Clinical Experience with Californium-252 (First Report)

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Cf-252の臨床経験（第1報）

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癌研究会附属病院は1973年10月米国 ERDA から ^{252}Cf Market Evaluation Program に参加することを認められ，各1—2 μg ^{252}Cf を含有する15本の ^{252}Cf 針と6本のセルの貸与を受けた．

放射線治療又は手術（又は両者合併）後の再発または残存癌10例に対して，刺入または表在照射を行ない，中性子線量として 500— 2,800ラド平均 1,300ラドの照射を行つた．その結果は観察期間も短かく結論的なことはいえないが一応有望と思われた．今後臨床的に有用な RBE 値の決定および線源の安全取扱方法について研究を進めたい．

Abstract

The Cancer Institute Hospital received a loan of 30 μg of Californium-252 small sources from the ERDA in October 1973 under the ^{252}Cf Market Evaluation Program, consisting of 15 needles and 6 afterloading cells of 1–2 μg of ^{252}Cf.

Ten secondary cases, who had recurrent or residual diseases developing from irradiated and/or operation scars of the tongue and various sites of the body, were treated by ^{252}Cf needling or by surface moulds. Neutron doses to the target volume varied from 500 to 2800 rads for an average of 1300 rads.

The overall initial results have been generally favorable and encouraging and good local tumor control could be obtained in most of the cases, but the follow-up period has been too short to permit final evaluation. The selection of clinically useful value of RBE and the establishment of a method for effective and safe handling of ^{252}Cf small sources should be studied in the future.

Introduction

In recent years, the challenge against cancers, heretofore considered radioresistant, has been made chiefly by two methods using unique radiobiological characteristics of high LET radiations in the field of radiology. The first method is the external irradiation of fast neutrons produced by particle accelerators such as cyclotrons, and the second one is the interstitial or intracavitary irradiation by the use of fast neutrons emitted from ^{252}Cf small sources, as have been done with gamma rays from ^{226}Ra and ^{192}Ir.

The Cancer Institute Hospital received the first loan of 30 μg of ^{252}Cf sources from the ERDA (former USAEC) in October 1973 under the ^{252}Cf Market Evaluation Program[1]. They consisted of 15 needles and 6 afterloading cells of 1–2 μg of ^{252}Cf (Table 1). The first year was devoted to the arrangement of the therapy room and various types of equipment necessary for safe handling on the part of the hospital personnel and to dosimetry for radiotherapy and radiation protection[2),3),4)].

Table 1. Cf-252 small sources loaned to the Cancer Institute Hospital from the ERDA (October, 1973)

Source type	Active length (mm)	Length (mm)	Capsule wall thickness 90% Pt, 10% Ir		External diameter (mm)	Intensity		Number
			inner (mm)	outer (mm)		μg	n/sec	
Needle, 2.4	30.00	40.00	0.15	0.30	1.65	2.505	5.800	5
	±0.50	±0.50	±0.012	±0.012	±0.025	±5.0%	$\times 10^6$	
Needle, 1.2L	30.00	40.00	0.15	0.30	1.65	1.223	2.834	5
	±0.50	±0.50	±0.012	±0.012	±0.025	±5.0%	$\times 10^6$	
Needle, 1.2S	15.00	26.00	0.15	0.30	1.65	1.256	2.910	5
	±0.50	±0.50	±0.012	±0.012	±0.025	±5.0%	$\times 10^6$	
Short after-loading cell 1.0	15.00	18.00	0.10	0.15	0.99	1.032	2.391	6
	±0.50	±0.50	±0.012	±0.012	±0.025	±5.0%	$\times 10^6$	

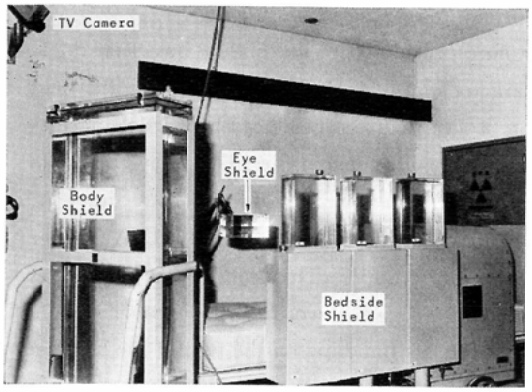
Between March 1974 and March 1975, ^{252}Cf sources have been used as implants or surface moulds applied to superficial accessible tumors in ten patients. Selected patients had recurrent or residual diseases developing from irradiated and/or operation scars. The success rate of radiotherapy is lower for these sites because of the higher percentage of hypoxic cells present. The overall initial results have been generally favorable and encouraging in this early period of study and will be reported here.

