Breast reconstruction after nipple-sparing mastectomy in the large and/or ptotic breast : a systematic review of indications, techniques, and outcomes

Breast Reconstruction after Nipple-Sparing Mastectomy in the Large and/or Ptotic Breast: A Systematic Review of Indications, Techniques and Outcomes.

Author list: Thierry **TONDU**, MD[1,2,3]; Guy **HUBENS**, MD, PhD[1], Wiebren TJALMA, MD, PhD[3,4], Filip **THIESSEN**, MD[1,2,3]; Ina **VRINTS**, MD[1,2,3]; Jana Van Thielen, MD[3], Veronique **VERHOEVEN**, MD, PhD[5]

ABSTRACT

Background:

Surgeons remain reluctant to perform nipple-sparing mastectomy in large breasts due to a higher risk of necrosis. We performed a systematic review of the literature to evaluate indications, techniques and outcomes in immediate or delayed breast reconstructions in large and/or ptotic breasts.

Methods:

The following search terms were used for both titles and key words: [nipple sparing mastectomy AND ("breast ptosis" OR "ptotic breast" OR “large breast” OR “breast hypertrophy” OR “gigantomastia”)]. All forms of breast reconstruction in large and/or ptotic breasts from 1990 through September 1st 2018 reporting indications, techniques and outcomes were included.

Results:

Thirty-one studies met the inclusion criteria, yielding 1128 nipple-sparing mastectomies (709 immediate and 419 delayed) in 629 patients for analysis. The overall complication rate was 29,08 percent. The mastectomy flap necrosis rate was 12 percent, the partial NAC necrosis 11 percent and the complete NAC rate 11 percent. The overall complication rate in one-stage versus delayed reconstructions was 37,52 versus 14,8 percent. The incidence of necrosis in one-stage versus delayed reconstructions was 5,36 versus 2,15 percent for partial, 5,08 versus 0,48 percent for complete NAC necrosis and 4,8 versus 1,43 percent for skin flap necrosis.

Conclusions:

The majority of studies being small and retrospective as well as the large variation in outcomes indicates that we lack consensus on timing of reconstruction or ideal technique. A noticeable difference in skin flap and NAC necrosis however is seen in favor of NAC delayed procedures. Randomized controlled trials are mandatory to prove this difference significantly.

Introduction

Early reports on subcutaneous mastectomy in large ptotic breasts date from the 1970's. Although efforts were made to obtain adequate skin flap thickness and reliable nipple areola bearing pedicles, using the remaining glandular tissue to ensure overlying dermal perfusion (1,2,3,4), these techniques do not comply with current surgical criteria for nipple sparing mastectomy (NSM) (5,6). Using careful oncological selection criteria as well as anatomical parameters, breast reconstruction

after NSM can be safely considered in prophylactic as well as therapeutic settings (7). In 2009 Spear recommends not to perform NSM on patients with positive lymph nodes, with tumors closer than 2 cm to the nipple and in patients with large or ptotic breasts (the Georgetown algorithm) (8). Jensen counterargues the contraindications of positive lymph nodes as well as a tumor to nipple distance less than 2 cm, based on the results of the National Surgical Adjuvant Breast and Bowel Project B.06 randomized trial in 1851 women (9). Jensen states that initial removal of the nipple does not prolong survival in the treatment of breast cancer: there is no difference in 20 years survival between the mastectomy, the lumpectomy or the lumpectomy with irradiation group (10). To ensure nipple perfusion Jensen describes staged nipple-areola complex delay in 2012 (11). Patients with a large body mass index (BMI), a larger mastectomy weight or an increased sternal nipple index (SNI) are at higher risk for skin envelope necrosis (12,13). We systematically report, guided by PRISMA guidelines, the indications, techniques, complications and outcomes of breast reconstruction after NSM in large and/or ptotic breast. The purpose of this review is to compare the necrosis rates between immediate and delayed breast reconstructions in large and/or ptotic breasts.

Patients and methods

Search methodology

PubMed and Science Direct databases were searched using the following search terms: [nipple sparing mastectomy AND ("breast ptosis" OR "ptotic breast" OR large breast OR breast hypertrophy OR gigantomastia)]. All studies from January 1st,

1990 until September 1st, 2018 were included. Duplicates were removed and references in the included articles were evaluated for further relevance (Figure 1).

