Thermal therapy with radiofrequency for the treatment of basal cell carcinoma: a pilot study

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Background: Basal cell carcinoma (BCC) is the most common type of skin malignancy. Hyperthermia is used as adjuvant therapy together with radiotherapy and chemotherapy in the treatment of some cancers. This study aimed to evaluate the efficacy and safety of thermotherapy in the treatment of BCCs.

Methods: This pilot trial was carried out on five patients with nodular or superficial BCCs on the scalp and face. Thermotherapy was done at 50° C for a duration of 30 seconds with a radiofrequency device (Thermomed 1.8 thermosurgery technologies). Thermotherapy treatment was applied only in one session. The first follow-up was one week after the procedure and then every month for six months. The last follow-up was one year after the procedure.

Results: All patients showed clearance of the tumors. Blisters, ulcers, crusts, and necrosis were the side effects, which healed with acceptable degrees of scarring. No recurrence was observed at the end of the study.

Conclusion: Thermotherapy was safe and efficacious for the treatment of BCCs on the scalp and face. It should be considered especially for the low-risk subtypes of this cancer.

Keywords: thermotherapy, basal cell carcinoma, radiotherapy, chemotherapy

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INTRODUCTION

Basal cell carcinoma (BCC) is the most common type of cutaneous malignancy and includes 70-80% of all skin cancers [1,2]. The incidence of BCC is estimated at around 110,000 adults in the UK [3] and there are reports of an increase in the incidence of BCC worldwide [4]. There are various subtypes of BCC, among which micronodular, morphoeic, and infiltrating are high-risk, and the most common sites of BCC are the head and neck [5,6]. The mortality of BCC is inconsiderable; however, it places a huge burden on healthcare systems [7].

Various treatment strategies have been proposed to treat BCC. Surgical excision with control of postoperative margins is currently the standard and treatment of choice in low-risk BCCs [1], providing a cure rate of 95%. The treatment of choice for high-risk BCC is Mohs surgery with an overall cure rate of 97-99% during 3-5 years of follow-up [8]. Curettage and cautery, cryotherapy, topical therapeutic agents (e.g., imiquimod), and photodynamic therapy are other options in the treatment of BCC. Radiotherapy is the last treatment option, commonly used when the tumor is not surgically operable or the patient's medical history contraindicates specific treatments. Vismodegib, which is an inhibitor of the hedgehog signal pathway, was approved in 2012 by the US Food and Drug Administration (FDA) for the treatment of recurrent, locally advanced,

and metastatic BCC [9].

The history of using hyperthermia as a treatment option for cancers initiated at least 5000 years ago. New noninvasive devices have recently drawn more attention to thermotherapy in different cancers [10]. Different sources of producing hyperthermia include electromagnetic energy, microwaves, sonic energy, laser, and radiofrequency [11]. This pilot study aimed to evaluate the efficacy and safety of thermotherapy in the treatment of BCC.

MATERIALS AND METHODS

This pilot study was conducted at Razi Hospital and the Center for Research & Training in Skin Diseases & Leprosy in Tehran, Iran from February 2016 to April 2017. The study was financially supported by the Center for Research & Training in Skin Diseases & Leprosy, affiliated with Tehran University of Medical Sciences. The research protocol was approved by the Ethics Committee (IR.TUMS.REC.1394.1777) of Tehran University of Medical Sciences.

Five patients aged above 18 years with the diagnosis of BCC tumor on the face and neck confirmed by a dermatopathologist on a non-excisional biopsy were eligible for recruitment in this pilot study. All volunteers provided written informed consent. The exclusion criteria were recurrent tumors, tumoral lesions on high-risk areas including the eyes, ears, and nose, size of tumor more than 15 mm, pregnancy, breastfeeding, intolerance to heat, diabetes mellitus and peripheral vascular disease, immunodeficiency, and the history of any treatment for BCC.

