# A MULTICENTRE RANDOMIZED CONTROLLED CLINICAL TRIAL FOR THE REDUCTION OF ACUTE SKIN REACTION IN ADJUVANT BREAST RADIATION IN LARGE BREASTED WOMEN USING A PRONE TECHNIQUE

*Version of May 11th, 2016*


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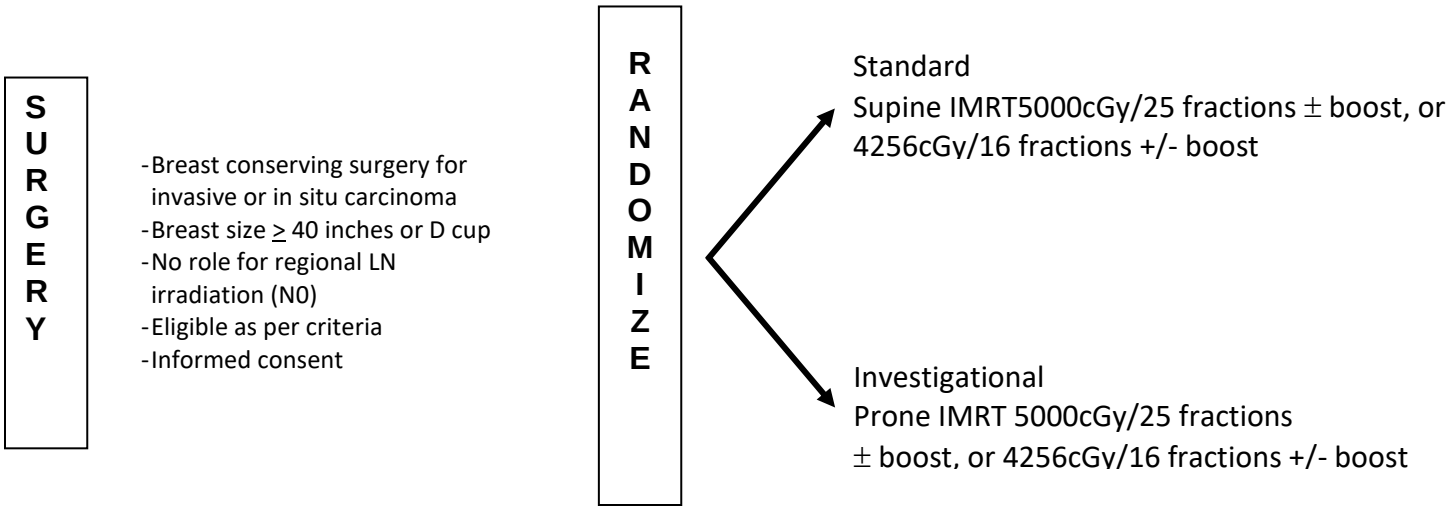
# Treatment schema



# 1. OBJECTIVES

## 1.1. Primary objective

To determine if treating women with adjuvant breast Intensity Modulated Radiation Therapy (IMRT) in the prone position reduces the occurrence of moist desquamation as graded on the Common Terminology Criteria for Adverse Events Version 4.03 scale (CTCAE) when compared to treating women in the supine position.

## 1.2. Secondary objectives:

Determine if breast IMRT in the prone position reduces the occurrence of acute radiation therapy side effects including:

1.2.1. ***Pain scores*** as graded on the Visual Analogue Scale (VAS) and CTCAE scale

1.2.2. ***Health related quality of life*** (HRQoL) using the European Organization for Research and Treatment of Cancer (EORTC) core QoL questionnaire (QLQ-C30) and the breast cancer module (QLQ-BR2)

1.2.3. Determine if adjuvant breast IMRT in the prone position produces improved ***dose distribution in regards to exposure to critical structures*** including heart, lung, liver and contralateral breast when compared to treatment in the supine position.

## 1.3. Future Goals (subject to future grant submission/renewal)

1.3.1. Determine if breast IMRT in the prone position reduces the occurrence of late skin and subcutaneous toxicities as graded on the CTCAE scale including skin telangiectasia, dryness, discoloration, breast edema, induration

1.3.2. Compare rates of local, regional and/or distant recurrence; and overall and disease-specific survival between patients treated in the prone and supine position.

1.3.3. Determine if treatment in the prone position improves long term cosmetic results compared to treatment in the supine position using Breast Cancer Treatment Outcome Scale (BCTOS), EORTC/CTCAE Breast Cancer Rating System for cosmesis assessment and Harvard Cosmetic Criteria tools.

# 2. RATIONALE

## 2.1. Why do women with breast cancer need adjuvant radiotherapy?

Breast cancer is the most commonly diagnosed cancer in Canadian women. The number of surgeries performed for newly diagnosed breast cancer is about 10,000 every year in Ontario, with nearly 2/3 (61%) receiving breast conserving breast

conserving surgery (BCS), which involves surgical excision of the tumour (as opposed to excision of the entire breast with a mastectomy) with postoperative/adjuvant radiation to the breast. The objective of adjuvant radiation therapy after breast conserving surgery is to provide loco-regional control rates equivalent to mastectomy, with good cosmetic results, minimal local toxicity, breast conservation, and hence improved Quality of Life. [1,2] Since the likelihood of survival following treatment of early stage breast cancer is high, it is increasingly important to minimize permanent side effects, negative impacts or complications from therapy.

## 2.2. What are the side effects of adjuvant breast radiotherapy?

### 2.2.1. *Incidence and impact of radiation-induced skin toxicity*

The delivery of XRT is painless. However, severe acute skin reactions are frequent ranging from simple redness of the skin to painful skin breakdown (moist desquamation). [3-9] In a study of 172 patients receiving standard doses of XRT (50 Gy), 38% of patients developed significant (i.e. ≥ grade 2 RTOG) acute skin toxicity, which includes the development of bright erythema with patchy moist desquamation, to confluent moist desquamation.[6] Skin breakdown occurs more frequently within the infra-mammary fold (IMF)[5], and radiation-induced skin toxicity may require temporary treatment interruptions, or occasionally early cessation of treatment.[9] Along with discomfort and pain, acute skin toxicity during breast XRT is associated with a significant decrease in Health Related QoL (HRQoL). For example, in the RTOG 97-13 study comparing best supportive care to Biafine in women treated with adjuvant breast XRT, patients with Grade 2 skin toxicity had a significantly worse HRQoL ($p=0.048$), and this continued through the end of XRT.[6]