Selection criteria

Inclusion and exclusion criteria were defined before data collection. Studies evaluating outcomes following NSM in large and/or ptotic breasts were included. All types of reconstruction were included and compared (tissue expander, implant, autologous flap, as well as a combination of methods). A mandatory inclusion criterion was the reported complication rate (or publication of sufficient data allowing this to be determined). At least one of the following postoperative complications had to be reported: hematoma, infection, wound dehiscence, partial or total necrosis of the skin and/or the nipple areola complex (NAC). We included case reports as well as prospective and retrospective studies. Two independent reviewers performed the article search and selection. The review is written and checked according to PRISMA guidelines.

Data collection and analysis

The following data were collected : authors, publication date, study name, study aim, location of study, journal of publication, type of study, inclusion criteria for NSM, number of patients, average age, age range, patients morphology (cup-size, BMI, SNI, Nipple-to-Inframammary Fold Distance (NIMF), Regnault Ptosis Grade), predisposing risk factors (diabetes, smoking, pre- and/or postoperative radiotherapy, previous breast reduction or mastopexy procedures), number of treated breasts, number of cancer breasts treated, number of prophylactic mastectomies, number of prophylactic mastectomies for genetic predisposition, number of BRCA-patients,

unilateral versus bilateral, type of reconstruction, incision type, prosthesis position, presence and kind of nipple delay technique, immediate or staged technique and number of stages, use of acellular dermal matrix (ADM) and the number of breasts treated, base of the nipple-areola complex (NAC) vascularization, pathology results and presence of intraoperative nipple biopsy, mastectomy weight, postoperative SNI, complications (wound dehiscence, hematoma, skin-flap epidermolysis or necrosis, NAC epidermolysis or partial or complete necrosis, infections, device-explantation), follow up time and late outcome (implant displacement, capsular contractures, locoregional recurrence, distant metastasis).

Results

Thirty-one studies were included for review (Figure 1). Twenty-six studies were retrospective and five prospective. The 31 studies included 629 patients and 1128 procedures. We noted 195 unilateral and 401 bilateral procedures. The sum of unilateral and bilateral procedures did not correlate exactly with the total number of procedures: the inclusion of specific article subgroups (large and/or ptotic breasts) meant it was not always possible to differentiate laterality. The average patient's age was 46.27 years. Tables 1 and 2 summarise the 31 included studies regarding patients, procedures, study type, stages, type of reconstruction and complication rates.

The indications for NSM were: invasive cancer, risk reducing mastectomy based on high family risk and/or genetic predisposition, carcinoma in situ, poor response to neo-adjuvant chemotherapy, mastectomy because of positive margins at re-excision,

diagnosed cancer in the opposite breast and disabling mastodynia. The varying inclusion and exclusion criteria are listed by study in Table 3. We report 357 therapeutic (26 studies) and 560 prophylactic procedures (29 studies) of which 94 had a genetic predisposition (16 studies): fifty-five of these patients were BRCA-positive (12 studies).

Morphologically, breast size varied from C to DD/E cup (7 studies). The average BMI was 26.11 kg/m^2 (15 studies). Two hundred and thirty-two patients had breast ptosis grade 2 and 119 patients had grade 3 (15 studies). Ninety-eight patients were considered grade 2 or 3 (3 studies). Grade 2 and 3 ptosis occurred in a total of 449 breasts. The average ptosis grade in 15 studies was 2,34. All included studies, however, classified their patients as high-risk due to ptosis or macromastia. Macromastia or breast hypertrophy was simply defined as a large breast. SNI was larger than 25 cm with a maximum of 35 cm in 11 studies. NIMF measurement was longer than 8 cm with a maximum of 15 cm in 7 studies. Average mastectomy weight was 557.11 g (13 of 31 studies). Ten patients were diabetic (17 studies) and 84 smoked (24 studies). Thirty-eight patients had preoperative radiotherapy (22 studies) whereas 37 underwent postoperative irradiation (20 studies). Seventy-one patients had a history of previous breast reduction or mastopexy (21 studies).

