A PROSPECTIVE TRIAL TO ASSESS TUMOR: BREAST RATIO AND PATIENT SATISFACTION IN FOLLOWING LUMPECTOMY VERSUS MASTECTOMY WITH RECONSTRUCTION

Washington University School of Medicine
Department of Surgery
660 S. Euclid Ave., Campus Box 8109
St. Louis, MO 63110

Version date: 09/07/2018

Principal Investigator: Terence M. Myckatyn, MD

Phone: (314) 996-8800
Email: myckatyn@ wustl.edu

Sub-Investigators: Marissa M. Tenenbaum, MD
Amy E. Cyr, MD
Julie A. Margenthaler, MD, FACS

A PROSPECTIVE TRIAL TO ASSESS TUMOR: BREAST RATIO AND PATIENT SATISFACTION IN FOLLOWING LUMPECTOMY VERSUS MASTECTOMY WITH RECONSTRUCTION

INDEX

1.0 BACKGROUND AND RATIONALE

1.1 Background

Patients with localized ductal carcinoma in situ (DCIS) and Stage I-IIIA breast cancers are usually candidates for either breast conservation therapy (BCT: lumpectomy with radiation) or mastectomy since survival outcomes are comparable. By its very name, BCT implies superior aesthetic outcomes as breast tissue is preserved. Not surprisingly, when offered, the majority of women will choose BCT over mastectomy with reconstruction, (~65% BCT vs. 35% with mastectomy of which <30% of those receive a reconstruction).

The degree of tissue loss with BCT however falls on a spectrum that is influenced by tumor size and the variable impact of radiation therapy. Large-breasted women are able to absorb a larger absolute tumor resection than smaller breasted women due to the relative size of their breast. Further, the majority of women note that the upper-inner pole of their breast is more aesthetically relevant than other quadrants. Therefore, BCT impacting this region may create a relatively greater degree of dissatisfaction. A recent survey performed by the American Society of Plastic Surgeons found that ~ 46% of women undergoing BCT were disappointed with their results. In another survey – the Breast Cancer Treatment and Outcomes Survey – increased breast asymmetry following BCT was correlated with depressed mood and a feeling of stigmatization. In another study, tumors involving >10% of breast volume, and particularly those located in the medial breast, were associated with decreased patient satisfaction. Unfortunately, quantification of tumor: breast ratio was imprecisely calculated, and patient satisfaction was not determined by a validated, breast-specific patient reported outcomes tool in any of these studies.

While the percentage of women undergoing mastectomy with reconstruction is still under 30%, and approximately 70% are not even informed of their options, there is increasing evidence that successful reconstruction offers a clear biopsychosocial advantage. Advanced reconstructive techniques including nipple-sparing mastectomy, immediate implant reconstruction, microvascular perforator flaps and adjunctive imaging and materials technologies have significantly improved patient outcomes in terms of pain, function, patient reported satisfaction, and lowered complication rates. Compared to national trends, the rate of reconstruction following mastectomy is 59% overall at our institution. Of the remaining patients who did not undergo reconstruction following mastectomy, 60% chose not to have it and 40% had medical contraindications that precluded it as an option.

Our ability to quantify patient satisfaction has also improved with the advent of the Breast Q. This instrument represents the most comprehensive and specific quantitative method for patient self-assessment following breast surgery. Specific modules for breast reconstruction and BCT are available. The Breast Q is superior to other previously validated instruments like

the Short Form (SF-36) which provides a generic psychometric overview of patient satisfaction on an 8 point scale but lacks items specific to breast surgery. The European Organization for Research and Treatment or Cancer's Quality of Life Questionnaire Breast Cancer Module (EORTC QLQ-30 Br23) does provide a breast cancer-specific module, but evaluates overall function and does not differentiate between breast conservation therapy and reconstruction. We believe that for patients who get BCT, the relative size of the tumor and volume of its resection will profoundly impact breast symmetry and therefore impact patient reported outcomes on the Breast Q.

1.2 Rationale

This study will show that many patients currently selected for lumpectomy will have better aesthetic outcomes when mastectomy with reconstruction is chosen. While the absolute dimensions of a breast cancer are relevant to staging and treatment, tumor: breast ratio is a key factor in determining patient satisfaction with lumpectomy, and in turn should determine when a mastectomy with reconstruction should be performed to yield an optimal result. It is the relative size of the tumor and volume of its resection that will profoundly impact breast symmetry and therefore impact patient reported outcomes following BCT. Tumor: breast ratios > 0.2 will be associated with progressively poorer patient satisfaction outcomes when treated with BCT than would be provided by mastectomy with reconstruction. Tumors in the superomedial breast will be even more sensitive to tumor: breast ratio. We hypothesize that BCT will be particularly sensitive to tumor: breast ratio whereas mastectomy with reconstruction will be less dependent. The results from this study will enable plastic and oncologic surgeons to identify a new cohort of patients, previously destined for BCT, to undergo a mastectomy with reconstruction to optimize their overall satisfaction with the aesthetic outcomes with equivalent treatment of their disease.

2.0 OBJECTIVES

2.1 Primary Objective

- At which tumor: breast ratio do patient reported outcomes justify performance of a mastectomy with reconstruction versus BCT in stage-matched patients?

2.2 Secondary Objectives

- Does tumor location impact the influence of tumor: breast ratio on patient reported outcomes following mastectomy with reconstruction or BCT?
- How does the pre and post-op Breast Q for the two groups (mastectomy + recon vs. BCT) reflect the tumor: breast ratio as calculated from 3D images rendered from MRI utilizing software-based algorithms?
- How does the pre and post-op Breast Q for the two groups (mastectomy + recon vs. BCT) reflect the VECTRA 3D generated mammometrics?

- What is the impact of radiation in BCT on Breast Q (Q-score before and after radiotherapy) and VECTRA (breast volume, nipple position, total breast skin surface area before and after radiotherapy)?
- How do complications that arise from each scenario (mastectomy + recon) vs. BCT impact patient satisfaction?
- What is the impact of tumor location and obesity as independent determinants of patient satisfaction in the two groups (mastectomy + recon vs. BCT) relative to tumor: breast ratio?

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

- Patient must be scheduled to undergo breast conservation therapy (BCT), mastectomy or mastectomy with immediate reconstruction (defined as initiating the reconstructive process at time of mastectomy) for ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), and early stage breast cancer (Clinical Stages IA-IIB). Stage IIB tumors are 2-5 cm with micrometastases 0.2 to 2.0 cm in lymph nodes; or 2-5 cm tumor with 1-3 positive axillary or internal mammary lymph nodes, or >5 cm with no lymph node involvement. Clinical staging, based on imaging and physical exam will be used for enrollment. Patients that are unexpectedly upstaged will be excluded at that time. For staging reference please see http://www.cancer.gov/cancertopics/pdq/treatment/breast/patient/page2#keypoint13.
- If multifocal/multicentric disease of the ipsilateral breast is encountered and patients are still deemed eligible for BCT or mastectomy per standard of care, then the tumor area will be calculated as the total volumes of the identified foci.
- Patient must be between 18-72 years old.
- Patient must be able to understand and willing to sign a written informed consent document.

