

**Title of study: Optical Coherence Tomography Guided Laser
Treatment of Basal Cell Carcinoma**

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STUDY PROTOCOL

Background & Purpose of the Research

The purpose of this research is to evaluate histological clearance of BCC due to laser treatment while also imaging the sub-surface structure of skin and to obtain information about the lesion such as depth, margin, and the size and density of investing tumor vasculature. This is a pilot study that will explore efficacy of laser treatment of BCC, determining how many treatments are needed to histologically clear the lesion. The current standard of treatment is to treat patients based on qualitative, visual characteristics of the skin lesion, such as vascularity, pliability, height, and pigmentation of the lesion. Imaging with OCT provides more information about the characteristics of the skin lesion, allowing for more precise approximation of depth and margins to treat BCC with laser coagulation. Our hypothesis is that Nd:YAG laser treatments of BCC will result in improved clinical outcomes when compared to other non-invasive treatment options in the standard of care, and potentially approaching that of surgery. The benefits of imaging to direct laser treatment to tumor tissue, and to accurately control delivery will help monitor successive treatment sessions until the tumor is successfully cleared.

The purpose of this study is to test the efficacy of laser treatment of basal cell carcinoma (BCC) histologically, accompanied by guidance from non-invasive skin imaging using Optical coherence tomography (OCT). However, there is a trade-off between aggressiveness of the laser treatment to achieve tumor clearance versus side effects of the treatment including pain and scarring. This study will utilize OCT and a 1064nm Nd:YAG laser from Sciton Inc. Data acquisition of the skin will monitor laser treatment effects and progress by providing information on skin lesion characteristics.

There have been shown to be many applications for OCT; one of which is the imaging of non melanoma skin cancer. OCT is being used to enhance the effectiveness of Mohs Micrographic Surgery of these cancers by elucidating more definitive tumor margins^{1,2}. BCC is a lesion of interest because, while it is malignant, its metastasis is quite rare, thus allowing for more flexibility in treatment options³. Many studies have explored the use of laser treatment of BCC⁴, but one recent study added OCT measurements and scans for only a single BCC patient in that study to validate the effectiveness of laser treatment of BCC⁵. We are hoping to push this further by using OCT to examine a whole cohort with laser treated BCC.

Imaging with OCT provides more information about the characteristics of the skin lesion (such as lesion depth, the subclinical lateral extent of the lesion, and the size and density of blood vessels), which could allow for more informed selection of margins to apply surgical or laser treatment to the entire area of lesions like BCC to help prevent recurrence. OCT can also be used to monitor regression of tumors undergoing treatment and which may no longer be clinically evident, so that more accurate decisions can be made regarding whether to terminate or to continue treatment⁶. Our proposed protocol would include the use of OCT to examine the BCC before and after laser treatment, and at follow up, in order to assess the efficacy of the treatment.

The following technologies will be used in this study:

1) Optical Coherence Tomography (OCT): OCT is an imaging modality that uses light to image turbid media such as living tissues, and has been successfully used to generate high resolution (~10 micron) cross-sectional images of tissue microstructure in the human retina, skin, gastrointestinal tract, and genitourinary tract^{10,6}. OCT systems are now commercially available for ophthalmic and dermatologic use, and several clinical reports on the use of OCT in the vascular system and aero digestive tract (HS#2003-3025), Ophthalmology (HS#2004-3555), Pleural disorder (HS#2006-4982), Neural tissue (HS#2005- 4775), Aneurysm healing (HS#2006-5031) and Oral Pathology (HS#2002-2805). This device focuses low power non-laser broadband infrared light onto tissue and does not involve input of significant amounts of energy into the subject; no temperature rise occurs. Because the wavelength of light used for imaging does not have adverse tissue effects, there is no risk.

Imaging with OCT provides information about the characteristics of skin lesions (such as depth, margin, and the size and density of investing vasculature). OCT poses no known risks to the patients. A number of studies have evaluated characteristics of squamous cell carcinoma and BCC using OCT. OCT has been used to diagnose skin cancer, classify subtypes of BCC, and to assess tumor margins for more accurate excision^{2,7-}

10. In these studies, OCT aided treatment and also provided a method to assess treatment outcome. Byers et al. noted that OCT was a robust, and non-invasive method for observing longitudinal dynamics of the subcutaneous microcirculation of tumors¹¹.

