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Clinical Experience with Californium-252  
(Second report)

by

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**$^{252}\text{Cf}$  小線源の臨床経験 (第2報)**

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1974年3月より1977年8月の間に  $^{252}\text{Cf}$  小線源によって治療された44例のまとめである。14例は初回治療として用いられ、30例は再発癌に用いられた。本治療の対象には以前の照射、手術によって瘢痕化した部に発生したものや、もともと組織学的に放射線抵抗性である病巣が選ばれた。線源は針状、シード状、管状のものがあり、組織内照射、間隔照射、腔内照射などが行なわれた。本線源のみのものと  $\gamma$  線、電子線照射に対する追加照射のものとがあつた。

結論として、2ヵ月後の局所所見で病巣消失(放医研の Early response score 1)のものは44例中23例であつた。症例は頭頸部腫瘍、皮膚腫瘍、悪性黒色腫、子宮頸部腺癌などであり、速中性子線量にして600rad以上に有効例が見られた。食道癌の腔内照射は全例不成功であつた。副作用としての皮膚、粘膜、骨の障害は特に高度のものはなかつた。 $^{252}\text{Cf}$  は組織的に見た放射線抵抗性癌にも有効であつたが効果の程度は今後の検討課題である。

### Introduction

This report presents our clinical experience with  $^{252}\text{Cf}$  brachytherapy from March 1974 through August 1977 on 44 cases, consisting of 14 primary and 30 secondary cases. Secondary cases were recurrent or residual diseases developing from irradiated and/or surgical scars. In these cases the success rate of conventional radiotherapy for these sites is considered to be very low because of possible higher percentage of hypoxic cells present. Four primary cases were also included; one case of malignant melanoma of the vulva and three cases of well differentiated papillary adenocarcinoma of the uterine cervix. These histological types are considered to be very radioresistant, their low radiosensitivity being confirmed in our past experience. These cases were also submitted to clinical trial in order to study the effectiveness of  $^{252}\text{Cf}$  irradiation.

### Method of Treatment

As alluded to in the first report<sup>1)</sup>, the Cancer Institute Hospital received the first loan of 30 ug of  $^{252}\text{Cf}$  sources from the USAEC in October 1973. Thereafter in March 1977 the second loan of 87 ug consisting of new types of  $^{252}\text{Cf}$  sources was received from the ERDA (presently, Department of Energy, U.S.A.) (Table 1).

During this period interstitial application of  $^{252}\text{Cf}$  needles was mainly made. In some cases, afterloading cells were also used interstitially by manual afterloading technique in order to reduce the therapist dose as much as possible.

Three-dimensional dose distribution was calculated by our physicist's group using a computer.<sup>1)2)</sup>

Table 1.  $^{252}\text{Cf}$  medical sources loaned to the Cancer Institute Hospital (Second loan)  
Received: March 1977

Source type	Active length mm	External length mm	Capsule wall 90% Pt 10% Ir		External diameter mm	Source strength		Number of sources	Total ug
			inner mm	outer mm		ug	n/sec		
Applicator tube	15.00 $\pm 0.50$	23.50 $\pm 0.25$	0.30 $\pm 0.012$	0.50 $\pm 0.012$	2.80 $\pm 0.05$	15.662 $\pm 5.0\%$	36.195 $\times 10^6$	3	46.99
Short after-loading cell	15.00 $\pm 0.50$	18.00 $\pm 0.50$	10.0 $\pm 0.012$	0.16 $\pm 0.012$	0.95 $\pm 0.025$	0.795 $\pm 5.0\%$	1.838 $\times 10^6$	10	7.95
Seed	4.00 $\pm 0.10$	6.00 $\pm 0.25$		0.16 $\pm 0.012$	0.80 $\pm 0.05$	0.380 $\pm 5.0\%$	0.878 $\times 10^6$	72	27.36
Total								85	82.30
Seed assemblies									
Seed assembly	Active length mm	External length mm	External diameter mm		Number of seeds		Number of seed assemblies	Total ug	
3-seed	26	60	1.05		0.38 ug $\times 3$		4	4.56	
4-seed	36	70	1.05		0.38 ug $\times 4$		4	6.08	
5-seed	46	80	1.05		0.38 ug $\times 5$		4	7.60	
6-seed	56	90	1.05		0.38 ug $\times 6$		4	9.12	

Assayed: September 27 to December 31, 1976.

