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References at the bottom are used in the answers to the reviewer's comments (the references used in the "changes in the text" sections are those that refer to the reference list of the original manuscript).

Reviewer A

The authors should be congratulated on performing the study and for applying these techniques in this challenging group of patients. Interesting paper, turning the oncologic/prophylactic and reconstructive pathway around. Please find enclosed the reviewer's comments

ABSTRACT

Presents the paper in a clearly written language and represent a digest of the content of the paper

INTRODUCTION/BACKGROUND

Comment 1: Presents a short work through of the literature. But fails to mention the more commonly used approach of performing a reduction/mastopexy without preshaping, followed by the skin-or nipple-sparing mastectomy. Moreover, there is no mention on the advantages of the preshaping (if any)

Reply 1: Dear colleague, I understand your point of view. This article deals specifically with staged approach in nipple sparing mastectomy and reconstruction in difficult breasts. I did not mention the discussion between immediate and staged approaches due to the technique used in this case series. However, I published a review in 2020 in JPRAS specifically on the outcome of immediate versus staged approach in difficult breasts (1). The last five years, the number of publications on this topic is growing, specifically because we encounter the difficulties in perfusion. The review shows a high overall complication rate of 29.08% and an tendence in

favor of staged procedures specifically in necrotic outcomes (skin envelope necrosis 1.43% versus 4.8% in immediate NSM in large breasts and NAC necrosis 0.48% versus 5.08 in immediate NSM in large breasts). However, most of the included publications are too small to draw significant conclusions. The advantage of preshaping the difficult breast is less necrosis.

References:

1. Tondu T, Hubens G, Tjalma WA, Thiessen FE. Breast reconstruction after nipple-sparing mastectomy in the large and/or ptotic breast: a systematic review of indications, techniques, and outcomes. *J Plast Reconstr Aesthet Surg*. 2020;73:469-485.

Changes in the text: line 113: Recent review shows tendence of less necrosis in a staged NSM approach (10)

ETHICS

Internal approval and written informed consent to participate in the study + photographs.

PATIENTS AND METHODS

Comment 2: The paper describes a rather low number of patients undergoing the procedure in the course of 7.5 years. The authors should mention why. Because the majority of the patients at the institution were undergoing autologous reconstruction (within the BMI-limit) and not implant-based or??? Judging from the clinical photos and the BMI-range mean 26.68 (19-35) some of the patients could have been offered autologous breast reconstruction. Judging from the information given the amount of co-morbidities in the patient population was not overwhelming…

Reply 2: The small amount of patients has several reasons. The indication is very limited, specifically in preventive surgery. Secondly the anatomy of our patients: most of our younger patients have an indication for an immediate approach in smaller, non ptotic breasts: in this population we perform a direct-to-implant reconstruction. We notice that the younger patients opt more for prosthetic

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reconstruction. Third: I completely agree that patients with larger breasts often have a good indication for a bilateral autologous reconstruction. We perform several DIEP flaps on a weekly basis. Nevertheless this specific population opted for a prosthetic reconstruction for several reasons: length of surgery, absence of donor scar, donor site morbidity, recovery period etc. Fourth: because of the risk of NAC necrosis in larger breasts: we always resect NAC in immediate primary DIEP flap reconstructions in large, ptotic breasts because the higher risk of NAC necrosis. I completely agree that several of the included patients had a good indication for autologous free flap reconstruction, but because of their objection and the demand of a nipple-sparing approach, we had to think of another solution.

Changes in the text:

Line 132-135: Although several patients also had an indication for autologous reconstruction, they opted for a prosthesis reconstruction because of length of surgery, absence of donor scars, no donor site morbidity and a shorter recovery period.

Surgical technique

Comment 3: First stage: the inferior pedicle is used for the mastopexy/reduction with maximal glandular resection – how is that defined in each individual? Expander placed subpectorally – please describe how – with release of the inferior border/ medial part of the muscle – and how much? Please provide the information from line 272 p 11 to the results section.

Reply 3: We use a dermal design width of 6 cm for an inferior dermoglandular pedicle (9). However, when incising the gland, we always notice that the glandular pedicle becomes smaller in width. From a safety point of view and referring to the anatomical studies of Van Deventer (2), this width is necessary to capture enough adequate perforators to supply NAC perfusion. The maximal glandular resection is performed as in a subcutaneous mastectomy, with infiltration of subcutaneous/ glandular plane. At the lateral border of the pedicle, the lateral pectoral border can be incised for the subpectoral insertion of the tissue expander. I added an extra figure with preoperative markings:

Figure: this becomes Figure 1 in the manuscript and the others are renumbered.

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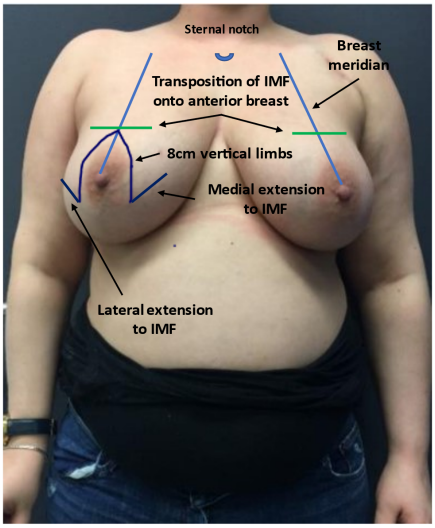

Changes in the text:

Line 159-160: The inferior pedicle has a width of 6 cm and preserves the anterior intercostal branches 4 to 6 originating from the internal thoracic artery

Line 162 to 164: The breast gland, besides the pedicle, is removed by scissors as in a subcutaneous mastectomy with infiltration of 0.5% of lidocaine and 1:200,000 epinephrine mixture, focusing on the dissection plane.

line 170 to 172: The expander is inserted through the lateral pectoral border and is completely covered by muscle. The inferior border and medial lower 1/3 of the pectoral muscle are released.

Line 210-211: The average filled expander volume was 396,3 cc (range 250 to 550 cc).

References:

2. Van Deventer PV. The blood supply to the nipple-areola complex of the human mammary gland. *Aesthet Plast Surg*. 2004;28:393-398.

Comment 4: Second stage: nipple sparing mastectomy/remaining glandular pedicle + exchange of expander to implant – is the definitive implant placed subpectorally again? Please specify. Would it have been beneficial to use an ADM in the second stage – decreasing the rate of capsular contracture??

Reply 4: The definitive implant is placed subpectorally. An ADM could have been used, but is not reimbursed in Belgium by health insurance, public nor private. The

cost per breast is around 1500 USD. Although an ADM may be beneficial for capsular contracture, it is until now not state of the art in reconstructive procedures because of its cost. Nevertheless we only report on 2 cases of Baker III contracture.

Changes in the text:

Line 183: subpectoral

Comment 5: How was the perfusion assessed in the individual surgeries? Clinical assessment in both procedures. Could indocyanine green angiography add any extra benefit? Comments, please including reference(s)?

