

# Radionuclide Therapy of Skin Cancers and Bowen's Disease Using a Specially Designed Skin Patch

Jong Doo Lee, Kwang Kyun Park, Min-Geol Lee, Eun-Hee Kim, Kyung Jin Rhim, Jong Tae Lee, Hyung Sik Yoo, Young Mi Kim, Kyung Bae Park and Jae Rok Kim

Departments of Diagnostic Radiology, Nuclear Medicine, Oral Biology and Dermatology, Yonsei University Medical College, Seoul; Department of Dermatology, Cyclotron Application Laboratory, Korea Cancer Center Hospital, Seoul; and Department of Radioisotope, HANARO Center, Korea Atomic Energy Research Institute, Taejon, Korea

Skin cancer is the most common malignancy in humans. Therapeutic modalities for skin cancer are local destruction, radiotherapy and surgery. External radiation therapy leads to good results, however, generally 5–6 wk of treatment is needed to deliver optimal radiation dose to tumors. In this study, a beta-emitting radionuclide,  $^{166}\text{Ho}$ , impregnated in a specially designed patch, was used on superficial skin cancers and Bowen's disease for local irradiation. **Methods:** Ten mice with chemically induced skin tumors were studied. Five-millimeter size patches containing 22.2–72.15 MBq (0.6–1.95 mCi)  $^{166}\text{Ho}$  were applied to the tumor surface for 1–2 hr. In a human trial, patients with squamous-cell carcinoma ( $n = 3$ ), basal cell carcinoma ( $n = 1$ ) and Bowen's disease ( $n = 1$ ) were treated with patches containing 273.8–999 MBq (7.4–27 mCi) of  $^{166}\text{Ho}$  for 30 min to 1 hr. Pathologic examination was performed 4–7 wk after treatment in an animal model. Skin biopsy was performed 8 wk post-treatment in four patients. **Results:** Tumor destruction was seen 1 wk post-treatment, however, radiation dermatitis or ulceration developed at the site of radionuclide application. Those reactions healed gradually with fibrosis or epithelialization, which was confirmed pathologically. No significant adverse reaction to radiation except subcutaneous fibrosis was found. **Conclusion:** Superficial skin tumors could be successfully treated by topical application of beta-emitting radionuclides.

**Key Words:** skin cancer; radiotherapy; radionuclide; holmium-166

**J Nucl Med 1997; 38:697–702**

The classical approaches to the treatment of skin cancer, which is the most common malignancy in humans, are local destruction, surgery and radiotherapy (1–2). Each method has its advocates; among them, radiotherapy is indicated when plastic repair is not easy due to its wide involvement. Radiotherapy with low-energy orthovoltage radiographs or megavoltage electrons has long been used in the treatment of malignant skin cancers (3). However, several factors such as total dose, fractionation regimens, field size and beam quality affect the treatment outcomes. In general, a total dose ranging 35–70 Gy with daily fractionations lying in the 2.0–3.5 Gy is accounted for the optimal therapeutic regimen (4–6). Instead of external irradiation, radon or radioactive cobalt applied as a surface mould, and interstitial radiation with radium needles, gold grain or iridium wire have been used (2–3). However, those methods are not widely used at present, since proper preparation of the moulds is not easy and interstitial implantation needs an invasive technique. In this study, a specially designed skin-patch uniformly impregnated with a beta-emitter,  $^{166}\text{Ho}$ , was developed for topical application. The aim of this study was to evaluate the tissue response to beta rays in an animal model and

determine the feasibility of beta-emitting radionuclides for the treatment of skin cancers in clinical trial.

## MATERIALS AND METHODS

### Production of Holmium-166 Skin Patch

Holmium-165 ( $\text{NO}_3$ )  $3.5\text{H}_2\text{O}$  (53.5 mg) dispensed in 0.4 ml of distilled water was reacted with 198 mg of  $\text{NaBH}_4$  in 2 ml of 0.2 *M* NaOH, which produced macroaggregates of holmium particles. Uniform size holmium particles (1–6  $\mu$ ) were obtained by ultrasonification, centrifugation, washing with water and acetone, drying at room temperature and finally microsieving of the  $^{165}\text{Ho}$  macroaggregates. The particles were uniformly affixed on an adhesive tape (approximately 50  $\mu$  in thickness) and then coated with a polyethylene microfilm (100  $\mu$  in thickness) to avoid leakage of the particles. The patches were bombarded in a nuclear reactor at a neutron flux of  $1 \times 10^{13}$  n/cm<sup>2</sup>.sec to convert  $^{165}\text{Ho}$  to  $^{166}\text{Ho}$ , which is a beta emitter ( $E_{\text{max}} = 1.84$  MeV) with a half life of 26.9 hr. Holmium-166 also emits gamma photons (5.4% of 0.081 MeV and 0.9% of 1.38 MeV).

### Dosimetry

Radiation dose from a  $^{166}\text{Ho}$  skin patch to skin tissue was estimated macrodosimetrically. The Monte Carlo code EGS4 was chosen for electron-gamma transport simulations.

**Calculation Model.** The geometrical model for simulation is shown in Figure 1. A cylinder is sectioned into two regions: one represents the skin tissue and the other represents the air over the outermost skin layer. The coin-like patch, containing 37 MBq  $^{166}\text{Ho}$ , was applied to the affected site of the skin. The transport medium is defined large enough to cover the electron range corresponding to the endpoint energy of the  $^{166}\text{Ho}$  beta spectrum. The holmium patch was the source organ and the target organ was designed to be a 1-mm height cylinder of the same radius as the source patch. The target is located at an 1-mm distance from the skin surface toward the deep skin layer perpendicular to the air-skin tissue boundary. Liquid water is used to simulate the particle transport in skin tissue.