3.2 Exclusion Criteria

- Cognitive impairment
- History of radiation to the chest wall or breasts
- Patients unable to undergo MRI due to metallic implant or claustrophobia
- Patients that are pregnant since breast MRI is contraindicated
- History of previous breast surgery other than primary cosmetic augmentation or breast reduction
- Identification of a concurrent or synchronous contralateral cancer during the enrollment period
- Any patient that would not have been considered for BCT or reconstruction
- BCT patients planning to proceed with reconstruction during their study participation timeline.

3.3 Inclusion of Women and Minorities

Only women will be enrolled due to the anatomical specificity of breast cancer. Members of all races and ethnic groups are eligible for this trial.

4.0 CONFIRMATION OF PATIENT ELIGIBILITY

The following information is required to confirm patient eligibility prior to registering patient:

1. Completed eligibility checklist, signed and dated by a member of the study team
2. Copy of appropriate source documentation confirming patient eligibility
3. Signed consent form
4. Documentation of informed consent process
5. Patient's race, sex, and DOB
6. Assignment of unique study identifier
7. Registering MD's name
8. Planned date of enrollment

5.0 REGISTRATION PROCEDURES

Patients must be registered in the Siteman Cancer Center database within one working day of enrolling physician signing off on patient eligibility.

6.0 PATIENT VISITS

6.1 Visit #1: Preoperative Evaluation with Surgical Oncologist

The surgical oncologists will discuss treatment options with patients during their initial consultation. Patients will be evaluated to determine whether their age, planned surgical procedure, and medical/surgical history meet the inclusion criteria specified in Section 3.1. Patients will also be evaluated to be sure they do not meet any of the exclusion criteria in Section 3.2. Patients meeting all study criteria will be approached about their ability to participate in this research trial.

The relevant Breast-Q Module is routinely administered pre-operatively to obtain baseline quality of life data on all patients being evaluated for breast cancer surgery. There are 3 distinct BREAST Q surveys based on the type of surgery planned. There is a "Breast Conservation Therapy" version, a "Mastectomy Only" version and a "Mastectomy with Reconstruction" version. Each version has surgery specific pre-operative and postoperative modules. All contain several domains that generate a Q-Score (0-100) enabling quantitative and validated comparison between groups for a particular domain (patient overall satisfaction, satisfaction with care, satisfaction with breasts, etc.). It should take 10-15 minutes for this self-administered

questionnaire to be completed.

6.2 Visit #2: MRI Visit

Diagnostic imaging visit with radiology is performed via MRI per standard of care prior to the surgical procedure that removes breast tissue via lumpectomy or mastectomy. The 3D reconstruction can be performed at any time after image acquisition as image data is stored per standard procedure, in the radiology department. The tumor: breast ratio calculation will be rendered from these images for the purposes of this study. It is possible some patients may have already had a MRI prior to enrollment into this study.

6.3 Visit #3: Plastic Surgeon Visit (*Group B Mastectomy + Reconstruction Only*)

The plastic surgeons will discuss reconstructive treatment options with patients. The plastic surgeons may order additional tests and imaging procedures during this evaluation as needed.

The Breast Q Reconstruction + Expectations Module will be administered pre-operatively to obtain baseline quality of life data if it was not completed at visit #1. It should take 10-15 minutes for this self-administered questionnaire to be completed. The Breast Q is given to all patients seeking breast surgery in the clinical practice and is not a research procedure.

6.4 Surgical Intervention (T=0)

Standardized operation techniques will be used in all treatment groups. All surgeries will be performed by surgical oncologists experienced with breast oncology and affiliated with the Siteman Cancer Center at Washington University. All reconstructions will be performed by one of two plastic surgeons who are also experienced with all forms of breast reconstruction (Drs. Tenenbaum and Myckatyn).

Operative notes and pathology reports will be collected.

Postoperative management is standard of care for all patients. Postoperative complications and need for re-excision will be recorded and monitored.

6.5 Visits #4 - 5: Post-Operative Visits

All patients will have routine follow up visits after surgery. Timing of follow-up will be variable among the three groups.

- **Group A:** The surgical oncologist will see the BCT group.
    - Post-Lumpectomy 1st Post-op Visit before Radiotherapy *(1-10 weeks after lumpectomy)*
        - Post-Op Breast Q will be administered and routine imaging taken to quantify volume and mammometric parameters

- Post-Lumpectomy Post-op Visit <u>after</u> Radiotherapy *(6- 18 months after radiation or the latest follow-up time point within the duration confines of our study period.)*
    - Post-Op Breast Q will be administered and routine imaging taken to quantify volume and mammometric parameters

Some patients will require no adjuvant chemotherapy following lumpectomy based on their pathology. These patients are typically radiated 4-10 weeks after lumpectomy. Other patients will require chemotherapy after lumpectomy but prior to radiation. Chemotherapy duration can vary depending on selected treatment regimen but can be between 8-18 weeks excluding Herceptin which typically is administered every 6 weeks for 1 year. Patients receive Herceptin during radiation and reconstruction and so the administration of Herceptin does not independently alter any study time points. Patients will not undergo chemotherapy or radiation until after re-excision is performed in cases where there is a positive cancer margin after lumpectomy per standard of care.

- **Group B:** Mastectomy with reconstruction patients will be seen in follow up with plastic surgery.
    - Post-mastectomy 1st Post-op Visit <u>before</u> Completion of Reconstruction *(1-10 weeks after mastectomy)*
        - Post-Op Breast Q will be administered and routine imaging taken to quantify volume and mammometric parameters
    - Post-mastectomy Post-op Visit <u>after</u> Final Reconstruction (*3-8months after final reconstructive procedure or the latest follow-up time point within the duration confines of our study period.*)
        - Post-Op Breast Q will be administered and routine imaging taken to quantify volume and mammometric parameters