Reply 5: Perfusion assessment was only clinical: skin color and capillary refill. I am absolutely convinced that ICG adds an extra benefit in the intra-operative evaluation. Absence or decrease of ICG fluorescence in NAC predicts necrosis (3). The first description, proving vascular NAC supply through a circumareolar scar by ICG, is by Alperovich in 2013 in 13 procedures (4). Strangely enough, in the key articles by Wapnir (5) and Dua (6), only 18% and 19% of NAC are directly perfused through the gland in contrast with the advantageous effect of two-staged techniques on NAC necrosis (1). Limitations of their studies is that we don't have any information on the size of the breasts. One could presume from their findings that, when NAC/ICG assessment preoperatively shows perfusion from the surrounding skin (V2) rather than from the underlying gland (V1), NSM could be performed with immediate reconstruction and Wise pattern incision, saving NAC's dermal blood supply on dermal pedicles. Our review on this indication has shown differently (1). Personally I would not be very enthusiastic for this immediate technique. Our review showed already the difference in necrosis outcome (1). Gunnarson (7), Alperovich (4), Spear (8) and our present series show the strength of delayed preconditioning of NAC. Even more, if only a small percentage of NAC is dominantly perfused through the gland, why don't we see much more NAC necrosis in breast reduction procedures, relying on glandular pedicles? Or is NAC perfusion dynamically adaptable? Does perforator perfusion take-over from the moment that dermal perfusion to NAC is blocked as it is done in a reduction pedicle? If so, is this triggered by distal ischemia at the end of the reduction pedicle where NAC is positioned ? From the above series, we know that the opposite is true. Prior breast reduction provides enough dermal neoperfusion through the circumareolar NAC scar to avoid necrosis: no

necrosis is seen in our series, neither in Gunnarson's series (4,7,8). The only condition is that one delays at least three to four months between both stages. Finally, I can suggest in the article that we could use ICG as an extra benefit, but since we did not use it (we lacked the ICG scanner in that era), it is perhaps not an extra added value to our article?

Changes in the text:

Line 266-273: NAC and skin flap evaluation in our study is only performed clinically, based on color and capillary refill. An additional tool in assessment of skin flap and NAC viability is the intraoperative use of near-infrared fluorescence angiography (27). Indocyanine green (ICG) was used as fluorescence dye. ICG angiography qualitatively shows the presence of dermal perfusion in real-time (28). Gorai et al. show a significant decrease in full thickness necrosis from 17.8% to 4.8% with the use of ICG angiography-guided skin trimming (29). In pedicled perforator flaps or for large skin paddles, intraoperative ICG angiography is strongly correlated with postoperative outcomes (30).

References:

3. Johnson AC, Solacoglu S, Chong TW, Mathes DW. Indocyanine green angiography in breast reconstruction: utility, limitations and search for standardization. Plast Reconstr Glob Open 2020; 8(3): e2694.
4. Alperovich M, Tanna N, Samra F, et al. Nipple-sparing mastectomy in patients with a history of reduction mammoplasty or mastopexy: how safe is it ? Plast Reconstr Surg. 2013; 131: 962-967.
5. Wapnir I, Dua M, Kieryn A, et al. Intraoperative imaging of nipple perfusion patterns and ischemic complications in nipple-sparing mastectomies. Ann Surg Oncol. 2014;21(1):100–106
6. Dua M, Bertoni DM, Nguyen D, et al. Using intraoperative laser angiography to safeguard nipple perfusion in nipple-sparing mastectomy. Gland Surg. 2015;4(6):497–505.

7. Gunnarson GL, Bille C, Reitsma LC. Prophylactic nipple-sparing mastectomy and direct-to-implant reconstruction of the large and ptotic breast: is preshaping of the challenging breast a key to success? Plast Reconstr Surg. 2017;140:449-454.
8. Spear SL, Rottman SJ, Seiboth LA, Hannan CM. Breast reconstruction using a staged nipple-sparing mastectomy following mastopexy or reduction. Plast Reconstr Surg. 2012;129:572-581.

RESULTS

Comment 6: The weight of the resections has a rather large range in 1. and 2. stage procedures. There is no information regarding the per-operative or final expansion volume – please provide.

Reply 6: The range is large because some breast were very ptotic and not that voluminous as others presented important breast hypertrophy. All expanders are intra-operatively filled with 120 cc of saline.

Changes in the text:

Line 172: After insertion, the expander is filled with 120cc of saline.

Line 210-211: The average filled expander volume was 396,3 cc (range 250 to 550 cc).

Comment 7: Did the resection weight in stage 1 and 2 correlate to the BMI, to the final volume of the expander or to the final volume of the definitive implant – please provide data and/or results.

Reply 7: I provided the data of the patients in an extra table 2.

Changes in the text: Table 1 will be added to the manuscript

Comment 8: The follow-up is stated to be from 4-11 years – is it follow-up from first or second stage procedure....

Reply 8: Follow up is from the second procedure.

Changes in the text:

Line 237-238: Follow up ranged from four to eleven years, after the second stage.

Comment 9: The authors report 10 complications in 41 procedures – were the

complications reported per breast or per patient – please specify in Table 1 and in the text. Moreover, the information on the complications (line 240 p 11), should be presented in the results section.

Reply 9: The complication are per procedure (per breast).

Changes in the text: Table 1. Patient characteristics and complication rates per breast in two stages (NA=Not Applicable)

And line 236: (table 2: complications per procedure).

And line 231-234: In our series three out of five reports of epidermolysis occur in the only two smoking patients (one of these two patients has a complete epidermolysis of NAC as well as an epidermolysis of the distal skin flap at the inverted T-point).

DISCUSSION

Comment 10: Please clearly state why the superior/superior pedicle was not used – several papers have shown this pedicle to be the safer one.

Reply 10: According to Van Deventer (2), the internal thoracic artery is the main and constant contributor of blood to the NAC by means of its perforating branches 1 to 4 and anterior intercostal branches 4 to 6. The most important are the branches originating from intercostal spaces 3 and 4. The anterior intercostal branches 4 to 6 run from the medial costochondral rib junction through the pectoral muscle into the inferomedial pedicle.

The idea of subpectoral tissue expander placement comes from the one stage augmentation/mastopexy I perform for the last 16 years. The use of a broad inferior pedicle includes these branches (Van Deventer describes this pedicle as inferomedial). Careful release of the medial inferior 1/3 of the pectoralis muscle possibly saves most of these anterior intercostal branches. Secondly the muscular perforators of pectoral muscle are included. Van Deventer also shows us interaction between branches derived from the lateral thoracic artery and the internal thoracic artery. Following this idea, one can easily release the inferior insertion of the pectoral muscle: these major cutaneous perforators are not the main source of pedicle perfusion (2). Nevertheless, when the inframammary fold can be kept intact, these perforating branches can add to the inferior pedicle perfusion. This is the same idea as in the one stage augmentation/mastopexy by Rod Rohrich. The use of an 8 cm wide inferior pedicle (we use 6 cm) includes the anterior intercostal

branches in his inferocentral pedicle and allows an eventless insertion of a definite breast prosthesis through the lateral pectoral border, immediately lateral from his inferior pedicle. He reports no NAC loss (9). Recently Jensen described in PRS Global Open a hybrid delay in 6 breasts (10): he uses an inferior dermoglandular pedicle and in the same first stage, he places the expander superior to the pedicle and above the muscle. Our case series is the first to describe a similar hybrid delay successfully in 41 procedures: we differ from Jensen in placing the expander subpectorally. If the same kind of approach is uneventful in augmentation/mastopexy, it is also a safe approach for reconstruction, since we use the same pedicle and the same implant/ tissue expander position.

