Dermatological high-dose-rate brachytherapy for the treatment of basal and squamous cell carcinoma

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Summary

Background. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are among the most common cancers in humans. Various therapies are currently being used to treat these tumours including surgery, topical treatments and radiotherapy. We describe a new treatment for BCC and SCC. This consists of superficial radiotherapy, using synthetic resin containing a radioactive β-emitting isotope. The resin is applied to the lesion to perform a selective β-irradiation brachytherapy treatment.

Methods. In total, 53 patients with histologically confirmed diagnosis of BCC and of SCC were enrolled for the treatment.

Results. In all treated cases, an apparent clinical remission occurred in approximately 3 months, and complete healing was obtained in 100% of the treated patients; in 82% of the cases, this occurred after a single application. No disfiguring scars or any side-effects were seen. After a follow-up of 20–72 months (mean 51 months), no clinical relapses were observed in the treated patients. Histological examination confirmed complete tumour regression.

Conclusion. The results indicated that brachytherapy is an effective treatment for BCC and SCC.

Introduction

Skin cancer is one of the most common forms of cancer, and basal cell carcinoma (BCC) is the most common cancer in white populations.[1] Squamous cell carcinoma (SCC) is the second most common form of skin cancer, and in European countries its annual rate of incidence is about 25/100 000 in the population. SCC is a more aggressive tumour than BCC, may metastasize to regional lymph nodes and is often locally recurrent.[2]

For both tumours, standard treatments such as curettage and cautery, surgery (including Mohs' surgery), cryosurgery,[3,4] topical chemotherapy, imiquimod and photodynamic therapy[5] are often proposed to patients. Radiotherapy, using low-energy X-rays (≤ 90 kVs) or electrons, and interstitial brachytherapy with γ-ray emitting sources placed across the tumour volume, have both been used in clinical practice.[6]

In this paper, we present a new treatment for BCC and of SCC. This consists of superficial radiotherapy, characterized by the use of a specially formulated, inert, synthetic resin containing radioactive β-emitting isotopes, which is able to adapt to skin surfaces without spreading beyond the tumour area, allowing accurate dose distribution and sparing of healthy tissue.

The treatment has been used in a large variety of BCC and SCC forms, from very large tumours to relapsing or recurrent forms, to multifocal lesions.

Methods

The treatments were routinely performed in the Nuclear Medicine Department of S. Eugenio Hospital. The method of preparing radioactive resin has previously been reported.[7,8] Briefly, carrier-free ^{188}Re (perrhenate)

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was obtained from a $^{188}W/^{188}Re$ generator (Oak Ridge National Laboratory, Oak Ridge, TN, USA) by elution with saline. A sterile nanocolloid (200–800 nm) of Re_2S_7 was obtained by reaction of perrhenate with hydrogen sulphide. The nanocolloid was thoroughly mixed with a synthetic acrylic resin (Meyer, Milan, Italy) to obtain homogeneous distribution of the radioactive nanocolloid.

The skin to be treated was protected by a thin layer of a protective cream (Tueor; SOFAR, Milan, Italy), and the radioactive resin was applied on top of this cream layer. After a few minutes, the resin solidified without appreciable shrinkage; the radioactive mould was kept on the lesions for the time necessary to impart the precalculated dose distribution.

The thickness of the resin and cream was accurately measured, in order to account for β-radiation absorption and self-absorption effects. For each application, the dose distribution depends on the initial radioactivity, the isotope emission energy, the surface of the lesion and the contact time. The applied radioactivity was measured using a dose calibrator (Model 4045; RadCal, Monrovia, CA, USA). A Perspex screen 10 mm thick was sufficient to protect the physician from β-radiation during the phase of application (1–3 min) to the patient. During the irradiation, typically lasting from 15 min to 2 hours, the patient was kept isolated; after the required irradiation time, a radioactivity test was performed on the treated lesions, which always showed a total absence of any measurable contamination.

Dosimetry

The ^{188}Re isotope is a mixed β–γ emitter, with a half-life of 16.98 hours; the β-particles have a maximum energy of 2.12 MeV and a mean energy of 764 keV, therapeutically effective only at short ranges. A γ-ray component of 155 keV accounts for 15% of the radiation intensity, and allows excellent control of any possible radioactive contamination.

The dose distribution of β particles in human tissue is described by complex multiexponential functions.[9–12] Vinkyer *et al.*,[13] and Sedda *et al.*,[14] proposed some modifications of the classic formulas, in order to increase the accuracy of dose distribution at distances comparable to the maximum range of the β particles.