Purpose

The final purpose of this study is to evaluate the potential advantages of ^{252}Cf small sources over ^{226}Ra or ^{192}Ir for brachytherapy, and to determine whether any significant improvement in therapeutic results could be observed. The difference in indications will be compared with those of external irradiation of fast neutrons produced by cyclotrons, including the use of booster therapy of ^{252}Cf small sources combined with other modalities of radiotherapy when indicated.

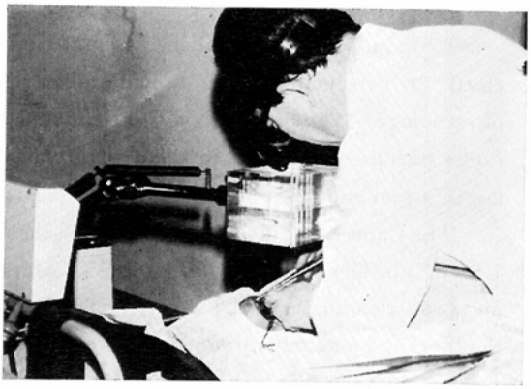
Average Therapist Dose

The dose received by the therapist, while directly loading and unloading ^{252}Cf sources, should be carefully checked, because the RBE value of high LET radiations increases sharply with decrease in dose



a) Body shild. b) Bedside shield: Water 20 cm in thickness reduces the neutron dose equivalent rates by about a factor of 10. c) Eye shield: "Lucite" block 20×12 cm in size and 10 cm in thickness reduces the neutron dose equivalent rates by about a factor of 3.

Fig. 1. Various kinds of equipment for radiation protection.



Implantation is made with the eyes shielded with a "Lucite" plate 10 cm in thickness. This reduces the neutron dose by about a factor of 3.

Fig. 2. The use of eye and bedside shields during ^{252}Cf implantation.

rate. This is especially true when the radiation hazards to the eye (radiation cataract) is taken into account. Accordingly, ^{252}Cf small sources should be handled very carefully in the therapy room, where various kinds of equipment necessary for safe handling are well provided[2] (Fig. 1, 2).

The ^{252}Cf gamma ray dose received by the therapist to his head (eye), breast, abdomen, back, lower lumber region, and fingers was measured with $CaSO_4$: Tm or BeO thermoluminescent dosimeters. These dosimeters are insensitive to neutrons. The product of the measured gamma ray dose and the measured ratio of neutron dose equivalent to gamma ray dose behind the bedside shield or eye shield was used as the estimated neutron dose equivalent.

With the therapist standing behind the bedside shield and eye shield while directly loading interstitial implants, the average total dose equivalent (neutron+gamma) to his head region was 4.3 mrem/μg ^{252}Cf implanted (Fig. 3). During the early stage, the numberof patients treated was limited to 5 or 6 cases a month, this being the number which could be implanted safely by one therapist within the legally permissible dose. The use of afterloading technique can reduce the dose equivalent to the therapist by about a factor of 2 or 3, by eliminating source handling in sterilization procedures, in needle threading, and in the surgical procedures. Incidentally, the average dose to the head region of the therapist while directly loading interstitial radium implants without shielding was 3 mR/mg ^{226}Ra implanted, excluding the dose exposed during the needle threading[5].

Clinical Cases and Method of Treatment

First ten patients, treated before March, 1975, were secondary cases, who had recurrent or residual diseases developing from irradiated and/or operation scars (Table 2). They consisted of four cases of tongue cancer and six other patients, who had cancer developing from the larynx, hypopharynx, floor of the mouth, uterine cervix and rectum, respectively.

