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Breast Reconstruction Outcomes With and without StratticE (BROWSE)- Long-term outcomes of a multi-centre study comparing Strattice™ immediate implant breast reconstruction with submuscular implant reconstruction.

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Strattice^{TM} Reconstructive Tissue Matrix, Allergan.

The Breast Reconstruction Outcomes With and without StratticE (BROWSE) (NCT02608593) study

Abstract

Background: Over half of immediate implant-based breast reconstructions (IBBR) are performed with an acellular dermal matrix (ADM), despite limited long-term outcome data.

Methods: The Breast Reconstruction Outcomes With and without StratticE (BROWSE) (NCT02608593) study was a retrospective multicentre cohort study comparing consecutive patients who had undergone immediate Strattice™ IBBR with those who had undergone immediate IBBR with a submuscular technique between January 2009 and December 2015.

Results: This study compared 553 Strattice™ reconstructions with 242 submuscular reconstructions, with a median follow-up of 4.3 years (range 2 - 9.3) and 5.7 years (range 2 - 8.1) respectively, demonstrating an equivalent total complication rate (Strattice™ 36.9% (n=204) *vs*. submuscular 31.8% (n=77),p=0.17) and implant loss rate (8.5% *vs*. 5.4%, p=0.12, respectively). Infection rates and wound dehiscence rates were higher in the Strattice™ cohort (20.6% (n=114) *vs*. 12.8% (n=31), p=0.009 and 16.3% (n=90) *vs*. 10.4% (n=25), p=0.03, respectively). Overall revision rates were comparable (46.7% (n=226) *vs*. 41.1% (n=79), p=0.2) but significantly less Strattice™ reconstructions required revision surgery for capsular contracture (5.3% *vs*. 15.6%, p<0.001).

Conclusions: Although the risk of complications associated with Strattice™ reconstruction is numerically higher than that for submuscular coverage, the difference is small and not statistically significant, and likely outweighed by the clear reduced rate of revision surgery due to capsular contracture when Strattice™ is used.

Introduction

Immediate breast reconstruction is routinely offered as a standard treatment for women facing mastectomy, with rates in England at 48.6% in women under 50, 46% in women age 50-70 and <5% in women over 70 [5]. Implant based breast reconstruction (IBBR) has become the most commonly used type of reconstruction in the UK and US in recent years [1-5]. The traditional technique for immediate IBBR is complete submuscular (subpectoral with or without serratus anterior) coverage, maintaining muscle attachments. This technique frequently requires a first stage procedure of tissue expander insertion, and is associated with several long-term complications including, implant displacement, excessive upper pole fullness, loss of lower pole projection and inframammary fold definition and capsular contracture [6-9]. Total submuscular reconstruction has gradually been superseded with a lower pole acellular dermal matrix (ADM) or mesh-based implant reconstruction in a partial subpectoral (with freeing of the lower part of pectoralis major) plane, and, more latterly the prepectoral plane [10, 11]. The use of ADM commenced in 2005 but has quickly gained acceptance as an alternative to complete submuscular coverage, now making up to 55% of implant based reconstruction in the UK [12]. ADM based IBBR has several perceived advantages including improved shape, a reduction in capsular contracture and the ability to perform a one-stage procedure [13]. Despite this significant change in practice there is a lack of data comparing submuscular reconstruction with ADM based reconstruction [14].

A meta-analysis reporting outcome data in IBBR with a variety of ADMs compared to a submuscular technique was limited by heterogeneity in the intervention and control groups, lack of predefined outcome measures, small sample size, short-term follow-up and predominantly single institution [14]. Alloderm™ (AbbVie Inc., North Chicago, Illinois) was first used as an

ADM in the US, but as human derived tissue it cannot be used for regulatory reasons in Europe which led to the use of porcine, bovine, and synthetic ADMs [9]. Strattice™ (AbbVie Inc., North Chicago, Illinois) is a porcine derived cross-linked ADM that has been widely used in Europe since being 2008 and is still the most widely used ADM in the UK [7]. However, there is only one single site study which compares the use of Strattice™ to submuscular implant reconstruction and this is limited by a patient sample size of 52 with follow-up of only 24 months [12].

BROWSE is a multi-centre study comparing the short and long-term outcomes of women undergoing submuscular IBBR reconstruction with and without the use of Strattice ™. The study focused on Strattice™ as this has the longest follow up data, is most widely used, and allowed us to minimise learning curve effects of newer products.

Materials and Methods

Study population

Breast Reconstruction Outcomes With and without StratticE (BROWSE) (NCT02608593) is a retrospective multicentre cohort study comparing patients who received immediate Strattice™ IBBR with those who received immediate IBBR with a submuscular technique (total, including dissection of serratus anterior or partial). Inclusion criteria recruited patients age 18 years or older at the time of surgery, who had undergone IBBR for cancer or risk reduction, with a minimum follow-up period of six months.

