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Electronic Brachytherapy (eBx)-Mohs Matched Pair - Cohort Study

A Multi-Center Retrospective-Prospective Matched Pairs Cohort Study to Assess Long-term Clinical Outcomes of Non-melanoma Skin Cancer Patients Treated with eBx Compared to Non-melanoma Skin Cancer Patients Treated with Mohs Surgery

Protocol Number:
CTPR-0014 Revision F

Co-Principal Investigators

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Scientific Advisor

Ahjay Bhatnagar, MD

Sponsor:
Xoft, Inc. – a subsidiary of iCAD, Inc.

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INVESTIGATOR AND SUB-INVESTIGATOR AGREEMENT

eBx-Mohs Matched Pair Cohort Study

A Multi-Center Retrospective-Prospective Matched Pairs Cohort Study to Assess Long-term Clinical Outcomes of Non-melanoma Skin Cancer Patients Treated with eBx Compared to Non-melanoma Skin Cancer Patients Treated with Mohs Surgery

PROTOCOL NUMBER: CTPR-0014 REV F

Signature below signifies Xoft – a subsidiary of iCAD has approved this Protocol:

_____ _____

John DeLucia Date
Vice President, RA, CA, QA
iCAD Inc. and Xoft Inc., a subsidiary of iCAD
98 Spit Brook Road, Suite 100
Nashua, NH 03062

The Study Principal Investigator's Signature or the study site's sub-investigator's signature signifies acceptance of this Multi-Center Retrospective-Prospective Follow-up Study of Patients Treated with Electronic Brachytherapy or Mohs Surgery for the treatment of Non-melanoma Skin Cancer (NMSC) and agrees to participate in the study in accordance with the protocol and Protocol requirements stated herein:

_____
Principal Investigator or Sub-Investigator Signature

_____
Printed Name

_____
City, State Zip

2 PROTOCOL SYNOPSIS

STUDY NAME	CTPR-0014 Rev F March 7, 2017: A Multi-Center Retrospective-prospective Matched Pairs Cohort Study to Assess Clinical Outcomes of Lesions Treated with eBx Compared to Lesions Treated with Mohs Surgery
CO-PRINCIPAL INVESTIGATORS	Rakesh Patel, MD and Robert Strimling, MD
SITES	Up to 5 sites will participate
STUDY DESIGN	This is a retrospective-prospective study design. Patients who completed treatment approximately 3 years (range of 2-4 years) at time of initial IRB approval of this study will be identified and any existing data in the patient's record will be collected in addition to conducting office visits for long-term follow-up. The study will include 2 parts: 1. Retrospective chart review: Collect data from patient records who completed treatment a minimum of 2 years prior to study onset and determine the feasibility of doing a matched pair cohort study comparison of eBx versus Mohs surgery. The history, demographic and treatment data will be retrospectively collected from up to 320 subjects previously treated with eBx for the treatment of NMSC and up to 320 subjects previously treated with Mohs surgery for the treatment of NMSC. 2. Prospective Follow-up: Patients will return for long-term follow-up visits for the investigators to assess the lesion site, document absence of recurrence/ absence of recurrence, toxicities, and collect patient reported outcomes.
SAMPLE SIZE	Up to 640 patients who will return for follow-up approximately 2 to 5 years post treatment so that at least 586 lesions have long term follow-up data collected. Follow-up may range from approximately 2 to 5 years post treatment. Up to 2 visits may be completed by each subject, one in 2016, and one in 2017-2018.
STUDY OBJECTIVES	1. To evaluate local recurrence of eBx and Mohs treated lesions. 2. To evaluate toxicities related to eBx and Mohs treatments. 3. To evaluate cosmetic outcomes for lesions treated with eBx and Mohs. 4. To assess the ability to deliver therapy with eBx and Mohs treatment modalities.
PRIMARY ENDPOINT	Absence of local recurrence at approximately 3 to 5 year follow-up (range is approximately two to five years) at treatment site(s).

