

RADIATION THERAPY ONCOLOGY GROUP

RTOG 98-04

PHASE III TRIAL OF OBSERVATION +/- TAMOXIFEN VS. RT +/- TAMOXIFEN FOR GOOD RISK DUCT CARCINOMA IN-SITU (DCIS) OF THE FEMALE BREAST

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Activation Date: **December 13, 1999**

Update Date: **October 15, 2004**

CTSU (R9804)

Version Date: **April 12, 2004**
(Broadcast Date: April 21, 2004)
Includes revisions 1-4

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SCHEMA

(1/15/02) (4/7/04)

The physician specifies tamoxifen use:

	<u>Age</u>		
	1. < 50		
S	2. ≥ 50	R	
T	<u>Final Path Margins</u>	A	<u>Arm 1</u>
	1. Negative (<i>re-excision</i>)		Observation +/- tamoxifen 20 mg per day for 5 years
R	2. 3-9 mm	N	
	3. ≥ 10 mm		
A		D	
	<u>Mammographic/Pathologic Size of Primary</u>		
T	1. ≤ 1 cm	O	<u>Arm 2</u>
	2. > 1 cm to ≤ 2.5 cm		Radiation therapy* to the whole breast +/- tamoxifen
I		M	20 mg per day for 5 years
	<u>Nuclei Grade</u>		
F	1. Low	I	
	2. Intermediate		
Y		Z	
	<u>Tamoxifen Use</u>		
	1. No	E	
	2. Yes		

*RT Dose: 1.8 Gy per fraction x 28 fractions, for a total dose of 50.4 Gy; **OR** 2.0 Gy per fraction x 25 fractions, for a total dose of 50.0 Gy; **OR** 2.656 Gy per fraction x 16 fractions, for a total dose of 42.5 Gy

Eligibility: (*See Section 3.0 for details*) (1/15/02) (4/12/04)

- Women ≥ 26 years of age.
- Unicentric mammographically detected DCIS. The DCIS must be detected by mammogram or detected as an “incidental” finding after a biopsy is performed for a benign histology (eg, fibroadenoma). **A mammogram will still be required pre study entry (See Section 4.2).**
- Lesions ≤ 2.5 cm in greatest dimension on mammogram or pathologic specimen; use the largest measured size from the pathology report to obtain the required measurement of ≤ 2.5 cm.
- Lesions must be classified as low or intermediate grade DCIS.
- Inked margins ≥ 3 mm.
- Clinically node negative.
- No active connective tissue disorders.
- No prior (*unless disease free ≥ 5 years*) or concurrent malignancy other than basal or squamous cell skin cancer or *in situ* cancer of the cervix.
- No concurrent hormone therapy (*other than tamoxifen*) at the time of study entry.
- Women may be taking tamoxifen, which may have begun up to four weeks preceding diagnosis of DCIS.
- If assigned to Arm 2, radiation must begin within 12 weeks after the final surgery.
- Not pregnant or lactating.
- Signed study-specific consent form prior to randomization.

Required Sample Size: 1790 12/3/01

RTOG Institution # _____

ELIGIBILITY CHECK (12/3/01) (4/12/04)

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(page 1 of 2)

RTOG Case # _____

- ____(Y) 1. Was the DCIS detected by mammogram or detected as an “incidental” finding after a biopsy is performed for a benign histology (eg, fibroadenoma)? **A mammogram will still be required pre study entry (See Section 4.2).**
- ____(Y) 2. Is the lesion ≤ 2.5 cm in its greatest dimension on mammogram or pathologic specimen? Use the largest measured size from the pathology report to obtain the required measurement of ≤ 2.5 cm
- ____(N) 3. Is the lesion palpable or multicentric?
- ____(NG1, NG2) 4. Using the Philadelphia Consensus Conference Guide (*Appendix VII of protocol*), how is the lesion classified?
- ____(Y) 5. Were the margins as assessed by India ink ≥ 3 mm?
- ____(Y) 6. Are the lymph nodes clinically negative?
- ____(Y) 7. Was the post op mammogram, including magnified views of the study breast, obtained within 12 weeks of final surgery?
- ____(Y) 8. Is the post op mammogram negative for any suspicious areas?
- ____(Y) 9. Will protocol radiation therapy begin within 12 weeks of final surgery if assigned to Arm 2?
- ____(Y) 10. Will the patient be free of any hormone therapy, including anti-estrogens, HRTs, birth control pills, at the time of study entry?
- ____(Y) 11. Is the patient 26 years of age or older?
- ____(N) 12. Any prior radiation therapy or chemotherapy?
- ____(N) 13. Except for basal or squamous cell skin cancer or *in situ* carcinoma of the cervix, is there a prior malignancy within the last 5 years?
- ____(N) 14. Is the patient pregnant or lactating?
- ____(N) 15. Does the patient have any active connective tissue disorders?
- ____(Y/N) 16. Is the patient taking tamoxifen?
- ____(N) If yes, was tamoxifen started more than 4 weeks prior to diagnosis of DCIS?

(continued on next page)

RTOG Institution # _____

ELIGIBILITY CHECK (1/15/02)

RTOG 98-04

(page 2 of 2)

RTOG Case # _____

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case?
- _____(Y) 2. Has the Eligibility Checklist (*above*) been completed?
- _____(Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed? (*must be prior to study entry*)
- _____ 5. Patient's Name
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Social Security Number
- _____ 11. Patient's Country of Residence
- _____ 12. Zip Code
- _____ 13. Patient's Insurance Status
- _____ 14. Will any component of the patient's care be given at a military or VA facility?
- _____ 15. Treatment Start Date (*if assigned to RT Arm*)
- _____ 16. Age (*< 50 vs. ≥ 50*)?
- _____ 17. Final Path Margins (*Negative vs. 3-9 mm vs. ≥ 10 mm*)?.
- _____ 18. Mammographic Size of Primary (*≤ 1 cm vs. > 1 cm to ≤ 2.5 cm*).
- _____ 19. Nuclei grade (*low vs. intermediate*)
- _____(N/Y) 20. Is physician planning Tamoxifen for this patient?
- _____ 21. Will patient participate in Epidemiology Study? (*yes vs. no*)
- _____ 22. Treatment Assignment

Completed by _____

Date _____

1.0 INTRODUCTION

- 1.1** With the growing acceptance of mammography as a screening tool, non-palpable duct carcinoma *in situ* is being diagnosed with a frequency of 20-25% in large breast practices. Retrospective studies suggest that good risk disease, i.e. small lesions, with a low-grade pathology classification, can be effectively treated with radiation or with observation.^{1,2,3,5} The NSABP B-17 trial designed to answer this question stratified patients by age, presence or absence of lobular carcinoma *in situ*, presence or absence of an axillary node dissection, and method of detection, i.e. palpable mass versus mammogram only. Size, margins and pathologic grade, recognized presently as important selection factors for possible treatment with observation only, were not factors in that trial.⁴ The NSABP B-24 trial, recently closed to accrual, places all patients on radiation and then randomizes them to post-radiation observation or tamoxifen, does not address the question of the efficacy of observation only in a subset of good-risk patients with duct carcinoma *in situ*.
- 1.2** Size, or extent of disease, margins, and pathology grade, are problematic selection factors because a number of pathology classification systems addressing duct carcinoma *in situ* have been proposed. Recently, a consensus conference was held with the purpose of defining pathologic criteria for this disease. A consensus was reached by the participating pathologists and we propose using this working system⁹ as a starting point to assure standardization in defining cases of pathologic "good-risk" disease. We propose distributing the consensus guidelines and an illustrative set of sample teaching cases using the format of glass slide sets for initial review and the RTOG web site for reference and reinforcement. Pathologists completing this "course" would then review a set of test questions and qualify to read slides for the purpose of determining entry criteria for this study. In an ancillary project, a limited sample of slides of patients on this study would be reviewed by a group of breast pathology experts to establish the effectiveness of this teaching technique and the reproducibility of the consensus working classification.
- 1.3** The mammogram is an important diagnostic test for this disease. We propose requiring that patients on this study have mammograms performed at an accredited facility.
- 1.4** Prospectively, in a non-randomized study of irradiated patients, age was associated with outcome. The breast treatment team at Memorial Hospital applied the criteria of 1) size less than 2.5 cm and 2) non-comedo, low-grade lesions to recommend observation in a given subset of patients. Women with larger lesions, or lesions with comedo features and high nuclear grade were irradiated. In comparing results, in a retrospective study, patient age at diagnosis impacted significantly on outcome, hence the reason for stratification in this study.⁶
- 1.5** The NSABP B24 trial recently reported a positive impact from tamoxifen in reducing the risk of both recurrent carcinoma-in-situ and invasive cancer in women treated with breast conserving surgery and radiation. A decrease in the risk of contralateral new breast cancers was also observed.⁷
- 1.6** Duct carcinoma *in situ* is emerging as a possible model for the prevention of progression of a cancer from the in-situ to the invasive form of the disease. Both tamoxifen and radiation will impact on biomarkers; tamoxifen is already formally under study in women at increased risk for breast cancer, and radiation is known to modulate these markers in organ systems. Family history of breast cancer, or ovarian cancer, especially with a genetic change such as BRCA 1,2, or other emerging markers, is likely to play a major role in the development and progression of this disease. This study will include a voluntary registry of patients by epidemiologic data for possible genetic or other biomarker studies at a later date. Both tissue and blood will be stored for future testing.
- 1.7** We propose to undertake a phase III randomized study, limited to patients with occult, "good risk" duct carcinoma *in situ*, comparing tamoxifen alone to the same 50 Gy whole breast radiation treatment used in both NSABP studies plus tamoxifen. To facilitate comparisons, we will adopt the same definition of a clear margin as is used in the open ECOG registry study for similar good-risk patients.
- 1.8** Women who fail primary treatment for this disease can go on to develop a recurrence of the *in situ* carcinoma, or may progress to the invasive form of the disease.^{4,8} Depending on the stage of the disease at the time of the recurrence, and the initial treatment, treatment of the recurrence may appropriately range from a repeat wide local excision and radiation to mastectomy and systemic chemotherapy or hormone therapy. While it is beyond the scope of this study to mandate a specific treatment plan, we propose establishing a "recurrence help hotline" through the use of e-mail and the Internet. This would give the physician of a patient on this study with a recurrence access to the expertise of the study chairmen for this protocol. We also propose tracking the therapy used in the treatment of the recurrence and establishing a tissue bank of patients who progress for later studies.

