UMSylvester
Comprehensive Cancer Center

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PHASE I TRIAL ASSESSING THE SAFETY AND FEASIBILITY OF PROPHYLATIC NIPPLE-AREOLA COMPLEX (NAC) IRRADIATION AFTER NIPPLE-SPARING MASTECTOMY AND IMMEDIATE RECONSTRUCTION IN PATIENTS WITH IN-SITU OR INVASIVE BREAST CANCER

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PROTOCOL SUMMARY

Overall rationale: Prophylactic NAC irradiation after nipple-areola sparing mastectomy and immediate reconstruction for patient with ductal carcinoma in-situ or invasive breast cancer will allow better cosmesis and patient's satisfaction.

Study design: Phase I trial assessing the safety, feasibility and toxicity of prophylactic NAC irradiation after nipple-areola sparing mastectomy and immediate reconstruction in patients with ductal carcinoma in-situ or invasive breast cancer.

Primary objective: To determine the recommended phase I dose of post-operative prophylactic NAC irradiation.

Secondary objectives: To provide extensive descriptive data regarding NAC-sparing surgery with reconstruction, including both surgeon experience and patient evaluation of cosmetic results. Survival and recurrence will be assessed.

Study size: Between 12 and 18 patients will be enrolled in the dose-escalation/de-escalation part of this phase I study. An additional ***expansion cohort of 12 patients*** will be enrolled at the **"potential" recommended phase II dose (RP2D)** over an expected accrual period of 2 years.

Treatment plan (07-15-2011)

Week 1	NAC-sparing mastectomy with immediate reconstruction
Between weeks 5 to 8	Prophylactic NAC irradiation twice daily, minimum of 4 hours apart, **for 5 days**, preferable in consecutive working days
2 weeks after irradiation	Chemotherapy, if indicated, at the discretion of the treating physician

Dose escalation/de-escalation design (section 4.2) (07-15-2011)

Dose levels†	Description
Dose Level I = 20 Gy	10 fractions of 2.0 Gy
Dose Level II = 25 Gy (starting dose)	**10 fractions of 2.5 Gy**
Dose Level III = 30 Gy	10 fractions of 3 Gy
Dose Level IV = 35 Gy	10 fractions of 3.5 Gy
† Treatment will be delivered twice a day, minimum of 4 hours apart, **for 5 days**, preferable in consecutive working days.	

The patients will be receiving postoperative NAC irradiation **starting at Dose level II**.

DLT (dose-liming toxicity), as defined in section 4.2.6, will be evaluated during radiation treatment period plus an **additional observation period of 30 days** following completion of NAC radiation.

A **modification of standard dose-escalation design,** treating cohorts of 2 to 6 patients per dose level of NAC irradiation, will be used. The main features of the proposed escalation design is that (1) no more than 2 patients will experience DLT at a given radiation dose and (2) escalation to a higher dose occurs only after a cohort of 6 patients have been evaluated at a given radiation dose.

Dose escalation/de-escalation rules	
Number of patients with DLT at a given dose level	**Escalation Decision Rule**
0 or 1 out of 6 patients	Enter 6 patients at the next higher dose level.
2 out of 2 to 6 patients	Dose escalation stops. However, if the dose tested is dose level II, the starting dose level, then de-escalation occurs. In this case, dose level I will be tested in 2 to 6 patients.
The highest dose tested at which ≤ 1 out of 6 patients experiences DLT will be declared the MTD and it will be the **recommended phase II dose**.	

Expansion cohort (section 4.2.7)

An additional ***expansion cohort of 12 patients*** will be enrolled at the **"potential" recommended phase II dose (RP2D)** over an expected accrual period of 2 years.

(See section 4.2 for further details.)

HYPOTHESIS:

- The use of NAC-sparing mastectomy followed by postoperative NAC (nipple-areola complex) external beam radiotherapy for selected patient with early stage invasive or in-situ breast cancers will be technically feasible and with acceptable complication rates.
- The cosmetic results after NAC-sparing mastectomy followed by postoperative external beam radiotherapy to the NAC will be better comparable with Skin Sparing Mastectomy.
- The local control rate in the NAC will be more than expected for a NAC sparing mastectomy without postoperative radiotherapy.
- The patient's satisfaction after NAC-sparing mastectomy followed by postoperative NAC external beam radiotherapy will be better than after Skin Sparing Mastectomy.

1.0 BACKGROUND

1.1 NAC-sparing Mastectomy:

Breast-conserving surgery is an option for the majority of patients with stage I/II invasive or noninvasive breast cancers. However, there are patients that require or elect to undergo mastectomy followed by a reconstruction. Skin-sparing mastectomy (SSM) has become a surgical option for an invasive or in-situ breast cancer requiring mastectomy or in high-risk patients undergoing prophylactic mastectomy. Several non-randomized series suggest that SSM does not add to the risk of local recurrence [1–3]. The SSM removes the breast, nipple-areola complex (NAC), previous biopsy incisions and skin overlying superficial tumors. The preservation of the skin of the breast and inframmary fold with SSM, greatly improves the aesthic results of the immediate breast reconstruction. The preservation of the nipple-areola complex (NAC) would lead to the best cosmetic result; however, the oncologic safety of lesser surgery is not yet proven. The incidence of occult involvement of the NAC in patients with established breast cancer has been reported in several published studies. Laronga and colleagues [4] reviewed a series of 286 mastectomy specimens at MD Anderson Cancer Center for the presence of occult NAC involvement. Occult tumor in the NAC was found in 5.6%. NSABP B-04 study (radical mastectomy versus total mastectomy ± radiation) noted the incidence of occult nipple involvement in 107 of 967 cases (11.1%) [5]. Santini and colleagues [6] reported the largest series of NAC involvement. 1,291 consecutive mastectomy specimens with primary invasive breast cancer were reviewed, showing a 12% NAC involvement. Several published studies identified features of the primary breast cancer to increase risk of occult NAC involvement [4-8], including tumors < 2 cm from the areola, dimpling of the areola, tumors > 4 cm, multicentric tumors, location beneath the areola, presence of positive axillary nodes, presence of extensive intraductal component (EIC), etc.

