Incorporation of Electronic Brachytherapy for Skin Cancer into a Community Dermatology Practice

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ABSTRACT
Objective: The introduction of an electronic brachytherapy delivery system into an existing general dermatology practice is described. Radiobiologic rationale for the dose fractionation schedule is detailed. Design: A miniaturized 50keV x-ray tube and delivery system are United States Food and Drug Administration cleared for nonmelanoma skin cancer. The device is introduced into an existing multi-physician dermatology practice in a standard unshielded treatment room. Setting: A multi-site, multi-physician dermatology practice Results: Fifteen months following introduction of the system, a total of 524 nonmelanoma skin cancer patients have been treated. At 12.5 months follow-up, there have been four recurrences and cosmesis has been excellent. Conclusions: Advances in radiobiology and radiotechnology permit the treatment course to be given in eight fractions over four weeks. Radiation therapy for nonmelanoma skin cancer can now be given in an office setting as an alternative to Mohs surgery for appropriately selected patients. Results are comparable or better than those of surgery. Advances in radiobiology and radiotechnology permit the treatment course to be given in as few as eight fractions over four weeks. Patients are pleased with the convenience of the short course of therapy given in the office. (J Clin Aesthet Dermatol. 2015;8(11):28–32.)

Radiation therapy and brachytherapy have been used for more than 100 years in the treatment of nonmelanoma skin cancer (NMSC). Radiation therapy for a large part of the 20th century was in the purview of dermatologists and surgeons until the division of general radiology into diagnostic radiology and therapeutic radiology in the mid-20th century began restricting the use of ionizing radiations exclusively to radiation oncologists. Simultaneously, the high cure rates of Mohs surgery and its inclusion in dermatology training programs promoted its increasing use. Dermatologists were pleased to offer their patients a convenient in-office therapy with a high cure rate without the need to refer aged and often debilitated patients to an outside radiation facility requiring weeks of daily visits.

Brachy- is from the ancient Greek word for short, which refers to the short distance between the radiation source and the target tissue. The first use of brachytherapy for skin cancer was the treatment of basal cell carcinoma of the face in 1903 with radium salts in St. Petersburg, Russia, five years after discovery of the element by Marie and Pierre Curie. The renowned French dermatologist Henri-Alexandre Danlos was the first physician to use brachytherapy clinically in 1901 when he applied a paste of radium and barium chloride to the skin to treat lupus.

External beam radiations for NMSC have been delivered with superficial energy photons (50–200Kev), orthovoltage photons (200–500Kev), and high-energy megavoltage photons and electrons (greater than 1MeV). This is referred to as teletherapy, tele- being from the ancient Greek word for long, referring to the distance between the source of the radiation and the target tissue.

Grenz rays, from the German word for border, refer to the border in the electromagnetic spectrum between ultraviolet light and ultra-low energy x-rays (10–20Kev). Grenz rays are not sufficiently penetrating to be used for NMSC.

Older teletherapy devices generate x-rays by acceleration of high-energy electrons into a tungsten target thus generating x-rays which are directed toward the tumor site. The x-rays are generated in the cathode tube approximately 10cm or more away from the target...
site creating significant scatter of x-rays throughout the treatment area. This creates a need for shielding in the walls, floor, and ceiling of the treatment room. The patient requires lead apron shielding and the radiation therapist must leave the room during the treatment. The generating machinery and shielding necessary for these treatments is bulky, costly, and immobile.

Traditional external beam radiation is a lengthy and costly procedure requiring daily treatments for 5 to 7 weeks. The devices cost up to several million dollars for a megavoltage linear accelerator. The shielding requirements are also substantial, requiring several millimeters of lead for all walls of the treatment room for superficial and orthovoltage and several feet of concrete and steel for megavoltage treatments. These treatment vaults are expensive to construct and design and cannot be moved or easily expanded. Skin cancer patients must travel on a daily basis for treatment to a radiation oncology department that primarily treats internal malignancies. Many of these patients are debilitated and cachectic, which can be a frightening experience for ambulatory and healthy NMSC patients.