2) 1064nm Nd:YAG laser by Sciton Inc. Skin conditions including vascular skin lesions, pigmented lesions, photoaging, and scarring have all benefited from laser treatment. It has also been employed for skin rejuvenation and hair removal. Recently, the use of lasers has been applied to the treatment of BCC⁴ The long pulse 1064nm Nd:YAG laser has been gaining traction in the treatment of BCC due to its ability to injure malignant cells at an adequate depth. The risk profile is minimal compared to other surgical methods, like ablative CO₂ laser and Mohs micrographic surgery, which are known to cause significant scarring and increased risk of infection^{5,12-14}. The pulsed dye laser (PDL) is also a treatment option for BCC, however, its inability to penetrate into the deeper dermis is a prominent shortcoming. It is relatively effective for the eradication of superficial BCCs, however, for tumors that extend into the dermis, it is unable to ablate the entire lesion¹⁵⁻¹⁷.

Another common treatment of BCC is excision, however, this can lead to minor adverse events, such as bleeding, redness, pain, and swelling, and major adverse events, such as wound infection and scarring in aesthetically sensitive regions. 1064 nm laser coagulation would not entirely eliminate these major risks; however, it would substantially decrease their likelihood of occurring. Laser treatment would also be an alternative for patients reluctant to undergo surgical excision of BCC. Our study would employ the use of the 1064nm Nd:YAG laser to treat biopsy proven nodular and/or superficial variants of BCC to determine histological clearance alongside OCT for approximation of the margins and visualization of the investing vasculature. If the experienced dermatologists involved in this study treating the BCC patient deem the BCC lesion too advanced for laser treatment or the OCT images of the lesion depth to be inconclusive, more invasive or aggressive treatments like standard excision would be utilized to remove the lesion, and the patient would not be enrolled in the study.

Multiple centers in the US and Europe have started using OCT to provide information about the skin. Laser coagulation is gaining traction as a treatment option for BCC^{5,12,13}. This information is not yet being used commonly to guide laser treatments.

Primary outcome variables include the complete histological clearance of the BCC lesion. Clearance of tumors will be verified clinically, dermoscopically, histologically, and via OCT. OCT and visual clinical examination will be used to check tumor clearance; once tumor clearance is deemed, histological confirmation will be scheduled for greater than three months after the patient's final laser treatment. Secondary outcome variables: significance of lesion depth (by OCT), lateral extent (by OCT), BCC subtype, and anatomical region, on rate of clearance and recurrence.

We will assess cosmetic outcome and any adverse effects of the laser treatment such as pain, redness, infection, skin discoloration, blistering, scarring, and scabbing. Cosmetic outcome will be rated on a 0-4 Likert scale, with 0 representing the worst cosmetic outcome and 4 resembling normal skin, upon follow-up of treatment. If tumors are persistent after the 3rd laser treatment as evidenced on clinical evaluation and OCT, then the patient will undergo biopsy or histological tissue harvest as part of more aggressive treatment methods, such as standard excision as determined by the treating physician. Histological analysis will determine laser treatment failure, validate or disprove interpretation of imaging. If histology shows tumor persistence, patient will then be removed from the study and will undergo further observation or treatment as determined by treating physician. This is considered a safe practice because the successive laser treatments, if needed, will be performed after the treated area has healed completely. Additional laser treatments will be separated from each other by 8-16 week intervals, which should provide ample time for healing. Since BCC is a relatively non-aggressive cancer, and the treated area should have plenty of time to heal, clinical inspection and OCT will be used to check if the tumor has shrunk in size, if there is remaining tumor, or if there is no response warranting additional treatments. Additional information is provided in the Research Procedures.

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Research Procedures

To clarify, Steps 1 and 2 are routine standard of care procedures, therefore research procedures are outlined starting at Step 3. Steps 1 and 2 are provided for context.

1. Focused medical history and a focused skin examination will be performed on the patient. This includes general questioning about the patient's health, well-being, allergies, and medications, and history of the skin lesion in question as identified by the patient and confirmed by the physician. The skin examination consists of a medical examination of the skin lesion in question. The patient will also be subject to signing a standard photograph release form, which is standard in our clinic.
2. If the lesion is suspicious for a BCC, a biopsy of the lesion will be performed by the physician and sent to dermatopathology in order to confirm the diagnosis. Type of diagnostic biopsy is to be determined by the treating physician according to standard of care.

