Available online at www.sciencedirect.com
ScienceDirect
Applied Radiation and Isotopes 66 (2008) 303–309
Applied Radiation and Isotopes
www.elsevier.com/locate/apradiso

Radioactivity and Radionuclide Applications

Design and bioevaluation of a ^{32}P-patch for brachytherapy of skin diseases

M.J. Salgueiro[a,*], H. Durán[b], M. Palmieri[c], R. Pirchio[d], J. Nicolini[e], R. Ughetti[e], M.L. Papparella[f], G. Casale[e], M. Zubillaga[a]

[a]*Radioisotope Laboratory, School of Pharmacy and Biochemistry, University of Buenos Aires, Buenos Aires, Argentina*
[b]*Radiobiology Department, National Atomic Energy Commission (CNEA) Buenos Aires, CONICET and School of Science and Technology, University of San Martín, San Martín, Argentina*
[c]*Biodiversity and Experimental Biology Department, School of Exact and Natural Sciences, University of Buenos Aires, Buenos Aires, Argentina*
[d]*Dosimetry Department, National Atomic Energy Commission (CNEA) Buenos Aires, Argentina*
[e]*Research and Development Department, Laboratorios Bacon SAIC, Argentina*
[f]*Pathology Department, School of Dentistry, University of Buenos Aires, Buenos Aires, Argentina*

Received 27 February 2007; received in revised form 22 August 2007; accepted 11 September 2007

Abstract

The purpose of this study was to design and evaluate a ^{32}P patch for brachytherapy of skin diseases. We employed Phosphoric-^{32}P-acid and Chromic ^{32}P-phosphate in combination with natural rubber or silicone to produce the patches. Stability studies *in vitro* to evaluate the leakage of radioactivity, autoradiographic studies to evaluate homogeneity and shielding, as well as therapeutic efficacy in an animal model of skin cancer of the selected ^{32}P patch were performed. The ^{32}P-silicone-patch demonstrated its safety for external application. Tumor growth was arrest and complete regressions of tumors were seen in some other cases with 40 Gy applied in a single-dose scheme. In conclusion, the ^{32}P-silicone-patch is easy to prepare and use in the treatment of skin diseases.

Keywords: ^{32}P; Brachytherapy; Skin cancer; Patch

1. Introduction

Skin diseases such as melanoma, non-melanoma skin cancer and keloids are very common in humans (Diepgen and Mahler, 2002; Kal and Veen, 2005; Locke et al., 2001). The most common treatment modalities for them are surgical excision, radiotherapy and chemotherapy (Diepgen and Mahler, 2002; Kal and Veen, 2005; Locke et al., 2001). Each therapeutic mode has its own advantages and disadvantages, but brachytherapy with beta emitting radionuclides such as ^{166}Ho, ^{90}Y and ^{188}Re incorporated in bandages has been reported as a promissory effective alternative (Chung et al., 1998, 2000; Lee et al., 1997, Mukherjee et al., 2002, 2003). The availability of this beta emitters, their cost and their physical characteristics are of importance when considering the possibility of a treatment employing them. The aim of our study is to design a ^{32}P patch, as this radioisotope is commercially available in South America, in order to evaluate its radiopharmaceutical characteristics to be applied in brachytherapy treatments of skin diseases. In this way, we planned different alternatives both for the matrix and the ^{32}P source of the patch and evaluated them with *in vitro* and *in vivo* studies.

2. Materials and methods

2.1. Production of ^{32}P-patches

10 mCi of ^{32}P was purchased as Phosphoric-^{32}P-acid (CNEA, Buenos Aires, Argentina) and its radiochemical purity was controlled (USP XXVIII, 2005a, b). The final whole size of each patch was approximately of

*Corresponding author. Tel.: +54 11 4964 8202x33; fax: +54 11 4964 8202x31.
E-mail address: jsalgueiro@ffyb.uba.ar (M.J. Salgueiro).