2.0 OBJECTIVES (12/3/01)

- 2.1 In the defined good-risk group, assess the role of whole breast radiation plus/minus tamoxifen compared to wide excision to negative margins alone plus/minus tamoxifen, in decreasing or delaying the appearance of local failure, both invasive and *in situ*, and preventing the need for mastectomy.
- 2.2 Assess distant disease free survival to affirm the hypothesis that the proportion of patients in either arm who fail with progression to invasive local disease can be successfully salvaged with further definitive local therapy and adjuvant systemic therapy as is appropriate to the individual case.
- 2.3 Adopt a working pathology classification system for DCIS, which can be taught to and uniformly applied by the community pathologist. This will include processing the specimen, assessing extent of disease, margin assessment, and the grading of the lesion. Pathologic relationship of any calcium present to the DCIS will also be noted.
- 2.4 Establish a registry for patients with an epidemiological questionnaire, for companion studies of biomarkers and genetics, to be done at a later time when research in this area has identified useful markers. Tissue and blood will be banked from each patient who agrees to participate in this aspect of the study.
- 2.5 Establish a tissue bank of patients who progress to local failure in the study breast.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (4/12/04)

- 3.1.1 Patients must be women.
- 3.1.2 The DCIS must be detected by mammogram and must be unicentric or detected as an “incidental” finding after a biopsy is performed for a benign histology (eg, fibroadenoma). **A mammogram will still be required pre study entry (See Section 4.2).**
- 3.1.3 Lesions ≤ 2.5 cm in greatest dimension on mammogram or pathologic specimen; use the largest measured size from the pathology report to obtain the required measurement of ≤ 2.5 cm if the information cannot be obtained from the mammogram.
- 3.1.4 Must be classified as low (*NG1*) or intermediate (*NG2*) nuclear grade DCIS, using the Philadelphia Consensus Conference Guidelines (*Appendix VII*), and necrosis in less than one third of the involved ducts.
- 3.1.5 Margins as assessed by the India ink method will be 3 mm or greater.
- 3.1.6 A post-operative mammogram will be taken within 12 weeks after the final surgery. It will include magnification views of the study breast and must show no suspicious areas.
- 3.1.7 Clinically node negative.
- 3.1.8 Patients must be ≥ 26 years of age to avoid the increased potential in the young patient for radiation to induce breast cancer later in life.
- 3.1.9 If assigned to Arm 2, radiation must begin within 12 weeks after the final surgery.
- 3.1.10 Patients must sign a study-specific consent form prior to randomization.

3.2 Conditions for Patient Ineligibility (12/3/01) (4/12/04)

- 3.2.1 Patients whose DCIS is palpable at the time of diagnosis, or multi-centric, or who have bloody nipple discharge.
- 3.2.2 Lesions measuring greater than 2.5 cm in greatest dimension on mammogram or pathologic specimen.
- 3.2.3 High-grade lesions (*NG3*) as classified by the Philadelphia Consensus Conference Guidelines or necrosis in greater than one third of the involved ducts.
- 3.2.4 Final pathology margins measuring <3 mm. If the patient undergoes a further re-excision and then meets selective criteria, she may be randomized to this study.
- 3.2.5 Pregnant or lactating women because of the potential risk to the fetus or child from breast irradiation.
- 3.2.6 Active connective tissue disorders, such as lupus or scleroderma.
- 3.2.7 Prior history of any malignancy, except basal or squamous cell skin cancers or *in situ* carcinoma of the cervix, unless disease-free ≥ 5 years.
- 3.2.8 Any prior irradiation or chemotherapy.
- 3.2.9 Patients whose post-operative mammogram shows findings for DCIS. If the patient undergoes a further re-excision and has a subsequent negative mammogram, she may be randomized to this study.
- 3.2.10 Other hormone therapy at the time of study entry, including raloxifene, hormone-replacement therapy, or birth control pills.
- 3.2.11 Tamoxifen begun > 4 weeks prior to diagnosis of DCIS

4.0 PRETREATMENT EVALUATIONS (12/3/01)

- 4.1** History and physical examination, including surgical history.
- 4.2** Radiological evaluation including one set of mammograms performed or evaluated at an accredited facility and post-operative magnification views.
- 4.3** Pathology slides read by a local pathologist (*See Section 10.1.5*).
- 4.4** Patients who agree to have blood and tissue banked must complete the Family History Assessment and Epidemiologic Questionnaire.

5.0 REGISTRATION PROCEDURES

5.1 RTOG Institutions

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 to a treatment arm 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
- Stratification Information
- Demographic Data
- Treatment Start Date

5.2 CALGB Institutions

Registration will be accepted through the Main Member Institution only. Confirm all eligibility criteria as listed in Section 5.0. Call the CALGB Registrar (919-286-4704, Monday - Friday, 9:00 a.m. - 4:30 p.m., Eastern Time). Registrations must occur prior to initiation of therapy. Call the CALGB Registrar (919-286-4704, Monday-Friday, 9 a.m.-4:30 p.m. Eastern Time) with the following information:

Your name
Study #
Institution #
Treating Physician
Patient's Social Security #, or hospital ID #
Patient's Name, I.D.#
Date of Signed Informed Consent
Race, Sex, Date of Birth
Zip code of residence
Method of payment
Diagnosis, Date of Diagnosis
Eligibility Criteria met (*Sec. 3.0*) (*yes, no*)
List of prior CALGB protocols
Date of most recent Institutional Review Board approval (*<1 year*)

The CALGB Registrar will then contact the RTOG Headquarters for treatment assignment, after which the CALGB Registrar will contact the institution with the treatment assignment. RTOG Headquarters will forward a confirmation of treatment assignment to the CALGB Registrar, who will subsequently forward the confirmation of treatment assignment to the main member institution.

5.3 CTSU Investigators (12/3/01, 10/15/04)

5.3.1 CTSU Address and Contact Information

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	For patient enrollments:	To mail study forms or data:
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone - 1-888-823-5923 Fax – 215-569-0206	CTSU Data Operations Center Phone – 1-888-462-3009 Fax – 1-888-691-8039 [For CTSU patient enrollments that must be completed within approximately one hour or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]	Westat CTSU Data Operations Center 1441 W. Montgomery Avenue Rockville, MD 20850-2062
<p>For patient eligibility or treatment-related questions contact the RTOG Research Associate for Protocol, Data Management section at 215-574-3214. The option remains to contact CTSU Help Desk for assistance in obtaining a response from the Group.</p>		
<p>All other questions (including forms-specific questions) should be communicated by phone or e-mail to the CTSU Help Desk at: CTSU General Information Line – 1-888-823-5923, or ctscontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</p>		
<p>The CTSU Public Web site is located at: www.ctsu.org</p>		
<p>The CTSU Registered Member Web site is located at http://members.ctsu.org</p>		

5.3.2 Registration / Randomization, CTSU Investigators

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol before they can enroll patients. Patients can be registered only after pre-treatment evaluation (*Section 4.0 of protocol*) is completed, all pertinent documents are approved and on file and eligibility criteria are met.

Requirements for RTOG 98-04 site registration:

- CTSU IRB Certification
- IRB/Regulatory Approval Transmittal Sheet
- Radiation Therapy Facility Inventory Form

NOTE: Radiation therapy facilities must participate in the RPC monitoring program to participate in studies sponsored by the CTSU.

Prestudy requirements for patient enrollment on RTOG 98-04:

- Patient must meet all inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- All baseline laboratory tests and prestudy evaluations performed.

CTSU Procedures for Patient Enrollment: (8/31/01) Contact the CTSU Patient Registration Office by calling 1-888-462-3009 to alert the CTSU Patient Registrar that an enrollment is forthcoming. To enroll the patient, the investigator should complete the following forms:

- CTSU Enrollment Coversheet
- RTOG 98-04 Eligibility Checklist

These forms should be faxed to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 am and 5:00 pm Eastern time. The CTSU registrar will verify that the investigator is CTSU credentialed and that all regulatory requirements have been met. The registrar will also check the enrollment forms for completeness and follow-up with the site to resolve any discrepancies.

Once investigator eligibility is confirmed and enrollment documents are reviewed for completeness, the CTSU will contact the RTOG to obtain a randomization assignment and assignment of a unique patient ID. The CTSU will then contact the enrolling site and convey the patient ID number (*to be used on all future forms and correspondence*) and the patient's treatment assignment. This will be confirmed by a RTOG-generated confirmation of registration e-mail to the enrolling site, followed by the mailing of a data submission calendar and case-specific labels with the patient ID number.

5.4 NCIC CTG Investigators (12/3/01)

5.4.1 Ethical and Regulatory Requirements

The following documentation must be on file at the NCIC CTG central office prior to randomization:

- Documentation of full board REB approval of the protocol and consent form
- A copy of the REB approved consent form (*on institutional letterhead*)
Please note: The REB approved consent form must include all required NCI US elements. Upon request and time permitting, consent forms may be reviewed by the NCIC CTG central office prior to REB submission.
- REB membership (*consistent with OHRP membership requirements*)
- A completed NCIC CTG Confirmation of Initial Ethical Approval Form
- A completed NCIC CTG participant's list
- A current curriculum vitae for all investigators (*principal and additional investigators*)
- A current Cooperative Project Assurance (CPA) or Federal Wide Assurance (FWA) number

Documented annual re-approval of the study is required as long as there are patients being followed on the study. Annual re-approval must be full board until accrual is complete and all patients have completed protocol treatments and/or protocol mandated interventions.

Central Office Contacts:

Ms. Cathy Sears
Intergroup Trials Associate
NCIC Clinical Trials Group
82-84 Barrie Street, Queen's University
Kingston, ON
Canada K7L 3N6
Phone: 613-533-6430
Fax: 613-533-2812
E-mail: csears@ctg.queensu.ca

Dr. Lois Shepherd
Hematologic Pathologist
Physician Coordinator
NCIC Clinical Trials Group
82-84 Barrie Street, Queen's University

Kingston, ON
Canada K7L 3N6
Phone: 613-533-6430
Fax: 613-533-2911
Email: lshepherd@ctg.queensu.ca

5.4.2 Registration Procedure

Registrations for all NCIC CTG centres will be done through the NCIC CTG Central Office. Registrations will be accepted on Monday to Friday between 8:00 AM and 6:00 PM Eastern Time. The eligibility checklist must be completed prior to registration. Registration may be done by telephone (613-533-6430) or by fax (613-533-2812). Once eligibility is confirmed by the NCIC CTG, RTOG will be contacted by the NCIC CTG between 9:30 AM and 6:00 PM Eastern Time to obtain the treatment assignment. The NCIC CTG will then relay the treatment assignment to the centre and confirm it in writing.

6.0 RADIATION THERAPY

6.1 Protocol Therapy (Arm 2) (12/3/01, 1/15/02)

All patients randomized to the radiation treatment arm shall receive a total of 50.4 Gy to the entire breast in 1.8 Gy fractions x 28 fractions, **OR** a total of 50.0 Gy in 2 Gy fractions x 25 fractions, **OR** a total of 42.5 Gy in 2.656 Gy fractions x 16 fractions. Radiation treatment will be delivered in uniform daily doses through standard tangent fields Monday to Friday for 3½ to 5 ½ weeks. No boost will be used.

