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13. ABSTRACT *(Maximum 200 words)*

This is an observational study of a cohort of patients who had undergone a modified radical mastectomy for primary breast cancer and then underwent a contralateral subcutaneous mastectomy at the time of reconstruction. The comparison of the survival and disease free survival of these patients to individuals who had not undergone contralateral mastectomy and reconstruction shows excellent survival through five years, suggesting a potential survival advantage to those who had elected this procedure. Selection bias and effects of confounding variables may account for some of the apparent survival advantage, although an important observation is that the maximum apparent benefit seen in the contralateral group is observed when the contralateral procedure is performed at shorter intervals from the primary procedure. This observation suggests that comparison to a cohort of patients with similar tumor characteristics in individuals who received tamoxifen should be carried out.

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PI - Signature Date

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INTRODUCTION

This project has involved the study of a unique cohort of patients who underwent modified radical mastectomy of a cancerous breast and contralateral glandular (subcutaneous) mastectomy followed by reconstruction of both breasts utilizing silicone-silastic implants. It is clear from the work of others as well as from the data of the present study, that the frequency of synchronous second cancers is insufficient to warrant the procedure. The basis on which the second procedure was undertaken in this series was to achieve optimal reconstructive symmetry, as well as to address and evaluate the presence of significant contralateral breast disease (1).

The ongoing controversy regarding silicone breast implants was a factor which was considered and, as predicted by the initial reviewers, introduced considerable obstacles to carrying out the proposed studies (see initial review, 4,5). The majority of these impediments were resolved by late spring 1998, but not without effecting the time course of the project. On the basis of many of the hypothetical concerns arising in the late 1980's concerning breast implants, the initial evaluation of the patients and the follow-up information which had been accrued in the late 1980's was intended to examine whether there was an adverse effect on patient survival, disease free survival or quality of life with contralateral subcutaneous mastectomy and silicone implants. The issue was initially whether women with breast implants developed connective tissue disorders (6,7,8), and some had suggested early in the controversy that there may be increased risk of cancer associated with silicone implants (9). The epidemiologic evidence is clear that there is no increased risk of cancer (10,11,12). Epidemiologic studies have supported the view that there is no increase incidence of connective tissue disease associated with silicone implants(13,14). In July 1998, the report of the United Kingdom Independent Review Group was published, strongly supporting the conclusion that there was no evidence to support any identified systemic disease from silicone breast implants (15).

The evaluation of the patients who had undergone contralateral mastectomy in the subject cohort suggested that there may be a survival advantage in the patients who underwent bilateral mastectomy as compared to a contemporary group undergoing unilateral mastectomy. This finding was not anticipated, as the question initially posed was whether there may be an adverse effect. In order to further evaluate the potential significance of the preliminary data, the present study was undertaken to compare the bilateral mastectomy cohort with additional control groups with similar tumors and patient characteristics, but treated with 1) unilateral mastectomy, 2) segmental mastectomy, or 3) segmental mastectomy with radiation which were evaluated under the auspices of the NSABP (16). The characterization of a substantial cohort of patients who underwent bilateral "prophylactic" mastectomy and who did not have cancer has enhanced the original proposal by providing a cohort for comparison of histologic changes observed in breasts contralateral to diagnosed cancer. The control group which had been utilized in the preliminary evaluation of the cohort consisted of matched patients treated with unilateral modified radical mastectomy. The survival advantage observed through five years follow-up in the contralateral cohort was accrued to those patients with less lead time to second mastectomy rather than to those with longer periods between procedures as would be predicted if the effect was due to lead

time bias. It has not been established whether a contralateral mastectomy has any effect on absolute, relative, or disease-free survival and selection bias for patients who elect this procedure as a part of achieving reconstructive symmetry complicates the interpretation of any observed differences in these outcomes. It remains critical that the full cohort be maintained through the full period of evaluation so that additional selection/loss bias is not introduced. The period of time since the preliminary data set construction is a major complicating factor in achieving this goal.