0969-8043/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.apradiso.2007.09.008

2 cm × 2 cm. ^{32}P-*Natural rubber-patch* was prepared mixing 5 mL of Phosphoric-^{32}P-acid and 5 mL of natural rubber (low ammonium latex, Lee, Malaysia) and desiccated at room temperature, in order to obtain a patch of 1 mm of thickness. ^{32}P-*resin untreated-patch* was prepared with a strongly basic anionic resin (Model HC-D208, Strongly Basic Anionic Exchange Resin, Hecheng, China) incorporated in a 20 cm glass-column and Phosphoric-^{32}P-acid was eluted and washed once, with saline. The ^{32}P incorporated to the resin was then mixed with an equal volume of natural rubber in order to obtain a patch of 1 mm of thickness which was desiccated at room temperature. ^{32}P-*resin treated-patch* was prepared in the same way than the former but the treatment consisted in washing the resin continuously during 24 h, with saline. The ^{32}P incorporated to the resin was then mixed with an equal volume of natural rubber in order to obtain a patch of 1 mm of thickness desiccated at room temperature. ^{32}P-*silicone-patch* was prepared with Chromic ^{32}P-phosphate (30–70 nm) obtained from Phosphoric-^{32}P-acid as previously described by Anghileri (1958, 1967), Anghileri and Marques (1967) and silicone (Silastic®J-White 80, Dow Corning, The Dow Chemical Company and Corning Inc., USA). Radiochemical purity of Chromic ^{32}P-phosphate was evaluated (USP XXVIII, 2005a, b) before using it. The Chromic ^{32}P-phosphate was previously washed with isopropilic alcohol (Anhedra, Argentina), centrifuged to 2000 rpm during 10 min and finally dried at 80 °C in order to obtain a powder. Afterwards, the Chromic ^{32}P-phosphate powder was mixed with a volume of silicone and dried at room temperature during 4 h in order to obtain a patch of 1 mm of thickness.

2.2. Autoradiographic studies

2.2.1. Homogeneity studies of the ^{32}P-silicon-patch

Autoradiographic studies were performed using a photographic paper (B/W RC paper Semi Matt, Multicontrast Premium, AGFA, Germany) and directly exposing a sample of the patch in a dark room during 4 min, in order to evaluate the distribution of ^{32}P in the matrix of the patch. Standard revealed techniques were used to obtain the photographs. All patches employed in therapeutic studies were assayed.

2.2.2. Range and shielding studies of the ^{32}P-silicon-patch

Autoradiographic studies were performed in the same way as described above, using a sample of the liquid mixture of the silicone patch which was introduced in a catheter of 1 mm of thickness. The sample was then first exposed during 30 min to the photographic paper interposing different thickness of water by immersion with an angle of 3.3°, in order to confirm the range of the beta particle in this medium. Subsequently, the sample was again indirectly exposed during the same period of time to the photographic paper, but interposing different thickness of aluminium in order to shield radiation.

2.3. Measurements

2.3.1. Activity concentration of ^{32}P-patches

A weighted sample of each patch was dissolved with 5 mL of hyamine hydroxide (MP Biomedicals, LLC, USA) at room temperature overnight. An aliquot exactly measured was added to a vial containing 3 mL of a complete phase combining system for liquid scintillation counting (PCS® Amersham Biosciences, USA). The activity measurement was performed in a liquid scintillation counter (Wallac 1410 Liquid Scintillation Counter, Pharmacia Wallac OY, Finland) according to the ^{32}P protocol, with a relative error $<1\%$. Results were expressed as MBq/cm^2 (or mCi/cm^2) taking into account the weight of the sample and the density of the patches.

2.3.2. ^{32}P samples

All samples from supernants of stability studies were measured in a liquid scintillation counter with a relative error $<1\%$, as described above.

2.4. Stability studies of ^{32}P-patches

Triplicate samples of each kind of ^{32}P-patches were placed each in a Petri dish containing 10 mL of: distilled H_2O, saline and dextrose 5%. A set of samples were incubated at room temperature and another one at 37 °C. The radioactivity leaching out of the patch was determined in an aliquot of the supernant after 0.5, 1, 3, 6, 12, 24 and 30 h. Additionally, the ^{32}P-silicone-patch was also treated with $HClO_4$ 70% (Merck, Argentina), HNO_3 65% (Ciccarelli, Argentina), NaOH 1 N (Anhedra, Argentina), ClH 1 N (Merck, Argentina) at room temperature in order to evaluate its performance under extreme hydrolysis conditions. Results are expressed as activity leakage percentage.