**Computer Simulation.** EGS4 allows tracing electrons and photons down to 10 keV and 1 keV, respectively. Since the electron range corresponding to 10 keV is about 2.5  $\mu\text{m}$  in liquid water, the cutoff energy at 10 keV is low enough to describe the local energy deposition from the 1-mm height target volume. Simulation is started by assigning the initial energy, direction and location to a beta particle emission. The energy of the beta particle emitted is chosen at random in the  $^{166}\text{Ho}$  beta energy spectrum. The initial direction of the emission is also chosen at random, over the 4 $\pi$  space. In controlling the transport simulation, the following parametric values were involved: IRAYL = 1, ESTEPE = 0.02, ECUT = 10 keV and PCUT = 1 keV. The number of histories was chosen at 100,000 for the outer four depth values (target at 0.5–3.5 mm depth). For a greater target depth, the number of histories were increased up to 4,000,000 so as to obtain the energy deposition

Received Jul. 9, 1996; revision accepted Sep. 11, 1996.

For correspondence or reprints contact: Jong Doo Lee, MD, Division of Nuclear Medicine, Dept. of Diagnostic Radiology, Yonsei University Medical College, 134, Shincheon-dong, Seodaemun-gu, Seoul, 120-752, Korea.

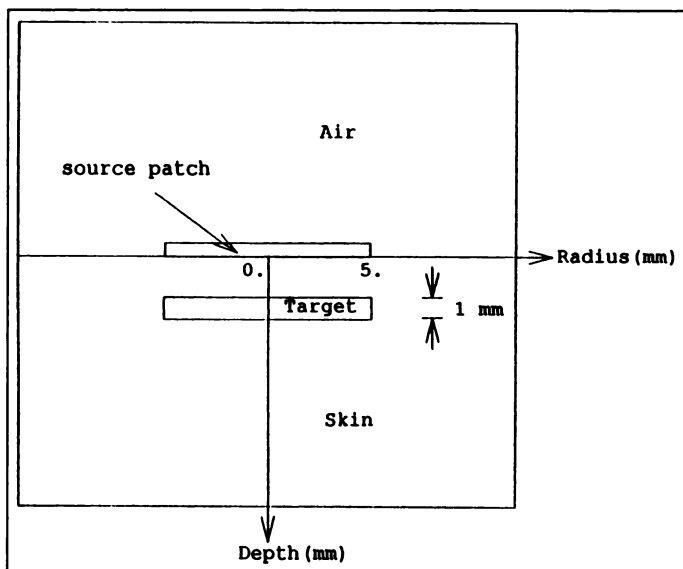


FIGURE 1. Geometrical model for EGS4 simulations.

records of over 2000. The approximate formulas provided by Prestwich et al. (7) were used to describe the beta energy spectrum and calculated the electron range in liquid water.

The dose estimates for 37 MBq hours of  $^{166}\text{Ho}$  were 35.01 Gy at 0.5 mm, 12.56 Gy at 1.5 mm and 5.4 Gy at 2.5 mm in depth (Table 1). Although  $^{166}\text{Ho}$  emits gamma photons, they are of a low enough photon yield to result in significant radiation doses. Therefore, photon emissions from  $^{166}\text{Ho}$  were excluded from the simulation.

#### Animal Model of Skin Tumors

Eight ICR and two hairless mice were used in this study; 15 mM of 12-O-tetradecanoyl-13-acetate (TDA) in 0.1 ml of acetone was topically applied to the skin of the mice. Then, 2  $\mu\text{mol}$  of 2'-(4-nitrophenoxy) oxirane (NPO) in 0.2 ml of acetone was applied once a week for two consecutive weeks and followed by TDA twice a week for 35 wk. Squamous-cell carcinomas ( $n = 3$ ) and keratoacanthomas ( $n = 7$ ) were developed. The tumor size was 4–8 mm in diameter and 3–4 mm in thickness.

#### Human Subjects

Five patients were used in this study (four women, one man; age range 41–95 yr). Three patients with superficial squamous-cell carcinoma on the scalp, face and neck, respectively, one patient with basal cell carcinoma at the nasolabial fold and one with Bowen's disease at toe were included. These patients had no distant metastasis and tumor infiltration was confined to epidermal or dermal layers.

#### Treatment of Skin Tumors

In the animal models, 5-mm size patches were applied over the skin tumors and firmly affixed with adhesive tape for 2 hr ( $n = 4$ )

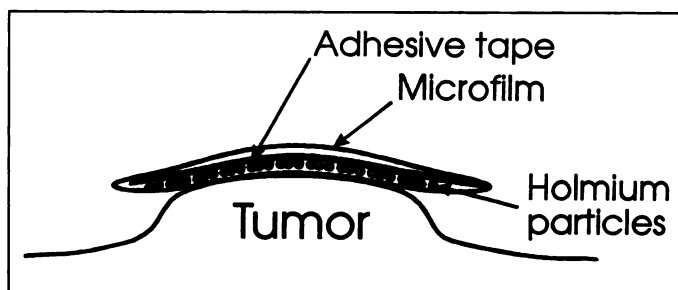


FIGURE 2. Schematic drawing of a  $^{166}\text{Ho}$  skin patch.

with 22.2 MBq and 29.6 MBq, and 1 hr ( $n = 5$ ) with 44.4 MBq and 48.1 MBq (radiation dose ranged 42–45 Gy at the tumor surface). In one mouse, the tumor was treated for 19 hr with 72.15 MBq, which is about 30 times higher dose, to evaluate tissue response to excessive radiation. The mice were killed at 2 ( $n = 3$ ), 4 ( $n = 5$ ) and 7 wk ( $n = 2$ ) after treatment for pathologic examinations.

