FACTORS INFLUENCING COSMETIC OUTCOME IN BREAST PRESERVATION THERAPY FOR EARLY STAGE BREAST CANCER

By

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CERTIFICATE OF APPROVAL

This is certify that the Master's Thesis, entitled

"Factors Influencing Cosmesis in Breast Conservation Therapy for Early Stage Breast Cancer"

by

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Abstract:

Introduction - Before 1985, total mastectomy was the standard treatment for early stage breast cancer (American Joint Committee on Cancer Stage I and II). Since then, randomized clinical trials challenged this prevailing approach to treatment by demonstrating equivalent 8-17 year survival outcomes in women with early stage breast cancer treated with mastectomy or breast preservation therapy (the combination of conservative surgery followed by radiation treatment). Consequently, breast preservation therapy and the goal of improved cosmetic outcome are gaining greater prominence in patient choice and treatment decisions. A better understanding of the long-term cosmetic results of women treated with breast preservation therapy is needed. Furthermore, a determination of what patient, tumor, and treatment factors predict for improved cosmetic outcome needs further definition to guide patients and their treating physicians. Prior single-institution studies have had methodological problems including unavoidably small numbers of patients or the use of inconsistent cosmetic rating criteria. This study sought to identify influential factors. Determining these factors will allow for the establishment of patient selection criteria and appropriate treatment modifications to improve cosmetic outcome for women who choose breast preservation therapy.

Methods - The retrospective cohort study included a cohort of 101 patients treated between 1984-2001 at Oregon Health & Science University's Department of Radiation Oncology. Data on long-term physician ratings of cosmetic outcome in 101 women with AJCC Stage I and II breast cancer who chose breast preservation therapy were examined. Patient clinical and tumor characteristics, as well as specifics of surgery, radiation, and chemotherapy treatment were

collected through chart review. These data was analyzed to identify independent factors that jointly influence cosmetic outcome.

Results – Factors found to be associated with impaired cosmetic outcome included hypertension (p=.035), axillary lymph node dissection (p=.040), total surgical volume (p=.001), radiation treatment break (p=.046), tumor size (p=.033). Marginal association was seen with follow-up time (p=.063). Tamoxifen use (p=.042) was found to associated with improved cosmetic outcome.

Introduction:

Breast cancer is the most common malignancy in women in the Western world, with approximately 183,000 new cases of invasive tumors diagnosed each year in the United States. Eight percent of women will develop breast cancer during their lifetimes, and the incidence is increasing. Mortality remains substantial, with overall survival rates of approximately 73% at five years and 59% at ten years. Indeed, it is the leading cause of death among women 40-55 years old. Although this remains the most widely diagnosed cancer in American women and despite these discouraging statistics, over the years its treatment has continually improved to better the quantity and quality of life after diagnosis. However, these changes in therapy have been constantly accompanied by controversy stemming from various medical and political forces. These include the earlier detection resulting in smaller tumors upon presentation, the expanding understanding of the biology of breast cancer, the use of chemotherapy, the use of radiation therapy, and the relatively new empowerment of breast cancer patients in making their own treatment decisions.

Breast cancer surgery was established in the 1890s by William Halsted who developed the radical mastectomy procedure. This surgery was based upon the theory that breast cancer spreads through local draining lymphatics. This was an extensive surgery that included an *en bloc* breast resection, as well as removal of overlying skin, pectoralis minor and major muscles, and all axillary lymph nodes. As patients continued to have high long-term mortality despite this comprehensive operative procedure, it was recognized that treatment failure actually resulted from metastatic spread before surgery rather than from inadequate resection. This resulted in an important shift in the

understanding of breast cancer's natural progression, the revision of this long-standing extreme surgery, and the development of the modified radical mastectomy.

Modified radical mastectomy involves removal of the entire breast, the pectoralis minor muscle if indicated, as well as a partial rather than complete axillary lymph node dissection. Retrospective studies showed equivalent survival between women treated with radical and modified radical mastectomy, which was then further confirmed through prospective randomized trials.[1] Throughout the 1970s, modified radical mastectomy had been the long-established and standard treatment for Stage I and II breast cancer. As some women refused to undergo mastectomy, anecdotal reports circulated regarding the relative merits of conservative surgery followed by radiation treatment. Conservative surgery includes the variously termed but clinically similar techniques of lumpectomy, wide local excision, partial or segmental mastectomy, quadrantectomy, or excisional biopsy—all with or without axillary lymph node dissection. Interestingly, breast preservation therapy was first performed in 1924 by Sir Geoffrey Keynes.

Until the early 1980s, early stage breast cancer continued to be primarily a surgical disease. However, in 1985 a randomized clinical trial by Fisher *et al* found that women with early stage breast cancer treated with conservative surgery resulting in negative margins, axillary node dissection, then followed by radiation had equivalent five-year survival. Moreover, disease-free survival after segmental mastectomy plus radiation was significantly better than that in women treated with total mastectomy alone. Indeed, 92.3% of women treated with radiation were disease-free at five years compared to 72.1% of those not receiving radiation.[2] Multiple continued follow-up reports of this initial randomized clinical trial have further demonstrated long-term equivalent eight and

17-year survival rates in women who were treated with either mastectomy or conservative surgery combined with radiation.[3] This combined treatment approach is now referred to as breast preservation therapy or breast conservation therapy (BPT). This approach consists of surgically removing the tumor with at least one centimeter margins, followed by moderate doses of radiation to eliminate any remaining microscopic disease. Further validation came with the National Institutes of Health Consensus Conference conclusion that breast preservation is the preferred treatment for most women with Stage I and II breast cancer. Specifically, this is the preferred treatment for women with adequate tumor-to-breast ratios who do not have multicentric tumors or diffuse microcalcifications.

Despite these clinical trials and consensus recommendations, adoption of conservative treatment has been controversial, incomplete, and has varied geographically. Over recent years, this slow paradigm shift has been facilitated by concurrent medical and social developments including the increased use of screening mammography, improved mammographic techniques, and greater awareness of breast cancer amongst women—these have all led to earlier diagnosis and the detection of smaller tumors. In terms of treatment, radiation therapy techniques and equipment have improved as well. Moreover, patients have become more actively involved in the medical management of their breast cancer, resulting in a greater emphasis on quality of life issues in the approach to breast cancer treatment.

Recommended guidelines for conservative treatment have been established jointly by the American College of Radiology, the American College of Surgeons, the College of American Pathologists, and the Society of Surgical Oncology.[4] Absolute

contraindications include two or more primary tumors located in separate breast quadrants or with diffuse malignant-appearing microcalcifications, previous radiation treatment in the affected breast area with additional treatment exceeding tissue tolerance, and positive margins after reasonable surgical attempts for complete excision. The latter may be a marker for an extensive intraductal component that suggests that the tumor may be multifocal and extends without being clinically detectable. Relative contraindications include multiple gross tumors in the same quadrant, indeterminate microcalcifications, tumor size >4-5 cm, large tumor size relative to breast size, and large breast size if patient setup is not consistently reproducible or if dose homogeneity can't be achieved. Lastly, a history of collagen vascular disease such as scleroderma or lupus is considered to be a relative contraindication since these patients tend to have poor tolerance to radiation.

Despite these guidelines, BPT unfortunately remains an underused treatment despite its great potential benefit for patients. There are factors that some practitioners have considered contraindications to conservative treatment although they have not been demonstrated to compromise survival. These include axillary node involvement, family history, and tumor location. Stage II breast cancer includes ipsilateral non-fixed nodal involvement, and it has been clearly shown that these women have equivalent survival with either mastectomy or BPT as previously discussed. In terms of location, subareolar tumor locations raise the concern of disease spread along the ductal system. However, even with the resection of the nipple-areolar complex needed for adequate clearance, patients can achieve preserved cosmesis with appropriate reconstruction.[5]

Lastly, conservative treatment does not preclude accurate evaluation for local recurrence, nor does it carry any appreciable risk for causing secondary malignancy.

Obedian *et al* performed a retrospective cohort study comparing two groups of patients each with >1000 patients who had either BPT or mastectomy. The 15-year risk of any second malignancy was nearly equivalent for both cohorts, 17.5% and 19.0%, respectively. More specifically, the rate of second breast cancer occurrence at 15 years was 10% for both groups, and the risk of a second nonbreast cancer was 11% for the BPT group and 10% for the mastectomy group.[6]

For patients who have the option of conservative treatment, it is necessary for them to work closely with their physicians to understand the risks and benefits of mastectomy versus BPT. This is especially true given the unique nature of each patient's clinical and personal circumstances. The patient must consider how treatment choice will impact her sense of control over preventing disease recurrence, self-esteem, body image, sexuality, and physical functioning which will collectively contribute to the overall quality of life following BPT. With equivalent survival outcomes, the factor of cosmetic outcome in patient choice and treatment considerations gains greater prominence.

The goals of BPT are to reduce the risk of recurrence, provide equivalent survival to mastectomy, while also obtaining excellent cosmetic outcome in the treated breast. Prior studies show that the majority of patients treated with BPT have preserved cosmesis. Among a group of patients receiving appropriately planned whole breast radiation with a dose of 4500-4600 cGy in daily fractions of ≤200 cGy, along with a boost dose of ≤1800 cGy, 73% had an excellent cosmetic outcome and 96% had an excellent or good cosmetic outcome at three years.[7] Cosmetic outcome is important since it is known that mastectomy produces varying degrees of psychological trauma in many patients. For women receiving conservative therapy, studies suggest that psychological

status during the one to two year period after treatment is better in terms of body image, body integrity, and self-esteem.

It has also been suggested that women choosing BPT over mastectomy have greater concern over body image and body integrity. One study reported that 96% of women chose breast conservation therapy because they wanted to avoid the feelings of disfigurement, mutilation, and insult to femininity they feared with modified radical mastectomy.[8] As BPT becomes a more prominent alternative in early stage breast cancer treatment and as a greater proportion of women diagnosed with breast cancer are at earlier stages, a better understanding of the factors that contribute to a favorable cosmetic outcome for patients is needed. Additional studies are needed as prior studies include patients treated at single institutions, perhaps affecting applicability to other patient populations and necessitating other studies to see if results are consistent.

Excellent cosmetic outcome can be attained with greater likelihood when patients are properly selected and optimal surgical and radiation treatment parameters are more clearly defined. Complications following surgery and radiotherapy are uncommon, but can involve breast edema, retraction, telangiectasia formation, and arm edema. Various studies have addressed the many treatment factors that determine cosmetic outcome. In general, breast retraction is considered to parallel overall cosmetic outcome most closely.

Predisposing patient characteristics as well as therapy techniques have been determined by retrospective studies to affect the cosmetic outcome after conservative surgery and radiotherapy for early stage breast cancer. These include tumor size, breast size, extent of surgical resection, external beam radiation technique, and boost type.[9] Taylor *et al*[10] found that surgical resection volume, radiation treatment volume, whole

breast dose >5000 cGy, and concurrent chemotherapy affect cosmesis. In this study, they identified the following factors as influential: patient age >60 years, increased weight, postmenopausal status, and African-American race were associated with lower scores. Factors not found to be significant by that study included daily radiation fraction size, use and type of boost, and sequential chemotherapy or adjuvant tamoxifen.

Since chemotherapy is an integral part of breast cancer treatment for many women, the optimal sequencing of chemotherapy and radiation therapy needs to be better understood in breast preservation therapy. Adjuvant chemotherapy has been shown to reduce 10-year mortality by 27% in women under age 50, 14% in those 50-59, and eight percent in those 60-69 years of age. Tamoxifen treatment has been shown to decrease the annual rate of death by up to 15%. While chemotherapy and hormonal therapy use are becoming more widespread and integral to multidisciplinary treatment, there is a relative paucity of information concerning the effects on survival and cosmetic outcome that may vary with sequencing of chemotherapy and radiation therapy.