SECONDARY ENDPOINTS	1. Comparison of long-term toxicities related to eBx vs. Mohs treatment; 2. Comparison of long-term cosmetic outcomes for lesions treated for NMSC with eBx vs. Mohs; 3. Comparison of Chronic toxicities; 4. Comparison of Patient Reported Outcomes (PRO) using a patient survey.
ESTIMATED STUDY PERIOD	Follow-up Visits #1: August 29, 2016 – August 31, 2017 Data Collection & Data Entry: August 29, 2016 – September 31, 2017
	Prospective Follow-up Visit #2: August 31, 2017- January 31, 2018 Data Entry: August 1, 2017 – February 28, 2018
SPONSOR & FUNDING PARTY	Xoft – a subsidiary of iCAD, Inc. San Jose, CA
STATISTICAL ANALYSES	Xoft – a subsidiary of iCAD, Inc. San Jose, CA
STUDY MANAGEMENT	Eminence Clinical Research, Inc. Colorado Springs, CO
ELECTRONIC DATA CAPTURE	Eminence Clinical Research, Inc. Colorado Springs, CO
MEDICAL WRITING ASSISTANCE	Eminence Clinical Research, Inc. Colorado Springs, CO

3 STUDY CONTACTS

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4 INTRODUCTION AND BACKGROUND

More than one million skin cancer cases occur annually.[1] Most of these forms of skin cancers are curable. Carcinoma is a medical word for a cancer that starts in a lining layer of cells such as the skin or the lining cells of the digestive system. There are many types of keratinocyte cancer, but two types of epithelial skin cancers are most common, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

Epithelial skin cancer is a common neoplasm that affects more than a half of a million people each year. The most serious of skin cancers is melanoma, which was diagnosed in approximately 60,000 people in 2007. However, the majority of these lesions, estimated to be eighty to ninety percent, are basal cell cancers and the remainder is categorized as squamous cell.

Both types of malignancies are related to ultraviolet light exposure from the sun.[1-3] Basal cell cancer begins in the lowest layer of the epidermis, the basal cell layer. About eight out of ten skin cancers are BCCs. They usually begin on areas exposed to the sun, such as the head and neck. BCC was once found mostly in middle-aged or older people, in the fourth decade of life and beyond. But now it is also being seen in younger people. This may be because people are spending more time in the sun without protecting their skin. BCC tends to grow slowly. It is very rare for a basal cell cancer to metastasize. But if left untreated, it can grow into nearby areas and spread into the bone or other tissues beneath the skin.

SCCs are more likely to spread into fatty tissues just beneath the skin. They are also more likely to spread to lymph nodes or to distant parts of the body than are BCCs, but this is not common. With thorough screening these neoplasms can be identified at an early stage. With the selection of the appropriate treatment option, these cancers can result in excellent local control with excellent cosmesis results.[1, 2]

There has been a diverse variety of modalities developed for the treatment of basal cell and SCC over the years, from surgical excision, to Mohs micrographic surgery, to radiation therapy. The location of the cancer and the extent of the disease effect the treatment options available to patients.[3] The following section provides an overview of the different treatment modalities published in the literature.

Lovett et al reported on 339 patients who were consecutively treated for histologically confirmed basal cell (71%) and squamous cell (29%) carcinoma.[5] A retrospective study was performed to assess local recurrence. The majority of the basal cell lesions (93%) and 97% of the SCCs were on the head. Radiation therapy was the initial treatment modality in 212 patients, and 127 patients were treated with radiation therapy after the initial surgical excision failed. Tumor control was analyzed by the type of external beam radiation therapy administered. The local control for superficial x-ray ranged from 91 to 100% reported categorically by tumor size. Electron beam ranged from 70 to 75% local control. Patients were stratified into groups by the

type of radiation beam used on the treatment. Excellent to good cosmesis was seen in 97% of the patients treated with superficial X-rays and in 78% of the patients treated with electrons, 78% of the patients treated with mixed beams, and in 80% of the patients treated with megavoltage photons. The overall complication rate (complications were defined as grade 4 toxicities[4]) for the 310 patients whose data was available was 5.5%. Of the 217 previously untreated patients, the complication rate was 3.2%.[, 5]

Silva et al report on a retrospective review of radiation therapy treatment for basal cell, squamous cell, and basal-SCC from 313 patients with 334 lesions treated. The objective of this study was to assess local control and late toxicities in patients treated with radiation therapy for the treatment of cancer of the pinna of the ear. For 270 patients, radiation therapy was the primary treatment, 50 patients received radiation therapy for recurrent cancer that had not previously undergone resection, and 12 patients received radiation therapy as an adjuvant treatment.[6]