6.2 Dose Specifications

The dose will be prescribed to a point at the lung-chest wall interface according to the method outlined below. This prescription method ensures that the PTV (*entire breast volume plus margin*) receives a minimum dose equal to the prescription dose. The CTV (*entire breast volume*) will be defined during simulation with the patient in the supine treatment position by palpating the periphery of the breast tissue and marking it with radio-opaque markers, such as lead wire. In a patient with surgical clips placed in the tumor bed, the clips must be within the CTV. The planning target volume (PTV) is the CTV plus a margin of 1.0 to 2.0 cm, superiorly, inferiorly, medially and laterally. Tangent fields with a coplanar posterior border will be used (*Figure 1, Appendix VI*). The prescription point at the lung-chest wall interface is defined in the following manner: A contour of the external patient surface is obtained for a transverse plane passing through the isocenter. On the simulation film or DRR, the location of the contour plane is determined and the distance of the lung-chest wall interface from the posterior border in the contour plane is measured and demagnified (*See Point A in Figure 2, Appendix VI*). On the patient contour, a line is drawn through the isocenter and perpendicular to the posterior border of the tangential fields. A point is then placed along this line at the distance, A, of the lung-chest wall interface from the posterior border as measured on the simulation films or DRR's (*Figure 1, Appendix VI*). Care should be taken to consider any collimator rotation of the tangential fields when defining both the contour plane on the simulation film and the posterior tangent field borders on the contour. If a CT scan through the isocenter is available, it is always possible to mark point A directly without using a measurement from a DRR.

6.3 Technical Factors

6.3.1 Equipment must have nominal photon energies between 4MV and 8MV.

6.3.2 Compensators, wedges, or dynamic therapy must be used to keep the maximum PTV dose within 15% of the prescription.

6.3.3 The beam may be shaped, with a margin, to the shape of the breast with cerrobend-type blocking or by using a multi-leaf collimator.

6.3.4 Fields will be designed using a simulator unit or CT simulator with appropriate patient immobilization for daily accuracy. Use of an Alpha-cradle would be one example, a mammorex board is another.

6.4 Critical Structure Dose

The maximum distance from the posterior or deep field border to the lung/chest wall interface will be 3.0 cm anywhere in the field.

6.5 Treatment Interruptions

If a treatment interruption is necessary for acute radiation toxicity of the skin, aggressive treatment of the area with a product like Duoderm is encouraged to minimize the treatment break. The total time to deliver the radiation therapy should not exceed seven weeks.

6.6 Supraclavicular Field

The use of a third field to cover the supraclavicular area is not allowed.

6.7 Documentation

All treated fields require filming on simulator or CT simulator units. Portal verification must be done for all treated fields. Copies of both simulator and portal fields must be submitted to RTOG Headquarters as specified in Section 12.0.

6.8 Side Effects

Fatigue is the anticipated systemic reaction to radiation. Skin erythema and desquamation may also occur. Breast edema and tenderness and myositis are also acute side effects. Possible long term complications include radiation pneumonitis, rib fractures, and for left sided lesions, cardiac complications.

7.0 DRUG THERAPY

7.1 Tamoxifen (Nolvadex)

7.1.1 Animal Studies

In the rat, mouse, beagle dog, and rhesus monkey, maximal blood levels of tamoxifen are seen 1-6 hours and 24-44 hours after an oral dose. The drug is hydroxylated in the liver to a number of different compounds and excreted in the bile. After a conjugation, an extensive enterohepatic circulation exists, and the conjugated metabolites are hydrolyzed to the unhydrolyzed metabolite, reabsorbed, and reconjugated. Eventually, the drug is excreted in the feces in the metabolized form. Very little drug is excreted in the urine. Biophasic half-lives of 5-12 hours and 62-170 hours were seen in the animal experiments. The antiestrogenic properties of the metabolite are unknown; however, the monohydroxyl metabolite is thought to have activity. Tamoxifen has been shown to cause liver tumors in rats, when they receive doses 20-100 times the human dose.

7.1.2 Human Studies

Using a method incorporating ion pair extraction, photochemical activation, and chromatographic analysis, maximal blood levels of tamoxifen and metabolite are found to occur within 3-12 hours after a single dose of tamoxifen of 10 mg. Preliminary data indicate a half-life after a single dose in excess of 24 hours. Metabolism in humans is similar to animals but with extensive enterohepatic circulation. Half-life after prolonged 10 mg b.i.d. dosage is variable but appears to be between 4 and 14 days.

7.1.3 Human Toxicity

Toxicity attributable to tamoxifen is minimal and consists mainly of hot flashes (20%), transient nausea (10%), and vaginal discharge (9%). Vaginal bleeding, skin rash, and edema occur rarely. A mild leukopenia or thrombocytopenia will develop in up to 20% of the patients, usually during the second week of therapy, which resolves spontaneously within a week and does not require discontinuation of the drug. Hypercalcemia developed in approximately 1% of patients.

Analysis of data from NSABP P-1E, an ancillary study to NSABP B-14 designed to evaluate ocular toxicity in women taking tamoxifen, and the Breast Cancer Prevention Trial suggests that women taking tamoxifen may be at a slightly increased risk for developing cataracts. In addition, women who have a cataract prior to tamoxifen may be more likely to have cataract surgery. Other eye problems, such as corneal scarring or retinal changes, have been reported in a few patients.

An association between tamoxifen therapy and thromboembolic events has been supported by case reports, and the findings of decreased antithrombin levels in patients receiving tamoxifen in some, but not all studies. Data from a large prospective placebo-controlled adjuvant tamoxifen trial shows that the incidence of thromboembolic events was 0.9% in tamoxifen-treated patients versus 0.2% in patients receiving placebo.

In placebo controlled adjuvant tamoxifen trials, no hepatocellular tumors have been observed in over 3000 tamoxifen-treated patients and over 3000 patients who received placebo. In a Swedish adjuvant trial in which patients received 40 mg/day of tamoxifen, 2/931 (0.2%) cases of liver cancer were observed in contrast to 0/915 cases in patients treated with placebo.

Tamoxifen has an estrogenic effect on the endometrium and cases of endometrial cancer in women on tamoxifen have been reported. Some of these resulted in death. The incidence of endometrial cancer is 0.3% (9/3097) in patients receiving 20 mg/day of adjuvant tamoxifen, in contrast to 0.1 (4/3091) in patients treated with placebo. The incidence of endometrial cancer was higher (1.4% versus 0.2%) in a Swedish adjuvant study which treated patients with 40 mg/day of tamoxifen.

Other adverse reactions reported infrequently include distaste for food, depression, dizziness, and light-headedness. Unpublished data suggest a possible increase in second cancers of the gastrointestinal tract among women receiving tamoxifen, and there have been a few reports of liver cancer that have occurred in women taking tamoxifen.

7.2 Drug Formulation and Availability

7.2.1 Formulation (12/3/01)

Tamoxifen is supplied in 10 mg or 20 mg tablets.

7.2.2 Storage and Stability

The drug substance is stable for at least five years under normal storage conditions and should be protected from light and moisture. Minimal shelf-life appears to be two years.

7.2.3 Administration (12/3/01)

If the physician specifies that tamoxifen will be used, patients will receive tamoxifen 20 mg per day for five years.

7.2.4 Supplier

The drug is commercially available for purchase. This drug will not be supplied by the NCI. Tamoxifen is available from Zeneca, Wilmington, Delaware, under the trade name Nolvadex.

7.3 Adverse Reaction Reporting (12/3/01)

7.3.1 The revised NCI Common Toxicity Criteria will be used to score acute radiation (≤ 90 days) toxicities.

7.3.2 A copy of the CTC version 2.X can be downloaded from the CTEP Home page (<http://ctep.info.nih.gov>). All appropriate treatment areas should have access to a copy of the CTC version.

This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

7.3.3 All deaths within 30 days of completion or termination of protocol treatment regardless of cause.

7.3.4 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.

7.3.5 All life-threatening (*grade 4*) toxicities 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.

7.3.6 Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report (FAX# 215/928-0153).

7.3.7 A MedWatch Form must be submitted on all life threatening (*grade 4*) or fatal (*grade 5*) toxicities resulting from protocol therapy and submitted to RTOG Headquarters within 10 working days of the telephone report. An NCI AML/MDS Second Malignancy Form is required if the patient is diagnosed with Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS) during or subsequent to treatment on NCI/CTEP-sponsored clinical trials. The form is available at <http://ctep.info.nih.gov> (See Appendix V).

7.3.8 CALGB Investigators: Adverse Drug Reactions (ADRs) for CALGB patients will be routed through the CALGB Central Office. The CALGB Central Office (773-702-9860) must be called for all toxicities that need to be reported by telephone. All written reports must be submitted within five working days to the CALGB Central Office, 208 South LaSalle Street, Suite 2000, Chicago, IL, 60604-1104, for tracking purposes. The CALGB Central Office will forward these reports to RTOG Headquarters.

7.4 CTSU Investigators (8/18/00)

7.4.1 Adverse Event (AE) Reporting (10/15/04)

This study will utilize the CTC version 2.0 for toxicity and Adverse Event (AE) reporting. A hyperlink to the CTEP home page that contains CTC information is available on the CTSU website. CTSU investigators are responsible for reporting adverse events according to the RTOG guidelines, including notification of their local IRB. All reporting should be conducted within the timeframes specified in the protocol.

For those AE's requiring **24-hour phone notification**, the CTSU investigator is responsible for reporting the event within 24 hours to the following persons/entities:

- CTSU Data Center at 1-888-462-3009
- RTOG Primary Study Chairman (*see cover page of protocol*)

7.4.2 Secondary Malignancies Reporting

All CTSU investigators are required to report secondary malignancies occurring on or following treatment on NCI-sponsored protocols. Events should be reported according to the RTOG guidelines and conducted within the timeframes specified in the protocol. Completed forms (*including pertinent pathology and cytogenetics reports*) should be submitted to the CTSU. Once received, the CTSU will send the forms to RTOG who will forward them to the appropriate agencies.

7.5 NCIC CTG Investigators (12/3/01)

Adverse Reactions must be reported according to the definitions in Sections 7.3.1 to 7.3.5 on the NCIC CTG Serious Adverse Event Form by telephone (613-533-6430) and/or fax (613-533-2812) within 24 hours of the event. Any second malignancies or myeloid dysplasia must be reported in writing on a NCIC CTG Serious Adverse Event Form within 15 working days of when the diagnosis is known to the investigator.

Adverse Reactions will be forwarded to RTOG Headquarters by NCIC CTG as required.

8.0 SURGERY (8/18/00)

- 8.1** Patients will have completed all breast surgical procedures prior to accrual into this protocol in order to establish eligibility criteria. Surgical issues and considerations in the breast excision(s) are important and have been covered in the *Standards of Breast Conservation Treatment*,⁸ a 1992 consensus booklet published by the American Cancer Society for Professional Education. The technical surgical aspects for DCIS are similar to those for invasive cancer and concern the kind of anesthesia, needle localization technique, placement of incision, use of cautery and its effects on margin assessment, approximation of edges of the excisional cavity, clip placement to indicate site of excision, closure of the skin, and orienting the specimen in the operating room to orient it for pathologic evaluation.
- 8.2** A copy of this booklet can be obtained from RTOG (Fax 215-574-0300).