Several studies have shown conflicting cosmetic results following the addition of chemotherapy.[11] Abner *et al* examined the effects of adjuvant chemotherapy (CT) combined with radiation therapy (RT) on cosmetic outcome. They compared a group receiving CT following RT to a group of patients undergoing only RT. At 36 months, they found improved cosmetic results in those treated with RT only (47% vs. 71% excellent).[12] Additionally, the CT group was subdivided according to the sequence of the therapeutic regimen. They found that only those treated concurrently rather than sequentially with CT and RT presented with more adverse effects. Of course local and

disease control, and ultimately survival, are more central to treatment decisions than are cosmetic results.

Some studies suggest that an increased interval of seven weeks or more between surgery and radiation, due to intervening chemotherapy, is associated with failure of local control. However, delays in starting chemotherapy have shown varying results in systemic control, a treatment issue of great concern given the potential for developing metastases. Ultimately, randomized clinical trials will answer questions of optimal treatment sequencing most definitively, and additional retrospective cohort studies may provide further insight.

Given the possible subjective aspects of determining breast cosmetic outcome, prior studies examining cosmetic outcomes for early stage breast cancer have noted poor inter-observer reliability amongst ratings by medical staff when standardized scales were not used. However, Sneeuw *et al* found a high degree of concordance between ratings by both oncology nurses and radiation oncologists when a four-point grading scale was used.[13] This confirmed similar studies that found high levels of inter-rater agreement when using similar quantifiable methods of measurement.[14]

General problems associated with these prior studies may be attributable to varied definitions of cosmetic endpoints assessed, as well as the varying time intervals to evaluation. Due to these potential inconsistencies, this study used a standardized scale established by the Joint Center for Radiation Therapy. Having been used in similar studies, this more objective and consistent rating system compares cosmetic alteration of the treated with the untreated breast on a four-point scale (excellent, good, fair, poor)

with specifically defined criteria that take into account overall appearance, breast edema, telangiectasias, retraction, and arm edema (*Appendix A*).

Since irradiation effects may become evident later than surgical effects, Harris and Recht suggest that three years of follow-up are ideal to assess long-term cosmetic outcome. This is the time interval during which breast appearance has most likely stabilized.[12] Indeed, Amichetti *et al* evaluated long-term radiation effects and resulting cosmetic outcome at a minimum of five years after treatment, and found that cosmetic results tended to decline with time.[15] This may reflect the progressive effects of breast edema, skin thickening, post-surgical fluid collection, late scarring, as well as fibrosis.

Study Objectives:

The primary objective of this study is to evaluate the long-term cosmetic outcomes of women with early stage breast cancer treated with breast preservation therapy (BPT), and to determine which patient, tumor, and treatment factors influence cosmetic outcome. The study hypothesis asserts that the independent variables of patient age, tumor stage, tumor excision volume, extent of axillary node dissection, use of chemotherapy, and total radiation dose are significant factors predicting the dependent variable of cosmetic outcome in women with early stage breast cancer treated with breast preservation therapy. Using the patient treatment registry at Oregon Health & Science University's Department of Radiation Oncology, all women with early stage breast cancer who completed BPT from 1984-2001 were identified for the following purposes:

(1) To collect data on long-term cosmetic outcomes assessed by physician ratings in women choosing breast preservation therapy.

(2) To determine patient, tumor, and treatment factors that predict for cosmetic outcome. These factors include age, menopausal status, ethnicity, breast size, tumor stage, pathology, excision volume, extent of axillary node dissection, surgical complications, interval between surgery and radiation, radiation dose and fractionation, photon energy, treatment volume, use of boost, chemotherapy and hormonal therapy use and timing of administration.

(3) To recommend patient selection criteria and appropriate treatment modifications to improve cosmetic outcome in women choosing breast preservation therapy.

Materials and Methods:

This retrospective cohort study examined determinants of long-term physician-rated cosmetic outcomes in women with early stage breast cancer choosing breast preservation therapy. The outcome of interest was cosmetic outcome, which was reported as excellent, good, fair, or poor. More importantly, this study examined which patient, tumor, and treatment factors (including age, menopausal status, ethnicity, breast size, tumor stage, pathology, excision volume, extent of axillary node dissection, surgical complications, interval between surgery and radiation, radiation dose and fractionation, photon energy, treatment volume, use of boost, chemotherapy and hormonal therapy use and timing of administration). Physician ratings of long-term cosmetic outcome were assessed during routine clinical follow-up at OHSU's Department of Radiation

Oncology. The data concerning patient, tumor, and treatment factors were collected through extensive medical chart review. This study received OHSU IRB approval.

Data Source and Data Quality:

All women with breast cancer treated at OHSU's Department of Radiation Oncology were listed in the department's patient treatment registry per standard practice. Those women who underwent BPT for unilateral stage I and II breast cancer, as defined by the American Joint Committee on Cancer, were identified (*Appendix B*). Their specific departmental as well as general hospital medical records were reviewed for study eligibility with pertinent patient, tumor, and treatment factors recorded using a standardized data form developed by the investigator. The investigator was trained in appropriate chart review and data abstraction. The data were entered (with repeated review for accuracy of data entry) into the confidential computer database for subsequent analysis.

Predictor Variables:

• Patient information included age, weight, ethnicity, past medical history pertinent to the study hypothesis (these included current tobacco use, hypertension, diabetes), and menopausal status at the start of radiation therapy. The way in which the patient first learned about the presence of breast carcinoma (self-exam, physician exam, or mammogram) was also noted, along with the quadrant location of the tumor determined by palpation, mammography, or ultrasound.

• Tumor data included tumor size, T and N staging as defined by the AJCC (*Appendix A*), nuclear grade (determined by the pathologist using the Bloom-Richardson scale), and immunohistological studies determining estrogen and progesterone receptor status.

• Surgical factors included initial tumor resection volume, use of re-excision, re-excision volume, total surgical volume, and surgical margins. Also noted were use of sentinel node biopsy, use of axillary lymph node dissection, the highest level of axillary lymph node dissection (defined by relation to the pectoralis minor muscle), number of positive and total nodes removed, and the presence of post-operative complications (cellulitis, hematoma). Approximate tumor resection volumes were cubic volumes, calculated using the dimensions of surgical specimens as measured by the pathologist. This was the approximation used since surgical specimens are not necessarily spherical and typically are found to conform to a variety of shapes.

• Adjuvant therapy factors included specific hormonal or chemotherapeutic drugs used, and their timing (before radiotherapy, concurrently, after radiotherapy, or sandwich scheduling), which were evaluated for association with cosmetic outcome.

• Radiation factors included total breast and tumor doses, daily fractionation, photon energy, use of mixed photons, isodose line, radiation treatment volume (two tangential or ≥3 fields including the internal mammary chain, posterior axillary boost, or supraclavicular fields), the use of CT-based lung correction, and the need for treatment break. The use of tumor bed boost, as well as its type and energy, were also noted.

Outcome Variables:

• One independent observer—the radiation oncologist who was responsible for treatment planning—was the source of clinical cosmetic assessment. At OHSU, determination of cosmetic outcome is a standard component of routine clinical follow-up after radiation treatment for evaluation of recurrent disease as well as to monitor the natural history of radiation changes occurring with breast preservation therapy. A previously established cosmetic scale has been used by the same radiation oncologist to determine cosmetic outcome throughout follow-up for the vast majority of patients included in the study.

• The radiation oncologist adheres to a standardized four-point scale based upon physical exam objective criteria, which was used for this study. This observer-based four-point scale grades the degree of cosmetic alteration of the treated breast compared with the untreated breast. Generally, it defines overall appearance as "excellent" if the treated breast is virtually indistinguishable from and symmetric with the opposite breast, "good" when there are minimal but still noticeable radiation therapy effects, "fair" when there are obvious and significant variations, and "poor" if there are severe tissue sequelae (see *Appendix B* for detailed definitions). These criteria take into consideration overall breast appearance, breast edema, telangiectasia formation, retraction, and arm lymphedema. Patients were classified by cosmetic outcome for comparison of the various patient and treatment factors (surgery, radiation, and chemotherapy) as detailed above.

Study Population:

During 1984-2001, women who chose to undergo breast preservation therapy for early stage unilateral breast cancer (AJCC Stage I and II) at Oregon Health & Science University were identified. BPT was typically recommended to women with solitary tumors that were small relative to breast size. The majority of these women received surgical treatment at OHSU primarily by three breast surgeons belonging to the multidisciplinary breast team. Surgical treatment for all patients involved procedures aimed at complete tumor removal with grossly negative margins. Surgical procedures included excisional biopsy, wide local excision, partial or segmental mastectomy, lumpectomy, and quadrantectomy. All women who received breast radiation at the Department of Radiation Oncology were identified through the department's treatment registry. From this population, there were 101 women (101 breasts) who met study eligibility requirements and who had continued routine clinical follow-up at the Department of Radiation Oncology after treatment completion.

Eligible patients were free of local recurrence or distant failure after twelve months of radiation completion since a second course of treatment may affect the cosmetic results of the initial treatment. However, patients with local recurrence had their treatment and cosmetic outcome information included until the time of subsequent evaluation and treatment. In this study, the minimum follow-up time from radiation completion was seven months. However, the mean length of follow-up time to last recorded cosmetic assessment was 29 months, with a range of 7-141 months.

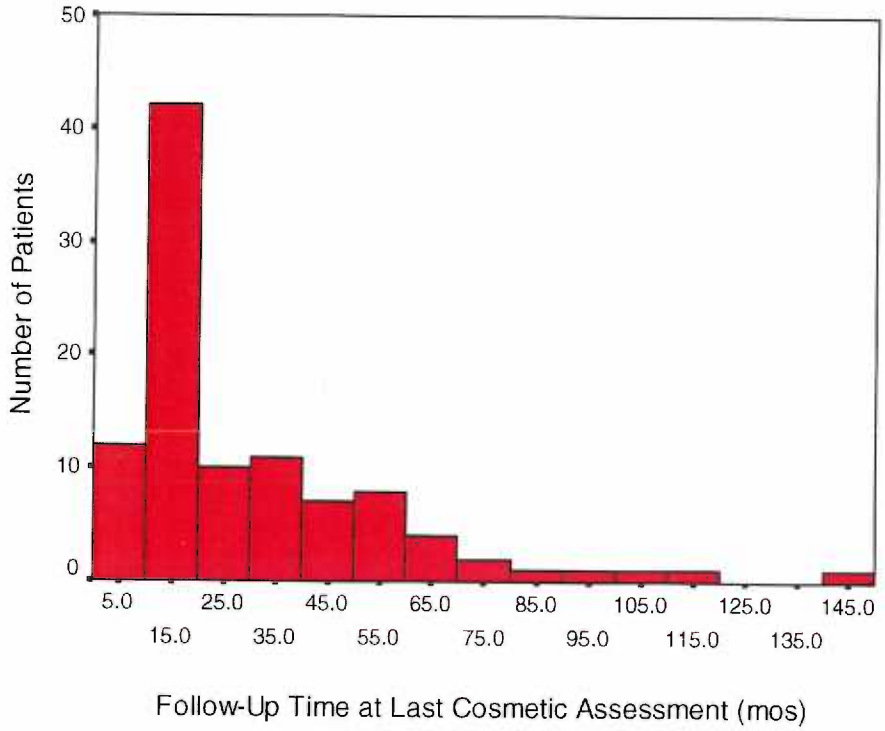

Figure 1: Study Population Length of Follow-Up in Months at Time of Last Recorded Cosmetic Assessment (n=101)

At the time of last follow-up of cosmetic assessment in the Department of Radiation Oncology, one hundred patients had no clinical evidence of disease and one patient had a local recurrence. These women did not have a history of prior chemotherapy nor other malignancy except for non-melanoma skin cancers or carcinoma *in situ* of the cervix. In addition, they did not have a prior history of breast surgery, reconstructive surgery after breast preservation therapy, or a history of previous radiation to the chest.