In the human trials, informed consents were obtained. The tumor tissue as well as surrounding normal tissue 0.5 cm beyond the tumor margin were included in the irradiation field. A patch uniformly impregnated with 273.8–999 MBq of  $^{166}\text{Ho}$  was applied to the tumor surface (Fig. 2). The total treatment time ranged from 30 min to 1 hr to have approximately 50 Gy in radiation absorbed dose. Two months after the treatment, skin biopsy on multiple sites were performed in four patients.

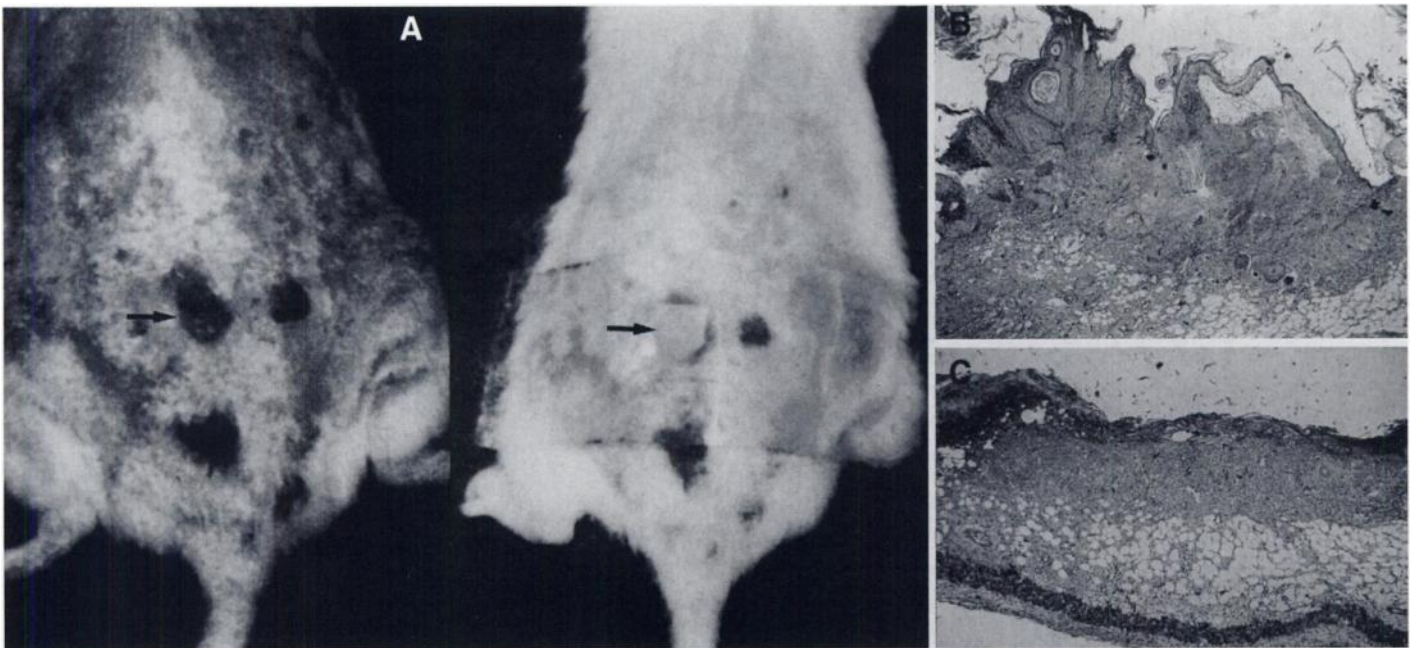
## RESULTS

#### Animal Models

Ten mice with squamous-cell carcinoma ( $n = 3$ ) or keratoacanthoma ( $n = 7$ ) were successfully treated with  $^{166}\text{Ho}$  skin patches without adverse injury on the underlying soft tissue or internal organs. Between 1 and 2 wk after the completion of  $^{166}\text{Ho}$  therapy, destruction of the tumor tissue was noted, however, acute radiation dermatitis or skin ulceration were developed in all cases. Pathologically, there was no viable tumor tissue but infiltration of inflammatory cells with edema and exudate (Fig. 3C). The radiation dermatitis or ulceration gradually healed with regeneration of epithelium until 7 wk post-therapy (Fig. 4). In one case, the tumor (8 mm) was larger than the patch size (5 mm) (Fig. 5A). At 4 wk post-therapy, tumor necrosis was found only at the patch application site. Discrete demarcation between irradiated and nonirradiated areas was seen microscopically (Fig. 5B,C). Another mouse, in which the tumor size was about 4 mm in diameter and thickness, was treated for 19 hr with 72.15 MBq. The estimated radiation dose was about 30 times higher than usual therapeutic dose. The tumor was completely destroyed with muscle necrosis beneath the skin layer up to 3 mm in depth (Fig. 6). No adverse injury was seen in underlying deep muscle or internal organs.