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY (12/3/01)

10.1 For All Patients (4/12/04)

- 10.1.1** Central pathology review is not planned for this protocol, however it is recognized that there are several significant issues related to the pathology of DCIS which have the potential to impact on the eligibility of patients for this trial.
- 10.1.2** The definition of "good risk" DCIS will utilize the guidelines accepted at a classification consensus conference of DCIS (*Appendix VII*). Patients will be ineligible if the DCIS is of high grade, greater than 2.5 cm in greatest diameter as measured on the preoperative mammogram or pathologic specimen, or with final pathologic margin < 3 mm.
- 10.1.3** High histologic grade will be defined by the presence of either of two features:
- 10.1.3.1** High nuclear grade, defined as nuclear size greater than 2.5 times lymphocyte or benign ductal epithelial cell nuclei, marked pleomorphism, irregular chromatin with single or multiple nucleoli and conspicuous mitoses.
- 10.1.3.2** Necrosis, defined by the presence of ghost cells with karyorrhectic debris, in one third or greater of the neoplastic ducts.
- 10.1.4** Relationship to the surgical resection margin is dependent on the surgical approach.
- 10.1.4.1** In cases where the surgeon submits separate samples from the wall of the biopsy cavity after removal of the excision specimen (*usually representing medial, lateral, superior, inferior, and deep aspects*), if no tumor is present in these biopsies, the margin will be considered adequate. The presence of tumor in any of these biopsies will be considered an inadequate margin for the purposes of this protocol.
- 10.1.4.2** In cases where no separate margin biopsies are submitted, the pathologist will ink the entire surface of the specimen. This may or may not employ multiple colored inks to aid in orientation. The narrow (*closest*) margin of the tumor to ink will be measured on the glass slide and must be greater than or equal to 3 mm for eligibility in this protocol.
- 10.1.5** In order to ensure reproducibility of histologic criteria, three tools will be employed in this study:
- 10.1.5.1** A "teaching" set of photomicrographs illustrating key diagnostic features of low/intermediate and high grade lesions has been prepared and is available on the RTOG website (www.rtog.org/qa/qa.html). This has been provided as a resource for the designated pathologist from participating institutions; however, mandatory credentialing is not a requirement for study participation.
- 10.1.5.2** A random sampling of 10% of cases will be reviewed by Dr. Sneige to assess the success of Section 10.1.5.1 in educating pathologists in the assignment of low or intermediate histologic grade as defined in this protocol. Any discrepancies identified will not render the patient ineligible but will provide information on the approximate frequency of undergrading in this study. **Material for**

central review must NOT be sent to RTOG (*Headquarters or Tissue Bank*) until requested by Dr. Sneige.

10.2 For Patients Participating in the Epidemiologic Component (Optional) (4/12/04)

10.2.1 Instructions for Plasma Collection and Handling (12/3/01)

Blood samples should be collected either before RT starts (Arm 2) or after registration (Arm 1). One purple top (*EDTA*) tube (*10 cc*) should be drawn, and the plasma separated from the cellular component by centrifugation. The plasma should be placed in a plastic freezing tube, which must be labeled with the patient's name, CALGB/RTOG patient numbers, CALGB/RTOG protocol numbers, date of collection, and specimen number. Samples should be stored at -20°C (*a standard refrigerator freezer*) until mailing.

Samples should be sent overnight express on dry ice. Be certain sufficient dry ice is in the mailing box to keep samples frozen for at least 48 hours. A completed original CALGB Form C-384, Specimen Routing Form (*for plasma*) should accompany each sample. A copy of Form C-384 will also be sent to RTOG, and a copy kept for your records.

Samples should not be sent on Fridays or on days before holidays. It is optimal to send samples in batches of 10-20 specimens for convenience and savings on shipping costs.

BE CERTAIN TO USE AT LEAST FIVE (5) POUNDS OF DRY ICE. ALSO, SHIP OVERNIGHT EXPRESS SO THAT SPECIMENS WILL NOT ARRIVE ON A WEEKEND OR HOLIDAY. SHIP TO:

**CALGB PCO
The Ohio State University
B054 Graves Hall
333 W. 10th Avenue Columbus, OH 43210
(614) 688-3495
Fax (614) 292-5618**

10.2.2 Instructions for Block Submission

One block shall be obtained by the participating institution to be submitted to the CALGB Pathology Coordinating Office (*PCO*). In cases where there are mixed types of DCIS, the highest grade areas should be submitted where possible.

The requested block must be labeled with the institutional surgical pathology number and should be sent in a properly packaged sturdy box along with copies of the original ER/PR report, institutional pathology report and consultative pathology reports (*if available*). A completed CALGB Tracking Form for Tissue Blocks (*C-490*) must also be sent with the above tissue specimens and pathology reports to the following address:

**CALGB PCO
The Ohio State University
B054 Graves Hall
333 West 10th Avenue
Columbus, OH 43210-1239
(614) 688-3495
Fax (614) 292-5618**

Please consider using a secure and temperature-safe method of packaging the specimens. Extreme heat precautions should be taken when packaging blocks. Use of a traceable shipping method is recommended. If the above requirements cannot be met, please include a detailed explanatory letter.

A copy of the C-384 (RTOG BS Form) and C-490 (RTOG PS Form) forms must also be sent to RTOG. Submitting institutions should also keep a copy of these forms for their records.

The CALGB has instituted special considerations for the small percentage (5%) of hospitals whose policy prohibits long-term storage of blocks, and the smaller percentage (4%) of hospitals whose policies prohibit release of any block. If due to institutional policy, a block cannot be sent, please call the CALGB PCO at 614-688-3495 to obtain a protocol to cut the sections at your institution. The CALGB PCO is committed

to being able to return blocks within 24 hours should the submitting institution need them for medical or medicolegal reasons.

The goal of the CALGB PCO is to provide investigators with quality histology sections for their research while maintaining the integrity of the tissue. All paraffin blocks that are to be stored at the PCO will be vacuum packed to prevent oxidation and will be stored 4°C to minimize degradations of cellular antigens. For these reasons it is preferred that the PCO bank the block until correlative studies have been initiated and the study investigator requests thin sections. Please contact the PCO if additional assurances are required by your hospital pathology department.

10.3 CTSU Investigators (12/3/01)

10.3.1 *Plasma Submission for Patients Participating in the Epidemiological Component, CTSU Investigators*
Blood samples should be collected before study treatment begins and shipped to the address in Section 10.2.1 of the protocol. A completed original Specimen Routing Form for Plasma C-384 (*RTOG-BS Form*) should accompany each sample. A copy of Form C-384 should also be sent to CTSU for forwarding to RTOG, and a copy kept for your records.

10.3.2 *Pathology Submission, CTSU Investigators*
All pathology materials are to be submitted directly to the CALGB Pathology Coordinating Office (*PCO*) according to instructions in Section 10.2.2 of the protocol. These should be accompanied by copies of the original ER/PR report, institutional pathology report, consultative pathology reports (*if available*) and a completed CALGB Tracking Form for Tissue Blocks C-490 (*RTOG PS Form*). Please submit a copy of all of the above-mentioned reports and forms to the CTSU for forwarding to RTOG, and keep a copy for your records.

10.4 NCIC CTG Investigators (12/3/01)

A limited sample of slides of patients on this study will be reviewed by a group of breast pathology experts. In addition to the possible request by RTOG for pathology material for central review (*as described in Section 10.1.5.3*), patients registered on this study will be asked for their consent to participate in Tissue Banking. Please refer to Section 10.2.2 of the protocol for a list of required forms and materials. At randomization, NCIC CTG will request submission of pathology materials as described in Section 10.2.2. The materials are to be clearly marked with the patient’s initials and NCIC CTG and RTOG patient and study numbers. **DO NOT INCLUDE PATIENT NAMES ON THE BLOCKS.** The blocks should be sent with a copy of the original ER/PR report and operative and pathology notes to:

**The NCIC CTG National Tumour Bank
Richardson Labs - Pathology 4th Floor
Queen's University
Stuart Street
Kingston, Ontario, Canada
K7L 3N6
ATTN: Mr. Troy Feener**

Please do not submit materials to RTOG.

Pathology material will be required at recurrence if available (*if biopsy is performed as part of normal patient care*). If the amount of tissue available is limited, unstained sections rather than paraffin blocks will be sufficient.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (12/3/01)

Procedure	Pre-Entry	Weekly During RT	In Followup
History & Physical	X		X ^a
Family History/Patient Epidemiological Questionnaire ^f	X		X ^d
Mammography	X ^b		X ^c
PreEntry Specimen Radiograph	X ^g		
Pathology	X		X ^e
Toxicity Evaluation		X	X ^a

- a. Visits may alternate between the radiation oncologist and the surgeon. Patient will be seen every 3 months from study entry for 1 year; q 6 months x 2 years, then annually. Also at progression/relapse and at death.
- b. Includes pre-biopsy and post-biopsy (*mag views also*).
- c. Yearly

- d. At 3 and 5 years.
- e. For local failure at study breast
- f. For patients who have consented to tissue/blood storage
- g. Recommended but not mandatory (*See Appendix VIII*)

11.2 Response

- 11.2.1** Local failure in the study breast will be defined as biopsy-proven recurrence in the quadrant of the original lesion, and classified as DCIS or invasive cancer.
- 11.2.2** Local failure in another quadrant, proven by biopsy, will be defined as a new primary lesion within the treated breast, and considered as another event within the treated breast.
- 11.2.3** Biopsy-proven failure in the skin of the treated breast will be defined as another event within the treated breast.
- 11.2.4** Distant failure will be defined as progression of the disease beyond the study breast and axillary lymph nodes, and should be proven by biopsy whenever possible.
- 11.2.5** Overall survival.
- 11.2.6** Mastectomy will be defined as removal of the study breast for any reason. Pathology of any lymph nodes removed during this procedure will be recorded, as well as any further therapy required.
- 11.2.7** Contralateral breast events.
- 11.2.8** Death from progression of disease.