At the time of radiation, these women ranged from 29-86 years of age, with a mean age 54.5 years. Reflecting the demographics of the area, the study population was 94.1% Caucasian, 3.0% African American, 2.0% Asian, and 1.0% Hispanic. In this group, 99 women had invasive ductal carcinoma and two had invasive lobular carcinoma.

Total radiation dose ranged from 5000-6650 cGy to the tumor bed using external beam opposed tangential fields and 6 mV photons. External boost was used for 97 patients, and no patients were treated with interstitial implant or breast brachytherapy.

Statistical Analysis:

Descriptive statistics were used to summarize patient demographic and clinical characteristics for the entire study population. The cosmetic outcomes of the patients included in this study were found to follow a non-normal distribution. For this study population, cosmetic outcomes at the last recorded clinical assessment were as follows: 58.4% excellent, 26.7% good, 12.9% fair, and two percent poor as illustrated in *Figure 2*.

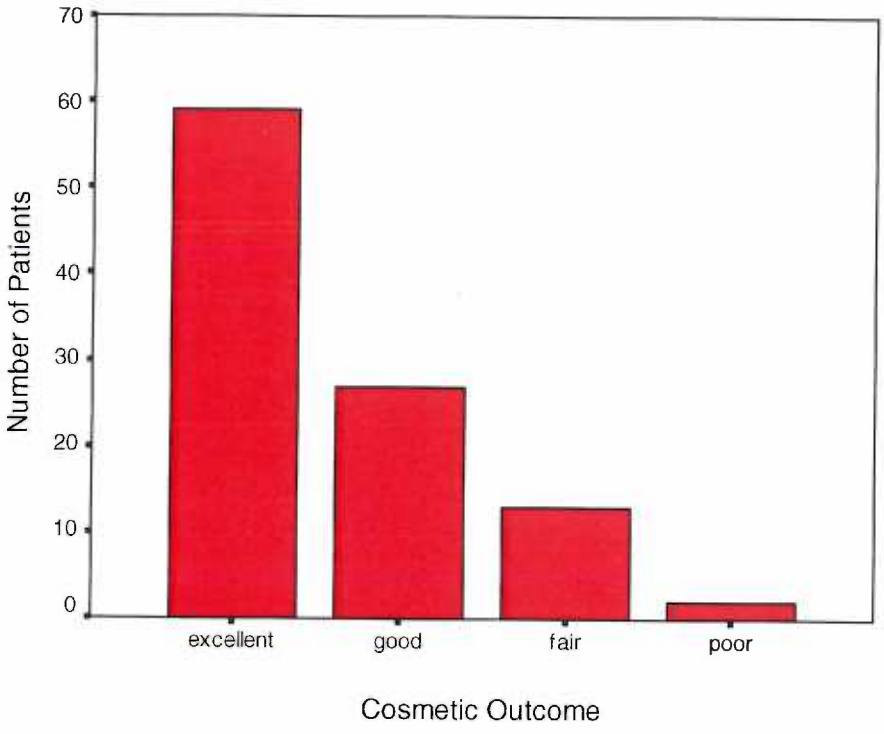

Figure 2: Distribution of Patient Cosmetic Outcome Following Breast Preservation Therapy at Time of Last Clinical Follow-Up (n=101)

Due to the non-normal and skewed distribution of cosmetic outcomes, this variable was converted to a dichotomous variable. The four variable categories were reduced to two, and therefore redefined as excellent and good/fair/poor to create statistically comparable groups as illustrated in *Figure 3*.

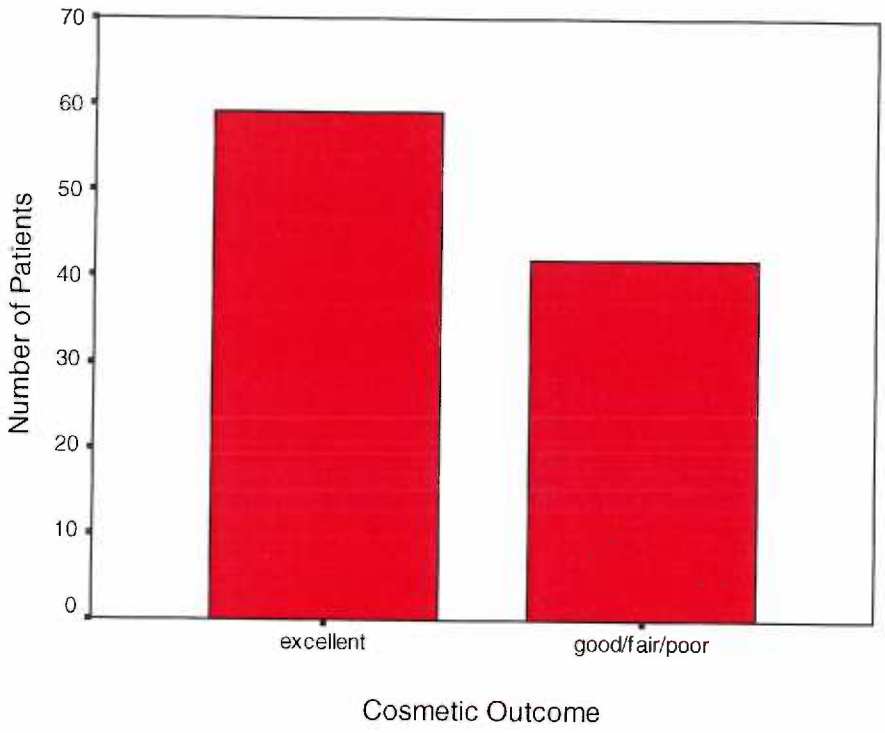

Figure 3: Distribution of Patient Cosmetic Outcome Dichotomized into Excellent vs. Good/Fair/Poor, Following Breast Preservation Therapy at Time of Last Clinical Follow-Up (n=101)

This revision of outcome categories made clinical sense as the multidisciplinary breast oncology team strives for an excellent cosmetic outcome for its patients.

Descriptive statistics were used to summarize characteristics of these two cosmetic outcome groups as well. Univariate statistical tests were used to identify influential factors to be included for model building in logistic regression analysis. For categorical variables, contingency tables classified by the dependent variable of cosmetic

outcome were created. The Pearson Chi-Square Test of Independence was performed to assess for relationships between cosmetic outcome and the various categorical variables (race, menopausal status, smoking, hypertension, diabetes, chemotherapy, tamoxifen, method of diagnosis, T stage, N stage, tumor stage, nuclear grade, ER status, PR status, history of axillary dissection, sentinel node biopsy, history of postoperative complications, history of re-excision, history of radiation treatment break, number of radiation treatment fields, use of radiation boost, and the use of mixed photons). For variables resulting in cell sizes of $n<5$ subjects, Fisher's Exact Test was used to assess association. A significance level of $p<.100$ was used as the criterion for inclusion in the logistic regression model, or clinical relevance as judged by the investigator. With both statistical tests, odds ratios with 95% C.I. were calculated. Odds ratios could only be calculated for dichotomous variables given the statistical nature of these tests. Variables with multiple levels were recategorized to create dichotomous variables when appropriate so that odds ratios could be calculated.

Continuous variables and their relationships with cosmetic outcome were assessed through the Mann-Whitney U test. This test is the nonparametric equivalent to the *t* test that similarly tests whether two independent samples are from the same population, but it does not require sample data to follow a normal distribution. Given the non-normal distribution of the majority of the continuous variables in this study, this test was also used. These variables included the number of positive lymph nodes, total number of lymph nodes removed, number of radiation treatment fields, radiation daily fraction, breast radiation dose, tumor radiation dose, and boost energy. An association level of

$p<.10$ was used as the criterion for inclusion in the logistic regression model, or clinical relevance as judged by the study investigator.

In order to identify all potential variables that predict cosmetic outcome, both categorical and continuous variables underwent repeat assessment via separate univariate logistic regression analyses. Unlike logistic regression analyses, the Pearson Chi-Square Test of Independence or Fisher's Exact Test contingency tables cannot calculate odds ratios for variables with more than two levels. In addition, univariate logistic regression analyses can provide us with more extensive statistical information about the variables in consideration. Specifically, univariate logistic regression is considered to be the optimal statistical test for assessing continuous variables. To more comprehensively evaluate continuous variables of interest (tumor size, total surgical volume, follow-up time), these variables were also converted to categorical variables based upon quartiles of data distribution. This allowed for the assessment of linear trends in risk. There were no potential effect modifiers identified which were clinically plausible; therefore, no interaction terms were used. For inclusion in the logistic regression model, the more statistically liberal Hosmer & Lemeshow's criterion for association as measured by the Likelihood Ratio Test $p<.25$ was used, or clinical relevance as judged by the study investigator.

Although this is a cohort study, the need to use these statistical tests and logistic regression allowed for the calculations of odds ratios only. Controversy exists regarding the use of the odds ratio as an estimate of the relative risk. However, Deeks asserts that the most appropriate use of the odds ratio is in case-control studies and logistic regression analyses, where they are considered to be the best estimates of relative risks that can be

obtained.[16] For logistic regression, odds ratios also allow for the examination of effects of other variables on that relationship, and it is similar to relative risk if there is no effect modification.

In addition, bivariate analyses of the independent variables were conducted to assess their relationships with each other. Correlations between independent variables were evaluated in order to evaluate for potential multicollinearity. Pearson's *r* correlation analyses were done to examine continuous independent variables. The gamma statistic was used to assess association between pairs of variables that included ordinal variables.

Statistically significant factors as well as those nonsignificant factors that were deemed clinically relevant were then included for logistic regression model building. Highly correlated variables were examined and excluded when appropriate in order to avoid multicollinearity. A multivariable logistic regression model was constructed. Procedures included both forward and backward stepwise model building using the Wald statistic. Predictive models resulting from both procedures were compared. After the final model was determined, the Hosmer-Lemeshow goodness-of-fit test was used to assess the model. All statistical analyses in this study were conducted using SPSS.

Sample Size and Power: A total of n=101 women were treated from 1984-2001. *Table 1* shows the *ad hoc* power calculations testing the null hypothesis that there is no association. These calculations assume that: (1) the excellent cosmetic outcome of 50% among the reference group (P0), (2) the proportion for the comparison group under the alternative hypothesis (P1), (3) a total sample size of N=100 women with $n1$=$n2$=50 for the two cosmetic outcome comparison groups, and (4) a significance level of α=.05.

Table 1: Two Proportions Power Analysis Testing the Null Hypothesis P0=P1 and Alternative Hypothesis P0≠P1 *

Power	Total N	P0	P1	Odds Ratio	Alpha	Beta
0.89	100	0.500	0.800	4.00	0.05	0.11
0.83	100	0.500	0.775	3.44	0.05	0.17
0.74	100	0.500	0.750	3.00	0.05	0.26
0.64	100	0.500	0.725	2.64	0.05	0.36
0.53	100	0.500	0.700	2.33	0.05	0.47

*Assumes equal comparison groups of $n1=n2=50$

Results:

For this study population, cosmetic outcomes at the last recorded clinical assessment were as follows: 58.4% excellent, 26.7% good, 12.9% fair, and two percent poor. The redistribution of cosmetic outcomes into two more evenly weighted comparison groups resulted in the following distribution: 58.4% of the women had "excellent" and 41.5% had "good/fair/poor" cosmetic results (*Figures 2* and *3*).

