A pilot study of ultrasound-guided electronic brachytherapy for skin cancer

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Abstract

Purpose: Electronic brachytherapy (eBT) has gained acceptance over the past 5 years for the treatment of non-melanomatous skin cancer (NMSC). Although the prescription depth and radial margins can be chosen using clinical judgment based on visual and biopsy-derived information, we sought a more objective modality of measurement for eBT planning by using ultrasound (US) to measure superficial (< 5 mm depth) lesions.

Material and methods: From December 2013 to April 2015, 19 patients with 23 pathologically proven NMSCs underwent a clinical examination and US evaluation of the lesions prior to initiating a course of eBT. Twenty lesions were basal cell carcinoma and 3 lesions were squamous cell carcinoma. The most common location was the nose (10 lesions). A 14 or 18 MHz US unit was used by an experienced radiologist to determine depth and lateral extension of lesions. The US-measured depth was then used to define prescription depth for eBT planning without an added margin. A margin of 7 mm was added radially to the US lateral extent measurements, and an appropriate cone applicator size was chosen to cover the target volume.

Results: The mean depth of the lesions was 2.1 mm with a range of 1-3.4 mm, and the mean largest diameter of the lesions was 8 mm with a range of 2.6-20 mm. Dose ranged from 32-50 Gy in 8-20 fractions with a median dose of 40 Gy in 10 fractions. All patients had a complete response and no failures have occurred with a median follow-up of 12 months (range of 6-22 months). Also, no prolonged skin toxicities have occurred.

Conclusions: A routinely available radiological US unit can objectively determine depth and lateral extension of NMSC lesions for more accurate eBT treatment planning, and should be considered in future eBT treatment guidelines.

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Key words: electronic brachytherapy, skin cancer, ultrasound.

Purpose

Non-melanomatous skin cancer (NMSC) affects over 3.5 million patients per year in the United States [1]. Treatment of NMSC can have significant effects on quality of life and cosmesis. There are several available treatment options including surgery, topical chemotherapies, external beam radiation therapy, and brachytherapy [2, 3, 5, 6]. Although effective, surgery can be disfiguring and morbid for lesions located on cosmetically sensitive areas of the body such as the face [2]. For these lesions and for medically inoperable patients, radiotherapy can offer an equally effective alternative to surgery.

Several radiation techniques are available to treat NMSCs. When using conventional megavoltage radiation, treatments can last between 3-6 weeks depending on size and location of the lesion [6, 7]. In addition, to ensure adequate margins and dose to the skin surface, water-equivalent bolus and clinical evaluation are commonly utilized [6, 7]. Superficial/orthovoltage radiation (40-300 kVp) has also been used to treat thin superficial NMSC [8, 9]. Finally, for large tumors with irregular shapes, high-dose-rate (HDR) brachytherapy molds, flaps, interstitial catheters, or radionuclide applicators can be used with an 192Ir source [3, 5, 10, 11, 12, 13, 14, 15].

Since 2009, electronic brachytherapy (eBT), a 50 kVp miniaturized X-ray source with specialized cone-shaped applicators has been used to treat superficial NMSC. Xoft eBT (Axcent eBx; Xoft – a subsidiary of iCAD, Inc., Sunnyvale, CA, USA) does not require a radioactive isotope and involves minimal shielding [16, 17, 18]. It also does not require the same regulations of a radioactive source such as 192Ir [19]. Xoft eBT uses a hypofractionated regimen as do other orthovoltage or HDR brachytherapy techniques [13, 17, 18, 20]. Another system similar to Xoft eBT is Esteya (Elekta AB, Stockholm, Sweden) but uses a 69.5 kV X-ray source [21, 22, 23]. Because of eBT low energy X-rays, the maximum dose is at the surface, and the dose at 5 mm depth is 50-60% of the surface dose depending upon the applicator, e.g., if the prescription depth is 5 mm then ~200% of dose is at the skin surface [24, 25]. In a previously published study...
using Xoft eBT for lesions 1-7 mm thick treated with 40 Gy in 8 fractions, treatment resulted in a local control of 100% and an excellent cosmesis in 93% of patients with no toxicity at a follow-up of 1 year [18]. In this particular study, CT scans were used to estimate the depth of treatment. In many clinics, however, a default depth is selected for eBT calculations and is used universally for all patients. The lateral extension is usually determined with visual inspection on the skin surface and a varying margin is applied based on the physician’s discretion [6, 7]. In our initial eBT experience, using clinical estimates of depth and lateral extent, led to complications such as grade 4 skin necrosis and prolonged wound healing, especially with thicker lesions and lower extremity lesions (Figure 1). This motivated us to investigate a more accurate approach in choosing an applicator size and dose depth prescription by utilizing clinically available ultrasound (US) to measure the depth and lateral extent in order to prevent overdosing the skin. Such US methods have been previously investigated with HDR-BT [13].