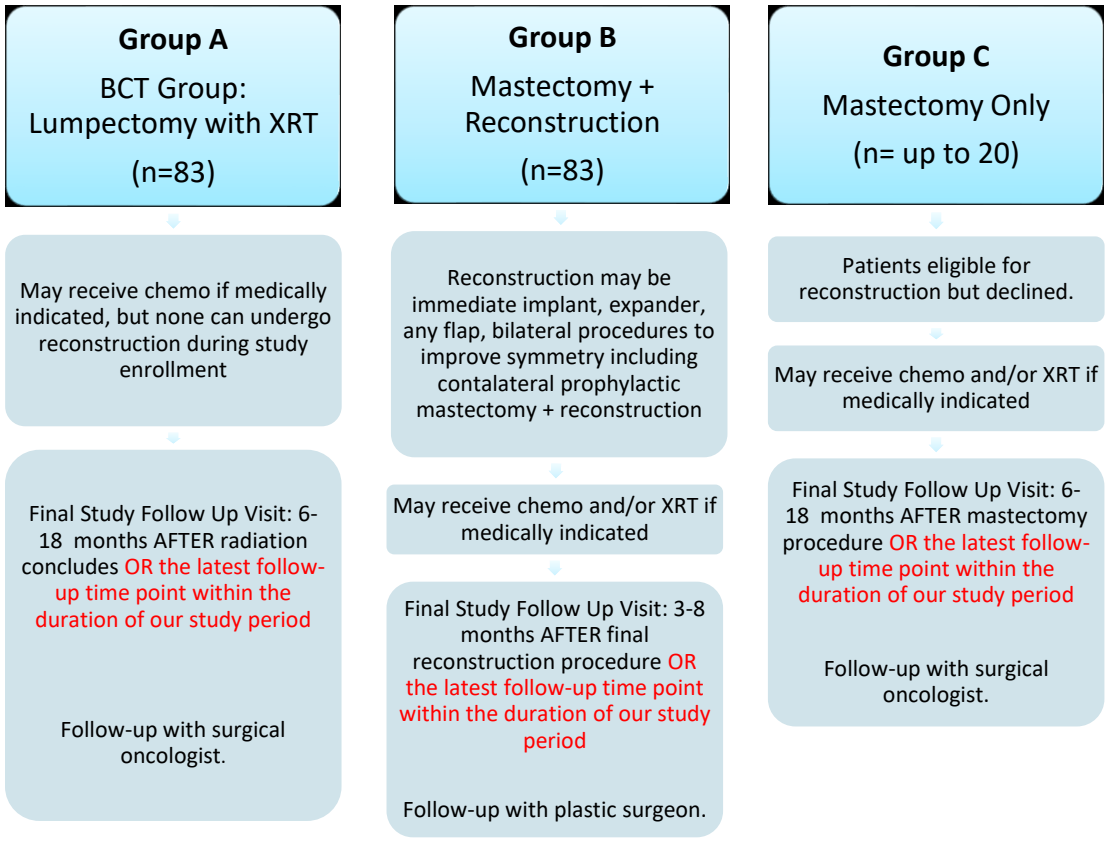
- **Group C:** The surgical oncologist will see the mastectomy only group.
    - Post-mastectomy 1st Post-op Visit *(1-10 weeks after mastectomy)*
        - Post-Op Breast Q will be administered and routine imaging taken to quantify volume and mammometric parameters
    - Post-mastectomy Post-op Visit *(6- 18 months after mastectomy or the latest follow-up time point within the duration confines of our study period.)*
        - Post-Op Breast Q will be administered and routine imaging taken to quantify volume and mammometric parameters

6.6 Variable Duration of Study Observation

Some patients may receive neoadjuvant chemotherapy prior to either lumpectomy or mastectomy. Adjuvant chemotherapy may also be required based on pathologic findings. If required, chemotherapy may begin approximately 6 weeks following surgery. Chemotherapy

duration can vary depending on selected agents but can be between 8-18 weeks. Radiotherapy if needed is usually scheduled for 6 weeks after the final chemotherapy and can last approximately 6 weeks. Treatment time may be lengthened for complications. Reconstruction procedures can happen in multiple stages, therefor extending the time to final completion. This variability in adjuvant treatment will affect the timelines for follow-up and will be recorded for study purposes.

Fig. 1. Study Arms and Duration

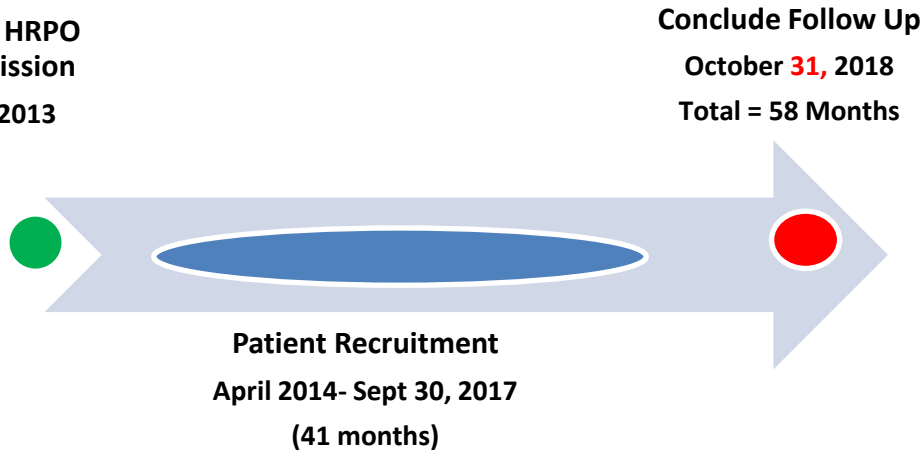


6.7 Criteria for Removal from Study

If the patient, at any time wishes to be removed from the study, they will be. This study does not propose any new interventions – it is an observational study of patients receiving normal, uninfluenced care for the treatment of breast cancer.

6.8 Anticipated Time Duration of Study

RECRUITMENT: 41 Months to recruit
FOLLOW-UP: MONTHS: Variable with minimum 12 months and maximum 4.5 years
TOTAL TIME TO CLOSURE: 58 MONTHS



7.0 REGULATORY AND REPORTING REQUIREMENTS

7.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

This is an observational study where diagnostic imaging and patient reported outcomes are measured in the context of routine breast cancer care. There will be no intervention that is unique to this study that does not normally occur with standard patient care. As such, there are no adverse events that are unique to this study.

Common complications associated with breast oncologic and reconstructive surgery will be tracked since we suspect that complications will be an independent risk for adversely affecting patient reported outcomes independent of tumor: breast ratio. Common complications will be obtained by reviewing the inpatient and outpatient electronic medical records in Clinical Desktop and Allscripts of all enrolled patients. We will therefore record anticipated morbidities such as anesthetic complications, bleeding, infection requiring readmission or surgery, wound healing problems requiring surgical intervention, need for re-excision in lumpectomy due to positive margins, and reconstructive failures due to flap loss or breast prosthesis explant for the purposes of this study. However, none of these are expected to be related to the performance of this study

and will not be summarized, graded or reported as traditional adverse event reporting in an interventional oncology trial.

