Full Title: Bioprosthetic Mesh to Expand the Lower Pole in Tissue Expander Reconstruction: A Blinded, Prospective, Randomized, Controlled Trial

1.0 Background

For years, plastic surgeons have struggled with two opposing goals in tissue expander breast reconstruction: protecting the implant from exposure under a thin mastectomy skin flap; and, creating an esthetically appealing breast with a full lower pole. For many surgeons, these two goals seemed mutually exclusive. Protecting the implant meant placing it completely underneath the pectoralis major and serratus muscle, forcing the implant into an unnaturally high position. On the other hand, releasing the pectoralis major muscle allows the implant to sit within the mastectomy skin flap, but exposes the lower pole of the implant to a purely subcutaneous plane.

In recent years, there has been a proliferation of bioprosthetic mesh products. Some of these products found their way into breast reconstruction[1,2,3,4]. Plastic surgeons began using bioprosthetic mesh as a sling to allow the pectoralis major muscle to be released and then reconnected to the inframammary fold. This hammock effect protects the implant from the subcutaneous plane, takes tension off of the precarious mastectomy flap skin, and allows better control of the inframammary fold and lateral border of the breast. The additional thickness of the bioprosthetic mesh also helps to even out the thickness of the tissue overlying the implant, which is skin and muscle above and skin and mesh below[6,7,8].

As experience with reconstruction using bioprosthetic mesh has grown, increasing evidence suggest that mesh products may be associated with increased complication rates, particularly seroma and infection, potentially effecting not only the reconstruction, but the course of cancer treatment by delaying chemotherapy or interfering with radiation protocols[5,9,11]. Because the mesh products consist of extracellular matrices that are created from different source materials (human, pig, cow), and are processed differently, it is logical to conclude that complication profiles, and possibly esthetic outcome, differ from product to product.

2.0 Objectives

Primary objective:

1. To determine the overall complication rate for each arm and compare the complication rate for the group of patients using different types of mesh.

Secondary objectives:

1. To determine whether esthetic outcomes differs based on the type of mesh used.

3.0 Patient Eligibility

All patients seen at the MD Anderson main campus (MDACC) and/or one of the MD Anderson regional care centers (MDACC) for immediate breast cancer reconstruction with tissue expanders will be eligible for the study.

Inclusion Criteria

Patients undergoing immediate tissue expander reconstruction following mastectomy by any of the surgeon co-investigators are eligible for the study.
Patients 18 years of age or older are eligible for the study.
Patients undergoing skin-sparing mastectomy utilizing bioprosthetic mesh are eligible for the study.
Patients who have not undergone autologous tissue breast reconstruction and intend to undergo implant only breast reconstruction.
Patients who intend to remain under the MDACC surgeon's care until completion of the reconstruction.

Exclusion Criteria

Patients with prior radiation to the breast/chest wall of the ipsilateral breast.
Patients who cannot be effectively reconstructed without the use of bioprosthetic mesh.
Patients who are current smokers.
Patients requiring additional intraoperative skin resections of greater than 1 cm beyond the skin edge as a result of mastectomy flap devascularization.
Patients who have a history of breast tissue expander or implant placement.

4.0 Risks and Benefits

Potential risks of each of the two arms of the study include bleeding, infection, implant exposure, implant malposition, seroma, delayed wound healing, mastectomy flap necrosis, and capsular contracture. This study may involve unpredictable risks to the participants.

There may be no benefits to participants in the study.

5.0 Study Design

This is a prospective, randomized-to-procedure, controlled, blinded-to-esthetic evaluator trial. Information recorded and evaluated will include:

Population Variables -
- age
- body mass index (BMI)
- breast size
- past medical history
- smoking history
- tumor size and location
- mastectomy surgeon
- mastectomy method

Operative Variables -
- plastic/reconstructive surgeon
- tissue expander
- tissue expander type
- quality of skin
- additional skin resection
- intraoperative fill volume
- method of lower pole expansion
- drains

Postoperative Variables -
- duration of drains
- chemotherapy
- radiation
- number of post-op visits
- time to first expansion
- number of expansions
- final fill volume
- time to exchange
- type and volume of implant placed
- contralateral procedures performed
- nipple (yes/no)

Outcome -
- infection
- seroma
- implant malposition
- capsular contracture
- hematoma
- histologic incorporation
- esthetic evaluation (photos, blinded evaluators)

6.0 Operative Technique

Intervention Arm:

After the mastectomy is performed, the pectoralis major muscle is elevated off the chest wall with electrocautery. After elevation superiorly and medially, the pectoralis major muscle is disinserted from the chest wall along its inferior border to the 3 or 9 o'clock position medially.

The skin envelope is evaluated. If the inframammary fold has been violated, sutures are used to secure it into its appropriate anatomic location. This is also done with the lateral breast skin.

Bioprosthetic mesh is then sewn into the inframammary fold and lateral chest wall. If Surgimend is used, then the 10 x 15 cm piece of fenestrated material is sewn to the fold, curved side along the fold, using a suture. If Alloderm (acellular dermal matrix) is used, a 6 x 12 cm piece or 6 x 16 cm piece is trimmed into a semicircle and sewn into the inframammary fold. The smooth side is placed against the implant.