2.5. Therapeutic studies

All animal experiments were performed in accordance with the "*Guide for the Care and Use of Laboratory Animals, US National Research Council, 1996*". The classical model of mouse two-stage skin carcinogenesis was reproduced (DiGiovanni, 1992; DuBowski et al., 1998; Aldaz et al., 1991). Briefly, the backs of 7–8-week-old female Sencar mice were shaven with surgical clippers at least 3 days prior to treatment and only mice in the resting phase of the hair cycle were used. Mice were initiated by a single topical application of 20 nmol of DMBA in 0.2 mL of acetone. Afterwards, they were topically treated twice a week with TPA 3.25 nmol in 0.2 mL of acetone, starting 10 days after initiation and over a period of 16 weeks. Animals were randomized in two groups with similar tumor initial sizes: treated (TG $n=7$) and controls (CG $n=6$). Although each animal has more than one tumor, treated and control tumor were selected from different mice, therefore CG did not received any treatment and TG received brachytherapy in one selected tumor.

The ^{32}P-silicone-patch was divided in pieces in order to adapt them to the size of tumors in the treated group. In this regard, for experimental purposes the patches were not shielded. Afterwards, each patch was applied into direct contact with lesions and further firmly affixed with a hypoallergenic adhesive tape to prevent displacement. The exposition time was determined by dosimetric calculation in order to deliver a physical dose of 40 Gy in a single-dose scheme (alternative (Chung et al., 1998, 2000; Lee et al., 1997; Mukherjee et al., 2002, 2003; Rio et al., 2005; Kal and Veen, 2005; Locke et al., 2001; Kwan et al., 2004; Ragoowansi et al., 2003). After treatment, mice from both groups continued receiving TPA as promoter during 30 days of follow-up and then, they were sacrificed in order to get samples of control and treated tumors for histological analysis.

2.6. Dosimetric calculations

Radiation dose from the ^{32}P-silicone-patch was estimated using the Monte Carlo MCNP5 code for simulation (MNCP Code, Version 5, 2003). The geometrical model was considered as a cylinder (0.1 cm height, 0.5 cm of diameter) with the density and chemical composition of the silicon (1.2 g/cm^3 and chemical composition of SiC_2H_6O). Since ^{32}P was uniformly distributed in the patch, beta particle emission was considered isotropic. The region of the skin was simulated as water (density 1 g/cm^3) and the other region as air. In all, 3×10^8 electron histories from the source were simulated with an uncertainty $<1\%$. The cut off energy considered for electrons and photons was 10 keV. Taking into account the activity concentration of the patch expressed as MBq/cm^2 and the total physical dose, exposition time was calculated. Similarly, dose rate at different skin depth (0.0001; 0.01; 4 and 7.5 mm) was estimated. Finally, the software was also used for calibrating the source according to the American Association of Physicists in Medicine (AAPM) recommendations (Nath et al., 1999). For this purpose, we considered concentric cells of 0.19–0.21 cm ratio cut with a cone of 1° angle and surrounded by a sphere of water with 20 cm ratio.

2.7. Histological analysis

Samples of all treated and control tumors were collected after sacrificed the animals and then, processed for paraffin sectioning and subsequent stained with haematoxylin and eosin. Photomicrographs of haematoxylin and eosin sections were taken at $\times 100$ magnification using a Canon PowerShot G5 camera (Japan).

3. Results

The results of *in vitro* stability studies showed that significant ^{32}P activity leakage was obtained with patches of natural rubber and both treated and untreated resin (Figs. 1–3). However, the ^{32}P-silicone-patch showed that less than 0,6% and 20% of the total activity was lost under mild or extreme hydrolysis conditions, respectively (Figs. 1–4). Therefore, the rest of the experiments were performed with the ^{32}P-silicone-patch.

Autoradiographic studies with samples of patches that were used in the therapeutic studies showed that ^{32}P was uniformly distributed over the surface of the ^{32}P-silicone-patch (Fig. 5). When shielding was evaluated, the autoradiographies revealed that the mixture of the silicone and the chromic ^{32}P-phosphate, did not modify the range of the beta particle emitted by ^{32}P in water (Fig. 6), which is 4 mm for median range and 7 mm for maximum (Evans, 1955). Additionally, we could determine the thickness of aluminium necessary to shield radiation in the opposite side of the therapeutic face, which was approximately of 2.55 mm (Fig. 7).