Anatomically, based on Van Deventer's findings, one could consider the superior approach less safe: the inferomedial pedicled gland is a direct arterialized perforator flap whereas the superior pedicle should be considered as a randomly perfused flap (2): "In 21 of the 27 breasts dissected, the NAC did not receive blood vessels superiorly. Therefore, a superiorly based flap would, in most cases, be considered random. Blondeel (11) reported incidences of 7.3% for partial nipple necrosis and 2.1% for complete necrosis of the NAC for patients in whom they used a superodermal pedicle (2)." Nevertheless, Gunnarson reports no NAC failure in 42 breasts using a superior pedicle (7).

Changes in the text:

Line 159-160: The inferior pedicle has a width of 6 cm and preserves the anterior intercostal branches 4 to 6 originating from the internal thoracic artery

Lie 289-301: The tissue expander can be safely placed in the same procedure as the inferior pedicle breast reduction (13,37). The internal thoracic artery is the main and constant contributor of blood to the NAC by means of its perforating branches 1 to 4 and anterior intercostal branches 4 to 6. The most important are the branches originating from intercostal spaces 3 and 4. The anterior intercostal branches 4 to 6 run from the medial costochondral rib junction through the pectoral muscle into the inferomedial pedicle. Secondarily it receives lateral mammary branches from the lateral thoracic artery that form an anastomotic ring with the internal thoracic branches superior and inferior of NAC (14). In addition, there is random

vascularization in the lower glandular part of the pedicle, which may be provided by the lower intercostal branches (14,38). However, Palmer and Taylor identify fixed skin areas around the perimeter of the pectoralis major muscle and the submammary fold. Major cutaneous perforators emerge in these areas, referred to as hypervascular zones (39).

References:

9. Beale EW, Ramanadham S, Harrison B, Rasko Y, Armijo B, Rohrich RJ. Achieving predictability in augmentation mastopexy. Plast. Reconstr. Surg. 2014;133:284e-292e, 2014.
10. Jensen JA, Giuliano AE. The hybrid delay: a new approach for nipple-sparing mastectomy in macromastia. Plast Reconstr Surg Glob Open 2020;8:e2940; doi: 10.1097/GOX.0000000000002940.

Comment 11: Please discus the other means of evaluating flap/skin perfusion.

Reply 11: I discussed the use of ICG since thermography is less practical in the evaluation of NAC perfusion. Thermographic images can be obtained after cooling the tissue locally. This makes it less useful in this setting. Moreover, ICG dermal perfusion mapping almost anatomically shows perfusion inflow as well as perfusion adequacy, expressed in absolute units or relative percentages (percentage of fluorescence of the measured point compared with the brightest fluorescent point on the screen).

Changes in the text:

Line 266-273: NAC and skin flap evaluation in our study is only performed clinically, based on color and capillary refill. An additional tool in assessment of skin flap and NAC viability is the intraoperative use of near-infrared fluorescence angiography (27). Indocyanine green (ICG) was used as fluorescence dye. ICG angiography qualitatively shows the presence of dermal perfusion in real-time (28). Gorai et al. show a significant decrease in full thickness necrosis from 17.8% to 4.8% with the use of ICG angiography-guided skin trimming (29). In pedicled perforator flaps or for large skin

paddles, intraoperative ICG angiography is strongly correlated with postoperative outcomes (30).

Comment 12: Could the perforating branches of the internal thoracic artery have been spared – please comment?

Reply 12: In the last version of the manuscript I noticed that "The subpectoral expander will only damage the branches of the intercostal arteries. " was wrongly expressed. I meant the major cutaneous branches in the IMF hypervascular zone, keeping the IC branches in the medial IC area intact. I changed the manuscript accordingly and made the anatomy more clear (I included references). Damaging the medial intercostal branches in a large inferior pedicle would possibly jeopardize the inferior pedicle. Thank you for pointing out this anatomical mistake.

Changes in the text:

Line 289-301:

The tissue expander can be safely placed in the same procedure as the inferior pedicle breast reduction (13,37). The internal thoracic artery is the main and constant contributor of blood to the NAC by means of its perforating branches 1 to 4 and anterior intercostal branches 4 to 6. The most important are the branches originating from intercostal spaces 3 and 4. The anterior intercostal branches 4 to 6 run from the medial costochondral rib junction through the pectoral muscle into the inferomedial pedicle. Secondarily it receives lateral mammary branches from the lateral thoracic artery that form an anastomotic ring with the internal thoracic branches superior and inferior of NAC (14). In addition, there is random vascularization in the lower glandular part of the pedicle, which may be provided by the lower intercostal branches (14,38). However, Palmer and Taylor identify fixed skin areas around the perimeter of the pectoralis major muscle and the submammary fold. Major cutaneous perforators emerge in these areas, referred to as hypervascular zones (39).

Comment 13: Line 272 p 11: if the pectoralis major is not released along its inferior border, how is the expander kept in the lower position, favoring the expansion of the inferior pole?

Reply 13: The pectoralis major muscle is released along its inferior border, but not transsected. The expander is only filled in the first stage with 120 cc of saline.

Because the insertion is not transsected, the expander may be high riding (1 to 2 cm) during the inflation period. However, when replacing it by a definite prosthesis in the second stage, the newly formed capsule is always incised on its lowest border, allowing the definitive prosthesis to position itself lower, at the height of the IMF. Until now, we never had to revise a patient for a high riding prosthesis.

Comment 14: Lines 286-295 p 12: ADM might have been useful in the second stage surgery. For instance if the implant-position was changed from subpectoral to prepectoral – please comment on breast animation deformity and implant-related discomfort. Please also comment on the advantages of using ADM to mitigate/lower the rate of capsular contracture. The authors state in lines 294-295 that not using ADM may lower the risk of infection – please comment on vascularity of the skin envelope and the safety of using ADMs and please provide references for the former statement.

Reply 14: In our patient population there was no report on breast animation deformity. One patient reported implant-related discomfort. Her reconstruction was converted to a bilateral autologous reconstruction. We did not actively inform about implant-related discomfort: the one reported patient spontaneously mentioned her discomfort. This bothered her that much that she wanted both implants removed. Therefore, I did not write that there was no implant-related discomfort nor breast animation deformity.

We did not actively check on breast animation deformity (BAD). I realize that BAD surely will be present in our reconstructed patient group. Since the article is focused on the reliability of the technique, more specific on the vascular safety of skin flaps and NAC, I did not actively inform about BAD. Surely prepectoral placement will diminish BAD, because the only sure factor that contributes to BAD is the retropectoral placement of the prosthesis. Would a subpectoral placement with an inferiorly placed ADM diminish BAD? Not according to Fracol and Kim (18): they saw an increase in BAD with an added ADM. I completely agree with the ideas of Scott Spear (18): keeping the inferior pectoral insertion intact surely diminishes BAD. Therefore, we start with a flat expander, only filled for 120 cc. In this way the capsule

in the lower pole fastly adheres to the lower muscle border. I do not transect the inferior pectoral insertion completely, but by incision of the distal adherence to the upper part of the rectus abdominis fascia, one can gently push the inferior pectoral muscle fiber adhesions more inferiorly. In this way, some attachment of the inferior pectoral muscle remains and the capsule progressively is formed, creating a pocket that is about 1 cm lower than the inferior pectoral insertion. In the second stage, the muscle and the capsule have been expanded. Quite often release of the inferior border of the capsule creates this extra 1 to 2 cm that is necessary to position the definite prosthesis on the level of the inframammary fold. If this is not enough, we indeed have to transect the complete inferior insertion of the pectoral muscle with a higher risk of noticeable BAD.