Patients who underwent IBBR with a Strattice™ or submuscular technique between 1st January 2009 and 31st December 2015 across three tertiary centres; Manchester Foundation Trust, Royal Victoria Infirmary, Newcastle, or Bradford Royal Infirmary were included in the study. These study sites were chosen as large volume centres, with long-term experience of Strattice™

reconstruction. The selection process for reconstruction type was on a case-by-case basis after discussion between the patient and surgeon. In all three centres the full procedure was completed by the same surgeon, in two centres this was by oncoplastic trained breast surgeons and in one, oncoplastic trained plastic surgeons. No objective assessment of mastectomy flaps was performed for either reconstruction type.

Data collection

A retrospective case note review was performed. Clinic letters, multidisciplinary team meeting outcomes, operation notes, anaesthetic charts, admission pathways, nursing notes, histology and radiology reports and all handwritten clinical documentations were reviewed. Ethical approval was granted by North West - Greater Manchester South Research Ethics Committee in April 2016 (16/NW/0082).

Definitions of post-surgical complications

Definitions were based on those used in the iBRA study, a UK multicentre prospective cohort study of implant based breast reconstruction to allow direct comparison [11]. The following definitions were used when compiling the data; *Suspected infection:* Clinical signs within the breast; hot, erythema, swelling, purulent discharge and/or systemic signs e.g. fever. *Wound dehiscence*: Separation of the skin edges at the wound site. *Haematoma:* Collection of blood beneath the incision/around the implant. The severity of complications was graded using the Clavien-Dindo classification [6] (Supplementary Table 1). *Implant loss:* Implant removal secondary to post-operative complications e.g. infection or wound dehiscence. *Planned further surgery:* Surgery that was planned as part of the overall reconstructive procedure i.e. exchange of tissue expander to definitive implant, nipple reconstruction, port removal or contralateral surgery.

*Unplanned further surgery: S*urgery that was not an anticipated step of the overall reconstructive procedure and required due to a complication consequent to the initial reconstruction.

Long-term complications requiring revision surgery

Data was captured from retrospective notes (clinic letters and operation note) on the reasons for further intervention. The reasons for revision surgery documented in this study were: capsular contracture, malposition, asymmetry, rupture, contour defects, rippling, animation, patient request to change style or size and other. There may have been more than one reason for the revision surgery.

Statistical analysis

Summary statistics are stratified by IBBR method and are presented as median (IQR) and number (percentage) for continuous and categorical variables, respectively. Differences between the two groups were tested using independent-samples t-test, chi-square, or Fisher's Exact test, as appropriate. Logistic regression was used to examine the relationship between IBBR method and the two outcomes, post-operative complication and implant loss, before and after adjusting for age, smoking status, BMI and operative time. Kaplan-Meier curves were used to visualise differences in time to revision surgery and were compared using log-rank test. Cox proportional-hazards regression was used to compare risk of revision surgery, before and after adjusting for haematoma, post-operative complication and radiotherapy. All tests were two-sided, with $p<0.05$ considered statistically significant. Statistical tests were performed using SPSS 22.0 (SPSS Inc, USA) and R version 4.0.1.

Results

Patient demographics

Between August 2016 and April 2018, data was collected for 585 patients across the three tertiary centres. Four patients were excluded as insufficient data was available. In total 394 patients underwent 553 Strattice™ reconstructions (159 bilateral cases) and 191 patients underwent 242 submuscular reconstructions (51 bilateral cases), five patients had one reconstruction of each type. The median age was 52 years (range 25 - 82) in the Strattice™ cohort compared to 56 years (range 32 - 80) in the submuscular cohort. There were significantly more younger patients in the Strattice™ cohort when compared to the submuscular cohort. Moreover, there was a smaller number of smokers in the Strattice™ cohort when compared to the submuscular cohort. However, no other significant differences in patient demographics and pre-operative risk factors were identified across the cohorts (Table 1). Median follow-up (accounting for deaths and patients lost to follow-up) for Strattice™ was 4.3 years (range 2 - 9.3) and 5.7 years (range 2 - 8.1) for submuscular reconstructions. There was an equivalence in the indication for surgery between the two cohorts and a lower median mastectomy weight in the Strattice™ cohort (335g *vs.* 390g, $p<0.001$) (Table 2).

Of the three centres involved in this study, centre one performed the largest number of reconstructions with 361 (65.3%) Strattice™ and 209 (86.4%) submuscular reconstructions (Figure 1A). Centre two performed 55 (9.9%) Strattice™ and 26 (10.7%) submuscular reconstructions. However, Strattice™ reconstructions were no longer performed at centre two after December 2013 (changed product used). Centre three performed 137 (24.8%) Strattice™ and 7 (2.9%) submuscular reconstructions. There was a gradual decrease in the use of submuscular reconstruction in favour of Strattice™ reconstruction from 2009-2015 (Figure 1B).