The present project was specifically intended to extend the follow-up of the cohort of patients who had undergone unilateral modified radical mastectomy followed by contralateral subcutaneous mastectomy and reconstruction with silastic/silicone implants to a minimum follow-up of ten years and to compare these to the control groups identified, now including examination of bilateral glandular mastectomy specimens not associated with carcinoma, and to catalogue the pathologic specimens and characterize the frequency and pattern of epithelial change observed in the contralateral breast.

METHODS

Contralateral Subcutaneous Mastectomy Population

The study group consists of 360 consecutive patients who underwent contralateral subcutaneous mastectomy between 1975 and 1986 at Duke University Medical Center performed by Dr. Nicholas Georgiade, Dr. Ronald Riefkohl or Dr. Gregory Georgiade. Of these patients, 67 demonstrated only in situ carcinoma. The mean age of the patients at operation was 42.9 years old. The primary breast cancers were treated by modified radical mastectomy. The second breast (contralateral) mastectomy was followed by bilateral reconstruction with silicone gel filled, silastic implants. Follow up was carried out in conjunction with the offices of the treating physicians to confirm the status of the patients regarding survival.

Control Groups

The initial control group used in the preliminary analyses were derived from a cohort of patients who underwent unilateral modified radical mastectomy for regional breast cancer at Duke University. These were consecutive patients drawn from the surgical schedule lists. Additional control groups were defined from the 1997 progress report assembled from patients from the NSABP statistical center protocol B-04 and B-06 to include matched controls for age, tumor type and stage treated with mastectomy (C2), tylectomy (C3), or tylectomy with radiation (C4). In C2-C4 selection of matched controls from the larger available population allows for the mean age to more closely match the age of the study group (43 years). Patients were excluded from the control groups (C1-C4) if they experienced metastatic disease within 3 months of diagnosis, or had previous or simultaneous breast cancer; subsequent contralateral breast cancer (diagnosed > 3 months following primary breast cancer). The bilateral glandular mastectomy group, who had not had breast carcinoma diagnosed prior to glandular mastectomy, is drawn from 1186 patients who

underwent this procedure from 1975 to 1988. The mean age of this group is 46.3 years. The present proposal does not consider the long term follow-up of this group although efforts are now underway to determine the feasibility of this.

Follow-Up Procedures

Follow-up contact of the contralateral cohort is by telephone interview combined with medical record reviews supervised by the patient's treating physicians and with the physician's permission and the patient's consent. Record abstraction includes verification of deaths by death certificates. The use of a missing person service was anticipated for up to 10% of the cohort, but as a result of area code changes and issues raised by the breast implant controversy the expected sourcing of information and contact base was significantly affected and the need for the use of search services extended to over 164 patients (46%). Internet direct and reverse number searches, claims data, as well as public records provided some resolution of the difficulty (96 patients). The remainder (68 patients) are likely to require the use of a similar service to that used in the original data evaluation which had been required for only 7 patients in 1991-2. This service requires several hundred dollars per person depending on the complexity of the search required.

Definitions

The variables are defined as follows:

1) Disease-free interval (DF-SURV) = Time in years from unilateral cancer surgery to either recurrence of disease or date of last follow-up, whichever comes first.

2) Survival (SURV) = Time in years from unilateral cancer surgery to last follow-up or death

3) Age at operation (AGEOP) = Age of patient in years at the time of unilateral cancer surgery.

4) Nodal status (NODES) = Number of involved lymph nodes observed at the time of unilateral cancer surgery.

5) Tamoxifen status (TMOX) = Whether or not the patient was treated with tamoxifen as part of cancer therapy.

6) Adjuvant therapy (ADJV) = Whether or not the patient received adjuvant therapy, type recorded; dichotomized use or no use.

7) Operation status (OP2) = Time-varying designation of whether or not a patient had undergone CSQM at any given point in time.