12.0 DATA COLLECTION (4/12/04, 10/15/04)

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

12.1 Summary of Data Submission - All Patients

<u>Item</u>	<u>Due</u>
Initial Evaluation Form (I1)	Within 2 weeks of study entry
Diagnostic Pathology Report (P1)	
Pathology Form (P4)	
Surgical Operative Notes (S2)	
Surgical Pathology Report (S5)	
Specimen Radiograph Form (SP)	
 <u>Preliminary Dosimetry Information</u> (<i>Arm 2</i>)	 Within 1 week of start of RT
RT Prescription (<i>Protocol Treatment Form</i>) (T2)	
Films (<i>simulation and portal</i>) (T3)	
Calculations (T4)	
 <u>Final Dosimetry Information</u> (<i>Arm 2</i>)	 Within 1 week of RT end
Daily Treatment Record (T5)	
Isodose Distribution (T6)	
Treatment Form (TF)	Within 1 week of RT end
Initial Follow-up Form (FS) (<i>Arm 2</i>)	At 13 weeks from study entry.
Follow-up Form (F1) (<i>Arm 1</i>)	At 13 weeks from study entry.
Follow-up Form (F1)	At 6, 9, 12 months; then q 6 months x 2 years, then annually. Also at progression/relapse and at death.
Pathology Report (P1)	At local failure in study breast, if applicable.
Pathology Slides/Blocks (P2)	
Autopsy Report (D3)	As applicable

12.2 For Patients Who Have Agreed to Tumor and Blood Storage

Family History (PQ)	Within 2 weeks of study entry
Epidemiology Assessment (PF)	At 3 and 5 years.
Blood Specimen Form (BS) (CALGB C-384)	Copy, original per Section 10.2.1
Pathology Specimen Form (PS) (CALGB C-490)	Copy, original per Section 10.2.2

12.3 CALGB Institutions

CALGB participants should submit all non-RT data forms to the CALGB Data Management Center for forwarding to RTOG Headquarters. Dosimetry materials will be submitted directly to RTOG at the address in Section 12.1. The CALGB Data Management Center address is:

**CALGB Data Management Center
First Union Plaza, Suite 340
2200 West Main Street
Durham, NC 27705**

12.4 CTSU Investigators (12/3/01)

12.4.1 Data Submission (10/15/04)

All case report forms (CRFs) and other documents associated with this study must be downloaded from the protocol number Web page located on the CTSU registered member Web site (<http://members.ctsu.org>). CTSU investigators must use the current version of the protocol-specific RTOG-98-04 forms and adhere to the RTOG-98-04 schedule for data submission per protocol section 12.0. CRFs and associated reports must be submitted to the CTSU in the following manner:

- Patient entry CRFs should be faxed to the CTSU according to the instructions in the CTSU patient enrollment procedures section of this Appendix.
- Refer to protocol section 10.3 for instructions on submission of blood, pathology, and associated reports and transmittals. Please include the Patient ID, patient initials, and protocol number on all pages of the pathology report and redact the patient's name.
- Original and amended CRFs, reports, and responses to query and delinquency letters must be mailed directly to the CTSU Data Operations Center accompanied by a properly completed CTSU Data Transmittal Form; the CTSU will forward all data submissions to the RTOG.
- Copies of reports submitted to the CTSU must include the Patient ID and protocol number on all pages of the report. The patient's name must be redacted.

A CTSU Data Transmittal Form must accompany all data submissions. Data submitted with an improperly completed CTSU Data Transmittal Form or without a CTSU Data Transmittal Form will be returned to the site for corrective action without being processed. An RTOG study/case label should be affixed to all case report forms and source documentation.

Send data submissions to the below address:

Westat
CTSU Data Operations Center
1441 W. Montgomery Avenue
Rockville, MD 20850-2062
Phone: 1-888-823-5923
Fax: 1-888-691-8039

12.4.2 Radiation Therapy Documentation Submission Instructions, CTSU Investigators(4/12/04)

Dosimetry materials and data (*preliminary dosimetry information and final dosimetry information*) are to be submitted directly to the Dosimetry Department, RTOG, at the address in Section 12.1 of the protocol. Please note that there are two separate intervals for submission: preliminary data (*T2, T3, T4*) within 1 week of start of RT and final data (*T5, T6*) within 1 week of completion of RT. See Section

12.0 of the protocol for a complete inventory of dosimetry items to be submitted. Treatment Form (TF) is considered a case report form and should be sent to the CTSU Data Center for forwarding to RTOG. A copy of the Dosimetry Transmittal Form also should be sent to the CTSU for tracking purposes. Any dosimetry questions should be directed to the Dosimetry Department at RTOG headquarters (215) 574-3219.

12.5 NCIC CTG Investigators (12/3/01)

RTOG Case Report Forms (CRFs), with the header modified by the NCIC CTG for their use, will be used by all NCIC CTG institutions.

A single set of case report forms (CRFs) will be sent to each centre (*for photocopying and use*) following local activation. CRFs should be completed and submitted directly to the NCIC CTG Central Office according to the submission schedule in section outlined in the protocol. In addition to the required forms as listed, a copy of the signed consent form must be submitted for each patient. RTOG and NCIC CTG patient numbers as well as patient initials must be recorded on each form. CRFs will be forwarded to the RTOG by the NCIC CTG. Do not send CRF's directly to RTOG, with the exception of radiation and films and forms which should be sent directly to RTOG to the address specified in section 12.0

The NCIC CTG address for the submission of forms is:

**National Cancer Institute of Canada Clinical Trials Group
82-84 Barrie Street
Queen's University
Kingston, Ontario
K7L 3N6**

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint

Local recurrence is defined as either invasive or non-invasive local recurrence.

13.1.2 Secondary Endpoint

- Overall survival
- Time to distant metastasis
- Invasive local recurrence
- Salvage mastectomy rate

13.2 Sample Size Determination

13.2.1 Overview

The study is designed to evaluate the efficacy of the additional whole breast radiation plus tamoxifen compared to wide local excision plus tamoxifen with respect to local recurrence. Silverstein and et al.¹² have reported a long term experience of DCIS treated breast conservation therapy (*excision alone or excision plus radiation*). The 5-year local recurrence-free survival for Van Nuys classification group 1 (*non-high grade DCIS without comedo-type necrosis*) is about 95% ($n=132$). The 5-year rate for group 2 (*non-high grade DCIS with comedo-type necrosis*) is about 90% ($n=111$). For our study design, we hypothesized that the 5-year local recurrence rate for the control arm, wide excision plus tamoxifen, is 5% and 10% for low and intermediate grades DCIS, respectively. In addition, we presume that a 40% or more reduction in the 5-year local recurrence rate with radiation therapy is of clinical importance. Thus, the projected local recurrence rates in the radiation arm with tamoxifen, are 3% and 6% for the low and intermediate groups respectively.

The results of the NSABP B-24 trial indicated a statistically significant benefit from tamoxifen for "good risk" DCIS patients. With an average follow-up of 62 months, the study showed a 34% reduction in the annual risk of all breast cancer recurrence. For this study, we assume that the hazard rate for patients in both arms will be reduced 34% during and after the tamoxifen treatment. Thus, the radiation arm maintains its 40% reduction in hazard rate compared to the observation arm, although their local recurrence rates are decreased.

13.2.1.1 (12/3/01) The accrual to this study has been slower than anticipated with an average of 5 patients per month. This prompted discussions at the summer 2000 and winter 2001 RTOG meetings. An informal survey of the RTOG members indicated that there were several institutions where women did not go on to the study because they did not want the tamoxifen. NCIC agreed to join the study, *if* the tamoxifen is optional. The UK DCIS trial presented at ASCO 2000¹³ has not yet shown a benefit in local recurrence rates with the addition of tamoxifen. Based on all of these reasons, the RTOG Breast Committee proposed to make the tamoxifen optional. This recommendation was subsequently approved by the RTOG Data Monitoring Committee at its April meeting.

The study design was revised assuming that the nuclei grade distribution will be ½ low grade and ½ intermediate grade, and that 2/3 of the patients will receive tamoxifen and 1/3 will not. Under these assumptions, with the recurrence rates listed in Table 1 and a 40% or more reduction in the five-year local recurrence rate with radiation therapy deemed to be of clinical importance, we will be comparing five-year local recurrence rates of 6% for wide excision vs. 3.5% with the addition of whole breast irradiation.

Table 1

Local Recurrence Rates without Whole Breast Irradiation

	<u>Nuclei Grade</u>	
	<u>Low</u>	<u>Intermediate</u>
Tamoxifen	3%	7%
No Tamoxifen	5%	10%

13.2.2 *Number of Local Recurrence Events Required* According to Kim and Tsiatis' group sequential design approach¹⁴ to 3 treatment comparisons (2 interim and 1 final analyses) using two-sided logrank test statistics, a maximum of 121 local recurrence events is required to detect the hypothesized 40% reduction in hazard rate by the addition of radiation therapy with a statistical power of 80% and significance level of 0.05.

13.2.2.1 (12/3/01) Due to the revision making the tamoxifen optional, 129 local recurrence events will now be required.

13.2.3 *Sample Size and Accrual and Follow-Up Period* To acquire 121 local recurrence events, the sample size required in this study is determined by the accrual rate, the lengths of accrual period and follow-up period, and the projected hazard rates for both arms. The following table lists the total sample sizes for various accrual rates, considering a 1% annual loss to follow-up after year five of the study and a total of 10% of ineligible and lack-of-data cases.

<u>Accrual Rate</u> <i>(monthly)</i>	<u>Years of</u> <u>Accrual</u>	<u>Years of Follow-</u> <u>up</u>	<u>Total Sample</u> <u>Size</u>
22.4	7	5	1880
27.6	6	5	1990
35.0	5	5	2100

With other cooperative groups joining the study, we expect to accrue an average of 25-30 cases per month. Thus **1990 women are required to be uniformly entered within 6 years with additional 5 years of follow-up.** If the average monthly accrual rate is around 35 cases, the study can close in five years (*with a sample size of 2100*).

13.2.3.1 (12/3/01) The hazard rates for local recurrence will depend on the distributions of nuclei grade and tamoxifen use. The following table lists the total sample sizes for various combinations of nuclei grade and tamoxifen use distributions with six years of accrual and five years of follow-up.

Table 2

**RTOG 9804 – DCIS Study: Sample Sizes* (Number of Failures)
for Given Distributions of Tamoxifen Use and Nuclei Grade**

	Distribution of Low (L) to Intermediate (I) Nuclei Grade				
Distribution of Tamox(T) to No Tamox(NT)	70 L – 30 I	60 L – 40 I	50 L – 50 I	40 L – 60 I	30 L – 70 I
2/3 T – 1/3 NT	2089 (131)	1891 (128)	1790 (129)	1716 (133)	1583 (133)
1/2 T – 1/2 NT	1965 (132)	1790 (129)	1716 (133)	1535 (127)	1482 (130)
1/3 T – 2/3 NT	1836 (130)	1700 (130)	1582 (130)	1482 (130)	1433 (130)
100% T Original Design	---	---	1990 (121)		

* Includes 10% ineligible/lack of data cases.

13.2.3.2 (12/3/01) With the revisions to this study, we expect to accrue an average of 25 cases per month. Under the assumed nuclei grade and tamoxifen use distributions in Section 13.2.1, **1790 women are required to be uniformly entered within six years with an additional five years of follow-up.** If the average monthly accrual rate is around 30 cases, the study can close in five years.

13.3 Randomization

The treatment allocation scheme described by Zelen will be used. The stratifying variables are age (<50 vs. ≥50), margin (3-9 mm, ≥10 mm, negative) and tumor mammography size (≤1 cm, >1 cm).

13.3.1 (12/3/01) Nuclei grade (low, intermediate) and tamoxifen use (yes, no) will be added as stratification variables.

13.4 Treatment Effect on Overall Survival

Solin et al.¹⁵ have reported the 15-year results of 268 patients treated for DCIS of the breast using breast-conserving surgery plus definitive breast irradiation. They showed 98%, 94% and 87% overall survival at 5 years, 10 years and 15 years since the start of definitive breast irradiation, respectively.

To provide an answer to the treatment difference in overall survival for the patients in this trial, an additional five years of follow-up are necessary to obtain sufficient survival information.

Using the overall survival rates of Solin’s series and the assumption of a 1% loss of follow-up after year 5, the proposed sample size of 1990 (10 years follow-up) would detect a 33% reduction in annual death rate due to RT with a statistical power of 80%. To protect the type I error, the survival advantage will be tested using a two-sided logrank statistics with a significance level of 0.025. Specifically, a 33% reduction translates a 10-year overall survival improvement from 91% in the excision alone arm to 94% in the excision plus RT arm.