7.2 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subject's research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

7.4 Serious Noncompliance

Definition: noncompliance that materially increases risks, which result in substantial harm to subjects or others, or that materially, compromises the rights or welfare of participants.

7.5 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.
Pre-approval of all protocol exceptions must be obtained from the Human Research Protection Office prior to the event.

7.6 Reporting to the Human Research Protection Office (HRPO) and the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.

- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event.

7.7 Timeframe for Reporting Required Events

Unanticipated Problems	
Any unanticipated events as described in Section 7.2	Immediately, within 24 hours to PI and within 10 working days to the IRB
Noncompliance and Serious Noncompliance	
All noncompliance and serious noncompliance	Immediately, within 24 hours, to PI and within 10 working days to the IRB

7.8 Anticipated Risks

There are no additional risks that this study poses to study participants relative to not participating. All enrolled patients are subject to the same risks as any other patient undergoing standard of care breast oncologic and reconstructive care.

8.0 DATA SUBMISSION SCHEDULE

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Eligibility Checklist RedCap Enrollment, Visit 1, Visit 2 MRI, and Visit 3 Plastics (if applicable)	Prior to surgery
RedCap Surgical Intervention	Following receipt of final operative and pathology reports
RedCap Follow-Up Forms Post-Operative Visit 1, Oncology Course, and Post-Operative Visit 2	**Group A:** ○ Post-Lumpectomy 1st post-op visit before Radiotherapy *(1-10 weeks after lumpectomy)* ○ Post-Lumpectomy post-op visit after radiotherapy *(6-18 months after radiation or the latest follow-up time point within the duration confines of our study period.)* **Group B:** ○ Post-mastectomy 1st post-op visit before completion of reconstruction *(1-10 weeks after mastectomy)* ○ Post-mastectomy Post-op Visit after final reconstruction (3-8 months after final reconstructive procedure *or the latest follow-up time point within the duration confines of our study period.*) **Group C:** ○ Post-mastectomy 1st post-op visit *(1-10 weeks after mastectomy)* Post-mastectomy post-op visit *(6-18 months after mastectomy or the latest follow-up time point within the*

	duration confines of our study period.)
Unanticipated Event via HRPO	At the time of any unanticipated event
MRI T:B ratio, Breast Q-Scores, and Vectra Mammometrics	The coordinators will ensure MRI performed, Breast-Q's completed and Vectra images captured during active patient phase. MRI T:B ratio will be performed late in the active study phase to allow for a limited number of staff to perform bulk of measurements to optimize standardization. There is also a possibility the software will be upgraded to automate the T:B ratio later in the study period. Breast-Q scores and Vectra mammometrics will be also evaluated in bulk late in the active study phase using SAS, SPSS, or another similar statistical program.

9.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC).

The Principal Investigator will review all patient data at least monthly and provide a semi-annual report to the Quality Assurance and Safety Monitoring (QASM) Committee. This report will include:

1. the protocol title, IRB protocol number, and the activation date of the study.
2. the number of patients enrolled to date
3. the date of first and most recent patient enrollment
4. a summary of all unexpected events
5. a response evaluation for evaluable patients
6. a summary of any recent literature that may affect the ethics of the study.

The study principal investigator and Research Patient Coordinator will monitor for unexpected events on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of a research related and unanticipated adverse event, it will be reported to the HRPO according to institutional guidelines.

10.0 STATISTICAL CONSIDERATIONS

10.1 Outcome Measures

- Tumor: breast ratio generated from MRI
- The Breast Q (pre and post op) outcome measurements
- Breast mammometrics generated from 3D imaging

10.2 Data Fields Recorded

- PATIENT VARIABLES : BMI, smoking history, patient age, race, previous history breast augmentation,
- CANCER VARIABLES: cancer stage, presence or absence of sentinel lymph node biopsy, receptor status, tumor location, multifocal
- RADIATION & CHEMOTHERAPY VARIABLES: radiation received, length of treatment, chemotherapy selected, complications causing radiation or chemotherapy delay or dose reduction
- BREAST VARIABLES :, standardized breast measurements (sternal notch to nipple, IMF to nipple, maximum areolar diameter, ptosis)
- SURGICAL VARIABLES: patients undergoing mastectomy with reconstruction as per routine will be recorded as immediate implant, expander-reconstruction, use of acellular dermal matrix, or flap including predominantly DIEP, but also free TRAM, latissimus, PAP, SIEA, TUG, or SGAP. Also balancing procedures will be considered like breast reduction/lift/augmentation/augmentation with lift, fat grafting, adjacent tissue transfer, pseudohernia repair, correction of malposition, implant exchange, capsulectomy, capsulorrhaphy, Ryan procedure,
- IMAGING VARIABLES: tumor: breast ratio, mammometrics (breast volumes, surface area, nipple position, chest wall morphology, vectors, anatomic landmarks)
- COMPLICATION VARIABLES: complications related to breast surgery will be recorded (anesthetic complications, bleeding, infection requiring readmission or surgery, wound healing problems requiring surgical intervention, need for re-excision in lumpectomy due to positive margins, and reconstructive failures due to flap loss or breast prosthesis explant). Patients with complications will be included as this is a key determinant of patient reported outcomes.

10.3 Study Design

All DCIS, LCIS and Stage IA-IIB breast cancers that are reasonably treated with mastectomy or BCT will be screened for eligibility for participation in this study. There will be significant heterogeneity within each group in terms of presence/absence, type, timing (adjuvant/neoadjuvant) and duration of chemoradiation administered. To standardize the timing of our outcome measurement, t=0 will always be in relation to the tumor surgery (lumpectomy or mastectomy). We will also obtain a late time point for last follow-up at least 6 months after the final intervention whether therapeutic or reconstructive, whichever is last. Data collected at this late time point – relative to the initial cancer resection at t=0 – is expected

to vary substantially (months-year) between subjects. We have carefully selected IIB patients as the most advanced stage of breast cancer included. This enables us to evaluate patients with large (>5 cm) tumors that are candidates for mastectomy or BCT which will be important since it is in the larger tumors we hypothesize that patient satisfaction and mammometric data would favor mastectomy + reconstruction over BCT.

Patients that meet the inclusion criteria but who opt for mastectomy without reconstruction are included as a control group to further evaluate the impact of post-mastectomy reconstruction.

10.4 Sample Size

Mammometrics will be converted to comparable data and then related to Q-Score as these are expected to be complex relationships.

We anticipate enrolling 83 subjects per study arm (166 total) with up to an additional 20 subjects undergoing mastectomy without reconstruction as a negative control for a total of 186 patients.

