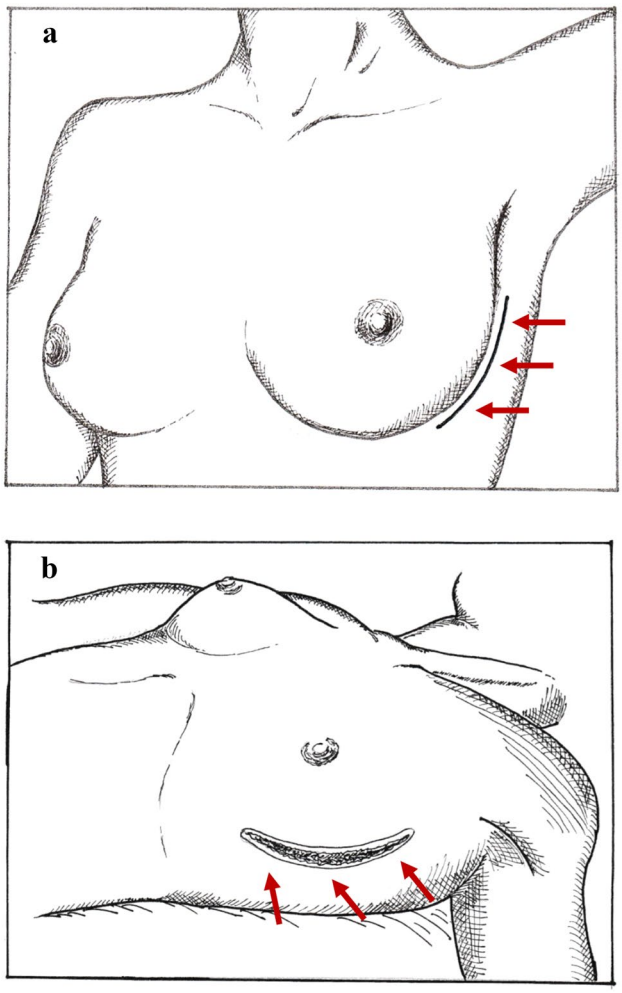

Fig. 2 Lateral inframammary fold incision (IMF) for NSM. **a** Schema of the lateral IMF incision line (*red arrows*) (left breast). **b** Overview of the lateral IMF incision (*red arrows*) after completion of NSM and removal of the surgical specimen

clear surgical margin of the sub-areolar region. The resected sub-areolar nipple ductal tissue on the surgical breast specimen from an NSM should be marked with a suture for subsequent pathologic examination [22, 36, 42]. At our hospital, the sub-areolar nipple duct margin is evaluated by intraoperative frozen section as well as postoperative permanent specimens. If the frozen section and the permanent pathology reveal in situ or invasive carcinoma of the ductal tissue, the carcinoma and NAC will be removed during the same operation and/or in a second surgical procedure.

After the entire resected breast specimen of the NSM is removed, the viability of the NAC and skin flap will be assessed by evaluating the color, temperature, and dermal blood flow of the skin flap. The viability of the local blood supply of a skin flap after a TM or NSM can also be assessed intraoperatively using a fluorescein imaging system with indocyanine green (ICG) dye, which can also detect axillary sentinel lymph nodes [43–45]. If the NAC and skin flap are both viable, breast reconstruction can be performed by reconstructive plastic surgeons using either the immediate direct-to-implant technique as one-stage reconstruction, or by tissue expanders that require a change of the expander to a definitive implant, as two-stage reconstruction.

Complications of NSM followed by IBBR

One-stage and two-stage IBBR

An IBBR is usually well tolerated and safe, with low rates of major and minor complications. The typical complications include skin necrosis, infection, infection requiring implant removal, and hematoma/seroma [33]. Several studies have shown that immediate reconstruction (one-stage IBBR) has the same postoperative complications as tissue expander/implant-based breast reconstruction (two-stage IBBR) [46]. However, historical data suggest that two-stage IBBR using the sub-muscular implant space is reliable, safe, and effective [47–49], and that the complication rates of one-stage IBBR tend to be higher [50–52].