Although staged delay perfectly permits to change from subpectoral to prepectoral position, it was not performed. We recently started preshaping large breasts before NSM followed by autologous reconstruction, with free flaps prepectorally positioned in the second stage. Although small in series (10 patients), no necrosis of NAC is reported until now. First, out of precaution we did not consider prepectoral prosthesis placement and ADM use. Second, ADM is not reimbursed in Belgium and has an important additional cost. In 2016 we had a huge political debate on breast reconstruction. Public opinion considered reconstruction completely covered by national health insurance without extra cost for the patient. Finally all types of breast reconstruction got completely reimbursed without any extra cost, besides ADM since no evidence based advantage could be shown. Until now, ADM is still not reimbursed and debate has gone silent because of Covid 19.

Both considerations brought us back to the safety issue: what if skin flaps brake down in large ptotic breasts? In this present technique, the capsule around the tissue expander works an ADM during both stages. In the second stage, we are clinically sure that our skin flaps as well as NAC are well perfused. Possible high riding expanders can be lowered by incision the inferior border of the capsule before definite prosthesis placement.

In addition one could add that intraoperative assessment of perfusion of skin flaps and NAC reinforces this safety issue. Your remark on ICG assessment is correct: it took us 4 years to negotiate with the hospital to buy a NIR-ICG scan which we finally

did. Its use will be implemented in our reconstruction protocol on arrival of the device in the hospital (and also in free flap surgery, trauma etc).

Capsular contracture:

In our series, two Baker 3 contractures were reported. This is within the range of capsular contracture reported with silicone implants (3-25%) (11). In 2016 Lee's meta-analysis on evidence for ADM use in breast reconstruction reinforced the benefit of decreased capsular contracture with ADM use (12). A separate meta-analysis of studies over the past decade further supports the finding of ADM associated decreased capsular contracture rates, citing the incidence of capsular contracture with ADMs at 0.6% by a pooled analysis of 16 studies (13). Nevertheless, referring to the above, although an ADM could be an additional tool in lowering the chance on capsular contracture, with the published evidence, a national task for could bring this discussion back on the Belgian political table.

Not using an ADM lowers infection rate:

We reported two infections (2/41 procedures) that resolved under oral antibiotics.

"Tissue grafts are foreign to the host, and postoperative complications following ADM insertion, including infection and seroma, have been well documented. When considering using ADM's in this setting, it is important to first consider patient-specific factors that could preclude their use, such as low body mass index, small breasts, or a history of radiation exposure to the breast tissue" (13). Zhao found that incorporation of ADMs increased the incidence of overall complications: the same study showed the rates of infection after ADM use to be 8.9 versus 2.1% for those patients who did not receive ADM (14). Kim et al showed an increased rate of total complications, seroma, infection, and flap necrosis in cases using human ADMs when compared with submuscular reconstructions (15). Lee performed a meta-analysis of 23 studies comparing the outcome of ADM use with traditional submuscular technique and reported significantly enhanced risks of infection and seroma with ADM use (16). Referring to the above, we also concluded that, if we would use an ADM and the patient had to pay it herself, it had to add an extra advantage/value to our technique. Because they were high-risk patients (Spear's Georgetown algorithm with anatomical contra-indications hypertrophy and ptosis), because the risk of

wound dehiscence existed in the inverted T, because we could only clinically evaluate the skin flap perfusion, because there remained a potential risk of NAC necrosis, why add the extra risk of an extra foreign body, besides the prosthesis/expander, with a significantly higher risk for infection? Therefore, we counted on the small and flat volume of the tissue expander, positioned under the muscle, completely covered by the muscle and overlied by a direct vascularized inferior dermoglandular pedicle flap. We counted on the capsule that would be formed and could act as a natural ADM in the lower outer pole of the pectoral muscle. Incising this capsule in its outer lower quadrant in the second stage, is safe because the overlying skin flaps have been proven well vascularized and moreover, they are challenged and delayed in the first stage. All the above made us conclude in this case series, not to use an ADM.

Safety of ADM:

I refer to the above explanation under ADM and infection.

Skin envelope and vascularity:

Breast reduction skin flaps are random flaps: there is no constant position of the arterial inflow (2). However, Van Deventer points out the importance of the intercostal branches (2 to 6) of the internal thoracic artery as well as perfusion by branches of the lateral thoracic artery. Most of these medial branches can be included in the medial skin flap; the lateral branches have a more inconsistent appearance. The medial intercostal perforating branches run very superficially between the gland and (within) the subcutaneous fat, at a maximal depth of 1.5 cm (2). Hydrodissection of the surgical glandular plane can prevent damage to these branches. An intraoperative visualization of skin flap perfusion would indeed add to the safety of the procedure. Interestingly a technical paper in PRS Global Open 2020 by Parus supports the idea of an ADM-wrapped prepectoral tissue expander in 12 breasts, covered by a wide dermal inferior NAC bearing flap. They completely rely on the intra-operative ICGA result of the inferior random dermal flap (17): the hypervascularized inframammary branches described by Palmer and Taylor, are not consistent and are no specific proven vascular source for NAC (18). I understand their technique, but our technique is more consistent in perfusion, because the inferior dermoglandular flap is anatomically arterialized and proven reliable (9).

Disadvantage is the two stages and the possible BAD and discomfort. Disadvantage of an one-stage inferior dermal flap that has to be assessed on perfusion intra-operatively, is the risk that a patient can wake up without a nipple: the patient has to be well informed that possibly a plan B has to be considered surgery.

Changes in the text:

Line 333: second stage and also avoids a major cost (44,45).

Line 334-338: One patient reports implant-related discomfort. Our study patients are not routinely checked for breast animation deformity (BAD), only when this is causing discomfort. However, we know that in reconstructive patients BAD is reported up to 80% with moderate to severe deformity (46,47). Further long-term outcome study will show BAD-severity of our reported technique.

Line 323-330: Gravina's meta-analysis supports the finding of ADM associated decreased capsular contracture rates, citing the incidence of capsular contracture with ADMs at 0.6% by a pooled analysis of 16 studies (42). Breast reduction skin flaps are random flaps, supplied by intercostal branches (2 to 6) of the internal thoracic artery as well as branches of the lateral thoracic artery (43): hypoperfusion can be noticed at their most distal flap end (inverted T point). However, poor vascular supply together with an acellular dermal matrix may be attractive for bacterial growth.

References:

11. Salzberg CA, Ashikari AY, Berry C, Hunsicker LM. Acellular dermal matrix-assisted direct-to-implant breast reconstruction and capsular contracture: a 13-year experience. Plast Reconstr Surg 2016; 138(02):329–337
12. Lee K-T, Mun G-H. Updated evidence of acellular dermal matrix use for implant-based breast reconstruction: a meta-analysis. Ann Surg Oncol 2016;23(02):600–610.
13. Gravina PR, Pettit RW, Davis MJ, Winocour SJ, Selber JC. Evidence for the use of acellular dermal matrix in implant-based breast reconstruction. Semin Plast Surg 2019;33:229-235.
14. Chun YS, Verma K, Rosen H, et al. Implant-based breast reconstruction using acellular dermal matrix and the risk of postoperative complications. Plast

Reconstr Surg 2010;125(02):429–436.