The different reconstructive techniques consisted of 214 autologous reconstructions, 398 expander-to-implant reconstructions, 268 permanent implant-expanders or Becker-prosthesis and 168 immediate implant reconstructions.

The most frequent skin incisions were: 333 Wise pattern incisions (29.5%), (302 immediate Wise pattern, 14 Wise pattern incisions secondary to an inframammary fold (IMF) incision, 10 after a vertical incision and 7 after supra-areolar delay), 254 six o'clock vertical (22.5%), 212 IMF incisions (18.8%) and 85 IMF combined with a circumareolar incision (7.5%) (Figure 2).

The implant position was subpectoral in 646 and prepectoral in 72 procedures. In 10 studies an ADM was used for implant coverage in 214 procedures. Vascular supply to the NAC was secured by a circumareolar dermal pedicle (13 studies with intact skin around the NAC), an inferior dermal/fat pedicle (10 studies), a bipedicled infero-superior dermal/fat pedicle (5 studies) and a superior dermal/fat pedicle (2 studies). Two studies used an inferior, or a superior fat-dermis and glandular pedicle respectively (Figure 3). Delayed techniques to secure vascular supply to the NAC were used in 14 studies. In the other 17 studies an immediate technique was performed.

Only 10 of the 31 studies used peroperative retroareolar frozen sampling. In the two staged studies using a glandular pedicle in the first stage (25,29), retroareolar frozen sampling was not possible because of the NAC-bearing pedicle. However, in these techniques retroareolar frozen sampling can be performed in the second stage. In one study frozen sampling was positive for carcinoma in situ in three breasts (36).

All studies reported on skin and nipple-areola-complex epidermolysis or necrosis. Overall complication rate was calculated from the total number of complications with respect to the total number of procedures. Two different complications occurring in

the same procedure were regarded as two separate complications. We found an overall complication rate of 29.08% (Figure 4).

Comparison between immediate and delayed procedures demonstrated an overall complication rate in one-stage immediate reconstructions in large breasts of 37.52% versus 14.8% in delayed techniques. There was a greater incidence of partial NAC necrosis in one-stage reconstructions compared with multiple stage reconstructions (5.36% versus 2,15%). The incidence of complete NAC necrosis was 5.08% in immediate procedures versus 0,48 % in delayed reconstructions. (Table 4).

Comparing the use of the Wise pattern in immediate and delayed procedures shows an overall complication rate in one-stage immediate reconstructions of 28,79 % versus 9,4 % in delayed techniques. There was a greater incidence of wound dehiscence, NAC epidermolysis and partial NAC necrosis in one-stage reconstructions compared with multiple stage reconstructions (8,33%, 8,33% and 9,09% versus 1,71%, 3,42% and 2,56%). The incidence of complete NAC necrosis was 2,27% in immediate procedures versus 0% in delayed reconstructions. (Table 5). Comparison of other incision types was not possible because there was no correlation between chosen incision type and related complications.

Ten studies including 214 procedures used ADM (11,12,13,24,25,30,34,37,38). In five (two direct-to-implant and three multi-staged), the complication rate was clearly defined (11,24,25,30,37) (Table 6). All implants were placed subpectorally.

Follow-up varied from 1 month to 22 years. Follow up was indicated in 17 of the 31 studies with a very large range (3 months to 21 years). Very few studies discussed

late outcome results: prosthesis displacement was noted in 1 breast (4 studies) and symptomatic capsular contraction in 8 breasts (6 studies). A local recurrence was noted in only 1 patient (8 studies, 272 procedures) giving an incidence of 0.37%. Distant metastasis was reported in 2 patients (0,74%).

Discussion

Oncologic criteria and indications

At present, clinical cancer stage, tumor biology and tumor location determine if the NAC can be spared (10). Anatomical criteria together with risk factor evaluation such as smoking, diabetes, need for radiotherapy or prior breast surgery will further guide the plastic surgeon in deciding whether to perform a NSM in larger breasts. Although most studies apply more or less similar oncological criteria, no universal agreement has yet been reached. A recent consensus meeting has recommended NSM as a good alternative for the treatment of early breast cancer and ductal carcinoma in situ (DCIS). Indeed, NSM is unanimously recommended as risk reducing surgery (7).