A recent meta-analysis found no significant difference between one-stage IBBR and two-stage IBBR in terms of complication rates of infection, seroma, hematoma, and capsule contracture, but the incidences of flap necrosis, reoperation, and implant loss were significantly higher after one-stage IBBR [46]. Other studies show that the postoperative complication rate for NSM is approximately 20–30% and that the rate of complications requiring treatment remains at approximately 10–12% [11, 26, 38, 53]. Moreover, the reported rate of complications involving an NSM followed by one-stage or two-stage IBBR ranges from 1.5 to 9% for surgical-site infection [38, 54–57], 1–5% for seroma requiring treatment [56–58], 1–3% for hematoma [56, 57], 4–20% for skin flap ischemia, and 3–12% for necrosis [38, 55, 56, 58]. The incidences of reversible ischemia and/or superficial epidermolysis of the nipple lesion range from 6 to 13% [55, 57, 58], and that of NAC necrosis resulting in nipple loss ranges from 1–5% [4, 26, 38, 55, 59]. Skin incisions for expander/implant placement away from the areola were reported to be associated with fewer ischemic complications of the NAC [11, 53, 60].

NSM followed by immediate IBBR is still a technically challenging surgical procedure, but several research groups have described individual and/or team learning curves for NSM based on patient selection, surgical judgment, technical expertise, and perioperative management [5, 53, 54].

Chemotherapy and radiotherapy

Adjuvant chemotherapy has been reported to increase the overall complication rate to 27–30% [61–63], whereas neoadjuvant chemotherapy has been reported to increase it to within the range of 15–33% [64, 65]. Moreover, definitive reconstruction failed in 38% of patients who received neoadjuvant chemotherapy because of infection or extrusion [64]. The safety of neoadjuvant chemotherapy remains a subject of controversy, although two studies reported that neoadjuvant chemotherapy did not increase the complication rate and was safe for IBBR [66, 67]. A systematic review found that even one-stage IBBR does not necessarily delay the start of adjuvant chemotherapy to a clinically relevant extent, suggesting that one- or two-stage IBBR is an effective option for patients with early stage breast cancer [68, 69]. On the other hand, although complications from a TM including SSM or NSM followed by one- or two-stage IBBR may delay the timing of postoperative adjuvant chemotherapy when initiating treatment, no impact of neo- or adjuvant chemotherapy on oncologic and cosmetic outcomes was observed [66, 67].

Patients with ipsilateral loco-regional recurrence after prior breast breast-conserving surgery plus radiotherapy are at higher risk of complications following TM including SSM or NSM with the one- or two-stage IBBR approach [54]. In a series of patients who had undergone prior whole-breast radiation and subsequent NSM followed by IBBR, the rate of infection was 20%, that of expander loss at the first stage was 15%, while that of implant loss was 5% [70]. A retrospective analysis revealed that the substantial rate of early postoperative complications in NSM patients who had received prior radiotherapy included an 18.8% rate of infection, necrosis, and hematoma requiring reoperation, a 7.2% rate of nipple necrosis, and a 4.3% rate of nipple loss [26]. In contrast, the rate of implant loss and surgical-site infection were approximately 15–22% and 9–31%, respectively, for patients who received postoperative radiotherapy [70, 71].

Our experience

We analyzed 71 patients who underwent TM as SSM or NSM, followed by one- or two-stage IBBR, at our hospital after 2013 and compared their clinical features and complication rates. As shown in Table 2, early stage (0–II) disease with minimal lymph node metastasis was diagnosed in all patients. Thirty-seven patients underwent TM, including 5 who underwent SSM, followed by two-stage IBBR; 18 who underwent NSM followed by two-stage IBBR; and 16 who underwent NSM followed by one-stage IBBR. The operation times were 236, 247.2, and 321 min, and the mean surgical blood loss was 60.4, 88.8, and 138 ml, respectively. Axillary surgery consisted of a sentinel lymph node biopsy in