The activity concentration of the ^{32}P-silicone-patch used in therapeutic studies was 10.6 MBq/cm^2 (289 μCi/cm^2). This patch was divided into small pieces according to the size of the tumors selected to be treated of the TG. Monte Carlo calculations estimated a time of exposition of 14 h for this scheme of single dose in order to deliver 40 Gy. Table 1 shows the results of dose rate estimates as a function of skin depth. According to AAPM recommendations, the calibration of the brachytherapy source resulted in a value of 0.105 Gy/(MBq h) (3.91 Gy/(mCi h)).

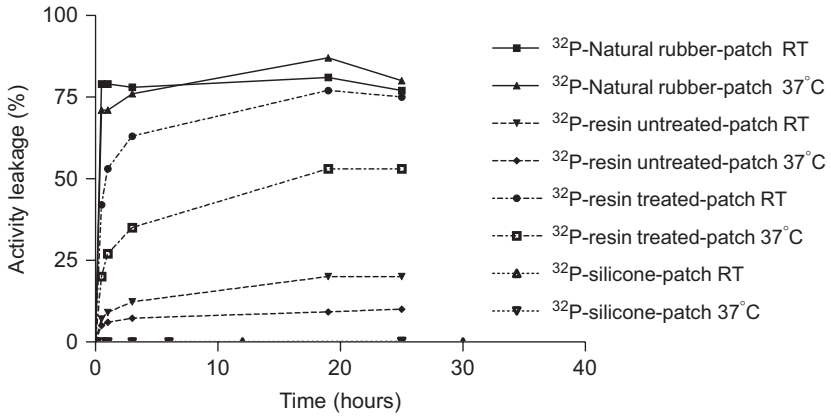


Fig. 1. Stability studies results for ^{32}P patches in saline at room temperature (RT) and 37 °C.

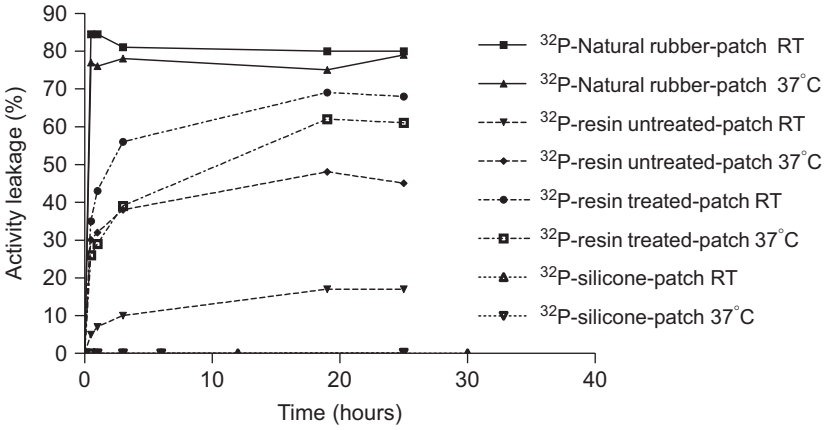


Fig. 2. Stability studies results for ^{32}P patches in dextrose 5% at room temperature (RT) and 37 °C.

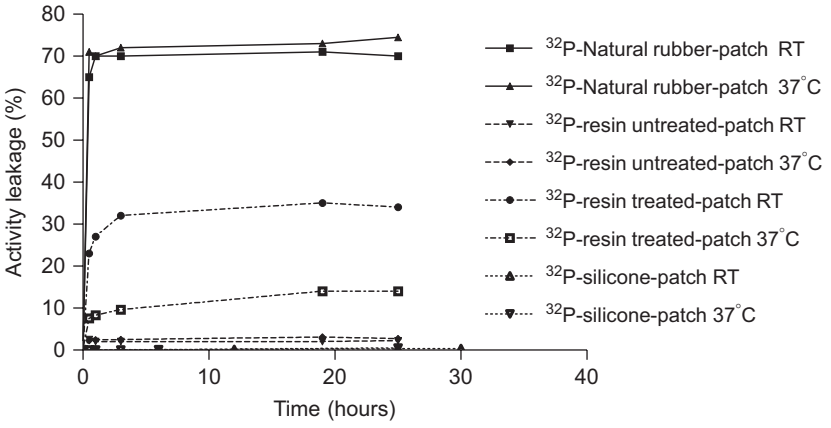


Fig. 3. Stability studies results for ^{32}P patches in distilled water at room temperature (RT) and 37 °C.