Post-operative complications

There was no significant difference in the total number of reconstructions that experienced post-operative complications when comparing Strattice™ 36.9% (n=204) *vs*. submuscular 31.8% (n=77), (p=0.17, chi-square test) cohorts (Figure 2).

Overall there was a higher number of reconstructions treated for suspected infection in the Strattice™ cohort than the submuscular (20.6% (n=114) *vs.* 12.8% (n=31), p=0.009). This was true for both grade two (requiring pharmacological treatment with drugs) and grade three (requiring surgical, endoscopic or radiological intervention) infections in the Strattice™ cohort compared to the submuscular cohort (14.8% (n=82) *vs.* 10.3% (n=25), p=0.09 and 5.4% (n=30) *vs.* 2.5% (n=6), p=0.07, respectively).

In total, more Strattice™ reconstructions experienced wound dehiscence compared to the submuscular reconstructions (16.3% (n=90) *vs.* 10.4% (n=25), p=0.03), in particular grade three (requiring surgical, endoscopic or radiological intervention) wound dehiscence (10.7% (n=59) vs. 2.5% (n=6), p<0.001).

The odds of having a post-operative infection or wound dehiscence is estimated at 1.61 times higher with a Strattice™ reconstruction (OR 1.61 (95% CI 1.13-2.31), p=0.009). Adjusting for age, smoking status, BMI and operative time, the odds were significantly higher in the Strattice™ cohort (OR1.58 (95% CI 1.03-2.44), p=0.037).

Overall rates of seroma (grade one, any deviation from normal post-operative course without the need for pharmacological, surgical, endoscopic or radiological intervention) were equivalent in the Strattice™ and submuscular cohort (23.3% (n=125) *vs*. 27.6% (n=67), p=0.2). However, in the clinically significant grade three seromas, rates were lower in the Strattice™ cohort (10.1%

(n=56) *vs*. 18.2% (n=44), p=0.002). Mastectomy flap necrosis occurred in 0.9% (n=5) of the Strattice™ reconstructions and 1.7% (n=4) of the submuscular reconstructions.

Implant loss rates were numerically higher with Strattice™ compared to submuscular reconstructions, however this difference was not significant (8.5% (n=47) *vs*. 5.4% (n=13) respectively, p=0.12), highlighting that if a true difference exists, it is small. Moreover, the 3-month implant loss rate for both techniques were below the UK quality criteria (<5% at 3 months), set by the Association of Breast Surgeons and British Association of Plastic Reconstructive and Aesthetic Surgeons in their guidelines for best practice in IBBR [14], at 4.3% implant loss for Strattice™ and 3.7% for submuscular reconstructions. The odds of having an implant loss were not significantly different between to the two groups (OR 1.78 (95% CI 0.96-3.57), p=0.083. Due to the small numbers of events, it was not possible to adjust for multiple factors together. When adjusting for age, the odds of implant loss were significantly higher in the Strattice™ cohort (OR 1.98 (95% CI 1.05-4.00), p=0.04) and similarly when adjusting for smoking status (OR 2.01 (95% CI 1.07-4.06), p=0.04). **The Hosmer-Lemeshow tests showed no evidence of poor fit for models in the logistic regression analysis, for both complications (unadjusted p=1, adjusted p=0.332) and implant loss (unadjusted p=1, adjusted p=0.456).**

Median time to implant loss was 88 days (range 14-993 days) in the Strattice™ cohort and 28 days (range 13-225 days) in the submuscular cohort. Implants were lost up to almost three years after the reconstruction in the Strattice™ cohort compared to a maximum of nine months in the submuscular cohort (log rank test, p=0.04).

In 2009 (the first year Strattice™ reconstructions were performed) the implant loss rate was significantly higher than in the submuscular group, 21.4% (n=6) vs. 4.3% (n=2), p=0.05, there was no difference in subsequent years. This probably reflects a learning curve.

Revision Surgery

During the total follow-up period 46.7% (n=226) Strattice™ reconstructions underwent revision surgery compared to 41.1% (n=79) submuscular reconstructions (p=0.2), however the hazard ratio of 0.77 (95%CI 0.59 – 0.99, p=0.042) suggests that the Strattice™ cohort had a significantly reduced risk of requiring revision surgery. After adjusting for a haematoma, post-operative complication (infection or wound dehiscence) and radiotherapy, the two groups no longer had a significantly different risk of requiring revision surgery (HR 0.79 (95%CI: 0.61-1, p=0.07).

There were significantly less revisions due to capsular contracture in the Strattice™ cohort when compared to the submuscular cohort (5.3% (n=21) *vs*. 15.6% (n=22) respectively, p<0.001) (Table 3). Revision surgery for malposition, asymmetry, contouring, patient request (size/style change), rupture, animation, rippling, improved cosmesis or other, were not found to be different across the cohorts. Median time to first revision surgery (calculated from date of definitive implant insertion) was 11 months (range 1 – 68) in the Strattice™ cohort and 14 months (range 1 – 68) in the submuscular (p<0.001). Assessment of the time to first revision for capsular contracture revealed that Strattice™ reconstructions have significantly greater longevity when compared to submuscular implants (p=0.01. HR 0.47 (0.25 to 0.90)) (Figure 3).

