RADIATION THERAPY ONCOLOGY GROUP

RTOG 95-17

A PHASE I/II TRIAL TO EVALUATE BRACHYTHERAPY AS THE SOLE METHOD OF RADIATION THERAPY FOR STAGE I AND II BREAST CARCINOMA

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AS THE SOLE METHOD OF RADIATION THERAPY  
FOR STAGE I AND II BREAST CARCINOMA  

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Arm 1: LDR 45 Gy/3.5-6 days  
Arm 2: HDR 34 Gy/10 fractions/5-7 days  
\( (3.4 \text{ Gy b.i.d. separated by 6 hours}) \)

Chemohormonal Therapy  
At discretion of treating institution, but cytotoxic chemotherapy is not to be started until at least 2 weeks post-brachytherapy. Tamoxifen can be started at once.

**ELIGIBILITY:** (see Section 3.0 for details)  
- Invasive ductal, medullary, papillary, colloid (mucinous), tubular histologies  
- Stages T1, T2, (lesions \( \leq 3 \text{ cm} \)) N0, N1 (up to 3 metastatic axillary lymph nodes with no extracapsular nodal extension \( \text{[a minimum of 6 nodes in specimen], or a negative sentinel node is acceptable]} \), M0  
- Six surgical clips placed at time of tylectomy to delineate target volume.  
- Unifocal breast cancer \( \text{(single focus which can be encompassed by one tylectomy)} \)  
- Unilateral breast cancer; no synchronous or previous contralateral breast cancer  
- Negative or close but negative microscopically-assessed surgical margins \( \text{(see Section 10.6)} \)  
- No extensive intraductal component \( \text{(see Section 3.2.16)} \)  
- No collagen vascular disease \( \text{(see Section 3.2.7)} \)  
- No known unresected residual carcinoma; no diffuse suspicious microcalcifications  
- No prior malignancy \( \text{(\( \leq 5 \text{ years prior to enrollment in study} \)) except non-melanoma skin cancer if continuously disease-free} \)  
- Negative post-tylectomy mammogram if cancer presented with malignancy-associated microcalcifications  
- Negative pregnancy test for women of child-bearing age  
- Time interval from final definitive breast surgical procedure to brachytherapy loading is less than 6 weeks  
- Signed study-specific consent form

**Required Sample Size:**  
46 to HDR  
46 to LDR  

2/14/00
"Rapid Turnaround Review" MUST be completed first, see Sections 5.1 and 6.14

1. Does the patient have an untreated (except for tylectomy) histologically confirmed cancer of the breast of the types specified in Section 3.1.7 and excluding those characteristics described in Section 3.2.2?

2. What is the AJC TNM classification? (Skip to Q4 if T1)

3. Specify the primary tumor size as determined by the pathologist (Section 10.3). Use clinical size only if pathological size is indeterminate.

4. Has the patient undergone tylectomy resulting in negative, or negative but close, tumor margins? (if yes, skip to Q6)

5. If no, is re-excision planned prior to introduction of radiation sources? (failure to meet all criteria subsequent to re-excision will result in ineligibility)

6. Any evidence of pre-excision breast microcalcifications in the initial mammogram?
   - (Y) If yes, was a postoperative mammogram done and found negative for residual suspicious microcalcifications?

7. Were six surgical clips placed delineating the margins of the tylectomy cavity?

8. Has the patient had at least six axillary nodes sampled with three or fewer nodes found positive and none with extracapsular spread, or a negative sentinel node?

9. Any evidence of multicentric breast tumor, unresolved suspicious synchronous tumors/calcifications or prior history of breast cancer?

10. Any evidence of Paget's disease of the nipple, tumor involving skin, internal mammary or supraclavicular lymph nodes or distant metastasis?

11. Have the conditions described in Sections 3.2.12, 3.2.13, 3.2.15 and all characteristics specified in Sections 3.2.16 and 3.2.21 been ruled out?

12. Any evidence of the conditions described in Section 3.2.7 (collagen diseases), Section 3.2.8 (life expectancy) and Section 3.2.9 (psychiatric disorders)?

13. Except for non-melanoma skin cancer, is there history of a prior malignancy within the past 5 years?

14. Any prior radiotherapy, chemotherapy or non-hormonal therapy for the present breast cancer?

15. Will the patient undergo protocol brachytherapy within 6 weeks of the definitive surgical procedure?

16. Is the patient pregnant or lactating?
The following questions will be asked at registration:

17. Institutional person registering this case?
18. Was the Eligibility Checklist (above) completed?
19. Is the patient eligible for this study?
20. Date the study-specific consent form was signed?
21. Patient's Name
22. Verifying Physician
23. Patient ID #
24. Birthdate
25. Race
26. Social Security Number
27. Patient’s country of residence
28. Zip Code (9 digit if available)
29. Method of Payment
30. Will any component of the patient’s care by at a military or VA facility?
31. Treatment Start Date
32. Dose Rate (LDR or HDR)?
33. Was a stereotactic biopsy done?
34. Date of catheter placement?
35. Date of source placement?
36. Will tamoxifen be started?
37. Is chemotherapy planned? (if yes, must not start < 2 weeks after removal of brachytherapy catheters)
38. What is the surgeon’s name?
39. Treatment Assignment

Completed by ____________________________  Date ____________________________
Within the last ten years, breast conserving therapy has become a major treatment modality for Stage I and II breast carcinoma. Seven studies, including NSABP B-06\(^1\) and the Milan trial,\(^2\) have demonstrated in a prospective randomized setting similar overall and distant disease-free survival for patients receiving breast conserving therapy, compared with patients treated by conventional mastectomy. Breast conserving therapy in both NSABP B-06 and the Milan study consisted of initial tumor excision with negative gross and histologic margins, axillary lymph node dissection, and whole breast external beam radiation therapy. The major advantages of breast conserving therapy are superior cosmetic outcome and the reduced emotional and psychological trauma afforded by this procedure compared with conventional mastectomy. The principal disadvantage of breast conserving therapy (BCT) is its more complex and prolonged treatment regimen requiring approximately 6 weeks of external beam radiation therapy which poses problems for some patients such as the working woman, elderly patients, and those who live at a significant distance from a treatment center. These factors, along with the patient's geographic location, result in only a small fraction of the patients who currently meet eligibility criteria for BCT actually receiving it, despite its cosmetic and probable psychological advantages. The logistical problems of BCT are primarily related to the protracted course of external beam radiation therapy to the whole breast. While some investigators reported what they believe to be acceptable local control rates in carefully selected patients treated by wide local excision without radiation therapy, the criteria for patient selection are controversial and poorly defined and probably restrict the access of many patients to breast conserving therapy. For instance, Crile et al.\(^3\) at the Cleveland Clinic and Liljegren et al.\(^4\) from the Uppsala-Orebro Breast Cancer Study Group treated patients with wide local excision and no radiation therapy with breast recurrence rates of 10.9% and 18.4% respectively. Both studies were quite restrictive in their criteria, treating only small tumors. These results are in sharp contrast to the tylectomy alone arm of the NSABP B-06 randomized prospective trial, which included patients with invasive cancers up to 4 cm in size with negative surgical margins, where the breast recurrence rate of 43% is considerably higher than the 10% breast failure rate of the tylectomy and whole breast irradiation arm.\(^1\) At ten years, the local recurrence rates were 53% and 12% respectively \(p < 0.001\).\(^5\)

Whole breast irradiation subsequent to tylectomy is postulated to reduce the breast recurrence rate through eliminating residual foci of cancer remaining in the peri-tylectomy site and occult multicentric areas of in-situ or infiltrating cancer in remote areas of the breast. Rosen et al. evaluated 203 mastectomy specimens and identified multicentric areas of in-situ or invasive cancer in 26% of breasts with index cancers ≤ 2 cm, and in 36% of breasts with index cancers of 2.1 to 4 cm.\(^6\) Holland et al. evaluated 217 mastectomy specimens and noted residual foci of cancer greater than 4 cm from the index cancer in 32% of patients with an extensive intraductal component (EIC) and in 12% of patients without EIC.\(^7\)

Despite the discovery of remote foci of cancer in 26% to 36% of patients in the above studies, the relationship of these foci to local control rates after breast conservation treatment is debatable. Sixty-five to 100% of breast recurrences reported after tylectomy and radiation therapy have been found in the same quadrant as the initial tumor, with an histology similar to the primary tumor, and probably representing residual viable cancer in the peritylectomy site not controlled by radiation therapy.\(^4,8,9,10\) Since breast recurrence rates after conservative surgery with negative surgical margins and whole breast irradiation have been approximately 10%,\(^8,10\) and since 65 to 100% of these local recurrences are in the immediate vicinity of the tylectomy site, it appears that only 0 to 3.5% of patients treated with tylectomy and radiation therapy relapse in remote areas of the breast. This 3.5% recurrence rate is far below the anticipated rate of remote recurrence predicted by the Rosen/Holland data on multicentricity. Is this absence of the expected number of remote breast recurrences due to the whole breast radiation therapy employed in these series or to the biological insignificance of occult cancer foci in remote quadrants of the breast?

To address this question, one must examine studies of breast conservation patients treated with surgery only and evaluate the number of remote recurrences. Fisher evaluated 110 patients with breast recurrence, initially treated by tylectomy without radiation therapy, and found that all relapses were in the immediate vicinity of the tylectomy site.\(^8\) Crile evaluated 32 patients with breast recurrence initially treated with segmental mastectomy alone; in 84% of these patients the recurrence was in the immediate vicinity of the segmental mastectomy scar.\(^3\) Liljegren et al. also evaluated 43 patients who recurred in the breast after wide local excision only and in 84%, the recurrence was in the immediate vicinity of the tylectomy site, defined as the surgical scar and the skin directly over the surgical field.\(^4\) From these data, one can infer that radiation therapy following tylectomy has as its maximal effect the reduction of breast cancer recurrence at or very near the tylectomy site.
If the above observations are valid and breast irradiation following tylectomy exerts its maximal effect in eradicating occult disease remaining in the immediate vicinity of the tylectomy site, can radiation therapy be directed only to the tissue surrounding the excision cavity of the breast, using brachytherapy alone? If so, the entire course of radiation therapy could be delivered over a 3 to 7 day period immediately following tylectomy and/or axillary dissection, thus markedly reducing treatment time. Brachytherapy also inherently provides a higher central dose to the volume most at risk for recurrence. In addition, there may be biological advantages to low dose rate continuous radiation over a short time interval.\textsuperscript{11} Cosmetic outcome after the use of a brachytherapy boost after external whole breast radiotherapy is comparable\textsuperscript{12} or slightly inferior\textsuperscript{13} to electron beam boost radiation therapy. The complication rate after standard implants is < 2\%.\textsuperscript{14}

The Ochsner Experience:
Reducing the duration of treatment time from 6 weeks to 4 days and confining irradiation to the tissue at greatest risk for tumor recurrence were the objectives of a prospective phase I/II trial designed to evaluate cosmesis, complications, and local tumor control following wide-volume double-plane iridium-192 breast implants.\textsuperscript{15} Since patients were assigned to receive low dose rate (LDR) or high dose rate (HDR) brachytherapy alternating in blocks of 10 patients, a comparison of these two methods with the same end points was undertaken.