Table 2. Californium-252 patients (10 cases)

Patient No.	Age and Sex	Primary Site and Stage	Site and Condition of Disease	Previous Treatment	Date	Method of Cf-252 Application	Dose Rate (hrs)*	Local and Side Effects
1	64 M	Tongue T3N0M0	tongue; recurrence	External Co-60 therapy followed by implantation of Ra needles and Rn seeds in 1972 Partial glossectomy in 1973 Second Ra implantation in 1973	'74.3	Double plane implant (10 μg) 0.99 μg/3.0 cm×5, 1.01 μg/1.5 cm×5	neutron(n): 12 rad/h, gamma(γ): 6.7 rad/h 5 days (120 hrs)	Well controlled for more than 1 yr Severe mucositis persisted for about 12 mos
2	72 M	Hypopharynx T1N1M0	right upper neck; recurrence	Linac X-ray and right radical neck dissection in 1973	'74.5	Double plane implant (8.6 μg) 0.80 μg cell×6, (Afterloading) 0.95 μg/3.0 cm×4	n: 5 rad/h γ: 3 rad/h 7 days (168 hrs)	Well controlled Slight ulceration of more than 4 mos; died of generalized metastasis 6 mos later
3	54 M	Larynx	lower neck; residual tumor adherent to the esophagus	Laryngectomy (with bilateral radical neck dissection) following Linac irradiation	'74.7	Surface mould (18.2 μg) 1.90 μg/3.0 cm×4, 0.93 μg/3.0 cm×4 0.95 μg/1.5 cm×4 0.78 μg cell×4	n: 10 rad/h γ: 5.6 rad/h at skin surface 80 hrs	Well controlled No skin reaction
4	51 F	Rectum	perineal region; recurrence	Radical operation followed by Linac X-ray in 1969	'74.8	Double plane implant (Ra 14 mg, Cf 11.9 μg) Ra: 2 mg/3.0 cm×5 1 mg/1.5 cm×4 Cf: 1.83 μg/3.0 cm×5 0.92 μg/1.5 cm×3	Ra-side n: 0.7 rad/h γ: 37 rad/h Cf-side n: 11 rad/h γ: 9.5 rad/h 8 days (192 hrs)	Well controlled Died of generalized metastasis 4 mos later
5	66 M	Tongue T2N0M0	left border of the tongue; primary case	External Co-60 therapy to the tongue cancer of the right side in 1970	'74.9	Single plane implant (9.0 μg) 1.80 μg/3.0 cm×3, 0.90 μg/1.5 cm×4	n: 17 rad/h γ: 12 rad/h 7 days (168 hrs)	Well controlled Mucositis subsided in about 1 mo

6	60 F	Floor of the mouth	mouth floor; recurrence in the operation susture	Ra implant in 1955 Double or radiation-induced cancer was found in 1973 X-ray irradiation followed by extended radical operation in 1973	'74.9	Single plane implant (6.2 μg) 1.77 μg/3.0 cm×1, 0.89 μg/1.5 cm×5	n: 17 rad/h γ: 11 rad/h 8 days (168 hrs)	Well controlled Slight mucositis
7	51 F	Tongue T3N0M0	tongue; recurrence	Ra implant in 1970	'74.10	Single plane implant (14.0 μg) 1.75 μg/3.0 cm×3, 0.86 μg/3.0 cm×5, 0.87 μg/1.5 cm×3	n: 11 rad/h γ: 6.3 rad/h 7 days (168 hrs)	No sign of activation at 5 mos Mucositis persisted for more than 5 mos
8	58 M	Lung T1N3M0	supraclav. node metastasis; residual mass of 4×3×3 cm	Linac X-ray irradiation to the right supraclavicular lymph node metastasis Residual tumor causing moderate neuralgia extending to the right upper extremity	'74.12	Double plane implant (6.6 μg) 0.82 μg/3.0 cm×5 0.84 μg/1.5 cm×3	n: 7.5 rad/h γ: 4.3 rad/h 3 days (68 hrs)	Lymph node metastasis decreased in size markedly and neuralgia was well controlled Marked pigmentation
9	54 F	Uterine cervix T_3NxM0	vaginal stump; residual disease	Radical operation in 1972 Ra-colpostat (stage 3) application for vaginal stump recurrence in 1974	'75.3	Intracavitary surface mould a) First cource (19.8 μg) 1.62 μg/3.0 cm×5 0.77 μg/3.0 cm×5 0.79 μg/1.5 cm×5 0.65 μg cell×6	n: 12 rad/h γ: 6 rad/h 41 hrs	Moderate mucositis corresponding to an RBE value of more than 6 not effective
						b) Second cource (13.6 μg) 1.62 μg/3.0 cm×5 0.79 μg/1.5 cm×2 0.65 μg cell×6	n: 9.4 rad/h γ: 4.8 rad/h 12 hrs	
						Volume implant (parametrium) (7.7 μg) 1.53 μg/3.0 cm×5	n: 15 rad/h γ: 7.7 rad/h 6 days (144 hrs)	
10	69 F	Tongue T3N0M0	tongue; recurrence	Double plane Ra implant in April, 1974	'75.3	Double plane implant (6.2 μg) 0.77 μg/3.0 cm×5, 0.79 μg/1.5 cm×3	n: 12 rad/h γ: 9 rad/h 4 days (96 hrs)	No sign of reactivation

