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Early clinical experience with a degraded 4 MeV electron beam in radiotherapy of superficial basal cell carcinoma

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ABSTRACT

The most common non-melanoma skin cancer is basal cell carcinoma (BCC). Surgery is the gold standard treatment but also non-surgical alternatives are needed. The purpose of this work was to present the early clinical experiences of degraded 4 MeV electron beam as a treatment method for superficial BCC. Twelve patients underwent two weeks radiation therapy treatment with either 5 × 7 Gy or 2 × 12 Gy. There were no significant differences in treatment outcome with different fractionations or lesion locations. The degraded beam method is a safe and valid non-surgical solution for suitable patients with superficial lesions.

1. Introduction

Radiation therapy (RT) has been used to treat skin tumors since the very early days of its history. The first curative results for RT were achieved with skin cancers [1]. There were two reasons for this. Firstly, external RT devices were X-ray tubes with limited penetration in deeper areas. Secondly, skin lesions were directly visible, so the RT field was easy to locate. Nevertheless, the popularity of RT in the treatment of skin cancer diminished in many countries during the 1970 s and 1980 s owing to advances in alternative treatment options and the risk of secondary cancer after RT. RT remains still, a good alternative to treat skin tumors, especially when surgery is not an option and for elderly people.

The most common non-melanoma skin cancer is basal cell carcinoma (BCC) that arises in the epidermis. Optimal treatment options for BCC are determined by tumor size, location, and histopathological subtype. Surgery with negative margins remains the gold standard [2–6]. Various RT-techniques are available for BCC lesions. The most common is external beam radiation therapy (orthovoltage X-rays, electron, and megavoltage photon treatment). Brachytherapy represents an alternative treatment strategy. RT can be considered as the primary treatment in BCC patients for whom surgery is not indicated due to locally advanced disease, co-morbidities, aesthetically unsatisfactory outcome, or patient preference [7–10].

The ideal treatment solution for superficial tumors would have an invasion depth of 0.5 cm or less, a uniform dose distribution, narrow penumbra, insensitivity to moderate density or geometry variations, and fast fall-off for areas deeper than 0.5 cm. All the existing techniques lack the combination of these optimal treatment features.

To achieve a treatment field with sharp penumbra the beam is typically collimated with conical collimators, when using electrons as a treatment beam for skin tumors. The diameter of the collimators ranges from 1 cm to 5 cm depending on the selected treatment method. For these collimators the field size is larger than the practical range of the electrons. As a result, falloff in dose is sharp beyond the maximum dose and spares critical organs deeper down. Typically, the loss of energy in water or water-equivalent material for electrons is 2 MeV/cm. For a superficial X-ray the falloff is approximately exponential because the maximum dose is at the skin level [11].

During the years 2019–2022, a clinical trial was conducted. The standard nominal 4 MeV electron beam from linear accelerator was modified with degrading filter to remove the lateral scatter and minimize the penumbra. A cylindrical collimator was attached to the electron applicator block holder level to define the beam. We evaluated whether a degraded 4 MeV electron beam was suitable for treating small

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Table 1
Patient characteristics, delivered fraction dose (d), total dose (D), and field size.

Patient no.	Sex	Age at recruitment	Target lesion	Fr	d/Fr(Gy)	D(Gy)	Target size(cm)	Size of the collimator (mm)
P-1	m	60	left upper back	5	7	35	1.5 × 1.3	25
			right lower back	5	7	35	2.5	40
P-2	f	62	right lower leg	5	7	35	1.7 × 2.5	40
P-3	m	70	right shoulder	5	7	35	2.0	30
			right upper chest	5	7	35	2.0	30
			right chest	5	7	35	2.0	30
			left clavicle	2	12	24	3.0	50
P-4	m	71	lef upper chest	2	12	24	2.0 × 1.5	30
P-5	f	73	left lower back	2	12	24	1.3	25
			right back thigh	2	12	24	1,7	30
P-6	m	81	left leg	5	7	35	2.5 × 1.5	40
P-7	m	71	right shoulder blade	2	12	24	1.5	30
P-8	m	40	right leg	2	12	24	1.5	30
P-9	m	78	right clavicle	2	12	24	1.0	25
			right clavicle	2	12	24	1.0	25
			left clavicle	2	12	24	1.0	25
P-10	m	74	left flank(side)	5	7	35	2.0	30
P-11	m	76	right upper arm	5	7	35	1.5	30
P-12	f	83	left upper arm	5	7	35	2.0	30

superficial BCCs of the body and extremities. Our aim was to assess, if these modifications can produce a competitive option for other non-surgical treatment modalities of superficial BCC.

2. Materials and methods

2.1. Electron beam modification

The standard 6 cm x 6 cm electron applicator from Elekta Versa HD (Elekta AB, Stockholm, Sweden) linear accelerator was modified to be suitable for treating small superficial skin targets. The aim was to keep the changes in the applicator and the increase of the weight as minimal as possible.