15. Kim JY, Davila AA, Persing S, et al. A meta-analysis of human acellular dermis and submuscular tissue expander breast reconstruction. Plast Recons Surg 2012;129(01):28–41.
16. Lee K-T, Mun G-H. Updated evidence of acellular dermal matrix use for implant-based breast reconstruction: a meta-analysis. Ann Surg Oncol 2016;23(02):600–610.
17. Parus A, Venturi ML. A strategic approach to nipple-sparing mastectomy reconstruction with a wide based inframammary fold flap. Plast Reconstr Surg Glob Open 2020;8:e3053; doi: 10.1097/GOX.0000000000003053.
18. Palmer JH, Taylor GI. The vascular territories of the anterior chest wall. Br J Plast Surg. 1986;39:287–299.

CONCLUSION

Comment 15: Lines 303-304 – this statement is only true for the patients described in this paper. As this is a retrospective, low patient number-study, firm conclusions may not be drawn.

Reply 15: I agree that the series is small and retrospective. However, several publications in the last five years try to find a solution for the problem of NSM in difficult breasts.

Gunnarson (7): “Targeted preshaping mastopexy/reduction of the large, ptotic and deformed breast prior to NSM/ SIR has proven to be a successful method to overcome the drawbacks of the procedure for this challenging group of patients”

Jensen (10): “Thus, nipple sparing can be accomplished in this high-risk group in 2 procedures without compromising oncologic safety, as all patients are left with complete oncologic mastectomies.”

Spear (8): “Having demonstrated a level of safety with the staged approach comparable to that of nipple-sparing mastectomy, we are comfortable offering this procedure to patients with moderately large or ptotic breasts. Nipple-sparing mastectomy may not be suitable for the very large or ptotic breast but may be possible using this staged approach.”

Changes in the text:

Line 346: In our series, preshaping of the large breast in a delayed NSM creates the ideal anatomical criteria for a reliable necrosis-free two-stage expander-to-prosthesis reconstruction.

Comment 16: Lines 306-307: None of the data presented in the paper may support this statement as no aesthetic follow-up or questionnaires is provided.

Reply 16: I presume you mean the statement at line 296: "Aesthetic outcome is pleasing without extra donor-site scars." I agree with your remark. I changed it accordingly.

Changes in the text:

Line 339: Staged NSM avoids extra donor-site scars.

Comment 17: Lines 314-315: none of the patients seem to have more than one co-morbidity. The patients with BMI < 30 may have been candidates for autologous reconstruction.

Reply 17: I completely agree. Autologous reconstruction was proposed to these patients, but refused because of length of surgery, hospital stay, overall recovery, extra donor site scars etc.

Reviewer B

I think this paper is well written introduce an interesting concept in challenging situtations (NSM in large ptotic breasts) and deserve publication with minor revisions, which will have to be accomplished before publications.

questions to the authors that need to be answered:

methods

Comment 18: Which was the follow-up for these patients?

Reply 18: Follow up ranged from four to eleven years.

Changes in the text:

Line 237-238: Follow up ranged from four to eleven years, after the second stage.

Comment 19:

Do you think there is an increased risk to “leave behind” same glandular tissue with this two-stage mastectomy approach?

Reply 19: According to the few available articles on remaining glandular tissue after nipple-sparing mastectomy, it is sure that glandular tissue is left behind. In 1973, Goldman and Goldwyn found residual glandular tissue in 83% of NSM: they performed 12 NSM procedures in cadavers through an IMF incision (19). More recently, in 1991, Barton compared 27 classic mastectomies with 28 NSM: he found no differences between the number of biopsies containing residual breast glandular tissue after conservative mastectomy (22%) and after total mastectomy (21%) (20). More specifically, breast cancer evolves from terminal duct lobular units (TDLU)(21). In 2005, Torresan reported that the risk of finding TDLU’s strongly increased for skin flaps thicker than 5 mm (22). At the level of NAC, the presence of TDLU’s varies from scarce to 26% and up to 61% (23,24,25). In a series by Van Verschuer, 21 primary breast cancers occurred after 6,044 prophylactic mastectomies. Of these, three occurred after a total mastectomy (0.6% of all total mastectomies), 17 occurred after a conservative mastectomy (0.3% of all subcutaneous mastectomies, NSM or SSM) in 24 studies (21). Van Verschuer points out that the majority of primary breast cancers did not originate near the NAC or skin flap. The 21 loco-regional primary breast cancers after 6,044 prophylactic mastectomies correspond with an incidence of 0.7% per woman who undergoes bilateral prophylactic mastectomy (0.35% per mastectomy). Most breast cancers that developed after conservative mastectomy were found at the chest wall or in the axilla. However, skin-flap and chest wall are in direct contact. Therefore, it is possible that the breast cancers developing at the chest wall, actually did originate in the skin flap. The surgical technique of SSM and NSM using small peri-areolar or inframammary incisions can be challenging. A suboptimal exposure may impede thorough removal of remaining breast glandular tissue in all quadrants and in the axillary tail (21). The classic inferior pedicle breast reduction approach in our technique creates a wide exposure of the complete breast gland, even the axillary tail can be properly approached in the first stage. In order to achieve the right dissection plane between gland and subcutaneous fat, we use

tumescent infiltration of 0.5% of lidocaine and 1:200,000 epinephrine mixture before incision. This not only reduces diffuse bleeding. Hydrodissection will also make it easier to dissect in the right plane. Nevertheless, glandular tissue will maintain to occur outside the dissection plane, in NSM as well as in classic mastectomy (26).

References:

19. Goldman LD, Goldwyn RM. Some anatomical considerations of subcutaneous mastectomy. Plast Reconstr Surg 1973;51:501-5.
20. Barton FE Jr, English JM, Kingsley WB, et al. Glandular excision in total glandular mastectomy and modified radical mastectomy: a comparison. Plast Reconstr Surg 1991;88:389-92; discussion 393-4.
21. Van Verschuer VMT, Maijers MC, Van Deurzen CHM, Koppert LB. Oncological safety of conservative breast surgery: skin-sparing and nipple-sparing versus total mastectomy. Gland Surg 2015;4(6):467-475
22. Torresan RZ, dos Santos CC, Okamura H, et al. Evaluation of residual glandular tissue after skin-sparing mastectomies. Ann Surg Oncol 2005;12:1037-44.
23. Stolier AJ, Wang J. Terminal duct lobular units are scarce in the nipple: implications for prophylactic nipple-sparing mastectomy: terminal duct lobular units in the nipple. Ann Surg Oncol 2008;15:438-42.
24. Kryvenko ON, Yoon JY, Chitale DA, et al. Prevalence of terminal duct lobular units and frequency of neoplastic involvement of the nipple in mastectomy. Arch Pathol Lab Med 2013;137:955-60.
25. van Verschuer VM, van Deurzen CH, Westenend PJ, et al. Prophylactic nipple-sparing mastectomy leaves more terminal duct lobular units in situ as compared with skinsparing mastectomy. Am J Surg Pathol 2014;38:706-12.
26. Bille C, Dalaei F, Thomsen JB. Identifying the dissection plane for mastectomy: description and visualization of our technique. Gland Surg 2019;8(Suppl 4):S276-S280 | http://dx.doi.org/10.21037/gs.2019.05.04

Comment 20: Does the complementary NSM mastectomy results in any complexity.

