

6-2014

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Donita Blanken-Little

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Recommended Citation

Blanken-Little, Donita, "Safety and Efficacy Study of Intra-Operative Radiation Therapy Using Xofig at the Time of Breast Conservation Surgery for Early Stage Breast Cancer" (2014). *Graduate Research Projects*. Paper 18.

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Safety and Efficacy Study of Intra-Operative Radiation Therapy Using Xoft at the Time of
Breast Conservation Surgery for Early Stage Breast Cancer

Donita Blanken-Little RN, BSN

June 12, 2014

A Paper Presented to Meet Partial Requirements

For NRSG 594

MSN Capstone

Southern Adventist University

School of Nursing

Chapter 1: Introduction

Breast cancer is uninhibited cellular growth that occurs within the breast. Although there are many different forms of breast cancer, the most common type of breast cancer found in women is ductal carcinoma in situ (DCIS). DCIS is a noninvasive form of breast cancer where malignant cells arise and proliferate within the breast ducts without invasion of the basement membrane. DCIS is a precursor for invasive ductal carcinoma and therefore if left untreated can invade the epithelial membranes of the surrounding tissue and becomes an invasive infiltrating type of breast cancer (Reynolds, 2013). Invasive ductal carcinoma may develop in 30 to 50% of all DCIS cases (Lee, Vallow, McLaughlin, Hines, & Peterson, 2012).

Description and Prevalence of the Problem

One out of every eight women will be diagnosed with breast cancer. These statistics make it the most frequently diagnosed cancer in women. The American Cancer Society projects that 295,240 breast cancer diagnoses will occur in 2014, this includes invasive and noninvasive breast cancer. The breast cancer mortality rate for 2014 is an estimated 13.6 % making it the second leading cause of cancer death in women (American Cancer Society, n.d.). With statistics such as these, it is not hard to comprehend why so much research is being done to find effective treatments, preventative measures, or a cure for this disease.

Survival rates for breast cancer are determined by the cancer staging at diagnosis. Research has show that an earlier diagnosis yields a better outcome. With the advancements in screening technology and treatment, more women are being diagnosed early at a localized stage and the average age range is 50 to 60. Most treatment regimens for breast cancer involve surgery, chemotherapy, and radiation. These modalities are dictated by the National Comprehensive Cancer Network (NCCN) guidelines. Given that these women are being

diagnosed at a younger age, the treatments take weeks and months to complete. This places these women with a hardship of treating their cancer while raising children, balancing a career, and living life. Conventional radiation techniques that are the standard of care currently state that women must have external beam radiation daily five days a week for an average of six weeks.

Purpose Statement

The goal of this research is to assess the efficacy of single-fraction intra-operative radiation therapy (IORT) using the Xoft Axxent System at time of breast conserving surgery for early stage breast cancer. PICO: Intra-operative radiation therapy (IORT) using the Xoft Axxent eBx System is no worse (non-inferior) than whole breast irradiation when used as stand-alone radiation treatment in breast conserving therapy in women with early stage breast cancer.

Rationale for Review

The primary efficacy endpoint for this research is to demonstrate that the local recurrence rate of intraoperative radiation therapy is non-inferior to external beam radiation. The potential benefits of IORT are; elimination of tumor tissue, decrease the likelihood of recurrence, reduce radiation delivered to non-target tissue, accelerated delivery system, reduced treatment time, improved cosmetic aesthetics post treatment, and decrease the incident of skin fibrosis.

Definition of Major Terms

Breast Cancer- Cancer that forms in the tissue of the breast.

Breast Conservation Surgery- An operation to remove the breast cancer but not the breast itself.

Types of breast-conserving surgery include lumpectomy (removal of the lump), quadrantectomy (removal of one quarter, or quadrant, of the breast), and segmental mastectomy (removal of the

cancer as well as some of the breast tissue around the tumor and the lining over the chest muscles below the tumor). Also called breast-sparing surgery (National Cancer Institute, n.d.).

Ductal Carcinoma in Situ- (DCIS) of the breast is characterized by malignant epithelia cells confined to the ductal system of the breast without evidence of invasion through the basement membrane into the surrounding tissue.