Conventional radiation teletherapy has a long and successful record for NMSC competitive with that seen with Mohs surgery. Five-year cure rates are 93 percent for previously untreated epithelial lesions irradiated with radiations in a university academic radiation oncology practice. Overall complication rate was 5.8 percent with 92 percent of lesions showing good or excellent cosmetic result.2

Mohs micrographic dermatologic surgery was introduced in the first half of the 20th century as an alternative to excision, electrodessication, and cryosurgery and radiation therapy. Patients and dermatologic surgeons found the technique attractive due to its outpatient nature, solitary treatment session, and use of local anesthesia. Two recent European studies showed a five-year recurrence rate after Mohs of 2.1 to 3.3 percent for primary basal cell carcinoma (BCC) and 4.9 to 5.2 percent for previously treated BCC.14 These studies showed that the recurrence rate of squamous cell carcinoma (SCC) after Mohs varies from 1.2 percent to as high as eight percent at five years for high-risk cases.14

Defects created by Mohs surgery with or without grafting may cause unacceptable cosmetic and functional results around the eyelid, the canthus, the nasal ala, the lips and vermilion border, and on thin skin overlying bony prominences and overlying tendons. The use of radiation therapy for cancer eradication at the above sites allows for improved cosmetic and functional outcome without tissue extirpation or skin grafting.

DOSE FRACTIONATION SCHEDULES FOR NMSC

Research at the Paris Curie Institute in the second quarter of the twentieth century by pioneering radiotherapists Claudius Regaud and Henri Coutard led to the standard dose fractionation schedules in recent use. Dose fractionation schedules for external radiations have been 60 to 66 Gy in 1.8 to 2.5 Gy fractions given 4 to 5 times a week over a 5- to 7- week period. Past dermatology office-based radiation therapy for NMSC has utilized these standard fractionation schemes with excellent cure rates and cosmetic outcomes, but with the patient inconvenience of 25 to 35 daily treatment visits. Five-year cure rates of 94.4 percent for BCC and 92.7 percent for SCC have been reported with dermatologist office-based conventional radiation teletherapy.5 Nasolabial fold involvement and size greater than 10 mm are independent predictors of BCC recurrence.5

By 1970, this dose fractionation scheme was being challenged by the concept of high dose rate (HDR). Delivering larger amounts of radiation per fraction of therapy allowed for fewer treatments. Treatments were separated by several days to permit repair of sublethal cell damage and recovery of normal tissues.7 Radiobiology studies on human cells showed that HDR therapy was effective in tumor eradication without an increase in late tissue toxicity.7

During the 1980s, the radiobiological basis of the factors concerning total treatment course time, effects of increasing dose per fraction, and delayed cell proliferation following irradiation were illuminated with increasing clarity and translated into clinical practice.8 These bench investigations along with clinical trials and experience have permitted a lesser number of treatments over a shorter course of time, a technique known as accelerated hypofractionation.

A vast amount of research, clinical experience, and technical innovations has now led to the worldwide current use of HDR technology and hypofractionation dose schedules in radiation therapy of cancers of the lung, breast, prostate, skin, and central nervous system.10–15 In recent years, attention turned to the use of accelerated hypofractionated HDR for NMSC. Treatments were given with HDR iridium192, with a half-life of 74 days and a high average energy of 380 keV. This half-life and energy require thick concrete and steel shielding in the treatment vault and costly source change every three months. Nonetheless, the clinical results from NMSC treated with HDR iridium192 have been outstanding with the advantage of requiring only 6 to 10 treatments over 2 to 4 weeks instead of the former 4 to 5 treatments a week over 5 to 7 weeks.16–21 Cure rates following HDR iridium192 brachytherapy for NMSC from 90.2 to 98 percent with 4- to 10-year follow-up. Severe late radiation skin toxicities have not been reported.22–25

Electronic brachytherapy has been used for skin cancer utilizing HDR and an accelerated hypofractionation schedule. Results have been reported for a series of 177 lesions.26 There were no recurrences at 10-month follow-up and cosmesis was judged as good to excellent in all cases. There were no cases of Radiation Therapy Oncology Group (RTOG) grade 4 acute skin toxicity. Treatments were delivered twice a week, separated by a minimum of 36 hours for four weeks. Two other electronic brachytherapy series, both utilizing accelerated hypofractionation and HDR for NMSC have been reported showing similar results.28–31