The tissue expanders are then placed in the subpectoral/subbioprosthetic pocket. A drain is placed along the inferior border between the bioprosthetic mesh and the tissue expander. The superior border of the bioprosthetic mesh is closed to the inferior border of the pectoralis major muscle with a suture. An additional drain is placed in the subcutaneous pocket. Saline solution is then injected into the tissue expander to an appropriate fill volume.

Skin closure is performed.

7.0 Statistical Considerations

Primary endpoint

The study is designed to evaluate the overall complication rate post-tissue expander reconstruction surgery using different types of mesh. Patients who are eligible for the study will be equally randomized to the following arms: 1) Alloderm; 2) Surgimend. The primary endpoint, overall complication after tissue expander implant is defined as any of the following complications: seroma; infection; implant malposition; capsular contracture; and, hematoma.

Sample Size

Patients who are seen at MDACC for immediate breast reconstructive surgery after mastectomy will be enrolled to the study and equally randomized to the two arms when the tissue expander is implanted: 1) Alloderm; 2) Surgimend. The randomization will be stratified by surgeon in order to avoid confounding between surgeon and surgical method. A total of 398 patients will be enrolled with 199 patients for each arm. The information on overall complication observed after tissue expander implant and before

the permanent implant will be collected. The rate of overall complication for the patients using Alloderm mesh (arm 1) will be compared to the patients using Surgimend mesh (arm 2). With 199 patients in each arm the study will have 80% power to detect the difference in complication rate between 10% in the Alloderm mesh group and 20% in the Surgimend mesh group with a two-sided type I error rate of 0.05 (calculated by nQuery Advisor 7.0). The secondary objective is esthetic evaluation. The main question for the esthetic evaluation is whether the overall shape of the reconstructed breast is good. Evaluators who are blinded to the arm assignment information will grade the patients using a 5-point Likert scale (strongly disagree, disagree, somewhat agree, agree, strongly agree). Their scores will be averaged for each patient.

Analysis Plans

Patient information including age, BMI, smoking history, tumor size and location, breast size, mastectomy method, mastectomy surgeon, plastic reconstruction surgeon, quality of skin, tissue expander type, intraoperative fill volume, method of lower pole expansion, chemotherapy, and radiation therapy will be summarized. Outcome variables which include complications and scores for esthetic evaluation will be studied. Summary statistics including mean, standard deviation, median, and range will be provided for continuous variables (such as age and BMI) while frequency counts and percentages will be provided for categorical variables (such as smoking history and tissue expander type). The overall complication rate for each arm will be calculated along with the 95% confidence intervals. Fisher's exact test or the Chi-square test will be used to evaluate the association between two categorical variables. Cochran-Mantel-Haenszel test will be used to access the association between treatment and outcomes by adjusting the stratification of surgeon's experience (<= 3 years and >3 years). Logistical regression model will be used to assess the effect of patient variables on overall complication. For each question of the esthetic evaluation, an average score will be calculated for each patient based on the scores from all evaluators. Summary statistics for the scores including mean, standard deviation, median, and range will be calculated. The scores will be compared between the two mesh arms using Wilcoxon rank sum test.

8.0 Data Collection

All population variables will be collected after enrollment in the study and prior to surgery. After the initial surgery, during which operative variables will be documented by the surgical team, patient data will be collected in clinic. At the postoperative week 1 visit, the patient will be assessed by the surgical team for incisional complications and mastectomy flap necrosis. At the postoperative week 2 visit, expansion will begin, absent complications preventing expansion. The patient will return to clinic for additional expansion, as determined by the a member of the surgical team, until the desired volume is reached. During each of these visits, the patient will be assessed for seroma and infection. After expansion, the patient will return in approximately 3 months for a preoperative visit, followed shortly by tissue expander exchange for a permanent implant. One to twelve months following implant exchange, 5 photographs

(standardized photographic views) will be taken and used for aesthetic evaluation (see Appendix D). Unique study numbers will be assigned to the photographs.

Population variables:

- age
- BMI
- breast size
- past medical history
- smoking history
- tumor size and location
- mastectomy surgeon
- mastectomy method

Operative Variables – These will collected from the operative note or at the time of surgery:

- plastic/reconstructive surgeon
- tissue expander
- expander type
- quality of skin
- additional skin resection
- intraoperative fill volume
- method of lower pole expansion
- drains

Postoperative Variables – These will be recorded at clinic visits or retrospectively from clinic notes:

- duration of drains
- chemotherapy
- radiation therapy (out of study)
- number of post-op visits
- time to first expansion
- number of expansions
- final fill volume
- time to exchange
- type and volume of implant placed
- contralateral procedures performed
- nipple (yes/no)

9.0 Outcome

The primary endpoint, overall complication after tissue expander implant is defined as any of the following complications: seroma, cellulitis, abscess, red breast syndrome, implant malposition, capsular contracture, and hematoma. These will be defined as follows:

Seroma: Any suspected fluid collection that is either radiologically confirmed by ultrasound or clinically confirmed by drainage, or both.