The total delivered dose was calculated individually and determined according to histology, location, size and conditions of the tumor bed.

### Clinical Cases and Results of Treatment

All the cases so far treated are presented in Table 2 with individual clinical course, previous treatment, method of application, delivered tumor dose, prognosis and tumor response score.

Score system used at the National Institute of Radiological Sciences was employed as shown in Table 3. The relationships between the local tumor response by early effect score and the number of cases in each group of the disease is shown in Table 4.

#### 1. Primary cases

Table 3. Radiation effect score for tumor control

(A) Early effect score
1. complete disappearance
2. regression, less than half of the original size
3. regression, larger than half size
4. no shrinkage
5. increasing in size
(B) Late effect score
1. complete disappearance with no sign of scar formation
2. complete disappearance with scar formation
3. residual but non-growing tumor
4. residual and slowly growing tumor
5. rapidly growing recurrent tumor

Table 4. Summary of local tumor response by early effect score 2 months after the completion of therapy

No. of cases assigned	Score		Score 4,5 or salvaged by operation	Scoring not possible	Total
	1	2 or 3			
<b>Primary cancer</b>					
<sup>252</sup> Cf only	Cervix uteri	3	—	—	3
	Vulva	1	—	—	1
	Esophagus	1	6	—	7
<sup>252</sup> Cf boost	Skin	1	—	—	1
	Lymph node	—	1	—	1
	Bronchus	—	1	—	1
<b>Recurrent cancer</b>					
Head and neck	13	1	2	2*	18
Uterus	2	3	2	—	7
Esophagus	—	2	—	—	2
Skin	1	—	1	—	2
Rectum	1	—	—	—	1
Total	23	14	5	2	44

\*One case died of intercurrent disease soon after the implant (Case 26), and the other case was treated <sup>252</sup>Cf prophylactically (Case 45)

Four out of 14 primary cases were treated solely with  $^{252}\text{Cf}$  (Table 4), and the remaining 10 cases were treated by Linac X-rays or  $^{60}\text{Co}$   $\gamma$ -rays supplemented with  $^{252}\text{Cf}$  boost therapy.

a) Neutron therapy only:

One case of malignant melanoma of the vagina (Case 13 in Table 2(3)) was controlled by  $^{252}\text{Cf}$  volume interstitial irradiation of neutron dose of 1440 rad in 6 days. Tumor disappeared completely but she died of other cause 1.5 years later.

Three cases of well differentiated papillary adenocarcinoma of the cervix uteri (Cases No. 22, 23 and 24 in Table 2(5)) were also treated with intracavitary application of  $^{252}\text{Cf}$ . A non-curative neutron dose of 430 rad was given in 6 fractions in 2 months to point A. Two out of 3 cases responded favorably, resulting in complete local control which lasted for more than 1 year, but the remaining case (Case 23) was salvaged by surgical removal due to recurrence 6 months later, probably attributable to low dosage. The dose at point A of Case 22 (T1b) was calculated to be 430 rad, but as the primary focus was small and located at the inner side of point A, the tumor dose was calculated to be 840 rad based on the dose distribution curve. The dose at point A was used as the tumor dose in Cases 23 and 24 (T3), because the primary tumor extended almost to point A. Case 22 has been in good health and asymptomatic for more than 2 years. It is noteworthy that very marked histological changes were observed very soon by successive histological examinations (Figs.4 and 5).

b) Neutron boost therapy:

Ten out of 14 cases were treated by neutron boost therapy, which consisted of 7 cases of esophageal carcinoma, one case out of cervical metastasis of lung carcinoma (Case 8), skin cancer (Case 19), and bronchial cancer (Case 46), respectively. External irradiation of 5000–7000 rad was given to the esophagus, followed by additional intracanalicular application of  $^{252}\text{Cf}$  for the eradication of the remaining radioresistant nests. Neutron doses of 60 to 260 rad were given to a point 0.5 cm from the center of the tube. For esophageal cancer, results more favorable than those of the external X-irradiated group could not be obtained. Three cases other than esophageal cancer showed favorable local control for 6 months or more than 2 years.