### 2.2.2. *Breast pain*

Chronic pain in the breast has been reported in 43% of patients treated with a combination of breast conserving surgery followed by adjuvant radiotherapy in two series.[3,10] This pain was present 5 years after the breast treatment, lasted at least 6 month in duration and was more frequently perceived as aching (61%), tenderness (52%) or cramping (45%).[11] The delivery of radiotherapy and the volume or area of the breast receiving an excessive dose have been identified on multivariate analysis to be significantly associated with the occurrence of pain.[10,12] Pain has a detrimental effect on the patient's QoL, impacting significantly on physical, psychosocial and relationship activities.[3] In another study a greater chronic breast pain was associated with greater depressive symptoms and lower QoL related to mental health.[6]

2.2.3. *Delayed skin and sub-cutaneous side effects*

In addition to the acute, generally temporary side effects described above, breast radiation therapy can result in delayed, generally permanent, side effects as well. Permanent side effects may involve the skin (telangiectasia, erythema, and discoloration), sub-cutaneous tissues (oedema, induration, breast atrophy and pain), arm (oedema) and more rarely adjacent structures (myocarditis, rib fractures, lung fibrosis). Skin and sub-cutaneous delayed side effects directly impact on the cosmetic outcome. Poorer cosmetic outcome and breast pain degrade the patient's Quality of Life.[6]

Skin telangiectasia and sub-cutaneous induration are the most frequent permanent side effects with reported rates of 31.4% and 6.7% respectively.[13] Telangiectasia is an objective and measurable side effect that is specifically induced by radiotherapy, independent of other breast treatments including surgery, hormone therapy or chemotherapy. It has a major impact on cosmetic outcome, such that the majority of studies reporting on delayed side effect of breast radiotherapy frequently report on telangiectasia as a primary outcome.

In 2007 Lilla analysed the factors associated with late normal tissue complications following breast radiotherapy. She found that patient age, ***occurrence of acute moist desquamation***, the radiation dose, and heavy smoking were associated with telangiectasia. She reported that patients with moist desquamation were at higher risk to develop telangiectasia with an odd ratio (OR) of 1.8 (95% confidence interval 1.0 – 3.1).[14] Exactly the same OR for the development of telangiectasia following moist desquamation was calculated by Bentzen and Overgaard after post-mastectomy radiotherapy.[3] Since improved dose homogeneity in breast radiation plans, as has been seen with the introduction of breast IMRT has a major impact on the occurrence of moist desquamation (as will be discussed in the following section) it may also have an impact on the occurrence of telangiectasia and eventually the cosmetic outcome.[14] Acute toxicity has therefore clearly been shown to be associated with late toxicity and decreased QoL, rationalizing efforts to minimize seemingly 'temporary' effects of breast radiotherapy.

## 2.3. What is breast IMRT?

Radiation therapy is typically delivered by two opposing tangential fields directed to the breast at an angle approximately parallel to the chest wall with the patient lying on their back (supine). During the last decade, there have been significant improvements in computerized treatment planning systems and modifications to linear accelerators, which can allow for three-dimensional (3D) dose compensation not possible previously with standard breast radiation, as metallic wedge-shaped beam attenuators that were previously used attenuated the intensity of the beam to accommodate the

changing contour of the breast in a two dimensional plane – thus leading to substantial dose gradients (with 'hot spots') in areas of the breast away from the central axis. Our group recently published results from a multicentre randomized controlled trial (RCT) showing IMRT significantly improves toxicity compared to standard XRT using wedges for missing tissue compensation.[15] We randomized 358 women to either standard breast XRT using wedges or IMRT and found that there was a significant decrease in acute toxicity during or up to 6 weeks after XRT treatment, as the rate of moist desquamation was 47.8% in women receiving standard XRT compared with only 31.2% in women treated with IMRT (P=0.002). In this study IMRT was used to improve the dose distribution homogeneity in the breast, as illustrated by the removal of the 'hot-spot;' that is typically seen in the IMF where moist desquamation is most common.[5] Our breast IMRT RCT also found that moist desquamation is correlated with pain (P=0.002) and reduced QoL (P=0.003). Furthermore, extensive moist desquamation due to XRT is also recognized to significantly increase the risk of late skin effects such as telangiectasia.[3,14,16] As a result of our study, techniques that improve dose homogeneity and thus decrease acute toxicity such as IMRT have become the standard of care for adjuvant breast XRT.[17]

## 2.4. Factors associated with the development of skin toxicity?

### 2.4.1. *Predictors of skin toxicity in all women*

The strongest predictor for the development of acute and late skin toxicity following breast XRT remains breast size[5-7] which is likely due to the fact that larger breast size leads to an increase in dose heterogeneity within the breast, and in particular areas of higher dose in the IMF.[18,19] In a retrospective review of 197 patients treated at the Royal Marsden Hospital, the factors predictive of acute skin toxicity were beam energy ("low" e.g. $^{60}$Co *versus* "high" e.g. 6-8 MV; RR=5.9), breast size (RR=5.7), inclusion of the axilla (RR=4.6), and total radiation dose (RR=0.2; NB: inverse relationship due to overriding effect of treatment technique: supine *versus* semi-supine).[5] Furthermore, dose variation in excess of 10% within the breast was found to be the most important predictor of skin toxicity with a RR of 9.7 (p=0.001). Synchronous chemotherapy (RR=1.67, p=0.1), and age below 50 years (RR=1.11, p=0.44) were not found to be related to an increase in acute skin toxicity. In support of these findings, in a prospective assessment of late changes in breast appearance among 559 patients, dose inhomogeneity was significantly associated with the development of moderate or severe late changes.[7] Similarly in our breast IMRT RCT, when comparing large (sizes > 38C) to small (sizes < 32C) breast size, the OR of developing moist desquamation was 10.9 (95% CI; 4.5 – 26.2; P < 0.001).[15] In multivariate logistic regression analysis, breast size remained strongly associated with moist desquamation, with an OR of developing moist desquamation of 1.2 per 100cm$^3$ increase in breast volume (P < 0.001), suggesting

that even with improved dose distribution homogeneity provided with IMRT, the risk of acute toxicity in women with large breast size remains unacceptable.