MATERIALS AND METHODS

Recent technological advances have resulted in the miniaturization of a 50 keV x-ray source tube (Xoft, San Jose, California) to 2.2 mm in diameter, narrow enough to fit inside a 5.4 mm in diameter flexible source catheter. The
source catheter fits into the stainless steel cone applicator, which is available in several different sizes, allowing treatment of lesions up to 5 cm in diameter. The applicator also contains a proprietary flattening filter at the apex of the cone, which ensures even dose distribution across the lesion surface. The source catheter is positioned within the applicator about 2 cm above the skin. The Soft Axzent® Electronic Brachytherapy System’s® components also include a computerized controller, the miniature electronic x-ray source contained within a flexible catheter, a miniaturized water pump cooling system for the x-ray source, and a series of stainless steel cone applicators that are applied to the skin lesion. The cone sizes are 10 mm, 20 mm, 35 mm, and 50 mm in diameter and have a plastic end cap to ensure a flat skin surface for dose homogeneity. The low source energy of 50 Kev in conjunction with the steel shaft eliminates heavy room shielding requirements allowing treatments to be given in a dermatology office room. Dosimetry studies document the homogenous nature of the photons generated by the device and the substantially lower doses delivered to surrounding tissues as compared to the doses reached by iridium 192 brachytherapy. 28–32

The miniaturized source was FDA cleared in January 2008 and the entire system has been thoroughly examined as a radiation delivery system. 29–34,36–37 The surface applicators for skin treatment were FDA cleared in March 2009.

The stainless steel applicators are applied over the skin after selecting the appropriate size applicator based on the size of the skin lesion. The applicator is held in place with the multi-jointed arm assembly with the end cap lightly touching the skin surface with the patient in a comfortable position. The miniaturized x-ray source as part of the flexible tube assembly is placed just above the surface of the skin. Following quality assurance checks, the x-ray source is activated and radiation treatments are delivered and monitored by the computerized controller. The average treatment time is 2 to 3 minutes. The vast majority of skin sites can be treated with the patient seated comfortably upright.

Because the source is encased by the stainless steel applicator during the treatment, the only exit for the x-rays is directly onto the skin. 50 Kev x-rays are low energy and have a half value layer of 5 to 6 mm of water. At 5 to 6 mm of tissue depth, the radiation dose has fallen by half so tissues underlying the skin receive minimal radiations. Scattered radiations are absorbed by the stainless steel applicator so the radiation therapist can remain in the room with the patient during the entire treatment to ensure that there is no shift of the applicator. Close real time supervision of treatment permits applicator selection to more tightly match lesion contours and therefore decrease the amount of normal tissue irradiated.

Flexible shields containing the equivalent of 0.44 mm of lead can be placed around the treatment site to shield sensitive superficial structures, such as the eye. Portions of the shielding material can be inserted into the nare during ala treatments to decrease the dose to the contralateral nasal wall. Tungsten eye shields can be inserted under the eyelids following topical lubrication and anesthesia of the cornea to protect anterior segment structures during lid radiation therapy.

The source is calibrated by the computerized controller prior to each treatment for quality assurance.

INTRODUCTION OF ELECTRONIC BRACHYTHERAPY INTO A CLINICAL DERMATOLOGY PRACTICE

A four-physician dermatology practice with three practice sites and on-site dermatopathologist analyzed their practice patterns regarding patient suitability for electronic brachytherapy for NMSC. A typical dermatology exam room was identified as the specific treatment room for locating the electronic brachytherapy system. Patient flow patterns were evaluated by the practice manager and the radiation therapist. The room was surveyed by the physics team to ensure that state dose limits to the surrounding patient and staff areas were not exceeded. The electronic brachytherapy system was secured and commissioned by the physics team after delivery to the dermatology office. 36–37

A radiation oncologist was identified and a radiation therapist was brought on site for the commissioning procedure. This practice was the first use site of the electronic brachytherapy system in San Diego, the first use of the electronic brachytherapy system in San Diego for skin cancer, and the first dermatology practice in the world to incorporate the system.

Following device commission, the first patients were seen by the radiation oncologist in the dermatology office. Consultation was performed, alternatives and risks presented, and written informed consent obtained. Face-to-face discussion by the radiation oncologist with the referring dermatologist and dermatopathologist regarding gross and microscopic margins occurred whenever necessary. It was noted that in the vast majority of lesions that less than 1 mm of tumor remained in the lesions following biopsy with or without curetting. The Dmax of the electronic brachytherapy system was therefore selected as the treatment depth. The lesion visible margins (clinical target volume) with a 2 to 5 mm margin (planning target volume) were marked and appropriate cone size was selected and fitted by the radiation oncologist. This clinical set up was reviewed, photographed, and prescription and request for physics consultation generated by the radiation oncologist. Medical radiation physicist performed dose calculations and created the treatment plan. The radiation therapist reviewed the plan and submitted it to the radiation oncologist for final review, approval, and signature.