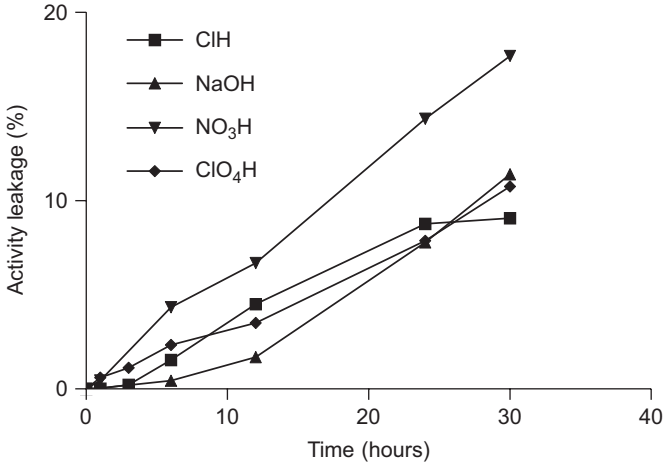


Fig. 4. Stability studies results for ^{32}P-silicone-patch under extreme hydrolysis conditions at room temperature.

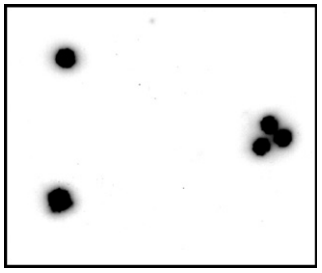
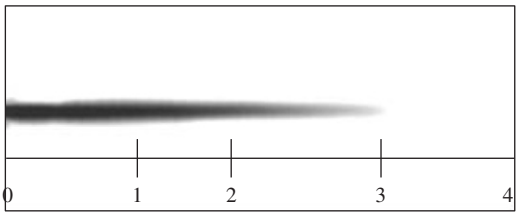


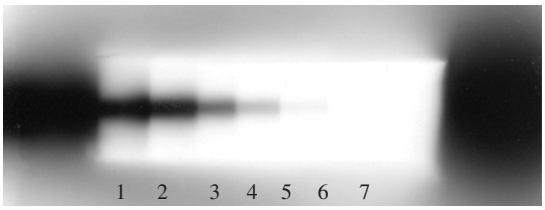
Fig. 5. Autoradiographic studies of samples of the ^{32}P-silicone-patches used in the therapeutic studies at 4 min of exposition. Dimensions of the patches were 6 mm (left-down angle), 5 mm (left-up angle) and a triangle formed by three pieces of 5 mm (middle right) of diameter.

The two-stage carcinogenesis protocol produced both papillomas and keratoacanthomas as describe elsewhere (Fig. 8), which were confirmed with histological analysis and (Fig. 9). After completion of therapy with the ^{32}P-silicone-patch, dermatitis and skin ulceration developed in few cases but they gradually healed with regeneration of tissue after 30 days of follow-up. Brachytherapy with the ^{32}P-silicone-patch provoked the macroscopic disappearance of four (Fig. 8) of the seven treated tumors, and the others significantly reduced their median diameter (data not shown). Histological analysis of treated tumors showed two total remissions and two partial remissions (Fig. 9) of the disappeared tumors and the rest were diagnosed as papillomas.



Portion	Thickness in water (mm)
0	0
1	2.3
2	3.4
3	6.0
4	7.9

Fig. 6. Autoradiographic studies of the mixture of silicone and Chromic ^{32}P-phosphate. The mixture with silicone did not modify the range of the beta particle emitted by ^{32}P in water as tissue simulation. The thickness of water increases from left to right of each portion and the table shows the bigger value of it. This is a scale picture which shows that median range of ^{32}P beta particle is located between portion 2 and 3 and that in portion 4 it reaches the maximum range in water.



Aluminium Z=13	
Line	Thickness (mm)
1	0.40
2	0.79
3	1.22
4	1.63
5	2.05
6	2.55
7	3.38

Fig. 7. Autoradiographic studies of shielding of the ^{32}P-silicone-patch. The picture revealed that 2.55 mm of aluminium is enough to shield the opposite side of the therapeutic face of the patch.