Initial plan is to use G*Power v 3.1, or a comparable statistical package. Based on an effect size d=of 0.45, Type I error α=0.05, and power (1-ß) =0.8, normal distribution, and 2-tails, we will require 83 subjects per arm (166 total). Assumptions: A difference in mean scores of 10 on a 100-point scale (Q-Score generated from Breast Q) was assumed to be significant. This is determined by assuming an SD of 20, with one-half of an SD being the threshold of discrimination for change in health-related quality of life.

Sample size calculations are based on 1) previously reported sample size calculations where data from the Breast Q for Breast Reconstruction was used with 2) the open-source statistical package G*Power 3.1.

10.5 Data Analysis

This is a longitudinal observational study to compare effects of two treatment groups on the quality of life and to explore how the treatment effects are modified by T:B ratio. For each study patient, we have a data vector D=(group, T:B ratio, location, Q(t), 3D(t), W), where group is a binary indicator for two comparison groups. T:B ratio is the tumor: breast ratio measured at a continuous scale, and location is a binary indicator of tumor location. Q(t) and 3D(t) are Q score and the VECTRA 3D generated mammometrics respectively, measured as continuous variables at t=(0,1,2), where t=0 is the pre-treatment baseline measurement. W is a set of patient characteristics – e.g., age, obesity, stage, etc. A longitudinal study generates correlations among the repeated measurements within the same individual, and observational study often comes with a biased estimate of the treatment comparison due to confounding. These two issues, the correlation of repeated measurements and confounding, must be taken into account in the data

analysis. Regression analyses of correlated data can simultaneously address these two issues. There are two families of statistical methods for regression analyses of correlated data – mixed effect model and generalized estimating equation (GEE). Both are appropriate for our study, even though the interpretations are different – population average vs subject specific. Data analyses for our study will be performed within this framework to adjust for the patient characteristics for unbiased comparison of treatment effect and to take into account the correlations.

10.5.1 Primary objectives:

For main effect of treatment group on Q-score: fit and test a model with Q score as the dependent variable and group as the independent variable, controlling for W in the model – (Model 1).

For the difference in Q score between two treatment groups modified by T:B ratio: fit and test a model with Q score as the dependent variable, and group, T:B ratio, and group-by-T:B ratio interaction as the independent variables, controlling for W in the model – (Model 2). The results can be better presented as a graph with two lines – Q score as a function of T:B ratio for these treated with BCT, and for those treated with Mastectomy+reconstruction.

10.5.2 Secondary objectives:

Does tumor location impact the influence of tumor: breast ratio on patient reported outcomes following mastectomy with reconstruction or BCT?

- Add location and three way interaction term –group-by-T:B ratio-by-location into Model 2 – (Model 3). The results can be better presented as two graphs – one for each location. See Model 2 for the graph.

How does the pre and post-op Breast Q for the two groups (mastectomy + recon vs. BCT) reflect the tumor: breast ratio as calculated from 3D images rendered from MRI utilizing software-based algorithms?

- Fit and test a model with Q-score as the dependent variable and 3D image data as the independent variable with appropriate non-linear terms for 3D (e.g. spline functions), with group and possible interaction of group-by-3D (Model 4).

How does the pre and post-op Breast Q for the two groups (mastectomy + recon vs. BCT) reflect the VECTRA 3D generated mammometrics?

- Both the Breast Q and the VECTRA 3 D generated mammometrics are continuous variables. The correlation between them will be quantified by Pearson or Spearman correlation coefficient with one sample t test for population correlation coefficient =0, and with Fisher Z transformation to test the population correlation coefficient not equal to zero.

What is the impact of radiation in BCT on Breast Q (Q-score before and after

radiotherapy) and VECTRA (breast volume, nipple position, total breast skin surface area before and after radiotherapy)?

- Perform the subgroup analyses of BCT patients comparing change in outcomes of interest before and after radiation.

How do complications that arise from each scenario (mastectomy + recon) vs. BCT impact patient satisfaction?

- Fit and test a model with Q-score as the dependent variable and complication and group, and possible group-by-complication interaction as independent variables controlling for W in the model.

What is the impact of tumor location and obesity as independent determinants of patient satisfaction in the two groups (mastectomy + recon vs. BCT) relative to tumor: breast ratio?

- Fit and test a model with Q-score as the dependent variable and group, T:B ratio, location, and obesity as the independent variables, controlling for W in the model. Obtain the standardized regression coefficients for location, obesity, and T:B ratio, and compare each other to determine their relative importance.

11.0 REFERENCES

1. Waljee JF, Hu ES, Newman LA, Alderman AK**.** Correlates of patient satisfaction and provider trust after breast-conserving surgery. *Cancer*. 2008;112(8):1679-87.
2. Waljee JF, Hu ES, Newman LA, Alderman AK**.** Predictors of breast asymmetry after breast-conserving operation for breast cancer. *Journal of the American College of Surgeons*. 2008;206(2):274-80.
3. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *The New England journal of medicine*. 2002;347(16):1233-41.
4. McGuire KP, Santillan AA, Kaur P, Meade T, Parbhoo J, Mathias M, et al. Are mastectomies on the rise? A 13-year trend analysis of the selection of mastectomy versus breast conservation therapy in 5865 patients. *Annals of surgical oncology*. 2009;16(10):2682-90.
5. Katipamula R, Degnim AC, Hoskin T, Boughey JC, Loprinzi C, Grant CS, et al. Trends in mastectomy rates at the Mayo Clinic Rochester: effect of surgical year and preoperative magnetic resonance imaging. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009;27(25):4082-8.
6. Vicini FA, Eberlein TJ, Connolly JL, Recht A, Abner A, Schnitt SJ, et al. The optimal extent of resection for patients with stages I or II breast cancer treated with conservative surgery and radiotherapy. *Ann Surg*. 1991;214(3):200-4; discussion 4-5.
7. Morrow M, Harris JR, Schnitt SJ**.** Surgical margins in lumpectomy for breast cancer--bigger is not better. *N Engl J Med*. 2012;367(1):79-82.