During the first visit, the baseline characteristics and clinical data including the site and number of BCCs, dimensions, anatomical locations, and histological subtypes were recorded. Then, the border of the selected tumor was examined primarily by a non-contact dermatoscope (Dermlite DL4) by two dermatologists prior to the thermotherapy to assess the border expansion of the tumor. The patterns that were used for diagnosis were arborizing vessels, superficial fine telangiectasias, blue-grey globules and ovoid nests, maple leaf-like areas, and spoke wheel areas [12]. The lesion and its expanded margins were marked and then anesthetized by local anesthesia with the injection of lidocaine 2%. After inducing anesthesia, lesions were made wet with sterile saline solution before thermotherapy was applied with a radiofrequency device (Thermomed 1.8 thermosurgery technologies, Phoenix, Az, USA).

The fact is that thermal cell death relates to different factors such as tissue sensitivity, temperature, and exposure time. It was shown that at the temperature of 50° C from just under 30 seconds, cell survival starts to diminish considerably [13]. Furthermore, time-temperature analysis of cell killing of baby hamster kidney (BHK) cells showed heating at temperatures in the range of 43.5° C to 57.0° C can cause cell death. Based on these findings and thermal isoeffect doses [14], we chose the mean temperature for inducing cell killing (50° C) with a duration of only 30 seconds for this study. Moreover, our previous study [15] on the treatment of warts (located anywhere except head and neck) with thermotherapy showed that the temperature of 50° C for 60 seconds led to blisters in most cases. Hence, we selected a shorter duration of thermotherapy to prevent this complication as much as possible. The Thermomed 1.8 device has a handpiece with two electrodes that were placed in direct contact with the tumor. A thermistor is placed in one of the electrodes to control the temperature. The handpiece of the device was moved a few millimeters away from the defined border and the treatment was repeated until the whole surface of the lesion had been treated. Thermotherapy treatment was applied only in one session without any prior curettage, shaving, or debulking of the tumor. No antibiotics were prescribed after the procedure.

The patients were followed up after one week and then every month for six months. The last session of follow-up was six months later for one year. In each follow-up, photography and dermoscopy (as a non-invasive method) were used to identify the response to treatment, presence or clearance of tumor, and possible recurrence of BCC.

The primary endpoint measurement of treatment was defined as the complete disappearance of the tumor. Biopsy was performed in the case of the presence of any clinical or dermoscopic signs of recurrence. The secondary endpoint was the satisfaction of patients with the procedure. The safety of the procedure was assessed by the record of any blister, ulcer, crust, scarring, necrosis, and post-inflammatory hyperpigmentation or hypopigmentation.

RESULTS

Thermotherapy was performed for five patients with BCC including two men and three women with a mean age of 69.4 years (range: 56 to 76 years). The baseline characteristics of the patients are shown in Table 1. All patients had a history of radiation for the treatment of tinea capitis in childhood. Out of the five tumors included in this pilot study, three tumors were nodular and two were superficial. The most common Fitzpatrick skin phototype was IV (4 out of 5). Only one tumor of each patient was treated by thermotherapy and the rest of the tumors were removed by surgery and reconstructed by either flaps or grafts. Moreover, one patient also had multiple small superficial BCCs that were treated by cryotherapy. The lesions in our study were all primary lesions.

All patients developed blisters (Figure 1a), ulcers, and crusts after thermotherapy, which healed with some degrees of scarring, but the scars improved in appearance considerably with time. Furthermore, one patient complained of pain at the site of the procedure that diminished over time. Necrosis was noticed only in one male patient, which completely healed with the prescription of fibrinolysin topical ointment. None of the patients had any signs of recurrence at the end of the study (Figures 1b, 2a, b), and all patients were satisfied with the thermotherapy.

DISCUSSION

To the best of our knowledge, this is the first report on the application of hyperthermia-induced by radiofrequency in the treatment of BCC. In this pilot study, the clearance of tumors was observed in all patients and none of the tumors had recurrence within one year of follow-up. At the end of the study, other tumors of patients that were treated by surgery did not show recurrences either. All of these patients stated that thermotherapy was much more convenient than a surgical procedure, even when the size of lesions treated with thermotherapy and surgery were the same. In this study, none of the patients developed an infection.