Reply 20: The complementary NSM in the second stage is straight forward. The immediate postoperative result after the first stage looks a bit strange: inner and

outer breast pole are empty; only skin flaps remain without any glandular filling. In the middle, the 6 cm wide pedicle remains. Since the initial position of NAC is referred to by the breast meridian (classic Wise pattern design), medial and lateral skin flap are brought together over the inferior pedicle on this meridian to create the vertical component of the Wise pattern. The pedicle underneath these skin flaps is positioned 3cm laterally and medially from this line. This makes it easier in the second stage to remove at least 3 cm of gland on each side of the vertical scar. Of course this is not an arbitrary measurement: intra-operatively you clearly recognize the scar tissue of the first surgery at the borders of the pedicle. Even more, one can clearly see the absence of glandular tissue laterally and medially from the pedicle, where the subcutaneous fat is sticking to the pectoral muscle. Secondly, complete muscular coverage of the tissue expander makes it easier to follow the muscular plane underneath the pedicle in the second stage, when removing this pedicle.

Comment 21: Do you infiltrate before mastectomy?

Reply 21: Yes, see reply 19.

Comment 22: Does cautery or scissors perform this.

Reply 22: We use scissors after tumescence, because in the scissors tip, one is able to feel the difference of the harder gland versus the softer subcutaneous fat.

The surgical technique paragraph should be improved by these details

Changes in the text:

Line 237-238: Follow up ranged from four to eleven years, after the second stage.

Line 162-164: The breast gland, besides the pedicle, is removed by scissors as in a subcutaneous mastectomy with infiltration of 0.5% of lidocaine and 1:200,000 epinephrine mixture, focusing on the dissection plane.

Line 192-202: The classic inferior pedicle breast reduction approach in our technique creates a wide exposure of the complete breast gland, even the axillary tail can be properly approached in the first stage. Nevertheless, glandular tissue will occur outside the dissection plane, in NSM as well as in classic mastectomy (15). The risk of finding terminal duct lobular units strongly increased for skin flaps thicker than 5 mm (16). In a series by Van Verschuer, 21 primary breast cancers occurred after

6,044 prophylactic mastectomies. Of these, three occurred after a total mastectomy (0.6% of all total mastectomies), 17 occurred after a conservative mastectomy (0.3% of all subcutaneous mastectomies, NSM or SSM) in 24 studies (17). Van Verschuer points out that the majority of primary breast cancers did not originate near the NAC or skin flap.

Discussion

Comment 23: Why did you prefer an inferior pedicle for the NAC transposition for your first stage surgery? Any reason not to use a superior pedicle based mastopexy (e.g. I wonder if the inf pedicle better protects the T-junction over the pec major from dehiscence?)

Reply 23: According to Van Deventer (2), the internal thoracic artery is the main and constant contributor of blood to the NAC by means of its perforating branches 1 to 4 and anterior intercostal branches 4 to 6. The most important are the branches originating from intercostal spaces 3 and 4. The anterior intercostal branches 4 to 6 run from the medial costochondral rib junction through the pectoral muscle into the inferomedial pedicle.

The idea of subpectoral tissue expander placement comes from the one stage augmentation/mastopexy I performed for the last 16 years. The use of a broad inferior pedicle includes these branches (Van Deventer describes this pedicle as inferomedial). Careful release of the medial inferior 1/3 of the pectoralis muscle possibly saves most of these anterior intercostal branches. Secondly the muscular perforators of pectoral muscle are included. Van Deventer also shows us interaction between branches derived from the lateral thoracic artery and the internal thoracic artery. Following this idea, one can easily release the inferior insertion of the pectoral muscle: these major cutaneous perforators are not the main source of pedicle perfusion (2). Nevertheless, when the inframammary fold can be kept intact, these perforating branches can add to the inferior pedicle perfusion. This is the same idea as in the one stage augmentation/mastopexy by Rod Rohrich. His use of an 8 cm wide inferior pedicle includes the anterior intercostal branches in his inferocentral pedicle and allows an eventless insertion of a definite breast prosthesis through the lateral pectoral border, immediately lateral from his inferior pedicle. He reports no NAC loss (9). Recently Jensen described this approach in PRS Global Open

as hybrid delay in 6 breasts (10): Jensen's approach only differs from our case series in placing the expander prepectoral and superior from the inferior pedicle. Our series is the first to describe this hybrid delay successfully in 41 procedures with retropectoral placement of the expander: according to the above anatomy, the medial intercostal branches are safed and the expander can be safely inserted behind the muscle.

Anatomically, based on Van Deventer's findings, one could consider the superior approach as less safe: the inferomedial pedicled gland is a direct arterialized perforator flap whereas the superior pedicle should be considered as a randomly perfused flap (2): "In 21 of the 27 breasts dissected, the NAC did not receive blood vessels superiorly. Therefore, a superiorly based flap would, in most cases, be considered random. Blondeel (11) reported incidences of 7.3% for partial nipple necrosis and 2.1% for complete necrosis of the NAC for patients in whom they used a superodermal pedicle (2)." Nevertheless, Gunnarson reports no NAC failure in 42 breasts using a superior pedicle (7).

Changes in the text:

Line 159-160: The inferior pedicle has a width of 6 cm to preserve the anterior intercostal branches 4 to 6 originating from the internal thoracic artery (14).

Lie 289-301: The tissue expander can be safely placed in the same procedure as the inferior pedicle breast reduction (13,37). The internal thoracic artery is the main and constant contributor of blood to the NAC by means of its perforating branches 1 to 4 and anterior intercostal branches 4 to 6. The most important are the branches originating from intercostal spaces 3 and 4. The anterior intercostal branches 4 to 6 run from the medial costochondral rib junction through the pectoral muscle into the inferomedial pedicle. Secondarily it receives lateral mammary branches from the lateral thoracic artery that form an anastomotic ring with the internal thoracic branches superior and inferior of NAC (14). In addition, there is random vascularization in the lower glandular part of the pedicle, which may be provided by the lower intercostal branches (14,38). However, Palmer and Taylor identify fixed skin areas around the perimeter of the pectoralis major muscle and the

submammary fold. Major cutaneous perforators emerge in these areas, referred to as hypervascular zones (39).

Comment 24: In case of CDIS diagnosis before the first surgery, do you think it is still safe for patients to wait until the entire gland is removed?