2.4.2. *Factors influencing skin toxicity in large breasted women*

Most women undergoing adjuvant breast XRT are treated in the supine position, as it has the advantages of being comfortable for patients, allows for easy visualization of skin markings and provides simple immobilization and reproducibility. However in women with a large chest diameter or pendulous breasts this position results in the horizontal spreading of the breast, increasing the separation from the medial to lateral aspect of the breast, eventually resulting in difficulties to achieve dose homogeneity despite the use of IMRT as discussed previously. It is also possible that as large and pendulous breast tends to spread over the IMF in supine position the skin sparing effect of megavoltage beam become ineffective. Both of these issues result in higher doses being deposited in areas at risk of significant toxicity, including the IMF, and have prompted renewed interest in looking at optimizing patient treatment position in large breasted women, including treatment in the prone position.[18-23]

## 2.5. Prone breast IMRT

2.5.1. *Prone breast radiation and skin toxicity*

Adjuvant breast XRT in the prone position was developed mainly to address the issues of treating large breasts in the supine position as described above. In this setting gravity pulls the breast downwards and anteriorly, thus both lengthening and narrowing it, resulting in improved radiation dose distribution homogeneity throughout the entire breast and reduction of hot spots in the IMF.[21-24] In addition, using breast IMRT along with the prone position results in a very homogeneous dose distribution throughout the breast.[20,25] Several centres have published their clinical experience with prone breast XRT. Mahe et al reviewed 35 patients with large breasts treated in the prone position and found it was well tolerated, with no treatment interruptions and only low grade skin reactions noted in approximately 1/3 of the patients, though descriptions and data of toxicity were not explicitly reported.[23] Grann et al initially reported Memorial Sloan Kettering (MSK) preliminary data of acute and late toxicity in 56 patients with large breasts treated in the prone position, and found improved treatment tolerance with only one patient requiring a treatment break due to moist desquamation.[21] The MSK experience was recently updated to include 245 women. It continued to show low levels of moist desquamation/radiation dermatitis, with only 16 % experiencing acute RTOG grade 2 skin toxicity (defined as "Tender or bright erythema,/moist desquamation") and 2% RTOG grade 3 toxicity ("confluent, moist desquamation other than skin folds).[26] Consistent with this are the findings of our own pilot

data. We have used the prone technique at Sunnybrook for the large breasted women, who in our previous breast IMRT study had an over 50% risk of developing moist desquamation. In reviewing the XRT therapy charts (which are updated weekly during clinic review), as well as hospital records for the patient's first post treatment visit, moist desquamation was documented in 12/36 women (33%) that were treated in the prone position between May 2009 and Sept 2011(Unpublished; *Table 1*). There is increasing cohort study evidence to suggest that there is decreased toxicity using a prone breast IMRT technique[27], and we propose to test this hypothesis in a multi-centre RCT.

2.5.2. *Additional potential benefits and possible drawbacks of prone breast irradiation*

The majority of the published prone breast XRT studies have focused on dosimetric aspects of treatment and exposure to organs at risk (OAR; lungs, heart). Prone breast XRT has been shown to provide lower doses to OAR such as the ipsilateral lung.[20,24,28-31] Although most studies have shown decreased exposure to the heart while treated in the prone position,[24,28,31] there is evidence to suggest that for left sided tumours that are close to the chest wall depending on the extent to the treatment field, the prone position has the potential to increase exposure to the heart.[32,33] The most recent and conclusive study that compared women planned in both the supine and prone position has demonstrated that treatment in the prone position decreased lung exposure in all patients, and decreased heart exposure in 85% of the women with left-sided tumours.[34] In the remaining 15% the heart exposure was either equivalent or increased for women in the prone position. Interestingly, women with a large breast volume in this study had minimal heart volume within the treatment field when in the prone position, suggesting that for large breasted women there is an added benefit compared to being treated supine. We will add to the literature by conducting OAR exposure analysis to compare exposure to organs at risk.

Minimizing heart exposure is the standard of care despite modern radiotherapy which has largely decreased the risk of long term cardiac events that were seen with less sophisticated treatment.[35-37] Several studies have explored using defined radiation planning targets that are suggestive of 'unacceptable' heart exposures,[38-40] which may prompts the use of alternate treatment techniques such as Active Breathing Control (ABC), where the breast is only irradiated during deep inspiration, as the inflated lungs displace the heart away from the treated chest wall. In our study, women having >10% of the total volume of the heart receiving 50% of the prescribed dose (termed V25Gy > 10%) will be considered ineligible given conservative model based estimates that predict this level of radiation exposure to the heart is associated with a <1% probability of cardiac mortality approximately 15 years after radiation therapy.[38] Patients excluded due to this

'excessive' heart exposure will be treated at the discretion of the treating physician.

### 2.6. Summary of Rationale for this Study

The risk of moist desquamation in large breasted women remains unacceptably high and reactions tends to be severe and produce significant permanent and delayed side effects.[16] In our breast IMRT RCT the risk of developing moist desquamation for women with breast sizes of 40 inches or greater or a cup size of D or greater was 51.8%.[15] (*Table 2*) The evidence described above suggests that the use of a prone breast IMRT technique has the potential to decrease the risk of moist desquamation in large breasted women to the levels that are now seen when average/smaller breasted women are treated with supine IMRT. As prone breast XRT is currently only offered at 6 of 15 of the Ontario Cancer Centres polled for the purposes of providing motivation for this study, a multicentre RCT is feasible to confirm and quantify the improvement provided by the prone technique and provide Level 1 evidence for it to be adopted world-wide.

## 3. WHAT IS THE PROPOSED STUDY?

A multicentre RCT single blinded trial is proposed. Patients will be randomized between a standard (supine) arm and an experimental (prone) arm. The randomization will be blocked on post-operative bed boost delivery in order to get adequately balanced arms. Acute toxicity (radiation dermatitis/moist desquamation and pain) will be assessed at baseline prior to the start of radiotherapy, weekly during treatment and then weekly up to 6 weeks post-treatment until acute skin reactions resolve. All patients will be seen 6-8 weeks post treatment as per the standard of care. QoL will be assessed at baseline, during the last week of treatment, and then at the standard 6-8 week follow-up appointment. Long term follow-up in regards to recurrence and late toxicity at 5 years will be the subject of future grant renewal.