Table 1
Dose rate estimates (Gy/h) for the ^{32}P-silicone-patch used in the therapeutic studies as a function of skin depth

Skin depth (mm)	Dose rate (Gy/h)
0.0001	14.02
0.01	11.7
4	2.3
7.5	1.2

4. Discussion

The classical approaches to the treatment of skin diseases involve local destruction with surgery or radiotherapy. Size, location, recurrence, depth, functional and cosmetic results, health status of patient and prior treatments all play a role in determining the appropriate treatment of skin diseases (Diepgen and Mahler, 2002; Rio et al., 2005; Kwan et al., 2004; Veness, 2005; Ragoowansi et al., 2003). Although surgery is usually preferred, recurrence rates are high and it is not always possible to be practiced.

Radiotherapy is usually indicated when plastic repair is difficult and it has been an excellent choice for skin cancer of central face (eyelids, nose and lips) because these are areas difficult to excise. However, it has several disadvantages such as the necessity of expensive radiation therapy units, protracted treatments and the adverse effects of penetration into underlying bone and soft tissue.

Radionuclide therapy may be considered as an alternative for or adjuvant to surgery, external radiation and chemotherapy. In the last years, there has been an expanding availability of radiopharmaceuticals, which can deliver radiation doses selectively into target tissues. Particularly, radionuclide therapy with beta emitters has some advantages over external radiation therapy, since the former does not need expensive therapeutic units, the procedure is simple and non-invasive and there is no adverse effect on underlying bone and soft tissue due to the physical characteristics of beta rays. Radionuclide treatment may also play an important role in patients with multiple lesions and/or when excision or external radiotherapy are not possible or recommended.

Some beta emitters such as ^{90}Y, ^{32}P, ^{188}Re, ^{186}Re and ^{166}Ho have been used both in animals and humans in attempts to treat various skin diseases such as melanoma and non-melanoma skin cancer, Bowen's disease, fibrosarcoma and keloids (Chung et al., 1998, 2000; Lee et al., 1997; Mukherjee et al., 2002, 2003). In terms of methodology, interstitial radiation, surface applicators and specially designed patches have been used. The main advantages of therapy with skin patches are that it can be used in inoperable cases, it is a low cost treatment, and the patch can be easy designed in accordance to the shape and size of the lesion as well as with regard to the activity concentration required for the selected therapeutic scheme. The disadvantage of this kind of therapy is that if there is invasion of the tumor and/or metastasis developed, it is not suitable as unique treatment. In these cases, surgery,

external radiation and chemotherapy are recommended, although the patch can be used as an adjuvant.

In this work, we used ^{32}P which emits β^- radiation ($E_{max} = 1.7$ MeV) with a half life of 14.3 days, a maximum range in tissue of 7 mm and it is produced in nuclear reactor. This beta emitter, extensively available in our country and South America, has similar characteristics to those used by other groups with the additional advantages of its long half life, low cost and the absence of gamma radiation. The described characteristics made ^{32}P-silicone-patch a valid option for a radiopharmaceutical to be dispensed from a centralized radiopharmacy for this kind of treatment with minimal risk of irradiation for physicians. ^{32}P was used as Phosphoric-^{32}P-acid or Chromic ^{32}P-phosphate, both easy to handle for these experiments. With regard to the matrix of the patch, we selected natural rubber and silicone because of their flexible condition in order to easy adapt the patch to the shape of the lesion. Production of all ^{32}P patches was simple, although immobilization of the radioactive source was only achieved in the silicone patch. Stability studies showed significantly leakage of radioactivity in patches with Phosphoric-^{32}P-acid even in mild hydrolysis conditions. The attempts to use the resin in order to capture the ^{32}P source failed. Pre-treatment with saline washes for eliminating the remaining ^{32}P did not avoid radioactivity leakage, since as ^{32}P was not retained in the patch matrix it continued leaching out. However, leakage was negligible in the case of the ^{32}P-silicone-patch, making it very safe for treatment of superficial lesions even when it was submitted to extreme hydrolysis conditions which do not represent those of its intended use. In this case, the combination of the silicone and Chromic ^{32}P-phosphate resulted in an open source, which behaves very similar to a sealed source. Additional studies of biodistribution, bioelimination and dermal toxicity are required to confirm these preliminary results of *in vitro* stability studies.