## 2. Secondary cases

Thirty secondary cases consisted of 18 cases of head and neck cancer, 7 cases of uterine cervix cancer, 2 cases of esophageal cancer, 2 cases of skin cancer and 1 case of rectal cancer. They were considered to be poor candidates for photon beam radiotherapy, because they had undergone previous operation and/or irradiation. Five out of 18 head and neck cases, including Cases 30 and 34, have been doing well for more than 1 year, except for Case 45, who has been under observation for less than 1 year. Local control was achieved in 7 out of 9 recurrent cancer cases of the tongue and floor of the mouth for more than 5 months. Local control was also achieved in 1 case of adenoid cystic carcinoma of the soft palate (Case 36), and in 1 case of malignant melanoma of the ethmoid (Case 34).

Two out of 7 cases of uterine cervix cancer showed early good effect (Score 1) but recurred after 3 and 6 months, respectively. Two cases of esophageal cancer could not be controlled and 1 case of skin cancer (Case 29) achieved local control but later developed brain necrosis due to cumulative excessive irradiation. Another skin cancer case (Case 20) received operation because of poor local effect.

Table 2 (1). List of individual cases treated with  $^{252}\text{Cf}$  Brachytherapy

Pat. No. Name	Age	Primary site Stage	Site, Local condition	Previous treatment	Date	Method of applica- tion, $\mu\text{g}/\text{active}$ length (cm) $\times$ number of sources	Dose rate, Time, Total neutron dose	Local and side effects, Survival time	Early effect score	Late effect score
									2 mos.	3 mos.
<b>CARCINOMA OF THE TONGUE AND FLOOR OF THE MOUTH</b>										
1 I.N.	64 M	Tongue T3N0M0	Tongue Recurrence	Ext. Co-60 therapy followed by implan- tation of Ra needles	Mar. '74	Double plane implant: 0.99 $\mu\text{g}/3.0 \text{ cm} \times 5$ , 1.01 $\mu\text{g}/1.5 \text{ cm} \times 5$	12 rad/h 120 h 1440 rad	Well controlled for 2 yrs. Marked mucositis for 1 yr. Second Cf-252 treatment for marginal extension in 1976. Died of recurrence in Nov. 1976.	1	1
5 M.S.	66 M	Tongue T2N0M0	Tongue Recurrence	Ext. Co-60 therapy for tongue ca. on at the left the right side in side	Sept. '74	Single plane implant: 1.80 $\mu\text{g}/3.0 \text{ cm} \times 3$ , 0.90 $\mu\text{g}/1.5 \text{ cm} \times 4$	17 rad/h 168 h 2580 rad	Well controlled. Mucositis subsided in about 1 mos. Died of cervical lymph node metastasis after 11 mos.	1	1
7 N.M.	51 F	Tongue T2N0M0	Tongue Recurrence	Single plane Ra implantation in 1970. Oct. 1970.	Oct. '74	Single plane implant: 1.75 $\mu\text{g}/3.0 \text{ cm} \times 3$ , 0.86 $\mu\text{g}/3.0 \text{ cm} \times 5$ , 0.87 $\mu\text{g}/1.5 \text{ cm} \times 5$	11 rad/h 168 h 1848 rad	Well controlled for more than 3 yrs. Mucositis persisted for 1 yr.	1	1
10 T.O.	69 F	Tongue T3N0M0	Tongue Recurrence	Double plane Ra implantation in Apr. 1974.	Mar. '75	Double plane implant: 0.77 $\mu\text{g}/3.0 \text{ cm} \times 5$ , 0.79 $\mu\text{g}/1.5 \text{ cm} \times 3$	12 rad/h 96 h 1152 rad	Tumor decreased in size, but remained for 2 yrs. with persistent mucositis.	3	3
6 A.T.	60 F	Floor of the mouth T2N0M0	Mouth floor Ra implantation in 1955. Recurrence? in the or radiation ca.? operation in 1973. Ext. irradia- tion followed by extensive surgical removal in 1973. Recurrence in the scar in Aug. 1974.	Double plane implant: 1.77 $\mu\text{g}/3.0 \text{ cm} \times 1$ , 0.89 $\mu\text{g}/1.5 \text{ cm} \times 5$	Sept. '74	17 rad/h 168 h 2856 rad	Well controlled for more than 3 yrs. Mucositis was slight probably due to the small target volume.	1	1	