Table 1. Baseline characteristics of the basal cell carcinoma (BCC) patients of this study

Patient No.	Age (years)	Gender	Place of tumor	Type of tumor	Skin phototype	Size	Number of BCC lesions
1	71	M	Frontal (Rt)	Nodular	IV	12×10 mm	2
2	75	M	Parietal (Lt)	Superficial	III	13×10 mm	2
3	69	F	Face (Rt cheek)	Nodular	IV	10×5 mm	2
4	56	F	Ear (Rt posterior)	Superficial	IV	11×5 mm	Multiple
5	76	F	Face (below Rt eye)	Nodular	IV	10×8 mm	Multiple

Figure 1. (a) Blister at the site of superficial BCC following thermotherapy; (b) complete disappearance of this lesion

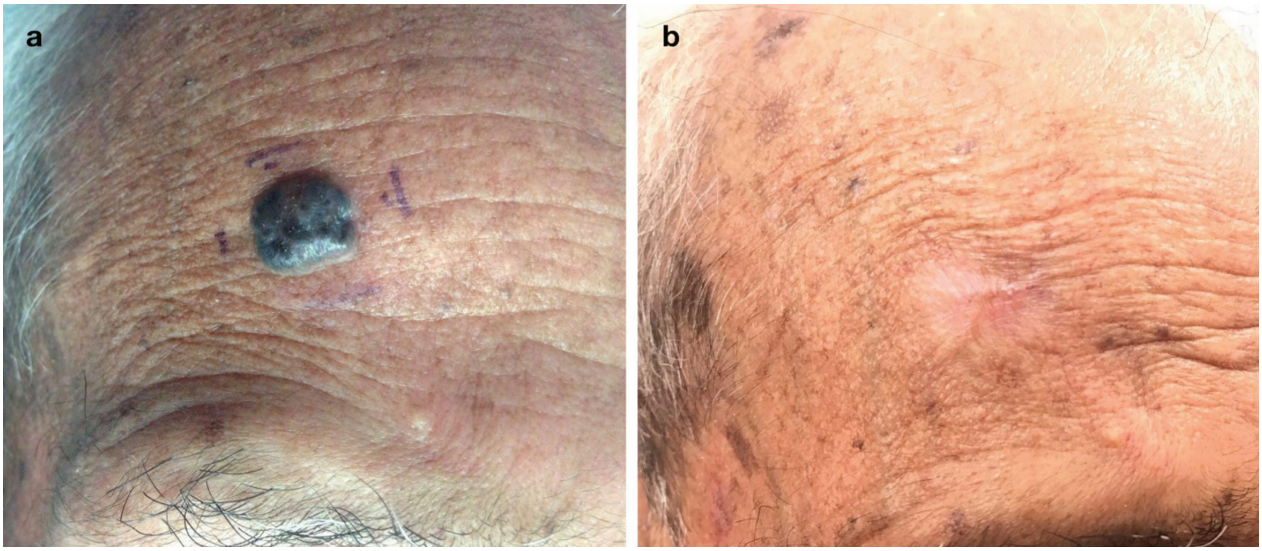

Figure 2. (a) Nodular BCC before treatment; (b) complete disappearance of the lesion.

Different studies have shown the effect of hyperthermia on neoplastic cells based on improving antitumor immune responses and increasing ATP tumoricidal activity. The most common mechanism that heat might affect malignant cells is apoptosis induction, while other important mechanisms are also involved, such as protein and cytoskeletal damage and production of reactive oxygen species. Furthermore, hyperthermia affects the environment around the tumor cells and causes an alteration in pH and blood flow, which might result in hypoxia and tumor cells' death. Heat shock proteins (HSPs) are responsible for repairing protein misfolding in cells. Exhaustion of HSPs is another mechanism through which thermal therapy may induce apoptosis in cancer cells [16-22].