Table 2 Clinical characteristics of the patients

	TM + TE (two-stage IBBR)	NSM + TE (two-stage IBBR)	NSM + direct-to-implant (one-stage IBBR)
No. of patients	37	18	16
Median age, yrs (range)	49 (35–76)	47 (30–61)	50 (42–74)
Pathological stage (%)			
Stage 0 (DCIS/LCIS) cases	5 (13.5)	8 (44.4)	4 (25)
Stage I cases	22 (59.5)	8 (44.4)	6 (37.5)
Stage II cases	10 (27)	2 (11.2)	6 (37.5)
Biologic subtype (%)			
Luminal cases	27 (72.9)	15 (83.2)	14 (87.5)
HER2-positive cases	8 (21.6)	2 (11.2)	1 (6.25)
Triple-negative cases	2 (5.5)	1 (5.6)	1 (6.25)
Operation time, mean	236.0 min.	247.2 min.	321.0 min.
Sentinel lymph node biopsy (%)	31 (83.8)	13 (72.2)	14 (87.5)
Axillary lymph node dissection* (%)	4 (10.8)	4 (22.2)	2 (11.8)
Blood loss, mean ml	60.4	88.8	138.0
Hospitalization, mean days	16.7	15.2	14.0
Chemotherapy (%)	16 (43.2)	8 (44.4)	6 (37.5)
Neoadjuvant/adjuvant	(2/14)	(1/7)	(1/6)
Adjuvant endocrine therapy (%)	26 (70.3)	11 (61.1)	7 (43.8)

TM: total mastectomy including skin-sparing mastectomy (SSM); NSM: nipple-sparing mastectomy; TE: tissue expander; IBBR: implant based breast reconstruction

*All cases: pN1a

31, 13, and 14 patients, respectively, and a sentinel node biopsy and/or axillary node dissection in 4, 4, and 2 patients, respectively. Neo- or adjuvant chemotherapy was given to 16 (43.2%), 8 (44.4%), and 6 (37.5%) patients, respectively, and adjuvant endocrine therapy was given to 26 (70.3%), 11 (61.1%), and 7 (43.8%) patients, respectively.

The complications in these three groups included infection (2.7%, 11.1%, and 6.3%), seroma/hematoma (0%, 5.6%, and 6.3%), flap necrosis (2.7%, 11.1%, and 12.5%), and loss of tissue expander or implant (2.7%, 5.6%, and 6.3%), respectively (Table 3). Specifically, one patient from the NSM + two-stage IBBR group, who had received radiotherapy after initial breast-conserving surgery, suffered nipple necrosis, and the nipple was lost in one patient from the NSM + one-stage IBBR group who was a heavy smoker (Table 2). The total complication rates were 8.1% for the TM + two-stage IBBR group, 38.9% for the NSM + two-stage IBBR group, and 31.3% for the NSM + one-stage IBBR group (Table 3).

These findings are consistent with those of previous studies and indicate that one-stage IBRR tended to increase the operating time and blood loss vs. two-stage IBRR and that there was no significant difference in the complication rate between one-stage and two-stage IBBR. In contrast, the complication rate might be higher when NSM is followed by IBBR than when TM with or without SSM is followed by IBBR.

Oncological outcomes of NSM followed by IBBR

The major oncologic concern about NSM followed by IBBR is the possibility that residues of primary cancer may be left in the breast tissue behind the NAC, which is usually preserved for blood supply. However, a review of ten studies of 1148 patients who underwent conventional TM indicated that the loco-regional recurrence rate was 2.8%, whereas that after NSM was 4.4% and 7.8% for patients with invasive breast cancer and ductal carcinoma in situ (DCIS), respectively [72, 73]. The 5-year rates of local recurrence of invasive ductal carcinoma (IDC) and DCIS in the NAC were 0.8% and 2.9%, respectively, which are lower than those of 3.6% and 4.9% in the chest wall [34, 72]. More recent single-institution studies, including our own retrospective analyses, clarified that the loco-regional recurrence rates at NAC sites and non-NAC sites ranged from 0% to 3.7% and from 0% to 8.2%, respectively (Table 4).

The results of our investigations are consistent with those of studies showing that loco-regional recurrence is less likely in the NAC regardless of whether patients undergo one-stage or two-stage IBBR following NSM. One of our 71 patients who underwent neoadjuvant chemotherapy was found to have distant lymph node metastases at the 24-month follow-up after NSM + two-stage IBBR; however, at the median 38-month follow-up, no loco-regional recurrence at the NAC or other distant recurrence were detected in any of the patients, irrespective of whether they underwent TM, NSM + one-stage IBBR, or NSM + two-stage IBBR.