Follow-up time was determined by the last clinical visit at which cosmetic outcome was recorded. Follow-up time ranged from 7-141 months, with a mean duration of 29.4 months for the entire study population (*Figure 1* and *Table 2*).

Table 2: Study Population Cosmetic Outcomes and the Follow-up Time at which Cosmetic Outcome was Assessed (n=101)

Variable	No.	%
Cosmetic Outcome		
Excellent	59	58
Good	27	26
Fair	13	13
Poor	2	2
Follow-up Time (months)		
<12	22	22
≥12	79	79
Mean	29	
Range	7-141	

To maintain sufficient numbers of study subjects for adequate statistical power, the 22 patients who had cosmetic outcomes assessed at 7-11 months were included. These 22 patients had a significantly higher proportion of excellent cosmesis at 77.3% compared to those with ≥12 months follow-up at 55.3% ($p<.042$). There was a greater likelihood of impaired cosmesis in the latter group (OR=3.00). As a continuous variable, follow-up time had borderline association with cosmesis ($p<.063$), with a slight elevation of risk (OR=1.02) associated with each month of follow-up. Follow-up time and year of treatment were not correlated ($p<.276$).

For this population, the distribution of breast cancer stage at treatment was as follows: 63.4% T1N0, 11.9% T1N1, 12.9% T2N0, and 11.9% T2N1. Therefore, 63.4% had Stage I and 36.6% had Stage II breast cancer (24.7% Stage IIA, 11.9% IIB).

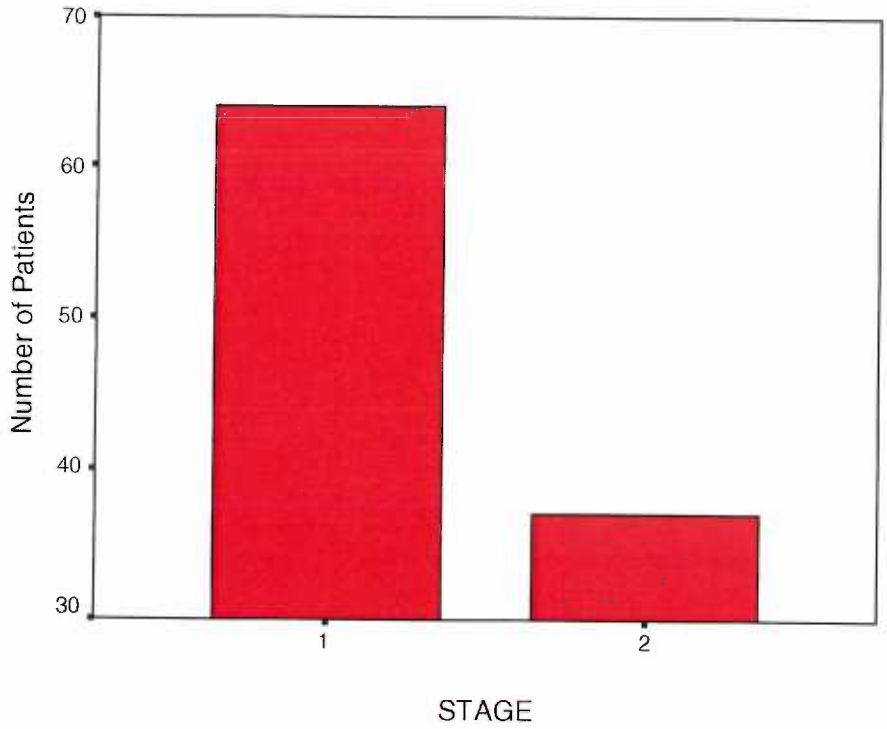

Figure 4: Distribution of AJCC Breast Cancer Stage upon Diagnosis (n=101)

T stage (based upon intervals of tumor size as defined by the AJCC) was not a predictor of cosmesis ($p<.223$). However, with univariate logistic regression it did meet Hosmer & Lemeshow standards of acceptability for inclusion in model building ($p<.226$). For the entire study population, the mean tumor size was 1.7 ± 0.92 cm as measured by the pathologist. This pathologic tumor size was found to have borderline significance as a predictor via Mann Whitney U testing ($p<.062$), and significant via univariate logistic regression ($p<.033$).

However, given that T stage is defined by intervals of tumor size as determined by the pathologist, these are obviously highly correlated variables. This was confirmed by their Pearson's correlation value of $r=.812$ ($p<.000$). While T stage as a predictive factor may be clinically more convenient since all patients are staged for determining prognosis and treatment, pathologic tumor size is more specific. Tumor size was found to be statistically significant through both statistical assessments. Therefore, T stage was not included in the model building process, whereas pathologic tumor size was included. Pathologic tumor size was also converted to a categorical variable according to quartile distribution, which upon univariate logistic regression analysis showed a non-linear risk pattern as it increased.

Table 3: Study Population Distribution of Cancer Stage at Diagnosis, Classified by American Joint Committee on Cancer (AJCC) Guidelines

Breast Cancer Stage	**No.**	**%**
Stage I	64	63.4
T1N0		
Stage II	37	36.6
T1N1 (IIA)	12	11.9
T2N0 (IIA)	13	12.9
T2N1 (IIB)	12	11.9

The 101 women included in this study ranged from 29-86 years of age at the time of radiation treatment, with a mean age 54.5 years. Age did not show any association with cosmetic outcome ($p<.450$) whether it was tested as a continuous or categorical variable using age intervals. The study population was 94.1% Caucasian, 3.0% African American, 2.0% Asian, and 1.0% Hispanic. The study population was predominantly Caucasian, making it statistically difficult to assess a relationship between race and cosmetic outcome. The Pearson Chi-Square Test of Independence when comparing all four racial groups was not significant ($p<.166$), but each non-Caucasian racial group had contingency table cells with $n<5$. Therefore, Caucasian subjects were also compared with all non-Caucasian subjects by combining all other racial groups into one single comparison category. The Pearson Chi-Square Test of Independence was again not significant ($p<.199$), and again the non-Caucasian subjects were classified into cells with $n<5$ since they fell into different categories of cosmetic outcome. Therefore, Fisher's Exact Test was assessed but was also nonsignificant ($p<.230$).

Although weight >160 pounds is considered to be a potential risk factor for worsened cosmesis, the study population mean weight was 164.5 pounds and had no influence ($p<.377$). Women with large breasts tend to have worse cosmetic outcome, as well as those women that weigh>160 pounds. Breast size information was not available for this study so this could not be assessed. Weight was not significantly associated with outcome ($p<.450$). Weight was converted to a categorical variable based upon the mean weight of 164.5 pounds to create two categorical comparison groups (<164.5 pounds, ≥164.5 pounds), but when tested was again nonsignificant ($p<.782$). Height was not available for all patients to calculate the body mass index.

Various features of medical history pertinent to the study hypothesis were evaluated. No patients had a history of collagen-vascular disease, which has been considered a risk factor for worsened cosmetic outcome with breast preservation therapy. Pre-menopausal women accounted for 29.7% of the study population, peri-menopausal for 3.0%, and post-menopausal for 67.3%. Current smokers comprised 67.3% of the study population. Patient medical history was significant for hypertension in 20.8% and diabetes mellitus in 5.0% of all study subjects. None of these medical history features were significant except for hypertension ($p<.034$) which negatively impacted cosmesis (OR=2.86). Hypertension was not significantly associated with any other factors known to impact cosmesis including tumor size and total surgical volume. These pertinent patient demographic and medical characteristics are presented in the following tables, as well as a summary of statistical testing of these factors for association with cosmetic outcome.

Table 4: Summary of Study Population Baseline Demographic Characteristics and Features of Medical Comorbidities Thought to Influence Cosmesis (n=101)

Variable	**No.**	**%**
Age (yrs)		
Mean	54.5	
Range	29-86	
Race (no.)		
Caucasian	95	94.1
African American	3	3.0
Asian	2	2.0
Hispanic	1	1.0
Wt (lbs)		
Mean	164.5	
Range	82-224	
Menopausal Status (no.)		
Premenopausal	33	32.7
Postmenopausal	68	67.3
Current tobacco use (no.)	33	32.7
Hypertension (no.)	21	20.8
Diabetes (no.)	5	5

Table 5: Summary of Study Population Demographic Characteristics and Medical History: Distribution of Age, Weight, Race, Menopausal Status, Medical Comorbidities, and Follow-Up Time by Cosmetic Outcome. Odds Ratios and Significance Values of these Variables when Evaluated for Association with Cosmetic Outcome.†

Variable	Cosmetic Outcome		*P*	OR [95% C.I.]*
	Excellent (n=59)	Good/Fair/Poor (n=42)		
Mean Age (yrs)	55.3	53.5	.450	
Mean Weight (lbs)	161.5	169.8	.311	
Race (no.)			.230**	***
Caucasian	57 (97)	38 (91)		
African American	0 (0)	3 (7)		
Asian American	1 (2)			
Hispanic	1 (2)			
Menopausal Status (no.)			.327	
Premenopausal	17 (29)	16 (38)		
Postmenopausal	42 (71)	26 (62)		
Smoking (no.)	21 (36)	12 (29)	.458	
Hypertension (no.)	8 (14)	13 (31)	.034	2.86 [1.06, 7.70]
Diabetes Mellitus (no.)	3 (5)	2 (5)	.941	
Follow-up Time (mos)			.042	3.00 [1.01, 8.92]
<12 mos	17 (77)	5 (12)		
>12 mos	42 (53)	37 (88)		

† Categorical Variables Assessed by Pearson's Chi-Square Test of Independence or Fisher's Exact Test; Continuous Variables Assessed by Mann Whitney U Test.
*OR provided if statistically significant difference between groups exists. O.R. could only be calculated from Pearson's Chi-Square Test of Independence or Fisher's Exact Test.
**Fisher's Exact Test calculated comparing Caucasian to non-Caucasian patients
***Odds ratio could not be directly calculated for variables with >2 levels.

Table 6: Summary of Study Population Demographic Characteristics and Medical History: Results of Univariate Logistic Regression Analyses of Age, Weight, Race, Menopausal Status, Medical Comorbidities, and Follow-Up Time for Association with Excellent Cosmetic Outcome

Variable	B	Se(β)	Wald *p*	Exp(β)= OR	Exp(β) 95% C.I.*	-2 log likelihood	LRT *p*
Age	-.013	.017	.449	0.99			.447
Wt	.004	.005	.379	1.00			.377
Race (White/Other)	1.098	.891	.218	3.00	[0.52, 17.20]	135.51	.202
Menopause Status	.419	.428	.328	1.52			.328
Smoking	-.323	.437	.459	0.72			.457
Hypertension	1.050	.506	.038	2.86	[1.06, 7.70]	132.69	.035
Diabetes	-.069	.936	.941	0.93			.941
Follow-up Time	.015	.009	.074	1.02	[0.999, 1.03]	133.69	.063

*Exp(β)=OR presented for factors deemed significant by Hosmer & Lemeshow's $p<.25$ criterion for inclusion in model building.

Regarding clinical presentation, the majority of women had tumors detected through breast self-exam (49.5%) or mammogram (44.6%), with only 5.9% having their tumors found incidentally upon physical exam by a physician. Unfortunately, correlating exam data were incomplete for those tumors that were discovered through mammogram, so we can conclude only that a minimum of 55.4% of patients had palpable tumors at presentation. No relationship between method of clinical presentation and cosmesis was found ($p<.831$). Consistent with established patterns of breast cancer occurrence, the majority (57%) of tumors in this study were located in the upper outer quadrant of the breast. There have been concerns that tumors residing in an upper inner quadrant or subareolar location may result in worse cosmesis. In this study, 14% and 1% of tumors were at these sites, respectively. Tumor location was not found to impact cosmesis.