Orthovoltage X-ray radiation therapy (100-250 kV) was used in 83% of the patients, and electron radiation therapy was used in approximately 12%. The rest were treated with megavoltage X-rays (primarily ^{60}Cobalt). The prescriptions were as follows: 17.5 Gy-20 Gy in one fraction, 35 Gy in five fractions with 7 Gy per fraction, 42-45 Gy in ten fractions with 4.2 to 4.5 Gy per fraction, and 50 to 60 Gy divided among 20 to 30 fractions with less than 3 Gy per fraction. Thirty-five (35) Gy was prescribed for 124 of the 313 patients. The follow-up ranged from 0.12 to 13.37 years. The primary endpoint was time to local failure, and the secondary endpoint was significant grade 4 late toxicities. Local control rate was reported to be 9% for patients who present with early stage cancer with tumor size 2cm or less in diameter. Orthovoltage X-ray radiation therapy has been shown to be efficacious primary treatment for squamous cell and BCC.[6]

Chan et al report on a single center experience for the treatment of basal cell and SCCs. They studied 1005 lesions treated with single fraction radiotherapy. This retrospective chart review took place ten years later to allow for follow-up. All patients were treated with 45-100 kV X-ray. The radiation doses administered were 22.5 Gy, 20 Gy and 18 Gy. The 18 Gy prescription was reserved for patients who were considered frail or had very small tumors. The study endpoints were recurrence and late necrosis over a ten-year period. There was no difference in the recurrence rate for the group treated with 20 Gy versus 22 Gy, but there was a significant increase in late skin necrosis rate ($p=0.002$). Most tumors were in the head and neck regions. One subgroup in this study, patients who received radiation therapy for the treatment of cancer of the inner canthus of the ear, showed a higher recurrence rate because of the concavity, or standoff, of the treatment area. Chan concluded that a standoff of 0.5 cm-1.5 cm would cause the radiation dose to decrease by six to 23%.[2]

Guix et al. published their series of 136 patients with basal cell or SCC of the skin of the face treated with surface molds and Ir-192 HDR brachytherapy with 98% 5-year local control rate with no severe early or late complications detected.[7]

Other treatment options for patients with basal cell or SCCs include curettage, Mohs surgery and conventional surgery. Curettage has been said to be quick, requires minimal equipment, and is associated with a cure rate of 90% or better for select low-risk skin cancers. With this strategy, however, there is no margin control, and healing and cosmesis can be variable; moreover, it is not a very effective treatment for high-risk tumors and tumors in certain locations.[3, 5, 6]

A common treatment for non-melanoma skin cancer (NMSC) has been Mohs surgery, which uniquely orients, maps, and processes removed tissue, permitting the microscopic evaluation of virtually 100% of the specimen margins. The completeness of this margin control permits the accurate identification and removal of all tumor extensions under the microscope. Tissues in Mohs surgery are processed as modified frozen sections which allow the accurate and rapid interpretation of most skin cancers.[6,9] Cosmesis may be adversely affected and the process of care can be lengthy. For those patients where surgical resection is not an option, primary treatment with radiation therapy was selected for patients whose data will be collected in this study. The treatment approach was individualized based on specific risk factors, and patient characteristics for the most acceptable cosmetic and functional outcome.[10, 11]

5 STUDY RATIONALE

Non-melanoma skin cancers, BCC and SCC, are the most prevalent of all skin cancers. Multiple publications have shown that radiation therapy using kilovoltage X-rays is a viable option for the treatment of BCC and SCC but treatment must be individualized to determine if radiation therapy should be an adjuvant therapy following surgical resection or if the radiation therapy is the primary treatment for skin cancer. Local recurrence rate varies depending on the histology, BCC versus SCC. SCC has a higher recurrence rate than BCC; deaths have been attributed to the recurrence of SCC.[2, 5, 6, 11-14]

Brachytherapy has the advantage of delivering a high dose to the tumor while sparing the surrounding normal tissues. With proper case selection and delivery technique, high-dose rate (HDR) brachytherapy has great promise, allows short treatment times, and can be performed on an outpatient basis.[15] The Xoft Axxent Electronic Brachytherapy (eBx) System allows for the administration of high dose rate brachytherapy treatments using an electronic source. The Xoft Axxent System Controller and Source are cleared by the United States Food and Drug Administration to deliver high dose rate X-ray radiation for brachytherapy.

It is important to understand the recurrence rates and cosmesis for this treatment option. The rationale for this retrospective data collection study is to understand longer-term outcomes in

patients treated with eBx for the treatment of both BCC and SCC NMSC and how the outcomes compare to Mohs surgery outcomes.

6 STUDY PURPOSE

The purpose of this retrospective-prospective study is to compare data after treatment for BCC or SCC NMSC with eBx to data after treatment with Mohs surgery in order to gain a better understanding of the clinical outcomes, cosmesis and durability, for this patient population.