TABLE 1  
Dose Estimates for 1 mCi Hours of Holmium-166 Uniformly Distributed in the Patch

Skin depth (mm)	Absorbed dose (Gy)	Dose fraction	Cumulated dose fraction	Relative percent dose
0.5	0.3501e + 02 ( $\pm 0.68\%$ )	0.6231e + 00	0.6218e + 00	100.0
1.5	0.1253e + 02 ( $\pm 1.2\%$ )	0.2230e + 00	0.8461e + 00	35.78
2.5	0.5425e + 01 ( $\pm 0.82\%$ )	0.9648e - 01	0.9425e + 00	15.48
3.5	0.2214e + 01 ( $\pm 2.3\%$ )	0.3937e - 01	0.9819e + 00	6.319
4.5	0.7751e + 00 ( $\pm 2.8\%$ )	0.1378e - 01	0.9957e + 00	2.212
5.5	0.2037e + 00 ( $\pm 2.9\%$ )	0.3623e - 02	0.9993e + 00	0.5815
6.5	0.3526e - 01 ( $\pm 4.0\%$ )	0.6271e - 03	0.9999e + 00	0.1006
7.5	0.3171e - 02 ( $\pm 11.0\%$ )	0.5640e - 04	0.1000e + 01	0.0091



**FIGURE 3.** Chemically induced squamous-cell carcinoma in an ICR mouse was treated with  $^{166}\text{Ho}$  patch (arrow, A). Pretreatment biopsy showed irregular proliferation and invasion of the tumor cells into dermis (B: HE, 40 $\times$ ), but complete destruction of tumor cells was demonstrated on post-treatment biopsy (C: HE, 40 $\times$ ).

### Clinical Cases

Successful tumor destruction was seen in all subjects. Desquamation, erythema or ulceration developed between 1–2 wk post-therapy. These acute radiation reactions were gradually healed with minimal fibrosis within 1 mo. There was no adverse reaction or recurrence during 8–20 mo follow-up periods.

A 89-yr-old woman had a 2-cm squamous-cell carcinoma on her scalp (Fig. 7A). Skin biopsy demonstrated irregular downward proliferation of epidermis and invasion of atypical cells with hyperchromatic and large nuclei. The tumor was treated with 555 MBq (15 mCi) of  $^{166}\text{Ho}$  for 40 min. One month after the treatment, tumor size decreased considerably (Fig. 7B). Complete destruction of the tumor with re-epithelialization was demonstrated on follow-up biopsy (Fig. 7C). Alopecia was the only postirradiation complication.

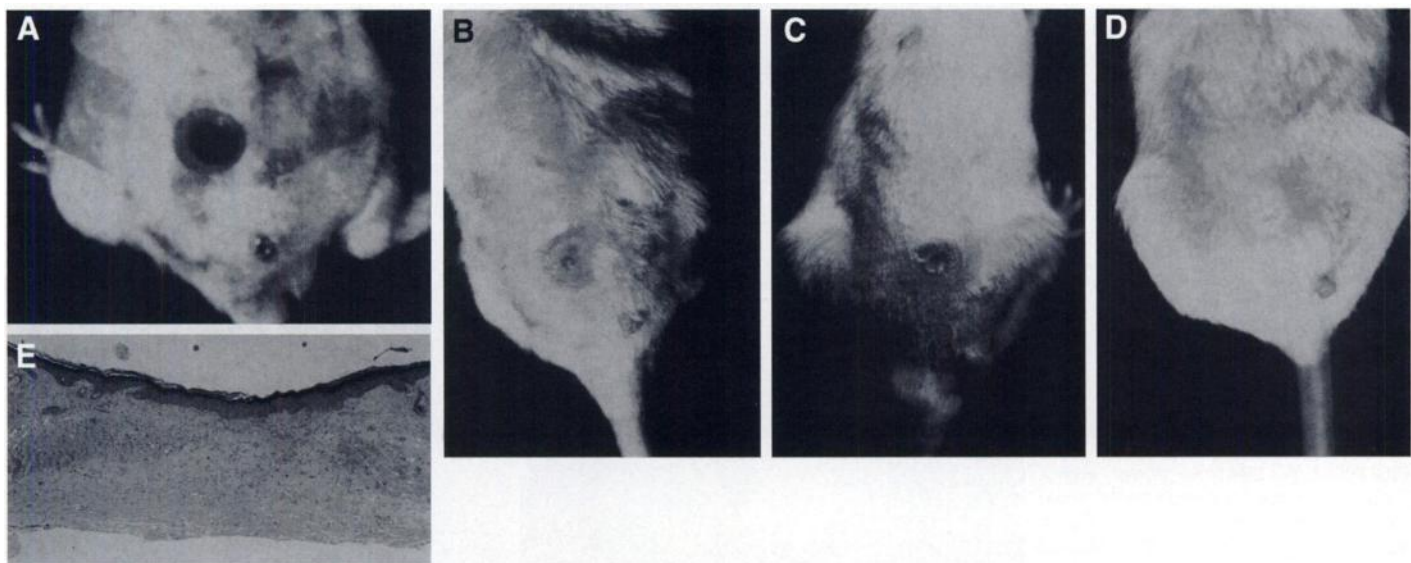
A 75-yr-old woman with a 1.3-cm squamous-cell carcinoma

on her neck was treated with 273.8 MBq (7.4 mCi) of  $^{166}\text{Ho}$  for 40 min. Complete destruction of tumor was seen with almost normal skin color and texture over the irradiated field (Fig. 8A-D). Re-epithelialization was observed at 3 mo post-treatment (Fig. 8E-F).

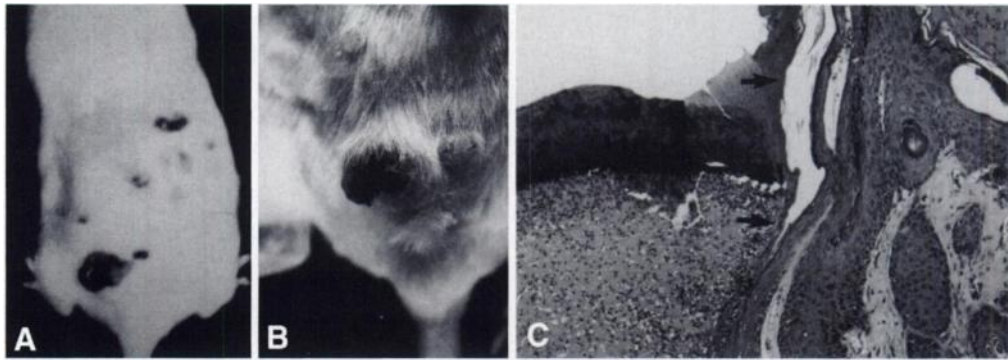
A 41-yr-old man suffered from recurrent Bowen's disease on the fifth toe despite cryosurgery or skin graft excision. Recently, a 2-cm lesion recurred and was treated with 740 MBq (20 mCi) of  $^{166}\text{Ho}$  for 30 min. After treatment, no residual lesion or recurrence was observed during the 13-mo follow-up period (Fig. 9).