*The maximum dose rate in the target volume was calculated by our computer as about 3 times the cited values in the table for single plain implant, and about 2 times for double plain or volume implant.

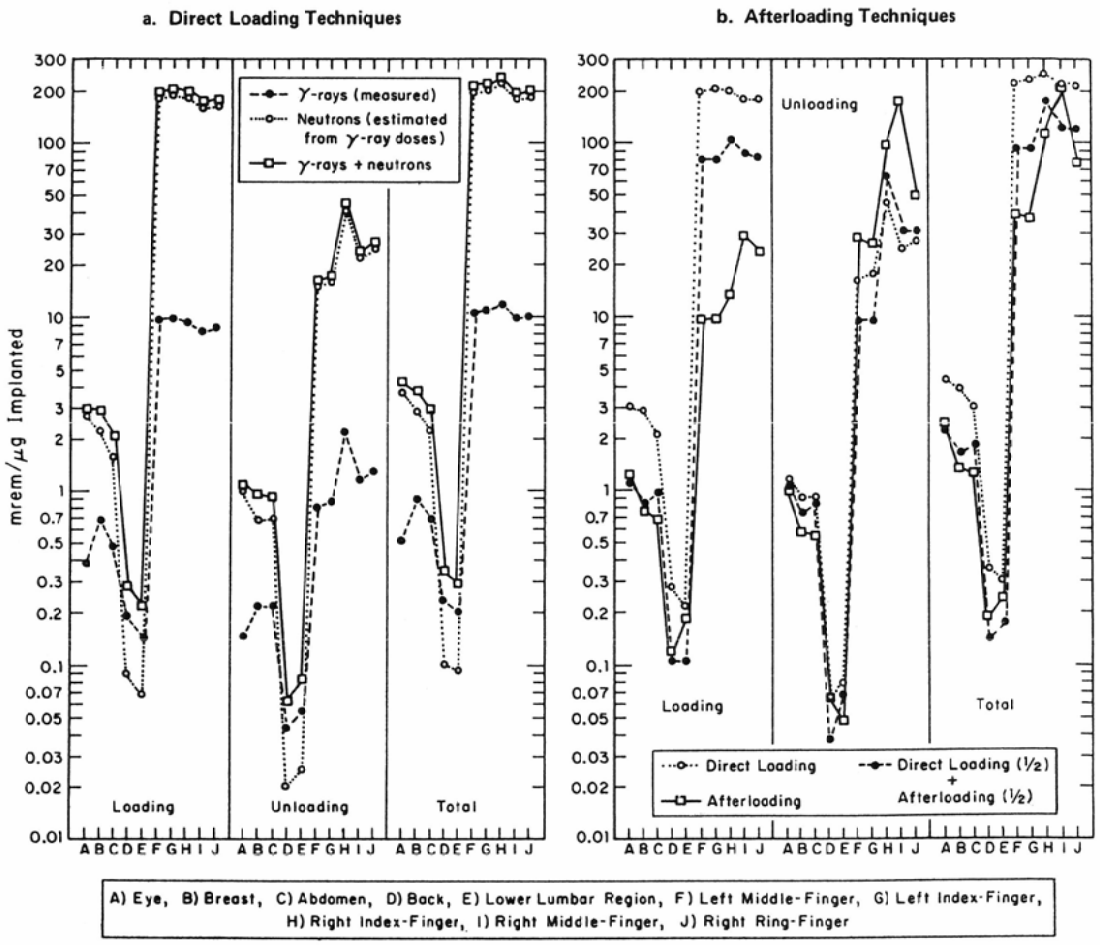


Fig. 3. Average dose equivalent received by therapist while loading ^{252}Cf sources.