Gerber and colleagues [9] published the largest series of NAC preservation, comparing the results of 112 patients undergoing SSM with preservation of NAC to 134 patients that had standard mastectomy. All tumors were > 2 cm from the nipple. After intra-operative frozen sections of the NAC-ground, they were able to preserve NAC in 61 patients (54.5%). There was no statistical difference in the rate of local recurrence with a follow up of 59 months. The subcutaneous mastectomy (SCM), which saves both the nipple and areola, has also been studied to treat established breast cancers and for risk-reduction operations. The number of studies using SCM in established breast cancer is small and appeared to show no difference in survival comparing from standard mastectomy, but with a higher incidence of local recurrence [10-15].

1.2 NAC-sparing Mastectomy followed by Prophylatic NAC Irradiation.

Petit and colleagues [16] reported a prospective study using nipple-sparing mastectomy (NSM) in association with intra-operative radiotherapy with electrons (ELIOT) given to the NAC, in attempt to decrease risk of local recurrence and increase patient's satisfaction and cosmetics. Frozen sections of the tissue under the areola were routinely sampled to exclude presence of tumor. A dose of 16 Gy was delivered intra-operative in the region of the NAC. Between March 2002 and September 2003, 106 NSM were performed in 102 patients, 63% with invasive carcinoma and 37% in situ carcinoma. In an average follow up of 13 months, only one local recurrence, located in the clavicular region, far from the NAC was observed. 15 patients (4.7%) lost their NAC due to total necrosis. Eleven patients (10.4%) developed moist desquamation, followed by spontaneous healing. A preliminary result of a psychological part of the study showed a very high satisfaction with the preservation of the nipple (97.6%).

1.3 Radiation Dose and Fractionation:

Several groups have recently published their data exploring the possibility of shortening the overall radiation treatment length after breast conserving surgery by increasing the fraction size, and decreasing treatment to the lumpectomy cavity with margins, where the majority of the recurrences occurred. 3D Conformal Radiation Therapy (3D-CRT) techniques have also been used in phase I/II trials. Formenti et al [17] published their experience treating 47 patients with early stage breast cancer after lumpectomy with 3D conformal partial breast irradiation. Patients received a total dose of 30 Gy at 6 Gy/fraction delivered in 5 fractions over ten days. At a median follow-up of 18 months, no patient developed a local recurrence, acute toxicity was modest (grade 1-2 erythema), with only grade 1 late toxicity. Baglan et al [18] also initiated a pilot study of 3D-CRT using doses of 34 Gy in 5 patients and 38.5 Gy in 4 patients, both delivered in 10 fractions, twice daily over 5 consecutive days. The acute toxicity was minimal. Radiobiological models suggest that this fractionation schedule of 38.5 Gy in 10 fractions using 3D-CRT external beam radiation should produce acceptable control rates in the breast and comparable late effects as with brachytherapy. These models estimate that the

regimen of 38.5 Gy in 10 fractions should provide a biologically equivalent dose (BED) of 45 Gy in 1.8 Gy fractions assuming a α/β ratio of 10. The Radiation Therapy Oncology Group (RTOG) has launched a phase III trial (0413), comparing whole breast irradiation delivered over 6 ½ weeks versus partial breast irradiation in shortened treatment length of 5 days, using different techniques as MammoSite HDR brachytherapy (34 Gy, 3.4 Gy fraction, in 10 fractions, minimum of 6 hours apart), 3D-Conformal Radiotherapy (38.5 Gy in 10 fractions, twice daily, 6 hours apart) or Intertitial Brachytherapy with High or Low Dose Rate Brachytherapy.

The proposed study will evaluate the use of external beam radiotherapy using electrons, which is a superficial radiation, for treatment of the nipple-areola complex, postoperative. The dose escalation level IV of 35Gy in 3.5 Gy fractions, for a total of 10 fractions, twice daily, minimum of 4 to 6 hours apart, has a Biological Effective Dose (BED) equivalent of the standard fractionation of 45 Gy in 1.8 Gy fraction (BED for early effects will be 45 Gy, assuming α/β of 10; BED for late effects will be 72.5 Gy, assuming a α/β of 3).

2.0 OBJECTIVES

2.1 Primary objectives

To determine the recommended phase II dose of post-operative prophylactic NAC irradiation after nipple areola-sparing mastectomy and immediate reconstruction in patients with ductal carcinoma in-situ or invasive breast cancer.

2.2. Secondary objectives

To provide extensive descriptive data regarding NAC-sparing surgery with reconstruction, including both surgeon experience and patient evaluation of cosmetic results. Survival and recurrence will be also assessed.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 Patients must have histologically confirmed in-situ or invasive breast carcinoma.

3.1.2 Tis, T1, T2 invasive or non-invasive carcinoma of the breast; lesion less than 4 cm.

3.1.3 Unifocal, multifocal or multicentric breast cancers that can be removed by nipple sparing mastectomy with negative surgical margins.

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3.1.4 No extensive intraductal component or patient with distant metastases.

3.1.5 Patients must be > 18 years of age.

3.1.6 No concomitant or history of nipple discharge or skin involvement.
3.1.7 No prior history of malignancy (less than 5 years prior to study entry), except non-melanomatous skin cancer.
3.1.8 No prior history of radiation to the chest.
3.1.9 No collagenous disease (systemic lupus erythematosis, scleroderma, dermatomyositis). No previous non-hormonal therapy including radiation or chemotherapy for current breast cancer.
3.1.10 No patients with Paget's disease of the nipple.
3.1.11 No patients with co-existing medical conditions with life expectancy < 2 years.
3.1.12 No pregnant or lactating women.
3.1.13 ECOG 0 - 2.
3.1.14 Signed study-specific informed consent form prior to the study entry.