Discussion

Strattice™ is the most widely used ADM in the UK [12] and this is the only published study to directly compare the long-term outcomes of Strattice™ reconstructions with a cohort of submuscular IBBR without the use of an ADM.

In terms of short-term outcomes, although there was no statistically significant difference in overall complication rates between Strattice™ and submuscular reconstructions, there were higher rates of suspected post-operative infections and wound dehiscences in the Strattice™ cohort. This however, did not translate into an increased implant loss rate. In the longer term, revision rates are similar in Strattice™ and submuscular cohort but in particular revision surgery for capsular contracture is performed less frequently in Strattice™ reconstructions.

Meta-analysis comparing ADM and submuscular IBBR suggested that ADM reconstruction is associated with significantly increased risks of infection, seroma, and mastectomy flap necrosis, but not associated with increased implant loss rates, unplanned reoperation, or total complications [14]. Our data corroborates these earlier findings, demonstrating broadly equivalent levels of implant loss and total complications in both groups. However, this study demonstrates no difference in mastectomy flap necrosis with low levels across both cohorts.

The finding that higher suspected infection rates (p=0.009) and wound dehiscence rates (p=0.03) in the Strattice™ cohort did not translate into increased implant loss rates may be due to higher clinical concerns in the Strattice™ reconstruction being reported, such as the 'red breast' syndrome' resulting in a reporting bias with a bias towards earlier intervention. Given the retrospective nature of the study it is not possible to prove what proportion of patients had a true infection.

During the first year that Strattice™ reconstructions were performed, the implant loss rate in the Strattice™ cohort was higher than the submuscular cohort and higher when compared to subsequent years in which Strattice ™ was used. This could possibly reflect a learning curve for this new technique that has been previously described [15]. Discounting the learning curve in 2009 results in an equivalent implant loss rate (7.8% in the Strattice™ cohort vs. 5.6% in the submuscular, p=0.4) between the two cohorts. This early increased rate of implant loss may be due to the learning curve of performing skin sparing mastectomy with no underlying protective vascularised muscle cover, and thus the viability of skin flaps determining the risk of infection to the underlying implant in an ADM reconstruction. In a complete submuscular setting a breach in the mastectomy flap will not necessarily contaminate the underlying implant as it is covered by vascularised muscle. This validates our decision to focus on units that had more long-term experience of Strattice, thus minimising the learning curve effect.

Strattice™ has been perceived to reduce the risk of capsular contracture [16] but this has not previously been demonstrated in a long-term comparative study such as this. Rates of revision surgery were equivalent between the Strattice™ and submuscular cohort for all other indications and the overall rate of revision surgery was no different between the two cohorts. Time to first revision was shorter in the Strattice™ cohort, 83% of them done within the first 24 months with the remaining performed in the following three years. In contrast, only 60% of the submuscular revisions were required in the first 24 months of the definitive implant being inserted, suggesting more of a consistent deterioration in the reconstruction and potentially higher rate of revision surgery in the even longer-term.

As expected, the data also highlights that Strattice™ allows a one-stage procedure in the vast majority of cases (87%) in contrast to the submuscular cohort (14%). This avoids repeated expansions in the clinic and a second surgery. However, in patients requiring a two stage procedure e.g. higher risk, large breasts, there are other benefits to be gained in using an ADM. The multi-centre nature of the study reduces the bias of single-centre studies, but also highlights the variance in outcome of implant-based reconstruction. In the UK alone there is great variation in outcomes with other centres reporting rates of implant loss as high as 17% [17]. However, our study implant loss rates in both cohorts fall below the national implant loss rate of 9% at 90 days [11] demonstrating in experienced hands, in a real world setting the outcomes from Strattice™ reconstruction are comparable to submuscular reconstructions without the use of ADMs.

This study has several inherent limitations. The Strattice™ cohort has a higher proportion of young patients and more bilateral cases, which may be accounted for by the higher rate of risk reducing surgery in this group or younger women are likely to have less co-morbidities therefore deemed more suitable to use an ADM. An adequate blood supply to the mastectomy skin flap is essential for integration of the ADM [18] therefore the significant reduction in smokers in the Strattice™ cohort is likely a reflection on the known impact smoking has on the microvasculature system [19, 20]. Despite higher stage disease in the submuscular cohort there was no difference in the percentage of patients receiving adjuvant radiotherapy which is a risk factor for capsular contracture. As expected with higher stage disease and more HER2 positive disease more patients received adjuvant chemotherapy and Herceptin in the submuscular cohort. There may again have been selection bias in this subgroup with the operating surgeons perceiving these patients to be higher risk and therefore not offering a Strattice™ reconstruction but impossible to account for in a retrospective study. Retrospective reporting of some outcomes such as infection rates has limitations because of definition problems, while the reasons for performance of revision surgery are not always clear as they are dependent on the quality of documentation. In addition, loss to follow up and transfer of patient care could be a source of inaccuracy. The study is also limited by a change in practice over the study period, with most of the submuscular reconstructions being performed in the earlier period, and at one centre and Strattice™ in the later period.