8) Waiting time (WAITTIME) = Time in years from unilateral cancer surgery to CSQM.

9) Histology of ipsilateral and contralateral specimen(s), breast cancer; epithelial lesions, and cystic change.

The cohorts are compared as those with unilateral invasive breast cancer who were exposed to contralateral subcutaneous mastectomy at a variable time after initial surgery and groups who were not exposed to contralateral subcutaneous mastectomy, separated into groups

treated with mastectomy, or tylectomy and radiation. The endpoints are the finding of death due to cancer, cancer recurrence, death not due to cancer or date of last follow-up. Death is corroborated by death certificate examination. Major prognostic factors for breast cancer survival (tumor size, type, and nodal status, stage) and waiting-time bias are accounted for in the analyses.

Because the contralateral subcutaneous mastectomies were not done on a randomized basis, these data constitute an observational study. There is no ideal group which can be used as a basis for comparison but the three selected can account for the major variables included in the analyses with the selection bias of patients who elect mastectomy or bilateral mastectomy as a variable which can not be adequately modeled. This selection bias extends to the higher socioeconomic status (SES) of the patients in the contralateral cohort.

Survival is compared as crude survival and simple stratification by potential confounding variables and by Co proportional hazards modeling of disease-free survival which allows for simultaneous investigation of several covariates (both fixed and time varying).

The primary quantifiable selection factors for performing a contralateral subcutaneous mastectomy indicate low nodal status and young age as principal factors. Other selection factors for contralateral subcutaneous mastectomy include the aforementioned high socioeconomic status (SES), positive family history of breast cancer, the patient's expressed wish for contralateral subcutaneous mastectomy, the presence of multicentric disease in the cancerous breast, and a history of multiple previous biopsies in the contralateral breast..

Progress:

This IDEA proposal was submitted in 9/95, and funds were first made available in late 8/96. The initial reviewers correctly predicted the problems which the implant controversy would provide, as well as the geographic constraints which flow from the geographic separation of Pittsburgh, PA and Durham, NC. The PI recognized this, as well as the potential for problems as a result of the period of time (four years) without direct organized contact with the cohort since construction. The complexity of the effect of the breast implant controversy on the study was considerably greater than expected until settlement of the major elements of the breast implant litigation occurred in 1998.

The solution to the geographic (logistic) concerns raised by the reviewers was achieved by the hiring of an interviewer, record abstracter based in Durham, NC who had worked extensively with both the PI and the principal treating physicians. The identification of the cohort and last contact point was achieved as per the planned timetable, however, the frequency where the last contact (1992) was no longer a valid telephone number was much greater than expected in part as a result of area code changes of 1997/98.

The project plan was and remained defined as six tasks. 1-Extend follow-up of contralateral cohort; 2-Acquire and compare additional control populations; 3-Model data sets; 4,5-Collate and catalogue pathology; 6-Evaluate the Resource availability

Task 1 - Extension of follow-up of patient cohort

Proposed (months 1-3): Verification of Addresses; contact points; completeness of data in initial set.

Status The initial contralateral cohort was verified with copies of primary documents and incomplete data requirements defined, addresses and phone number at last known were compiled for . The cohort data was completed to the last contact point available in September 1997.

Proposed (months 1-2): Review of follow-up protocols

Status The protocol was finalized to acquire survival status and most recent clinical evaluation of tumor status, current medications and whether any additional cancer treatments had been used. Menopausal status and date (the vast majority of the original cohort have now entered menopause). Family history revaluation was made to determine if any new family members have had cancer diagnosed in the interval since the previous follow-up.

Proposed (months 4-16): Patient follow-up contact; verify death certificates; chart reviews; missing person searches.