In past studies, researchers have mainly examined the effect of hyperthermia as an adjuvant therapy to radiotherapy or chemotherapy in cancers [10,23]. Heat therapy has a potential synergistic effect on the cytotoxicity of chemotherapy and promotes the response to radiotherapy [17,24]. Different methods of hyperthermia for different oncological cancers have been described with successful results [10].

There are reports of Nd:YAG laser-induced hyperthermia in the treatment of cancers. A study compared the efficacy of Nd:YAG laser with heating in a water bath on tumor cell killing. Interestingly, heat for 10-15 minutes of 47°C was enough to induce cell killing while a short laser exposure with 44°C caused significant tumor cell killing [25]. Panjehpour *et al.* demonstrated the efficacy of this laser in four pets with superficial head and neck tumors (three with squamous cell carcinoma and one with melanoma). The temperature was maintained between 43.2-43.5 °C for 1 hour. Although complete regression was observed, two satellite lesions developed afterward [26].

Another study demonstrated the efficacy of the Nd:YAG laser in the treatment of 37 patients with BCC. The temperature was set at 45°C for 1 minute, and a minimum of two and a maximum of four sessions were performed. It revealed 97% tumor clearance over five years of follow-up. Side effects were burning sensation, infection, hypo- and hyper-pigmentation, alopecia at the site of laser application, recurrence of the tumor, and a permanent depressed scar [11].

Transpupillary thermotherapy was utilized for the treatment of retinoblastoma and ocular melanoma with promising results. The applied temperature (60-65°C) was provided by an infrared diode laser [27].

Investigations on BCC revealed that hyperthermia induces apoptosis in a different way than two major apoptotic pathways, i.e., the extrinsic (caspase 8) and intrinsic (caspase 9) pathways. Instead, hyperthermia kills BCC cells through the pathway of the endoplasmic reticulum. This non-conventional pathway paves the way toward a new approach of treatment by thermotherapy for a synergistic effect in the treatment of cancers [28,29].

Even though hyperthermia has been proven to be efficacious, it has been remained obsolete so far due to its time-consuming and technologically challenging nature as well as difficulties for the patients [23]. Our work revealed that heat therapy with radiofrequency is very convenient for patients. Also, it has lower morbidity with the greater preservation of normal tissue surrounding the tumor, improving the quality of life during the period of the healing process and causing less scarring.

A larger study with more participants and a longer duration of follow-up is needed for a better evaluation of benefits and comprehension of the risks of thermotherapy in the treatment of BCCs. Moreover, further studies for other more invasive subtypes of BCCs including micronodular, basosquamous, and morpheaform are recommended. All five patients who participated in this study had a history of radiotherapy due to tinea capitis in their childhood. Radiotherapy is only one risk factor out of several other factors [7]. Although a previous study suggested that BCCs in these patients have more aggressive behavior [30], all patients in our study had a complete response to the thermotherapy. Nevertheless, there is a need to design further studies to assess the response of BCCs induced by other risk factors. The maximum size of tumors treated by thermotherapy in this study was 13 mm. Further studies for larger tumors are required to evaluate whether there is any limitation of the size of tumors treated by this method. Moreover, we did not evaluate high-risk tumors in the H-zone of the face. Finally, we evaluated tumor recurrence by dermoscopy, but histological evaluation might be more sensitive for assessing tumor recurrence.

CONCLUSION

In conclusion, this pilot study showed that the application of radiofrequency heat therapy for patients with BCC is simple and effective, with rapid healing, minimal side effects, and no recurrence. This method can provide a decrease in bleeding, tissue damage, time of the procedure, and scarring. Although the efficacy of thermotherapy in eradiating the tumor can be less than standard surgical treatment of BCC, many unwilling patients for surgical treatment or those who cannot tolerate surgery would benefit from it. This treatment is suitable for patients who have small nodular or nodulo-ulcerative BCCs and are not good candidates for surgery for any reason. On the other hand, morphea-type BCCs or lesions very close to sensitive anatomic areas (e.g., on the eyelids) are poor candidates for this treatment.

Conflict of interest: None declared.

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