Note that since Solin's series included all subtypes of DCIS and without the use of tamoxifen, the real overall survival rates for the patients in this trial may be higher than we assumed. The consequence would be that the proposed sample size may detect a larger treatment difference in overall survival than we projected.

- 13.4.1 (12/3/01)** With the revised sample size of 1790 patients, allowing up to a total of 10% ineligible and lack-of-data cases, and assuming 1% loss to follow-up annually after year 5, the study could detect a 35% reduction in the annual death rate with 80% statistical power. In addition, a 33% reduction could be detected with 78% power. This equates to a ten-year survival improvement from 90.87% in the excision alone arm to 93.98% in the excision plus RT arm.

13.5 Epidemiological Considerations

Women registered in the study may opt for the epidemiological portion of the study by agreeing to bank tumor tissue and blood. The questionnaire includes information about personal health, family history, and personal habits. Patients who agree to participate will be followed to provide any subsequent changes.

Unlike most early epidemiology studies²⁰ that tried to establish the association between the incidence of breast cancer (*or DCIS*) and many risk factors, this study tries to investigate the potential risk factors that affect the treatment outcome, i.e., what increases the risk of developing local recurrence under one treatment. The risk factors include, not exclusively, age, race, age at pregnancy, menopausal status, breast cancer family history, body mass index and habits of cigarette and alcohol use.

We project that 30%-50% patients in the study will complete the epidemiological questionnaire. Thus, we expect to have 300-500 patients from each treatment arm to examine the risk factors proposed.

- 13.5.1 (12/3/01)** In this revision of the study, we expect to have 250-450 patients from each treatment arm to examine the epidemiological risk factors proposed.

13.6 Analysis Plan

13.6.1 Statistical Methods

Cumulative incidence methods¹⁶ will be used to estimate the 5-year rates of local recurrence, distant metastasis, and invasive local recurrence and salvage mastectomy. Overall survival will be calculated by Kaplan-Meier method¹⁷. The treatment effect by radiation therapy with respect to all the endpoints will be done using logrank test statistics¹⁸. All eligible and evaluable patients will be included in the intent-to-treat analysis.

Cox's proportional hazards models¹⁹ will be utilized in analyzing the risk factors proposed in epidemiological considerations.

13.6.2 Interim Reports(4/12/04)

Interim reports are prepared every six months until the closure of the study. In general, the interim reports will include:

- the patient accrual rate including the rates in each stratum;
- treatment compliance
- the frequencies and severity of the toxicities.

- 13.6.2.1 (12/3/01)** The nuclei grade and tamoxifen distributions will be reported every six months:

- Two years after tamoxifen becomes optional, the distributions of nuclei grade and tamoxifen use will be evaluated and if necessary, a recommendation will be made to the data monitoring committee to change the sample size accordingly.
- If the difference between low and intermediate grade is more than 10% in favor of the low grade, then it will be recommended to the DMC to increase the sample size.
- If the use of tamoxifen is closer to 1/3, then it will be recommended to the DMC to decrease the sample size.

13.6.3 Interim Analysis for Early Stopping

Two such interim analyses shall be performed when we observe 25% and 67% of the 121 required local recurrences. The first interim analysis is projected to take place when 70% total accrual is reached. The second interim analysis is projected to take place at the third year (*2 years after the closure*) during follow-up. For each of these interim analyses, toxicity, treatment delivery and efficacy statistics will be reported to the RTOG DMC. The boundary for early stopping (*or the nominal significance level for the test*) will be computed based on the observed number of local recurrence events according to alpha spending function approach. If the difference is highly significant, i.e., across the boundary or p value less than the nominal level, the responsible statistician will recommend to the DMC that the study be closed (*if open at the time*) and be written up for publication.

- 13.6.3.1 (12/3/01)** The two interim analyses now will be performed when we observe 25% and 75% of the 129 required local recurrences. The first interim analysis is projected to take place when 63% of total accrual is reached. The second interim analysis is projected to take place with one year of follow up (*1 year after closure*).

13.6.4 The First Analysis for Reporting Treatment Effects The analysis will be done after the end of the follow-up period or 121 local recurrence events are observed (*see Section 13.2.3*) unless the study is stopped early according to Section 13.6.3. The report should be able to answer the questions about the primary endpoint that is whether excision plus tamoxifen and radiation improves the local control of DCIS breast cancer compared to excision and tamoxifen.

13.6.4.1 (12/3/01) The analysis now will be done after the end of the follow-up period or when 129 local recurrence events are observed.

13.6.5 The Second Analysis for Reporting Treatment Effects in Survival Outcome
The survival analysis will be done when each patient in the study has been followed for at least 10 years. Besides giving updated information in local control and other disease status, it should provide a more definitive answer to the treatment effect on overall survival status of the patients.

13.7 Inclusion of Minorities

In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we have also considered the possible interaction between race and treatments. Based on RTOG breast studies (*RTOG 83-06 and RTOG 97-02 [CALGB 9343]*), we project that 90% of women in the study will be white, 5% will be black (*not of Hispanic origin*), 1.5% will be Hispanic, 3% will be Asian or Pacific Islander, and 0.5% will be American Indian or Alaskan Native. The following table lists the projected accrual for each group. If this percentage remains the same in women who have had local recurrences at the time of analysis, the statistical power for detecting the hypothesized difference is 77% and 14% for white and non-white, respectively. With a projected 13 local recurrence events in non-white population, we will be able to detect a 73% hazard reduction by radiation therapy for the subset of non-white with statistical power of 50%.

Planned Gender and Minority Inclusion

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female	9	60	100	30	1791	0	1990

The projected number of local recurrence events in the non-white population is now 14. The revised Planned Gender and Minority Inclusion Table is below: (12/3/01)

Planned Gender and Minority Inclusion

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female	8	54	90	27	1611	0	1790

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APPENDIX I-A

RTOG 98-04

**PHASE III TRIAL OF OBSERVATION +/- TAMOXIFEN VS. RT +/- TAMOXIFEN FOR
GOOD RISK DUCT CARCINOMA IN-SITU (DCIS) OF THE FEMALE BREAST**

SAMPLE CONSENT FOR RESEARCH STUDY

THERE IS A RESEARCH STUDY ABOUT YOUR CONDITION AND ITS TREATMENT. THIS CONSENT FORM WILL TELL YOU ABOUT THIS STUDY AND HOW THE TREATMENT MAY OR MAY NOT HELP YOU.

IT IS IMPORTANT THAT YOU READ AND UNDERSTAND THIS FORM, THE STUDY AND THE TREATMENT BEFORE YOU DECIDE TO BE PART OF THIS STUDY. IF YOU HAVE ANY QUESTIONS ABOUT THIS STUDY, THE TREATMENT OR HOW IT WILL AFFECT YOU, PLEASE ASK YOUR DOCTOR.

RESEARCH STUDY

You have the right to know about the procedures used in this research study and the risks, benefits and alternatives to the treatment in this study. You should know and understand the treatment proposed in this study, how it will be given, how the treatment may help you, how the treatment may harm you, and the choices available to you. This form will tell you about the study, the benefits, the risks and the alternatives so you can decide whether to be a part of this research study.

PURPOSE OF THE STUDY (12/3/01)

You have been diagnosed with a breast cancer in the very early stage. Radiation therapy, a form of cancer treatment using high-energy x-rays, may decrease the chance of a breast cancer coming back in your breast. The anti-estrogen hormone tamoxifen also may be appropriate for your condition after a surgeon has carefully removed this small cancer. It has recently been shown that tamoxifen reduces the risk of this cancer returning. Your physician and you will decide if your treatment will include tamoxifen. In this study, observation with or without tamoxifen will be compared to breast radiation therapy with or without tamoxifen.

Also, a small part of the tissue removed by your surgeon and one tube of blood will be stored for future research. In the future, this may be able to predict which women may get this kind of cancer. It may also predict which women with this kind of cancer will benefit from the different treatments available.

DESCRIPTION OF PROCEDURES (1/15/02)

This study involves at random (*by chance*) assignment to one of two treatment arms. It is not clear right now which of the two is better. For this reason the therapy that is to be offered to you will be based upon a method of selection called randomization. Randomization means that your physician will call a statistical office that will assign you one of the two treatments by computer. The chance of receiving one of the two treatments is approximately equal.

If your doctor and you decide that your treatment will include tamoxifen, you will be assigned to one of the following:

After post-operative evaluation of your breast tissue by a pathology doctor and a post-operative mammogram of your involved breast show that all signs of the cancer have been removed, you will receive tamoxifen every day for five years. You will be carefully observed by physical examinations and yearly mammograms.

OR

After post-operative evaluation of your breast tissue by a pathology doctor and a post-operative mammogram of your involved breast show that all signs of the cancer have been removed, you will receive 16-28 treatments of radiation to your involved breast. It will be given once a day for five days a week (*except Saturday and Sunday*) for 3½ to 5½ weeks. You

will also take tamoxifen every day for five years. You will be carefully observed by physical examinations and yearly mammograms.

If your doctor and you decide that your treatment will not include tamoxifen, you will be assigned to one of the following:

After post-operative evaluation of your breast tissue by a pathology doctor and a post-operative mammogram of your involved breast show that all signs of the cancer have been removed, you will be carefully observed by physical examinations and yearly mammograms.

OR

After post-operative evaluation of your breast tissue by a pathology doctor and a post-operative mammogram of your involved breast show that all signs of the cancer have been removed, you will receive 16-28 treatments of radiation to your involved breast. It will be given once a day for five days a week (*except Saturday and Sunday*) for 3½ to 5½ weeks. You will be carefully observed by physical examinations and yearly mammograms.

You are being asked to also donate a small amount of the tissue removed at the time of surgery, and one tube of blood, to a tissue bank. At some time in the future, when biology research doctors know best what “markers” to look for, the tests which might predict how a patient with tumors like yours respond to a treatment, will be carried out at no additional cost to you. If you agree to this, you must sign a separate consent form for this purpose. You will also be asked to complete a questionnaire about your health, family history, and whether you smoke or drink. You will complete one questionnaire when you join the study. The next one will be done three years later. One more will be required two years after that. Your answers may provide information about how possible risk factors affect your health.

RISKS AND DISCOMFORTS

Cancer treatments often have side effects. The treatment used in this study may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Tamoxifen

Adverse reactions to tamoxifen are infrequent. They are seldom severe enough to require discontinuing treatment. The following information discusses the side effects that have been observed:

Frequent Side Effects: hot flashes, nausea and/or vomiting, menstrual irregularities including vaginal bleeding, vaginal discharge, and dryness.