Status As of September 1998, 68 of the individuals in the cohort have not been located based on last known address or on medical records. Attempts at contact at the last known contact were not successful for 129 patients, requiring phone number searches, claims and medical record searches, including reverse searches. To date there remain 68 individuals with no available contact information since the 1991-92 contact. There have been only five confirmed additional deaths from breast cancer beyond those known in 1992, three of whom were classified as alive with disease in the previous accounting. Three additional patients have been document as having died of other causes. The missing contacts may represent patients who have died and if analyses were based on the assumption they were dead of disease, this would increase the number dead of disease by 18%, to a number greater than the proportion seen in any of the control groups. It is therefore

imperative that their status be verified. The option of missing person searches, used for a smaller number of patients in the original analyses is beyond the budgetary constraints of the project for the number of patients involved although sources for the support of this effort are being sought. The treating physician's office is attempting to identify other means of making contact.

Proposed (months 17-24): Status

Verification of data sets; data analyses.
The data entry compared to primary documents has been undertaken for the patients successfully contacted. Data analyses to this point is preliminary only in view of 68 unknown status individuals. The inability to locate an individual may be modeled as either a proportion of those lost to contact as DOD or as those lost to contact as all either DOD or of other causes. The number of individuals involved in either case make data analyses speculative beyond the last point of contact in 1991/2. In the alternative the unknown status in 1998 can be modeled as the last date of contact, in either case providing a less than satisfactory basis for comparison at this time. For this reason we are continuing to pursue avenues to achieve contact.

Task 2 -

Acquire and compare additional control populations

The NSABP biostatistical center has appropriate control populations which match the initial cohort of CSQM. Preliminary analyses of matched patients treated with either mastectomy or tylectomy radiation had been done based on the data to five years of follow-up. The exploration of the data set requires that the cohort which will be used in the final analyses be defined and in particular the decision for the accounting of the nearly 20% without follow up be made. The crude absolute survival of the CSQM to five years was 96% while additional known deaths from breast cancer is 5 patients with 68 patients with unknown status, three dying from causes other than breast cancer, thus the crude absolute survival at ten years could be between 92 - 70%. Control groups at this interval drawn from B06 both demonstrates similar survivals at 10 years of approximately 71-73% whether treated with total

mastectomy or segmental mastectomy with radiation therapy (segmental only not consider as appropriate control) and model even more closely considering age and nodal status. It is readily apparent that analyses of the CSQM cohort requires the characterization of a substantial proportion of the remaining individuals and decision regarding at what point the remaining patients will be considered as lost to follow-up.

Task 3 - Status

Model data analyses sets; establish parameter comparisons

The variables of age at operation, nodal status, tumor characteristics, adjuvant therapy, socioeconomic status, time to second operation, are the primary variables. Considerable effort has gone into considering the potential impact of a significant loss of the CSQM follow-up with the recognition that if the proportion with last follow-up over five years earlier remains substantial the ability to compare outcomes will be severely limited and would present the undesirable alternative that the data be presented descriptively. In the initial data presentations there are remarkable survival curves which are superficially upheld with the follow-up accomplished. Presentation of the data with censored follow-up at last visit without considering the reasons for loss has the potential for providing seriously misleading conclusions on a critically important issue of effect on survival.

Task 4 & 5- Data analyses

Collate and catalogue the pathologic specimens

Data analyses to this point has been restricted only to the analyses of the histologic material. The analyses of the cohorts for DFS and Survival will be greatly influenced by the assignment of the status of the 68 individuals who are currently lacking contact points to verify status. The control groups from the NSABP have been identified and will be compared using the parameters outlined in methods. This is the endpoint of the evaluation of this resource and requires that the status identification be identified or the primary outcome of the study, the evaluation of the resource should the remaining patients be considered lost to follow-up, would be that the resource is of limited value in evaluating the significance of contralateral mastectomy on the critical issues of effect on outcome.

Task 6: Provide a means to make resource available to qualified investigators
Stored frozen samples remain from the contralateral breast cohort for 138 cases.