3.2 Exclusion Criteria (08-06-2013)

3.2.1 Retroareolar breast cancer lesions within one cm. depth from the skin surface.
3.2.2 Concomitant or history of nipple discharge or skin involvement.
3.2.3 Patient with distant metastases.
3.2.4 Patient with extensive intraductal carcinoma.
3.2.5 Any previously irradiated ipsilateral breast cancer.
3.2.6 Patients with Paget's disease of the nipple.
3.2.7 Patients with collagenous diseases, as systemic lupus erythematosis, scleroderma or dermatomyosis.
3.2.8 Other malignancy, except non-melanomatous skin cancer, less than 5 years prior to participation in this study.
3.2.9 Patients who are pregnant or lactating due to potential exposure of the fetus to RT and unknown effects of RT to lactating females.
3.2.10 Positive surgical margins following nipple sparing mastectomy

3.3 Enrollment Procedures (07-03-2012)

To enter a patient, the investigator or study team will contact the CRS representative. All eligibility requirements must be reviewed prior to the patient entering the study. The following information must be provided to the CRS representative:

1) Completed and signed protocol-specific eligibility checklist;
2) All pages of the original signed informed consent forms (ICFs), including HIPAA Form B.
3) Relevant source documents such as: subject medical history and physical exam, admission or discharge notes, diagnostic

reports, pathologic confirmation of diagnosis, and relevant subject-specific written communication.

3.3.1 Cancellation Guidelines

If a patient does not receive protocol therapy, the patient may withdraw. Contact the CRS representative, or e-mail the information including the reasons for withdrawal within 10 working days.

3.3.2 Emergency Registration

If an emergency registration takes place after business hours, the items listed in section 3.3 above must be submitted by the next business day.

4.0 TREATMENT PLAN

Week 1	NAC-sparing mastectomy with immediate reconstruction
Between weeks 5 to 8	Prophylactic NAC irradiation twice daily, minimum of 4 hours apart, **for 5 days**, preferable in consecutive working days;
2 weeks after irradiation	Chemotherapy, if indicated, at the discretion of the treating physician

4.1 Surgery

4.1.1 NAC-sparing mastectomy: Subcutaneous Mastectomy (SCM) to be performed, preserving the nipple and areola complex, after a frozen section of the tissue underneath the nipple-areola complex is sampled and found to be negative for tumor.

4.1.2 Axillary Dissection or Sentinel Node Biopsy (SNB) will be performed at surgeon's discretion.

4.1.3 Reconstruction: Immediate reconstruction of the breast will be performed by the plastic surgeon's discretion and patient's desire.

4.2 Radiation Therapy

4.2.1 Dose levels and schedule

Dose levels†	Description
Dose Level I = 20 Gy	10 fractions of 2.0 Gy
Dose Level II = 25 Gy (starting dose)	**10 fractions of 2.5 Gy**
Dose Level III = 30 Gy	10 fractions of 3 Gy
Dose Level IV = 35 Gy	10 fractions of 3.5 Gy
† Treatment will be delivered twice a day, minimum of 4 hours apart, **for 5 days**, preferable in consecutive working days.	

4.2.2 Treatment Planning and Imaging: Treatment planning and delivery should be performed with the patient in supine position, on a breast board. A treatment planning CT scan will be required to define the clinical target volume (CTV) which will include the nipple-areola complex. At the time of CT Simulation, the NAC will be marked on the skin, to be seen on the CT images for planning. A second simple simulation might be performed to verify treatment parameters and treatment field on the patient, according to plan.

4.2.3 Beam Angles/Treatment Position: The patient will be treated in supine position, with electrons. The energy of the electrons assigned for treatment will be dependent on the plan to cover the area of NAC appropriately, as per radiation oncologist's discretion.

4.2.4 External Beam Equipment: Megavoltage equipment is required with a range of electrons energy.

4.2.5 Dose escalation/de-escalation design

The following are the four possible dose levels to be tested in the study:

Dose level I: 20 Gy total (2.0 Gy for 10 fractions)
Dose level II: 25 Gy total (2.5 Gy for 10 fractions) (Starting Dose)
Dose level III: 30 Gy total (3.0 Gy for 10 fractions)
Dose level IV: 35 Gy total (3.5 Gy for 10 fractions)

The patients will be receiving postoperative NAC irradiation using electrons **starting at Dose level II**. Dose levels will be escalated by 0.5 Gy per fraction for an overall 5 Gy increase per level up to 3.5 Gy per fraction and a total dose of 35 Gy. **Evaluable patients** will be defined as any eligible patient that begins NAC irradiation treatment.

DLT (dose-liming toxicity), as defined in section 4.2.6, will be evaluated during radiation treatment period plus an **additional observation period of 30 days** following completion of NAC radiation.

We propose **a modification of standard dose-escalation design, treating cohorts of 2 to 6 patients per dose level of NAC irradiation**. The main features of the proposed escalation design is that (1) no more than 2 patients will experience DLT at a given radiation dose and (2) escalation to a higher dose occurs only after a cohort of 6 patients have been evaluated at a given radiation dose.

Dose escalation/de-escalation rules	
Number of patients with DLT at a given dose level	**Escalation Decision Rule**
0 or 1 out of 6 patients	Enter 6 patients at the next higher dose level.
2 out of 2 to 6 patients	Dose escalation stops. However, if the dose tested is dose level II, the starting dose level, then de-escalation occurs. In this case, dose level I will be tested in 2 to 6 patients.
The highest dose tested at which ≤ 1 out of 6 patients experiences DLT will be declared the MTD and it will be the **recommended phase II dose**.	

Thus, as stated in the dose escalation/de-escalation rules above, if 0 or 1 patient experiences DLT (as defined in section 4.2.6) among 6 patients, the dose level will be judged to be acceptable. If this occurs, then a new cohort of 2 to 6 patients will be accrued at the next higher dose level. If 2 patients experience DLT among 2 to 6 patients at a given dose level, then the corresponding dose will be declared to be unacceptable. If the **starting dose level** (dose level II) proves to be unacceptable, then de-escalation occurs to dose level I and 2 to 6 patients will enrolled at dose level I.

The **maximum tolerated dose (MTD),** among the doses tested, will be determined as the highest **NAC irradiation** dose level at which ≤1 out of 6 patients experiences DLT. The MTD will be declared the ***"potential"* recommended phase II dose (RP2D)** of post-operative prophylactic NAC irradiation after NAC-sparing mastectomy **with reconstruction** in patients with ductal carcinoma in-situ or invasive breast cancer.

Simultaneous enrollment: Simultaneous enrollment will be permitted under the following circumstance:

- If j (j≤4) patients have been treated at a given dose and there are no DLTs, patients (j+1) and (j+2) may be enrolled simultaneously at the same dose level.