Research procedures begin here.

3. If the diagnostic biopsy returns that the lesion in question meets the inclusion/exclusion criteria, the patient will be asked to return to the clinic for treatment.
4. The patient will be screened upon their next visit according to inclusion and exclusion criteria and will be asked to consent to this study and may take as long as needed to do so.
5. If the patient consents, the BCC will be photographed by digital photography. If the study area is on the face, subjects will be offered to protect their identity.
6. Non-invasive imaging will be performed with OCT using the VivoSight Dx (Michelson Diagnostics, Kent, UK). Each individual scan with OCT takes about 30 seconds to complete, and multiple scans may be performed on larger lesions. The lesion depth will be recorded, and the lateral extent of the lesion will be mapped.
7. The laser will be prepared with settings to coagulate the mapped tumor while minimizing side effects.
8. The total treatment area and margins will be outlined using a pen.
9. Laser treatment of the targeted area will be performed with the long pulse 1064nm Nd:YAG laser (Sciton Inc., Palo Alto, CA). The laser treatment may be recorded using video.
10. A follow-up will be performed 8-16 weeks after the initial treatment. During this visit, a focused skin examination will be performed to evaluate the destruction of the tumor. Photography and OCT of the treated area will be performed with optional, additional laser treatments to be performed at the discretion of the treating physician and the patient.
11. The number of follow-ups is also determined at the discretion of the treating physician and the patient but could range from 1 to 6 depending on the response of the lesion to treatment. The lesion will be treated as necessary to obtain complete lesion clearance as judged by OCT imaging. If tumors are persistent after the 3rd laser treatment as evidenced on clinical evaluation and OCT, then the patient will undergo biopsy or histological tissue harvest as part of more aggressive treatment methods, such as standard excision as determined by the treating physician. Histological analysis will determine laser treatment failure, validate or disprove interpretation of imaging. If histology shows tumor persistence, patient will then be removed from the study and will undergo further observation or treatment as determined by treating physician.
12. When OCT image analysis deems the treated area clear of tumor patient to receive a skin biopsy of the area of skin identified in photographs from step 4 where the center of the lesion was originally located, at a time at least 3 months after the final laser treatment. This biopsy will be used to histologically confirm clearance of the lesion. Lesions will also be followed clinically, dermoscopically, and via OCT to track clearance and monitor recurrence up to 12 months after final laser treatment.

The first visit should take no more than 1.5 hours: approximately 20 minutes for a medical history and focused skin examination, 30 minutes for imaging including photographs, and 30 minutes for laser treatment. These times are all maximums and will likely be shorter. The patient may take as long as needed to consent and is permitted to take the consent form home and return another day to sign and enroll. Some subjects may be asked to participate in more than one imaging session. They will have the option of refusing participation in additional sessions.

Study Design

This is a longitudinal pilot study. The patients will undergo treatment with the 1064nm laser and follow-up evaluations using OCT over the course of 12 months depending on whether clearance is deemed clear with OCT. Patients will additionally receive a skin biopsy (either shave biopsy or 3 mm punch biopsy, at physician's discretion) for histological confirmation of laser treatments and OCT results. There is no placebo and no randomization, and patients will not be blinded. OCT measurements, clinical, and dermoscopic evaluation of the lesion of interest will be used to validate the improvement results. Histological examination will be used to validate the treatments and imaging at a time greater than 3 months after the final laser treatment.

Primary endpoint: the complete histological clearance of the BCC lesion. Patients will undergo a skin biopsy for histological confirmation of clearance via gold standard histological diagnostics, confirming laser treatment efficacy and imaging results. Secondary Endpoint: We assess cosmetic outcome and any adverse effects of the laser treatment as a result of the laser treatment such as pain, redness, infection, skin discoloration, blistering, scarring, and scabbing. Cosmetic outcome will be rated on a 0-4 Likert scale, with 0 representing the worst cosmetic outcome and 4 resembling normal skin, upon follow-up of treatment. Is (i) BCC subtype (ii) lesion depth measured by OCT (iii) lesion lateral extent measured by OCT (iv) anatomical region:

Trunk/Arms/Legs or Scalp/Neck/hand/foot/genitalia or Face, a significant factor affecting the rate of tumor clearance (number of treatments required to achieve clearance by skin biopsy) and recurrence rate (number of patients with lesion recurrence over total number of patients).