In the past, NMSC lateral extension and depth measurements have commonly been determined by visual estimation during clinical examination [6, 7] but this method can be quite subjective and physician-dependent. Measurements from punch biopsies have also been utilized but have led to questions regarding its accuracy [26].

This study reports on the feasibility of using standard US technology as a measuring tool to determine the diameter and the depth of a lesion in order to adequately prescribe radiation dose in eBT treatment planning.

Material and methods

From December 2013 to April 2015, 24 patients with 28 biopsy confirmed NMSCs were referred for definitive Xoft eBT. The depth and lateral extension for all lesions were assessed with US imaging. Five lesions, 4 basal cell carcinomas (BCC), and 1 squamous cell carcinoma (SCC), could not be visualized on US and therefore they were not included in this study. These were treated at a default depth of 1 mm and with a radial margin based on the biopsy scar.

Due to limitation of the eBT technique (low energy and high surface dose), the lesions treated were limited to a depth of < 5 mm. In addition, the largest available Xoft applicator size is 50 mm in diameter, so the largest lateral dimension of any treated lesion was limited to 36 mm due to inclusion of a 7 mm radial margin to cover microscopic disease and setup errors. Lesions were ineligible if evidence of clinical or pathologic positive lymph nodes, metastatic disease, or melanoma histology.

Radiation oncology and radiology records, referring physician documentation, and hospital records were examined. Data was gathered on: patient demographics, pathology, physical examination, photographs, three-dimensional (3D) tumor measurements with US, and radiation treatment planning sheets, calculations, and quality assurance (QA). There were 23 eligible skin lesions in 19 patients for this study. Lesions were staged based on the American Joint Committee on Cancer staging manual 7th edition [27]. Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4. This retrospective study was approved by our institutional review board. Written consent from each patient was received to publish their data and photographs.

**Lateral extension and depth measurements**

A patient with a suspicious skin lesion first underwent a shave biopsy by a dermatologist. After a diagnosis of NMSC was rendered, the patient was referred for radiotherapy and underwent a consultation with a board-certified radiation oncologist. The patient was then sent for US imaging of the lesion for lateral extent and depth measurements, which were documented in a report within an accessible electronic medical record.

**Fig. 1.** Default prescription depth toxicity. Two lesions on the lower extremity were treated to 40 Gy in 8 fractions (5 Gy per fraction) twice per week using a 35 mm cone based on clinical exam and default depth of 3 mm in our early electronic brachytherapy (eBT) experiences. The patient developed a non-healing grade 4 ulceration that persisted even after 4 months post-eBT. Although this toxicity could be due to a number of contributing factors, it illustrates the need for a more precise and accurate depth of prescription. **A)** Pre-treatment, **B)** 4 months post-eBT
Focused US of the lesions was performed by a board-certified radiologist using either: the LOGIQ E9 (GE Healthcare, Milwaukee, WI, USA) or S-3000 US units (Acuson; Siemens Medical Solutions, Mountain View, CA, USA). Linear array transducers with upper frequencies of 14 and 18 MHz were utilized to obtain sonograms. Imaging was performed using either a custom made gel standoff pad or copious amounts of cold US gel acting as a standoff, especially on body parts where the gel pad could potentially cause image degradation due to poor apposition. Scanning was done gently to avoid distortion of lesions. Two-dimensional (2D) B-mode images were acquired with transverse and longitudinal sweeps across the lesion. The US probe was oriented along the longest dimension of the lesion to obtain sagittal and transverse measurements. Measurements of depth were made at the most vertical extension of the NMSC in either plane.