The applicator was modified in three ways. Firstly, 6 mm thick Plexiglas (polymethyl methacrylate, PMMA) plates were added in top level of the applicator. The plates were perpendicular to the treatment beam, and they reduced the lateral scatter from the treatment head. Secondly, another 6 mm thick PMMA plate was placed parallel to the treatment beam in the second aperture plate of the applicator. This plate reduced the energy and worked as an energy degrader. To collimate the beam, an additional 5 cm long PMMA collimator was added, just below the degrader. The third modification was that 6 cm long PMMA collimators were attached to 1 cm thick brass baseplates and located to the standard block holder level to minimize penumbra. The inner diameters of the collimators were 2.5, 3, 4 and 5 cm. The modification of the electron beam has been described previously in more detail [12].

The beam output factors (OF) were reduced significantly in modification as compared with the standard 10 cm × 10 cm 4 MeV open field (OF = 1.000) [12]. This resulted in quite a low dose rate and long delivery time, for instance 7 Gy dose at dose maximum took 10 min at 600 MU/min for the 30 mm collimator.

2.2. Eligible patients

Patient recruitment for our trial was done at the Department of Dermatology by a dermatologist. Eligible patients had a local superficial (thickness below 5 mm) BCC tumor with a diameter below 5 cm. The dose maximum for our treatment energy was 8 mm. All the tumors were located on the body or extremity. The skin at BCC site was required to be in a good condition. The patient performance status had to be WHO 0–2 [13]. The diameter of the targeted lesion was measured and photographed. An optimal collimator which covered the whole lesion with a minimum clinical margin of 3 mm was chosen by the investigating dermatologist. Patients signed an informed consent before participating.

Twelve patients with a total of 19 BCC lesions were recruited in the study, Table 1. Of these 12 patients, nine were male and three women. Mean age at diagnosis was 73.3 years (range 40–82 years). Six patients received 5 × 7 Gy and seven patients received 2 × 12 Gy. One patient had BCC lesions treated with both fractionations. The total number of treated lesions was ten for group I and nine for group II. The BCC lesion was mostly in the body. The mean clinical size of the lesions was 1.8 cm (range 1–3 cm). Histopathology of BCC was confirmed in 18 of 19 cases. Histopathologic subtype was superficial in 15 patients, and mainly superficial with nodular components in three patients. All the BCC lesions, including the one without histopathologic verification, were clinically superficial. One patient had received photodynamic therapy (PDT) for BCC ten years ago, whereas all the other patients had not received any other previous treatments for these BCC lesions.

2.3. RT treatment delivery and follow up

RT consisted of either five fractions of 7 Gy totaling to 35 Gy 2–3 times per week (group I), or two fractions of 12 Gy totaling to 24 Gy once per week (group II). There are remarkable variations in α/β values reported for BCC, ranging between values 0.6 Gy - 13.8 Gy. [14]. Biologically 2 Gy equivalent dose with $\alpha/\beta = 3$ Gy ($BED_{2\ Gy}$) was approximately 70 Gy for both groups I and II. When $\alpha/\beta = 10$ Gy was used $BED_{2\ Gy}$ was 67 Gy for group I and 44 Gy for group II. The difference between calculated $BED_{2\ Gy}$ values with different α/β values is not so large and does not differ from traditional fractionation pattern dose [15–17] that it is possible to use any of these fractionations. The five fractions treatment was the more conventional approach, while the two fractions schedule was a leap to hypofractionated path. So, it was important to compare both. Shorter treatment is easier for the patient and comparable to other non-surgical treatment methods like PDT. RT was delivered with the Elekta Versa HD linear accelerator 4 MeV electrons and modified electron applicator.

The patient's treatment position, gantry angle, and fixation were decided at the first fraction. The aim was to achieve as perpendicular line between target volume and treatment beam as possible. At the first treatment fraction, the oncologist verified the target volume, with the help of images, taken at the dermatologist's appointment. After verification, the target volume was marked with skin marker pen, to be able to setup the patient in other fractions. Patients were carefully supervised through a monitor during every treatment fraction and halfway of the fraction the patient's position was checked. The treatment was given as a fixed source to skin distance (SSD) of 100 cm.

Follow up consisted of dermatologist appointments at one month and six months after the end of RT. The patients were interviewed, and the treated BCC was photographed. The skin condition was evaluated