Fifty-one women with 52 breast cancers were entered into the trial. Eligibility criteria included intraductal or invasive carcinomas less than or equal to 4 cm in size, 0 to 3 positive axillary nodes, and negative inked microscopic surgical margins. A double-plane implant was placed under direct visualization of the excision cavity or with ultrasound guidance, and the catheters extended 2 cm beyond the cavity in all peripheral dimensions. LDR patients received 45 Gy in 3.5 to 6 days, while HDR patients received 32 Gy in 8 fractions over 4 days. The prescription isodose curve for the first 17 patients was selected by the physicians as the curve best covering the target volume. Thereafter, the ICRU dosimetry guidelines which establish the gradient between the mean central dose rate and the peripheral or reference dose rate at 15\% were consistently used. Cosmesis was strictly evaluated by a three person panel from photos taken every 6 months according to established criteria which is described in Section 11.3.1. Median follow-up is 50 months (range = 30 - 62 months) as of March 1997.

There have been 3 grade 3 complications (5.8\% overall, 3.8 \% LDR, 7.7 \% HDR). Two HDR patients experienced severe fat necrosis, one requiring a mastectomy and the other a quadrantectomy with flap coverage. One LDR patient developed an abscess from an infected seroma at 4 months which was incised and drained. There were 2 grade 2 complications: both symptomatic fat necroses not requiring surgery. Cosmesis was excellent in 44\%, good in 28\%, fair in 19\%, and poor in 9\% of the patients. The rate of good/excellent cosmesis was 78\% in LDR, 67\% in HDR (p = 0.39). Fat necrosis developed in 5 of 10 patients receiving chemotherapy as compared to 5 of 42 patients without chemotherapy (p = 0.008), and in 8 of 46 (17\%) with acceptable dosimetry versus 2 of 5 patients (40\%) with unacceptable dosimetry, defined as a dose gradient greater than 30\%. With four year median follow-up period there have been no local breast tumor recurrences. Refinements in dosimetry and increasing the number of HDR fractions to 10 (5 days) may improve the cosmesis and decrease the complications. At the Ochsner Clinic, LDR brachytherapy including hospitalization, offers a reduction of 23\% in Medicare allowable fee collections when compared to a standard 6 week course of external beam irradiation.

The Guy's Hospital and Christie Hospital Trials
Two trials from Great Britain investigated the use of small field irradiation in breast cancer. The Guy's Hospital trial included patients with lesions up to 4 cm in size, grossly excised margins which were not evaluated, complete axillary dissection, and 55 Gy in 5 1/2 days low dose rate (LDR) brachytherapy.\textsuperscript{16} There were 2 isolated local regional recurrences (7.5\%) and 2 with distant metastases (7.5\%). Cosmetic results were 96\% Excellent/Good according to patients and 80\% judged by the physicians. Complications included 4 wound infections, 3 skin necroses, 7 temporary erythema, 2 frozen shoulders, and 1 patient with claustrophobia.

Important differences between the Guy's trial and this RTOG study include: requiring inked microscopic margin assessment, large volume implants, (typically 17 catheters compared to a median of 9 wires in the Guy's trial), a total prescribed dose 10 Gy lower in RTOG, the use of free-hand technique rather than templates, and the exclusion of patients with an extensive intraductal component (EIC) and lobular histologies. Stricter patient selection criteria and broader volume implants in the RTOG study may result in a lower breast recurrence rate, and the lower total dose may reduce the complication rate and improve cosmesis.
The Christie Hospital and Holt Radium Institute randomized 708 patients with lesions 4 cm or less in diameter and without an axillary dissection to receive either: (1) quadrant irradiation, typically 10 MeV electron beam to an average field of 6 x 8 cm, 42.50 Gy in 8 fractions; or (2) tangential whole breast 4 MV photon beams to 40 Gy in 15 fractions. The primary tumor was completely excised in only 80% of the cases. The actuarial 5 year breast recurrence-free rates were 94% in the wide field arm and 87% in the local field. Lobular carcinomas in the local field arm had a 20% recurrence rate. Axillary recurrences occured in 14% of the locally treated patients and 4% in the wide field treatment arm. Ten patients in the local field and 2 in the wide field group had fat necrosis. These results are difficult to extrapolate to this RTOG study, because of the differences in patient selection and surgical technique, as well as the inherent physical differences in electrons and brachytherapy. Most critical are the smaller treatment volumes and the probable underdosing of the deeper tissues with 10 MeV electron beams which fall off steeply at a depth of 2.5 cm.

Patient selection criteria in this RTOG breast brachytherapy protocol has been chosen to minimize the risk of multicentricity and a remote breast recurrence. The key factors are the exclusion of patients with microscopic extension of tumor cells to the inked surgical margins, lobular histologies, tumors larger than 3 cm, and patients having an extensive intraductal component. Patients with involvement of 4 or more axillary lymph nodes have a significant risk for supraclavicular or infraclavicular nodal relapse. Most radiation oncologists treat such patients to these nodal sites with 5 weeks of external beam radiation therapy. These patients would lose the logistical advantage of a 3 to 7 day breast treatment regimen. Even with these strict selection criteria, approximately 71,000 women per year in the United States would be candidates for this protocol.

The radiobiological similarity between the proposed 10 fraction 5 day HDR treatment schedule and the 45 Gy 4 1/2 day LDR treatment has been calculated for both tumor control and late normal tissue effects by two independent scientists, based on the linear quadratic model.18, 19

2.0 OBJECTIVES
This study will evaluate the technical feasibility and reproducibility, cosmetic results, complication rates, and local control rate of brachytherapy when used as the sole method of radiation therapy for patients with stage I and II (≤ 3 cm) carcinoma of the breast (non-lobular histology) treated with tylectomy, with histologically assessed negative surgical margins, less than 4 positive nodes at axillary dissection, and without extra-capsular nodal extension or extensive intraductal component (EIC) by the Harvard definition. 

2.1 Hypotheses
2.1.1 For selected patients with stage I and II breast carcinoma, radiation therapy delivered with brachytherapy alone is technically feasible and reproducible with acceptable complication rates in a multi-institutional trial.

2.1.2 Cosmetic results after brachytherapy as the sole radiation therapy technique following tylectomy will be comparable to that obtained after whole breast external beam radiation therapy.

2.1.3 The local tumor control rate in the breast after brachytherapy as the sole radiation therapy technique following tylectomy will be comparable to that of conventional external beam radiation therapy, with less inconvenience and cost to the patient, given the selection criteria which minimizes the risk of clinically significant multicentric or extensive residual carcinoma following tylectomy.

2.2 End Points
2.2.1 Evaluation of the prescription isodose curves, dose inhomogeneity, and coverage of the target volume, as defined by surgical clips placed at the time of tylectomy to delineate the target volume.

2.2.2 The evaluation of cosmetic results as judged by the patient, surgeon, and radiation oncologist at stated follow-up intervals and by an independent panel who will judge cosmesis from serial photography.

2.2.3 Assessment of patient satisfaction with the procedure, as measured by a questionnaire.

2.2.4 The evaluation of tylectomy wound healing after low dose rate and high dose rate brachytherapy and the overall complication rate.

2.2.5 Ipsilateral breast recurrence rate in patients treated with both high dose rate and low dose rate brachytherapy following tylectomy with negative surgical margins. Disease status will be evaluated at routine patient follow-up appointments, including yearly mammography.

2.2.6 Freedom from mastectomy

2.2.7 Cost benefit analysis of this treatment method compared with standard external beam treatment at the discretion of the participating institution. (planned for future Phase III Trial).
3.0 PATIENT SELECTION CRITERIA

Investigators are encouraged to evaluate all women having tylectomy for AJC stage I or II (T1N0, T2N0, T1N1, T2N1) histologically confirmed non-lobular, non EIC20 (extensive intraductal component) carcinoma of the breast for inclusion on this protocol.

3.1 Eligibility Criteria (2/14/00)

3.1.1 AJC stage I or II (T1N0, T2N0, T1N1, T2N1) histologically confirmed invasive carcinoma of the breast with a lesion ≤ 3 cm, treated with tylectomy and axillary dissection (see Section 8.0). Tumor size is determined by the pathologist (Section 10.3). Use clinical size only if the pathologic size is indeterminate.

3.1.2 Surgical clips in place delineating the margins of the tylectomy cavity.

3.1.3 Signed study-specific informed consent for participation in the study (Appendix I).

3.1.4 Negative, or close but negative, inked histologic margins of tylectomy or reexcision specimen to be confirmed prior to introducing the radiation sources. Margins generally are positive if there is invasive or noninvasive tumor at the inked resection margin, close but negative if the tumor is within 2 mm of the inked margin and negative if the tumor is at least 2 mm away from the inked edge.22

3.1.5 Negative post-tylectomy or post-reexcision mammography if cancer presented with malignancy-associated microcalcifications; no remaining suspicious microcalcifications in the breast before brachtherapy. If the catheters are placed at the time of reexcision, the criteria may not be feasible but a post brachtherapy mammogram should be obtained as soon as is practical and the results recorded on the data form.

3.1.6 Less than four positive axillary nodes with no extracapsular extension, and at least 6 axillary lymph nodes sampled, or a negative sentinel node.

3.1.7 Invasive ductal, medullary, papillary, colloid (mucinous), or tubular histologies.

3.1.8 Tamoxifen therapy is allowed. Chemotherapy planned for ≥ 2 weeks after removal of brachtherapy catheters is permitted.

3.2 Ineligibility Criteria

3.2.1 Patients with distant metastases.

3.2.2 Patients with invasive or in-situ lobular carcinoma or pure ductal carcinoma in-situ or nonepithelial breast malignancies such as sarcoma or lymphoma.

3.2.3 Patients with proven multicentric carcinoma (tumors in different quadrants of the breast, or tumors separated by at least 4 cm) with other clinically or radiographically suspicious areas in the ipsilateral breast unless confirmed to be negative for malignancy by biopsy.

3.2.4 Patients who are pregnant or lactating.

3.2.5 Patients with more than 3 histologically confirmed positive axillary nodes in the ipsilateral axilla. Palpable or radiographically suspicious contralateral axillary, supraclavicular, infracervical, or internal mammary nodes, unless there is histologic confirmation that these nodes are negative for tumor.

3.2.6 Prior non-hormonal therapy for the present breast cancer, including radiation therapy or chemotherapy.

3.2.7 Patients with collagen vascular diseases, specifically systemic lupus erythematosis, scleroderma, or dermatomyositis with a CPK level above normal or with an active skin rash.