For each application, a calculation of the dose-distribution curve imparted to the skin was performed by a point source algorithm, but in selected cases an intercomparison of different calculation methods was performed, by comparing the results obtained using EGS4 Monte Carlo software, a point source numerical integration algorithm, and *ab initio* integration calculations of point sources of β rays. An agreement of the dose-distribution curves obtained from the different models within ± 5% was found.

Treatments

In total, 53 patients (29 men, 24 women) with histologically confirmed diagnosis of BCC (37 patients) or SCC (16 patients) were enrolled. These were patients in whom a relapse of the tumour had occurred, or for whom surgery was considered impossible or aesthetically unacceptable. Nine patients had multiple BCC lesions and three patients had multiple SCC lesions. Within the study group, 70% of the tumours were present on the head or neck, 22% on the upper and lower limbs, and 8% on the trunk and back. Most of the superficial BCCs on the head were located on the nose and temporal area. Tumours of the nodular or infiltrative type made up 32% of the total. Further details on patients are shown in Table 1.

A thorough clinical and dermoscopical examination of the lesional area was performed, and histological information was used to evaluate the mean depth of tumours and the limit of the histologically healthy tissue of the lesions. High-resolution digital photographs of the tumours were collected before and at various intervals after the treatment to evaluate and document clinical healing.

For each patient and for each lesion, the dose-distribution curve was always calculated, using a point source integration program. Mean doses of 40–60 Gy were given, to depths of 300–600 μm from the epidermis, depending on histological indications. Some typical examples of dose distribution curves are reported in Figure 1. The activity used for each treatment ranged

Table 1 Overview of patient data and treatments.

Tumour	BCC	SCC
Treatments (no. of patients)		
1	32	11
2	4	4
3	1	1
Mean ± SD area (cm^2)	7.04 ± 8.9	14.6 ± 10.6
Follow-up (no. of patients)		
1–2 years	6	3
3–4 years	14	4
≥ 5 years or more	12	4
Previous surgical treatment (*n*)		
No	20	8
Yes	12	3

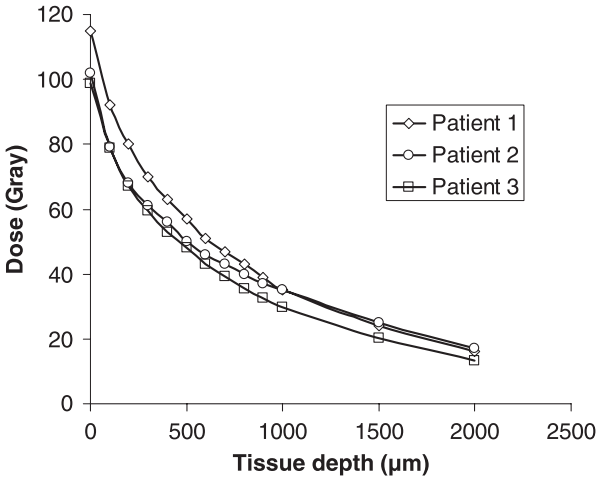

Figure 1 Example of ^{188}Re dose distribution curves in three different patients.

from 40 MB of ^{188}Req in the smaller lesions up to about 2000 MBq in larger lesions. The required application times varied from a few minutes to 2 hours, depending on the applied radioactivity, the size of the lesion, and the calculated dose-distribution curve.

Results

Immediately after the irradiation, mild erythema was visible in the irradiated area, which completely disappeared 2–7 days after the treatment. Bleeding was often present in large lesions; this ceased 10–30 days after treatment, a scab was formed, and the lesion gradually healed. Most of the patients only needed a single treatment; in some cases two or three treatments were required for complete healing (Table 1). The number of treatments required for healing is apparently related to the thickness of the lesion; thicker tumours generally required two or even three treatments.

In some cases, clear neoangiogenic development was seen in the dermoscopic examination of the tumour area, especially in SCC cases, which gradually disappeared after the treatment.

In all treated cases, apparent complete clinical remission occurred after 3–5 months; in all the cases in which a second or even a third treatment was performed, the ulcerations rapidly disappeared after the first treatment, and the tumour residue appeared as a hard nodule. After successive treatments, a gradual flattening and softening of the lesion was observed, ending with complete healing (some examples of clinical results are reported in Figs 2–4).