### DISCUSSION

Radionuclide therapy is a unique cancer treatment modality, which is alternative for or adjuvant to external radiation and chemotherapy. Recently, expanding availability of suitable



**FIGURE 4.** (A) Holmium-166 patch was applied to a skin tumor of an ICR mouse. (B) Erythema at the irradiated region and ulceration at tumor site were developed within 1 wk, but postradiation skin reactions were gradually improved (C: 1 mo, D: 7 wk post-treatment). Pathologic examination demonstrated regeneration of epithelium with fibrosis and loss of subcutaneous fat tissue (E: HE, 40 $\times$ ).



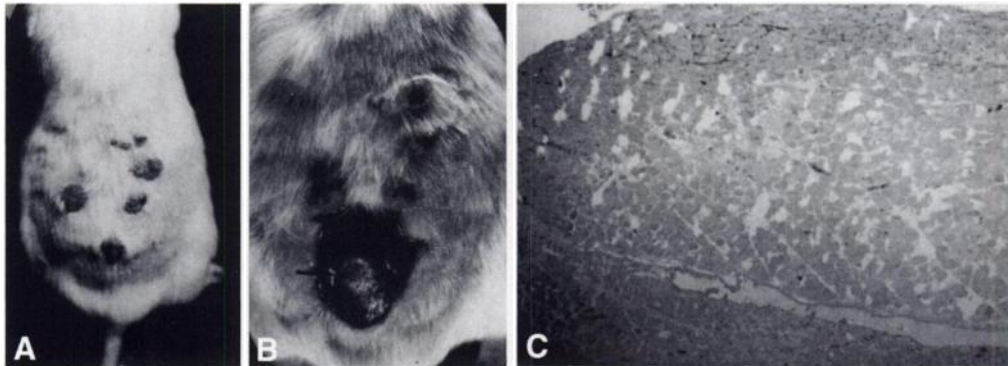
**FIGURE 5.** (A) An 8-mm keratoacanthoma was treated with a 5-mm  $^{166}\text{Ho}$  patch. (B) Tumor destruction is seen only at the irradiated area. (C) Pathology depicted sharp demarcation between irradiated and nonirradiated areas (arrows).

radiopharmaceuticals in oncology and endocrinology enable the use of radionuclide therapy. In nuclear oncology, specific tumor-seeking radiopharmaceuticals are being used since they can deliver radiation doses selectively into the target tissues.

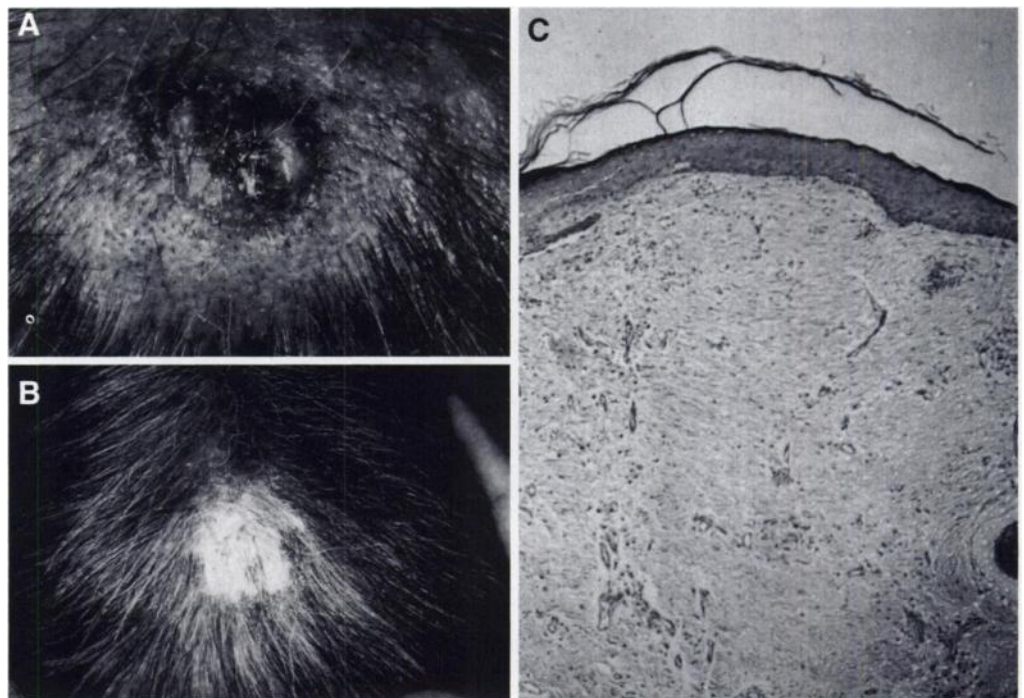
In terms of the methodology of radionuclide therapy, intravenous or intra-arterial injection and intracavitary instillation of radiotracers are the preferable methods (8). However, beta emitters such as  $^{90}\text{Sr}$ ,  $^{32}\text{P}$  and gamma emitters such as  $^{106}\text{Ru}$ ,  $^{182}\text{Ta}$ ,  $^{125}\text{I}$  and  $^{60}\text{Co}$  have been used for topical application to

treat ophthalmologic disease (9,10). Specially designed applicators have been used for ocular melanoma at the Royal Marsden Hospital (9). The applicators are still being used for the treatment of corneal vascularization. In this article, a beta-emitting radionuclide,  $^{166}\text{Ho}$ , impregnated in a skin patch, was used for local radiation therapy of superficial skin cancer and Bowen's disease.