7 STUDY DESIGN, ENROLLMENT, AND DURATION

7.1 Study Design

This is a retrospective-prospective study design. Patients who completed treatment approximately 3 years (range of 2-4 years) at time of IRB approval of this study will be identified and any existing data in the patient's record will be collected in addition to conducting office visits for long-term follow-up.

The study will include:

Identifying patients, retrospectively, who completed treatment a minimum of 2 years prior to study onset. The history, demographic and treatment data will be collected from up to 320 subjects previously treated with eBx for the treatment of NMSC and up to 320 subjects previously treated with Mohs surgery for the treatment of NMSC. Data will be collected from enough patients to achieve the required sample size of 293 lesions in each treatment group. Patients will then return for long-term follow-up visit for the investigators to assess the lesion site, document absence of recurrence, chronic toxicities, and collect patient reported outcomes.

7.2 Sample Size

Up to 320 subjects treated with eBx and up to 320 subjects treated with Mohs surgery will have data collected retrospectively from the patient's medical records, and prospectively at the time of the follow-up visit for those who agree to participate in this study.

7.3 Study Objectives

i. To evaluate long-term local recurrence of eBx and Mohs treated lesions.
ii. To evaluate long-term toxicities related to eBx and Mohs treatments.
iii. To evaluate long-term cosmetic outcomes for lesions treated with eBx and Mohs.

7.4 Primary Endpoint

i. Freedom from local recurrence at the prospective follow-up visit in this study.

7.5 Secondary Endpoints

i. Comparison of long-term toxicities related to eBx vs. Mohs treatment;
ii. Comparison of long-term cosmetic outcomes for lesions treated for NMSC with eBx vs. Mohs;
iii. Chronic toxicities;
iv. Patient Survey for reporting Patient Reported Outcomes (PRO)

7.6 Eligibility Criteria

7.6.1 Inclusion Criteria

All answers must be YES to have lesions included in this study.

1. Previously completed treatment for non-melanoma skin cancer using Xoft eBx Electronic Brachytherapy System or Mohs surgery;
2. Provides informed Consent;
3. Greater than 40 years of age;
4. Pathological diagnosis confirmed to be squamous cell or basal cell carcinoma prior to treatment;
5. Cancer Staging included in this study:
    - Stage 0: Tis, N0, M0
    - Stage 1: T1, N0, M0
    - Stage 2: T2, N0, M0 and ≤ 4cm in diameter

7.6.2 Exclusion Criteria

All answers must be NO to have lesions included in this study.

1. Target area is adjacent to a burn scar
2. Any prior definitive surgical resection of the cancer, prior to Radiation Treatment
3. Known perineural invasion
4. Actinic Keratosis
5. Known spread to regional lymph nodes
6. Known metastatic disease

8 METHODOLOGY

8.1 Identifying the Population

The first phase of this study will be to identify patients who completed treatment with eBx or Mohs treatment approximately 3 years ago or more prior to study onset and collect history and demographic data, and eligibility and treatment planning and treatment data retrospectively from the patient records and on source worksheets to complete a matched pair cohort study comparison.

This phase will include a review of the site's patient medical records to determine if the source documentation contains the variables that are needed to determine eligibility and which will be used in the endpoint analyses. These variables include:

- Patient Age (within ≤ 15 year brackets)
- Pathology report for evidence of:
  - Lesion size (cm)
  - Lesion diagnosis (BCC, SCC)
- Last treatment date for each location
- Lesion location (e.g. face, extremities, neck, nose, scalp, torso)
- Toxicities at time of prospective follow-up visit

Matching will be performed according to:

- Calendar year of treatment for equivalent follow-up
- Patient age bracket [15-year brackets or less]
- Lesion diagnosis (BCC, SCC)
- Lesion size range (< 1 cm, ≥1 and <2 cm, ≥2 and <3 cm, ≥3 and ≤4 cm)
- Location according to the methodology below:
  - Scalp
  - Face (includes neck)
  - Nose
  - Ear
  - Torso
  - Upper extremities (Arms, hands, fingers)
  - Legs (Thighs, lower leg, feet, toes)

Data Collected Prospectively:

- Cosmesis rating by physician
- Cosmesis rating by the patient
- Recurrence of cancer
- Chronic toxicities
- Patient reported outcomes (PRO) survey

Patients who return for long-term follow-up will be required to provide informed consent for both the retrospective data and the prospective data that are collected at the time of the visit.