Despite the limitations of this retrospective study, it is likely to be a true reflection of surgical practice across multiple sites during this period of practice change.

Surgical practice is constantly evolving, with a move currently towards prepectoral reconstruction with total ADM coverage rather than the subpectoral technique detailed in this study. It is vital that our practice is evidence-based, efficacious and in the best-interests of our patients [21]. The Cumberlege report of device management in the UK suggests "A central patient-identifiable database should be created by collecting key details of the implantation of all devices at the time of the operation. This can then be linked to specifically created registers to research and audit the outcomes both in terms of the device safety and patient reported outcomes measures". Further studies are required on other ADMs and meshes to investigate whether they have similar long-term benefits to that of Strattice™ and this dataset will provide a valid comparison for future studies involving alternative meshes/ADM used in the pre- or sub-pectoral setting.

This study demonstrates both short and long-term outcomes of patients undergoing Strattice™ based immediate implant breast reconstruction, thus allowing clinicians to be clear in advising patients of the likely long-term sequelae. Although overall complication rates, including implant loss rate, were numerically higher in the Strattice™ group, this did not reach statistical significance. This may reflect that the study is underpowered to detect a small difference in complication rate, however any possible difference may be outweighed by the clear advantage in terms of reduced revision surgery.

References

1. Lang, J.E., et al., *Trends in post-mastectomy reconstruction: a SEER database analysis.* Journal of surgical oncology, 2013. **108**(3): p. 163-168.
2. Leff, D.R., et al., *Trends in Immediate Postmastectomy Breast Reconstruction in the United Kingdom.* Plastic and reconstructive surgery. Global open, 2015. **3**(9): p. e507-e507.
3. Albornoz, C.R., et al., *A paradigm shift in U.S. Breast reconstruction: increasing implant rates.* Plast Reconstr Surg, 2013. **131**(1): p. 15-23.
4. Mennie, J.C., et al., *National trends in immediate and delayed post-mastectomy reconstruction procedures in England: A seven-year population-based cohort study.* Eur J Surg Oncol, 2017. **43**(1): p. 52-61.
5. McNeill F., I.T., *Get It Right First Time National Report on Breast Surgery.* 2019.
6. Champaneria, M.C., et al., *The evolution of breast reconstruction: a historical perspective.* World J Surg, 2012. **36**(4): p. 730-42.
7. Cordeiro, P.G. and C.M. McCarthy, *A single surgeon's 12-year experience with tissue expander/implant breast reconstruction: part I. A prospective analysis of early complications.* Plast Reconstr Surg, 2006. **118**(4): p. 825-831.
8. FDA. *Breast Implants – Certain Labeling Recommendations to Improve Patient Communication Final Guidance*. 2020; Available from: https://www.fda.gov/medical-devices/implants-and-prosthetics/breast-implants.
9. Nahai, F. and J. Bostwick, 3rd, *Aesthetic aspects of breast reconstruction.* Aesthetic Plast Surg, 1982. **6**(2): p. 61-7.

10. Clavien, P.A., et al., *The clavien-dindo classification of surgical complications: Five-year experience.* Annals of Surgery, 2009. **250**(2): p. 187-196.

11. Potter, S., et al., *Short-term safety outcomes of mastectomy and immediate implant-based breast reconstruction with and without mesh (iBRA): a multicentre, prospective cohort study*. Lancet Oncol, 2019. **20**(2): p. 254-266.

12. Mylvaganam, S., et al., *Variation in the provision and practice of implant-based breast reconstruction in the UK: Results from the iBRA national practice questionnaire.* Breast, 2017. **35**: p. 182-190.

13. Hallberg, H., et al., *Benefits and risks with acellular dermal matrix (ADM) and mesh support in immediate breast reconstruction: a systematic review and meta-analysis.* J Plast Surg Hand Surg, 2018. **52**(3): p. 130-147.

14. Lee, K.-T. and G.-H. Mun, *Updated Evidence of Acellular Dermal Matrix Use for Implant-Based Breast Reconstruction: A Meta-analysis.* Annals of Surgical Oncology, 2016. **23**(2): p. 600-610.

15. Lardi, A.M., et al., *Immediate breast reconstruction with acellular dermal matrix: factors affecting outcome.* J Plast Reconstr Aesthet Surg, 2014. **67**(8): p. 1098-105.