## 4. WHAT IS THE STUDY FEASIBILITY?

Using our previous breast IMRT trials experience, 33% of women accrued were classified as being 'large breasted' with a bra size of 40 inches or D cup or greater.[15] (*Table* 2). Between the 4 participating centres (Sunnybrook Odette Cancer Centre (Sunnybrook), R.S. McLaughlin Durham Regional Cancer Centre at Lakeridge Health Centre in Oshawa (Lakeridge), Simcoe Muskoka Regional Cancer Program at Royal Victoria Hospital in Barrie (RVH), BC Cancer Agency Vancouver Island Centre (BCCA-VIC), approximately

2650 women are treated with adjuvant breast XRT each year (Sunnybrook = 1400; RVH = 350; Lakeridge = 450; BCCA-VIC = 450). Using SEER data estimates for 2010, approximately 60% of all breast cancers are diagnosed at a localized stage.[41] Assuming that 60% of these women are treated with BCT and adjuvant XRT to the breast alone as suggested by Ontario ICES data,[42] approximately 315 women will be eligible for accrual each year (2650 women X 0.60 localized X 0.6 BCT X 0.33 large breasted) With a conservative estimate of 40% of eligible patients not being accrued (patient/doctor refusal, wound infection, unable to lie prone, unable to cover the postoperative bed with very medial tumours given interference with the prone breast board), we expect accrual at a minimum of 189 patients per year, easily achieving our goal of accruing 378 patients over 3 years.

# 5. STUDY POPULATION AND SAMPLE SIZE

## 5.1. Patient eligibility

5.1.1. Eligibility: Patients referred to one of the participating centres; Sunnybrook, Lakeridge RVH, BCCA-VIC for adjuvant XRT to the breast only with: (i) confirmed histological diagnosis of breast carcinoma or ductal carcinoma in situ (DCIS); (ii) treated with BCT; (iii) no indication for treatment of regional LN; (v) Women with a bra size of 40 inches or greater, or a pre-surgery cup size of D or greater

5.1.2. Ineligibility: (i) Regional LN XRT indicated; (ii) Bilateral breast cancer; (iii) unhealed wound (skin not closed and/or infection); (iv) previous XRT to the same breast; (v) unable to lie prone; (vi) presence of active connective tissue disease; (vii) pregnancy; (viii) unacceptable heart exposure (as measured by > 10% of the heart receiving 50% of the prescribed dose, i.e. V25Gy > 10%); (ix) adequate coverage of postoperative tumour bed not technically possible

## 5.2. Sample size

Sample size calculation for the current study assumes a moist desquamation rate of 50% for large breasted women treated supine given the rates seen in our IMRT trial (*Table 2*).[15] We hypothesize that prone breast IMRT may result in a relative reduction of acute skin toxicity by 30% (i.e. absolute change from 50% to 35%), given our preliminary evidence in the 36 patients treated prone in our centre between May of 2009 and Sept 2011 (*Table 1*). A total of 340 patients, 170 patients treated supine and 170 patients prone could test the hypothesis with a two tailed level of significance of 5% and a power of 80%. Accounting for a 10% loss of follow-up a total of 378 patients (189 per group) will effectively test the primary hypothesis.

### 5.3. Patient inclusion

Patients will be offered the study at time of post-surgical consultation for adjuvant radiotherapy. The trial will be fully explained to patients who will then be provided the Informed Consent. This study and consent will be reviewed again just prior to radiation planning at a separate appointment such that all questions are answered before obtaining written informed consent.

# 6. STUDY ENDPOINTS

### 6.1. Primary Outcome:

The primary outcome of this study is the incidence of maximum skin toxicity (moist desquamation) as per the CTCAE scale (*Table 3*)

### 6.2. Secondary outcomes of this study are:

6.2.1. Maximum acute breast pain: patient reported as per the VAS scale (*Appendix A)* and CRA reported pain as per the CTCAE scale (*Table 3*)

6.2.2. Change in health related Quality of Life as per the EORTC core QoL questionnaire (QLQ-C30; *Appendix B*) and the breast cancer module (QLQ-BR23; *Appendix C*) (defined in more detail in Section 6.1.3)

6.2.3. Differences in radiation exposure of adjacent normal OAR (heart, lung, liver, contralateral breast).

### 6.3. Endpoints evaluation

6.3.1. *Moist Desquamation*

The maximum skin toxicity will be assessed weekly during treatment, weekly for up to 6 weeks for patients being followed for toxicity resolution, and at 6-8 weeks post-treatment. Acute skin toxicity will be scored using the CTCAE scale for moist desquamation (*Table 3*). The maximum diameter of skin toxicity will be recorded. The area of skin toxicity (as defined by the maximum two perpendicular dimensions of the area involved) and the maximum skin toxicity of each area will also be recorded. Eight breast areas are at risk of skin toxicity: IMF, axilla, nipple area, breast divided into 4 quadrants (upper-outer, upper-inner, lower-outer and lower-inner quadrants), and if applicable the area of boost. The time of onset will be calculated in days from date of first treatment to the date of toxicity assessment. The duration of symptom will be calculated in days from the date that toxicity was first documented to the assessment date whereby the lesion has healed.

6.3.2. *Breast Pain*

Maximum breast pain will be assessed weekly during treatment, weekly up to 6 weeks for patients followed for toxicity resolution, and at 6-8 week post-treatment. Acute pain will be scored quantitatively by asking patients to rate its intensity using a Visual Analog Scale (VAS) ranging from 0 (no pain) to 10 (unbearable pain) (A*ppendix A*).[43] For quality control purposes the CTCAE pain scale will be used by the CRA to quantify breast pain using a four point scale; no pain; mild pain; moderate pain limiting instrumental activity of daily life (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.), and severe pain limiting self care of daily life (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden). (*Table 3*).

6.3.3. *Quality of Life*

QoL will be assessed using the EORTC core QoL questionnaire (QLQ-C30) and the breast cancer module (QLQ-BR23), which are well validated and widely used QoL questionnaires available in multiple languages.[44-47] QLQ-C30 is composed of 30 questions that represent 5 functional scales (physical, role, cognitive, emotional and social), 3 symptom scales (fatigue, nausea and vomiting, and pain), and a global health / QoL scale. The breast cancer module (QLQ-BR23), concentrating on QoL in breast cancer patients, consists of 23 questions addressing 4 functional scales (body image, sexual functioning, sexual enjoyment, future perspective) and 4 symptom scales (systemic side effects, breast symptoms, arm symptoms, hair loss). Questionnaires will be completed by patients at time of radiation simulation as baseline, in the 5th week of XRT (during routine review) and at 6-8 week follow-up.