Intra-Operative Radiation Therapy- (IORT) is a single fractional dose of radiation that is delivered directly to the tumor bed during breast conservation surgery.

Total Mastectomy- Surgery to remove the entire breast and surrounding lymph tissue.

Whole Breast Radiation Therapy (WBRT) or External Beam Radiation Therapy (EBRT)- Uses high-energy x-ray (linear accelerator) to directly deliver radiation to the tumor.

Theoretical Framework

In researching the different treatment options available for breast cancer the theoretical framework that seems to assess all aspects of the patient is Betty Neuman's Systems Model. Neuman's System theory includes the following concepts; a wholistic client, an open system, and stressors. The patient is viewed as a whole, whose body is in constant interaction with the with the evolving environment, other people and within themselves (Neuman & Fawcett, 2002). The interaction between any of these concepts can induce stress to the patient and disrupt wholeness.

Stressors are viewed as anything that interrupts stability of an individual and poses a risk to the body's normal line of defense. The individual's reaction to the stressor is dependent upon the time of occurrence, the present and past condition of the individual and the individual's ability to adapt to the stressor. Stressors may be intra, inter, and extra-personal (Neuman&

Fawcett, 2002). The stressors in regards to breast cancer and cancer treatment are discussed in the following paragraphs.

Intrapersonal stressors are internal environmental forces occurring within the patient. Examples of intrapersonal factors in relation to breast cancer that could pose stress to a client are the initial diagnosis of cancer and the uncertainty of survival. The pain associated with surgical removal of the cancer and any associated radiation treatments, alteration in body image and disruption of the woman's sexuality.

Interpersonal stressors are external environmental interaction forces occurring outside the client (Neuman & Fawcett, 2002). Interpersonal stressors related to breast cancer may include changes in role expectation within the family unit, or conflicts related to surgery, procedures and treatments. Disruption to daily living by cancer treatment can cause the patient to have increased stress and progress to requiring extra energy to adapt to this stressor.

Extrapersonal factors are external factors or interactions occurring outside of the patient at a distant range, (Neuman & Fawcett, 2002). Hospitalization, frequent trips to the physician, and radiation treatment are just a few examples of this type of stressor.

The ultimate goal of Neuman's System Models in relation to breast cancer it to help the patient deal with the interpersonal, intrapersonal, and extrapersonal stress factors. Positive interaction with any of the stressor will help the patient cope with cancer and promote wellness within, which will in turn return the person back to a whole.

Chapter 2: Literature Review

The literature search was accomplished using the CINAHL, Academic Search Premier, and MEDLINE databases. Search words included "breast cancer," "ductal carcinoma in situ," "Xoft," and "intraoperative radiation therapy," during the time period of 2004-2014. The

inclusion criteria for this review were articles that focused on defining breast cancer and ductal carcinoma in situ, and the modalities of treatment. All literature had to be scholarly and peer reviewed. The reference lists of the selected articles were also reviewed and were included. The literature is comprised of 1791 pertinent scholarly articles of breast cancer, types of breast cancer and modalities of treatment.

Once considered to be a rare breast lesion, DCIS now constitutes 20 % of all newly diagnosed breast cancer cases. One case of DCIS will be detected in every 1300 screening mammograms (Siziopikou, 2013). Patients with DCIS can be asymptomatic at the time of presentation (mammogram) or present with symptoms as a palpable mass or nipple discharge. Prior to the advent of widespread screening mammograms DCIS was diagnosed by surgical removal of a suspicious breast mass. The incidence of DCIS has markedly increased, primarily due to improved screening and imaging techniques. This has led to a shift in disease presentation from in the past where patients presented with symptomatology to the current period where the disease is detected solely by abnormal mammographic finding (Moran et al., 2012).

Conventional mammography is the gold standard modality used for annual breast cancer screening to detect calcifications as well as any soft tissue changes (Reynolds, 2013). On a mammogram, DCIS appears as clustered microcalcifications. These calcifications differ in density, form and size and are grouped together in linear or segmental arrangements reflecting their presence in the ducts (Lee, Vallow, McLaughlin, Hines, & Peterson, 2012).