It is generally considered that the tumor-to-nipple distance should be 2 cm or larger. Preoperative MRI-imaging shows NAC involvement and tumor to nipple distance (15,20,40). Rivolin allows a distance of up to 10 mm from the NAC when there is negative histological examination of the underlying major duct (20). Wang even allows a smaller distance to NAC if the MRI demonstrates no NAC involvement (40). Recent literature shows safe tumor to nipple margins of up to 5 to 10 mm (42,43). Retroareolar frozen section will demonstrate NAC involvement intra-operatively. In ten studies using frozen section, there were only three positive cases in 292

procedures. No NSM was performed in these cases. This supports the recent idea of treating the nipple margin like any other margin (7). Tumor size, tumor to nipple distance, extensive DCIS and multicentricity are predictors of nipple involvement (44). In staged procedures with a dermoglandular pedicle, intra-operative frozen section is only possible in the second stage (25,29). Tumors close to the NAC are therefore not an ideal indication for this approach. On the contrary, prophylactic procedures with negative imaging or peripherally localized tumors can be managed by these staged procedures.

Radiation therapy is considered a relative contraindication for NSM due to the risk of wound dehiscence and decreased dermal vascular supply. Thirty-eight patients in 13 studies received preoperative radiotherapy (11,13,16,22,23,28,30,31,32,36,37,38,40). Overall complication rates vary from 0 to 46.91%. Since no correlation was made between overall outcome and preoperative radiation therapy in any of the included articles, no conclusions can be made.

Anatomical factors

Large ptotic breasts are often considered a relative contraindication for NSM based on anatomical factors (13,45). Skin excision, with possible compromise of vascular supply, is usually necessary. Large and ptotic breasts are thought to be more prone to develop NAC or skin flap necrosis (46). Ideal candidates for NSM have a low body mass index and absence of breast ptosis (12,13). Ptosis grade 2 or 3 was noted in 449 procedures. In only 7 studies was a cup size of C or larger reported. Average mastectomy weight was 557.11 g. The overall complication rate was 29.08 % which confirms the procedure in these indications is challenging.

Incision site

The chosen incision not only facilitates both mastectomy and reconstruction, but it must also preserve blood supply to skin flaps and NAC. Although numerous incision types have been described, the Wise anchor pattern (as primary incision or as an incision contained within previous mastopexy or reduction scars) was most frequently used. This pattern allows an easy approach to mastectomy and facilitates remodeling and skin reduction. Inframammary or periareolar incisions do not easily allow remodeling (28,29,40). The higher complication rate in immediate reconstructions using Wise pattern incisions can be explained by reduced skin perfusion. Delaying will induce collateral vascularization as well neovascularization (Table 5).

Prosthetic or autologous reconstruction

Due to the higher complication risks in large breasts, it is understandable that there is widespread use of expanders or permanent implant-expanders (398 and 268 procedures respectively). Staged inflation will diminish the vascular stress of the mastectomy flaps and NAC. Immediate implantation, however, is challenging due to breast volume and ptosis. The major pectoral muscle will not easily adapt and muscle damage can be expected in primary, larger volume reconstructions. Coverage of the implant in the lower lateral pole will be incomplete. Prepectoral placement can result in upper pole emptiness or rippling of the implant, resulting from limitations in size or from the thickness of the skin flap (6). Wound dehiscence due to insufficient skin vascularization can easily result in prosthesis exposure with prepectoral placement. This can explain the reported use of only 72 implants in the prepectoral position in 168 immediate implant reconstructions. A reduction in NAC vascular compromise is achieved in delayed prosthetic procedures by using an

adjustable device: inflation starts when the wounds are healed. Jensen delays the NAC with its dermal pedicle by using a thin silicone sheet (11). Preshaping of the breast has the additional advantage of providing a dermoglandular supply to the NAC in a first stage (25,29). This delay allows complete circumareolar dermal neovascularization to the NAC before a NSM is performed a few months later. Free flaps create an immediate well vascularized matrix underneath the mastectomy skin. Full thickness necrosis of the skin flap often heals per secundam from the remaining dermal layer of the free flap. The nipple areola complex will progressively receive additional vascularization from the flap (23).