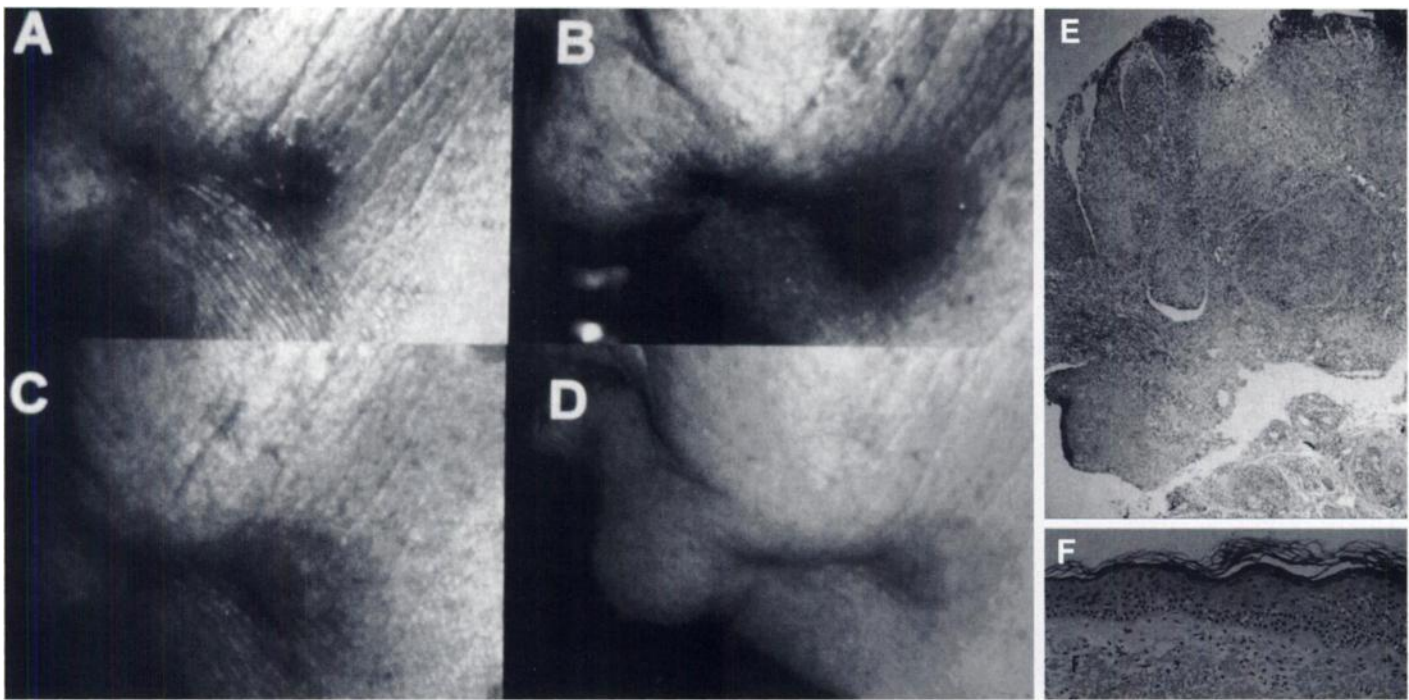
Holmium-166 emits beta-rays ( $E_{\text{max}} = 1.84 \text{ MeV}$ ) with a maximum soft-tissue range of 8.7 mm (average 2.1 mm) (11).



**FIGURE 6.** A keratoacanthoma was treated with an extremely high radiation dose (A: before treatment). Complete tumor necrosis was found, but there was a hard mass beneath the skin layer (arrow) due to muscle necrosis and fibrosis (B,C).



**FIGURE 7.** An 89-yr-old woman with a 2-cm squamous carcinoma on the scalp (A) was treated with 15 mCi  $^{166}\text{Ho}$ . Tumor was completely destroyed, but alopecia developed (B; 3 mo after treatment). Biopsy showed complete regeneration of epithelium without viable tumor cells (C: HE, 100 $\times$ ).