Eight patients were treated by plane or volume implants lasting from 4 to 8 days. The other two patients were treated by surface moulds. The implantation technique was similar to that for ^{226}Ra implants.

A formula for computer calculation of the three-dimensional isodose distribution around a ^{252}Cf source has been developed and applied for each individual case. The three-dimensional isodose distribution around the implants was calculated in rads for both neutron and gamma rays. Next, the biological equivalent dose was calculated corresponding to RBE values of 3, 5 and 7. This dose permitted a closer comparison with the response of tumor and contiguous normal tissues. Neutron doses to the tumor varied from 500 to 2800 rads, for an average of 1300 rads.

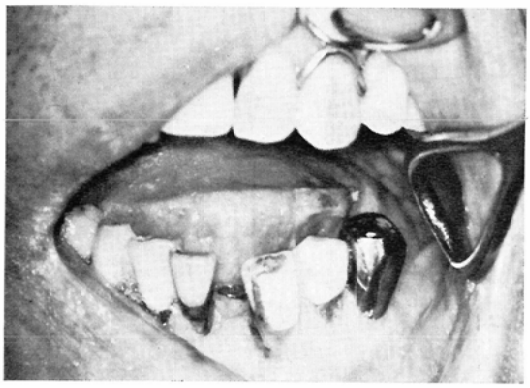
Case 1. T.N., male, aged 64 years, carcinoma of the tongue, T3N0M0.

Histology: Squamous cell carcinoma.

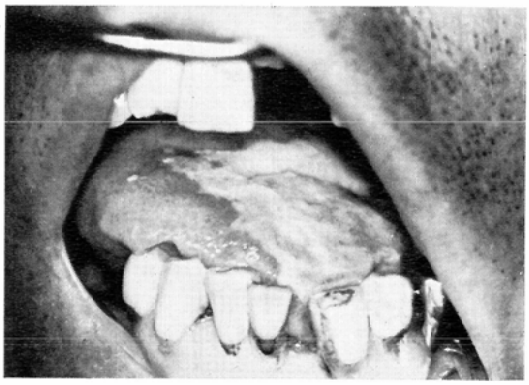
He was first seen in February, 1972, with cancer of the left border of the tongue at another hospital, where the telecobalt external irradiation of 5400 rads in 9 weeks (at interval of 3.5 weeks) was given.

He was referred to our hospital on March 22 for radium implantation. He had a residual tumor, measuring 1×4 cm in size and extending from the left lateral border to the base of the tongue, which formed a shallow ulceration in the middle. A single plane radium implant (2 mg×2, 1 mg×4) was made delivering a dose of 4500 rads in 6 days, with an additional implantation of radon seeds (1 mCi×4) into the base of the tongue 2 and 3 months later, respectively.

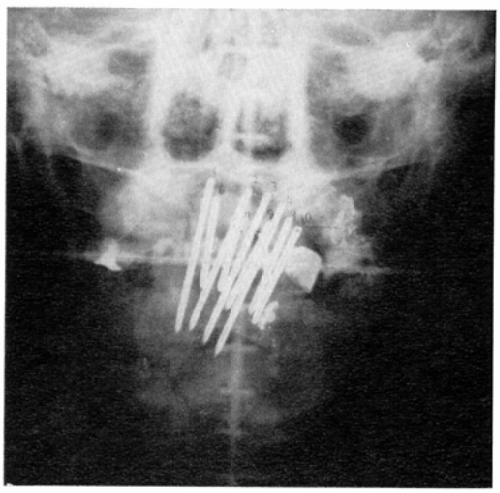
On September 5, partial glossectomy was performed to eradicate the remaining tumor extending into the base of the tongue with partial removal of the floor of the mouth and left anterior faucial arch.