Use of an ADM

When choosing a direct implant reconstruction in large breasts, there can be difficulty in creating a pocket that is not only large enough, but also provides well vascularized coverage of the prosthesis. This coverage needs to be able to support the weight of a larger prosthesis. This is less of a problem when an expander is gently inflated over time. In addition the capsula formed around the expander will create more prosthesis coverage, as well as lower pole support. Recently the creation of an ADM makes it possible to create this pocket immediately. By attaching it to the lower border of the pectoral muscle a subpectoral hammock is created that will support the lower pole (47). Due to its acellular nature, care must be taken to avoid infection. An ADM is an option in immediate larger breast reconstruction, although necrosis in a less vascularized skin flap can cause exposure. There are only a few large series of ADM use in large breasts (28,29,40).

Frozen section of the subareolar tissue

NSM is oncologically safe (7,46). Retroareolar biopsy confirms safe margins (10,11). However, only one third of the included studies reported on the intra-operative use of frozen section pathology (12,20,21,28,33,34,36,38,39,41). Nine studies reported no retroareolar involvement. Bertoni described 3 cases of positive frozen sections that were excluded from their series (36). Since inclusion criteria often describe the requirement for a minimal distance between tumor and areola, one can understand the frequent absence of frozen section pathology. From a surgical point of view a positive intra-operative retroareolar frozen section requires removal of the nipple. This may jeopardize the vascular skin supply when the chosen incision is remote from NAC (48). Petit et al. reported a novel technique in which, after intra-operative frozen section, a 16 Gy dose electron-beam was delivered to the nipple-areola complex, followed by immediate reconstruction (49).

Local recurrence and distal metastasis

Only 8 studies reported on local recurrence, distant metastasis as well as on follow up (15,17,18,21,26,29,32,34). Follow-up varied widely from 3 months to 22 years. On 272 procedures, Nava is the only author describing 2 local recurrences and 2 patients with distant metastasis in follow-up at 24 to 84 months (21). Although Spear reports a wide variation in local recurrence rates (1.4 to 24.1%) with an average of 1.8% in 6003 procedures (46), we are unable to draw conclusions from the 272 procedures included in our review due to very large variability in follow-up.

Complications

Complication rates vary widely from 0 to 46.91 % (18,40). The overall rate of 29.08% for the included series is high: we focused on large ptotic breasts, as these are

considered a relative contra-indication for NSM. With increasing breast volume (>500g) or breast ptosis, the NAC or mastectomy skin flaps are at higher risk for necrosis (12,45). The average mastectomy weight of 557,11 g can be considered as an indicator for larger breasts.

Primary nipple sparing prosthetic breast reconstruction can be performed in one or in multiple stages. Single-stage reconstruction is straight forward with a lower cost (50). The two-stage methods improve symmetry in a second operation. This review demonstrates an increased overall complication rate in one-stage versus multi-staged reconstructions in large breasts (37.52% versus 14.8%). The included immediate procedures show a higher total necrosis rate of 14.95 % compared with the multi-staged procedures (Table 4). Even with a large prosthesis or free flap, skin excision is usually necessary to obtain a natural result: excess of skin in direct-to-implant reconstructions will easily result in upper pole emptiness when a prosthesis is placed prepectorally. When the implant is positioned retropectorally, the excess of skin can produce a high-riding prosthesis with sagging of the skin in the lower pole. NAC necrosis rates vary from 0 to 21.4%. There is also a remarkable increase in NAC necrosis in one-stage reconstructions compared with multi-staged reconstructions (Table 4). These results are compatible with the increased vascular stress and tension on mastectomy skin flaps in immediate reconstructions as well as with the inability of immediate reconstructions to induce neovascularization to the nipple areola complex.