3.2.8 Patients with coexisting medical conditions in whom life expectancy is < 2 years.

3.2.9 Patients with psychiatric or addictive disorders which would preclude obtaining informed consent or tolerating confinement of several days duration for brachtherapy (low dose rate) or completing the full series of brachtherapy treatments on an outpatient basis (high dose rate).

3.2.10 Patients with Paget's disease of the nipple.

3.2.11 Patients with skin involvement, regardless of tumor size.

3.2.12 Patients with a breast unsatisfactory for brachtherapy. For example, if there is little breast tissue remaining between the skin and pectoralis muscle after surgery, placement of catheters is technically problematic.

3.2.13 Patients with tylectomy so extensive that the cosmetic result is fair or poor prior to brachtherapy.

3.2.14 Patients whose tylectomy cavity is not delineated by surgical clips.

3.2.15 Surgical margins which cannot be microscopically assessed or are positive at pathological evaluation.

3.2.16 Extensive intraductal carcinoma by the Harvard definition, i.e. 1) more than 25% of the tumor is DCIS and there is DCIS in adjacent breast tissue, or 2) an intraductal carcinoma with microinvasion.

3.2.17 Any previously treated contralateral breast carcinoma or synchronous bilateral breast carcinoma.

3.2.18 Other malignancy, except non-melanoma skin cancer, ≤ 5 years prior to participation in this study; the disease free interval from any prior carcinoma must be continuous.

3.2.19 Time between final definitive breast procedure to radioactive source loading of the brachtherapy catheters is greater than 6 weeks.

3.2.20 Patients with diffuse (>1 quadrant or >5 cm in diameter) suspicious microcalcifications.
3.2.21 Patients with suspicious microcalcifications remaining on the post-tylectomy mammogram.

4.0 PRETREATMENT EVALUATIONS

4.1 History including family history of breast carcinoma and method of detection of the breast tumor (clinical, mammographic, or both).

4.2 Physical examination with the location and palpable size of the tumor in cm.

4.3 Mammogram of both breasts with a careful measurement of the lesion size in cm.

4.4 Post-tylectomy ipsilateral mammogram, if microcalcifications were initially present, to confirm complete removal. This will not be required, if the implant is placed at the time of tylectomy/reexcision but a post-brachy mammogram is required.

4.5 Chest x-ray, CBC, platelets, alkaline phosphatase, SGOT, serum calcium.

4.6 Bone scan if the alkaline phosphatase is elevated and/or the patient complains of bone pain or has other symptoms possibly associated with skeletal metastasis.

4.7 Abdominal CT if the liver function blood tests are elevated.

4.8 Photographs of the patient's breast prior to placement of the catheters and with the catheters in place. 35 mm slides are preferred; polaroids are acceptable. If catheters are placed at the time of the tylectomy, photographs should be taken at the time of the removal of the brachytherapy catheters, in order to judge surgical cosmesis. In any case, the first photo should be a closeup encompassing only the breast to be treated at a 45° oblique with arms elevated over the patient's head. The second photo should be a straight frontal view of both breasts taken in either a standing or seated position with the patient's hands on her hips, taking care to exclude her face. The third photo should be taken of the breast with catheters in place, in a position best exhibiting the geometry of the implant. Label each slide or photograph with the date and RTOG patient case number.

5.0 REGISTRATION PROCEDURES

5.1 Preparation

5.1.1 Brachytherapy Credentialing
Before patients can be accessioned to this protocol, a Brachytherapy Institution Questionnaire (BIQ) (see Appendix VII) must be completed and submitted to RTOG Headquarters who will, in turn, forward the BIQ packet to the Radiation Physics Center (RPC). Do not submit the BIQ packet directly to the RPC. Allow at least four weeks turnaround. The RPC will notify both the institution and RTOG Headquarters in writing when the BIQ is approved.

5.1.2 Videotape
A copy of the "how to" brachytherapy videotape available from Dr. Kuske should be viewed by the involved radiation oncologist, physicists and nurses prior to placing the first patient on protocol.

5.1.3 Per Case Approval
In addition, "rapid turnaround" review (Section 6.14) is required prior to registration of each patient. You will be notified when this review is completed and you may not register the patient until you have been notified that the review is complete. Dr. Kuske will also notify RTOG Headquarters via fax of rapid turnaround approvals.

5.2 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. The patient will be registered and a case number will be assigned and confirmed by mail.

The following information must be provided:
- Institution Name & Number
- Patient's Name & ID Number
- Verifying Physician's Name
- Eligibility Criteria Information
- LDR or HDR plan
- Surgeon's name
- Catheter placement date
- Anticipated date when catheters will be loaded with radioactive sources
- Has the patient had a core biopsy (9/8/98)
- Whether tamoxifen or systemic chemotherapy is included in patient's plan
- Demographic Data
6.0 RADIATION THERAPY

6.1 Brachytherapy

6.1.1 Catheters may be placed at the time of the initial tylectomy or reexcision, at the time of the axillary dissection, or under local anesthetic with intravenous sedation, but the patient must be informed that if histologic assessment of margins and axillary nodes renders them ineligible for this treatment, the catheters will be removed or used as a boost method off-protocol. Radioactive implants following tylectomy are intended to deliver a cancerocidal dose to the target volume. The delineation of this target volume through the use of surgical clips is essential for prescribing a dose and dose distribution capable of sterilizing occult tumor foci in the breast tissue surrounding the excision cavity.

6.1.2 Placing the implant under direct visualization at the time of tylectomy or reexcision facilitates adequate coverage of the target volume.

6.2 Definition of Target Volume (9/8/98, 2/14/00)

6.2.1 The target volume will be defined as the volume encompassed by an irregularly-shaped surface 2 cm outside the excision cavity peripherally, and including points 1 cm superficial (or to skin surface if less than 1 cm) and 1 cm deep in the cavity as defined by large surgical clips (see Section 8.1.11) or omnipaque contrast. Ultrasound (see breast brachytherapy videotape) or CT scans can be used optionally to further define the excision cavity in relation to the catheters. The use of these imaging techniques is highly recommended.

6.3 Designing the Implant Geometry (9/8/98, 2/14/00)

6.3.1 A double plane implant must be used. A minimum of two planes is required; more planes may be added if justified by the volume. Single plane or planned three-plane implants are not allowed. If in treatment planning, a wide separation between planes is observed, a few additional catheters between, or outside, the two planes may be added in order to achieve dose uniformity within the target volume (see Section 6.4 below).

6.3.2 The deep plane is placed at the level of and parallel to the bottom of the excision cavity. The superficial plane is placed at the level of, and parallel to, the superficial border of the cavity. Optimized values of the interplanar spacing are given for a range of implant sizes by Zwicker et al. Within a given plane, the separation between catheters is 1.0 to 1.5 cm. and catheters must extend beyond the edge of the target volume or at least 2 cm beyond clips.

6.3.3 Occasionally, a large seroma or hematoma (more than 2.5 cm in thickness) may appear to require a 3 plane implant, which would exclude the patient from participation in this trial. In such a case, needle aspiration of the seroma can be performed prior to placing the catheters to reduce the seroma to a size appropriate for adequate coverage of the target volume with a 2 plane implant (see the breast brachytherapy videotape).

6.3.4 For adequate peripheral coverage, the number of catheters is chosen so that at least one catheter on each side is placed 1 cm or more beyond the target volume. Note that this guideline requires at least 3 to 4 catheters beyond the surgical clips. The other dimension of peripheral coverage is determined by the length of the active sources within each catheter as discussed in Section 6.6. The skin entry and exit points should extend at least 2 cm beyond the edge of the target volume, while still allowing a "dead space" (no radioactive sources) of 1 - 2 cm near the skin entry and exit wounds, preventing "pock" marks and late telangiectasia.

6.3.5 The catheters must be parallel and as straight as possible.

6.3.6 Rigid templates may be used, but are not required. The advantage of templates is precise geometrical source distributions, but there may be a problem with coverage of a curved, irregularly-shaped target volume. Free-hand technique, especially with the wound open, permits catheter placement which conforms to the shape of the tylectomy cavity, but results in less uniform isodose distributions.

6.4 Correcting a Cold Spot Noted on The Isodose Curves

If a wide separation between catheters or planes is noted, or if a peripheral edge at the target volume is not covered by the prescription isodose curve, it is preferable to insert additional catheter(s) under local anesthesia to avoid protocol deviation (see Section 6.12). Use of dose optimization algorithms in HDR are acceptable, but not to correct for inadequate implant geometry.

6.5 Timing of Source Loading (9/8/98)

Note: Sources may be loaded into the catheters as soon as the pathology report confirms that the patient meets all eligibility requirements. Prevention of infection by proper catheter care is important during the delay between catheter placement and source loading. The study-specific consent form must be signed by the patient prior to loading the sources into the catheter. See Sections 5.2 and 6.1.4.3.

6.6 Active Length of Sources

The measurement of skin surface to skin surface length must be accurate for each catheter. This is done using dummy seeds with 1 cm seed separation, a radiopaque button or wire at the skin entry/exit sites, and
orthogonal or directly appositional radiographs of the implant (Section 6.9). In order to achieve the desired 1 to 2 cm of dead space at each end, subtract a minimum of 2 to 4 cm from this length to determine the number of seeds (LDR) or number of dwell positions (HDR) required, being careful that the target volume is encompassed by sources in all peripheral dimensions. To achieve adequate target volume coverage, there should be at least two LDR seeds or 1.5 - 2.0 cm of HDR dwell positions beyond the edge of the target volume. This implies that 3-to 4 LDR seeds or 3.5 to 4.0 cm of HDR dwell positions are required beyond the surgical clips. Note that the entry and exit points of the catheters must be beyond the target volume, in order to prevent a conflict between target volume coverage and the dead space requirements.

6.7 Source Activity
For low dose-rate implants, the activity of the Ir-192 sources should be ordered to provide a minimum peripheral dose-rate of approximately 45 cGy/hr, with an acceptable range of 30-60 cGy/hr. A typical order of seed strands is 0.45 mg radium equivalent per seed (0.8 mCi). High dose-rate implants will use the activity of the source at the time of treatment, which is in the range 2 - 10 Ci.

6.8 Dose Prescription.
6.8.1 Low dose-rate: A total dose of 45 Gy will be prescribed to the target volume, and an appropriate implant time determined (ideally 100 hours with an acceptable range of 75 - 140 hours).
6.8.2 High dose-rate: A total dose of 34 Gy will be prescribed to the target volume. Two fractions per day, each of 3.4 Gy, separated by at least 6 hours, given in 5 consecutive working days, will sum to 10 fractions and 34 Gy total dose.