Margin for clinical target volume and planning target volume

In order to cover potential subclinical disease, a margin of 5 mm was added radially to the gross tumor volume (GTV) diameter measurements to create the clinical target volume (CTV), even though dermato-pathologic data has shown that the lateral extent estimate derived from US measurements tends to overestimate the extent of the lesion [28]. Since eBT is a contact therapy with the applicator applied directly and firmly to the skin, there was no expected movement during treatment but an inter-fractional error in positioning the applicator was possible. Therefore, a 2 mm margin was added to the CTV to create a planning target volume (PTV). However, when treating difficult anatomical sites (e.g. eyelid, lip), CTV and PTV were reduced based on practicality and clinical judgment. With 4 eBT applicator sizes available (10, 20, 35, and 50 mm), we used the cone size that adequately covered the PTV.

No extra margin was added to depth based on US measurements and Mohs pathology data showing that US may overcompensate for depth by about 27% [28], and there was no expected setup error in the vertical dimension.

Radiation doses and fractionation

The median dose used was 40 Gy in 10 fractions delivered every other day; median fraction size was 4 Gy. Two lesions on the upper lip and tip of the nose received a more protracted course of 50 Gy in 20 fractions of 2.5 Gy per fraction due to central anatomical locations and greater depths. One patient stopped her treatment after 32 Gy due to grade 3 erythema.

Treatment procedure

During simulation, an immobilization device was fabricated depending upon the location of the NMSC. Patients with lesions on the face were immobilized using an aquaplast facemask (CIVCO Medical Solutions, Coralville, IA, USA) and the area to be treated was cut out from the facemask. Lesions on the extremities were stabilized using a knee roll or wedge cushion. Photographs were taken at the time of setup to aid in treatment setup verification.

When using eBT, the maximum dose occurs at the skin surface due to the use of low energy X-rays, therefore output of the source was defined as the dose rate (Gy/minute) at the skin surface for each applicator. This X-ray source calibration for each applicator followed the American Association of Physicists in Medicine (AAPM) task group (TG) 61 protocol [24, 25]. The beam-on time was computed by the ratio of prescribed dose over the product of dose rate and vendor provided percent-depth-dose (PDD) values. Therefore, for a given prescription dose, 2 parameters were essential in treatment planning calculations: prescription depth determined the PDD value while the lateral extension determined the applicator size.

At the time of treatment, after the patient was setup on the treatment couch, the lesion was demarcated with a fine tip marker by the physician and compared to photographs taken during simulation. Then the applicator was placed firmly against the skin and treatment initiated. The patient was monitored by 2 therapists and a physicist who remained in the room to ensure the patient kept the same position as planned. Aloe vera gel (RadiaGel Hydrogel, Medline Industries, Inc., Mundelein, IL, USA) was provided for the treated area during the eBT course and as long as the radiation-induced erythema persisted (usually a month).

Effects on surface dose

The percent of prescription dose at the surface is considered for clinical purposes (Table 1). Surface dose increases with increasing depth. Cone applicator size with a constant depth also shows small variation in percent of prescription dose at the surface.

| Table 1. Skin surface dose |
|---------------------------|
| Prescription depth (mm)  | 10 mm cone | 20 mm cone | 35 mm cone | 50 mm cone |
| 1                        | 113.0%     | 115.2%     | 112.1%     | 111.7%     |
| 2                        | 127.9%     | 132.5%     | 125.6%     | 124.4%     |
| 3                        | 144.5%     | 151.5%     | 140.4%     | 137.9%     |
| 4                        | 163.4%     | 172.1%     | 156.7%     | 151.7%     |
| 5                        | 184.5%     | 194.2%     | 174.2%     | 166.1%     |

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**Results**

*Patient and lesion characteristics*

This study included 23 eligible NMSCs in 19 patients. The mean age was 68 years. Seventeen patients were ≥ 60 years old. All patients were Caucasian. Twenty lesions were BCC and 3 lesions were SCC. All tumors were staged as T1 or T2. The most common location was the nose (10 lesions). The characteristics of 23 lesions are summarized in Table 2.