Nuclear grade appeared to be a statistically significant predictive factor ($p<.027$), but only 85 patients had this information recorded. In theory, nuclear grade may possibly be a correlate of tumor size and total surgical excision volume since tumors of higher nuclear grade are more aggressive. They may therefore be larger upon presentation, thus requiring more extensive surgery. Grade III tumors did not appear to be confounded with these other study variables since they were not statistically associated with higher T stage, tumor size, or total surgical volume. Therefore, no direct clinical explanation for a direct relationship to cosmetic outcome was evident. Also, because multivariate logistic regression analysis excludes any cases with missing data, it was unclear whether nuclear grade should be included in the model building process. Ultimately, due to its statistical significance, a separate stepwise regression analysis was performed to assess its influence

on cosmetic outcome within the multivariate model. These findings are reported in the end of the Results.

Hormonal receptor status did not impact cosmesis for the 78 patients whose tumors underwent immunohistochemistry testing. Throughout the duration of the study, the clinical use of immunohistochemistry progressively became a standard part of clinical assessment. Consequently, patients treated in the earlier years of the study were less likely to have this pathologic information available. Both ER positive tumors ($p<.583$) and PR positive tumors ($p<.183$) were not significant predictors.

Table 7: Summary of Study Population Baseline Tumor Characteristics Including Clinical Presentation, Location, Pathologic Grade, and Hormonal Receptor Status

Variable	**No.**	**%**
Initial Diagnosis (no.)		
Breast self-exam	50	49.5
Physician exam	6	5.9
Mammogram	45	44.6
Tumor Location (no.)		
UOQ	57	56.4
UIQ	14	13.9
LOQ	10	9.9
LIQ	8	7.9
Other (upon axis)	11	10.9
Nuclear Grade (no.)		
I	26	25.7
II	39	38.6
III	18	17.8
Receptor Status (no.)		
ER+	78	77.2
PR+	69	68.3

Table 8: Summary of Study Population Breast Tumor Characteristics: Distribution of Presentation, Tumor Size, Nodal Involvement, Stage, Nuclear Grade, and Hormonal Receptor Status by Cosmetic Outcome. Odds Ratios and Significance Values of these Variables when Evaluated for Association with Cosmetic Outcome.†

Variable	Cosmetic Outcome		*p*	OR [95% C.I.]*
	Excellent (n=59)	Good/Fair/Poor (n=42)		
Method of Diagnosis (no.)			.831	
Breast Self-Exam	30 (58)	20 (48)		
Physical Exam	4 (7)	2 (5)		
Mammogram	25 (42)	20 (48)		
Mean Tumor Size (cm)	1.6	2.0	.033	1.62 [1.03, 2.56]
Nodal Involvement	14 (24)	10 (24)	.978	
Mean Total Nodes	16.0	16.3	.881	
Stage I (no.)	40 (68)	24 (57)	.273	
Stage II (no.)	19 (32)	18 (43)		
Nuclear Grade (no.)	48	35	.027	**
I	20 (42)	6 (17)		
II	17 (35)	22 (63)		
III	11 (23)	7 (20)		
ER Positive (no.)	43 (73)	35 (83)	.588	
PR Positive (no.)	36 (61)	33 (79)	.183	

† Categorical Variables Assessed by Pearson's Chi-Square Test of Independence or Fisher's Exact Test; Continuous Variables Assessed by Mann Whitney U Test.
*OR provided if statistically significant difference between groups exists. O.R. could only be calculated from Pearson's Chi-Square Test of Independence or Fisher's Exact Test.
**Odds ratio could not be directly calculated for variables with >2 levels.

Table 9: Summary of Study Population Breast Tumor Characteristics: Results of Univariate Logistic Regression Analyses of Tumor Size, Stage, Nuclear Grade, and Hormone Receptor Status for Association with Excellent Cosmetic Outcome

Variable	B	Se(β)	Wald *p*	Exp(β)= OR	Exp(β) 95% C.I.*	-2 log likelihood	LRT *p*
Tumor Size	.482	.233	.039	1.62	[1.03, 2.56]	132.59	.033
T stage	.563	.465	.226	1.76	[0.71, 4.37]	135.67	.226
N stage	.004	.474	.993	1.00			.993
AJCC Stage	.457	.418	.275	1.58			.274
Nuclear Grade	.419	.314	.181	1.52	[0.82, 2.81]	111.19	.177
ER Positive	-.305	.564	.589	0.74			.586
PR Positive	-.675	.517	.192	0.51	[0.19, 1.40]	123.05	.183

*Exp(β)=OR presented for factors deemed significant by Hosmer & Lemeshow's $p<.25$ criterion for inclusion in model building.

Surgical features included the use of sentinel node biopsy for 11 patients (10.9%), with two of these patients found to have positive nodes. The relatively low number of patients undergoing sentinel node biopsy reflects the extensive time period of this study and the evolution of standard practice during this period. This procedure gained clinical acceptance only in the later years of the study period. Axillary lymph node dissection was performed for 88 of the patients, 24 of whom were found to have nodal involvement upon pathologic evaluation. The use of axillary lymph node dissection was found to worsen cosmesis with an OR=4.60 ($p<.030$). A mean of 16 total nodes were removed for all patients undergoing dissection, and there was an average of 2.4 positive nodes for the 24 patients for whom axillary dissection found tumor spread. Nodal involvement and total number of lymph nodes removed were not significant predictors ($p<.978$ and $p<.830$, respectively). Level of axillary lymph node dissection was surgically documented for only 34 of the 88 patients (38.6%) who underwent dissection, and was therefore not assessed for association.

For all patients in this study, including those who underwent re-excision procedures, the mean total surgical excision volume was 154 cm^3. Patients with T1 tumors had a mean total surgical excision volume 127 cm^3, those with T2 tumors had a mean of 231 cm^3, and the total excision volumes were significantly different between these two groups ($p<.001$). When total surgical volume was converted to a categorical variable based upon quartiles, it showed a strong positive linear risk relationship in univariate logistic regression analysis that confirmed this association. Increasing volume by quartile had a significant adverse effect in this population, with an OR=3.07.

Fifty-one patients underwent re-excision at a separate procedure from the primary surgery, with five of them left with close margins and one with positive margins. Having re-excision performed did not negatively influence cosmesis ($p<.259$). Those undergoing re-excision had a greater mean total surgical excision volume of 162 cm^3, compared with 142 cm^3 if only one single surgical procedure was performed. This volume difference was not significantly different ($p<.100$) between the two groups. Although re-excision volume had a statistically significant association with cosmetic outcome ($p<.002$), it is a component of the sum total surgical volume, rendering it a redundant variable. This is demonstrated by their extremely strong correlation (Pearson's $r=.895$, $p<.000$). Therefore, re-excision volume was excluded from the model building process. A total of eight study subjects had postoperative complications, all of which were cellulitis. This was not found to affect cosmetic outcome.

Table 10: Summary of Study Population Surgical Treatment Characteristics Regarding Axillary Node Evaluation, Re-Excision, Total Surgical Volume, and Postoperative Complications

Variable	**No.**	**%**
Sentinel Node Biopsy (no.)	11	10.9
Positive Biopsy	2	18.2
Axillary Dissection (no.)	88	87.1
Nodal Involvement	24	23.8
Number of Positive Nodes		
Mean	0.57	
Range	0-13	
Total Nodes Removed		
Mean	16	
Range	1-40	
Re-excision (no.)	51	50.5
Total Surgical Volume (cm^3)		
Mean	152	
Range	4-756	
Postoperative Complications (no.)	8	7.9
Cellulitis	8	7.9

Table 11: Summary of Study Population Surgical Characteristics: Distribution of Patients According to Lymph Node Evaluation, Excision Volumes, and Postoperative Complications by Cosmetic Outcome. Odds Ratios and Significance Values of these Variables when Evaluated for Association with Cosmetic Outcome.†

Variable	Cosmetic Outcome		*p*	OR [95% C.I.]*
	Excellent (n=59)	Good/Fair/Poor (n=42)		
Sentinel Node Biopsy (no.) Axillary Dissection (no.)	9 (15) 48 (81)	2 (5) 40 (95)	.095 .067	4.58 [0.96, 21.9]
Nodal Involvement (no.) Mean Total Nodes	14 (24) 16.0	10 (24) 16.3	.978 .881	
Re-excision (no.)	27 (46)	24 (57)	.259	
Mean Re-excision Volume (cm^3)	84	174	.001	1.01 [1.00, 1.02]
Mean Total Surgical Volume (cm^3)	113.1	207.2	.001	1.01 [1.00, 1.01]
Postoperative Complications (no.)	4 (7)	4 (10)	.615	

† Categorical Variables Assessed by Pearson's Chi-Square Test of Independence or Fisher's Exact Test; Continuous Variables Assessed by Mann Whitney U Test.
*OR provided if statistically significant difference between groups exists. O.R. could only be calculated from Pearson's Chi-Square Test of Independence or Fisher's Exact Test.

Table 12: Summary of Study Population Surgical Characteristics: Results of Univariate Logistic Regression Analyses of Lymph Node Evaluation, Excision Volumes, and Postoperative Complications for Association with Excellent Cosmetic Outcome

Variable	B	Se(β)	Wald *p*	Exp(β)= OR	Exp(β) 95% C.I.*	-2 log likelihood	LRT *p*
Axillary Dissection	1.522	.798	.056	4.58	[0.96, 21.89]	132.43	.056
Total Nodes Removed	.006	.026	.830	1.01			.830
Re-excision	.458	.407	.261	1.58			.259
Total Surgical Volume	.006	.002	.003	1.01	[1.00, 1.01]	122.83	.001
Postoperative Complication	.370	.738	.616	1.45			.617

*Exp(β)=OR presented for factors deemed significant by Hosmer & Lemeshow's $p<.25$ criterion for inclusion in model building.

Chemotherapy did not impact cosmetic outcome ($p<.934$). For adjuvant therapy, 37.6% of patients underwent chemotherapy and 40.6% underwent hormonal therapy with

tamoxifen; 19.8% of the women were treated with both chemotherapy and hormonal therapy with tamoxifen. Thirty-eight women completed chemotherapy with regimens including adriamycin/cytoxan (AC), cyclophosphamide/methotrexate/5-fluorouracil (CMF), and more rarely cyclophosphamide/adriamycin/5-fluorouracil (CAF). Taxol was variably added to the AC and CAF regimens. The majority of the thirty-eight women who underwent chemotherapy completed AC (42%) and CMF (29%) regimens, with an additional 16% of these women having had AC followed by Taxol. The range of completed cycles was two to eight, with a median of four cycles. Two patients had chemotherapy concurrent with radiation, and seven had a sequential "sandwich" regimen.

The use of tamoxifen was found to influence cosmetic outcome ($p<.042$), with an apparent protective effect (OR=0.43). Interestingly, tamoxifen had a marginally significant association with lower T stage ($p<.071$) as well as a significant association with lower total surgical volume ($p<.020$). Chemotherapy combined with tamoxifen had no association with cosmetic outcome ($p<.326$).