There are several risk factors associated with DCIS. Less educated women had a greater cumulative incidence of DCIS than women with a higher education. Breast cancer registry data consistently show that the incidence of DCIS increases until age 65-69 then declines. According to the World Health Organization Collaborative Study on Neoplasia and Steroid Contraceptive

there is a significant increase of DCIS in women over the age of 35 that used oral contraceptives. Women with four or more children had a 38 % decreased risk of DCIS (Virnig, Shamliyan, Tuttle, Kane, & Witt, 2009).

The management and treatment of DCIS is very controversial for many reasons. There are no prospective randomized trials comparing mastectomy, breast conservation with radiation and breast conservation without radiation for the treatment of DCIS. Retrospective data suggest survival is similar among all methods of treatment (Lee, Vallow, McLaughlin, Hines, & Peterson, 2012).

As the incidence of DCIS increases, the treatment options continue to evolve. Traditional treatment for DCIS was total mastectomy, which often required cosmetic reconstruction surgery. Previous standards of care have transitioned from radical surgery only (total mastectomy) to bimodality treatments consisting of breast conservation surgery (BCS) partial mastectomy, lumpectomy with external beam radiation treatment (EBRT) (Ash, Williams, Wagman, & Forouzannia, 2013). The modality of treatment is based on type and stage of breast cancer the patient has.

Mastectomy was traditionally the standard of care for DCIS and historical data demonstrated the risk of local recurrence post mastectomy is extremely low. Simple mastectomy remains a treatment option however results from the National Surgical Adjuvant Breast and Bowel Program (NSABP) B17 study established that breast conservation surgery followed by radiation as a standard treatment option for DCIS (Siziopikou, 2013).

Breast conservation surgery for DCIS combined with external beam radiation therapy can reduce the risk of local recurrence but is associated with significant cost. Treatment modality of using EBRT timespan ranges from five to seven weeks and is associated with interruption of

daily life and financial burdens. Transportation to a radiation center, physical limitations and or lack of family support may prevent many patients from selecting breast-conserving therapies. In addition, EBRT is associated with potential acute and chronic toxicities to the surrounding normal tissue such as dermatitis, soft tissue fibrosis, rib fractures, hyperpigmentation, and volume loss of breast tissue in the treated breast and an increase risk of cardiac disease in patients with left sided breast cancers (Ash, Williams, Wagman, & Forouzannia, 2013).

A therapeutic alternative to EBRT would be a treatment that has equivalent efficacy while reducing overall toxicity and treatment duration. Intraoperative radiotherapy (IORT) is radiotherapy that delivers radiation to the tumor bed during surgical excision of cancerous lesions (Reitsamer et al., 2008). This treatment can reduce or eliminate the need for external beam radiation therapy. This treatment approach has the potential to significantly reduce normal tissue toxicity. IORT avoids radiation to the skin and limits radiation exposure to normal breast tissue. Radiation dose to deep structures, such as heart, ribs and lungs is reduced since IORT utilizes electron or low energy x-ray (Ash, Williams, Wagman, & Forouzannia, 2013). A highly favorable aspect of IORT is direct visualization of the target volume need to ensure appropriate treatment coverage needed and this visualization reduces the risk of geographic oversight (Sinha, 2008).

Ductal carcinoma in situ is a disease with heterogeneous clinical behaviors and successful treatment of DCIS requires a multidisciplinary approach. At the present time no well-established studies to direct the change of treatment or to predict the clinical behaviors of DCIS. Several clinical trails such as Xoft and the TARGIT trail are ongoing and show many improved strategies for treating breast cancer.

Chapter 3: Methods

Design

This is a single-arm, historical controlled, non-randomized, non-inferiority study of subjects treated with single fraction, intra-operative radiation therapy at the time of breast conserving surgery for early stage breast cancer. This is a multicenter study being conducted at The Sara Cannon Cancer Center at Parkridge Medical Center in Chattanooga Tennessee and multiple centers across the United States, Spain and Germany. The Primary Investigator for the Sarah Cannon Cancer Center is Dr. Stephen Golder a Radiation Oncologist and Sub Investigator is Dr. Laura Witherspoon a specialty train breast surgeon.