For instance, the first two patients could be enrolled simultaneously, that is, patient 2 could be enrolled within <30 days apart after patient 1 has completed the radiation treatment. As another example, If the first patient to receive a NAC radiation dose level does not experience DLT, within the DLT evaluation period of minimum 35 days, patients 2 and 3 may be enrolled simultaneously at the same dose level; that is, patient 3 can be enrolled before patient 2 has been fully evaluated for DLT within <30 days apart after patient 2 has completed the radiation treatment.

4.2.6 Definition of dose limiting toxicity (DLT)

Dose limiting toxicity (DLT) is defined as any of the following toxicities occurring during radiation treatment period plus an **additional observation period of 30 days** following completion of NAC radiation:

a) Grade 4 skin rash

b) Grade 4 pain

c) NAC necrosis

d) Any toxicity requiring interruption of the NAC irradiation by > 2 weeks (14 calendar days), except if interruption is secondary to LINAC machine or unpredictable weather problems or unrelated medical conditions that would prevent the subject to come for treatment.

e) Any grade 4 or 5 treatment-related toxicity

4.2.7 Expansion cohort

An additional expansion cohort of 12 patients will be enrolled at the ***"potential"*** recommended phase II dose (RP2D) **to confirm its safety.**

If safety is confirmed in the total 18 patients (6 from dose-finding part of study plus 12 from the expansion cohort) treated at the ***"potential"*** (RP2D, the corresponding dose will be declared the **RP2D**.

4.3 Chemotherapy

4.3.1 Chemotherapy, if indicated by oncologist, will be delivered at least 2 weeks from the last radiation treatment.

4.3.2 The type of chemotherapy will be at discretion of the oncologist physician.

5.0 Clinical and Laboratory Evaluations

5.1 Preoperative assessment:

Preoperative assessment includes general medical status and organ function as well as tissue diagnosis and a work up for metastatic disease if applicable. The assessment will include standard history and physical examination, histology, laboratory and radiological tests as deemed appropriate by the operating surgeon.

5.2 Intraoperative parameters

Intraoperative events and findings will be reported as routinely done in the operative report. Pathologic examination of the frozen section of the tissue underneath the NAC will be performed at the time of surgical procedure and results will be recorded in the study records. If pathology is positive, the patient will be taken off the study as screen failure.

5.3 Perioperative parameters

The surgical team will monitor for complications in the usual manner and any complication will be treated accordingly. Duration of hospital stay, complications will be recorded.

5.4 Pathologic evaluation of specimens

Pathologic examination of the frozen section of the tissue underneath the NAC will be performed at the time of surgical procedure and results will be recorded in the study records. If pathology is positive, the patient will be taken off the study as screen failure. If pathology is negative, the surgeon will then perform a Skin Sparing Mastectomy, sparing the NAC. If the patient's NAC tissue biopsy is negative by frozen, but positive after standard hematoxylin and eosin, the patient will be taken off the study and the discussion will be done with the patient about options of removal of the NAC or postoperative irradiation of NAC outside the protocol.

5.5 Photographs (07-15-2011)

5.5.1 Photographs shall be taken at the discretion of the P.I. and Sub-P.I.

5.6 Patient enrollment data

5.6.1 Complete history and physical examination
5.6.2 Mammographic reports
5.6.3 Pathology reports

5.7 Patient treatment data

5.7.1 Operative reports from mastectomy and reconstruction.
5.7.2 Toxicity reports: skin reaction(s) to radiation therapy including erythema, desquamation, etc.; any acute or unusual severe side effects of surgical procedures or radiation treatment
5.7.3 Radiation treatment: prescribed and delivered doses
5.7.4 Copies of dosimetry calculations
5.7.5 At least one photograph of the treated breast prior to initiation of treatment

5.8 Patient follow-up

5.8.1 Vital status
5.8.2 Disease status, classified local, regional, or distant
5.8.3 Site(s) and date of first failure in each category above
5.8.4 Relationship of the recurrence to the irradiated volume
5.8.5 Cosmetic evaluation by patient and physicians
5.8.6 Effects of treatment
5.8.7 Follow-up physical examination
5.8.8 Photographs will be taken at the discretion of the P.I. and Sub-P.I.
5.8.9 AE and Concomitant Medication reporting from post-operative visit up to 30 days post radiation treatment.

5.9 RESPONSE CRITERIA

5.9.1 The definition of local recurrence is histologic evidence of recurrent carcinoma, either invasive or non-invasive in the nipple-areola complex in the ipsilateral breast.

5.9.2 Clinical evidence of carcinoma by physical exam and/or mammograms/MRI will not be evidence of local recurrence until biopsy proof.

5.9.3 Overall survival time is defined from the date of surgery until the date of death due to any cause. In the absence of death, follow-up time will be censored by the date of last contact.

5.9.4 Disease-free survival time is defined from the date of surgery until the date of documented recurrence (local or distant) or breast cancer-related death, whichever occurs first. Patients who die without documentation of recurrence will be considered to have had disease recurrence at the time of death, unless there is documented evidence that no recurrence occurred before death. In other words, ‘unknown cause of death’ will be considered an event for the disease-free survival analysis. In the absence of any event defining disease recurrence, follow-up time will be censored at the date of last documented recurrence-free status.

5.10 DEFINITIONS OF LEVELS OF COSMETIC OUTCOME (07-15-2011)

5.10.1 Cosmesis will be graded by the patient and by the radiation oncologist or the surgeon prior to radiation (baseline), and 1, 3, 6 and 12 months after completion of radiation therapy as follows: Plus or minus 2 weeks.

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

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

Fair: there is obvious difference in the size of shape of the reconstructed breast. This change involves ¼ or less of the breast.

Poor: marked change in the appearance of the treated breast involving more than ¼ of the breast tissue.

Clarification: (Evaluation of the treated nipple-areola complex)

Color: Natural Score 0 or 1

Shape: Round Score 0 or 1

Nipple: Central Score 0 or 1

Nipple: Everted Score 0 or 1Total Score Report;

4 =excellent
3= good
2 = fair
1=poor

6.0 TOXICITIES AND COMPLICATIONS

6.1 Surgery

6.1.1 General risks of Surgery

The general risks of surgery include anesthetic risk, bleeding, infection, pulmonary and cardiac complications and death. These general risks will be explained in detail to the patient and a separate standard surgical consent form will be completed prior to enrollment.