Table 13: Summary of Study Population Chemotherapy Regimens and Sequencing

Variable	**No.**	**%**
Chemotherapy	38	37.6
Regimen		
AC	16	15.8
AC + Taxol	6	5.9
CMF	11	10.9
CAF	4	4
CAF + Taxol	1	1
Chemotherapy		
Before Radiation	27	26.7
Concurrent with Radiation	2	2
"Sandwich" with Radiation	7	6.9
After Radiation	2	2
Tamoxifen		
Concurrent with Radiation	41	40.6
Sequential with Radiation	60	59.4
Chemotherapy + Tamoxifen	19	18.8

Table 14: Summary of Study Population Chemotherapy and Tamoxifen Regimens and Sequencing: Distribution of Adjuvant Treatment by Cosmetic Outcome. Odds Ratios and Significance Values of these Variables when Evaluated for Association with Cosmetic Outcome.†

Variable	Cosmetic Outcome		*P*	OR [95% C.I.]*
	Excellent (n=59)	Good/Fair/Poor (n=42)		
Chemotherapy	22 (37)	16 (38)	.934	
Tamoxifen	40 (68)	20 (48)	.042	0.43 [0.19, 0.98]
Chemotherapy + Tamoxifen	13 (22)	6 (14)	.326	

† Categorical Variables Assessed by Pearson's Chi-Square Test of Independence or Fisher's Exact Test; Continuous Variables Assessed by Mann Whitney U Test.
*OR provided if statistically significant difference between groups exists. O.R. could only be calculated from Pearson's Chi-Square Test of Independence or Fisher's Exact Test.

Table 15: Summary of Study Population Chemotherapy and Tamoxifen Regimens and Sequencing: Results of Univariate Logistic Regression Analyses of Adjuvant Treatment for Association with Excellent Cosmetic Outcome

Variable	β	Se(β)	Wald *p*	Exp(β)= OR	Exp(β) 95% C.I.*	-2 log likelihood	LRT *p*
Chemotherapy	.034	.416	.934	1.04			.934
Tamoxifen	-.840	.416	.044	0.43	[0.19, 0.98]	133.00	.042
Chemotherapy + Tamoxifen	-.528	.541	.330	0.55			.320

*Exp(β)=OR presented for factors deemed significant by Hosmer & Lemeshow's $p<.25$ criterion for inclusion in model building.

While previous studies have shown worsened cosmesis with large fraction sizes and higher radiation doses, these treatment parameters were relatively uniform throughout this study population: 75 patients received 180 cGy daily fractions and 26 patients received 200 cGy daily fractions, to a total mean dose of 6045 cGy to the tumor bed. Treatment was delivered using 6 MV photons for 97 patients, and 97 patients received an electron boost.

The majority had two tangential opposed fields, but 28 patients had three treatment fields and two had four treatment fields. More radiation fields are thought to impact cosmetic outcome because matchline fibrosis may be seen in patients treated with three fields. Matchline fibrosis is inflammation and scarring at sites of overlapping radiation fields. In addition, patients receiving nodal irradiation are treated with greater than two radiation fields. This may result in a greater likelihood of breast edema, along with the requisite nodal dissection, that could also impair cosmesis.

Ninety-six patients received an electron boost to the tumor bed, with median boost energy at 11 MeV. The only radiation factor associated with cosmesis was the use of a treatment break ($p<.046$)—all eight of these patients had moist desquamation. No other radiation treatment complications were noted. Features of radiation treatment planning and technique were relatively uniform throughout the study population.

Table 16: Study Population Radiation Treatment Characteristics: Treatment Volume, Radiation Dose, and Technique (n=101)

Variable	**No.**	**%**
Radiation Treatment Volume (no. of fields)		
2	71	70.3
3	28	27.7
4	2	2
Fraction		
180 cGy	75	74.3
200 cGy	26	25.7
Total Breast Radiation (cGy)		
Mean	4874	
Range	4460-5220	
Total Tumor Radiation (cGy)		
Mean	6045	
Range	5000-6640	
Mixed Photons (no.)	4	4
Radiation Boost (no.)	96	96
Boost Energy (MeV)		
Mean	10.8	
Range	6-20	
Bolus (no.)	0	0

Table 17: Summary of Study Population Features of Radiation Treatment: Distribution of Radiation Volumes, Fractionation, Dose, Boost, and Need for Treatment Break by Cosmetic Outcome. Odds Ratios and Significance Values of these Variables when Evaluated for Association with Cosmetic Outcome.†

Variable	Cosmetic Outcome		*p*	OR [95% C.I.]*
	Excellent (n=59)	Good/Fair/Poor (n=42)		
Radiation Volumes (no.)			.438	**
2	40 (68)	31 (74)		
3	18 (31)	10 (24)		
4	1 (2)	1 (2)		
Radiation Fraction (no.)				
180 cGy	45 (76)	30 (71)		
200 cGy	14 (24)	12 (29)		
Breast radiation (cGy)	4880	4864	.232	
Tumor Radiation Dose (cGy)	6048	6041	.749	
Radiation Boost	57 (97)	40 (95)	.727	
Boost Energy (mV)	10.8	11.5	.251	
Radiation Treatment Break	2 (3)	6 (14)	.046	4.75 [1.91, 24.83]

† Categorical Variables Assessed by Pearson's Chi-Square Test of Independence or Fisher's Exact Test; Continuous Variables Assessed by Mann Whitney U Test.
*OR provided if statistically significant difference between groups exists. O.R. could only be calculated from Pearson's Chi-Square Test of Independence or Fisher's Exact Test.
**Odds ratio could not be directly calculated for variables with >2 levels.

Table 18: Summary of Study Population Features of Radiation Treatment: Results of Univariate Logistic Regression Analyses of Radiation Volume, Fractionation, Dose, Boost, and Need for Treatment Break for Association with Excellent Cosmetic Outcome

Variable	β	Se(β)	Wald *p*	Exp(β)= OR	Exp(β) 95% C.I.*	-2 log likelihood	LRT *p*
Radiation Vol.	-.289	.796	.466	0.74			.462
Radiation Vol.	-.292	.446	.424	0.75			.513
Fractionation	.013	.023	.584	1.01			.584
Tumor Radiation Dose	.00	.001	.902	1.00			.902
Boost Energy	.092	.075	.222	1.10	[0.95, 1.27]	131.72	.218
Mixed Photons	.354	1.021	.729	1.43			.729
Radiation Break	1.556	.844	.065	4.75	[1.91, 24.83]	133.14	.045

*Exp(β)=OR presented for factors deemed significant by Hosmer & Lemeshow's $p<.25$ criterion for inclusion in model building.

The final results of using these various statistical tests for assessing association between independent variables with cosmetic outcome were combined with the consideration of clinical relevance for inclusion or exclusion in model building. This resulted in the following set of variables to be included in stepwise regression procedures: hypertension ($p<.035$), tumor size ($p<.033$), axillary lymph node dissection ($p<.056$), total surgical volume ($p<.001$), tamoxifen use ($p<.042$), radiation treatment break ($p<.046$), boost energy ($p<.218$), and follow-up time ($p<.063$). For continuous variables in consideration for multivariate logistic regression model building, Pearson correlations were reassessed to uncover any multicollinearity of variables. Although tumor size and total surgical volume had a statistically significant correlation ($p<.015$), the Pearson correlation was weak with $r=.243$. Therefore, it is reasonable to conclude that these factors while having an obvious clinical relationship are statistically independent factors influencing cosmesis for the purposes of model building.

The forward Wald stepwise multivariate logistic regression resulted in a predictive model including the following variables: hypertension, total surgical volume, and radiation treatment break. The backward Wald stepwise multivariate logistic regression resulted in an identical set of variables. The forward and backward stepwise procedures produced these similar multiple logistic regression models, respectively:

$$COSMESIS = -1.431 + 1.011*HTN + .005*TOTALSURGICALVOL + 1.192*BREAK$$

$$COSMESIS = -1.490 + 1.251*HTN + .005*TOTALSURGICALVOL + 2.009*BREAK$$

A separate model building analysis was performed for the population of patients who had follow-up time of at least one year. This population was assessed using the same set of independent variables found to have statistically significant or clinically relevant

associations with cosmetic outcome. The forward and backward Wald stepwise multivariate logistic regression procedures produced the following models, respectively:

$$COSMESIS = 1.077 + 0.126*SIZE + 0.001*TOTALSURGICALVOL + 0.515*BREAK$$

$$COSMESIS = 1.077 + 0.126*SIZE + 0.0009*TOTALSURGICALVOL + 0.515*BREAK$$

While the coefficients for total surgical volume and treatment break were different from the model based upon the entire population, the model itself was different given its inclusion of tumor size rather than hypertension. Total surgical volume and treatment break appeared to convey a higher risk in the entire study population rather than those who had follow-up time of less than one year. The difference in models made this comparison of the coefficients indirect.

Nuclear grade had also been found to have a significant association with cosmetic outcome ($p<.027$). However, only 85 patients had nuclear grade reported. This presented a problem since multivariate logistic regression excludes any cases with missing data. Therefore, including nuclear grade in the model building process would mean conducting the analysis with only these 85 patients rather than the entire study population. However, in order to better assess the role of nuclear grade in determining cosmetic outcome, this variable was added to the previously determined set of variables under a separate model building process. This produced a predictive model that included the same set of variables hypertension, total surgical volume, and radiation treatment break. This model retained its overall significance ($p<.001$) as well as the significance of each variable within the model. Therefore, nuclear grade did not appear to be an independent risk factor for cosmesis.

The final logistic regression model was also assessed for fit. The Hosmer-Lemeshow goodness-of-fit test for this model was not significant ($p<.745$)—therefore,

we do not reject the null hypothesis that the observed and expected values are close, and conclude that the model fits the data well.

Discussion:

Similar to previous investigation at other institutions, greater than 55% of the women in this study had an excellent cosmetic outcome at a mean follow-up time of 2.4 years. This reinforces the rationale of using breast preservation therapy to provide a high likelihood of maintaining breast appearance as well as equivalent survival benefit as mastectomy. One of the foundational issues in the design of this study concerns the follow-up time at which cosmetic outcome was assessed. Due to the small study population and the need to accrue an adequate number of patients for meaningful statistical analysis, 22 patients with follow-up time of 7-11 months were included. These patients were found to have a significantly higher proportion of excellent cosmesis than those with ≥12 months follow-up. Those with longer follow-up times had greater likelihood of worsened cosmesis (OR=3.00) only when compared as a dichotomous variable.

When follow-up time was assessed as a continuous variable using univariate logistic regression, it had a borderline association with cosmesis ($p<.063$). Although the elevation of risk (OR=1.02) appeared small, due to the method of calculation, this risk was actually based upon each month of follow-up. This would result in an appreciable cumulative risk with time. These results are consistent with the fact that cosmesis is known to decline for the first three years after completing treatment, but then tends to stabilize. Most long-term radiation effects become evident during that three-year

period.[17] It is possible that long-term radiation changes such as edema, telangiectasias, and breast retraction had not yet developed in the subset of patients whose cosmetic outcomes were recorded at the shorter follow-up interval.

Another potential explanation for worsened cosmesis associated with longer follow-up centers upon the timing of patient accrual into the study. If follow-up time was shorter for patients most recently enrolled into the study, then these patients would potentially be different from their predecessors. Specifically, they may have benefited from optimal surgery, chemotherapy, and radiation treatment compared to patients enrolled during the initial years of BPT. However, there was no significant correlation between follow-up time and the year of treatment ($p<.276$), nor significant association between year of treatment and cosmetic outcome ($p<.526$).

Recommendations regarding BPT and patient age have been controversial for various reasons. In this study, age did not show any association with cosmetic outcome. While many reports have not shown age to be related to cosmesis, Taylor *et al* found that age >60years at diagnosis adversely affected cosmetic outcome. They postulated that postmenopausal breasts may undergo greater retraction from radiation due to the higher proportion of adipose relative to glandular tissue.[10]

On the opposite end of the age spectrum, previous analyses have showed that younger women more often have lymph node involvement, larger tumors, and decreased likelihood of hormone receptor expression.[18] These features reflect the aggressive nature of breast cancer in younger women. This raises the question of whether BPT should be recommended to younger women over mastectomy. Unfortunately, due to the constraints of retrospective cohort design, the incidence of locoregional recurrence as well as

survival following conservative treatment in younger women could not be addressed in this study. Therefore, the important question of whether BPT should be recommended to younger women could not be answered. Further study is needed given the fact that younger women typically express greater interest in conservative treatment.