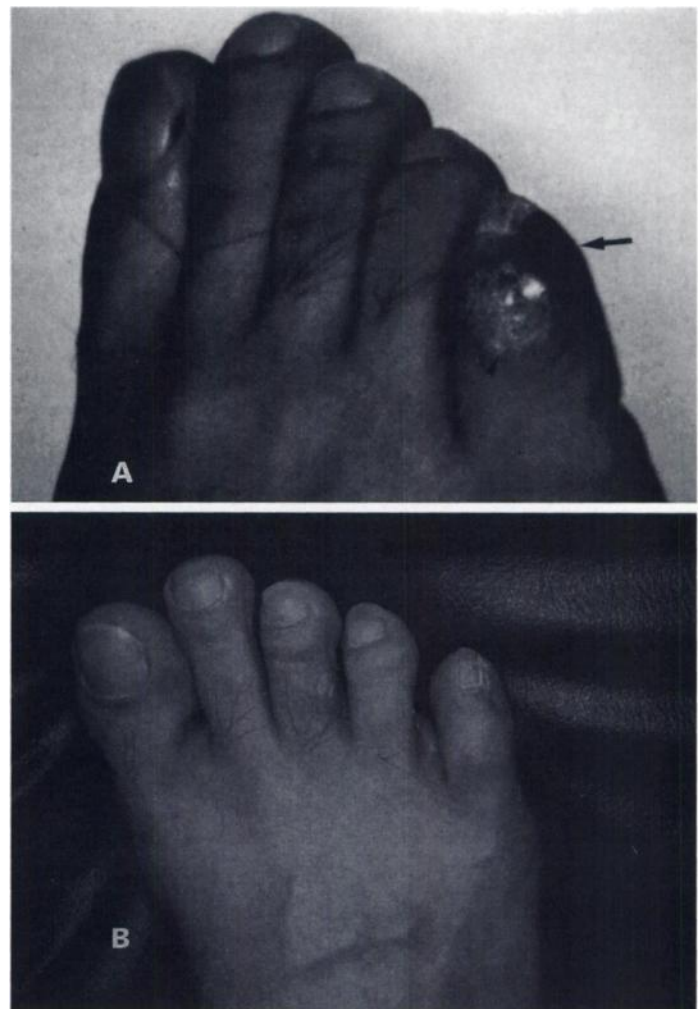


**FIGURE 8.** A 75-yr-old woman with a 1.3-cm squamous carcinoma on the left neck (A). Radiation dermatitis was seen within 1 mo post-therapy (B), but gradual healing of the radiation reaction was demonstrated without complication (C: 2 mo post-Tx, D: 3 mo post-Tx). Irregular proliferation of tumor tissue (E; HE, 40 $\times$ ) seen on pretreatment biopsy was completely destroyed with skin regeneration (F; HE, 40 $\times$ ).

Due to its favorable physical characteristics,  $^{166}\text{Ho}$  has been used for internal radiation therapy of primary hepatoma or liver metastasis and for radiation synovectomy (12–14).

In our study, all skin tumors of both humans and animals were successfully treated using the  $^{166}\text{Ho}$  skin-patch in a relatively short period without injury to the surrounding normal tissue. On the basis of our study, radionuclide treatment with beta-emitters has some advantages over external radiation therapy, since the former does not need expensive therapeutic units and the procedure is simple and noninvasive. Production of  $^{166}\text{Ho}$  is simple and less expensive compared with  $^{90}\text{Y}$  or  $^{89}\text{Sr}$ , since  $^{165}\text{Ho}$  is a naturally abundant element. In addition, radionuclide treatment may play an important role in patients with multiple lesions when excision or external radiotherapy of the lesions is not possible. Another advantage is that there is no adverse effect on underlying bone and soft tissue due to the physical characteristics of beta-rays, high linear energy transfer and rapid fall off. Our study in animals had minimal injury to the adjacent tissues, except fibrosis confined to the beta-ray penetration length, despite an extremely high radiation dose (Fig. 6B,C). Although acute forms of skin reactions to radiation such as erythema, desquamation and ulceration may occur, it usually heals gradually with epithelial regeneration or fibrosis. Hyperpigmentation of irradiated skin may develop as a chronic reaction within a couple of months after completion of the irradiation, but this reaction will fade. It may also progress to a vitiligo appearance in some patients (3). Skin necrosis is a serious late complication of radiation, but 90% of the subjects are known to have healed spontaneously (15). Therefore, long-term follow-up is required to evaluate chronic complications and secondary malignancy.

In the treatment of large protruding tumors, beta emitters have a limitation due to their limited penetration range (maximum 8.6 mm). Ninety percent of the energy deposits within 2.1 mm and 10% within 2.1–8.6 mm (11). For these subjects, external radiotherapy is preferable, but a higher radiation dose or fractionated treatment using beta emitters may be effective. Therapeutic response to the fractionated treatment in large



**FIGURE 9.** A 2-cm recurrent Bowen's disease on the fifth toe (arrowheads) in a 41-yr-old man was completely cured by the  $^{166}\text{Ho}$  patch (A, before therapy; B, 3 mo post-therapy). An area of skin discoloration can be seen anterior to the lesion (arrow) due to prior excision and skin graft.

tumors is being evaluated in our hospital. Therefore, beta-emitters such as  $^{166}\text{Ho}$ ,  $^{32}\text{P}$ ,  $^{90}\text{Y}$  or  $^{89}\text{Sr}$  can be used in the treatment of superficial malignant tumors of the skin.

## ACKNOWLEDGMENTS

We thank J.W. Chang and C.H. Kim for excellent technical assistance and E.W. Park and K.H. Han for preparing the patches. This study was supported by Korea Atomic Energy Research Institute grant 92C-121.