Reply 24: There is still controversy about NSM. First of all, it would depend on the location of DCIS. When DCIS is diagnosed within the pedicle or close to NAC, it is not a good idea to perform this technique. One can alter the pedicle's position: Gunnarson reports no necrosis with a superior pedicle (7). When situated behind NAC (within 2 cm margin), a nipple-sparing approach is not a good idea. The discussion about NSM versus lumpectomy and radiotherapy is already pending for several years: this discussion alone is not only an important article on itself, but it would need very large prospective studies as well as large retrospective reviews. The main problem in this, is what to compare. Even in our own university hospital, it is still the source of lively discussion. This is the reason why I focused this article on the technique itself, but I am well aware that DCIS and even more early stage breast cancer, will remain subject of discussion. The second part of your question is whether we can wait. A safety margin of three months is taken in our technique as well as by Gunnarson (7) and Spear (8): this can be considered for preventive surgery or when DCIS is found in the resection specimen in the first stage. DCIS has to be removed with enough normal gland margin. We perform the same in oncoplastic surgery. One has to consider that in oncoplastic surgery, resection is followed by radiotherapy within four to six weeks. In our staged technique, one has to wait six weeks longer. Spear points out that he would perform the second stage already after 4 weeks, but in his article all patients undergo the second stage the earliest after 3 months (8). Until now, no one performed the second stage after 4 weeks. What if perfusion is not adequate after 4 weeks? It would not mean a serious problem in autologous reconstruction; however in prosthesis reconstructions it may result in a disaster or at least, in several stages of consecutive surgery and one could only hope that the prosthesis does not get infected.

When DCIS is well localized and no other lesions are shown, one can consider this technique: NCCN guidelines support mastectomy for pure DCIS (27). DCIS on more than one location is not an indication for this technique.

Considering all the above, it is wise, not only from a medicolegal point of view, to have an agreement of the oncologists and the breast surgeons, to perform this technique when a DCIS is diagnosed before the first stage. In our university breast clinic, this is mandatory before including a patient for this staged technique. With the above indication (unilocalized DCIS, distant from pedicle and NAC and intra-operatively proven complete resection on pathology and intra-operative X-ray of the specimen), we perform this staged technique when DCIS is diagnosed before the first stage.

References

27. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Updates in Version 4.2021 of the NCCN Guidelines for Breast Cancer:DCIS-1, https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf; 2021 (accessed 16 June 2021).

Comment 25: Line 264 when detailing the perfusion and the perforators nourishing the inferior pedicle please cite this work on different NAC perfusion pedicles in mastopexy: “Systematic review of outcomes and complications in nonimplant-based mastopexy surgery. Di Summa PG, Oranges CM, Watfa W, Sapino G, Keller N, Tay SK, Chew BK, Schaefer DJ, Raffoul W.J Plast Reconstr Aesthet Surg. 2019 Feb;72(2):243-272”

Reply 25: I cited the suggested work

Changes in the text:

Line 298: which may be provided by the lower intercostal branches (28,50).

Comment 26: Images

- Could you add pre-operative markings pictures?

Reply 26: I added an image with simulated preop markings, according to Scott Spear’s design of a Wise pattern design mastopexy.

Changes in the text:

Line 158-159: In the first stage, an inferior pedicle breast reduction with Wise pattern skin reduction was performed (13) (Figure 1).

Reviewer C

This is a very well planned and well written paper. I don't have many comments, and I congratulate you on your nice work.

However, I would like some technical clarifications. It is difficult to understand how exactly the first and second glandular excision are planned.

Comment 27: In the first stage, an inferior pedicle with wise pattern skin reduction is used. How do you plan the pedicle? Width? Thickness (is it dermal or dermoglandular)? Do you preserve the vessels of the breast septum?

Reply 27: The pedicle we use, is an inferior dermoglandular pedicle. It is the same pedicle as in an inferior pedicled breast reduction or mastopexy: I use Wise pattern markings according to Scott Spear's design of a Wise pattern design mastopexy (9). For the reader's convenience, I added an extra figure with preop simulated markings of the shown patient. The dermal width of the pedicle base is 6 cm. I preserve the vessels of the breast septum as described by van Deventer (2) in his cadaver study.

Changes in the text:

Line 158-159: In the first stage, an inferior pedicle breast reduction with Wise pattern skin reduction was performed (13) (Figure 1).

Comment 28: During the second stage, you describe that the vertical scar is re-used, and that the remaining glandular pedicle is resected. Do you preserve the inferior fat-dermal pedicle - and how do you avoid damaging that pedicle when using the vertical incision? (the inferior pedicle is right underneath that scar)

A short explanation or a schematic drawing would be sufficient.

Reply 28:

The anatomical key behind the two stage technique is not the pedicle itself. We just

need a reliable (preferably arterialized) pedicle for NAC to survive until the circumareolar neovascularization is sufficient. The key of the technique is the power of hypoxia-driven delay with neovascularization induction in the surrounding NAC scar. NAC is delayed at the distal end of the arterialized inferior dermoglandular pedicle and is subject to relative ischemia. This causes hyperemia in the pedicle, especially in its distal end. This relative hypoxia will also accentuate neovascularization in the circular scar around NAC. This same neovascularization will secondly be triggered by the relative hypoxia at the distal end of the medial and lateral random skin flap, although, according to van Deventer's cadaver results (2), branches of medial IC arteries 2-6 will make the medial skin flap less random. Keeping this idea in mind, the pedicle is of no use anymore after three months: the dermal neovascularization will perfuse NAC adequately, indepently from its inferior (or any other) pedicle. Therefore, there is no reason to save the inferior dermal pedicle: one can easily reuse the vertical scar to have a broad approach to the glandular pedicle as well as to the undersurface of NAC to resect all the necessary glandular tissue. We incise vertically through the inferior dermal pedicle. This also easily allows intra-operative pathology sampling of the retroareolar NAC surface.

Comment 29: Have you considered using a direct-to-implant reconstruction using dermal sling and nipple-areolar graft instead of a two-stage procedure?

Reply 29: Both dermal sling and NAC graft rely on random perfusion. Unfortunately I saw too many problems with hypoperfusion of NAC, wide dermal flaps, exposed prostheses. As a plastic surgeon, we are always questioned about suboptimal results or reconstructive results that fail. In a direct to implant reconstruction, the patient (public opinion) will never question the surgeon who performs the mastectomy, but always the surgeon that is not able to deliver a nice result in the same procedure. In small breasts, I admit, this is seldom a problem. In large breasts, this is the contrary: I refer to our review on NSM in large breasts. We reported on an overall complication rate of 29.08%. More specifically, " 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 15 immediate procedures show a higher total necrosis rate of 14.95 % compared with the multi-staged procedures (Table 4)."

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Reconstruction Type	Procedures (n=breasts)	Complications								TOTAL
		Wound-dehiscence	**Skin**		**Nipple-areola complex**			Infection	Hematoma	
			Epidermo-lysis	Necrosis	Epidermo-lysis	Partial Necrosis	Complete Necrosis			
Delay	419	13	0	6	16	9	2	10	6	62
%		*3,1*	*0*	*1,43*	*3,82*	*2,15*	*0,48*	*2,39*	*1,43*	*14,8*
Immediate	709	29	28	34	33	38	34	61	9	266
%		*4,09*	*3,95*	*4,8*	*4,65*	*5,36*	*5,08*	*8,6*	*1,27*	*37,52*
Total	1128	42	28	40	49	47	36	71	15	328
%		*3,72*	*2,48*	*3,55*	*4,34*	*4,17*	*3,19*	*6,29*	*1,33*	*29,08*

Table 4 : Complication rates in delayed versus immediate procedures (%=percentage of n procedures)

For your convenience, I included the table out of the preproof manuscript: in the official manuscript, the table is published in an oblique manner. The total amount of only necrosis in DTI reconstruction is almost 10%, as in a two staged procedure only 2% (1).