6.1.2 Specific risks of NAC-sparing Mastectomy

The operative procedure is performed under general anesthesia and following standard breast cancer operation. The NAC sparing during mastectomy will add a frozen biopsy of the tissue underneath the NAC is expected to prolong the anesthesia for approximately ½ hour. A small risk of NAC necrosis postoperative exists due to possibility of decrease in vascularization.

6.2 General risks of Breast Reconstruction with Implants or Autologous Tissue.

The general risks of plastic surgery reconstruction include anesthetic risk, bleeding, infection, loss of the reconstructed breast with autologous tissue secondary to necrosis, capsulitis of the breast implant, cardiac and pulmonary complications and death.

6.2.1 Specific risks of NAC-sparing Mastectomy with Immediate Reconstruction with Implants or Autologous Tissue followed by prophylactic NAC Irradiation

Besides the general risks of mastectomy and plastic reconstructive surgery with implants or autologous tissue, postoperative prophylactic NAC Irradiation will give a small increased risk of NAC necrosis, which in some cases will resolve spontaneously or in some cases will require a second operation. The aesthetic result of NAC-sparing Mastectomy with Immediate Reconstruction with Implant or Autologous Tissue followed by Prophylatic NAC Irradiation might alter the cosmetic results secondary to skin fibrosis or discoloration.

6.3 General risks of Radiation

Fatigue is anticipated systemic reaction to radiation treatment. Skin erythema, hyperpigmentation and desquamation (dry or moist) may also occur, and they are usually temporary. Edema and tenderness are possible side effects of treatment. There is a rare possibility of development of secondary malignancy.

6.3.1 Specific risks of Prophylatic NAC Irradiation after NAC-sparing Mastectomy and Reconstruction.

The addition of Prophylatic NAC irradiation after NAC-sparing Mastectomy and Reconstruction include necrosis of NAC, with a need for additional surgical procedure for repair; delayed wound healing, poor cosmesis secondary to permanent hypopigmentation or hyperpigmentation of the skin of the NAC or skin fibrosis.

7.0 Adverse Event Reporting

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for adverse event reporting. A copy of the CTCAE version 3.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/reporting/ctc.html).

7.1 Definitions:

7.1.1 ***Adverse events*** (AE's) will use the descriptions and grading scales found in the NCI Common Toxicity Criteria in Appendix II.

Adverse events: Any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the treatment or procedures; also and "unanticipated problem" of any nature (e.g., psychological or social harm)

7.1.2 A ***serious adverse event*** (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

The definition of serious adverse event (experience) also includes ***important medical events***. Medical and scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or **may require intervention** to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

7.1.3 **Expected events** are those that have been previously identified as resulting from administration of the treatment.

7.1.4 An adverse event is considered ***unexpected*** when either the type of event or the severity of the event is *not* listed in: the current NCI Agent-Specific Adverse Event List; the investigator's brochure or the information section of this protocol.

7.1.5 The definition of ***related*** is that there is a reasonable possibility that the drug caused the adverse experience.

7.2 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Note: Chemotherapy **related** adverse event reporting will not be performed for patients receiving standard of care chemotherapy in the follow-up period starting 2 weeks post radiation. Adverse events are reported in a routine manner at scheduled times during a trial (please follow directions for routine reporting provided in the Data Reporting Section). The following sections provide information about reporting.

7.2.1 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

7.2.2 Steps to determine if an adverse event is to be reported in an expedited manner:

Step 1: *Identify the type of event using the NCI Common Toxicity Criteria (CTC).*

The CTC provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTC can be downloaded from the CTEP home page (http://ctep.cancer.gov). Additionally, if assistance is needed, the NCI has an Index to the CTC that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTC.

Step 2: *Grade the event using the NCI CTC.*

Step 3: *Determine whether the adverse event is associated to the protocol therapy (investigational or commercial)*.

Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event*.

Step 5: *Review 10.2 to determine if there are any protocol-specific requirements for reporting of specific adverse events that require special monitoring.*

Step 6: *Determine if the protocol treatment given prior to the adverse event included investigational agent(s), a commercial agent(s), or a combination of investigational and commercial agents.*

7.3 Reporting Methods

7.3.1 All serious, unusual life-threatening or lethal adverse which may be study related will be reported within 24 hours by telephone to the Principal Investigator and must be followed by a written report which must be received by the Principal Investigator within 10 business days. The Principal Investigator shall also be responsible for promptly notifying the local Institutional Review Board of all such serious adverse events. For all fatal events (Grade 5) while on study or within 30 days of treatment, a written report will follow within 10 working days.

7.3.2 IRB Reporting

7.3.2.1 All unexpected adverse events, serious adverse events, events that are more severe than anticipated, events that are more frequent than anticipated, and deaths must be reported to the IRB within ten (10) working days of being made known to the Principal Investigator.

8.0 CRITERIA FOR DISCONTINUATION OF A PATIENT FROM THE STUDY

8.1.1. Disease progression

8.1.2. Unacceptable surgical adverse event that preclude administration of radiation treatment.

8.1.3. Patient decides to withdraw from the study

8.1.4. At any time, the patient or his/her physician may discontinue participation in the study if this is believed to be in the patient's best interest.

9.0 DATA REPORTING

Basic forms include

- On-study information, including patient eligibility data and patient history
- Flow-sheets, tumor/disease assessment forms or other forms for interim monitoring
- Specialty forms for pathology, radiation or surgery
- Off-study summary sheet, including a final assessment by the treating physician
- Follow-up forms when requires.

The following can be used for the location if using SCCC forms.

Data must be submitted according to the protocol requirements for ALL patients registered. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

A list of forms to be submitted, as well as expectation dates, is found in Appendix IV.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Size

For the purpose of dose escalation of NAC-radiation treatment, **evaluable patients** will be defined as any eligible patient that begins NAC irradiation treatment. However to evaluate feasibility of the NAC-sparing mastectomy with reconstruction, any patient who undergo surgery will be considered evaluable.