On treatment Day one, patient setup was checked by the radiation oncologist with the radiation therapist prior to treatment delivery. The radiation therapist reviewed the treatment plan and machine treatment parameters. Source calibration occurred before each treatment. The treatment plans were electronically transmitted by medical radiation physics to the electronic brachytherapy system further reducing the chance for human error in machine setup. The miniature x-ray source was inserted into the applicator...
catheter and clamped in place. Programmed treatment time was then delivered with the radiation therapist present in the room to monitor the machine and any patient motion. A total of 40 Gy in eight fractions over four weeks was delivered to each lesion. 50 keV radiations were delivered to Dmax and treatments separated by a minimum of 36 hours.

Two adjoining exam rooms were dedicated to the electronic brachytherapy program. The electronic brachytherapy system was stored and utilized in one room, the second adjoining room was used for consultations and treatment setups. These rooms were utilized as usual by the dermatology staff when brachytherapy activities were not occurring. Film dosimeters in the rooms and in adjacent rooms were analyzed every three months. There was no measurable radiation exposure.

Treatments, setups, and consultations were given on Tuesdays and Thursdays initially. Patient load rapidly increased so that by the end of the second month, Mondays and Wednesdays were opened for treatments, consultations, and follow-ups. Patients had a choice of a Monday–Wednesday or a Tuesday–Thursday for their treatments as long as treatments were separated by a minimum of 36 hours.

RESULTS
Fifteen months following treatment of the first patient, a total of 524 lesions had been treated. All were BCC, SCC, or SCC in situ with a single case of keratoacanthoma and a single case of vertex scalp pleomorphic stromal sarcoma. All were T1 or T2. None had palpable adenopathy.

The program was initiated in July 2012 and as of October 2013 with a median follow-up of 12.5 months, only four local recurrences have been seen.38,39

Most patients experienced mild skin reddening that peaked a week after the eighth and final treatment. Petrolatum and hydrocortisone cream were prescribed as needed based on skin erythema. Two patients developed a moist desquamative reaction requiring dressing changes. Both patients were on anticoagulation and both healed well with no obvious sequelae at first follow-up. Three-month follow-up on the initial patients treated showed excellent cosmetic results utilizing the Common Terminology Criteria for Adverse Events.

CONCLUSION
We have shown that electronic brachytherapy for NMSC can be easily integrated into an existing dermatology practice under the supervision of radiation oncology with minimal disruption of existing patient flow. Patients are pleased with the convenience of treatment in the dermatology office and with the avoidance of surgery. The electronic brachytherapy system is easily rolled from room to room and can be transported from one facility to another if required. The electronic brachytherapy system requires minimal shielding, and the radiation therapist can remain in the room with the patient during treatment.

Standard fractionation teletherapy radiations and HDR iridium186 radiations have been shown to be effective treatment for NMSC. Electronic brachytherapy is a combination of HDR low-energy radiations and the radiobiological technique of accelerated hypofractionation. Current results, albeit with short follow-up, show improvement in local control over teletherapy and HDR studies.38–41 Postulated reasons for this include the radiobiological superiority of accelerated hypofractionation, the close collaboration by radiation oncologists with dermatologists to identify margins, and the presence of the therapist in the room during treatment which minimizes patient motion and therefore geographic miss. Further improvements in local control are expected with further advances in technology and radiobiologic understanding of the complex relationship between the immune system and irradiated cancer cells.

NMSC treatable with standard fractionation teletherapy, Mohs, or excision can be treated with electronic brachytherapy with comparable cure and complication rates. Sensitive areas on the pinna, lip, nasolabial fold, nasal ala, and canthus and eyelids are easily treated with electronic brachytherapy, thus avoiding the need for tissue excision and grafting.

Patients and physicians are pleased with the ease and convenience of electronic brachytherapy treatments and with the short eight-fraction treatment course. Dermatologists are now able to offer this effective, low-morbidity therapy in their office for appropriately selected NMSC patients.

REFERENCES


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