# 7. PATIENT RISK

## 7.1. Physical

There is no anticipated additional physical risk for patients participating in this study, given both arms will receive the same "standard" radiation dose and fractionation, with radiation planning constraints based on current accepted centre guidelines. Patients that do not fulfill these constraints (e.g. excessive heart dose of V25Gy > 10%) will not be eligible for randomization and offered alternate treatment by the most responsible radiation oncologist as per the standard of care.

### 7.2. Psychological

It is possible that lying in the prone position may be associated with mild temporary discomfort for some patients. Patients treated prone may therefore not be as comfortable throughout treatment as those patients treated while supine.

### 7.3. Financial

Patients that experience acute toxicity will be asked to return to the cancer centre weekly (for up to 6 weeks) until resolution of their toxicity. To minimize additional personal costs to patient, patients will be reimbursed for parking for any visit required within the first 6 weeks after radiation has completed (i.e. for follow-up that is considered outside of the standard of care). Given there are no further differences in treatment regimens between arms, all of which is consistent with the standard of care (i.e. 5 weeks of daily radiation) there are no additional financial risks for patients.

## 8. RESEARCH METHODOLOGY

### 8.1. Consent and Randomization

A CRA will approach and give study information to all eligible patients, get informed consent, and register consenting patients into a secured database associated with a coded study number. Data collected will be entered into a separate secure database that identifies patients by their study number. Prior to CT Simulation, a radiation dosimetrist at the respective participating centre will contact the Sunnybrook data manager to determine which treatment arm the patient has been randomized into. Randomization will be performed, with blocking on the presence/absence of boost to the surgical bed using a software based randomization algorithm (SAS Version 9.1; SAS Institute, Cary, NC, USA).

### 8.2. Radiation Planning

All patients will receive an adjuvant XRT dose to the breast of 5000cGy in 25 fractions or 4256 cGy in 16 fractions (at the treating physician's discretion) using an IMRT technique. In both arms, boost to the surgical bed using a mini-tangent technique will be delivered at the treating oncologist's discretion. The boost dose and fractionation can be delivered sequentially, or delivered via a simultaneous intergrated boost during whole breast radiotherapy, as per the treating oncologist's preference. All patients will undergo CT Simulation. Patients randomized to the supine arm will be positioned supine on an angled breast board, with the ipsilateral arm abducted over her head. Patients randomized to the prone arm will be positioned prone on a prone breast board (PB06-S; Donaldson Marphil Medical, Brossard, Quebec) with both arms immobilized above the patient's head using a cushion-like Vacloc™ device. The prone breast board has an opening that allows the affected breast to be suspended into the

treatment fields as well as a supporting structure to help maintain the contralateral breast away from the treatment portal. Radiation beams will be shaped to encompass the breast volume requiring treatment in both arms. Dose distributions will be calculated using commercial planning systems (Sunnybrook and RVH: Pinnacle[3], Philips Medical Systems Inc., Cleveland OH; Durham – XiO/Focal, Elekta, Stockholm, Sweden; BCCA-VIC - Varian Eclipse, Palo Alto CA). Dose homogeneity optimization across the different breast volumes will be achieved using a standard forward-planned IMRT for both supine and prone patients. Patients that are found to have a heart V25Gy > 10%, will be deemed ineligible for study inclusion.

### 8.3. Acute Toxicity/QoL Measurement

Consistency in assessing skin toxicity between centres is required to minimize bias. At each centre only one CRA will be involved in toxicity assessment. The CRAs from all centres will have an initial training session prior to patient accrual to standardize skin toxicity assessment, pain and QoL instruments utilized in this study. To ensure consistency throughout the study, there will be training/case review sessions every 6 months starting at 1 year, with the last session at 30 months. Another potential source of bias comes from the assessment of acute skin toxicity assessment by an unblinded CRA. He/she has to be protected against unblinding regarding the treatment arm that the patient receives, and will never have access to the technical chart. Patients on treatment will be assessed in a separate clinic run by the CRA to avoid unblinding. All patients will have toxicity scores (as described previously in section 5) entered on a standardized toxicity reporting sheet, which denotes patients by their coded study number and month and year of birth (*Appendix D*). All toxicity score sheets will be signed off by the treating physician to ensure accuracy.

### 8.4. Data Management

All toxicity scores and QoL questionnaires will be entered by the respective CRAs into an on-line password protected, secure website based database. The database resides on a server which is a part of the Sunnybrook network which is protected by a standard firewall environment. The web interface is using the secure https protocol enabled by a website's security certificate (SSL). The database is accessible by authorized users only. The access is controlled by an authentication process in each session (user ID/password requirement) and session management (time-out after a certain period of inactivity). The patients in the study are managed using coded unique study identifiers. Information of the patients from different institutions are seen and managed by the members of those institutions only. For example, being logged in, a Sunnybrook physician can access only the Sunnybrook patients' information. The core study coordinators (PI, Sunnybrook data-manager) will have authority to view all patients entered for the purposes of data analysis. Copies of toxicity scores and QoL questionnaires will be couriered by registered mail to the

central organizing centre (Sunnybrook) for independent data quality assurance, with the original copies being maintained in a locked cabinet at the respective centres. An independent data monitorer will have access to the copied coded data sheets, and will only be able to view coded study identifiers and entered data in the online database (i.e. will have 'read-only' rights, therefore cannot edit the data). Discrepancies will be flagged, and brought to the attention of the respective treating centre's CRA for verification of data entered using the original copy of the data entry sheet. All changes in data entry will be automatically captured and noted.