6.9 Localization Films and Calculation Planes
Either orthogonal or 2 variable-angle films of the implanted breast, with dummy seeds in each catheter, will be taken prior to dosimetry calculations. An additional film whose plane is as parallel to the implant plane as possible should be taken, to aid in visualization of the target dimensions (the x-ray central axis is perpendicular to the catheter planes). These films, with surgiclip identified, are used to define the target volume and produce computer generated isodose curves. Five planes of calculation for the isodose curves are required. The clips and target volume must be clearly delineated on the central and sagittal planes of calculation, along with the peripheral isodose lines (HDR) or isodose-rate line (LDR), as specified in Section 6.14.

6.9.1 Central or transverse plane is defined as the plane through the geometric center of the implant, slicing perpendicularly through the catheters. The DHI must be calculated and reported for this plane (see Section 6.11.2).
6.9.2 Coronal plane is defined as the plane midway between the two implant planes, and parallel to them.
6.9.3 Sagittal plane is defined as the plane perpendicular to the other two planes.
These are shown in the following diagram:

The coronal and sagittal planes are orthogonal to the central plane and to each other and may not be strictly anatomic in relation to the patient.

6.9.4 Extreme planes are located 1 cm from each edge of the target volume and parallel to the central (transverse) plane.

6.10 Photography Documenting Implant Geometry (7/22/04)
At least one 35 mm slide or polaroid photograph with catheters in place is required, a close-up encompassing the treated breast only in a position which optimally exhibits the implant geometry, taking care to exclude the patient's face. Label each photograph with the date and RTOG study and case numbers and mail directly to the RT Quality Assurance Department at RTOG headquarters.

6.11 ICRU Dosimetry Guidelines
6.11.1 The ICRU (International Commission on Radiation Units and Measurements) has prepared a draft report for the purpose of unifying dose and volume specifications and providing common terminology and methodology in the reporting of interstitial implants. ICRU guidelines are followed in this protocol.
6.11.2 Definitions (9/8/98)

**Mean central dose (MCD)** - the average of all the local dose minima, or geometric center doses (GCD), in the central plane of the implant. In a double plane implant, the GCDs occur at the point within a triangle, formed by neighboring catheters, which has the minimal distance from the three catheters. The MCD is the arithmetic mean of the GCDs in the implant.

\[
MCD = \frac{GCD_A + GCD_B + GCD_C}{3}
\]

The spread in the GCDs expressed as a percentage of the MCD is a useful parameter for assessing dose uniformity. The GCDs are to be reported on the RTOG Treatment Form.

**Prescribed Dose** - the dose the physician intends to give and enters into the patient's treatment chart. For LDR implants, an analogous term, prescribed dose-rate, is used to calculate the duration of the implant.

**Peripheral dose (PD)** - the peripheral dose is the minimum dose at the periphery of the clinical target volume. Ideally, this is the same as the prescribed dose. The peripheral isodose is the isodose surface corresponding to the peripheral dose. It defines the treatment volume and should encompass the clinical target volume. For LDR implants, an analogous term peripheral dose rate is useful to describe the implant.

**High Dose Region** - defined as the area \((cm^2)\) encompassed by the isodose corresponding to 150% of the mean central dose around the sources in the central plane. The area is considered significant if it encompasses 2 or more sources. The dimension of all such regions are to be reported on the RTOG treatment forms.

**Low Dose Region** - defined as the region within the clinical target volume encompassed by an isodose corresponding to 90% of the prescribed dose. The maximum dimensions of any low dose regions are to be reported.

**Dose Homogeneity Index (DHI)** – Although the ICRU defines the DHI as the ratio of peripheral dose to mean central dose, for the purposes of this protocol, the DHI shall be calculated and reported as the ratio of the prescribed dose to the mean central dose. An analogous term, dose-rate homogeneity index, is useful for describing low dose rate implants. This index must be calculated in the central plane and reported on the RTOG treatment form. The recommended goal for implants on this protocol is 0.85. For example, in an HDR implant where the MCD is 400 cGy for a peripheral dose of 340 cGy, the DHI is 0.85.

For a typical LDR implant, when the MCD rate is 53 cGy per hour, you would ideally prescribe to the 45 cGy per hour isodose rate curve to achieve a DHI of 0.85.

6.11.3 Determining Mean Central Dose in the Central Plane

Use interactive graphics of the treatment planning computer to select the optimum central plane of calculation in which the catheters are viewed "end-on", and are aligned with the coordinate axes.

A) For low dose rate implants, depending upon the activity of the seeds, the isodose-rate lines are computed and plotted. From these, the geometric center dose rates are determined and averaged to yield the mean central dose rate. The peripheral isodose-rate line is selected and the treatment time
determined using the prescribed treatment dose of 45 Gy divided by the peripheral isodose-rate line. The dose rate homogeneity index is computed and should ideally be in the range of 0.85 (see Protocol Deviations, Section 6.12 and the example in 6.12.2).

B) For high dose rate implants, the treatment plan may or may not be be geometrically optimized using available computer optimization techniques. If optimized, care must be taken to insure that focal hot spots are not introduced by the optimization routine. It is usually necessary to compute several plans, comparing the mean central dose and the peripheral dose for each, in order to achieve a plan with the desired dose homogeneity index of 0.85. The HDR source dwell times are obtained from the final treatment plan which must be carefully examined to insure that the prescribed isodose line encompasses the target volume.

6.12 Deviations from Protocol Prescription (9/8/98)

The definitions of protocol deviations are based on an analysis of two of the three orthogonal planes through the center of the implant, the central and sagittal planes. The coronal plane is not quantitatively analyzed due to difficulties often arising from the curved geometry of actual implants. Define the Average Peripheral Dose (APD) as the average of the four doses at the intersection of the coordinate axes with the sides of the target volume. If any of the four doses (PD1, PD2, PD3, or PD4) exceed the prescribed dose, then use the prescribed dose for that value. Thus, in computing the APD, all of the peripheral dose values must be less than, or equal to, the prescribed dose.

If D_pr is the prescribed dose, then the absolute value of the percentage deviation of APD from D_pr is given by:

\[ D = \frac{100 \times |APD - D_{pr}|}{D_{pr}} \]

If D is determined for the central plane (Dc) and the sagittal plane (Ds), then the average percentage deviation for the two planes is expressed:

\[ D_{AV} = \frac{(Dc + Ds)}{2} \]

6.12.1 Acceptable Implant

D AV is less than or equal to 10%, and the dose homogeneity index in the central plane is greater than or equal to 0.75.

Examples of acceptable implants are 1) an LDR average peripheral dose in the range of 4050 to 4950 cGy; 2) an HDR average peripheral dose in the range of 3060 to 3740 cGy; and 3) an MCD of \( \leq 6000 \) cGy LDR or \( \leq 4530 \) cGy HDR (453 cGy per fraction) if the peripheral = prescription isodose line.

6.12.2 Marginally Acceptable Implant - Minor Protocol Variation

a) D AV is more than 10%, but less than 20%, and DHI is greater than 0.65, or

b) D AV is less than 10% and the DHI is between 0.65 and 0.75 (See block diagram below).

Examples:
Case a) LDR - an average peripheral dose within the range 3600 to 4050 cGy or 4950 to 5400 cGy, and a DHI greater than 0.65.
HDR - an average peripheral dose within either the range 2720 to 3060 cGy or 3740 to 4080 cGy, and a DHI greater than 0.65.
Case b) LDR - an average peripheral dose within the range 4050 to 4950 cGy and a DHI between 0.65 and 0.75.
HDR - an average peripheral dose within the range 3060 to 3740 cGy and a DHI between 0.65 and 0.75.
6.12.3 Unacceptable Implant-Major Protocol Deviation, See Section 6.3 for how to correct and avoid unacceptable implants)

a) \(D_{AV}\) is greater than 20% (regardless of the value of DHI) or

b) the DHI is less than 0.65 (regardless of the value of \(D_{AV}\)).

Examples:

Case a) LDR - An average peripheral dose less than 3600 cGy or more than 5400 cGy regardless of the DHI.

HDR - an average peripheral dose less than 2720 cGy or more than 4080 cGy regardless of the DHI.

Case (b) LDR - would be a mean central dose greater than 6923 cGy (when the peripheral dose matches the prescribed dose).

HDR - a mean central dose greater than 5230 cGy (when the peripheral dose matches the prescribed dose).

The above conditions may be represented by the diagram below, in which A = acceptable implant, M = marginally acceptable implant, and U = unacceptable implant.

![Diagram showing conditions for acceptable, marginally acceptable, and unacceptable implants based on \(D_{AV}\) and DHI values.]

6.13 Dosimetry Monitoring

A copy of the final dose calculations and isodose curves clearly showing the target volume, surgical clips, if used, with the catheters and the active treatment lengths identified must be submitted, as well as polaroid photographs or 35 mm slides of the implanted breast.

6.14 Rapid Turnaround is Required

6.14.1 Prior to loading the sources, fax copies of the dose calculations and the isodose curves showing surgical clips and target volumes clearly labeled in the central, coronal, and sagittal planes. Isodose curves must include the lines corresponding to the peripheral dose, the prescribed dose (if different), the mean central dose, 150% of the MCD and 90% of the prescribed dose, all of which should be clearly labeled. Map out the edge of the tylectomy cavity with the guidance of the surgical clips, using ultrasound or CT scans for additional confirmation, if necessary.

6.14.2 Fax all required information at least 24 hours before inserting the radioactive sources to (504) 842-2037. Include the name of your facility and phone number of the contact person to receive approval or make corrections if necessary.

6.14.3 Only after the requirement for rapid turnaround has been fulfilled and approval obtained by fax from Ochsner Clinic can patient be registered and the radiation sources loaded.

6.15 Toxicity Reporting:

Acute side effects and complications of treatment should be promptly recorded on an RTOG Data Form. Any Grade 3, 4, or 5 toxicity should be immediately reported both to Dr. Kuske and to RTOG Headquarters (See Appendix V).

6.16 Catheter Care and Nursing Issues (call Ochsner R.N. at 504/842-2029)

6.16.1 Patient Education: To assist the patient's understanding of brachytherapy catheter placement, a plastic model of a breast with plastic brachytherapy catheters in place or the catheters themselves without needles are used as an illustration of the procedure. If possible, develop pamphlets describing treatment and treatment effects of the selected treatment arm, either LDR or HDR.

6.16.2 Signs and symptoms of infection must be discussed with the patient. Names and phone numbers of personnel should be provided in the event that problems are identified after hours. To patients who are treated with HDR, reinforce instructions for appropriate care of the indwelling catheter sites each day. Patients are instructed to measure their oral temp b.i.d. and to call if there is a fever over 101°F, pus, redness, chills, or other symptoms of infection. At least once a day and at each dressing change, the catheter sites are carefully inspected for signs of infection or edema, especially where the buttons rest directly against the skin.
6.16.3 When catheters are placed prior to obtaining definitive pathologic evaluation or in the event that there is a delay in loading the implants with iridium-192 sources, patients should be instructed not to touch the site, to leave all bandages in place, and to keep the area dry. The patient is asked to return on day 3 after catheters are placed, for nursing inspection and care.