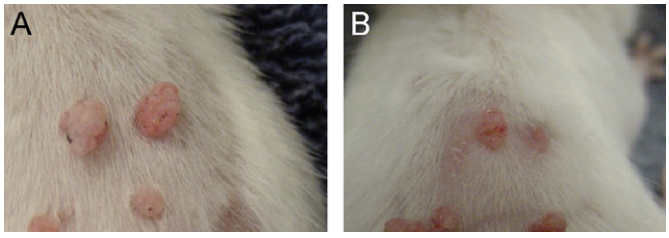


Fig. 8. Panel A shows a treated tumor (right) selected in one of the mice of TG group of therapeutic studies, before (panel A) and after (panel B) patch application. On the left side there is a tumor of the same animal, which was not treated. Both tumors have approximately 5 mm of diameter at the beginning of the study but after patch application the treated tumor was completed regressed.

Autoradiographic studies confirmed that the mixture with silicone did not modify the physical characteristics of ^{32}P and resulted in the production of a homogeneous source. Additionally, we could determine the appropriate shielding which would be required for the patch to protect the physician and the patient during treatment using aluminium. These experiments have important implications for the dosimetry involved in the treatment planning and for sanitary considerations about radioprotection.

In order to evaluate the therapeutic performance of this patch, we used the two-stage carcinogenesis protocol in Sencar mice. Although the radiation dose used in our therapeutic scheme is in the down extreme of ranges

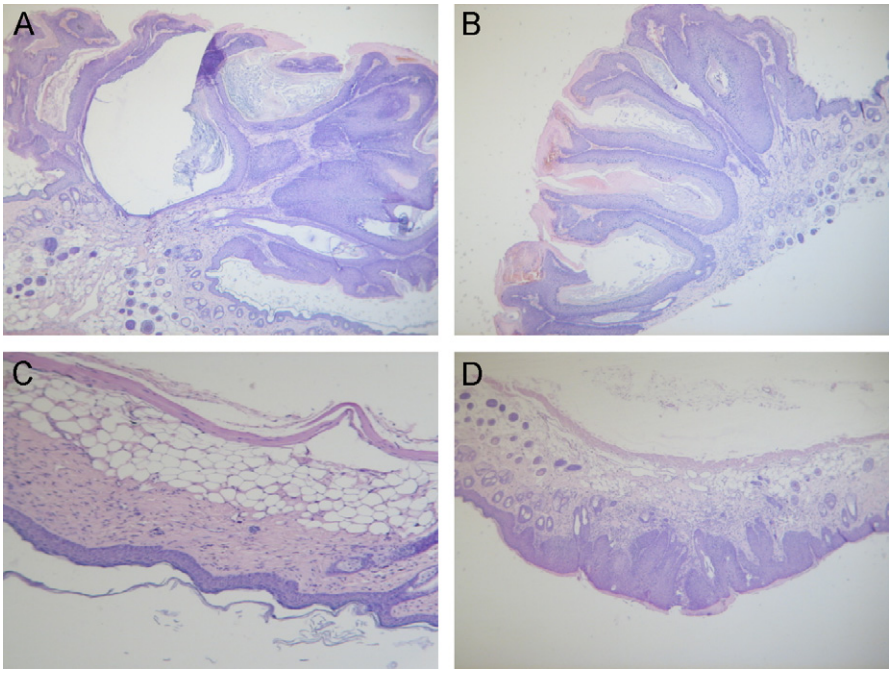


Fig. 9. Skin section of control and treated tumors. Panel A shows a papilloma, panel B shows a keratoacanthoma, panel C shows a complete remission and panel D shows a partial remission.

reported for skin cancer, the single-dose treatment with 40 Gy could arrest tumor growth as well as achieved complete regressions of tumors in some other cases. Additional experiments would be required to assayed different therapeutic schemes (single dose or fractionated) and radiation doses in order to obtain complete destruction of tumors with minimal harm to normal surrounding tissues, as well as the performance of the patch in the treatment of other skin diseases.

In conclusion, this radioactive ^{32}P-silicone-patch is easy to prepare and use in the treatment of skin diseases. Although it is an open source it behaves very similar to a sealed one, making it very safe for employing it in superficial lesions. The therapeutic efficacy for different skin diseases requires additional studies but preliminary results obtained in the two-stage carcinogenesis protocol in Sencar mice are promissory.