**8.5. Data Analysis**

Descriptive statistics will be calculated for all variables of interest. Continuous measures such as age will be summarized using means and standard deviations (SD) whereas categorical measures will be summarized using counts and percentages. The primary analysis will be done on the basis of intention to treat. Sample size calculation is explained in section 5.2. The test of the primary hypothesis will be a comparison of the frequency of grade 2-3 CTCAE acute moist desquamation between women randomized to the supine arm compared to those randomized to the prone arm. This will be carried out using a two sample two-sided test of proportions which will also provide an odds ratio (OR) and it is associated 95% confidence interval (CI). The homogeneity of the OR across strata (boost delivered) will be assessed using Breslow-Day statistics. Multivariable logistic regression analysis will evaluate the relative risk of acute skin toxicity (dependent variable), and various independent variables: use or not of prone breast IMRT, breast separation, previous chemotherapy, age, Body Mass Index (BMI), total dose (boost versus no boost) and boost technique (sequential versus simultaneous) adjusting for the correlation among patients seen at the same centre. Identical analysis will be performed for the secondary aim, with comparison of frequency for grade 2-3 CTCAE pain. Patient reported pain as per the VAS scale will be analyzed as a continuous variable using a linear regression model.

The EORTC Scoring Manual will be adhered to for the scoring and analysis of QLQ-C30 and QLQ-BR23. All scores will be linearly converted to a 0 to 100 scale. For the functional and global health status / QoL scales, higher scores represent a better level of functioning. For the symptom scales, higher scores represent a greater degree of symptoms. The primary QoL analysis will be comparison of mean change in scores of the breast symptom scale of QLQ-BR23 between the two study arms. This will be carried out with a linear regression model comparing the scores between groups adjusting for the correlation among patients seen at the same centre. Our hypothesis is that a reduction in the IMF acute skin toxicity in the prone IMRT planned patients will be reflected in improved scores in the breast symptom, as compared to the supine IMRT planned patients. We will also examine whether there are differences in the physical function scale, pain symptom scale and global health status / QoL of QLQ-C30

as a result of the expected reduction in the skin toxicity using linear models. All analyses will be carried out using SAS Version 9.1 (SAS Institute, Cary, NC, USA).

Patients that consent to being contacted for future studies/analysis will be asked to complete the Breast Cancer Treatment Outcome Scale (BCTOS; [13] and the CRA will rate breast cosmesis using the Harvard Cosmetic Criteria and CTCAE Breast Cancer Rating System for cosmesis assessment prior to the start of radiation to provide baseline cosmetic results (*Appendix E*).[48] Although this data will be collected and stored in the research study database, it will not be used in the current analysis and patients will be explicitly told that it may or may not be used for future research if they consent to being contacted at some point in the future.

# 9. REGULATORY ISSUES

### 9.1. Funding of the study

The study is funded by the Canadian Breast Cancer Foundation (Ontario Chapter) through a peer reviewed grant. There is no conflict of interest for the investigators in participating in the study. Sunnybrook will act as the Trial sponsor. Outside centres will be provided 'per-case' funding that will be calculated to encompass all aspects of accruing, monitoring, data capture and data entry which will be expected from the participating centres.

### 9.2. Institutional Research Ethic Board approval

Ethics approval will be obtained from the Institutional Research Ethics Board in each participating site prior to the respective centre's study involvement.

### 9.3. Data management and Privacy

Patient's data will be entered into a secure database as fully described in Section 8 and hosted and maintained on the secure Sunnybrook network. After central patient randomization, patients will be assigned a coded unique study identifier that will be maintained in a separate secure password protected file within the database structure that can only be accessed by the study investigators and respective CRAs with appropriate levels of authority (which is built into the database). All toxicity data accumulated at the participating centres will be entered onto datasheets that use the coded study number as identifier (i.e. there will be no direct patient identifier in the study database or toxicity forms), and then entered into the online password protected web-based database. Copies of toxicity and QoL datasheets will be periodically sent to Sunnybrook using registered courier mail for data monitoring purposes, with original copies maintained at the respective treating centre in an organized locked cabinet.

### 9.4. Study registration

The study will be registered to the ClinicalTrials.gov website.

### 9.5. Publication policy

The results of this study will be published in peer reviewed journals. It will be the responsibility of the PI to ensure that results are published within a reasonable time of study completion. No material may be submitted for presentation and publication without prior review and a written approval by the study PI.

### 9.6. Trial committee

The trial committee includes Drs Vesprini, Olivotto, Truong, Stevens, El Mallah, Davidson, Sixel, Ms Bosnic, M. Tran and the trial biostatistician, Alex Kiss (Institute of Clinical Evaluating Sciences, Toronto). The committee have been involved with overall trial design and have finalised this version of the clinical trial.

### 9.7. Data Safety Monitoring Board (DSMB)

Although not expected, given the evidence discussed in Section 7.1, study completion will not be possible if prone breast IMRT increases toxicity. Data will therefore be analyzed and reviewed by an independent DSMB twice prior to study completion, after 1/3 and 2/3 patient accrual targets are met. The DSMB consists of: external radiation oncologist (Dr Jean-Michel Caudrelier – Ottawa Hospital Cancer Centre): internal breast surgical oncologist (Dr Claire Holloway – Sunnybrook Odette Cancer Centre): internal radiation oncologist (Dr Andrew Loblaw – Sunnybrook Odette Cancer Centre). The presence/absence of grade 2-3 moist desquamation as per the CTCAE scale (objective 1) will be compared between the experimental (prone) and standard (supine) arms using a chi square analysis to test for a statistical difference. The DSMB will be blinded to treatment arm, though will have the ability to request unblinding if any concerning excess toxicity is seen in either arm to determine appropriateness of trial continuation.

# 10. AMENDMENT HISTORY

### 10.1 – Oct 28th, 2013 amendment

This amendment allows for both sequential and simultaneous integrated (SIB) fractionation regimens to be utilized for those patients that are undergoing a breast 'boost'. This change was undertaken to increase accrual given mandatory sequential boost fractionation was shown to be a barrier. In addition, since the protocol was initially written SIB has become more widely adopted, so the investigators agreed to allow for alternate boost treatments to better reflect standard practice and experience. Given randomization is blocked on presence/absence of boost, this change will not affect the overall results though will be included in multi-variate analysis to ensure it does not have a confounding effect.