This prospective study is sponsored and monitored by Xoft Axxent eBx Systems. Subject that enrolled in this study will be only treated with the Xoft Axxent eBx System at the time of breast conserving surgery.

Population

This phase IV clinical trial is currently enrolling up to 1,600 eligible participants in fifty centers across the United States and Europe. The trial period will be ongoing during June 2012 to June 2014 and will be comprised of females greater than or equal to forty years of age.

Variables

The variables under study for this research are the following: age, sex, biopsy proven invasive ductal carcinoma or ductal carcinoma in situ of ipsilateral or bilateral breast with tumors less than or equal to 3.0 cm in greatest diameter. Cosmesis of bilateral breast using the Harvard Scale and skin assessment is performed at baseline and during month 6, 12, 18, year 2 and then annually through 10 year follow up. The rate and severity of adverse events, disease free and

overall all survival rates will be assessed during the ten-year follow up. Other variables assessed were quality of life pre and post treatment. All these variables were compiled to evaluate the success of intervention of Xoft intraoperative radiation therapy for breast cancer.

Measurements

The analysis of the primary endpoint of breast tumor recurrence at five and ten years will be done by utilizing a random effects model for joint analysis of survival proportions reported at multiple time points during the study. Patient baseline characteristics for age at enrollment, ethnicity, menopausal status, tumor size, grade and classification, prior cancer history, family history of breast cancer, pregnancy history, volume of tissue excise and medications will be summarized. These comparisons are presented in order to identify any major baseline site or therapy differences that could affect outcomes.

Descriptive statistics for continuous variables will consist of the mean, median, standard deviation, minimum and maximum values. When comparisons are presented a Chi-Square test for categorical variables, one-way ANOVA for continuous variables will be used or the equivalent non-parametric test in the case where there is no identifiable distribution.

The Xoft Axxent Electronic Brachytherapy System and balloon applicator and sources are FDA cleared. An independent Data and Safety Monitoring Board will review safety and adverse events throughout the duration of the trial.

Results and Discussion

How Role Evolved

I first was made aware about this current research by speaking with Kassie Britton RN who is the research coordination with the Sarah Cannon Cancer Center at Parkridge Medical Center. I discussed with her my desire to get involved with some research project and she told

me about some research projects going on within her department. This evolved as a beginning point to be involved with the Xoft phase 4 clinical trials for early-staged breast cancer.

Role as Research Assistant

As a research assistant for this study I performed chart reviews on patients who were diagnosed early stage breast cancer, ductal carcinoma in situ (DCIS) during a three-month period of 2014. I audited and compiled the outcome variables of pre and postoperative visits. I performed over 60 hours reading, interpreting, synthesizing and logging in data. I also assisted the researcher in other ways such as organizing, storing, and filing paperwork for this study.

I was very fortunate to be able to follow one subject from the first interview for possible participation to being involved during her surgical procedure and seeing first hand the intraoperative radiation treatment. At her one month follow up I was able to assess her quality of life post surgery and cosmeis of her breast post surgery and post IORT.

Findings

This study is still in the collection phase of its findings therefore no findings are available to report at this time. The target enrollment date is completed and subject's data will be followed for a period of ten years.

Chapter 4: Evaluation

Overall I learned a great deal from this experience. This was my first experience with research and synthesizing information from charts and interviewing subject for a study. I found I gained more knowledge about breast cancer and cancer treatments. When I began my chart reviews I found I had to look up a lot of information so I could understand what I was reading from radiological reports, pathology reports and CT scans. Just simple terminology was hard to interpret at first but the more I became familiar with anatomy of the breast and the various tools

being used during the procedures I found I was quicker by the end. Overall this was a great experience and it opened my eyes on how hard it is to conduct research and then to follow through with the findings. This clinical trail has finished its enrollment period and subjects will be followed during the next ten years and hopefully this research will aid in the advancement of breast cancer treatment.

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