Following the dose escalation/de-escalation procedure described in section 4.2, we anticipate that 12 to 18 evaluable patients will be enrolled in this phase I study *during the dose-finding part*. The **number of evaluable patients** that will be needed depends on the number of times the NAC-radiation dose is escalated or possibly de-escalated. If the escalation occurs from dose level II up to dose level IV, between14-18 evaluable patients will be required. If the dose is de-escalated after dose level II been evaluated in 6 patients, then 12 evaluable patients will be required, assuming 6 patients would be evaluated at dose level I. With 6 evaluable patients, the probability of not escalating when the true DLT rate is 35% is 68%. If the true DLT rate is 20%, the probability that the dose will be escalated is 66%.

A maximum of 6 patients per year is expected to be enrolled, since each patient must be evaluated for a minimum of 35 days and at most two patients will be enrolled simultaneously (within < 30 days after completion of the 5 days NAC radiation treatment). Thus, the expected accrual period is between 2-3 years.

An ***additional expansion cohort of 12 patients*** will be enrolled at the **"potential" recommended phase II dose (RP2D)** over an expected accrual period of 2 years.

To gather data on recurrence and survival, all patients will be followed at their clinic visits as clinically indicated.

10.2 Planned Analysis

Patient demographics (age, race/ethnicity), **laboratory parameters, disease characteristics** (such as, tumor stage, grade), will be summarized using descriptive statistics: counts and percentages, range, median, mean, and standard deviation, as appropriate [23].

Toxicities resulting from radiation treatment will be tabulated by type, grade, duration, and attribution to treatment according to NCI CTCAE version 3.0, and by administered NAC radiation dose. A patient-level summary by worst grade toxicity will be included. Any grade 3, 4 or 5 or unexpected lower grade toxicities will be reported.

Intraoperative parameters and perioperative parameters (complications, events, and findings) will be described in the operative report as routinely done.

Surgery success rate, defined as the proportion of patients who had successful NAC sparing surgery with reconstruction divided by the total number of study patients, will be determined.

Cosmetic results will be assessed by both the physician(s) and the patients at 3, 6 and 12 months, using a 4-category ordinal scale (excellent, good, fair, and poor). Data will be summarized in terms of number and % of patients in these 4 possible categories at those assessment times separately for assessment by physician and by patient. Statistical analysis methods for contingency tables will be used to compare changes over time for each evaluator (physician or patient), and also to compare agreement between physician and patient assessment at a given time. [24]

To gather data on recurrence and survival, all patients will be under follow-up for a minimum of 5 years, unless they withdraw consent or die within that time.

Given the small study size and the expected low incidence of recurrence, we do not expect any such recurrences within 5 years. However, if patients do recur, the **number of recurrences** will be reported, along with corresponding summary regarding time to recurrence, type of recurrence -- local (ipsilateral nipple-areola recurrence in-field, peripheral, or extra-field location) or distant, irradiated volume, and radiation dose. If the number of events allows, **disease-free survival and overall survival** will be estimated by the Kaplan-Meier method. [25]

10.3 Interim Monitoring

10.3.1 Role of the Research Team and the DSMC

The Research Team will continuously monitor study accruals and adverse events from both surgery and radiation treatment. In particular, for the purpose of escalation and de-escalation (section 4.2) patients will be monitored closely during the 30 days after completion of NAC radiation treatment, and subsequently for any toxicity or adverse reaction to treatment. All toxicities, regardless their grade, will be recorded in the patient case report form using NCI/CTEP Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

The Sylvester Comprehensive Cancer Center's Data and Safety Monitoring Committee (DSMC) will monitor this protocol according to the Cancer Center's DSM Plan. In its oversight capacity, the DSMC bears responsibility for suspending or terminating this study.

DSMC oversight of the conduct of this trial includes ongoing review of accrual and adverse event data. The guidelines appearing in Sections 10.3.2, and 10.3.3 are offered for DSMC consideration in assessing accrual, adverse events. In addition, the DSMC will review reports from all audits, site visits, or study reviews pertaining to this clinical trial and take appropriate action.

10.3.2 Safety: Early stopping due to radiation-related toxicity

During the dose escalation/de-escalation for radiation dose-finding, there is no radiation-related toxicity that would suggest stopping the study early due to radiation-related toxicity beyond the dose escalation/de-escalation stopping rules described in section 4.2.5.

Expansion cohort:

An additional expansion cohort of 12 patients will be enrolled at the "potential" recommended phase II dose (RP2D).

If a radiation-related (possible, probable, or definite) death (grade 5 toxicity) occurs, enrollment will be suspended and continuation of the study will be reassessed by the DSMC.

Unacceptable radiation-related toxicity (possible, probable, or definite) is defined as grade 3, 4, or 5 adverse events, excluding grade 3 adverse events that resolve or down grade to grade 2 within 14 days.

Unacceptable radiation-related toxicity (possible, probable, or definite) is expected

to occur in no more than 10% of patients. If there is evidence that the true rate of this toxicity exceeds 20%, then the study should be suspended or possibly terminated early. Specifically, we suggest as a guideline for early termination a posterior probability of 90% or higher that the true rate exceeds 20%. The table below shows specific instances where this guideline is met, suggesting early termination, and due to evidence of excessive toxicity.

Number (%) of patients experiencing unacceptable radiation-related toxicity[#]	Total patients evaluated
3	3 to 5
4	6 to 9
5	10 to 12

[#]:Radiation-related toxicity (possible, probable, or definite) is defined as grade 3 or higher adverse events, excluding grade 3 adverse events that resolve or down grade to grade 2 within 14 days.

To illustrate the stopping guidelines, suppose that 5 evaluable patients in the expansion cohort have been assessed for radiation-related toxicity and 3 of them have experienced grade 4 unacceptable toxicity. (See row 1 of the above table.) Under this circumstance, the observed rate of unacceptable toxicity is 60%, resulting in a posterior probability of 92.7% (not shown) that the true underlying rate exceeds 20%, thereby suggesting early termination.

Posterior probabilities for the above table are calculated under a weak prior beta distribution with parameters β_1 = 0.2 and β_2 = 1.8, which corresponds to an expected unacceptable radiation-related toxicity rate of 20% based on very limited information, roughly equal to having studied 2 patients. This prior distribution implies also a priori chance of only 18% that true rate is 20% or greater.