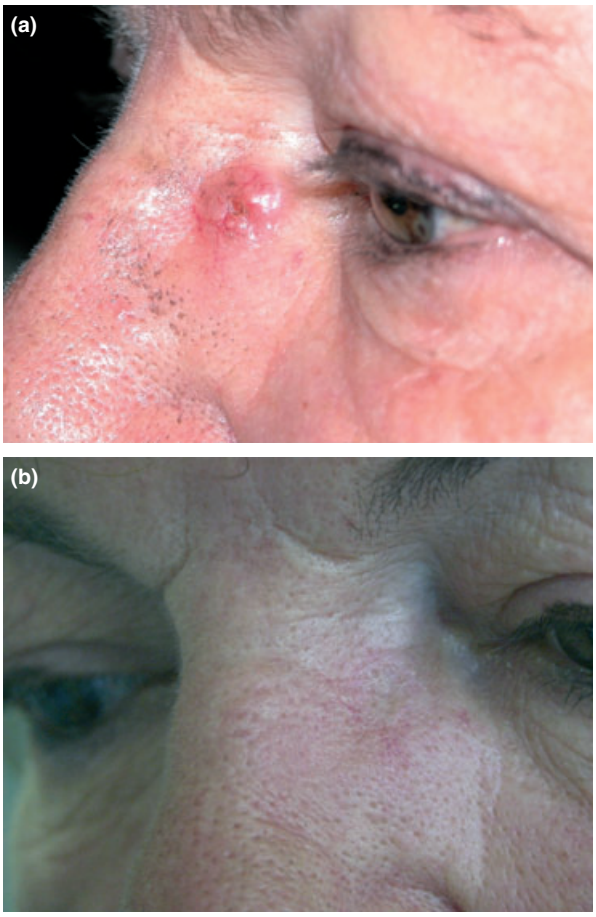

Figure 2 Basal cell carcinoma on the nose (a) before and (b) 120 days after a single treatment. Estimated imparted dose was 50 Gy at 450 μm.

After a follow-up of 20–72 months (mean 51) complete healing was seen in 100% of the treated cases; in 82% of the patients, this occurred after a single application. In the remaining cases, a maximum of three treatments was used (Table 1). No disfiguring scarring, pain or side-effects were seen. After the treatment, the patients were discharged home without any further prescriptions.

Follow-up included a control visit at 1 week, 3–4 weeks, 3 months, 6 months, and finally 1 visit/year. For each visit, photographic documentation of the lesion appearance was always collected. After a follow up of 20–72 months, no systemic nor topical side-effects had occurred, and no relapses were seen.

Moreover, treatment was successful not only for superficial tumours, but also for nodular, infiltrative, ulcerating and relapsing tumours, which showed relatively rapid and complete healing. Histological

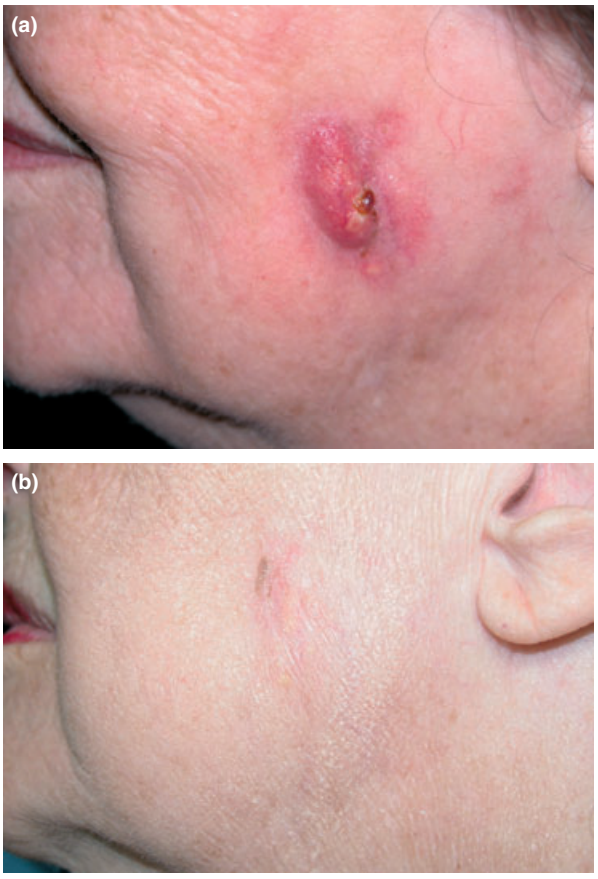

Figure 3 Squamous cell carcinoma on the cheek (a) before and (b) 60 days after a single treatment. Estimated imparted dose was 50 Gy at 600 μm.