8.1.1 Step by Step Instructions

1. The eBx patients will be determined first. They are called consecutively based on the length of follow-up required by this protocol.

2. As patients are called back for consenting and follow-up visits begin, the patients treated with Mohs are called consecutively and asked to come back who match those treated with eBx.

8.2 Long-term Follow-up Visits

Each patient agreeable to participating in this study will be asked to return for an office visit for prospective data collection. There may be up to two (2) visits over the next years.

Since the subjects have already received treatment, the study cannot include a randomization design. Each lesion from the eBx treatment group will be matched to a lesion treated with Mohs surgery. The variables used for matching will be:

- Calendar year of treatment for equivalent follow-up
- Patient age bracket [Attempt to ensure 15-year brackets or less]
- Lesion diagnosis (BCC or SCC)
- Lesion size range (< 1 cm, ≥1 and <2 cm, ≥2 cm and <3 cm, ≥3 and ≤4 cm)
- Lesion Location

It is not expected that there will be an equal number of patients treated with eBx and Mohs at each site, as some practices may not use both types of treatment modalities. To ensure that a minimum of 293 lesions are matched, the participating sites will be asked for a list of all patients treated approximately 2 to 4 years prior to study onset including the variables being used for matching. The study sponsor will then compare all the available data from the participating sites and notify each site which patient and lesion data will be included in the study.

8.3 Study Methodology Schema for Initial Follow-up Visits

Please see Figure 1 on page 14.

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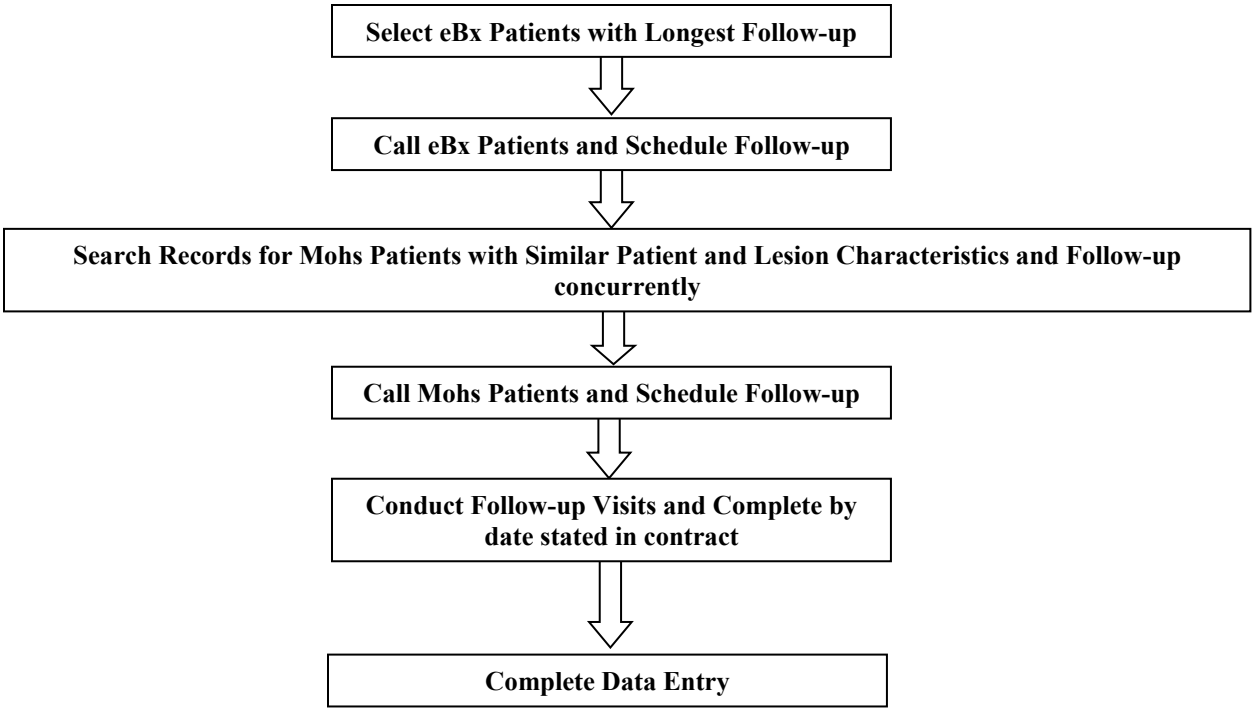
Figure 1. Study Schema



9 SITE REQUIRMENTS AND SELECTIONS

The sites will conduct the study following approval by an Institutional Review Board (IRB) and in accordance with 45 CFR 160 and 164 [Human Subjects Protection].