6.16.4 If definitive breast surgery has previously been performed and final pathologic evaluation is available prior to catheter placement, the patient is brought to radiation oncology for orthogonal films on the same day as the interstitial catheters are placed. A major focus should be maintenance of optimal patient comfort by administering prescribed narcotic medications (PRN), helping the patient find a comfortable position, and providing reassurance.

6.16.5 Catheter sites are cleaned with Microklenz or similar antimicrobial wound cleaner, taking care to prevent any liquid from entering the catheter. The Ochsner Clinic found betadine solution to be too drying and irritating. Betadine or Neosporine ointment is then applied to each catheter entrance and exit site. All catheters are completely covered with abdominal pads held in place by a surgical bra or tubular net dressings. The use of tape should be avoided. After each HDR treatment or daily for LDR patients, Neosporine is applied to all entrance and exit sites of the catheters. The protruding ends of the catheters are loosely placed inside the bandage, making sure no kinks are produced, for patient comfort.

6.16.6 Be aware that some women have transient breast edema after catheter placement. If any button is too tight, indenting the skin, the physician and dosimetrist should be notified. Instead of flat buttons, spherical or hemispherical buttons are preferable and are available commercially. Sometimes the button is repositioned in an outward direction to prevent skin erosion and scarring, or inward if they are too loose. The physicist and dosimetrist must remeasure and recalculate the dose prescription for that catheter, after an adjustment is made.

6.16.7 Catheter removal: After the last HDR treatment, or after achieving the prescribed dose of LDR, catheters are removed. Anxious patients are premedicated with their prescribed post-surgical pain medication approximately one hour before catheter removal. After the LDR sources are removed, with the source pig out of the room, scanning with a Geiger counter or other dosimeter is obligatory, to ensure that no seeds remain in the patient. The short-end of the catheter is then cut with scissors at or below the skin surface, and the catheters quickly pulled out through the skin. If the skin appears erythematous or there are other signs of infection, buttons are cut off at the opposite end and pulled towards the inflamed site to minimize the possible spread of infection. Under no circumstances should the catheter be cut under both buttons, since this will necessitate surgical removal. Avoid pulling the contaminated protruding end of a catheter through the breast tissue. If using LDR sources, avoid cutting through the source-carrying catheter. Pressure is applied to the breast over the center of the implant for 5-15 minutes to extract as much serous drainage as possible to decrease formation of a seroma and to prevent hematoma. This is the most uncomfortable part of the procedure, but few patients require additional pain medication. Bleeding rarely occurs when catheters are removed, but simply applying pressure for 15-20 minutes and using a pressure bandage should alleviate this. The patient is instructed to apply pressure if bleeding begins again at home and to call the physician on call if the bleeding continues after pressure is applied. Inform the patient that clear yellow drainage is common for the first day or two and to keep a clean, dry dressing in place.

6.16.8 After care: Following catheter removal and before the patient leaves the department or hospital, she is given complete verbal and written instructions for home skin care and infection prevention. The exit and entrance sites should be cleansed daily with Microklenz or a solution of 1/2 hydrogen peroxide and 1/2 water, after which Neosporin is then applied to all catheter sites. Bathing should be avoided until catheter sites are completely closed, usually 2-3 days. The patient is instructed to moisturize the treated breast twice daily for one month then once daily for at least a year post treatment.

6.16.9 Treatment effects: Occasional transient pain as well as a sensation of heaviness or engorgement in the treated breast related to inflammation, healing, and edema may occur periodically for the first year. For symptomatic patients, prescription strength ibuprofen or similar drug can be helpful.

6.16.10 Return appointments are made for patients 2 weeks and 6 weeks post treatment to evaluate acute toxicities, if any, and to monitor healing of the catheter sites.
8.0  SURGERY-TYLECTOMY GUIDELINES

8.1 These guidelines have evolved from the NSABP experience, and implementation will result in improved cosmesis. These guidelines are suggestions and are not mandatory for patient entry or protocol compliance.

8.1.1 Lesions located in the upper half of the breast. It is recommended that circumferential curvilinear incisions be performed directly over the tumor site (see Appendix VI, Figure 1).

8.1.2 Lesions in the lower half of the breast. Radial incisions tend to provide superior cosmesis. This is also illustrated in Appendix VI, Figure 1.

8.1.3 Figure 2 depicts incisions which are to be avoided, including radial incisions in the upper half of the breast. Such incisions tend to result in unacceptable cosmesis. Similarly, circumferential curvilinear or transverse incisions in the lower half of the breast may result in cosmetic deformity.

8.1.4 The initial biopsy should be performed as if it were a lumpectomy, i.e., precautions should be taken to ensure that the margins of the resected tissue are grossly free of tumor, avoiding a reexcision of breast tissue if the biopsy is positive for cancer, and the final margins are histologically negative. A frozen section should be done to confirm the diagnosis of cancer, and surgical clips should be placed to define the margin of the excision cavity (see Section 8.1.11). Margins generally are deemed positive if there is invasive or noninvasive tumor at the inked resection margin, close but negative if the tumor is within 2 mm of the inked margin, and negative if the tumor is at least 2 mm away from the inked edge.

8.1.5 Regardless of the type of incision, extensive undermining of the skin should be avoided. The dissection of thin skin flaps adjacent to the incision may result in unsatisfactory cosmesis. Unless the tumor is very superficial, excision of a skin ellipse is not recommended as it degrades cosmetic outcome and skin recurrences are rare. This is also true for the reexcision.

8.1.6 Following excision of the tumor, it is urged that the breast tissue not be reconstructed or approximated. The use of breast sutures to obliterate the dead space can result in unnecessary deformity.

8.1.7 Drainage of the breast wound, either with penrose drains or suction catheters, is not recommended. Drainage of the axilla, however, is recommended.

8.1.8 Careful approximation of the skin incision is essential. It is recommended that subcuticular closure be utilized in most cases. For large volume incisions or if the skin closure is close to the brachytherapy implant (within 2 cm), closure with 5-0 nylon simple interrupted sutures provides a more secure closure with acceptable cosmesis. The sutures should be placed no more than 3 - 4 mm from the skin edge to avoid "cross-hatching." Avoid vertical mattress sutures.

8.1.9 In the majority of instances, it is recommended that the incision for the tylectomy and that for the axillary dissection be separate. A single continuous incision is to be avoided, such as the continuous incisions demonstrated in Appendix VI, Figure 2. An exception to this recommendation is a lesion in the axillary tail where a continuous incision could be utilized.

8.1.10 In all cases, the surgeon should mark specimens with removable sutures at the superior (12 o'clock) and lateral positions of the resected breast tissue, short for superior and long for lateral allowing delineation and assessment of the surgical margins by the pathologist.

8.1.11 (9/8/98, 2/14/00) Surgical clips should be placed by the surgeon at the time of the tylectomy to define the excision cavity. If clips were not placed in a patient otherwise eligible for this protocol, marker seeds, clips, or wires may be placed under ultrasound or stereotactic guidance. These clips should be as large as possible since small clips are often difficult to visualize on the dosimetry films. It is recommended that only extra large (1 cm) clips be used, with the superficial and deep positions marked with a double clip. Clips are placed marking the superficial, deep, lateral, medial, superior, and inferior dimensions of the tylectomy or reexcision cavity. Use of clips permits target volume evaluation, is useful in conjunction with intraoperative ultrasound, and helps to guide the placement of catheters along the superficial and deep boundaries of the cavity using intraoperative fluoroscopy.

8.1.12 If margins are positive or unknown, a reexcision is required prior to study entry. Frequently, the radiation oncologist will place the brachytherapy catheters at the time of the reexcision, but it is mandatory to evaluate the reexcision margins histologically and to confirm that they are negative prior to loading the radioactive sources. In some cases, a second reexcision may be required to achieve negative surgical margins, and pre-brachytherapy cosmesis must be re-evaluated.

8.1.13 If the size of the tylectomy cavity is too large for a 2 plane implant, (thickness over 2.5 cm) aspirating the seroma/hematoma under ultrasound guidance will usually reduce the cavity to a size appropriate for a 2 plane implant. See Section 6.3. This procedure is demonstrated in the breast videotape available when institutional approval is obtained to participate in the study (2/14/00).
8.2 **The Axillary Dissection:** as defined by this protocol consists of the excision of the axillary contents at levels I and II. An anatomic delineation of the scope of dissection is the latissimus dorsi muscle laterally, the axillary vein superiorly, and the medial margin of the pectoralis minor muscle medially. The nerves to the serratus anterior and latissimus dorsi muscles should be identified and preserved. The axillary vein should be visualized and followed under the pectoralis minor muscle to the medial border. These are minimal limits for dissection. The extent of axillary dissection should not vary with the operative procedure performed for the resection. Axillary sampling, i.e., partial non-anatomic removal of axillary contents, is not in compliance with study criteria. At least 6 nodes or a negative sentinel node must be identified by the pathologist (2/14/00).

8.3 Any toxicity related to the tylectomy must be reported on the RTOG data forms.

9.0 **OTHER THERAPIES**

9.1 Tamoxifen is allowed at any time after biopsy or tylectomy, prior to, during, or immediately after brachytherapy, at the discretion of the patient's medical oncologist or other physicians.

9.2 The use of chemotherapeutic agents prior to or during brachytherapy is not allowed (see Sections 3.1 and 3.2).

9.3 Chemotherapy regimens should be started no earlier than 2 weeks after the removal of the brachytherapy catheters.

10.0 **PATHOLOGY**

10.1 Pathology review at the participating institution and review by a pathologist at the participating institution of any specimen obtained from referring surgeons from outside institutions will be considered sufficient for the purposes of this study. Central pathology review will not be undertaken. However, all blocks should be preserved, in case at some future date, central review is necessary as a quality control measure.

10.2 Measurement of the anteroposterior (AP), transverse, and superior-inferior (SI) dimensions of the resected breast specimen should be obtained and recorded.

10.3 The pathologist must find the dominant mass in the resection specimen and measure the tumor in 3 dimensions.

10.4 If the diagnosis has not been previously established, a small central portion of the dominant mass or suspicious area should be removed for frozen section. If the lesion is benign, the protocol does not apply.

10.5 If of adequate size, tumor should be harvested for estrogen and progesterone receptor determination. Immunohistochemical staining is an alternative.

10.6 Multiple blocks of the primary tumor and of breast tissue from the inked margins should be taken, the latter to confirm 6 negative margins: 1) anterior, 2) posterior, 3) medial, 4) lateral, 5) superior, 6) inferior. Margins generally are **positive** if there is invasive or noninvasive tumor at the inked resection margin, **close but negative** if the tumor is within 2 mm of the inked margin, and **negative** if the tumor is at least 2 mm away from inked edge.