## REFERENCES

1. Wilder RB, Kittelson JM, Shimm DS. Basal cell carcinoma treated with radiation therapy. *Cancer* 1991;68:2134-2137.
2. Mackie RM. Squamous-cell carcinoma of the skin. In: Champion RH, Burton JL, Ebling FJG, eds. *Textbook of dermatology*, 5th ed. London: Blackwell Scientific Publications 1992;1497-1504.
3. Shimm DS, Cassady JR. The Skin. In: Cox JD, ed. *Moss' radiation oncology: rationale, technique and results*, 7th ed. St. Louis: Mosby-Year Book Inc. 1994;99-118.
4. Shimm DS, Wilder RB. Radiation therapy for squamous cell carcinoma of the skin. *Am J Clin Oncol* 1991;14:383-386.
5. Petrovich Z, Parker RG, Luxton G, Kuisk H, Jepson J. Carcinoma of the lip and selected sites of head and neck skin: a clinical study of 896 patients. *Radiother Oncol* 1987;8:11-17.
6. Nevrlka E, Newton KA. A survey of the treatment of 200 cases of basal cell carcinoma (1959-1966 inclusive). *Br J Dermatol* 1974;91:429-433.
7. Prestwitt WV, Nunes J, Kwok CS. Beta dose point kernels for radionuclides of potential use in radioimmunotherapy. *J Nucl Med* 1989;30:1036-1046.
8. Hoefnagel CA. Radionuclide therapy revisited. *Eur J Nucl Med* 1991;18:408-431.
9. Lederman M. Some application of radioactive isotopes in ophthalmology. *Br J Radiology* 1956;29:1-23.
10. Packer S, Rotman M. Radiotherapy of choroidal melanoma with iodine-125. *Ophthalmology* 1980;87:582-590.
11. Johnson LS, Yanch JC, Shortkroff S, Barnes CL, Sitzer AI, Sledge CB. Beta-particle dosimetry in radiation synovectomy. *Eur J Nucl Med* 1995;22:977-988.
12. Mumper RJ, Ryo UY, Jay M. Neutron-activated holmium-166-poly(L-lactic acid) microspheres. A potential agent for the internal radiation therapy of hepatic tumors. *J Nucl Med* 1991;32:2139-2143.
13. Turner JH, Claringbold PG, Klemp PEG, et al. Holmium-166 microsphere liver radiotherapy: a preclinical SPECT dosimetry in the pig. *Nucl Med Commun* 1994;15:545-553.
14. Johnson LS, Yanch JC. Absorbed dose profiles for radionuclides of frequent use in radiation synovectomy. *Arthritis Rheum* 1991;34:1521-1530.
15. Traenkle HL. A study of late radiation necrosis following therapy of skin cancer. *Arch Dermatol* 1995;72:446-453.

# Clinical Decision Making Based on Radionuclide Determined Ejection Fraction in Oncology Patients

Nan-Jing Peng, Ranjana Advani, Susan Kopiwoda, George Fisher and H. William Strauss

Department of Nuclear Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan; Division of Nuclear Medicine, Departments of Oncology and Radiology, Stanford University Medical Center, Stanford, California

Decreased left ventricular ejection fraction (LVEF) is a relative contraindication for the use of potentially cardiotoxic chemotherapy. A resting LVEF of 50% is usually used as the lower limit of normal values. The decision to change chemotherapy, however, is complex and is affected by many factors, including ejection fraction.

**Methods:** To determine how LVEF data were used by clinical oncologists in clinical decision making, we performed a retrospective analysis of patients referred for ejection fraction measurements from the hematology/oncology divisions of Stanford University from March 1992 through March 1995. The records of 565 patients treated with potentially cardiotoxic chemotherapy were evaluated.

**Results:** LVEFs <50% were found in 153 patients. The charts of patients with reduced ejection fractions were reviewed to determine if the radionuclide measurement resulted in either discontinuation of the cardiotoxic agent or substitution of a less cardiotoxic drug or mode of administration. These specific changes in therapy occurred in only 43 of the 153 (28%) patients with ejection fractions below 50%; 24 of the 43 (57%) had ejection fractions  $\leq$ 40%. Patients with lower ejection fraction values were more likely to have their therapy changed than those with LVEFs close to normal. Patients with ejection fractions  $\leq$ 30 generally had cardiotoxic agents discontinued. Of patients who had a resting LVEF <50% and whose therapy was not changed, 81% had a normal increase in LVEF with exercise.

**Conclusion:** In clinical practice at our institution, ejection fraction <50% is not used as an absolute contraindication to cardiotoxic chemotherapy. When the LVEF is less than 40%, potentially cardiotoxic therapy is most often discontinued or omitted. Radionuclide evidence of cardiac reserve may account for decisions to continue cardiotoxic agents despite ejection fractions <50% in the majority of patients. Further study will be needed to establish standard criteria. Reserve function, as measured by the change in ejection fraction from rest to stress may be an important parameter used by

oncologists to help select patients for continued therapy in spite of a reduced ejection fraction. Our results argue that use of fixed criteria may be too restrictive.

**Key Words:** cardiotoxicity; left ventricle ejection fraction; equilibrium gated radionuclide angiography

**J Nucl Med 1997; 38:702-705**

Cardiac toxicity due to chemotherapy with anthracyclines and anthraquinones is a serious adverse effect associated with substantial morbidity in some patients who are fortunate enough to survive their cancer (1-10). Recommendations for the "safe" use of anthracyclines have included either not exceeding a defined cumulative dose (e.g., for doxorubicin 400 mg/m<sup>2</sup>) or ensuring adequate cardiac function by limiting treatment to patients with ejection fractions >50% (usually defined by quantitative radionuclide angiography). The threshold dose is an unreliable predictor of cardiotoxic risk and, furthermore, varies with the mode of anthracycline administration [i.e., bolus versus continuous infusion (11)], as well as the exact drug administered. Pharmacologic advances in cancer chemotherapy have resulted in new ways of safely administering higher cumulative doses of anthracyclines. Dexrazoxane ameliorates anthracycline-induced cardiotoxicity and has recently been approved for use in women with metastatic breast cancer who have received a cumulative dose of doxorubicin of >300 mg/m<sup>2</sup> (12). Liposomal doxorubicin preparations have also received recent approval and result in significantly less cardiotoxicity (13). A study of endomyocardial biopsies of patients receiving liposomal doxorubicin administered to cumulative doses of up to 860 mg/m<sup>2</sup> revealed no evidence of significant anthracycline specific cardiotoxicity (14). Thus, the cumulative dose criteria for establishing safe limits of anthracycline exposure will likely decline in clinical value while objective studies

Received Jul. 9, 1996; revision accepted Sep. 11, 1996.

For correspondence or reprints contact: H. William Strauss, MD, Division of Nuclear Medicine, Dept. of Radiology, Stanford University Medical Center, Rm. H0101, Stanford, CA 94035-5281.