27 Y.S.	65 Tongue M T2N0M0 Adenoca.	Tongue Recurrence in 1975.	Ext. Co-60 therapy	Mar. Single plane implant: '76 1.2 µg/3.0 cm × 2, 0.6 µg/1.5 cm × 5	10 rad/h 119 h 1190 rad	Well controlled. Recurrence was suspected 10 mos. later. Surgical removal revealed no remaining cancer.	1 1
28 S.S.	31 Tongue M T3N0M0 Sq. c. ca.	Gum Recurrence	Ext. Co-60 therapy and Ra implantation in Oct. 1974. Radical neck dis- section in Feb. 1975. Total glos- sectomy in Dec. 1975.	Mar. Volume implant: '76 1.16 µg/3.0 cm × 5, 0.60 µg/1.5 cm × 5, 0.58 µg/3.0 cm × 5 and surface mold to the gum, 0.49 µg cell × 6	10 rad/h 96 h 960 rad	Recurrence after 3 mos. Died of cancer 6 mos. later.	1 1
32 T.N.	45 Tongue Sq. c. ca.	Tongue Recurrence	Ra implantation followed by cryo- surgery in 1971.	Jun. Single plane implant: '76 0.54 µg/3.0 cm × 1, 0.56 µg/1.5 cm × 5	5.5 rad/h 167 h 920 rad	Slight induration 5 mos. later. Surgical removal with no cancer remaining.	1 1
33 M.M.	70 Tongue M T2N0M0 Sq. c. ca.	Tongue and floor of the mouth	Ext. Co-60 and electron therapy in 1974. Recurrence in 1976. Re- irradiation not effective in June 1976.	Jul. Two plane implant: '76 1.00 µg/3.0 cm × 3, 0.50 µg/1.5 cm × 5	10 rad/h 71 h 710 rad	Tumor controlled for more than 1 yr. Ulcer developed at the junction of tongue and floor of the mouth.	1 2
2 T.M.	72 Hypopharynx M T1N1M0 Sq. c. ca.	Right upper Ext. linac X-ray neck and radical neck dissection in 1973.	May Double plane implant: '74 0.81 µg cell × 6, (afterloading), 0.95 µg/3.0 cm × 4	5 rad/h 168 h 840 rad	Well controlled. Slight ulceration for more than 4 mos. Died of metastases 6 mos. later.	1 2	
3 T.K.	54 Larynx M T3N0M0 Sq. c. ca.	Right lower neck Residual tumor ad- herent to the esopha- gus	Laryngectomy with bilateral neck dis- section following ext. linac X-ray irradiation.	Jul. Surface mold: '74 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	10 rad/h 80 h 800 rad	Well controlled. No skin reaction. Died of pulmonary metastases 10 mos. later.	1 1

Table 2 (2).

Pat. No. & Name	Age	Primary site Stage Sex histology	Site, Local condition	Previous treatment	Date	Method of applica- tion, $\mu\text{g}/\text{active}$ length (cm) $\times$ number of sources	Dose rate, Time, Total neutron dose	Local and side effects, Survival time	Early effect score 2 mos. later	Late effect score 3 mos. later
CARCINOMA OF THE HEAD AND NECK OTHER THAN THE TONGUE										
12 K.N.	57	Larynx Sq. c. ca.	Right upper neck Recurrence	Preoperative irradiation followed by total laryngectomy with left RND in Apr. 1974. Right RND in Sept. 1974. Reoperation of the right neck metastases in Apr. 1975.	Jun. '75	Single plane implant: 1.44 $\mu\text{g}/3.0 \text{ cm} \times 5$ , 0.72 $\mu\text{g}/3.0 \text{ cm} \times 5$ , 0.75 $\mu\text{g}/1.5 \text{ cm} \times 5$	4 rad/h 90 h 360 rad	Ineffective. 2nd implant after 5 weeks.	5	3
26 T.O.	77	Soft palate Sq. c. ca.	Soft palate Recurrence	Ext. Co-60 therapy in 1972. Rn seed implant in 1973. Ext. linac X-ray irradiation in 1974.	Feb. '76	Single implant: 0.62 $\mu\text{g}/1.5 \text{ cm} \times 5$ , Ra 1 mg/1.5 cm $\times 2$	8 rad/h 163 h 1304 rad	Died of heart attack 3 days later.	—	—
36 K.A.	61	Hard palate M T3N2M0 Adenoid cystic ca.	Post. wall of the oropharynx Recurrence	Ext. linac X-ray irradiation followed by operation in 1972. Ext. irradiation to pulmonary metastases in 1975. Electron therapy (4800 rad) to the recurrent tumor at the posterior wall of the oropharynx with no effect in Aug. 1976.	Sept. '76	Single implant: 0.66 $\mu\text{g}/3.0 \text{ cm} \times 5$ , 0.68 $\mu\text{g}/1.5 \text{ cm} \times 5$	6 rad/h 146 h 876 rad	Tumor disappeared. Died of general weakness 12 mos. later.	1	1
37 F.T.	72	Middle ear Sq. c. ca.	Middle ear Recurrence	Operation followed by ext. irradiation of 6000 rad in Jan. 1977. Recurrence in Jul. 1977.	Sept. '76	Intracavitary applica- tion: 9 $\mu\text{g}$ (in total)	7.7 rad/h 165 h 1270 rad	Ineffective. Died of general weakness 3 mos. later.	4	3