11.0 **PATIENT ASSESSMENTS**

11.1 Study Parameters

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<tr>
<td>Bone scan, Abd. CT.</td>
<td>Xa</td>
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<td>Xb</td>
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<tr>
<td>Cosmesis, Patient</td>
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<td>X</td>
<td>X</td>
<td>Xb</td>
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<tr>
<td>Cosmesis, Rad Onc</td>
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<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>Xb</td>
</tr>
<tr>
<td>Cosmesis, Surgeon</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>Xb</td>
</tr>
</tbody>
</table>
a. If appropriate (indications).
b. Yearly thereafter.
c. Clinical examination and disease status assessment at 3 month intervals for the first year, 4 months for the 2nd year, 6 months (years 2 to 5), and yearly intervals thereafter.

11.2 Response Criteria - Treatment failure

11.2.1 The definition of a treatment failure is: histologic evidence of recurrent carcinoma, either invasive or non-invasive (except LCIS) in the ipsilateral breast.

11.2.2 Clinical evidence of recurrent carcinoma by physical examination and/or mammogram will not be construed as evidence of treatment failure without biopsy proof, but will be considered as suspicious for recurrence. Ipsilateral breast recurrences will be considered local (infield) if they occur within the prescription isodose volume, peripheral if between the prescription isodose volume and a volume 2 cm outside of the prescription isodose volume. Ipsilateral recurrences will be considered non-contiguous or extrafield if they are beyond the peripheral volume described above.

11.2.3 Ipsilateral axillary, intraclavicular, internal mammary, or supraclavicular recurrence or distant metastases will not be considered a treatment failure unless accompanied by ipsilateral breast recurrence.

11.3 Definitions of Levels of Cosmetic Outcome:

11.3.1 (7/28/04) Cosmesis will be graded by the patient, the radiation oncologist, and the surgeon 6 and 12 months after completion of therapy and at yearly intervals thereafter. Cosmesis will also be evaluated from the photographs submitted to the RT Quality Assurance Department at RTOG headquarters at required intervals; however, the Cosmesis Forms will be sent only to RTOG HQ.

11.3.2 Excellent - when compared to the untreated breast, there is minimal or no difference in the size, shape or texture of the treated breast. There may be mild thickening or scar tissue within the breast or skin, but not enough to change the appearance.

11.3.3 Good - there is mild asymmetry in the size or shape of the treated breast as compared to the normal breast. The thickening or scar tissue within the breast causes only a mild change in the shape.

11.3.4 Fair - there is obvious difference in the size and shape of the treated breast. This change involves 1/4 or less of the breast.

11.3.5 Poor - marked change in the appearance of the treated breast involving more than 1/4 of the breast tissue.

11.4 Photographs (7/28/04)

11.4.1 Routine photographs must be taken of the post-surgical breast prior to catheter placement. In the event catheter placement is done at the time of the tylectomy, when the wound is open, photographs of the breast after catheters are removed will suffice. In any case, at least one photograph of the breast with catheters in place, prior to loading the radioactive sources, is required. Photographs should also be taken and sent to the RT Quality Assurance Department at RTOG headquarters at 3 and 6 months, 1 year, and yearly thereafter. Also, for any visible complication, degradation, or improvement of cosmesis or local/regional treatment failure for documentation purposes. 35 mm slides are preferred; polaroids are acceptable. Post surgical (pre-catheter) and all follow-up photographs should always follow the guidelines specified in the next section.

11.4.2 The first photograph should be a closeup encompassing only the treated breast at a 45° oblique with arms elevated over the head. The second photograph should be a straight frontal view of both breasts taken in either a standing or seated position with the patient's hands symmetrically placed on her hips, taking care to exclude her face and framing or focusing on both the treated and untreated breast to allow optimal comparison of the breasts for symmetry. Label each photograph with the date and RTOG patient case number. These photographs must be submitted directly to the RT Quality Assurance Department at RTOG headquarters.

11.5 Patient Enrollment Data.

11.5.1 Complete history and physical examination.
11.5.2 Mammographic report(s).
11.5.3 Pathology reports.
11.5.4 Initial radiation therapy consult note.
11.5.5 Rapid turnaround isodose curves and dose calculations (see Section 6.14) faxed and evaluated.

11.6 Patient Treatment Data.

11.6.1 Operative reports, including tylectomy, any reexcisions, axillary dissection, and catheter placement.
11.6.2 Toxicity reports: Skin reaction(s) to brachytherapy, including erythema, desquamation, etc. and any acute radiation complications or unusual or severe side effects of treatment.
11.6.3 Radiation treatment prescription.
11.6.4 Daily dose record sheets for HDR patients.
11.6.5 Copies of dosimetry calculations.
11.6.6 Isodose distributions in five planes (see Section 6.9) for treatment planning with target volume and surgical clips outlined.

11.6.7 At least one photograph of the breast showing the geometry of the implant prior to initiation of brachytherapy.

11.6.8 Explanation for any deviation in technique or administered dose of brachytherapy.

11.6.9 Brachytherapy information sheet.

11.6.10 Surgical cosmesis form.

11.7 **Patient Follow-Up:**

11.7.1 Vital status. If patient has expired, a data form must be submitted.

11.7.2 Disease status, classified local, regional, distant.

11.7.3 Site(s) and date of first failure in each category above.

11.7.4 Relationship of breast recurrence to implant volume (infield, peripheral, extrafield, see Section 11.2.2).

11.7.5 Cosmetic evaluation.

11.7.6 Effects of treatment.

11.7.7 Follow-up physical examination and mammographic results.

11.7.8 Photographs (preferably 35 mm slides, polaroids are acceptable) at 3 and 6 months, 1 year, and yearly thereafter (see guidelines in Section 11.4).

12.0 **DATA COLLECTION** (2/14/00, 7/28/04)

12.1 **Summary of Data Submission**

(RTOG, 1818 Market Street, Suite 1600, Philadelphia, PA 19103, FAX#215/928-0153)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 wks of start of treatment</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Diagnostic Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Surgery Form (S1)</td>
<td></td>
</tr>
<tr>
<td>Surgical Operative Note (S2)</td>
<td></td>
</tr>
<tr>
<td>Surgical Pathology Report (S5)</td>
<td></td>
</tr>
<tr>
<td>PreOp Mammogram Report (I2)</td>
<td></td>
</tr>
<tr>
<td>PostOp/Post Brachy Mammogram Report (I2)</td>
<td>If done (See [Section 3.1.5])</td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td>Within 13 weeks from implant</td>
</tr>
<tr>
<td>Brachytherapy Treatment Form (BT)</td>
<td></td>
</tr>
<tr>
<td>Brachytherapy Localization Films (T0)</td>
<td></td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>At 6 and 12 months after implant, then q 3 months for 1 year; q 4 months x 1 year, q 6 months x 3 years, then annually. Also at progression/relapse and at death</td>
</tr>
<tr>
<td>Cosmesis Forms</td>
<td>At 6 and 12 months after completion of therapy, then yearly.</td>
</tr>
<tr>
<td>Patient Form (PQ)</td>
<td></td>
</tr>
<tr>
<td>Surgical Oncologist (FS)</td>
<td></td>
</tr>
<tr>
<td>Radiation Oncologist (QP)</td>
<td></td>
</tr>
<tr>
<td>Autopsy Report (D3)</td>
<td>As applicable</td>
</tr>
</tbody>
</table>

12.2 **Data Submission** (7/28/04)

(directly to the RT Quality Assurance Department at RTOG headquarters)

Photographs (T7)

Preliminary Dosimetry Information:

Supplemental Calculations (TL)

Isodose Distribution (T6)

After surgery but before catheter placement or after catheter removal (if implant done at time of surgery), with catheters in place and at 3, 6, and 12 months. Yearly thereafter.

Prior to start of treatment (by fax to Dr. Kuske, 504/842-2037)
13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Reproducibility of Brachytherapy Techniques
Reproducibility is the primary endpoint because whether or not the technique is widely applicable in a multicenter setting must be demonstrated prior to undertaking a phase III trial. Specific tools to measure the quality of brachytherapy technique have been developed in Section 6. The ability of various clinical sites to perform brachytherapy within the guidelines delineated in this protocol will provide a measure of feasibility for this technique. With the rapid turnaround procedure as described in Section 6.0, a high percentage of acceptable treatments is expected. Since treatments from Ochsner, the study chair’s institution, are most likely to be scored acceptable, the accrual from Ochsner will be capped at 25% in each dose rate arm (see Section 13.2).

13.1.2 Toxicities
Toxicities resulting from brachytherapy will be collected and graded. Any toxicities grade 3 or higher will be promptly reported as specified in Appendix V.

13.1.3 Cosmesis
Cosmetic results will be assessed by both the physician and the patient at three, six and twelve months, then annually. Photographs are to be taken at these time points according to the specifications in Section 11.4 and sent to the RT Quality Assurance Department at RTOG headquarters. To maintain confidentiality of results of patient's cosmesis assessment, copies of the Cosmesis Forms will not be sent to Dr. Kuske with the photographs.

13.1.4 Disease-Free Survival and Mastectomy-Free Survival
All disease recurrences and surgical interventions will be recorded. In disease-free survival, any tumor recurrence or death is considered a failure. In mastectomy-free survival, the failures are mastectomy and death. Ipsilateral breast recurrence rate, subdivided by in-field, peripheral and extra-field locations as defined in Section 11.2.2, ipsilateral nodal recurrence rate and distant metastasis rate will be calculated.

13.1.5 Overall Survival
Death from any cause is considered a failure.

13.2 Study Design
The sample size will be determined by the first endpoint in Section 13.1, namely, the reproducibility of the brachytherapy techniques. There will be two central reviews by the study chair for the brachytherapy after surgery, one is the initial review of the treatment plan during the rapid turnaround period (see Section 6.14), the other is the final review after the treatment is delivered. In both of these reviews the brachytherapy will be scored by the study chair as acceptable, marginally acceptable or unacceptable, using the criteria in Section 6.12. If, during the initial review, a treatment plan is graded unacceptable or marginally acceptable, the study chair will ask the institution to make appropriate changes. The sample size calculation will be based on the final review of the delivered treatment. Since HDR and LDR are two different procedures, we will proceed as if we have two separate trials, one for HDR and the other for LDR. Each institution can enter patients on both treatment arms. The following design is for both HDR and LDR, separately.