10.3.3 Safety: Early stopping due to surgery-related toxicity

We propose the following guidelines for the DSMC in its review of accumulating data on surgery-related toxicity. These guidelines were developed using Bayesian methods, which can be applied at any stage of enrollment without pre-specification of the number of interim analyses to be performed, or the number of patients evaluable for toxicity or survival at the time such assessments are made (26,27). Under the Bayesian method, we assign a prior probability (level of belief at the start of the trial) to a range of possible values for the true rate. As data on treated patients become available, this probability distribution is revised and the resulting posterior probability becomes the basis for recommending either early termination or continuation of the study. In the sections that follow, we provide specific stopping guidelines based on posterior probabilities for interim monitoring of surgery-related toxicity over the course of this trial. Underlying assumptions for the prior distribution are also presented.

If a surgery-related (possible, probable, or definite) death (grade 5 toxicity) occurs, enrollment will be suspended and continuation of the study will be reassessed by the DSMC.

Unacceptable surgery-related toxicity (possible, probable, or definite) includes grade 3-4 bleeding, infection, NAC necrosis, and any unexpected grade 3.

Unacceptable surgical-related toxicity (possible, probable, or definite) is expected to occur in no more than 10% of patients. If there is evidence that the true rate of this toxicity exceeds 20%, then the study should be suspended or possibly terminated early. Specifically, we suggest as a guideline for early termination a posterior probability of 90% or higher that the true rate exceeds 20%. The table below shows specific instances where this guideline is met, suggesting early termination, and due to evidence of excessive toxicity.

Number (%) of patients experiencing unacceptable surgery-related (possible, probable, or definite) toxicity	Total patients evaluated
3	3 to 5
4	6 to 9
5	10 to 12
6 (55 to 60%)	13 to 16
7	17

To illustrate the stopping guidelines, suppose that 5 evaluable patients have been assessed for surgical-related toxicity and 3 of them have experienced grade 4 unacceptable toxicity. (See row 1 of the above table.) Under this circumstance, the observed rate of unacceptable toxicity is 60%, resulting in a posterior probability of 92.7% (not shown) that the true underlying rate exceeds 20%, thereby suggesting early termination.

Posterior probabilities for the above table are calculated under a weak prior beta distribution with parameters $\beta_1 = 0.2$ and $\beta_2 = 1.8$, which corresponds to an expected unacceptable surgery-related toxicity rate of 20% based on very limited information, roughly equal to having studied 2 patients. This prior distribution implies also a priori chance of only 18% that true rate is 20% or greater.

11.0 INVESTIGATOR'S RESPONSIBILITIES

11.1 INVESTIGATOR RESPONSIBILITY/PERFORMANCE

The investigator will ensure that this study is conducted in accordance with all regulations governing the protection of human subjects.

The investigator will ensure that all work and services described in or

associated with this protocol will be conducted in accordance with the investigational plan, applicable regulations, and the highest standards of medical and clinical research practice.

11.2 CONFIDENTIALITY

The investigator must ensure that each subject's anonymity will be maintained and each subject's identity will be protected from unauthorized parties. A number will be assigned to each subject upon study entry and the number and the subject's initials will be used to identify the subject for the duration of the study. The investigator will maintain all documents related to this study in strict confidence.

11.3 INFORMED CONSENT AND PERMISSION TO USE PROTECTED HEALTH INFORMATION

It is the responsibility of the investigator to obtain written informed consent from each subject participating in this study after adequate explanation, in lay language, of the methods, objectives, anticipated benefits, and potential hazards of the study. The investigator must also explain that the subject is completely free to refuse to enter the study or to discontinue participation at any time (for any reason) and receive alternative conventional therapy as indicated. Prior to study participation, each subject will sign an IRB approved informed consent form and receive a copy of same (and information leaflet, if appropriate). For subjects not qualified or able to give legal consent, consent must be obtained from a parent, legal guardian, or custodian.

The investigator or designee **must** explain to the subject before enrollment into the study that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and the IRB. It is the investigator's (or designee's) responsibility to obtain permission to use protected health information per HIPAA from each subject, or if appropriate, the subjects' parent or legal guardian.

11.4 SOURCE DOCUMENTATION AND INVESTIGATOR FILES

The investigator must maintain adequate and accurate records to fully document the conduct of the study and to ensure that study data can be subsequently verified. These documents should be classified into two separate categories: (1) investigator study file and (2) subject clinical source documents that corroborate data collected on the CRF's. Subject clinical source documents would include hospital/clinic patient records; physician's and nurse's notes; appointment book; original laboratory, ECG, EEG, radiology, pathology, and special assessment reports;

pharmacy dispensing records; subject diaries; signed informed consent forms; and consultant letters. When the CRF or any form is used as the source document, this must be clearly stated in the investigator study file.

Minimally, the following be documented in source documents:

- Medical history/physical condition and diagnosis of the subject before involvement in the study sufficient to verify protocol entry criteria
- Study number, assigned subject number, and verification that written informed consent was obtained (each recorded in dated and signed notes on the day of entry into the study)
- Progress notes for each subject visit
- Documentation of treatment
- Laboratory test results
- Adverse events (action taken and resolution)
- Condition and response of subject upon completion of or early termination from the study

11.5 RECORDING AND PROCESSING OF DATA

If using hard copies of CRF's, study center personnel will complete individual CRF's in black ink. All corrections to entered data will be made by drawing a single line through the information to be corrected without obscuring it. All corrections will be initialed, dated and explained, if necessary. **Do not use "white-out" or obscuring correction tape.** A CRF is required for every patient who received any amount of study treatment. The investigator will ensure that the CRF's are accurate, complete, legible and timely. Separate source records are required to support all CRF entries.

11.6 NON-PROTOCOL RESEARCH

No investigative procedures other than those described in this protocol will be undertaken on the enrolled subjects without the agreement of the IRB.

11.7 Ethics

The investigator agrees to conduct the study in compliance with the protocol, current good clinical practices, and all applicable (local, FDA, ICH) regulatory guidelines and standard of ethics.

11.8 Essential documents for the conduct of a clinical trial

Essential documents are those documents with individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator with the standards of Good Clinical Practice and with all applicable regulatory requirements.