16. Salzberg, C.A., C. Dunavant, and N. Nocera, *Immediate breast reconstruction using porcine acellular dermal matrix (Strattice): long-term outcomes and complications.* J Plast Reconstr Aesthet Surg, 2013. **66**(3): p. 323-8.

17. Barber, M.D., et al., *Outcome of the use of acellular-dermal matrix to assist implant-based breast reconstruction in a single centre.* Eur J Surg Oncol, 2015. **41**(1): p. 100-5.

18. Gaster, R.S., et al., *Histologic analysis of fetal bovine derived acellular dermal matrix in tissue expander breast reconstruction.* Ann Plast Surg, 2013. **70**(4): p. 447-53.

19. Rossi, M., et al., *Impact of long-term exposure to cigarette smoking on skin microvascular function.* Microvasc Res, 2014. **93**: p. 46-51.

20. Leone, A. and L. Landini, *Vascular pathology from smoking: look at the microcirculation!* Curr Vasc Pharmacol, 2013. **11**(4): p. 524-30.

21. Cumberlege, J., *First Do No Harm. The report of the Independent Medicines and Medical Devices Safety Review.*

Figure Legends

Figure 1. **Total number of Strattice™ and submuscular reconstructions per centre (A) and over time (B).**

Figure 2. **Rates of complications by Clavien-Dindo classification between Strattice™ and submuscular reconstructions. Clavien-Dindo Classification defined in supplementary table 1 [10]**

Figure 3. **Kaplan Meier curve showing time to first revision for capsular contraction comparing Strattice™ and submuscular reconstructions.**

Tables

Table 1 **Patient demographics and pre-operative risk factors**

Table 2 **Summary of operative data per breast**

Table 3 **Reason for revision surgery comparing Strattice™ and submuscular reconstructions for all procedures performed during the follow-up period**

Table 1 Patient demographics and pre-operative risk factors

	Strattice™ n (%) (n=394)	**Submuscular n (%) (n=191)**	***p* value**
Median follow-up (years) [IQR] (years, months)]	4.3 [2,9-5,4]	5.7[3,10-7,1]	<0.001‡
Unilateral	235 (60)	191 (73)	
Bilateral	159 (40)	51 (27)	<0.001
Median Age (years)[IQR]	52 [45-61]	56 [48-65]	<0.001‡
<40	62 (15.7)	11 (5.8)	
40-59	230 (58.4)	108 (56.5)	
≥60	102 (25.9)	72 (37.7)	
Median BMI (kg/m^2)[IQR]	24 [22.1-26.8]	24.1 [21.7-28.2]	0.4‡
≤17.9	4 (1.0)	6 (3.1)	
18.0-24.9	231 (58.6)	108 (56.5)	
25.0-29.9	115 (29.2)	46 (24.1)	
30.0-34.9	30 (7.6)	24 (12.6)	
≥35.0	11 (2.8)	7 (3.7)	
Unknown	3 (0.8)	0 (0)	
Smoking Status			<0.01
Smoker	56 (14.2)	46 (24.1)	
Non-smoker	293 (74.3)	133 (69.6)	
Ex-smoker	44 (11.2)	12 (6.3)	
Unknown	1 (0.3)	0 (0)	
Diabetes	9 (2.3)	4 (2.1)	1
Previous chest wall radiotherapy	16 (4.1)	11 (5.8)	0.4
Pre-reconstruction chemotherapy	36 (9.1)*	12 (6.3)**	0.3

*21(5.3%) were neo-adjuvant chemotherapy and 15(3.8%) were adjuvant chemotherapy after breast conserving surgery immediately before reconstruction **9(4.7%) were neo-adjuvant chemotherapy and 3(1.6%) were adjuvant chemotherapy after breast conserving surgery before reconstruction. ‡ t test, all other analyses used chi2 test.

Table 2 Summary of operative data per breast

	Strattice™ n (%) (n=553)	**Submuscular n (%) (n=242)**
Reason for surgery		
Therapeutic	301 (54.4)	147 (60.7)
Invasive cancer	218	118
In situ carcinoma	83	29
Risk reduction	252 (45.6)	95 (39.3)
Type of Mastectomy		
Skin-sparing	424 (76.7)	164 (67.8)
Nipple-sparing	119 (21.5)	43 (17.8)
Simple	10 (1.8)	35 (14.4)
Completion mastectomy	94 (17)	44 (18.2)
Reconstructive Procedure		
Strattice™ (sub pectoral)	527 (95.3)	0
Strattice™ (pre pectoral)	26 (4.7)	0
Total submuscular	0	199 (82.2)
Partial submuscular	0	37 (15.3)
Subcutaneous	0	6 (2.5)
Incision		
Horizontal	396 (71.6)	152 (62.8)
Wise pattern	14 (2.5)	37 (15.3)
Inframammary fold	64 (11.6)	20 (8.3)
Other	79 (14.3)	33 (13.6)
Median specimen weight (g) [IQR]	335 [237 – 480] [1]	390 [220 – 604] [2]
Median operative time (mins) [IQR]	155 [120 – 190]	120 [95 – 155]
Prosthesis		
Tissue expander	74 (13.4)	203 (83.9)
Expander implant e.g. Beckers	96 (17.4)	20 (8.3)
Implant	383 (69.2)	19 (7.9)
Axillary Procedure		
Nil	274 (49.5)	101 (41.7)
Sentinel Node Biopsy	224[3] (40.5)	118[4] (48.8)
Axillary node sample	3[5] (0.5)	8[6] (3.3)
Axillary node clearance	52[7] (9.4)	38[8] (15.7)
Antibiotics		
Pre-operatively	550 (99.3)	241 (99.6)
Post-operatively (prophylactic)	544 (98.4)	226 (93.4)