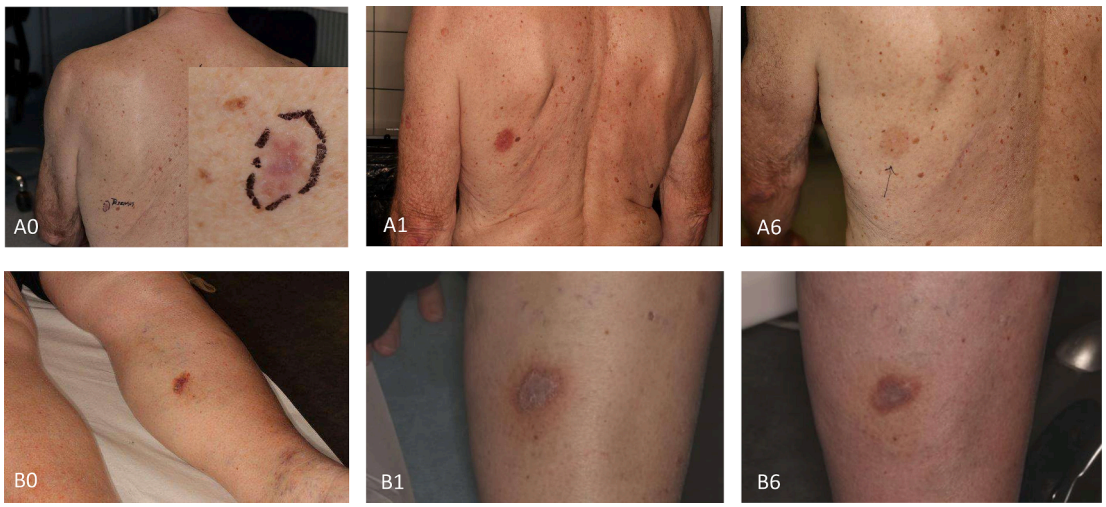

Fig. 1. The best (A) and worst (B) clinical outcome of group I. A0/B0 is the baseline (before the treatment). For same patients the images at one (A1/B1) and six (A6/B6) months after the radiation.

according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0 [18]).

3. Results

3.1. First clinical experiences

One month after the end of RT, BCC lesions were purple and dry. The patients had no pain or ulcering, see Fig. 1. No major difference was observed in BCC lesion appearance regarding different fractionation patterns, location, or size. Notably, one patient in group I with 1.5 cm x 2.5 cm lesion in left shin and severe leg edema, had a complete response after RT without adverse events.

After six months of treatment, a complete clinical response of RT was observed in all patients. Hyperpigmentation was more common in group I. Patient satisfaction was good, without any reports of pain or adverse events.

4. Discussion

The degraded 4 MeV electron beam do have extra collimation which gives it favorable properties to treat superficial skin lesions. There is no deeply penetrating dose "tail" as with orthovoltage x-rays or Ir-192 brachytherapy. And as the nominal energy is lower, the surface dose is higher than with nondegraded electrons. The similar effect for superficial dose and electron penetration could be achieved with a 5–7 mm thick tissue equivalent bolus, but especially with small lesions the degraded electron field has steeper lateral borders. The penumbra is 0.4 mm wider for normal 4 MeV electron beam with 6 cm x 6 cm applicator than degraded beam with extra collimation.

One problem with this solution is quite long delivery time. This also causes a small drop in beam output that can be seen with measured OFs and low dose rate. To make this solution even more optimal it might be reasonable to increase dose rate to decrease treatment time. With standard accelerator the increase from 600 MU/min to 1000 MU/min is usually feasible. The application of this kind of a collimator even with FLASH electron beams would be beneficial.

The criteria for the BCC lesions treated in this study were a depth of less than 5 mm. Even though we did not have the data of the actual histological depth of BCC in our targeted lesions, they were all except one histologically verified to be superficial subtype with or without some nodular component. From the studies with PDT, it is known that these low-risk BCCs seldom invade the skin deeper than 2 mm [19]. Moreover, our lesions were also clinically very thin (at the same level as surrounding skin) confirming that the inclusion criteria for a thickness less than 5 mm in our study were met.

In the current study, a clinical complete response of BCC lesion after RT was observed in all patients. The clinical outcomes were equivalent in both RT groups. These response rates are equivalent as seen for PDT (80 % to 100 %) as Lien et al. reported [20]. It may be interesting to study if there is a correspondence between early response and long-term surveillance as Raasch noticed in her study [21]. Patient satisfaction and treatment tolerance were excellent. This makes our degraded beam method a valid and potentially competitive non-surgical treatment option especially for patients with superficial BCC lesions in lower limbs where other treatment options can cause post treatment complications and limit patient compliance. These complications are reported in Lien et al. [15] and Raasch [21].

Even though the time period was short, and the group of patients was small we were able to get promising results of treatment outcome and tolerance. Because of this degraded beam method can give new non-surgical treatment option for patients for whom treatment options otherwise are limited. After this successful first clinical experiences, we are planning to start a response study with superficial BCC lesions next year.

CRediT authorship contribution statement

Assi Valve: Conceptualization, Methodology, Writing – original draft. **Sari Koskenmies:** Resources, Investigation, Visualization, Writing – review & editing. **Mikko Tenhunen:** Supervision. **Heidi Nurmi:** Conceptualization. **Micaela Hernberg:** Writing – review & editing. **Samuli Salminen:** Writing – review & editing. **Anu Anttonen:** Project administration, Resources.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Assi Valve has received research grant from Helsinki Cancer Center. Other authors have no conflict of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.].

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