45 K.Y.	29 M sinus Fibrosa.	Ethmoid sinus Residual	Incomplete operation of the right upper gum followed by intra- cavitory Co-60 $\gamma$ -ray irradiation in 1965. First recurrence was treated in 1975. For second recurrence surgical removal was followed by ext. cyclotron neutron irradiation (1320 rad/12F/25d) at NIRS in Jul. 1977. Re- sidual tumor highly suspected.	Aug. '77 cation by afterloading technique: 0.65 $\mu\text{g}$ cell $\times$ 10, 0.34 $\mu\text{g}$ cell $\times$ 6	Intracavitory appli- cation by afterloading at 1 cm depth 96 h 576 rad	6 rad/h at 1 cm depth 96 h 576 rad	No recurrence	Scoring impossible
CARCINOMA OF THE SKIN								
20 T.A.	72 F	Skin Root of the nose Sq. c. ca.	Skin Recurrence Primary	Surgical removal in May 1975 and Jun. 1976. Electron ir- radiation for re- currence 4750 rad /23F/6w in Aug. 1975.	Oct. '75 0.56 $\mu\text{g}$ cell $\times$ 4	Surface mold: at 3 mm in depth 35 h /3F/2w 525 rad	15 rad/h Ineffective. Surgical removal.	2 3
19 A.K.	23 F	Skin Arm Sq. c. ca. induced by burn	Skin Primary	Electron irradiation 3900 rad/14F/4w in Aug. 1975.	Sept. '75 1.16 $\mu\text{g}/3.0 \text{ cm} \times 5$ , 0.58 $\mu\text{g}/3.0 \text{ cm} \times 5$ , 0.60 $\mu\text{g}/1.5 \text{ cm} \times 5$ (boost therapy)	6 rad/h 168 h 1008 rad	Well controlled for 6 mos. Died of local and distant metastases 7 mos. later.	1 2
29 S.K.	47 M	Skin Scalp Sq. c. ca. induced by burn	Skin Recurrence	Ext. fast neutron (cyclotron) irradia- tion 1600 rad/15F /4.5w in Feb. 1976.	Apr. '76 1.14 $\mu\text{g}/3.0 \text{ cm} \times 5$ , 0.59 $\mu\text{g}/1.5 \text{ cm} \times 5$	8 rad/h 120 h 960 rad	Locally well controlled. Died of brain necrosis 3 mos. later	1 2

Table 2 (3).