8. Arriagada R, Le MG, Rochard F, Contesso G**.** Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institut Gustave-Roussy Breast Cancer Group. *J Clin Oncol*. 1996;14(5):1558-64.
9. Blichert-Toft M, Rose C, Andersen JA, Overgaard M, Axelsson CK, Andersen KW, et al. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. Danish Breast Cancer Cooperative Group. *J Natl Cancer Inst Monogr*. 1992(11):19-25.
10. Poggi MM, Danforth DN, Sciuto LC, Smith SL, Steinberg SM, Liewehr DJ, et al. Eighteen-year results in the treatment of early breast carcinoma with mastectomy versus breast conservation therapy: the National Cancer Institute Randomized Trial. *Cancer*. 2003;98(4):697-702.
11. van Dongen JA, Voogd AC, Fentiman IS, Legrand C, Sylvester RJ, Tong D, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst*. 2000;92(14):1143-50.
12. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*. 2002;347(16):1227-32.
13. Wang HT, Barone CM, Steigelman MB, Kahlenberg M, Rousseau D, Berger J, et al. Aesthetic outcomes in breast conservation therapy. *Aesthetic surgery journal / the American Society for Aesthetic Plastic surgery*. 2008;28(2):165-70.
14. Morrow M, Jagsi R, Alderman AK, Griggs JJ, Hawley ST, Hamilton AS, et al. Surgeon recommendations and receipt of mastectomy for treatment of breast cancer. *JAMA : the journal of the American Medical Association*. 2009;302(14):1551-6.
15. Waljee JF, Hu ES, Ubel PA, Smith DM, Newman LA, Alderman AK**.** Effect of esthetic outcome after breast-conserving surgery on psychosocial functioning and quality of life. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2008;26(20):3331-7.
16. Cochrane RA, Valasiadou P, Wilson AR, Al-Ghazal SK, Macmillan RD**.** Cosmesis and satisfaction after breast-conserving surgery correlates with the percentage of breast volume excised. *The British journal of surgery*. 2003;90(12):1505-9.
17. Losken A, Fishman I, Denson DD, Moyer HR, Carlson GW**.** An objective evaluation of breast symmetry and shape differences using 3-dimensional images. *Ann Plast Surg*. 2005;55(6):571-5.
18. Moyer HR, Carlson GW, Styblo TM, Losken A**.** Three-dimensional digital evaluation of breast symmetry after breast conservation therapy. *J Am Coll Surg*. 2008;207(2):227-32.
19. Han J, Grothuesmann D, Neises M, Hille U, Hillemanns P**.** Quality of life and satisfaction after breast cancer operation. *Archives of gynecology and obstetrics*. 2010;282(1):75-82.
20. Arndt V, Stegmaier C, Ziegler H, Brenner H**.** Quality of life over 5 years in women with breast cancer after breast-conserving therapy versus mastectomy: a population-based study. *Journal of cancer research and clinical oncology*. 2008;134(12):1311-8.
21. Clough KB, Lewis JS, Couturaud B, Fitoussi A, Nos C, Falcou MC**.** Oncoplastic techniques allow extensive resections for breast-conserving therapy of breast carcinomas. *Annals of Surgery*. 2003;237(1):26-34.
22. Rizzo M, Iyengar R, Gabram SG, Park J, Birdsong G, Chandler KL, et al. The effects of additional tumor cavity sampling at the time of breast-conserving surgery on final margin status, volume of resection, and pathologist workload. *Annals of surgical oncology*. 2010;17(1):228-34.

23. Veiga DF, Veiga-Filho J, Ribeiro LM, Archangelo I, Jr., Balbino PF, Caetano LV, et al. Quality-of-life and self-esteem outcomes after oncoplastic breast-conserving surgery. *Plast Reconstr Surg*. 2010;125(3):811-7.
24. Kalbhen CL, McGill JJ, Fendley PM, Corrigan KW, Angelats J**.** Mammographic determination of breast volume: comparing different methods. *AJR. American journal of roentgenology*. 1999;173(6):1643-9.
25. Katariya RN, Forrest AP, Gravelle IH**.** Breast volumes in cancer of the breast. *British journal of cancer*. 1974;29(3):270-3.
26. Harris JR, Levene MB, Svensson G, Hellman S**.** Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. *Int J Radiat Oncol Biol Phys*. 1979;5(2):257-61.
27. Aaronson NK, Bartelink H, van Dongen JA, van Dam FS**.** Evaluation of breast conserving therapy: clinical, methodological and psychosocial perspectives. *Eur J Surg Oncol*. 1988;14(2):133-40.
28. Cardoso MJ, Cardoso J, Amaral N, Azevedo I, Barreau L, Bernardo M, et al. Turning subjective into objective: the BCCT.core software for evaluation of cosmetic results in breast cancer conservative treatment. *Breast*. 2007;16(5):456-61.
29. Cardoso MJ, Cardoso JS, Vrieling C, Macmillan D, Rainsbury D, Heil J, et al. Recommendations for the aesthetic evaluation of breast cancer conservative treatment. *Breast Cancer Res Treat*. 2012;135(3):629-37.
30. Kronowitz SJ, Feledy JA, Hunt KK, Kuerer HM, Youssef A, Koutz CA, et al. Determining the optimal approach to breast reconstruction after partial mastectomy. *Plast Reconstr Surg*. 2006;117(1):1-11; discussion 2-4.
31. Bostwick J, 3rd**.** The patient and surgeon. In: Bostwick J, 3rd, ed. Plastic and Reconstructive Surgery. 2nd ed. St Louis, MO: Quality Medical Publishsing; 2000:30-4.
32. Losken A, Seify H, Denson DD, Paredes AA, Jr., Carlson GW**.** Validating three-dimensional imaging of the breast. *Ann Plast Surg*. 2005;54(5):471-6; discussion 7-8.
33. Quan M, Fadl A, Small K, Tepper O, Kumar N, Choi M, et al. Defining pseudoptosis (bottoming out) 3 years after short-scar medial pedicle breast reduction. *Aesthetic plastic surgery*. 2011;35(3):357-64.
34. Small KH, Tepper OM, Unger JG, Kumar N, Feldman DL, Choi M, et al. Re-defining pseudoptosis from a 3D perspective after short scar-medial pedicle reduction mammaplasty. *Journal of plastic, reconstructive & aesthetic surgery : JPRAS*. 2010;63(2):346-53.
35. Tepper OM, Karp NS, Small K, Unger J, Rudolph L, Pritchard A, et al. Three-dimensional imaging provides valuable clinical data to aid in unilateral tissue expander-implant breast reconstruction. *The breast journal*. 2008;14(6):543-50.
36. Tepper OM, Small KH, Unger JG, Feldman DL, Kumar N, Choi M, et al. 3D analysis of breast augmentation defines operative changes and their relationship to implant dimensions. *Annals of Plastic Surgery*. 2009;62(5):570-5.
37. Tepper OM, Small K, Rudolph L, Choi M, Karp N**.** Virtual 3-dimensional modeling as a valuable adjunct to aesthetic and reconstructive breast surgery. *American journal of surgery*. 2006;192(4):548-51.
38. Tepper OM, Unger JG, Small KH, Feldman D, Kumar N, Choi M, et al. Mammometrics: the standardization of aesthetic and reconstructive breast surgery. *Plastic and Reconstructive*