The optimal two-stage design by Simon\(^23\) will be used. Let \( p \) be the true probability that the final review is acceptable or marginally acceptable. A \( p \) close to 1 implies that the brachytherapy technique is reproducible in a multi-center setting. If \( p \) is less than or equal to 80%, the goal is to have at most a 5% probability of concluding that the technique is reproducible. On the other hand, if \( p \) is greater than or equal to 95%, the desired level, the goal is to have at most a 10% probability of concluding that the technique is not reproducible. With these specifications, 19 eligible patients will be required in the first stage. It is required that Ochsner enter no more than 5 eligible patients for this stage. If 3 or more brachytherapy treatments are scored unacceptable, then early stopping will be recommended to the study chair. Otherwise the trial will continue until a total of 42 eligible patients are accrued. The maximum Ochsner can enter is 10 eligible patients on each arm. If 5 or more of the 42 treatments are scored unacceptable, the technique will be considered not reproducible, and a phase III study will not be pursued. Otherwise, we will consider a further randomized phase III study comparing brachytherapy with standard external beam radiation therapy. This two-stage design has an expected sample size of 24.4. When \( p \) is 80%, this design minimizes the expected sample size among all designs satisfying the same specifications.

13.3 Patient Accrual
The patient accrual will be simultaneous for the HDR and the LDR arms. Each institution may choose to participate in either or both of the arms. Because of the large patient population base, we expect to finish the accrual for both treatment options within two years. After one year, patient accrual by dose rate will be assessed. If fewer than 12 patients were entered on a dose rate arm, the feasibility of continuing that arm will be evaluated by the RTOG Research Strategy Committee. For the maximum sample size of 42 eligible patients on each dose rate arm, we expect to accrue about 46 patients, taking into account the
ineligible cases. No more than 10 eligible patients in each arm will be from Ochsner (see Section 13.2). After the accrual of the first stage of 19 eligible patients is completed, the two-stage design calls for suspension of patient accrual until the results of the first stage are known. But, if from initial reviews of treatment plans and partial reviews of the final treatments, the study chair is certain that early stopping boundary will not be crossed, then no suspension of accrual will occur.

13.4 Schedule of Analyses

The following schedule will be applied to both the LDR and the HDR arm, separately. While patients are being accrued to this study, there will be semi-annual reports published in the RTOG Group Meetings Reports. These reports will give the updated information on patient accrual and toxicity. After 19 eligible patients have finished their treatment, the study chair will come to the headquarters to review the dosimetry together with other data. If 3 or more brachytherapy treatments are unacceptable, early stopping will be recommended. Three to five years after the early stopping, an analyses on all the endpoints will be made.

Without early stopping, the first analysis will be made one year after the completion of accrual of 42 eligible patients. This first analysis will focus on the first three endpoints in Sections 13.1.1 through 13.1.3. The results will be used to determine whether a further phase III study is appropriate. Analysis on all the endpoints will be made three to five years after completion of accrual, possibly together with initial analysis of the phase III study.
REFERENCES


APPENDIX I
RTOG 95-17
A PHASE I/II TRIAL TO EVALUATE BRACHYTHERAPY AS THE SOLE METHOD OF RADIATION THERAPY FOR STAGE I AND II BREAST CARCINOMA

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so I have an opportunity to decide whether or not to undergo the procedure after knowing the risks, benefits and alternatives. This disclosure is an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

I understand that I have cancer of the breast. I may be eligible for breast conservation therapy. Studies have shown that radiation therapy after surgery to remove the cancer (lumpectomy) improves control of the cancer within the breast. I understand that standard therapy after breast conservation surgery is 5 to 6 weeks of external radiation therapy to my breast. I understand that I am offered the opportunity to participate in a trial of brachytherapy (radioactive implants) delivered over a 3 to 7 day period as the only radiation treatment of my breast after removal of the cancer. The purpose of this study is to test whether or not radiation therapy delivered by brachytherapy as the sole radiation therapy treatment after removal of the cancer gives comparable local control of disease, acceptable appearance of the breast after treatment, and side-effects and complications of treatment similar to those after lumpectomy (removal of the cancer) and external radiation therapy.

DESCRIPTION OF PROCEDURES

Radiation therapy can be delivered on an inpatient or outpatient basis, using catheters (plastic tubes) which will contain the radioactive sources. Treatment can begin either the day after catheters are placed or later, depending upon the extent of surgery performed at the time of the implant. The catheters will remain in place between 3 to 7 days, depending on the type of brachytherapy and when the procedure is done. The catheters are usually placed in the breast at the time of the axillary dissection (removal of lymph nodes under the arm on the same side as my breast cancer), at the time of further surgery at the biopsy site, or under local anesthesia as a separate procedure. There are two types of brachytherapy:

1) **Low dose rate breast brachytherapy** - Following surgical removal of my breast cancer, the radiation oncologist with the assistance of the surgeon will place a series of small hollow plastic tubes called catheters around the site of my surgical procedure. These tubes penetrate through the skin and will be secured with buttons at the surface of the skin. Providing that the findings of the pathologist are consistent with the requirements of this study, a ribbon of small radioactive sources, iridium -192, will be inserted into each catheter. If the pathologist finds evidence of cancer at the edge of the specimen or other conditions which make me ineligible for this study, I will be removed from this study and treated with standard therapy. Once loaded, the iridium sources will be left in place as long as necessary to deliver the prescribed dose of radiation, usually 3 to 5 days. After the prescribed dose has been reached, the iridium sources and catheters will be removed.

During the period when the catheters contain the radioactive sources and my dose is being delivered, I will remain in the hospital in a private room, with limited visiting privileges, in order to minimize the exposure of other persons to radiation. I will be given instructions on the care of the catheter sites and I agree to follow those instructions carefully.

2) **High dose rate breast brachytherapy** - Following surgical removal of my breast cancer, the radiation oncologist with the assistance of the surgeon will place a series of small hollow plastic tubes called catheters around the site of my surgical procedure. These tubes penetrate through the skin and will be secured with buttons at the surface of the skin. If the pathologist finds evidence of cancer at the edge of the specimen or other conditions which make me ineligible for this study, I will be removed from this study and treated with standard therapy. After confirmation by the pathologist of my eligibility for the study, at least 4 to 6 days after excision or reexcision of the site of my cancer in the breast, I will begin my twice daily brachytherapy treatments.
A small radioactive source, iridium -192, will be inserted into each catheter by a special machine. Treatment times vary, but I will plan to spend approximately 30 minutes each morning and afternoon, at least six hours apart, in the Radiation Oncology Department for a total of 5 days. Because the radiation source is not continuously present, I do not need to be hospitalized for the treatments. After my final treatment, the catheters will be removed. I will be given instructions on the care of the catheter sites and I agree to follow those instructions carefully.

3) **Other aspects of treatment** -

   a) Chemotherapy and/or hormonal therapy may be necessary, depending on the size and extent of my tumor and other risk factors. My participation in this study will not influence whether or not I receive such additional treatment.

   b) If I agree to participate in this research study, I will have a physical examination and other screening tests and procedures before treatment. If I am still menstruating and am sexually active, a pregnancy test will be required prior to enrollment in the study.

   c) In order to evaluate the effectiveness of this treatment, I agree to have post-treatment physical examinations at three months, six months, one year, and at least yearly thereafter. Mammograms will be taken 6 months after treatment and yearly thereafter. Additional blood tests, x-rays, and scans will be done as necessary. In order to evaluate the appearance of my breast, I agree to allow photographs of my breasts to be taken, before and during treatment, at 6 and 12 months after treatment, and yearly thereafter.

   d) I also agree to fill out a questionnaire to evaluate the appearance of my breast at different time points and my satisfaction or dissatisfaction with the outcome of my treatment.

**RISKS AND DISCOMFORTS**

Both surgery and implanted catheters can lead to infection, bleeding, and the formation of fluid accumulation in the excision cavity called seroma or hematoma. Radioactive implants can delay wound healing at the site of my surgical excision. I may develop skin thickening or changes in the color of the skin overlying the catheters.

There may be small scars appearing as tiny white or red spots where the catheters penetrate the skin under the buttons. Scarring (fibrosis) can be a long-term complication of radiation therapy and some firmness, tenderness, pain, or deformity in the treated area of my breast may develop in the future. In the excision cavity, areas of fat necrosis (fatty tissue dissolving from the effect of radiation and forming a mass that can be felt in the breast until it is gradually reabsorbed) or fibrosis (scar tissue causing thickening and firming of the breast in the affected area) may form after treatment where the highest dose is concentrated. These problems may require surgical intervention ranging from needle aspiration of the fluid to mastectomy with surgical reconstruction. If I become pregnant during this study, I may have a miscarriage, and there is increased risk of congenital malformations of the fetus and an increased chance of future malignancies in the child. Inflammation of the lung (radiation pneumonitis) and inflammation of the sac around the heart (pericarditis) are rare but possible complications. This treatment will result in an increased risk of a future malignancy in the untreated breast. This risk, if it truly does exist, is quite small. In the breast treated on study, there may be an increased risk of tumor recurrence over treatment with external beam radiation. Recurrent tumors are usually treated with mastectomy (removal of the breast). Chronic chest wall pain, weakening of the ribs leading to possible fracture, and skin ulceration are other potential complications.

"Low dose" radiation received by some portions of the treated breast outside the main area treated by brachytherapy might increase the risk of a new cancer in the treated breast. I understand that there may be an increased risk of local recurrence in the breast or radiation induced cancers with brachytherapy alone as compared with standard therapy of 6 weeks of external beam radiation therapy. Standard treatment for local (breast) recurrence is mastectomy. While many, if not most, patients are cured with a mastectomy for local recurrence, some patients may not be cured.

I understand that these side effects are possible. I may experience no side effects, some of them, or most of them. Although I will be closely monitored, not all side-effects can be predicted and unforeseen problems can arise. I understand that there may be some unknown or unanticipated discomforts or risks in addition to those specified above, because this procedure has seldom been used before in this manner and is an attempt to advance medical knowledge.
CONTACT PERSONS

In the event that injury occurs as a result of this research, treatment will be available. I understand, however, I will not be provided with reimbursement for medical care other than what my insurance carrier may provide nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. ______ the investigator. In addition, I may contact ______________________ at ______________________ for information regarding patients' rights in research studies.

BENEFITS

Since the effectiveness of brachytherapy (radioactive implants) as the only method of radiation therapy after breast conserving surgery is being investigated, I know that no assurances can be made that it will benefit me or other breast cancer patients, but my physician will take every precaution compatible with the best medical practice. The procedure does offer a much shorter duration of treatment, and the study will test whether local breast cancer control rates and the appearance of the breast are comparable to these factors after 5 or 6 weeks of standard external beam radiation therapy. As in any research study, I am aware that these probable benefits may not occur and that, in the future, additional treatment for my breast cancer may become necessary, possibly including mastectomy, chemotherapy, hormonal therapy and/or further external beam radiation therapy.

ALTERNATIVE TREATMENTS

As an alternative to enrolling in this study, I have been offered several standard options for the treatment of my breast cancer: modified radical mastectomy (removal of the whole breast and adjacent axillary lymph nodes located under the armpit of the side on which the breast cancer was diagnosed) with or without breast reconstruction; or breast conserving surgery with axillary lymph node removal and 5 to 6 weeks of external beam radiation therapy, with or without a boost of additional radiation to the tumor bed. The above treatments also have risks, which may be more or less than those involved with brachytherapy. An additional alternative is to choose no further treatment, which has a risk of further growth or spread of my tumor. I have been told that I should feel free to discuss my disease and my prognosis with my doctor. A physician involved in my care will be available to answer any questions I have concerning my treatment now or in the future.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care. In the event of a research-related injury, I understand my participation has been voluntary.