Adjuvant therapy		
Chemotherapy	101 (35.1)*	65 (43.3)**
Herceptin	34 (11.8)	29 (19.3)
Endocrine	177 (61.5)	99 (66)
Radiotherapy	43 (13.5)†	21 (13.7) ††

[1]22 not recorded [2]3 not recorded [3]66 were at the WLE or pre-reconstruction [4]16 were at the WLE or pre-reconstruction [5]1 was at the WLE or pre-reconstruction [6]1 was post reconstruction [7]29 were at WLE, pre-reconstruction or post-reconstruction [8]27 were at WLE, pre-reconstruction or post-reconstruction *15 (5.2%) and **3 (2%) received chemotherapy after their WLE, before the reconstruction, †Number of reconstruction that received radiotherapy from a total of 316, one was for local recurrence during the follow-up

Table 3 Reason for revision surgery comparing Strattice™ and submuscular reconstructions for all procedures performed during the follow-up period

	Strattice™ n(%) (n=226 breasts)	**Submuscular n(%) (n=79 breasts)**	***p* value**
Total number of revision procedures	364*	133**	
Capsular contracture	21 (5.3)	22 (15.6)	<0.001
Malposition	24 (6)	5 (3.5)	0.3
Asymmetry	111 (27.8)	42 (29.8)	0.2
Contouring	58 (14.5)	16 (11.3)	0.3
Patient request (size/style change)	53 (11.3)	22 (15.6)	0.5
Rupture	3 (0.8)	1 (0.7)	1.0
Animation	14 (3.5)	4 (2.8)	0.7
Rippling	18 (4.5)	3 (2.1)	0.2
Improve cosmesis	55 (13.8)	19 (13.5)	0.9
Other	39 (9.8)	8 (5.7)	0.1

*32 cases had two reasons for the revision **8 cases had two reasons for the revision. Chi2 or Fischers exact if n<6

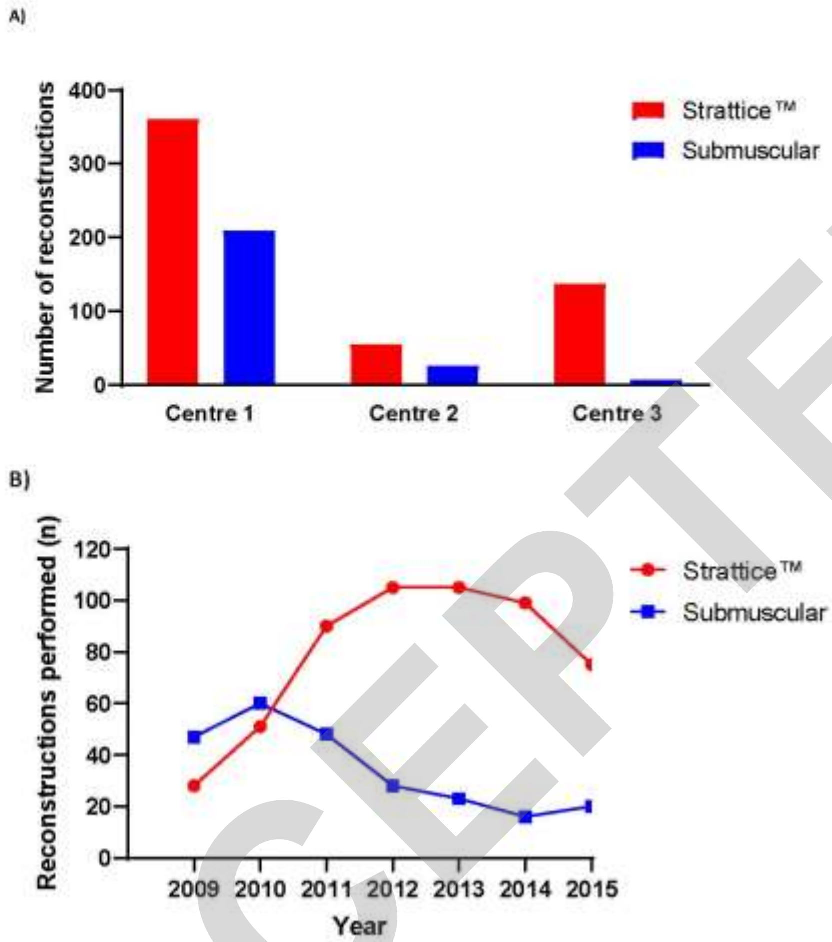

Figure 1. Total number of Strattice™ and submuscular reconstructions per centre (A) and over time (B).