Secondary Cancer

1. Endometrial cancer - Tamoxifen may cause changes in the lining of the uterus. An early sign of these changes may be abnormal vaginal bleeding or pelvic pain. You should report such symptoms to your physician immediately. The level of increased risk of uterine cancer associated with tamoxifen is still uncertain. After an average of 8 years of follow-up, the annual (*per year*) risk observed in a large-scale trial of breast cancer patients taking 20 mg of tamoxifen daily is about 2 per 1,000 women. This means that on the average, two cases of endometrial cancer were diagnosed among every 1000 women receiving tamoxifen during each year of the study and follow-up. This level of risk is approximately three times greater than that of a similar group of women in the general population. Uterine cancer may be life-threatening illness. Some breast cancer patients who develop uterine cancer while taking tamoxifen in the above studies have later died from uterine cancer. However, most of these cancers have been diagnosed at an early stage when treatment is highly effective. The treatment is surgical removal of the uterus, fallopian tubes, and ovaries. Radiation therapy may also be necessary. In view of this risk, it is recommended that all patients receiving tamoxifen have a pelvic exam before starting treatment and at least yearly thereafter. If you have already had a total hysterectomy, there is no risk of getting uterine cancer.
2. Other cancers - One large U.S. study showed no increase in other (*non-uterine*) cancers in women taking tamoxifen. However, other unpublished data suggest a possible increase in second cancers of the gastrointestinal tract among women receiving the drug. There have been a few reports of liver cancer. Although tamoxifen can cause liver cancer

in rats, it is not known to be a cause of liver cancer in humans. Whether an increased risk for other (*non-uterine*) cancers is associated with tamoxifen is still uncertain and continues to be studied.

Infrequent Side Effects:

Blood Clots - Some studies have shown that tamoxifen causes an approximate 1% increase in inflammation or blood clots in the vein and pulmonary embolism (*loss of blood flow to the lungs*). Rarely, death has occurred from such events. Patients with an existing history of such problems should discuss tamoxifen treatment carefully with their physician.

Liver toxicity - Abnormal liver function tests including rare cases of more severe liver abnormalities such as fatty liver, cholestasis (*back up of bile*), hepatitis, and hepatic necrosis (*destruction of liver cells*) have been observed. A few of these serious cases resulted in death but whether tamoxifen was the cause of these problems is uncertain.

Eye changes - Women taking tamoxifen may be at a slightly increased risk for developing cataracts (*a clouding of the lens inside the eye*). As women age, they are more likely to develop cataracts whether or not they take tamoxifen. Cataracts may lead to a decrease in vision. Eye surgery may be required to remove the cataract and improve vision. Women who have a cataract before beginning to take tamoxifen may be more likely to have cataract surgery. Other eye problems, such as corneal scarring or retinal changes, have been reported in a few patients. You must report any changes in your vision, or other eye problems, to your physician.

Endometrial (*uterine lining*) changes including polyps, hyperplasia (*tissue thickening*), and endometriosis (*endometrial cells outside the uterus*), or a decrease in platelet counts making you more prone to bleeding. Bone and tumor pain and sometimes high calcium occurred in those patients treated for metastatic disease. Patients with increased pain requires more or stronger pain relievers. Often such symptoms signaled a good response to treatment and these symptoms usually went away quickly.

Other infrequent side effects include skin rash, swelling of your hands or feet, genital itching, depression, dizziness and light-headedness, headache, hair thinning and/or partial hair loss. Ovarian cysts have been noted in premenopausal women.

Radiation Therapy

Radiation therapy may cause 1) **Fatigue**: tiredness for no apparent reason is a temporary effect going away within a month or two after completion of radiation. 2) **Skin damage**: within the area of radiation, the skin may develop a sunburn-like area within 2-6 weeks after treatment. This will go away. The skin may also become slightly thick compared to skin on the untreated breast. Treated skin will also be more sensitive to sun exposure in the future. 3) **Swelling**: the breast will feel heavy, almost like a pre-menstrual breast, during treatment and for several months afterwards. 4) **Muscle tightness**: muscles in the chest wall under the treated breast can sometimes feel "sore" or tight during and after radiation treatments. 5) Although uncommon, radiation may cause a cough and difficulty breathing in that part of the lung under the treated breast. A radiologist may see a slight change in this part of your lung on chest x-ray or CT scan or similar imaging of your chest. It is very unlikely that this will cause any decrease in exercise tolerance. 6) Although uncommon, pericarditis, (*irritation of the sac surrounding the heart*), myocarditis (*irritation of the heart muscle*), or rib fractures may occur long after completion of the radiation treatments.

Your physician will be checking you closely to see if any of these side effects are occurring. Side effects usually disappear after the treatment is stopped. In the meantime, your doctor may prescribe medication to keep these side effects under control.

COSTS

Routine scans will be done to evaluate your breasts. If injury occurs as a result of this research, treatment will be available. The use of medication to help control side effects could result in added costs. This institution is not financially responsible for the treatment of side effects caused by the study treatment. You will not be reimbursed for medical care other than what your insurance carrier may provide. You will not be paid for your participation in this research study.

CONTACT PERSONS

(This section must be completed)

For information about your disease and research-related injury, you may contact:

Name	Telephone Number
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For information about this study, you may contact:

Name	Telephone Number
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For information about your rights as a research subject, you may contact:

(OPRR suggests that this person not be the investigator or anyone else directly involved with the research)

Name	Telephone Number
------	------------------

ALTERNATIVES

Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) tamoxifen; (3) surgery; or (4) no treatment. These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. You should discuss your condition and the expected outcome with your doctor. Your doctor will be available to answer any questions. You are encouraged to ask your doctor any questions you have about this research study and the choices of treatment available to you. If you have any questions at all, please ask your doctor.

If your disease becomes worse, if side effects become very severe, or if developments occur that indicate the research study is not in your best interest, the treatment would be stopped. Further treatment would be discussed at that time.

BENEFITS

Tamoxifen has been shown to decrease the risk of breast cancer coming back after surgery. For this reason, it was approved by the Food and Drug Administration for treatment of postmenopausal women with breast cancer. It is also approved for treatment of metastatic breast cancers in women and men. Studies have also shown that tamoxifen can reduce the occurrence of second breast cancers. In addition, it has been shown to lower the level of cholesterol and other fats in the blood. This may reduce the risk of heart disease. Loss of bone minerals is also slowed by tamoxifen. This may result in fewer bone fractures as women age. Also, radiation has been shown to dramatically decrease the risk of cancer returning within the breast after breast-conservative surgery.

The information from this study may also help others by providing information about your type of cancer and its response to treatment. The information will be used scientifically. A possible personal benefit of this research study may be a decreased risk of disease recurrence and a longer survival. None of these possible benefits is certain or guaranteed.

VOLUNTARY PARTICIPATION

You do not have to take part in this research study. You are free to withdraw or withhold your consent from taking part in this research study at any time. If you refuse to participate, there will be no penalty or loss of benefits. You may seek care from a doctor of your choice at any time. If you do not take part in this study or if you withdraw from the study, you will continue to receive care.

CONFIDENTIALITY (8/18/00)

Records of your progress while on the study will be kept in a confidential form at this institution and 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 this study may have access to medical records that contain your identity. If you are participating in this study through the Cancer Trials Support Unit (*CTSU*), a record of your progress will also be kept by the CTSU. However, no information by which you can be identified will be released or published.

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient Signature (*or legal Representative*)

Date

TISSUE AND BLOOD TESTING

I agree to the use of my blood and tumor tissue and have signed a separate consent form for that purpose.

Yes

No

Patient Signature (*or legal Representative*)

Date

If yes, a signed and dated form must be attached to this form.

APPENDIX I-B

RTOG 98-04

PHASE III TRIAL OF OBSERVATION +/- TAMOXIFEN VS. RT +/- TAMOXIFEN FOR GOOD RISK DUCT CARCINOMA IN-SITU (DCIS) OF THE FEMALE BREAST

CONSENT TO COLLECT AND STORE BLOOD AND TUMOR TISSUE

The RTOG would like to keep some of your blood and tumor tissue that is not needed for your care. If you agree, the RTOG will keep the samples in a specimen bank. They may be used in future research to learn more about cancer. Researchers are trying to learn more about cancer, such as what causes cancer, how to prevent it, how to treat it better, and how to cure it. Causes of cancer may come from the environment or from genetic causes. Genetic causes are causes that people are born with and that can also affect other family members. Your cancer may come from one or both of these causes. You may be concerned that research about genetic causes may give information not only about yourself, but also about your relatives and other groups of people who are like you. If genetic testing is done on samples from the bank, the testing will be done with only coded samples so that your identity remains unknown. Because the value of the research is not known at this time, and the researcher will not know who you are, your results will not be given to you or your doctor. Even if the research that is done on your blood and/or tissue cannot be used to help you, it might help other people who have cancer or other medical problems.

The RTOG will be responsible for making sure your samples and information are protected and kept confidential in the specimen bank. Your samples will be given a code number to protect your identity. The samples will only be given to researchers approved by the RTOG. The research study must also be approved by the Institutional Review Board (*IRB*) at your hospital. An IRB is a group of people who look after the rights and welfare of people taking part in research.

The choice to let the RTOG keep your blood and tissue for doing research is up to you. **No matter what you decide to do, it will not affect your care.** If you decide that your blood and tissue can be kept for research but you later change your mind and tell your doctor, the specimen bank will destroy any of your samples that they still have. Otherwise, the blood and tissue may be kept until they are used up, or until the RTOG decides to destroy them.

The people who use your samples to do research may need to know more about your health both before and after your tamoxifen and radiation treatment (*if you are assigned to radiation treatment*). You will be asked to complete a questionnaire about your family history three times: at study entry, then 3 years later, then 2 years after that. If researchers ask for reports about your health, the RTOG will not provide them with your name, address, or phone number unless you are willing to be contacted in the future to take part in more research. There are laws that require that research records that have your name on them be shown to people who make sure that the research is being done correctly. As mentioned before in this consent form, the RTOG, the NCI, and the FDA will be allowed to review and copy your medical records as related to this research.

Your blood and/or tissue will be used only for research and will not be sold. Some new products might be made because of the results of the research that uses your samples. These products might be sold sometime in the future, but you will not get paid. There will be no cost to you for any specimens collected and stored in the RTOG specimen bank.

(continued on next page)

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all predisease activities without restriction (<i>Karnofsky 90-100</i>).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (<i>Karnofsky 70-80</i>).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (<i>Karnofsky 50-60</i>).
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (<i>Karnofsky 30-40</i>).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (<i>Karnofsky 10-20</i>).