Surgery. 2010;125(1):393-400.
39. Sneeuw KC, Aaronson NK, Yarnold JR, Broderick M, Regan J, Ross G, et al. Cosmetic and functional outcomes of breast conserving treatment for early stage breast cancer. 1. Comparison of patients' ratings, observers' ratings, and objective assessments. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 1992;25(3):153-9.
40. Karanicolas PJ, Bickenbach K, Jayaraman S, Pusic AL, Coit DG, Guyatt GH, et al. Measurement and interpretation of patient-reported outcomes in surgery: an opportunity for improvement. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract*. 2011;15(4):682-9.
41. Pusic AL, Reavey PL, Klassen AF, Scott A, McCarthy C, Cano SJ**.** Measuring patient outcomes in breast augmentation: introducing the BREAST-Q Augmentation module. *Clinics in Plastic Surgery*. 2009;36(1):23-32, v.
42. Pusic AL, Klassen AF, Scott AM, Klok JA, Cordeiro PG, Cano SJ**.** Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q. *Plastic and Reconstructive Surgery*. 2009;124(2):345-53.
43. Macadam SA, Ho AL, Cook EF, Jr., Lennox PA, Pusic AL**.** Patient satisfaction and health-related quality of life following breast reconstruction: patient-reported outcomes among saline and silicone implant recipients. *Plastic and Reconstructive Surgery*. 2010;125(3):761-71.
44. Pusic AL, McCarthy C, Cano SJ, Klassen AF, Kerrigan CL**.** Clinical research in breast surgery: reduction and postmastectomy reconstruction. *Clinics in Plastic Surgery*. 2008;35(2):215-26.
45. Al-Ghazal SK, Fallowfield L, Blamey RW**.** Does cosmetic outcome from treatment of primary breast cancer influence psychosocial morbidity? *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*. 1999;25(6):571-3.
46. Al-Ghazal SK, Fallowfield L, Blamey RW**.** Patient evaluation of cosmetic outcome after conserving surgery for treatment of primary breast cancer. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*. 1999;25(4):344-6.
47. Choi M, Unger J, Small K, Tepper O, Kumar N, Feldman D, et al. Defining the kinetics of breast pseudoptosis after reduction mammaplasty. *Annals of Plastic Surgery*. 2009;62(5):518-22.
48. Cano SJ, Klassen AF, Scott AM, Cordeiro PG, Pusic AL**.** The BREAST-Q: further validation in independent clinical samples. *Plastic and Reconstructive Surgery*. 2012;129(2):293-302.
49. Pusic AL, Klassen A, Cano SJ, Kerrigan CL**.** Validation of the breast evaluation questionnaire. *Plastic and Reconstructive Surgery*. 2007;120(1):352-3.
50. Pusic AL, Klassen AF, Cano SJ**.** Use of the BREAST-Q in clinical outcomes research. *Plastic and Reconstructive Surgery*. 2012;129(1):166e-7e; author reply 7e.
51. Zhong T, McCarthy C, Min S, Zhang J, Beber B, Pusic AL, et al. Patient satisfaction and health-related quality of life after autologous tissue breast reconstruction: a prospective analysis of early postoperative outcomes. *Cancer*. 2012;118(6):1701-9.
52. Clauson J, Hsieh YC, Acharya S, Rademaker AW, Morrow M**.** Results of the Lynn Sage Second-Opinion Program for local therapy in patients with breast carcinoma. Changes in management and determinants of where care is delivered. *Cancer*. 2002;94(4):889-94.

53. Staradub VL, Hsieh YC, Clauson J, Langerman A, Rademaker AW, Morrow M**.** Factors that influence surgical choices in women with breast carcinoma. *Cancer*. 2002;95(6):1185-90.
54. Chang JH, Vines E, Bertsch H, Fraker DL, Czerniecki BJ, Rosato EF, et al. The impact of a multidisciplinary breast cancer center on recommendations for patient management: the University of Pennsylvania experience. *Cancer*. 2001;91(7):1231-7.
55. Elmore L, Myckatyn TM, Gao F, Fisher CS, Atkins J, Martin-Dunlap TM, et al. Reconstruction Patterns in a Single Institution Cohort of Women Undergoing Mastectomy for Breast Cancer. *Annals of surgical oncology*. 2012.
56. Martin-Dunlap T., Myckatyn T, Margenthaler J**.** Who benefits from oncoplastic surgical techniques?. . *Current breast cancer reports*. In Press.
57. Garsa AA, Ferraro DJ, Dewees T, Margenthaler JA, Naughton M, Aft R, et al. Cosmetic Analysis Following Breast-Conserving Surgery and Adjuvant High-Dose-Rate Interstitial Brachytherapy for Early-Stage Breast Cancer: A Prospective Clinical Study. *Int J Radiat Oncol Biol Phys*. 2012.
58. Faul F, Erdfelder E, Buchner A, Lang AG**.** Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behavior research methods*. 2009;41(4):1149-60.
59. Buck, D. W., 2nd, Shenaq, D., Heyer, K., Kato, C. & Kim, J. Y. Patient-subjective cosmetic outcomes following the varying stages of tissue expander breast reconstruction: the importance of completion. *Breast* **19**, 521-526 (2010).
60. Salzberg, C. A. Nonexpansive immediate breast reconstruction using human acellular tissue matrix graft (AlloDerm). *Ann Plast Surg* **57** (2006).
61. Breuing, K. H. & Colwell, A. S. Inferolateral AlloDerm hammock for implant coverage in breast reconstruction. *Ann Plast Surg* **59**, 250-255 (2007).
62. Zienowicz, R. J. & Karacaoglu, E. Implant-based breast reconstruction with allograft. *Plast Reconstr Surg* **120**, 373-381 (2007).
63. Salzberg, C. A., Ashikari, A. Y., Koch, R. M. & Chabner-Thompson, E. An 8-year experience of direct-to-implant immediate breast reconstruction using human acellular dermal matrix (AlloDerm). *Plastic and Reconstructive Surgery* **127**, 514-524 (2011).
64. Spear, S. L. & Onyewu, C. Staged breast reconstruction with saline-filled implants in the irradiated breast: recent trends and therapeutic implications. *Plastic and Reconstructive Surgery* **105**, 930-942 (2000).
65. Kim, H. J. *et al.* Nipple areola skin-sparing mastectomy with immediate transverse rectus abdominis musculocutaneous flap reconstruction is an oncologically safe procedure: a single center study. *Annals of Surgery* **251**, 493-498 (2010).
66. Cense, H. A., Rutgers, E. J., Lopes Cardozo, M. & Van Lanschot, J. J. Nipple-sparing mastectomy in breast cancer: a viable option? *Eur J Surg Oncol* **27**, 521-526 (2001).
67. Paepke, S. *et al.* Subcutaneous mastectomy with conservation of the nipple-areola skin: broadening the indications. *Ann Surg* **250**, 288-292 (2009).
68. de Alcantara Filho, P. *et al.* Nipple-sparing mastectomy for breast cancer and risk-reducing surgery: the memorial sloan-kettering cancer center experience. *Annals of surgical oncology* **18**, 3117-3122 (2011).
69. Ashikari, R. H., Ashikari, A. Y., Kelemen, P. R. & Salzberg, C. A. Subcutaneous mastectomy and immediate reconstruction for prevention of breast cancer for high-risk patients. *Breast Cancer* **15**, 185-191 (2008).