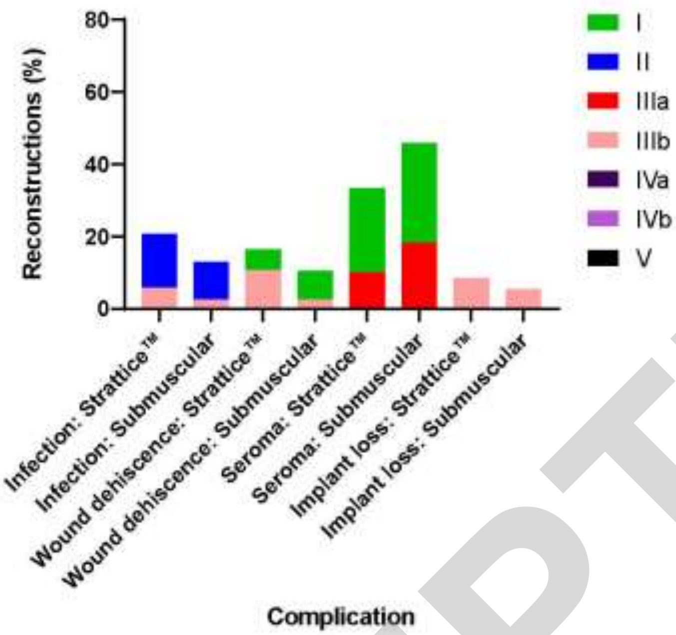

Figure 2 Rates of complications by Clavien-Dindo classification between Strattice™ and submuscular reconstructions. Haematoma (grade CD3b) not plotted as observed only in 2.2% for Strattice™ and 1.2% for submuscular.

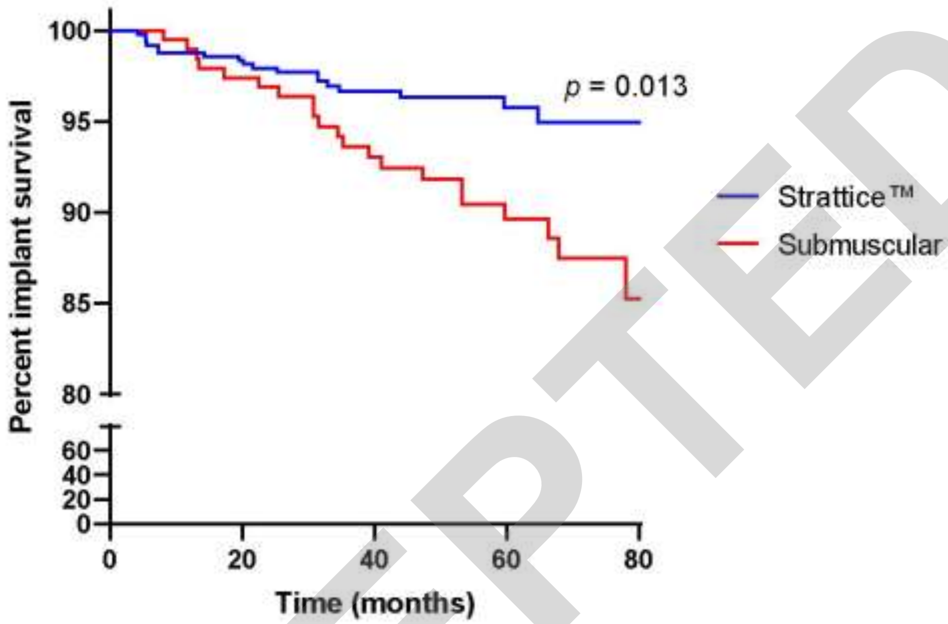

Figure 3 Kaplan Meier curve showing time to first revision for capsular contraction comparing Strattice™ and submuscular reconstructions. Curve comparison, Log-rank (Mantel-Cox) test.

Supplementary Table 1. **Clavien- Dindo Classification**

Grades		Definition
I		Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens include antiemetics, antipyretics, analgetics, diuretics and electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
II		Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III		Requiring surgical, endoscopic or radiological intervention
	IIIa	Intervention not under general anesthesia
	IIIb	Intervention under general anesthesia
IV		Life-threatening complication (including CNS complications)* requiring IC/ICU-management
	IVa	single organ dysfunction (including dialysis)
	IVb	Multiorgan dysfunction
V		Death of a patient