APPENDIX III

AJCC STAGING SYSTEM BREAST, 5th 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 <i>in situ</i> : intraductal carcinoma, lobular carcinoma <i>in situ</i> , or Paget's disease of the nipple with no tumor.
T1	Tumor 2 cm or less in greatest dimension
T1mic	Microinvasion 0.1 cm or less in greatest dimension
T1a	Tumor more than 0.1 but not more than 0.5 cm in greatest dimension
T1b	Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
T1c	Tumor 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 size with direct extension to (a) chest wall or (b) skin, only as described below.
T4a	Extension to chest wall
T4b	Edema (<i>including peau d' orange</i>) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
T4c	Both (<i>T4a and T4b</i>)
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 (<i>e.g., previously removed</i>)
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 (<i>e.g., previously removed, or not removed for pathologic study</i>)
pN0	No regional lymph node metastasis
pN1	Metastasis to movable ipsilateral axillary lymph node(s)
pN1a	Only micrometastasis (<i>none larger than 0.2 cm</i>)
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

APPENDIX III (cont'd)

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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 (<i>includes metastasis to ipsilateral supraclavicular lymph node[(s)]</i>)

STAGE GROUPING

Stage 0	Tis	N0	M0
Stage I	T1*	N0	M0
Stage IIA	T0	N1	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

* Note: T1 includes T1mic

** 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 supersede 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 (\geq *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 (\geq *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 10 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

EXAMPLE OF A TREATMENT PLAN USING WEDGES AND TWO TANGENT FIELDS:

Transverse Section at the Level of the Breast

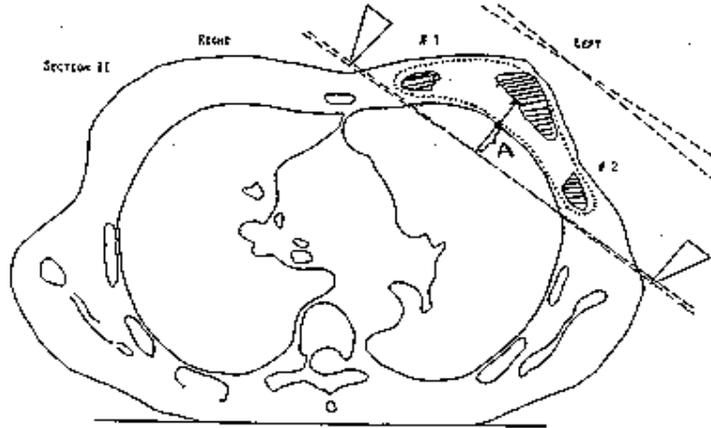


Figure 1: Modified from ICRU Report 50: Prescribing, Recording, and Reporting Photon Beam Therapy. Issued: 1 September, 1993. "A" indicates distance of lung-chest wall interface prescription point from posterior border. The position of "A" is determined from the simulation films as indicated in Figure 2 below. Dotted lines indicate the CTV. Shaded areas indicate expected regions of inhomogeneity.

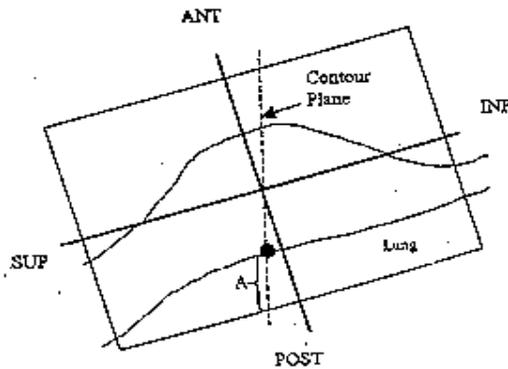


Figure 2: Diagram of simulator film indicating the determination and position of the lung-chest wall interface prescription point "A".

APPENDIX VII (8/18/00)

Classification of Ductal Carcinoma In Situ⁹

A. Low grade nuclei (NG 1)

Appearance: Monotonous (*monomorphic*)
Size: 1.5-2.0 normal RBC or duct epithelial cell nucleus dimensions
Features: Usually exhibit diffuse, finely dispersed chromatin, only occasional nucleoli and mitotic figures. Usually associated with polarization of constituent cells.
Caveat: The presence of nuclei that are of similar size but are pleomorphic precludes a low grade classification.

B. High-grade nuclei (NG 3)

Appearance: Markedly pleomorphic
Size: Nuclei usually >2.5 RBC or duct epithelial cell nuclear dimensions
Features: Usually vesicular and exhibit irregular chromatin distribution and prominent, often multiple nucleoli. Mitosis may be conspicuous.

C. Intermediate grade nuclei (NG 2)

Nuclei that are neither NG 1 nor NG 3

Necrosis Quantification

Comedonecrosis: Any central zone necrosis within a duct, usually exhibiting a linear pattern within ducts if sectioned longitudinally.
Punctate: Non-zonal type necrosis (*foci of individual cells necrosis visible under 10X, 40X is not needed*)

APPENDIX VIII

RECOMMENDED METHOD OF PATHOLOGIC EVALUATION (12/3/01)

A. Specimen Handling:

A flow diagram for this procedure is outlined in Figure 1.

The breast specimen when received should be measured and grossly inspected for any orientation designated by the surgeon. The specimen, still intact, should be placed on an x-ray plate and a radiograph should be taken. The radiograph should be evaluated with comparison to the patient's mammogram, which showed the suspicious microcalcifications and/or abnormal soft tissue densities (*ASTD*). This is best evaluated by a radiologist. If calcification/*ASTD* are identified which correspond to those observed mammographically, the surgeon should be informed immediately as the procedure is finished. If no calcifications or *ASTDs* corresponding to those seen on mammogram are identified, then a second radiograph of serial sections should be reviewed before proceeding with any further surgery. The oriented breast specimen should then be inked (*multiple colors may be used to identify various margins of resection.*) Tissue is sequentially sectioned in 3-5 mm thick sections and laid down, in order, on an x-ray plate (*keeping coherent orientation*). A second radiograph is taken and evaluated for the presence of microcalcifications and/or *ASTDs*. If calcifications or *ASTDs* corresponding to the mammogram are not identified, additional tissue must be removed after relocalization procedure. If corresponding calcifications or *ASTDs* are identified, no further procedure is required.

It is strongly suggested that no frozen sections of these tissue specimens be performed (*unless an identifiable lesion of adequate size [more than 1 cm] becomes apparent with serial sectioning*). These specimens should be examined on permanent sections. For relatively small specimens (*less than 5 cm in diameter*), all of the tissue specimen can be easily submitted for evaluation. Comparison of serial tissue sections with the corresponding radiograph should allow identification of tissue segments, which contain microcalcifications and/or *ASTDs*. The cassettes into which these areas are submitted should be identified in the gross dictation. For larger specimens, permanent sections should include 1) all areas containing microcalcifications and/or *ASTDs*; 2) all areas of fibrous parenchymal tissue 3) tissue margins of resection.

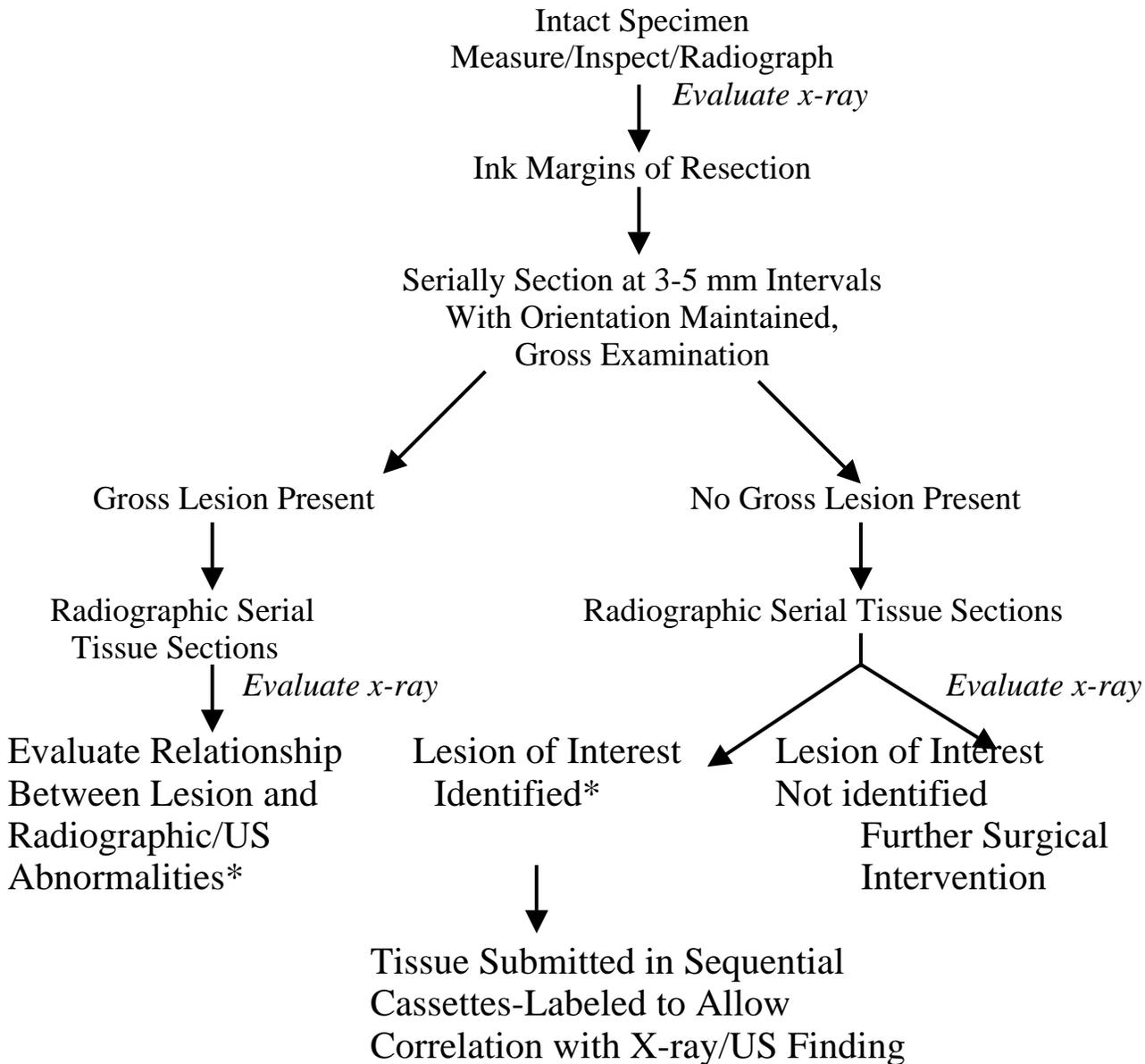
B. Microscopic Examination:

Microscopic examination should include the following:

- 1) Extent of DCIS – Provide the number of sections containing DCIS as well as the largest dimension of DCIS lesion on a glass slide
- 2) Nuclear Grade – See the grading system in Appendix VII. The system is based on the Consensus Conference on the Classification of DCIS.
- 3) Necrosis – Necrosis is defined by the presence of ghost cells and necrotic debris and is categorized as central or punctate (*see below for definition*).
- 4) Margins of Resection – Record closest margin as: $\geq 3\text{-}9\text{mm}$, $\geq 10\text{ mm}$, or a re-excision margin
- 5) Cell Polarization – Reflects the radial orientation of the apical portion of the tumor cells towards intercellar (*lumen-like*) spaces. Polarization is characterization of low-grade cribriform DCIS, bridges, arcades and micropapillae
- 6) Architectural Pattern – These include comedo, cribriform, papillary, micropapillary and solid. They should be listed in order of decreasing amounts, and the notation made that there are several patterns
- 7) Calcifications – State the relationship of any calcifications or *ASTDs* to the DCIS

APPENDIX VIII (cont'd)

Figure 1: PATHOLOGIC EVALUATION OF BREAST SPECIMENS



* Lesion at margin: Additional tissue should be removed and submitted as a new margin