The dermal sling can be made more reliable when using intra-operative perfusion assessment tools as near-infrared perfusion mapping with indocyanine-green dye (ICGscan). The problem however remains that one will only know the adequate perfusion of the dermal sling intra-operatively. I feel more comfortable with the certainty of an adequate perfusion before planning surgery.

NAC graft will survive by imbibition, as any free graft does. Again, I feel more comfortable with the idea of an adequate perfusion in advance. I cannot rely on a publication, but in my practice I use inferior dermoglandular pedicles up to a sternal-nipple distance of 40 cm without necrotic problems. Whenever possible, I try to avoid grafts because of vascular unreliability.

Reviewer D

Comment 30: After inserting the tissue expander, I wonder how the inflation protocol was proceeded. If you have had full inflation from the expander insertion, please describe the difference between using the ADM and inserting the implant immediately.

Reply 30: After insertion, the tissue expander is filled with 120 cc of saline. Then we wait three weeks before starting to fill the expander. We aim to fill the expander by the patient's desired volume over a period of two months on a weekly basis before scheduling the second stage. The main reason is to allow the formed capsule to adapt to expansion: we want the capsule to expand together with the pectoral muscle because we don't use an ADM. I completely agree with you that a completely filled expander intra-operatively in the first stage has the same result as ADM with an immediate prosthesis. In Belgium, the use of an ADM is not reimbursed by health insurance: an unilateral ADM costs about 1500 USD. This is also one of the reasons why we had to think about another solution for these indications.

Secondly, we rely on a two stage procedure for reason of perfusion. In large breasts, this is quite often a problem: I refer to our review on NSM in large breasts. We reported on an overall complication rate of 29.08%. More specifically, " 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 15 articles on immediate procedures show a higher total necrosis rate of 14.95 % compared with the multi-staged procedures (Table 4)."

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Reconstruction Type	Procedures (n=breasts)	Complications								TOTAL
		Wound-dehiscence	Skin		Nipple-areola complex			Infection	Hematoma	
			Epidermo-lysis	Necrosis	Epidermo-lysis	Partial Necrosis	Complete Necrosis			
Delay	419	13	0	6	16	9	2	10	6	62
%		*3,1*	*0*	*1,43*	*3,82*	*2,15*	*0,48*	*2,39*	*1,43*	*14,8*
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Table 4 : Complication rates in delayed versus immediate procedures (%=percentage of n procedures)

For your convenience, I present you the table out of the preproof manuscript: in the official manuscript, the table is published in an oblique manner. The total amount of necrosis in DTI reconstruction is almost 10%, as in a two staged procedure only 2% (1).

Comment 31: If the remaining glandular pedicle is removed at the second stage, won't the capsule be removed as well, making the lower pole thinner?

Reply 31: Since the expander remains completely muscle-covered, the capsule cannot be removed without removing the muscle. In the first stage, the pectoralis major muscle is released along its inferior border, but not transsected. The expander is only filled in the first stage with 120 cc of saline. Because the insertion is not transsected, the expander may sometimes be high riding (1 to 2 cm) during the inflation period. However, when replacing it by a definite prosthesis in the second stage, the newly formed capsule is always incised om its lowest border, allowing the definitive prosthesis to position itself at the height of the IMF. As a conclusion, the second stage never removes the capsule and the thickness of the lower pole is remained through the pectoral muscle and the capsule thickness.

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Comment 32: If it is confirmed before surgery that there is a tumor in the remaining dermoglandular pedicle, can this method be used?

Reply 32: There is still controversy about NSM. Important is what you define as a tumor. We propose this technique for localized DCIS and early stage breast cancer. First of all, it would depend on the location of DCIS. When DCIS is diagnosed within the pedicle or close to NAC, it is not a good idea to perform this technique. One can alter the pedicle position: Gunnarson reports no necrosis with a superior pedicle (7). When situated behind NAC (within 2 cm margin), a nipple-sparing approach is not a good idea. The discussion about NSM versus lumpectomy and radiotherapy is already pending for several years: this is not only an important article on itself, but it would need very large prospective studies as well as large retrospective reviews. The main problem in this, is what to compare. Even in our own university hospital, it is the source of lively discussion. This is the reason why I focused this article on the technique itself, but I am well aware that DCIS and even more early breast cancer, will remain subject of discussion. The second part of your question is whether we can wait. A safety margin of three months is taken in our technique as well as by Gunnarson (7) and Spear (8): this can be considered for preventive surgery or when DCIS is found in the resection specimen in the first stage by coincidence. DCIS has to be removed with enough healthy margin. This is what we also do in oncoplastic surgery. One has to consider that in oncoplastic surgery, resection is followed by radiotherapy within four to six weeks. In our staged technique, one has to wait six weeks longer. Spear points out that he would perform the second stage already after 4 weeks, but in his article all patients undergo the second stage the earliest after 3 months (8). Until now, no one performed the second stage after 4 weeks. What if perfusion is not adequate after 4 weeks? It would not mean a serious problem in autologous reconstruction; however in prosthesis reconstructions it may result in a disaster or at least, in several stages of consecutive surgery and one could only hope that the prosthesis does not get infected.

When DCIS is well localized and no other lesions are shown, one can consider this technique: NCCN guidelines support mastectomy for pure DCIS (27). DCIS on more than one location is not an indication for this technique.

Considering all the above, it is wise, not only from a medicolegal point of view, to

have an agreement of the oncologists and the breast surgeons, to perform this technique when a DCIS is diagnosed before the first stage. In our university breast clinic, this is mandatory before including a patient for this staged technique. With the above indication (unilocalized DCIS, distant from pedicle and NAC and intra-operatively proven complete resection on pathology and X-ray of the specimen), we perform this staged technique when DCIS is diagnosed before the first stage. I must admit that until now, we only performed this in a few cases.

The same argument can be taken into account for early stage breast cancer. Nevertheless this article is focused on the technical reliability of the technique.

Reviewer E

Comment 33: Why do you need to expand the space the implant space?

Reply 33: After insertion, the tissue expander is filled with 120 cc of saline. Then we wait three weeks before we start filling the expander. We aim to fill the expander by the patient's desired volume over a period of two months on a weekly basis before scheduling the second stage. The main reason to expand the implant space is to allow the formed capsule to adapt to expansion: we want the capsule to expand together with the pectoral muscle because we don't use an ADM. In Belgium, the use of an ADM is not reimbursed by health insurance: an unilateral ADM costs about 1500 USD. This is one of the reasons why we had to think about another solution.

Secondly, we rely on a two stage procedure for reason of perfusion. In large breasts, this is quite often a problem: I refer to our review on NSM in large breasts. We reported on an overall complication rate of 29.08%. More specifically, " 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 15 articles on immediate procedures show a higher total necrosis rate of 14.95 % compared with the multi-staged procedures (Table 4)."

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Table 4 : Complication rates in delayed versus immediate procedures (%=percentage of n procedures)

For your convenience, I present you the table out of the preproof manuscript: in the official manuscript, the table is published in an oblique manner. The total amount of only necrosis in DTI reconstruction is almost 10%, as in a two staged procedure only 2% (1).

References underneath are used in the answers to the reviewer's comments (the references used in the "changes in the text" sections are those that refer to the reference list of the original manuscript):

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