Cellulitis: Any redness of the breast that resolves with antibiotics, or requires surgical removal of implant, but does not contain a purulent fluid collection.

Abscess: Any purulent fluid collection confirmed during surgical removal of implant.

Red breast syndrome: Any prolonged redness of the breast, without other symptoms of infection, which does not resolve with antibiotics, and does not go on to require removal of the implant.

Malposition: Any surgeon perceived, postoperative movement of the expander outside of the surgically created pocket.

Capsular Contracture: Any postoperative capsule formation, classified according to the Baker classification, as follows: Baker 1: normal beast; Baker 2: palpable, minimally firm capsule; Baker 3: visible, easily palpated, moderately firm capsule; Baker 4: painful, hard and breast distorted.

Hematoma: Any postoperative collection of blood requiring surgical drainage.

Secondary endpoints are related to esthetic evaluation of postoperative, standardized five (5) view clinical photos.

Esthetic Evaluation

The esthetic evaluation will be based on five standardized photographic views: frontal; right lateral; left lateral; right three-quarter: and, left three-quarter. Photographs will be taken against a blue background, standard in all clinic rooms, at a distance of five feet from the patient.

Evaluators will include three attending plastic surgeons who are not taking care of any patients in the study, three plastic surgery fellows, and three physician assistants. Their scores will be averaged for each statement. Unilaterals and bilaterals will be judged separately.

Questionnaires will evaluate the breast esthetics based on a 1 to 5 scale (strongly disagree, disagree, somewhat agree, agree, strongly agree) of the following statements:

1. The overall shape of the reconstructed breast is good.
2. The overall symmetry with the other breast is good.
3. The upper pole transition is natural in appearance.
4. The lower pole has adequate fullness and ptosis.
5. The inframammary fold is in the appropriate position.
6. The lateral border of the breast has good contour.

7. The medial border of the breast has good contour.
8. The breast mound is in the appropriate position.
9. The breast surface contour is generally smooth.
10. There is minimal visible rippling of the implant.

10.0 Number of Patients

Approximately 398 patients will be enrolled in this study.

11.0 Criteria for Removal from the Study

Patients will be removed from the study if they change their mind about participation for any reason.

12.0 Reporting Requirements

Institutional guidelines for reporting of adverse events will be followed.

13.0 Data Confidentiality Plans

The confidentiality of the subjects will be preserved at all times. In no way will any individual subject be identifiable upon discussion or presentation of the data. HIPAA identifiers will be collected but will be replaced by unique study numbers in the analytical file. The data will be stored in a password-protected computer with firewall protection. Data will only be known to the PI and research staff. Study records will be destroyed within five (5) years after study publication.

14.0 References

1. Breuing KH, Warren SM. Immediate bilateral breast reconstruction with implants and inferolateral AlloDerm slings. *Ann Plast Surg*, 55(3):232-9, 2005.
2. Gamboa-Bobadilla GM. Implant breast reconstruction using acellular dermal matrix. *Ann Plast Surg*, 56(1):22-5, 2006.
3. Topol BM, Dalton EF, Ponn T, et al. Immediate single-stage breast reconstruction using implants and human accelular dermal tissue matrix with adjustment of the lower pole of the breast to reduce unwanted lift. *Ann Plast Surg*, 61(5):494-9, 2008.
4. Maxwell GP, Gabriel A. Possible future development of implants and breast augmentation. *Clin Plast Surg*, 36(1)167-72, 2009.
5. Becker S, Saint-Cyr M, Wong C, et al. AlloDerm versus DermaMatrix in immediate expander-based breast reconstruction: a preliminary comparison of

complication profiles and material compliance. *Plast Reconstr Surg*, 123(1):1-6, 2009.
6. Stump A, Holton LH 3rd, Connor J, et al. The use of acellular dermal matrix to prevent capsule formation around implants in a primate model. *Plast Reconstr Surg*, 124(1):82-91, 2009.
7. Namnoum JD. Expander/implant reconstruction with AlloDerm: recent experience. *Plast Reconstr Surg*, 124(2):387-94, 2009.
8. Grabov-Nardini G, Haik J, Regev E, et al. AlloDerm sling for correction of synmastia after immediate, tissue expander, breast reconstruction in thin women. *Eplasty*, 9:e54.
9. Chun YS, Verma K, Rosen H, et al. Implant-based breast reconstruction using acellular derma matrix and the risk of postoperative complications. *Plast Reconstr Surg*, 125(2):429-36, 2010.
10. Chen WF, Barounis D, Kalimuthu R. A novel cost-saving approach to the use of acellular dermal matrix (AlloDerm) in postmastectomy breast and nipple reconstructions. *Plast Reconstr Surg*, 125(2)479-81, 2010.
11. Lanier ST, Wang ED, Chen JJ, et al. The effect of acellular dermal matrix use on complication rates in tissue expander/implant breast reconstruction. *Ann Plast Surg*, 64(5):674-8, 2010.