The following documents should be on file:

CV's and license of all investigators
IRB documentation/correspondance
Documentation of IRB certification

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APPENDIX I (02-21-2013)

STUDY PARAMETER TABLE (See Section 5.0 for details)										
	SURGERY			PRIOR to RT	DURING RT	FOLLOW-UP AFTER TREATMENT				Long-term Follow-up
Assessment	Pre-Op	Intra-Op	Post-Op	PRIOR to RT		From END of RT				From End of RT
		Week 1-4		Week 1-7	Week 5-8	1 Mo ± 1 wk.	3 Mo ± 2 wks	6 Mo ± 2 wks	12 Mo ± 2 wks	Thereafter, Every 6 Mo (± 1 Mo) and in years 2-5 at the discretion of the Investigator
Informed Consent	X									
Biopsy	X									
Surgical Frozen Section Path		X								
Pathology	X		X							
History/Physical	X		X	X	X	X	X	X	X	X
ECOG 0-2	X			X		X	X	X	X	X
Mammogram	X									
Pregnancy test	X									
Labs per MD discretion	X									
Radiological tests per MD discretion	X	X								
Operative Report			X							
Photographs *				X		X	X	X	X	
NAC sparing mastectomy		X								
RT Treatment Plan					X					
Cosmesis				X		X	X	X	X	
AE Evaluation			X	X	X	X				

* Photographs will be taken at the discretion of the PI and Sub-PI

APPENDIX II:

NATIONAL CANCER INSTITUTE (NCI) COMMON TOXICITY CRITERIA (CTC)

The NCI CTC can be viewed on-line at the following NCI web site:

http://ctep.cancer.gov/reporting/ctc.html

APPENDIX III:

DATA AND SAFETY MONITORING PLAN

The Sylvester Comprehensive Cancer Center (SCCC) Data and Safety Monitoring Committee (DSMC) will monitor this clinical trial according to the Cancer Center's DSM Plan. In its oversight capacity, the DSMC bears responsibility for suspending or terminating this study.

DSMC oversight of the conduct of this trial includes ongoing review of accrual and adverse event data, and periodic review of response to treatment or other study endpoint. The guidelines appearing in Section ***10.3.1 to 10.3.3*** are offered for DSMC consideration in assessing surgery-related toxicities. In addition, the DSMC will review reports from all audits, site visits, or study reviews pertaining to this clinical trial and take appropriate action.

The SCCC DSM Plan to which this study is subject can be obtained by call the CRS office at (305) 243-4903.

Appendix IV:

DATA SUBMISSION SCHEDULE

FORM	TO BE COMPLETED
BASELINE	
Eligibility Checklist	Prior to registration
SCCC Protocol Enrollment Form	
Consent Forms Signed/dated	
On-study Form	Within 30 days of registration
DURING PROTOCOL THERAPY	
	Due every week for phase I studies, every cycle for phase II-IV studies
AFTER PROTOCOL THERAPY	
Off Treatment Form	Within 14 days of discontinuation/completion of protocol therapy
FOLLOW-UP SCHEDULE (for studies with long term follow-up)	
Follow-up Form	1 month, 3 month, 6 month, 1 year, then every 6 months (+/- 1 month) and in years 2-5, at the discretion of the Investigator.
Progression/Relapse	Within 4 weeks of knowledge of progression/relapse
Notice of Death Form	Within 4 weeks of knowledge of death
Subsequent Malignancy	Within 4 weeks of knowledge of another malignancy

NOTE: FORMS WILL BE CONSIDERED PAST DUE 14 DAYS AFTER THE DUE DATE.

APPENDIX VI

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 pre-disease activities without restriction (Karnofsky 90-100).
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 (Karnofsky 70-80).
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 (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).

APPENDIX VII

AJCC STAGING SYSTEM BREAST, 6th Edition

DEFINITION OF TNM
Primary Tumor (T)

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. 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 measurements, are used, the subsets of T1 can be used. Tumors should be measured to the nearest 0.1 cm increment.

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
Tis (DCIS)	Ductal carcinoma *in situ*
Tis (LCIS)	Lobular carcinoma *in situ*
Tis (Paget's)	Paget's disease of the nipple with no tumor

Note: Paget's disease associated with a tumor is classified according to the size of the 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, not including pectoralis muscle
T4b	Edema (including peau d' orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

APPENDIX VII (CONT'D)

Regional Lymph Nodes (N)
Clinical

NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral axillary lymph node(s)
N2	Metastasis in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis
N2a	Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastasis only in clinically apparent* ipsilateral internal mammary nodes and in the *absence* of clinically evident axillary lymph node metastasis
N3	Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the *presence* of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastasis in ipsilateral infraclavicular lymph node(s)
N3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastasis in ipsilateral supraclavicular lymph node(s)

* Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.

APPENDIX VII (cont'd)

AJCC STAGING SYSTEM
BREAST, 6th Edition

Pathologic (pN) [a]

pNX Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)

pN0 No regional lymph node metastasis histologically, no additional examination for isolated tumor cells (ITC)

Note: Isolated tumor cells (ITC) are defined as single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but which may be verified on H&E stains. ITCs do not usually show evidenced of malignant activity e.g., proliferation or stromal reaction.

pNO(i-) No regional lymph node metastasis histologically, negative IHC

pNO(i+) No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2mm

pNO(mol-) No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)[b]

pNO(mol+) No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)[b]

[a] Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," e.g., pNO(i+) (sn).

[B] RT-PCR:reverse transcriptase/polymerase chain reaction.

APPENDIX VII (cont'd)

AJCC STAGING SYSTEM
BREAST, 6th Edition

pN1	Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
pN1mi	Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
pN1a	Metastasis in 1 to 3 axillary lymph nodes
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
pN1c	Metastasis in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent.** (If associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden).
pN2	Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent* internal mammary lymph nodes in the *absence* of axillary lymph node metastasis
pN2a	Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastasis in clinically apparent* internal mammary lymph nodes in the *absence* of axillary lymph node metastasis
pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent* ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastasis to the infraclavicular lymph nodes
pN3b	Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes

APPENDIX VII (cont'd)

AJCC STAGING SYSTEM
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*_Clinically apparent_* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

**_Not clinically apparent_* is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

Distant Metastasis (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

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 N0 M0

T4 N1 M0

T4 N2 M0

Stage IIIC Any T N3 M0

Stage IV Any T Any N M1

* Note: T1 includes T1mic

Note: Stage designation may be changed if post-surgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.