References

Aldaz, C.M., Conti, C.J., Chen, A., et al., 1991. Promoter independence as a feature of most skin papillomas in Sencar mice. Cancer Res. 51, 1045–1050.

Anghileri, L.J., 1958. In: Second International Conference of Peaceful Uses of Atomic Energy, Génova, Italia, vol. 15, 1575pp.

Anghileri, L.J., 1967. ^{32}P en ratones. Influencia del tamaño de las partículas. Informe No. 158. Comisión Nacional de Energía Atómica.

Anghileri, L.J., Marques, R., 1967. New colloidal chromic radiophosphate (^{32}P) for local irradiation of the central nervous system. Int. J. Appl. Radiat. Isot. 18, 97–100.

Chung, Y.L., Bang, D., Lee, J.D., et al., 1998. Treatment of multifocal Bowen′s disease with a specially designed radioactive skin patch. Br. J. Dermatol. 139, 938–939.

Chung, Y.L., Lee, J.D., Bang, D., et al., 2000. Treatment of Bowen's disease with a specially designed radioactive skin patch. Eur. J. Nucl. Med. 27, 842–846.

Diepgen, T.L., Mahler, V., 2002. The epidemiology of skin cancer. Br. J. Dermatol. 146 (Suppl.), 61–66.

DiGiovanni, J., 1992. Multistage carcinogénesis in mouse skin. Pharmacol. Ther. 54, 63–128.

DuBowski, A., Johnston, D.A., Rupp, T., et al., 1998. Papillomas at high risk for malignant progression arising both early and late during two-stage carcinogenesis in Sencar mice. Carcinogenesis 19, 1141–1147.

Evans, R.D., 1955. The Atomic Nucleous. McGraw-Hill Book Company, NY, USA.

Kal, H.B., Veen, R.E., 2005. Biologically effective doses of postoperative radiotherapy in the prevention of keloids. Strahlenther. Onkol. 181, 717–723.

Kwan, W., Wilson, D., Moravan, V., 2004. Radiotherapy for locally advanced basal cell and squamous cell carcinomas of the skin. Int. J. Radiat. Oncol. Biol. Phys. 60, 406–411.

Lee, J.D., Park, K.K., Lee, M., et al., 1997. Radionuclide therapy of skin cancers and Bowen's disease using a specially designed skin patch. J. Nucl. Med. 38, 697–702.

Locke, J., Karimpour, S., Young, G., et al., 2001. Radiotherapy for epithelial skin cancer. Int. J. Radiat. Oncol. Biol. Phys. 51, 748–755.

Mukherjee, A., Pandey, U., Sarma, H.D., et al., 2002. Preparation and evaluation of 90Y skin patches for therapy of superficial tumors in mice. Nucl. Med. Commun. 23, 243–247.

Mukherjee, A., Pandey, U., Sarma, H.D., et al., 2003. Bioevaluation of radioactive bandages in a murine model of melanoma. Int. J. Radiat. Biol. 79, 839–846.

Nath, R., Arnols, H., Coffey, C., et al., 1999. Intravascular brachytherapy physics: report of the AAPM Radiation Therapy Committee Task Group No. 60. Med. Phys. 26, 119–152.

Ragoowansi, R., Cornes, P., Moss, A., et al., 2003. Treatment of keloids by surgical excision and immediate postoperative single-fraction radiotherapy. Plastic Reconstr. Surg. 111, 1853–1859.

Rio, E., Bardet, E., Ferron, C., et al., 2005. Intersticial brachytherapy of periorificial skin carcinomas of the face: a retrospective study of 97 cases. Int. J. Radiat. Oncol. Biol. Phys. 63, 753–757.

USP XXVIII, 2005a. CD version—Monograph Phosphoric-^{32}P-acid.

USP XXVIII, 2005b. CD version—Monograph Chromic Phosphate ^{32}P Suspension.

Veness, M.J., 2005. Treatment recommendations in patients diagnosed with high-risk cutaneous squamous cell carcinoma. Australas Radiol. 49, 365–376.

X-5 Monte Carlo Team, 2003. MCNP—A General Monte Carlo N-Particle Transport Code, Versión 5. Los Alamos National Laboratory, Los Alamos, NM, USA.