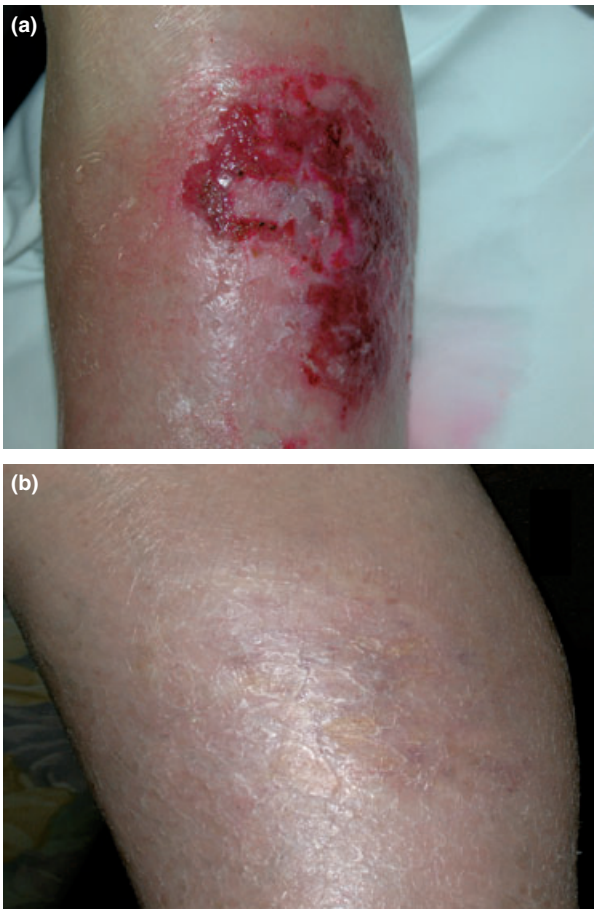

Figure 4 Squamous cell carcinoma on the leg (a) before and (b) 120 days after a single treatment. Estimated imparted dose was 50 Gy at 500 μm.

examination performed after the treatment (for about 60% of the patients) confirmed complete tumour regression.

Discussion

There is general agreement that surgery is the treatment of choice for BCC and SCC. Alternative treatments offer cost and clinical advantages in selected cases, such as for tumours located in high-risk areas or difficult sites (nose, ears, eyelids), or for patients with a large number of lesions, and older, infirm, or otherwise inoperable patients.

Irradiation of BCC by photons has been used in clinical practice in selected cases; high cure rates have been obtained, with values almost comparable to Mohs' micrographic surgery.[1,5] However, classic photon radiotherapy faces the problem of relatively inaccurate irradiation of tumour margins, due to the lack of individually moulded radiation collimators, and can be harmful to adjacent organs, due to the penetrating nature of γ photons or X-rays. Classic γ brachytherapy requires complex software programs for treatment planning and calculation of dose distribution to obtain an individually adjusted dose distribution, but the dose distribution remains far from ideal, due to the penetrating nature of the photons, and a large number of sessions (30–40) are usually required.[6]

The use of β radiation embedded in a tailor-made irradiation mould, such as the technique we describe here, appears able to override the drawbacks of classic radiotherapy. In fact, not only can the margin of irradiation be easily controlled by the present technique, but the dose-distribution curve obtained by beta particles (Fig. 1) almost follows the typical distribution of tumour invasion in dermal tissue, administering the therapeutic dose only at the required depths, without

unnecessary dose deposition in the subdermal tissue, independently of the complexity of the lesion shape or the number of lesions.

It must be noted that in our treatments the mean dose distribution curve (Fig. 1) showed a clear reduction in dose from a nominal value of 100–120 Gy at the epidermis to < 20 Gy at a depth of only 2 mm, a depth at which invasion from tumour cells is usually present.

Although it is difficult to reconcile such superficial treatment with the excellent clinical results we obtained, it must be noted that single-fraction radiotherapy has been used for the treatment of small superficial BCCs and SCCs in > 800 patients, obtaining an overall disease-free rate at 5 years of 84%; the optimum applied dose for such a lesion on a flat surface was 20 Gy,[15,16] which suggests fairly high radiosensitivity for these class of tumours.

Animal studies also indicate that ionizing radiation may exhibit immunomodulatory properties by enhancing antitumour immune response; radiation upregulates the expression of various cytokines (e.g. interleukins 1a, 1b, 2 and 12, and tumour necrosis factor-α and -β) in tumour, stromal and infiltrating cells.[17]

It has recently been recognized that doses of radiation lower than or equal to those that cause direct cytolysis may alter the phenotype of target tissue, by upregulating gene products that may make tumour cells more susceptible to T-cell-mediated immune attack.[18] Thus a synergistic mechanism may be present in the clinical and histological healing of tumour lesions apparently thicker than the therapeutic range of the β particles.

Apart from the underlying mechanism, the clinical results obtained with the technique we describe were satisfactory for the whole cohort of treated patients, in spite of the relatively small observation group. The proposed technique should be considered a new clinical treatment, and an alternative to both surgical and medical treatments. Its main advantage lies in the usefulness in all types of BCC and SCC, without restriction by site, dimension, clinical or histological type, or the patient's clinical situation. It is a rapid treatment, usually performed in a single treatment session, without discomfort for the patient, and offers complete aesthetic *restitutio ad integrum*.

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