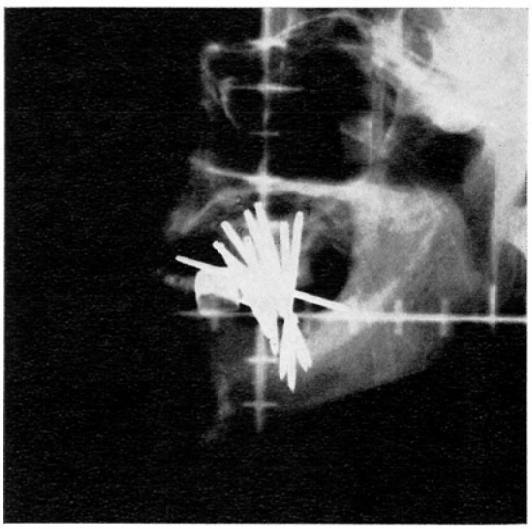


a) Local findings of tongue cancer prior to implantation. A mass 1×4 cm in size was palpated on the left tongue margin.



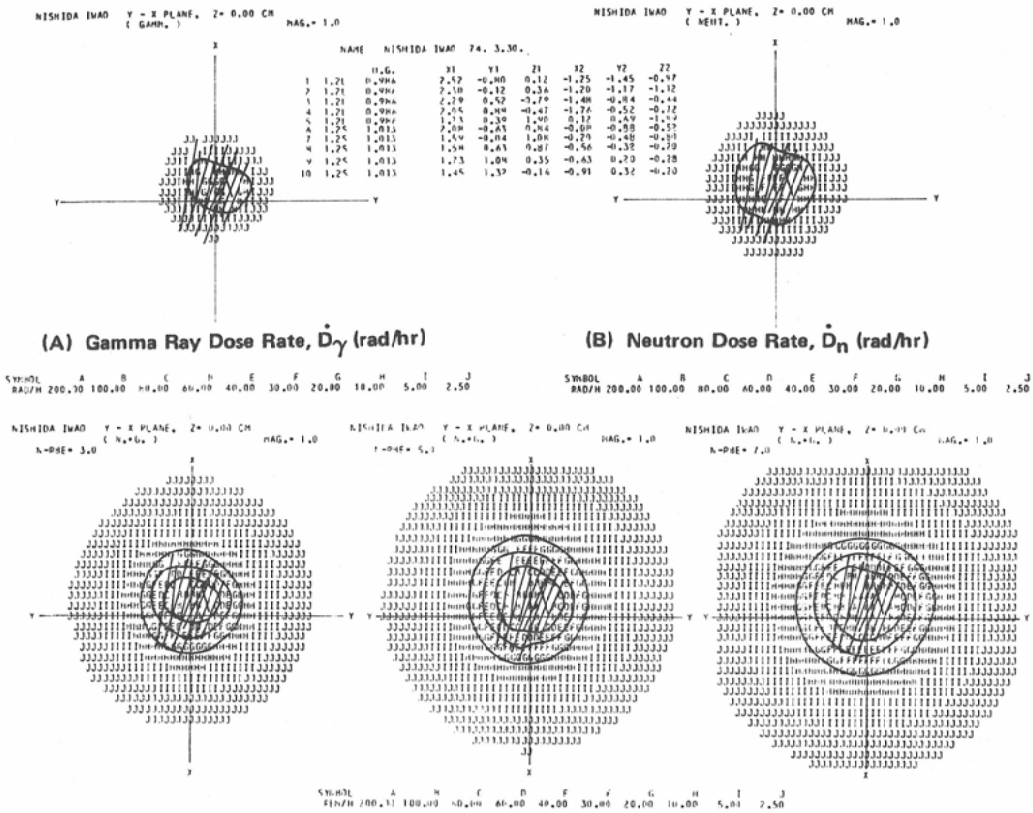
b) Local findings after removal of ^{252}Cf sources. Severe epithelitis developed at the site of implantation, but this epithelitis disappeared about one year later together with the tumor. The course thereafter for 1–1.5 years has been favorable.





c) Verification X-ray film of implanted ^{252}Cf needles. Left is AP X-ray film and right is lateral X-ray film. A total of 10 needles (effective length of 3 cm) of 1.2 μg and 6 short needles (effective length of 1.5 cm).