None of the patients in this study had a history of collagen-vascular disease, so this could not be evaluated for its relationship with cosmesis. In previous studies it has been considered a risk factor for worsened outcome due to the effects of small-vessel vasculitis or already existing skin changes that might worsen with the insults of surgery and radiation. The presence of collagen vascular disease is a relative contraindication to BPT, with recommended precautions such as the use of higher energy photons to improve homogeneity of dose distribution, reduction of skin dose, and minimization of matchline fibrosis.[19] Hypertension is the only feature of patient medical history in this study that had a significant negative impact upon cosmesis. The proposed pathophysiology of this effect also centers upon small vessel disease impairing adequate blood circulation to healing tissues.

The highly correlated features of tumor size, re-excision volume, as well as total surgical volume all had significant negative impact upon cosmetic outcome, which confirms established findings from previous similar studies. Axillary lymph node dissection was performed for the majority of patients in this study. Eighty-eight patients underwent the procedure, with an average of 16 nodes removed, only to result in 24 patients with nodal involvement. It was considered whether the high rate of lymph node dissection and the high number of nodes removed reflected previous standard practice, before the acceptance of sentinel node biopsy. Although the use of axillary lymph node

dissection was found to worsen cosmesis considerably, this could potentially have less current clinical relevance since patients more commonly undergo sentinel node biopsy for initial node exploration. However, in this study there was no relationship between the total number of lymph nodes removed and year of treatment ($p<.221$).

The use of chemotherapy as well as combined chemotherapy and tamoxifen regimens were not shown to adversely affect cosmesis. This assessment may have been limited by the fact that there were varying regimens delivered in varying sequences to the 38 women who underwent chemotherapy. These regimens included AC, AC+Taxol, CMF, CAF, and CAF+Taxol, yet they needed to be grouped together for the purposes of statistical analysis.

Importantly, tamoxifen in combination with BPT was found by the National Surgical Adjuvant Breast and Bowel Project B-24 trial to provide additional protection from breast cancer recurrence. This study was published in 1999, and since that time tamoxifen has become a standard part of therapy for women with breast cancer expressing hormonal receptors.[20] In this study, tamoxifen treatment alone was found to have an association with improved cosmetic outcome. In fact, tamoxifen was the only variable in this study found to have a favorable association.

Prior studies have shown conflicting effects of tamoxifen on cosmesis, but it has been postulated by Wagner *et al* that there may be an interactive effect on normal tissue recovery leading to postradiation fibrosis caused by tamoxifen-enhanced secretion of TGF-β.[21] These investigators initially found a marginally significant association ($p<.06$) between tamoxifen and adverse cosmesis, and upon an expanded follow-up study there was no association. Wazer *et al* found a borderline significant trend of adverse cosmesis

with tamoxifen due to retractive fibrosis.[22] The association with excellent cosmetic outcome in this study is therefore surprising. Given that tamoxifen became an established part of standard therapy only recently with the NSABP B-24 study, the confounding of tamoxifen with progressive treatment advances in surgery, chemotherapy, and radiation must be considered. Upon evaluation however, tamoxifen use was not associated with the year of treatment in this study ($p<.261$).

Tamoxifen may in fact be a confounder since it was found to have a marginally significant association with lower T stage ($p<.071$) as well as a significant association with lower total surgical volume ($p<.020$). By definition, patients who undergo therapy with tamoxifen have estrogen receptor positive tumors, which are known to be less aggressive in nature. Therefore, the apparent association with excellent cosmesis likely reflects a tendency for these tumors to be smaller at the time of diagnosis, and consequently a tendency for these tumors to require less extensive surgical resection.

All radiation treatment factors assessed did not show any association with cosmetic outcome except for the use of a treatment break. All patients in this study who had treatment temporarily stopped had developed moist desquamation. This was not particularly informative since it meant that the patient had a substantial treatment complication. The radiation toxicity evident in the skin reflects severe tissue toxicity that could result in breast tissue fibrosis and retraction.

The lack of other radiation treatment factors associated with cosmetic outcome may reflect the standardized nature of breast radiation treatment for early stage breast cancer and the homogeneity of treatment within the study population. Standardized practice results in minimal variation in treatment technique, radiation dose, and dose

fractionation. The use of radiation boost treatment to the lumpectomy site and its additional radiation dosage has been shown by other investigators to adversely affect cosmesis.[22] However, in this study 95% of patients received a boost, thus preventing assessment of a relationship to impaired cosmesis.

In addition to the statistical analyses of all variables of interest, the formation of a predictive clinical model was also attempted. Both the forward and backward stepwise Wald multivariate logistic regression analyses resulted in the same model. This model included the predictive factors of hypertension, total surgical volume, and radiation treatment break. The selection of these clinically marginal factors highlights the important role of clinical judgment in model building and the inclusion/exclusion of particular variables. For instance, total surgical volume is a well-established predictor of cosmetic outcome, but has limited clinical utility as it is not easily determined before surgery given the possibility of re-excision for positive margins. Similarly, the need for radiation treatment breaks is not easily predicted before therapy begins.

Therefore, these variables selected by the forward and backward Wald stepwise multivariate logistic regression analyses do not necessarily result in clinically rational or useful models. This is a common criticism of stepwise procedures as they can yield biologically implausible models with irrelevant variables, as in this case. Although a concise clinical model to predict cosmetic outcome is appealing, the results of this study instead support the consideration of the larger constellation of significantly associated variables to make clinical recommendations. According to the findings of this study, these variables include tumor size, total surgical volume, axillary lymph node dissection, and the presence of hypertension.

Study Design Limitations:

The most significant potential limitation involves the rating of cosmetic outcome. At Oregon Health & Science University's Department of Radiation Oncology, the principal investigator of this study is also the physician who treats the majority of the breast cancer patients. In addition, this physician is the sole observer determining cosmetic outcome. Consequently, in this study there was the potential for observer bias since she evaluated the treatment she had planned. Generally, no second observer ratings are recorded during routine follow-up, nor is it the standard practice of this department to take clinical photographs to document breast appearance after treatment completion. It would not have been feasible to schedule patients for appointments during which cosmetic outcome could be assessed solely for the purposes of this study. Moreover, such appointments and subsequent cosmetic outcome ratings would be subject to greater observer bias as they could theoretically be influenced by knowledge of the study objectives and variables.

However, given the treating radiation oncologist's expertise and experience in breast radiation therapy, she was also the best qualified and appropriate physician available to determine overall cosmetic outcome and to clinically assess possible long-term radiation effects. Although she was the sole observer, as part of her standard practice she used an established four-point scale to judge cosmesis. This scale has been shown to have good reproducibility between observers.[13] However, with the use of a single observer in this study, there was no inter-rater variability.

It is standard practice to determine and record cosmetic outcome during routine follow-up after radiation therapy. Therefore, this assessment was not done for the purposes of this study, thus diminishing the potential for observer bias. Since this was a retrospective study, at the time of assessment the physician did not know the treatment variables that would subsequently be studied. Therefore, she would not have used knowledge of these variables to shape her assessment.

Despite these limitations of a single observer, there is internal consistency in ratings as the principal investigator was the treating physician for the majority of the study period and used consistent cosmetic rating criteria as defined by the Joint Center for Radiation Therapy. Similarly, the majority of women in this study were treated at this institution according to its standard treatment practices by its multidisciplinary team, providing greater clinical consistency in terms of surgery, chemotherapy and radiation therapy treatment. However, this may perhaps affect the applicability of results to other institutions with different practitioners and practices. In terms of external consistency, the rate of excellent cosmetic outcome seen in this patient population was similar to other previous studies.

Another potential limitation concerning cosmetic rating is the absence of patient self-evaluation of cosmetic outcome. In addition to the variability of assessments by different physicians, the difference between physician and patient ratings of breast cosmetic results has also been investigated. Ultimately, patient self-evaluation is obviously of paramount importance, for it is the patient who must adjust to and live with the results of her treatment. Perhaps surprisingly, patients typically rate the cosmetic results more favorably than do physicians.[23] Due to the fact that patient ratings tend to be

higher, this study and its use of physician ratings have likely underestimated the occurrence of excellent cosmetic outcomes.

Various factors have been proposed to explain this lack of concordance. Methodological factors include physician use of objective standardized scale scoring that compares the treated and untreated breasts according to specific physical criteria. In contrast, patient ratings are characteristically and unavoidably subjective in nature. Patient evaluation reflects overall satisfaction with breast cosmetic results that is difficult to separate from the state of physical, psychosocial, and psychosexual functioning after breast cancer treatment[24]. In other words, patient assessment of cosmetic outcome has been shown to correlate closely with overall psychosocial and physical well-being.

Given the fact that the impact of breast cancer diagnosis and treatment reaches far beyond just cosmetic appearance, better understanding of the psychosocial, psychosexual, and physical adjustments is of course needed. Fundamental to this understanding is patient self-evaluation, which is absent in this study. However, the strength of this study design in determining factors influencing cosmetic appearance relies upon the assumption of greater objectivity and consistency in physician ratings, as defined by specific physical criteria. Moreover, it would not be possible to assess predictive factors against the pooled self-ratings of cosmetic outcome as these women would be making individual assessments that would be less systematic, and therefore less comparable in nature.

As discussed in the Introduction, a landmark study published in 1985 determined that breast preservation therapy resulted in equivalent survival outcomes compared to mastectomy. The time of this treatment paradigm shift coincided with the beginning of this study. Consequently, these patients were treated within the context of the same

therapeutic approach and philosophy. However, as this is a retrospective cohort study spanning the years 1984-2001, there is an immeasurable degree of potential heterogeneity of treatment as techniques and approaches changed with time. These potential changes include decreased breast excision volume as BPT became more accepted, decreased extent of axillary node dissection with the advent of sentinel node biopsy, refinement of radiation techniques with computerized tomography planning, as well as the use and scheduling of different chemotherapy regimens and hormonal therapy.

Another limitation centers upon the demographics of the study population. Reflecting the population demographics of the Portland, Oregon area, the vast majority (94.1%) of women treated with breast preservation therapy at OHSU in this study were Caucasian, with low representation of other racial groups. This study attempted to assess association between cosmetic outcome and ethnicity, but the racial distribution of the study population precluded any meaningful analysis. In addition, it may limit the applicability of study findings to other racial groups. However, given the relative uniformity of this study's patient population, its results can perhaps be more confidently applied to patients who share a similar demographic background.

Other potential limitations center around problems inherently associated with retrospective cohort studies. As this study depends upon a cohort of patients who have all undergone baseline assessment, treatment, and continued long-term follow-up, it may have selected for a population with greater compliance as well as health care access. In addition, there may have been patients who were lost to follow-up who had outcomes and treatment factors differing significantly from this study population. The strength of the retrospective design lies in its ability to identify a cohort of patients representing all

possible cosmetic outcomes, without bias selecting for patients with the desired outcome of interest.

Another potential limitation concerns data analysis. Since the distribution of cosmetic results was unequal, such that dichotomization into "excellent" and "good/fair/poor" was required for meaningful statistical analysis, the conclusions made regarding factors predicting cosmetic outcome were less specific. However, these cosmetic outcomes were consistent with prior investigation cited in the Introduction that demonstrated how the majority of women undergoing BPT have excellent results. This supports the external consistency of this study's distribution of cosmetic outcome with other institutions, and therefore the decreased likelihood of observer bias dictating cosmetic assessment.

This study did not address other potentially influential factors including breast size because this information was not available. The relative size of tumor to the breast is a recognized potential determinant of cosmesis. For example, earlier studies have suggested the negative influence of large breast size due to radiation dose inhomogeneity. Conversely, small breast size however, improved radiation techniques appear to have eliminated this problem through the use of increased radiation treatment energy. This study did not address radiation factors including matchline fibrosis or tangential chest wall separation. The latter is an index of relative dose inhomogeneity within the entire breast treatment field. It has been associated with worsened cosmesis.