10.2 – May 16th, 2016 amendment

This amendment allows an additional radiation fractionation scheme to be utilized. This change was undertaken given the lack of ability of the treating physicians to use a shorter (hypofractionated) schedule has been identified as significant barrier to study accrual. This schedule was not included initially given large breasted women were not included in the randomized trials that compared the traditional 25 fraction course to the shorter 16 fraction course. There is now a significant amount of literature to suggest that there is no excess acute or late toxicity in women treated with the shorter schedule, including women with larger breast sizes. Given this, in consultation with the study statistician, the addition of this extra variable into planned multivariate analysis does not result in a need to increase sample size, and will be controlled for in the final analysis. This amendment also clarifies wording of the dose and fractionation of the breast boost, as multiple equivalent protocols are acceptable and not associated with significant differences in toxicity. This amendment removes Dr Pignol being the Study Co-chair given he is no longer at Sunnybrook, though he will continue to be academically involved as a member of the trial committee. His name has therefore been removed from the Informed Consent Form as one of the Principal Investigators. Dr Melanie Davidson, the lead physicist on this study has been designated the Study Co-chair in replacement of Dr Pignol. Given the Southlake Regional Cancer Centre joined the trial since the last amendment Dr Daria Comsa (a medical physicist) has been added to the Trial Committee as the representative from this centre.

Other minor changes to the Informed Consent Form are made to reflect the changes above as well as set the new time line in regards to expectation of study completion given the slower than expected accrual.

# 11. TABLES

11.1. **Table 1** – Sunnybrook Odette Cancer Centre Prone Breast Experience – May 2009 – Sept 2011

| pt# | Year | laterality | Moist Desquamation | Description | Dose | Boost | Boost dose |
|---|---|---|---|---|---|---|---|
| 1 | 2009 | Rt | Y | severe | 4256 | Y | 1250 |
| 2 | 2009 | Rt | N | | 4256 | N | |
| 3 | 2009 | Lt | Y | patch | 5000 | Y | 1000 |
| 4 | 2009 | Lt | N | | 4256 | Y | 1600 |
| 5 | 2009 | Rt | N | | 4256 | N | |
| 6 | 2009 | Rt | Y | superficial | 5000 | N | |
| 7 | 2009 | Lt | N | | 4256 | Y | 1250 |
| 8 | 2009 | Lt | Y | minimal | 5000 | Y | 1600 |
| 9 | 2009 | Lt | N | | 4256 | Y | 1250 |
| 10 | 2009 | Lt | N | | 4256 | N | |
| 11 | 2009 | Lt | N | | 4256 | Y | 1600 |
| 12 | 2009 | Lt | N | | 4256 | Y | 1000 |
| 13 | 2009 | Lt | N | | 4256 | N | |
| 14 | 2010 | Lt | N | | 4256 | N | |
| 15 | 2010 | Rt | N | | 5000 | Y | 1600 |
| 16 | 2010 | Rt | N | | 5000 | N | |
| 17 | 2010 | Rt | N | | 4256 | Y | 1250 |
| 18 | 2010 | Lt | N | | 5000 | N | |
| 19 | 2010 | Lt | N | | 5000 | N | |
| 20 | 2010 | Rt | Y | patch | 5000 | Y | 1000 |
| 21 | 2010 | Rt | N | | 4256 | N | |
| 22 | 2010 | Lt | N | | 5000 | N | |
| 23 | 2010 | Lt | N | | 4256 | Y | 1000 |
| 24 | 2010 | Lt | N | | 4256 | Y | 1250 |
| 25 | 2010 | Rt | Y | patch | 5000 | Y | 1000 |
| 26 | 2010 | Rt | N | | 4256 | Y | 1000 |
| 27 | 2010 | Rt | N | | 4256 | N | |
| 28 | 2010 | Lt | Y | patch | 5000 | Y | 1000 |
| 29 | 2010 | Lt | Y | patch | 5000 | N | |
| 30 | 2010 | Lt | N | | 4256 | N | |
| 31 | 2011 | Lt | Y | minimal | | N | |
| 32 | 2011 | Rt | Y | none given | 5000 | Y | 1000 |
| 33 | 2011 | Rt | N | | 5000 | N | |
| 34 | 2011 | Lt | Y | patch | 4256 | Y | 1000 |
| 35 | 2011 | Lt | N | | 4256 | N | |
| 36 | 2011 | Lt | Y | moderate | 4256 | N | |

11.2. **Table 2 -** Risk of moist desquamation according to breast size in women treated in the breast IMRT randomized controlled trial

| | | | Breast Size | | |
|---|---|---|---|---|---|
| | N | All patients (N =331) | Small (N=56) | Medium (N=165) | Large (110) |
| IMRT: | 170 | 31.2% | 3.5% | 27.1% | 51.8% |
| Wedges: | 161 | 47.8% | 22.2% | 41.3% | 70.4% |

Breast Sizes: Small breast size $\leq$ 36A; Medium breast size = 32C to 38B; Large breast size = >38B, D cup; IMRT = Intensity Modulate Radiation Therapy; Wedges = physical wedged shaped objects placed in the radiation beam's path to attenuate dose on uneven volumes such as the breast while patient is lying supine.

11.3. **Table 3 -** Adverse event measurements using the CTCAE 4.03 scale

| | **CTCAE Grade** | | | | |
|---|---|---|---|---|---|
| Adverse Event | 0 | 1 | 2 | 3 | 4 |
| **Radiation Dermatitis** | None | Faint Erythema or dry desquam ation | Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema | Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion | Life threatening consequences; skin necrosis or ulercation of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated |
| **Pain due to radiation** | None | Mild pain | Moderate pain; limiting instrumental ADLs (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.) | Severe pain; limiting self care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden) | |

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# APPENDIX A

## Patient reported pain measurement using the Visual Analogue Scale (VAS)

**The Visual Analogue Pain Scale is a simple assessment tool consisting of a 10 cm line with 0 on one end, representing no pain, and 10 on the other, representing the worst pain ever experienced.**


*No pain* *Maximum pain tolerable*

# EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

---

| | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 1. | Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. | Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. | Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. | Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. | Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

## During the past week:

| | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 6. | Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. | Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. | Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. | Have you had pain? | 1 | 2 | 3 | 4 |
| 10. | Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. | Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. | Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. | Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. | Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. | Have you vomited? | 1 | 2 | 3 | 4 |
| 16. | Have you been constipated? | 1 | 2 | 3 | 4 |

Please go on to the next page

| **During the past week:** | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