Sites selected have expressed an interest in the conduct of a controlled study to collect and report long-term outcomes and compare clinical outcomes of eBx versus Mohs surgery for the treatment of non-melanoma skin cancer.

Source worksheets will be used to collect data not found in the patients' records. The data from the source worksheets and the patient records will be entered into the EDC. ECR will have a unique user name and password, and the EDC system is 21 CFR 11 compliant.

10 CO-PRINCIPAL INVESTIGATORS AND SUB-INVESTIGATORS

CO-PRINCIPAL INVESTIGATORS

Rakesh Patel, MD and Robert Strimling, MD

SUB-INVESTIGATORS

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Erica Ventrella PA-C - San Diego Dermatology and Laser Institute, San Diego CA

11 INVESTIGATOR RESPONSIBILITIES

The following responsibilities are required for investigators participating in this study:

1. Willingness to work with study project manager to facilitate study progress;
2. Adherence to applicable IRB requirements and willingness to comply with all applicable regulations and applicable good clinical practice guidelines;
3. Protocol compliance, including willingness to complete all relevant study documentation legibly;
4. Maintenance of confidentiality at all times;
5. Willingness to allow clinical monitors, at reasonable times agreed upon by the site and sponsor, to inspect all records pertaining to this trial; and
6. Willingness to agree to and sign the Investigator Agreement Page in this protocol indicating the protocol will be followed.

12 STATISTICAL CONSIDERATIONS

12.1 Data Collection

Data will be collected at the study site on case report forms and will be entered into the online database by ECR personnel. The following data collection requirements are listed below:

Table 1. Case Report Forms

Form # and Name	Retrospective Chart Review	Prospective Follow-up and Data Collection
Demographics and History	X	
Eligibility	X	
Treatment Planning and Treatment	X	
Follow-up Including Cosmesis, Chronic Toxicities, Recurrence		X
Patient Reported Outcomes (PRO) Survey		X

12.2 Statistical Analyses

This is a multi-center, retrospective-prospective study comparing non-melanoma skin cancer treatment (basal cell carcinoma and squamous cell carcinoma) using Xoft electronic brachytherapy (eBx) results compared to a Mohs micrographic surgery. The lesion data will be matched on 4 categories as outlined in Section 8 and the results will be compared between the two treatment groups.

A sample size calculation comparing treatment of NMSC with eBx to treatment with Mohs micrographic surgery was done using a 1.5% historical 3-year recurrence rate for NMSC treated with Mohs, and a 2.5% non-inferiority margin. A total of 293 lesions for each treatment group will provide 80% power with a 0.05 alpha level of significance. Data from up to three hundred-twenty (320) subjects with each type of treatment will be collected to ensure a sufficient number of lesions to adequately power the study. There may be more than one lesion per patient that is matched to another lesion in the other treatment group. The total lesions will be compared in this study and the lesion count determines the number of patients that are ultimately enrolled.

The primary endpoint of freedom from recurrence and the secondary endpoints will be summarized for each treatment group and Chi-square tests performed as applicable. All tests will be 2-sided, with significance level set at 0.05, and performed using SAS (version 9.4 SAS Institute, Inc., Cary, NC).

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13 GLOSSARY

TERM OR ABBREVIATION	DEFINITION
BCC	Basal Cell Carcinoma
21 CFR Part 11	Title 21, Code of Federal Regulations Part 11: Electronic Records, Electronic Signatures https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11
CRF	Case Report Form
eBx	Electronic brachytherapy treatment with Xoft
EDC	Electronic Data Capture-internet based secure electronic CRF
N0	No lymph node involvement
M0	No metastases
PRO	Patient Reported Outcomes
SCC	Squamous Cell Carcinoma
Tis	Tumor in stage 0; abnormal cells are found in the squamous cell or basal cell layer of the epidermis; also called carcinoma in situ.
T1	Lesions ≤ 2cm
T2	Lesions > 2 and ≤ 5cm

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15 APPENDICES

15.1 INFORMED CONSENT FORM

Attached separately in Microsoft® Word® format for edits by IRB and sites.

15.2 CASE REPORT FORM

Provided as a separate document in the form of a worksheet to use as a source document. The final case report form will be electronic data capture.

15.3 PATIENT REPORTED OUTCOMES (PRO) SURVEY

Provided as a separate document to be used as a source document with this protocol. The PRO survey results shall be entered into the EDC.