The study design precluded any meaningful examination of rates of local recurrence, distant metastasis, or survival outcomes. Since follow-up time was defined as

the last clinical follow-up visit during which cosmetic outcome was recorded, it is an artificial end-point used for the purposes of this study. Follow-up time ranged from 7-141 months, and was therefore highly variable amongst the study population. Moreover, these patients are a highly selected group who met the eligibility requirement of ≥12 month disease free interval from the time of radiation completion, as well as continued close follow-up, and they therefore may not represent the entire population of early stage breast cancer patients.

Conclusion: Public Health Implications

While this study aimed to identify those factors influencing cosmetic outcome so that patients can be given appropriate treatment recommendations, the problem remains that many women who are eligible for conservative treatment are not given this option. This is despite equivalent survival rates as well as the preservation of body image, body integrity, and self-esteem. Lazovich *et al* examined trends in the use of breast conservation therapy following the 1991 NIH Consensus Development Conference on the treatment of patients with early stage invasive breast carcinoma.[24] Based upon the evidence from several randomized controlled trials described in the Introduction, this conference recommended that breast conservation therapy be used for the majority of women with Stage I and II cancer. This conference also urged physicians to consider women's preferences in making decisions with regard to the type of surgery.

It is estimated that conservative treatment can be recommended to 50-75% of all women with operable breast cancer, but that it is persistently underutilized.[25] Data from the Surveillance, Epidemiology, and End Results Program showed that in 1991, <50% of

women with Stage I breast cancer and <30% of women with Stage II breast cancer were treated with BPT.[25] More encouraging news was found by Lazovich *et al* upon comparing data from nine various state cancer registries in five year time periods before and after the NIH Consensus Development Conference. They found that the use of postoperative radiation increased from 35% to 50% in Stage I disease, and from 19% to 39% for Stage II disease. Rates increased but still reflected the underutilization of conservative therapy, and substantially lower use amongst Stage II patients remained. They also noted striking regional variation in treatment practices—for Stage I patients, the use of conservative treatment ranged from 41.4-71.4%, and for stage II patients its use ranged from 23.8-48.0%.[26]

Unfortunately, geographic differences were persistent and could not be accounted for solely by differences in patient age, disease stage, and race between different state tumor registries in that study. BPT is more often performed in urban than rural areas, in teaching hospitals than in non-teaching hospitals, as well as in larger hospitals. Proposed explanations include geographic lack of access to radiation treatment facilities and variation in physician attitudes about breast conservation therapy. Kiebert *et al* noted that physician attitudes varied depending upon their field—surgeons tended to prefer radical surgery whereas medical oncologists and radiation oncologists tended to favor more conservative approaches. Beyond specialty, they also noted that physician attitudes regarding patient involvement in decision making also influenced recommendations. Those who were amenable to patient involvement in treatment decisions tended to favor conservative surgery more often.[27]

While we must refine our understanding of which patients will have excellent cosmetic outcome from conservative therapy, we must also work to address this fundamental issue—to ensure that women are provided this option and the counseling needed to make an informed decision. To this end, the NIH Consensus Conference public health recommendations still remain valid and necessary—to increase physician and patient education, to encourage objective presentation of treatment options to patients, to adopt multidisciplinary treatment approaches that include consultation with a radiation oncologist, to improve access to radiation treatment facilities, and to provide counseling to patients to empower them in the decision-making process.

Appendix A: Joint Center for Radiation Therapy Cosmetic Scoring Criteria

Excellent: When compared to the untreated breast, minimal or no difference in size or shape or consistency (texture) on palpation, of the treated breast. There may be mild thickening or scar tissue within the breast or skin, but not enough to change the appearance.

Good: Mild asymmetry between the breasts (slight difference in the size or shape of the treated breast as compared to the opposite breast). Mild reddening or darkening of the breast. The thickening or scar tissue within the breast causes only a mild change in the shape.

Fair: Moderate deformity with obvious difference in the size and shape of treated breast. This change involves ¼ or less of the breast. There is moderate thickening or scar tissue of the skin and the breast, and obvious color changes.

Poor: Marked change in the appearance of the treated breast involving more than ¼ of the breast tissue. The skin changes are very obvious. There is severe scarring and thickening of the breast. In retrospect, mastectomy would have been a better option.

Appendix B: American Joint Committee on Cancer TNM Staging Guidelines (1999)

Primary Tumor (T)

T0	No evidence of primary tumor
Tis	Carcinoma in situ (intraductal/lobular/Paget's disease of the nipple with no tumor)
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2cm but not more than 5cm in greatest dimension
T3	Tumor more than 5cm in greatest dimension
T4	Tumor of any size with direct extension to (a) chest wall, (b) skin, (c) both, or (d) inflammatory carcinoma

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral axillary lymph nodes
N2	Metastasis to ipsilateral axillary lymph node(s) fixed to one another or to other structures
N3	Metastasis to ipsilateral internal mammary lymph nodes

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis (includes metastasis to ipsilateral supraclavicular lymph node[s])

Stage Grouping

Stage I	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0

References:

[1] Maddox W, Carpenter J, Laws H, *et al.* "A Randomized Prospective Trial of Radical (Halsted) Mastectomy versus Modified Radical Mastectomy in 311 Breast Cancer Patients." *Ann Surg* 1983:198:207.

[2] Fisher B, Bauer M, Margolese R, Poisson R, *et al.* "Five-Year Results of a Randomized Clinical Trial Comparing Total Mastectomy and Segmental Mastectomy With or Without Radiation in the Treatment of Breast Cancer." *New England Journal of Medicine* 1985:312:667-673.

[3] Fisher B, Redmond C, Poisson R, Margolese, *et al.* "Eight-Year Results of a Randomized Clinical Trial Comparing Total Mastectomy and Lumpectomy With or Without Irradiation in the Treatment of Breast Cancer." *New England J Medicine* 1989:320:822-828.

[4] American College of Radiology, American College of Surgeons, College of American Pathologists, and the Society of Surgical Oncology. "Standards for Diagnosis and Management of Invasive breast Carcinomas." *CA Cancer J Clin* 1998:11:1545.

[5] Recht A, Danoff BS, Solin LJ, *et al.* "Intraductal Carcinoma of the Breast: Results of Treatment with Excisional Biopsy and Irradiation." *J Clin Oncol* 1985:3:1339-1343.

[6] Obedian E, Fischer DB, Haffty BG. "Second Malignancies after Treatment of Early-Stage Breast Cancer: Lumpectomy and Radiation Therapy versus Mastectomy. *J Clin Oncol* 2000:12:2406-12.

[7] De la Rochefordiere A, Abner A, Silver B, Vicini F, Recht A, Harris J. "Are Cosmetic Results Following Conservative surgery and Radiation Therapy for Early Breast Cancer Dependent on Technique?" *Int J Radiat Oncol Biol Phys* 1992:23:925.

[8] Wolberg WH, Tanner MA, Romsaas EP, *et al.* "Factors Influencing Options in Primary Breast Cancer Treatment." *J Clin Oncol* 1987:5:68-74.

[9] Abner AK, Recht A, Vicini F, Silver B, *et al.* Cosmetic Results after Surgery, Chemotherapy, and Radiation Therapy for Early Breast Cancer." *Int J Radiat Oncol Biol Phys* 1991:21:331-338.

[10] Taylor M, Perez C, Halverson K, Kuske R, *et al.* "Factors Influencing Cosmetic Results after Conservation Therapy for Breast Cancer." *Int J Radiat Oncol Biol Phys* 1995:21:753-764.

[11] Rose MA, Olivotto I, Cady B, Koufman C, *et al.* "Conservative Surgery and Radiation Therapy for Early Breast Cancer: Long-Term Cosmetic Results." *Arch Surg* 1989:124:153-157.

[12] Harris JR, Recht A. "Conservative Surgery and Radiotherapy." *Breast Diseases*. Ed Harris JR, Hellman S, Henderson IC, Kinne DW. (Philadelphia: Lippincott, 1991) 394-395.

[13] Sneeuw KC, Aaronson NK, Yarnold JR, *et al.* "Cosmetic and Functional Outcomes of Breast *Conserving* Treatment for Early Stage Breast Cancer: Comparison of Patients' Ratings, Observers' Ratings and Objective Assessments." *Radiotherapy and Oncol* 1992:25:153-159.

[14] Bartelink H, Van Dam F, Van Dongen J. "Psychological Effects of Breast Conserving Therapy in Comparison with Radical Mastectomy." *Int J Radiat Oncol Biol Phys* 1985:11:381-385.

[15] Amichetti M, Busana L, Caffo O. "Long-Term Cosmetic Outcome and Toxicity in Patients Treated with Quadrantectomy and Radiation Therapy for Early-Stage Breast Cancer." *Oncology* 1995:52:177-181.

[16] Deeks J, Bracken M, Sinclair J, Huw T, *et al.* "When Can Odds Ratios Mislead?" *Brit Med J* 1998:317:1155-6

[17] Olivotto I, Rose M, Osteen R, *et al.* "Late Cosmetic Outcome after Conservative Surgery and Radiotherapy: Analysis of Cosmetic Failures." *Int J Radiat Oncol Biol Phys* 1989:17:747-753.

[18] Winchester D. "Breast Cancer in Young Women." *Surg Clin North Am* 1996:76:279-287.

[19] Recht A. "Selection of Patients with Early Stage Invasive Breast Cancer for Treatment with Conservative Surgery and Radiation Therapy." *Semin Oncol* 96:23(suppl 2):19-30.

[20] Fisher B, Dignam J, Wolmark N, Wickerham, *et al.* "Tamoxifen in Treatment of Intraductal Breast Cancer: National Surgical adjuvant breast and Bowel Project B-24 Randomised Controlled Trial." *Lancet* 1999:353:1993-2000.

[21] Wazer D, Morr J, Schmid C, Ruthazer R, Schmidt-Ullrich R. "The Effects of Postradiation Treatment with Tamoxifen on Local Control and Cosmetic Outcome in the Conservatively Treated Breast." Cancer 1997:80:732-740.

[22] Wazer D, DiPetrillo T, Schmidt-Ullrich R, Weld L, Smith T, Marchant D, Robert N. "Factors Influencing Cosmetic Outcome and Complication Risk after Conservative Surgery and Radiotherapy for Early-Stage Breast Carcinoma." *J Clin Oncol* 1992:10:356-363.

[23] McCormick B, Yahalom J, Cox L, Shank B, Massie M. "The Patient's Perception of Her Breast Following Radiation and Limited Surgery." *Int J Radiat Oncol Biol Phys* 1989:17:1299-1302.

[24] Al-ghazal, SK, Fallowfield L, Blamey RW. "Patient Evaluation of Cosmetic Outcome after Conserving Surgery for Treatment of Primary Breast Cancer." *Eur J Surg Oncol* 1995:25:344-346.

[25] Lazovich D, Solomon C, Thomas D, Moe R, White E. "Breast Conservation Therapy in the United States Following the 1990 National Institutes of Health Consensus Development Conference on the Treatment of Patients with Early Stage Invasive Breast Carcinoma." *Cancer* 1999:86:628-637.

[26] "Use of Lumpectomy for Breast Cancer." Surveillance, Epidemiology and End Results Program. *J Natl Cancer Inst* 1995:87:339.

[27] Kiebert G, de Haes J, van de Velde C. "The Impact of Breast-Conserving Treatment and Mastectomy on the Quality of Life of Early-Stage Breast Cancer Patients: A Review." *J Clin Oncol* 1991:9:1059.