Fig. 4. Case 1, 64-old- male, carcinoma of the tongue.



(A) (B): A tubular listing of dose rates on grid point in the plane.
(C) (D) (E): Plotted or labeled isodose curves for both neutron and gamma ray physical dose rates plus biological equivalent dose rates with varying RBE's (3, 5 and 7).

Fig. 5. Dose distributions for interstitial ^{252}Cf implants (Case 1).

On December 12, recurrence developed again along the operated scar extending to the anterolateral part of the tongue, and the second plane radium implantation (1 mg×5, 2 mg×5) was made for 5 days without success, unfortunately.

On March 25, 1973, a volume implantation of Cf-252 needles (1.01 μg×5, 0.99 μg×5) was made covering the site of marginal recurrence along the left border of the tongue (Fig. 4a, b, c). A tumor dose of 5,000 or 10,000 rem in 5 days was given with the value of RBE of Cf-252 neutrons assumed to be 3 or 6 (Fig. 5).

The local lesion was found to be well controlled without ulceration in May, 1975.

Case 6. A.T., female, aged 59 years, carcinoma of the floor of the mouth, T1N0M0.

Histology: Squamous cell carcinoma.

Past history showed that she had a single plain radium implant for tongue cancer of the left anterior border of the tongue in 1955, followed by left radical neck dissection in 1956. She continued in good

condition until she noticed a 1.0×1.0 cm hard, deeply infiltrating tumor at the left anterior part of the floor of the mouth (T1N0M0, squamous cell carcinoma). This is considered to be a double or radiation-induced cancer.

The tumor was irradiated externally by 12 MeV electron beams for a total tumor dose of 3360 rads in 5 weeks, followed 2 months later by extended surgical removal of the remaining tumor including the anterior one-third of the floor of the mouth and accompanying muscles and partial resection of the jaw, which was partly reconstructed by a deltoid-pectral flap. The specimen showed a 12×9 mm lesion.

On September 25, a small carcinomatous granulation measuring 0.5 cm in diameter was noticed at the posterior margin of the operation-scar. A single plane Cf-252 implant (0.9 μg×5, 1.8 μg×1) was made, delivering a tumor dose of 8000 (16000) rem in 8 days, postulating the value of RBE of Cf-252 neutrons to be 3 (or 6). The accompanying mucositis was not severe and disappeared 2 months later.

More than 6 months later in May 1975, she appeared to be in good condition. Mucositis which developed was severe and remained for about a year, but underlying tumor infiltration disappeared gradually and no evidence of disease was found in May, 1975.

Results and Discussion

In three patients (Cases 1, 2 and 7), early response has progressed to severe mucositis or slight ulceration which persisted for more than 4 and 6 months, respectively. Fortunately, no untoward late gross ulcerated lesions suggestive of overexposure have been encountered.

Two patients (Cases 2 and 4) died at 4 and 6 months, respectively, with generalized metastasis, but with good control in the ^{252}Cf implanted area.

In one patient (Case 9), a direct comparison of the early skin response was made between ^{252}Cf and ^{226}Ra implants. An RBE value of about 6 was assumed for ^{252}Cf implants lasting 8 days.

The foregoing clinical findings may be summarized as follows[6),7),8)].

1. Overall initial results for radioresistant tumors were generally favorable and encouraging, but the follow-up period was too short to permit final evaluation.

2. The selection of clinical useful values of RBE should be determined on a larger number of cases and under varying local conditions.

3. We expect to establish a method for effective and safe handling of ^{252}Cf small sources to reduce the therapist dose. The use of afterloading cell assemblies supplied by the ERDA and remotely controlled afterloading apparatus should be considered[9),10)].

In both the United States[9)] and England[11)], the early trials ^{252}Cf brachytherapy have demonstrated encouraging results than those of low LET radiation for radioresistant or recurrent tumors. The search for true indications for ^{252}Cf brachytherapy is considered to be an interesting and challenging problem for the future, and it should be mentioned that a randomized controlled trials have been commenced under a 3-year program in the United States[12)].

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