**Measurement of lateral extension and depth of non-melanomatous skin cancer using ultrasound images**

Normal anatomy: The layers of skin: epidermis (thickness 0.06-0.6 mm), dermis (thickness 1-4 mm), and hypodermis (subcutaneous tissues; thickness 5-20 mm) can be visualized on US. The epidermis appears as the most superficial, well-defined, hyperechoic, linear band producing the “entry echo” between the US gel and skin (epidermal entry echo [EEE]). The dermis below the epidermis is also hyperechoic, usually less echogenic than epidermis, and with hypoechoic hair follicles, vessels, and sebaceous glands. The hypodermis is hypoechoic with intervening hyperechoic connective tissue septa separating fat lobules. Underneath the skin, superficial fascia covering muscle may be identified as a linear hyperechoic structure [29, 30]. Figure 2B illustrates each layer described on US.

**Ultrasound of non-melanomatous skin cancer**

US provides 2D or 3D images of deep dermal or subdermal layers by measuring differences in sound impedance [31]. On high resolution US, BCC is a solid, heterogeneous and hypoechoic mass that shows irregular margins containing echogenic foci of keratin nests. SCC also appears hypoechoic but may be more aggressive at the time of presentation with infiltration of deeper tissues [29, 30]. Figure 2A and B shows a NMSC on the forehead and US image depicting the clarity and capability of US in providing measurements for eBT prescriptions.

**3D measurements with ultrasound and electronic brachytherapy**

The mean largest diameter of all lesions was 8 mm (range 2.6-20 mm). The mean depth of all lesions was 2.1 mm (range 1-3.4 mm). For BCC, the largest lateral extent ranged from 2.6-12 mm and depth ranged from 1-3.4 mm. For SCC, the largest lateral extent ranged from 8-20 mm and depth ranged from 2.5-3.1 mm. The only upper extremity lesion had the largest lateral extent (20 mm). With US depth measurements, prescription depth could be rounded or prescribed to the fractional depth (e.g. 1.5 mm rather than every millimeter). Figure 3A and B shows the largest lateral extent and the second largest lateral extent, and also depicts the largest diameter and depth for each lesion using US-determined measurements for eBT. No correlation between location, lateral size, and depth was seen in our study.

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**Results of treatment**

All patients have had a complete response, and with a median follow-up of 12 months (range 6-22 months), there have been no failures. More importantly, there have been no cases of grade 4 skin necrosis or delayed healing. Figure 4 shows progressively worsening radiation-induced erythema during eBT for a patient with BCC. This grade 2 erythema usually resolves by the 1 month follow-up.

**Discussion**

In this methodology paper, we describe the use of commonly available US for determining the lateral extent and depth of a pathologically proven NMSC, and the clinical application of such measurements to guide eBT planning. Without a standard objective mode of measuring NMSCs, many clinicians determine prescription depth and applicator size based on clinical judgment [6, 7] or biopsy information [26]. When using small contact applicators, the determination of applicator size should be based on the maximal dimension of the lesion rather than the depth [6].

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**Table 2. Characteristics of non-melanomatous skin cancer lesions**

| # Lesions | % Lesions |
|-----------|-----------|
| **Histology** | |
| BCC | 20 | 87 |
| SCC | 3 | 13 |
| **Tumor stage** | |
| T1 | 12 | 52.2 |
| T2 | 11 | 47.8 |
| **Location of lesion** | |
| Nose | 10 | 43.5 |
| Cheek | 3 | 13 |
| Forehead | 2 | 8.7 |
| Scalp | 2 | 8.7 |
| Lip | 2 | 8.7 |
| Extremity | 2 | 8.7 |
| Ear | 1 | 4.3 |
| Abdomen | 1 | 4.3 |
| **Depth (mm)** | |
| 1-1.9 | 9 | 39.1 |
| 2-2.9 | 8 | 34.7 |
| 3-3.9 | 6 | 26 |
| 4-4.9 | 0 | 0 |
| ≥ 5 | 0 | 0 |
| **Largest lateral Extent (mm)** | |
| 1-5 | 4 | 17.3 |
| 6-10 | 16 | 69.5 |
| 11-15 | 1 | 4.3 |
| 16-20 | 2 | 8.7 |