Predictors of treatment outcome include BCC subtype and anatomical region. We would like to see if there is a difference between clearance rates of different BCCs, such as nodular and superficial BCC, and among the different regions of the body such as the trunk, head, neck, upper extremities, and lower extremities. Subtype of BCC is to be determined via prior biopsy.

STATISTICAL ANALYSIS PLAN

Statistical Analysis Plan Primary Endpoint: The histological clearance rate at greater than 3 months after final laser treatment will be calculated and also the clearance rate after 1 treatment. Secondary Endpoint: We will assess cosmetic outcome and any adverse effects of the laser treatment as a result of the laser treatment such as pain, redness, infection, skin discoloration, blistering, scarring, and scabbing. Cosmetic outcome will be rated on a 0-4 Likert scale, with 0 representing the worst cosmetic outcome and 4 resembling normal skin, upon follow-up of treatment. Is (i) BCC subtype (ii) lesion depth measured by OCT (iii) lesion lateral extent measured by OCT (iv) anatomical region: Trunk/Arms/Legs or Scalp/Neck/hand/foot/genitalia or Face, a significant factor affecting the rate of tumor clearance (number of treatments required to achieve clearance by skin biopsy, and recurrence rate (number of patients with lesion recurrence over total number of patients).

Statistical Methods:

Calculate the percentage of all lesions that were histologically clear of BCC tumor at greater than three months after the final laser treatment (1). Calculate the percentage of all lesions that were clear of BCC tumor by OCT after 1 treatment (2). (This is equivalent to the efficacy without the benefit of OCT imaging to control treatment) Determine whether (1) is significantly greater than (2) ($P < 0.05$), to show the benefit of OCT guided treatment. Histological clearance rate (%) using of laser therapy will be compared using a one-sample binomial test for non-inferiority against established benchmarks from the extant literature¹⁸. Null hypotheses assume a 100% clearance rate at greater than 3 months post final laser treatment and a 90% clearance rate after one treatment.

Secondary Outcomes:

Calculate average treatment cycle success rate and calculate correlation coefficient with (i) lesion depth by OCT (ii) lesion lateral extent by OCT. Calculate average treatment cycle success rate. We will use descriptive statistics to estimate the average lesion depth and lateral extent (in mm), the clearance rate (% cleared and number of treatments required to clear), prevalence (%) of optimal cosmetic outcome, and incidence (%) of recurrence among those who achieved tumor clearance. Clearance rate will also be compared by BCC subtype and anatomical region.

Sample Size Determination:

Literature indicated that long pulse 1064nm laser treatment of BCC yields a high degree of clearance. Ten subjects were treated by Ortiz et al. 2015 with a long-pulsed Nd:YAG laser, achieving complete clearance in 92% of patients after a single laser treatment. At higher fluences, 100% clearance was achieved in 1 treatment. Further studies by the same group achieved 90% clearance after a single treatment and 100% clearance overall. There is a history of laser treatment of basal cell carcinoma. For example, the El-Tonsy et al. 2004 study achieved complete BCC clearance in 36 of 37 of patients with only a single case of recurrence using a continuous wave Nd:YAG laser. Each patient required between 2-4 treatment sessions. Power analyses are based on the primary endpoints of tumor clearance by histology. Using a one-sided binomial test for non-inferiority with a significance level of 0.05, a sample size of 29 achieves 80% power to detect a 12-month clearance rate of no less than 90% and a sample size of 19 achieves 80% power to detect a 12-month clearance rate of at least 85%, assuming a population proportion under the null hypothesis of 99.9% clearance. Based on this power analysis, we will employ 30 patients for a clearance rate of no less than 90% under the null hypothesis of 99.9% clearance. To ensure that this sample size and statistical power is achieved, any refusal of histology at such point that the patient is exiting the study will need to result in removal of the patient from the study, and replacement of the patient to ensure the appropriate number of histological samples are gathered to establish treatment efficacy.