## For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

# EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

| **During the past week:** | | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|---|
| 31. | Did you have a dry mouth? | 1 | 2 | 3 | 4 |
| 32. | Did food and drink taste different than usual? | 1 | 2 | 3 | 4 |
| 33. | Were your eyes painful, irritated or watery? | 1 | 2 | 3 | 4 |
| 34. | Have you lost any hair? | 1 | 2 | 3 | 4 |
| 35. | Answer this question only if you had any hair loss: Were you upset by the loss of your hair? | 1 | 2 | 3 | 4 |
| 36. | Did you feel ill or unwell? | 1 | 2 | 3 | 4 |
| 37. | Did you have hot flushes? | 1 | 2 | 3 | 4 |
| 38. | Did you have headaches? | 1 | 2 | 3 | 4 |
| 39. | Have you felt physically less attractive as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 40. | Have you been feeling less feminine as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 41. | Did you find it difficult to look at yourself naked? | 1 | 2 | 3 | 4 |
| 42. | Have you been dissatisfied with your body? | 1 | 2 | 3 | 4 |
| 43. | Were you worried about your health in the future? | 1 | 2 | 3 | 4 |

| **During the past four weeks:** | | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|---|
| 44. | To what extent were you interested in sex? | 1 | 2 | 3 | 4 |
| 45. | To what extent were you sexually active? (with or without intercourse) | 1 | 2 | 3 | 4 |
| 46. | Answer this question only if you have been sexually active: To what extent was sex enjoyable for you? | 1 | 2 | 3 | 4 |

Please go on to the next page

| **During the past week:** | | **Not at All** | **A Little** | **Quite a Bit** | **Very Much** |
|---|---|---|---|---|---|
| 47. | Did you have any pain in your arm or shoulder? | 1 | 2 | 3 | 4 |
| 48. | Did you have a swollen arm or hand? | 1 | 2 | 3 | 4 |
| 49. | Was it difficult to raise your arm or to move it sideways? | 1 | 2 | 3 | 4 |
| 50. | Have you had any pain in the area of your affected breast? | 1 | 2 | 3 | 4 |
| 51. | Was the area of your affected breast swollen? | 1 | 2 | 3 | 4 |
| 52. | Was the area of your affected breast oversensitive? | 1 | 2 | 3 | 4 |
| 53. | Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)? | 1 | 2 | 3 | 4 |

Study ID - PB __ __ - __ __ __ DOB: Month _____, Year _____

RT Start Date _____ Date of visit _____

Week of assessment _____ ☐ Baseline ☐ On Treatment ☐ Post Treatment FU

## CRA assessed skin toxicity (place X in appropriate box)

| CTCAE Grade | | | | | |
|---|---|---|---|---|---|
| Adverse Event | 0 | 1 | 2 | 3 | 4 |
| Moist Desquamation | None | Dry desquamation | Patchy moist desquamation, mostly confined to skin folds and creases | Moist desquamation in areas other than skin folds and creases | Life threatening consequences; skin necrosis or ulceration of full thickness dermis; |
| Erythema | None | Faint | Moderate to Brisk | - | - |
| Oedema | None | Localized, no disability or functional impairment | Moderate Localized; limiting instrumental ADLs | Severe localized; limiting self care ADL | - |

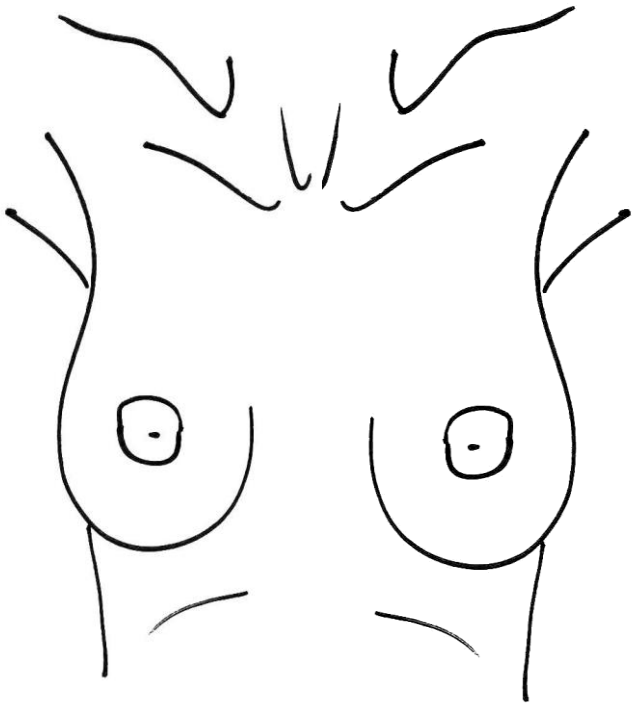
## Moist Desquamation

Max diameter (mm) _____
Perpendicular diameter (mm)_____

Note Location on diagram and on list below

Infra-mammary fold _____
Axilla _____
Nipple _____
Quadrant
- Upper-outer _____
- Upper-inner _____
- Lower-outer _____
- Lower-inner _____

Area of boost _____



Study ID - PB __ __ - __ __ __ DOB: Month _____, Year _____

RT Start Date _____ Date of visit _____

Week of assessment _____ ☐ Baseline ☐ On Treatment ☐ Post Treatment FU

## CRA assessed breast pain (place X in the appropriate box)

| | CTCAE Grade | | | | |
|---|---|---|---|---|---|
| Adverse Event | 0 | 1 | 2 | 3 | 4 |
| Pain | None | Mild pain | Moderate pain; limiting instrumental ADLs (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.) | Severe pain; limiting self care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden) | |

## Patient reported pain measurement using the Visual Analogue Scale (VAS)

"Please rate the worst amount of pain (if any) that you have had over the past 7 days in the treated breast, by placing a vertical line in the scale below. 0 means no pain, a line on 10 means the worse pain tolerable, and a line in between means less than the maximum tolerable"

0 ◆——————————————◆ 10

*No pain* *Maximum pain tolerable*

CRA VAS scale measurement (in mm) _____

**Medication prescribed** – (Yes/No) – Medication Name _____

**Is this the last radiation treatment examination?** ☐ Y ☐ N

If YES → Select one of these 3 follow up plans:

☐ Patient does not have any severe skin toxicities. Patient booked to return 6 weeks post radiation treatment for follow up.

☐ Patient has some skin toxicities. Patient to be contacted by phone weekly (up to 6 weeks) post radiation treatment until skin toxicities diminishes.

☐ Patient has severe skin toxicities. Patient to return weekly for examination of skin until skin toxicities diminishes.

_____ _____

Signature of CRA completing the form Date of Signature

_____ _____

Signature of Investigator Date of Signature