CONFIDENTIALITY

I understand that records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, may be sent to a central office for review and research investigation associated with this protocol.

I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient Signature (or Legal Representative) ______________________

Date ______________________
### APPENDIX II

**KARNOFSKY PERFORMANCE SCALE**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints; no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some sign or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most personal needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalization is indicated, although death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospitalization necessary; active support treatment is necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>
APPENDIX III

BREAST STAGING, AJCC 4th Edition

DEFINITION OF TNM

Primary Tumor (T)

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. The telescoping method of classification can be applied. If the measurement is made by physical examination, the examiner will use the major headings (T1, T2, or T3). If other measurements, such as mammographic or pathologic, are used, the examiner can use the telescoped subsets of T1.

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ: intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no tumor.
T1 Tumor 2 cm or less in greatest dimension
  T1a 0.5 cm or less in greatest dimension
  T1b More than 0.5 cm but not more than 1 cm in greatest dimension
  T1c More than 1 cm but not more than 2 cm in greatest dimension
T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3 Tumor more than 5 cm in greatest dimension
T4 Tumor of any sizes with direct extension to chest wall or skin.
  T4a Extension to chest wall
  T4b Edema (including peau d’orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
  T4c Both (T4a and T4b)
  T4d Inflammatory carcinoma

Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

Regional Lymph Nodes (N)

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

Pathologic Classification (pN)

pNX Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0 No regional lymph node metastasis
pN1 Metastasis to movable ipsilateral axillary lymph node(s)
  pN1a Only micrometastasis (none larger than 0.2 cm)
  pN1b Metastasis to lymph node(s), any larger than 0.2 cm
    pN1bi Metastasis in one to three lymph nodes, any more than 0.2 cm and all less than 2 cm in greatest dimension
    pN1bii Metastasis to four or more lymph nodes, any more than 0.2 cm and all less than 2 cm in greatest dimension
    pN1biii Extension of tumor beyond the capsule of a lymph node metastasis less than 2 cm in greatest dimension
    pN1biv Metastasis to a lymph node 2 cm or more in greatest dimension
pN2 Metastasis to ipsilateral axillary lymph nodes that are fixed to one another or to other structures
pN3 Metastasis to ipsilateral internal mammary lymph node(s)
**Distant Metastasis (M)**

- MX: Presence of distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis *(includes metastasis to ipsilateral supraclavicular lymph node(s))*

**STAGE GROUPING**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tis, T1, T2, T3, T4</th>
<th>N0, N1, N2, N3, Any N</th>
<th>M0, M1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>NO</td>
<td>M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1, T2, T3, T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T0, T1, T2, T3</td>
<td>N1, N0, N2, N1, N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2, T3</td>
<td>N1, N0, N2, N1, N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T0, T1, T2, T3</td>
<td>N2, N0, N1, N2, N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T4</td>
<td>Any N, T, Any N</td>
<td>M0</td>
</tr>
</tbody>
</table>

*Note: The prognosis of patients with N1a is similar to that of patients with pN0.*
APPENDIX V
ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supercede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
   a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.

2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.

3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).

4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.

5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of RTOG-coordinated intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.

7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.

8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.
C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

i. Any fatal (grade 5) or life threatening (grade 4) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.

ii. Unknown adverse reactions (> grade 2) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.

iii. All neurotoxicities (> grade 3) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.

iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (IDB)
P. O. Box 30012
Bethesda, MD  20824
Telephone number available 24 hours
(301) 230-2330      FAX # 301-230-0159

i. Phase I Studies Utilizing Investigational Agents

- All deaths during therapy with the agent. Report by phone within 24 hours to IDB and RTOG Headquarters.
  **A written report to follow within 10 working days.

- All deaths within 30 days of termination of the agent. As above

- All life threatening (grade 4) events which may be due to agent. As above
- First occurrence of any toxicity (regardless of grade). Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters. **A written report may be required.

ii. **Phase II, III Studies Utilizing Investigational Agents**

- All fatal (grade 5) and life threatening (grade 4) **known** adverse reactions due to investigational agent. Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours. **A written report must be sent to RTOG within working days with a copy to IDB. (Grade 4 myelosuppression not reported to IDB)

- All fatal (grade 5) and life threatening (grade 4) **unknown** adverse reactions resulting from or suspected to be related to investigational agent. Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**. **A written report to follow within 10 working days.

- All grade 2, 3 **unknown** adverse reactions resulting from or suspected to be related to investigational agent. **Report in writing** to RTOG Headquarters and IDB within 10 working days.

**See attached (if applicable to this study) NCI Adverse Drug Reaction Reporting Form**
APPENDIX VI

SUGGESTED
TYLECTOMY/REEXCISION INCISIONS

FIGURE 1

Recommended
APPENDIX VI

SUGGESTED
TYLECTOMY/REEXCISION INCISIONS

FIGURE 2
# BREAST BRACHYTHERAPY INSTITUTION QUESTIONNAIRE

**RTOG PROTOCOL 95-17**

**I. Institution Name:**

RTOG Institution #: _______________________________

Address:   

Telephone (Voice) (   )

Telephone (Fax) (   )

**II. Treatment Technique to Be Used:**

HDR only_______   LDR only_______   Either HDR or LDR___________

**III. Brachytherapy Sources and Equipment:**

1. Please complete the following:

**FOR HDR ONLY:**

Manufacturer and model of HDR afterloading unit: __________________________

Frequency of HDR source replacement: _____________________________________

**FOR LDR ONLY:**

State method used: Wire or seeds in ribbons or LDR remote afterloading

Radiation sources are purchased from: ___________________________________

Radiation sources are special ordered for each case or prepared from in-house inventory ,specify  __________________

_______________________________________

If remote, give make and model of unit: ________________________________

Manufacturer and model of treatment planning computer: ________________

_______________________________________

Does computer have interactive graphics capability? ______________________

Describe interstitial catheters to be used (manufacturer, size, lumen, etc.:

_______________________________________
Describe techniques used to verify position of catheters and/or sources within the target volume. _____________________________________________________
_____________________________________________________________________
_____________________________________________________________________

IV. Brachytherapy Personnel

1. Radiation Oncologists, Voice and Fax Numbers

_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________

2. Brachytherapy Physicist(s), Voice and Fax Numbers

_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________

V. Quality Assurance (attach the following)

a) Source strength verification:

Submit a description of the procedures followed to verify the calibration of the source(s). Include:

• Description of dosimetry system.

• Confirmation that calibration meets national standards.

• Measurement and calculation techniques, including conversion of the above standard into the source specification units, used by your treatment planning computer.

• Frequency of calibration.

b) Source positioning in the catheter (principally for remote afterloading systems):

• Describe quality assurance (Q.A.) procedures used to verify that source positions within the catheters are known and reproducible.
c) Dosimetry Procedure:

• Describe the exact procedure followed to assure that the dose calculations are in accordance with the requirements of the protocol.

d) Other quality assurance procedures:

Describe any hand calculations done to verify the accuracy of the computer-generated treatment plan.

Describe any other Q.A. procedures pertinent to study objectives.

VI. Benchmark Case

Submit dosimetry calculations on the following benchmark case.

The benchmark is a breast treatment utilizing a double plane implant. The superficial plane consists of seven parallel catheters, 1.5 cm apart, and 10 cm total length each. The deep plane, 2 cm below the superficial plane, consists of eight parallel catheters, 1.5 cm apart, and 12 cm total length each.

"Start and stop" all sources 2 cm from the skin surface on all catheters. The sagittal and coronal views, as obtained from "ideal" orthogonal films and with dummy seeds in the catheters, are shown in the figures on the following page. The locations of four small and two large surgical clips are also shown. Perform the following procedure for either an LDR or HDR or for both types of treatment as determined by your institutional preference. See Question II.

LDR Treatment:

Using 0.8 mCi seeds with a spacing of 1 cm, calculate the dose-rate distributions in the three orthogonal planes through the center of the implant (see Sec. 6.9). Use a magnification factor of 1.5 to improve the precision of the review. The prescription dose is 45 Gy. Use the clip positions to draw the excision cavity and the target volumes on the three planes, following protocol requirements (see Sec. 6.2). Select an isodose-rate line as your prescription dose-rate and calculate the treatment time required to deliver the prescription dose to the target volume.

Determine the Geometric Center Dose Rates, the Mean Central Dose Rate, the Peripheral Dose Rate, and the Dose Homogeneity Index. Determine the percentage deviations of the Prescribed Dose in the central and sagittal planes, and the average percentage deviation. On the isodose curves, show the lines corresponding to the MCD, the PD, the Prescribed Dose (if different), 150% of the MCD, and 90% of the Prescribed Dose, and these should be clearly labeled. State whether or not this implant is acceptable, marginally acceptable, or unacceptable, based on protocol definitions (Sec. 6.12). If marginal or unacceptable, describe actions that could be taken to make it acceptable.
HDR Treatment:

Using 0.5 cm dwell positions and a 10 Ci source, calculate the dose distributions in the three orthogonal planes through the center of the implant (see Sec. 6.9). Use a magnification factor of 1.5 to improve the precision of the review. The prescription dose is 3.4 Gy. Use the clip positions to draw the excision cavity and the target volumes on the three planes, following protocol requirements (see Sec. 6.2). Determine the Geometric Center Doses, the Mean Central Dose, the Peripheral Dose, and the Dose Homogeneity Index. Calculate the total time required to deliver the prescription dose to the target volume for the first treatment. Determine the percentage deviations of the Prescribed Dose in the central and sagittal planes, and the average percentage deviation. On the isodose curves, show the lines corresponding to the MCD, the PD, the Prescribed Dose (if different), 150% of the MCD, and 90% of the Prescribed Dose, and these should be clearly labeled. State whether or not this implant is acceptable, marginally acceptable, or unacceptable, based on protocol definitions (Sec. 6.12). If marginal or unacceptable, describe actions that could be taken to make it acceptable.

VII. Submit to:

RTOG HEADQUARTERS
ATT: ELAINE PAKURIS
1101 Market Street, 14th Floor
Philadelphia, Pa 19107

ALLOW AT LEAST FOUR WEEKS FOR REVIEW AND APPROVAL,
INCOMPLETE SUBMISSIONS WILL TAKE LONGER
Deep (12 cm)

Sup. (10 cm)

Small clips: a) 2.5 cm from origin
b) 2.0 cm from origin

CORONAL PLANE

Sup. (10 cm)

Deep (12 cm)

Large clips 0.75 cm from origin

SAGITTAL PLANE