70. Sacchini, V. *et al.* Nipple-sparing mastectomy for breast cancer and risk reduction: oncologic or technical problem? *J Am Coll Surg* **203**, 704-714 (2006).
71. Gerber, B., Krause, A., Dieterich, M., Kundt, G. & Reimer, T. The oncological safety of skin sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction: an extended follow-up study. *Ann Surg* **249**, 461-468 (2009).
72. Gerber, B. *et al.* Skin-sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction is an oncologically safe procedure. *Ann Surg* **238**, 120-127 (2003).
73. Garwood, E. R. *et al.* Total skin-sparing mastectomy: complications and local recurrence rates in 2 cohorts of patients. *Ann Surg* **249**, 26-32 (2009).
74. ASPS (2012) [news bulletin]. http://www.plasticsurgery.org/News-and-Resources/Press-Release-Archives/2012-Press-Release-Archives/ASPS-Applauds-Introduction-of-Legislation-to-Empower-Women-with-Breast-Cancer-to-Better-Understand-Their-Care-Choices.html
75. Hershman, D. *et al.* (2011) Influence of Hospital Factors, Physician Factors and Type of Health Insurance on Receipt of Immediate Postmastectomy Reconstruction in Young Women with Breast Cancer [news bulletin]. http://www.sabcs.org/PressReleases/Documents/Hershman.pdf

APPENDIX A: Group A — BCT + XRT ARM STUDY VISIT SCHEDULE

	Screening Oncology Surgeon	**Radiology**	**Breast Conservation Therapy (BCT)**	**Postop Visit Oncology Surgeon**	**Final Study Visit Oncology Surgeon**
	Visit #1[2]	**Visit #2**[4]	**T=0**	**Visit #4**[5]	**Visit #5**[6]
Past medical history[1,2]	X				
Physical Exam[2,3]	X			X	X
Informed Consent[2]	X				
Discussion of therapeutic options (Breast Surgery, sentinel node biopsy, XRT &/or chemo)	X			X	
Breast-Q [2] (BCT vs.)	X (Preop Vs.)			X (Post Op Vs.)	X (Post Op Vs.)
MRI[4]		X			
Photography[2]	3D			3D	3D
Documentation of lumpectomy findings [7]			X		
Monitor for Unexpected Events			X	X	X

[1]Study-relevant past medical and surgical history
[2]Screening procedures to be completed within 90 days of surgery.
[3]Baseline height, weight, clinical stage, biopsy results from pre-surgical physical examination
[4]MRI may be completed prior to Visit #1.
[5]This is done 1-10 weeks after lumpectomy where the surgical margins were cleared.
[6]Done 6- 18 months after radiation therapy has concluded *or the latest follow-up time point within the duration confines of our study period.*
[7]Final pathological stage, document if re-excision is needed
Note: No required Visit #3 for Group A.

APPENDIX B: Group B — MASTECTOMY + RECONSTRUCTION ARM STUDY VISIT SCHEDULE

	Screening Oncology Surgeon	**Radiology**	**Screening/Baseline Plastic Surgeon**	**Mastectomy + Reconstruction**	**Postop Visit Plastic Surgeon**	**Final Study Visit Plastic Surgeon**
	Visit #1[2]	**Visit #2**[4]	**Visit #3**[2]	**T=0**	**Visit #4**[5]	**Visit #5**[6]
Past medical history[1,2]	X		X			
Physical Exam[2,3]	X		X		X	X
Informed Consent[2]	X		X			
Discussion of therapeutic options (Breast Surgery, sentinel node biopsy, XRT &/or chemo)	X				X	
Breast-Q [2] (mastectomy and reconstruction vs.)	X (Preop Vs.)		X (Preop Vs.)		X (Post Op Vs.)	X (Post Op Vs.)
Discussion of reconstruction options			X			
MRI[4]		X				
Photography[2]	3D		3D		3D	3D
Documentation of intraoperative findings [7,]				X		
Monitor for Unexpected Events				X	X	X

[1]Study-relevant past medical and surgical history
[2]Screening procedures to be completed within 90 days of surgery. May be completed in Group B at Visits #1 and/or #3.
[3]Baseline height, weight, clinical stage, biopsy results from pre-surgical physical examination
[4]MRI may be completed prior to Visit #1.
[5]This is done 1-10 weeks after the first reconstructive intervention, typically at time of mastectomy.
[6]This is done 3-8 months after the final reconstructive intervention, or the latest follow-up time point within the duration confines of our study period.
[7]Final pathological stage, presence or absence of sentinel lymph node biopsy and the outcome of biopsy

APPENDIX C: Group C — MASTECTOMY STUDY VISIT SCHEDULE

	Screening Oncology Surgeon	**Radiology**	**Mastectomy**	**PostOp Visit Oncology Surgeon**	**Final Study Oncology Surgeon**
	Visit #1[2]	**Visit #2**[4]	**T=0**	**Visit #4**[5]	**Visit #5**[6]
Past medical history[1,2]	X				
Physical Exam[2,3]	X			X	X
Informed Consent[2]	X				
Discussion of therapeutic options (Breast Surgery, sentinel node biopsy, XRT &/or chemo)	X			X	
Breast-Q [2] (mastectomy vs.)	X (Preop Vs.)			X	X (Post Op Vs.)
MRI[4]		X			
Photography[2]	3D			3D	3D
Documentation of intraoperative findings [7,]			X		
Monitor for Unexpected Events			X	X	X

[1]Study-relevant past medical and surgical history
[2]Screening procedures to be completed within 90 days of surgery.
[3]Baseline height, weight, clinical stage, biopsy results from pre-surgical physical examination
[4]MRI may be completed prior to Visit #1.
[5]Visit #4 should occur 1-10 weeks after mastectomy.
[6]Visit #5 should occur 6- 18 months after mastectomy *or the latest follow-up time point within the duration confines of our study period*.
[7]Final pathological stage, presence or absence of sentinel lymph node biopsy and the outcome of biopsy
.
Note: No required Visit #3 for Group C.