BCC – basal cell carcinoma, SCC – squamous cell carcinoma
Fig. 2. Clinical setup and ultrasound image. A right forehead basal cell carcinoma (A) delineated with a pen (dotted line) and (B) on ultrasound found to have a hypoechoic lesion that measures 7.5 mm in the transverse dimension, 3 mm in depth and 5 mm in the sagittal dimension (not shown). A 20 mm applicator was chosen to treat to a depth of 3 mm. A hyperechoic epidermis (thin arrow), a hypoechoic dermal layer with a more echoic signal from subcutaneous fat beneath (arrowhead), and the strongly echoic layer below subcutaneous fat is bone that creates shadowing so nothing deeper is anatomically distinguishable (thick arrows).

Fig. 3. Ultrasound (US) measurements of lateral extensions and depth. The largest lateral extent (mm) and second largest lateral extent (mm) of each non-melanomatous skin cancer measured with US and used for electronic brachytherapy planning are shown (A). The largest lateral extension (mm) and depth (mm) of each non-melanomatous skin cancer measured with US and used for electronic brachytherapy planning are shown (B).

Fig. 4. Non-melanomatous skin cancer treated with electronic brachytherapy. A scalp lesion measured to be 6.3 mm × 4 mm × 2 mm with ultrasound was treated with a 35 mm applicator to a 2 mm depth. The dose regimen was 40 Gy in 10 fractions every other day and the lesion is shown: (A) prior to initial treatment, (B) after 5 fractions, (C) after completion of 10 fractions, and (D) after 1 month follow-up. There was progressively worsening erythema over the course of electronic brachytherapy that resolved after 1 month.

cators, this clinical approach bears potential issues such as inadequate lateral coverage and/or under-treating the NMSC or the alternative of over-treatment, which may lead to unnecessary toxicity (skin necrosis or delayed healing). Ballester-Sánchez et al. [26] used punch biopsy then US in order to evaluate depth for NMSC. However,
this leads to questions about whether the punch biopsy removes the deepest portion of the lesion prior to US measurement for eBT. In our study, shave biopsies were used for pathologic verification allowing a greater chance that the remaining NMSC depth and margins were adequately assessable by US.

Unfortunately, there are few available modalities that can be used for non-invasive and accurate measurement of a superficial lesion’s lateral extent and depth. A prior study has discussed US use for NMSC treated with HDR-BT [13]. There has been report of using CT for depth assessment in prior eBT studies [17, 18] but in our experience, CT does not have enough discrimination for accurate depth determination when dealing with superficial thin lesions.

We conducted this pilot study to provide an element of QA and guidelines for accurate treatment planning that is currently not performed routinely rather than proving clinical outcomes. We have found that US evaluation can visualize and measure thin NMSCs in the range of 1-5 mm. Thus, we advocate that rather than using clinical exam measurements (the current standard of care), which can be subjective based on practitioner, objective depth, and lateral extent US measurements that should be used as guidance when prescribing radiotherapy for these superficial cancers. The detailed use of US for NMSC eBT planning has not been described before and is an important consideration for future eBT skin cancer guidelines.

Our intent for this conceptual paper is to describe a more standard technique for prescribing eBT for NMSC; however, we do feel it is important to provide our preliminary clinical outcomes data in order to show that the use of US does not worsen local control or cosmesis compared to previously published studies [17, 18]. Compared to previously published data with median follow-ups ranging from 4.1 to 10 months, the 1 year patient outcomes data for our study shows 100% local control and no significant toxicity, essentially similar to reported data [17, 18]. Compared to previously published studies [17, 18] but in our experience, CT does not have enough discrimination for accurate depth determination when dealing with superficial thin lesions.

Conclusions

Ultrasound technology provides an easy and objective modality to determine the diameter and depth of a lesion when treating thin NMSC lesions with Xoft eBT. The suggested guidelines provide a set of simple parameters to follow when treating superficial skin cancers over cosmetically sensitive parts of the body where skin toxicity could jeopardize the anticipated good cosmetic results.

Disclosure

Authors report no conflict of interest.

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