Implant-related systemic disease

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a rare disease that may occur in women who have had an implant inserted as part of the reconstructive operation. An increased risk of BIA-ALCL in women with breast implants was first described in 2006. A significant association between breast BIA-ALCL and textured implants has been noted, as IBBR remains a common method of breast reconstruction worldwide for patients with breast cancer as well as for women who undergo breast augmentation with silicone implants. BIA-ALCL is an anaplastic lymphoma kinase (ALK)-negative and CD30-positive T cell lymphoma that arises in either the fluid or capsule surrounding the implant. The first case of BIA-ALCL in Japan was also recently reported [74, 75].

Table 3 Postoperative complications expressed as percentages (total number of each complication)

	TM + TE (two-stage IBBR)	NSM + TE (two-stage IBBR)	NSM + direct-to implant (one-stage IBBR)
Total complication rate	8.1 (2)	38.9 (7)	31.3 (5)
Infection	2.7 (1)	11.1 (2)	6.3 (1)
Seroma/hematoma	0	5.6 (1)	6.3 (1)
Flap ischemia/necrosis	2.7 (1)	11.1 (2)	12.5 (2)
TE/implant loss	2.7 (1)	5.6 (1*)	6.3 (1#)
Nipple necrosis/loss	–	5.6 (1)	6.3 (1)

*The patient underwent prior radiotherapy after initial breast-conserving surgery

#The patient was a heavy smoker

Table 4 Oncologic outcomes of nipple-sparing mastectomy followed by implant-based breast construction

Data	Year of publication	No. of breasts operated on	Median follow-up in months	Local regional recurrence rate (%)	
				NAC*	Not NAC (e.g., skin flap, chest wall)
Kim [81]	2020	251	68 (mean)	0.4	4
Krajewski [5]	2015	236	24	0	1.7
Eisenberg [80]	2014	208	33 (mean)	0.5	0.5
Sakurai [24]	2013	788	78	3.7	8.2
Coopey [4]	2013	315	22	0	2.6
Peled [38]	2012	412	28	0	2
Spear [83]	2011	49	30 (mean)	0	0
Kim [21]	2010	152	60	1.3	2
Our own[#]	–	34	38	0	0

*At the nipple–areolar complex

[#]Data included NSM followed by one-stage or two-stage reconstruction

Other systemic diseases are occasionally observed after IBBR, and several studies have described an association between breast implants and connective tissue disorders, immune dysregulation, cancer (including breast cancer), and neurological diseases [76–78]. Some cases were recorded as alleged breast implant-related deaths [79]. An implant used for cosmetic breast augmentation may interfere with the detection of breast cancer and impact the patient's survival [80].

Limitations

This review has several limitations. First, most of the studies we reviewed were performed at single institutions, and thus the data may tend to be biased. Second, we lacked the long-term maintenance data necessary to identify the rate of complications and disadvantages related to IBBR, including data about ruptures, leaks, the symmetry of implants in unilateral reconstruction, and capsular contracture.

Conclusion

With a better understanding of tumor biology and the use of increasingly effective neoadjuvant and adjuvant therapies, the oncologic outcome data are encouraging. There are currently low loco-regional recurrence rates after the surgical treatment of breast cancer using NSM followed by IBBR. The NSM technique is an attractive procedure both for high-risk patients with BRCA mutations and for use in conjunction with contralateral prophylactic mastectomy for patients with unilateral breast cancer. The NSM may become a standard surgical procedure, and its complications are comparable to those of the traditional TM. Nevertheless, it is important to inform patients appropriately about the oncologic safety, complications, and cosmetic outcomes of the various options. The choice of whether to perform an NSM or TM followed by IBBR should be individualized in the appropriate setting, as well as with careful preoperative management in accordance with the patient's preferences, including considerations of patient satisfaction and reasonable expectations.

Compliance with ethical standards

Conflict of interest U. Toh received honoraria and research funding from Chugai, Kyowa Kirin, Taiho and Eisai. The remaining authors have no conflicts of interest to declare.

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