The initial 5-Year Survival Data demonstrated a difference in disease free survival advantage for the patients diagnosed before age 50 for the CSQM. The difference in disease-free survival was greatest and most beneficial for CSQM patients compared to UNI patients plots when: Age < 50; Node positive- 1-3 Nodes positive; Tumor size > 2cm; Node positive and tumor size > 2cm. Efforts to reduce the number of individuals with follow-up to 1991/2 are continuing as the current deficit of 68 individuals would effectively obscure or reverse the observed differences of survival.

CSQM patients were treated at private hospitals and the majority had some form of medical insurance. This factor provides a potential point of follow up contact to determine status, i.e. claims data.

Five Year Data
Table 1

Crude Kaplan Meier Results:
Absolute survival CSQM 96% Orig Uni 70% NSABP B06TM 82% B06SMXR 84%
The difference in DFS is greatest for CSQM when Age<50; Node +=1-3, and Tumor size>2cm
A time between procedures of <2years provided the maximum benefit
Proportional Hazards modeling:
Maximum benefit of CSQM if Node +, no adjuvant therapy, <2 years between procedures

Table 2: Contralateral Cohort Available as of 8/14/98

	Contralateral Subcutaneous Mastectomy
Originally identified	360
Initial Misclassification	Delete 7 CSQM (-7C)
IN-SITU Breast Ca	Delete 67 CSQM (-67C) (LCIS, DCIS)
Missing Values	Delete 68 CSQM (-68C)

Table 3 Histology Contralateral Cohort Including In Situ Pts(353 Patients)
Histological Diagnosis of Original Tumors

Infiltrating Ductal	77% Grade I-18% of Infiltrating Ductal tumors GradeII 52% GradeIII-30%
Intraductal	16%
Lobular Invasive carcinoma	5%
Lobular Carcinoma In Situ	2%

Table 4 Histologic Findings In the Contralateral Breast

	Contralateral Patients	Bilateral Subcutaneous Patients (684)
Cystic Duct Dilatation		
Macrocysts Microcysts	31% 61%	50% 50%
Duct Ectasia	10%	10%
Sclerosing Adenosis	38%	24%
Ductal Epithelial Hyperplasia	26%	11%
Moderate-Severe Atypia	15%	5%
Atypical Lobular Hyperplasia	18%	4%
Moderate-Severe Atypia	7%	3%
Calcifications	19%	14%
Synchronous 2nd Carcinoma (clinically occult)	7.5%	
Clinically Occult Carcinoma in Glandular Mastectomy		6%

Conclusions:

The initial data set supports the rationale for the study. The project has experienced severe difficulties as a result of concerns raised associated with the breast implant controversy but the greatest impediment has been the time interval from the original cohort construction. The number of patients remaining alive among the contacted patients remains remarkable (only five additional patients were identified as DOD), but this enthusiasm is tempered with concern that the patients not contacted may include a significantly disproportionate number who are dead of disease, although most were disease free at last contact. For a number of reasons, the breast implant litigation resulted in greater complexity in obtaining follow up through their physicians office until after the resolution of the major issues in 1998. This was predicted by the original reviewers of this proposal.

It is relevant that the observation of an apparent survival advantage in this cohort, with appropriate additional control groups identified, is still noted, although a number of potential confounding variables (selection bias most importantly) remain to be explored. It is for this reason that continued support for the interviewer has been secured by the PI and funds to continue to pursue completion of the follow-up will be found. Until the complement of the cohort is established, meaningful analyses of the data set is unlikely to be productive and this becomes a descriptive study, considerably less than its full potential.

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Personnel Receiving Salary Support from budget

Dr. Kenneth S. McCarty, Jr.	10% effort (full year)
Beata Pietrzak	50% effort

Participants not receiving Salary Support from first year budget

Dr. Nicholas Georgiade	5% effort
Dr. Gregory Georgiade	5% effort
Donna B. Silva	20% effort - Contribution in kind from funds - Dr. McCarty