The intra-operative decision to convert a one stage to a multi-stage procedure can create difficulty with the vascular supply, especially when the incision pattern has to be changed. Evaluation of skin flap viability is a safe option. This can be achieved

intraoperatively using indocyanine green angiography. Gorai et al. showed a significant decrease in full thickness necrosis from 17.8% to 4.8% with the use of indocyanine green angiography-guided skin trimming (43,51). Since the NAC will always be positioned at the distal end of the flap, an increase in NAC necrosis in larger or ptotic breasts can be expected. Remarkably, complication rates in multi-stage procedures show an opposite trend. Delaying or pre-shaping of the skin envelope and the NAC will enhance the dermal vascular flow and will improve neovascularization to the distal end of the flaps.

The absence of an implant in the first stage can create more adhesions due to decreased tension on the skin flaps. Therefore, using an ADM is a helpful tool in the reconstruction of the implant pocket. Stress yielding of myofibroblasts will diminish late capsular contraction when an ADM is used. The slow repopulation of the ADM will delay the inflammatory response and diminish late capsular contraction (52,53). Ten studies included in this review used an ADM. The complication rate is clearly described in five of these (15,28,29,34,40). Although the numbers are small, the incidence of necrotic complications doubles in immediate reconstructions. Infections occur five times more with the immediate approach. The number of patients identified in this review is too small to make significant conclusions (Table 6), but theoretically, poor vascular supply together with an ADM is attractive for bacterial growth. It might be prudent in larger breasts to use only skin expanders with or without ADM-coverage, instead of an immediate prosthesis. Expansion itself will work as an adjuvant inducing increased blood flow to the overlying skin (52,53). Salibian recently advocated the two-stage suprapectoral placement of the

expander/prosthesis, especially in larger ptotic breasts, as this will reduce skin tension by contraction of the capsula (6).

Implant exposure results in salvage surgery, often with multiple procedures. Vascular supply, tension on the skin flap or infection can cause implant exposure. Adding a non-vascularized matrix in a setting with poorly vascularized skin flaps can trigger the attraction of bacteria. Neither antibiotics nor leucocytes will easily reach the affected skin area or prosthesis pocket. Although direct-to-implant series show an 8.6% rate of infection (versus 2.39% in delayed), the number of removed implants differs only one percent (3.10% versus 2.15%) (Table 4). In the direct-to-implant series using ADM, however, infection rates are five times higher (28.79% versus 4.2%). Implant removal occurs three times more in direct-to-implant series using ADM (9.09% versus 2.52%). Although these series are too small to compare or to draw conclusions, the difference between immediate versus delayed reconstructions using ADM may be explained as above (Table 6).

Most studies are retrospective: only five studies are prospective (12,20,23,29,32). There is a very large variation in reported outcomes, follow up, recurrence and late results. Larger retrospective studies as well as prospective randomized controlled trials embodying the same inclusion criteria are needed to derive significant conclusions. We nevertheless note a downward tendency in complication rates towards delayed techniques.

Conclusion

Decision-making in nipple sparing mastectomy in large ptotic breasts is complex. Oncological as well as anatomical parameters have to be considered. Early diagnosis and genetic counselling provide further indications for prophylactic and early breast cancer stage procedures. Gentle expansion as well as preshaping of the skin envelope will enhance local neovascularization. Preoperative breast imaging as well as preoperative retroareolar biopsy are extra tools in the prevention of positive margins. The ideal flap thickness should preserve the dermal blood supply: anatomical structures will guide the reconstructive surgeon into a correct dissection plane. NSM in large breasts remains challenging with an overall complication rate of 29.08 %. A noticeable difference in skin flap and nipple areola complex necrosis is seen in favor of nipple areola complex-delayed procedures in primary breast reconstruction. Evenmore immediate remodeling using a Wise pattern incision triples the incidence of wound dehiscence and partial NAC necrosis. The majority of recent publications dealing with NSM in large ptotic breasts are small and retrospective. Since there is a large variation in outcome rates, universal consensus is needed on indications, timing of reconstruction and ideal technique to be used.

Financial Disclosure Statement: The authors have nothing to disclose. No funding was received for this article.

Presented at:

The results of the manuscript are accepted for presentation at the Annual Meeting of the American Society of Plastic Surgery in San Diego on Friday, September 20th, 2019. In case of acceptance, please accept for publication after the congress date.

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