Pat. No. & Name	Age	Primary site Stage Histology	Site, Local Previous condition treatment	Date	Method of applica- tion, $\mu\text{g}/\text{active}$ length (cm) $\times$ number of sources	Dose rate, Time, Total neutron dose	Local and side effects, Survival time	Early effect score 2 mos. later	Late effect score 3 mos. later
<b>CARCINOMA OF THE SKIN continued from page 377</b>									
30 A.H.	42 F	Lower lip Sq. c. ca. occurring in lupus erythematosus	Lip Recurrence injection in 1970. X-ray irradiation 500 rad $\times$ 5 in 1970. Electron irradiation 5100 rad/17F/5w in Oct. 1975.	May '76	Single plane implant: 1.12 $\mu\text{g}/3.0 \text{ cm} \times 5$ , 0.58 $\mu\text{g}/1.5 \text{ cm} \times 5$	10 rad/h 95.5 h 955 rad	Recurred 4 mos. later. Removed surgically	1	1
<b>MALIGNANT MELANOMA</b>									
13 K.S.	69 F	Vulva T1N0M0 Malig. melanoma	Vulva Primary	No treatment	Jun. '75	Volume implantation: 0.72 $\mu\text{g}/3.0 \text{ cm} \times 5$ , 0.74 $\mu\text{g}/1.5 \text{ cm} \times 1$	10 rad/h 169 h 1690 rad	Well controlled for more than 1.5 yrs. Died of other causes.	1 1
<b>CARCINOMA OF THE LUNG AND RECTUM</b>									
34 A.M.	35 F	Ethmoid sinus T1N0M0 Malig. melanoma	Ethmoid sinus Postopera- tive (pro- phylactic)	Pre-operative Co-60 4100 rad/20F/23d in Mar. 1976. Ext. fast	Jul. '76	Postoperative intra- cavitory irradiation (ethmoid sinus) by afterloading technique	8 rad/h 72 h 576 rad	Well controlled. Died of distant metastases 10 mos. later.	1 1
4 Y.Y.	51 F	Rectum Adenoeca.	Perineal region	Radical operation followed by ext. linac X-ray irradia- tion in 1974.	Aug. '74	Double plane implant: (Ra 14 mg, Cf 11.9 $\mu\text{g}$ ) Ra: 2 mg/3 cm $\times$ 5 1 mg/1.5 cm $\times$ 4 Cf: 1.83 $\mu\text{g}/3.0 \text{ cm} \times 5$ 0.92 $\mu\text{g}/1.5 \text{ cm} \times 3$	Ra side: n: 0.7 rad/h : 37 rad/h Cf side: n: 11 rad/h : 9.5 rad/h 192 h	Well controlled, died of generalized metastasis 4 mos. later. Biological effects of both sources were compared. Ra and Cf were implanted in inguinal skin area in order to determine the relative RBE of skin response.	1 1

8 T.A.	58 Lung M T2N0M10 Sq. c. ca.	Supraventricular lymph node metastasis. Residual mass of 4 × 3 × 3 cm tumor causing moderate neuralgia extending to the arm.	Ext. linac X-ray irradiation to the supraventricular lymph node	Dec. Double plane implant: '74 0.82 µg/3.0 cm × 5, 0.84 µg/1.5 × 3	7.5 rad/h 68 h 500 rad	Tumor decreased in size and pain disappeared. Living 3 yrs. without recurrence at this region.	2 2
46 S.Y.	39 Lung M T3N0M0 Sq. c. ca.	Left main bronchus tumor Residual tumor	Ext. linac X-ray irradiation of 8000 rad to the left hilar mass in Jun. 1977. Effect was poor.	Aug. Intrabronchial application by remote afterloading technique: 12.8 µg Tube × 1 5F/4w poor.	40 rad/h (at the bronchial wall), 6h/5F/4w 240 rad	Moderately effective.	2 3
<b>CARCINOMA OF THE ESOPHAGUS</b>							
14 F.T.	73 Esophagus F T2NXM0 Sq. c. ca.	Thoracic esophagus Recurrence Nov. 1974.	Ext. irradiation 6250 rad/25F/9w in	Jul. '75 Intracanalicular; 2 tandems containing 3 × 0.58 µg cells each	3 rad/h (at a point of 0.5 cm from center of the tube) 1.6 rad (at 1.0 cm) 22h/3F/2w 66 rad	Ineffective. Died after 8 mos.	3 4
15 T.I.	57 Same as M above T2NXM0	Thoracic esophagus Recurrence Jun. 1974.	Ext. irradiation 7000 rad/30F/8w in	Jul. '75 Intracanalicular; 2 tandems containing 3 × 0.58 µg cells each	1.6-3 rad/h 44h/3F/2w 32 rad	Suppressed progression for 8 mos.	3 4
17 S.K.	73 Same as M above T2NXM0	Thoracic esophagus Primary	Ext. irradiation 5800 rad/25F/6w in Jul 1975.	Aug. '75 Intracanalicular; 2 tandems containing 3 × 0.58 µg cells each (boost therapy)	1.6-3 rad/h 21h/3F/2w 63 rad	Ineffective. Died after 4 mos.	2 4
16 T.I.	71 Same as M above T2NXM0	Thoracic esophagus Primary	Ext. irradiation 6900 rad/23F/12w in Apr. 1970.	Jul. '75 Intracanalicular; 2 tandems containing 3 × 0.58 µg cells each (boost therapy)	1.6-3 rad/h 39h/4F/7w 117 rad	Ineffective. Died after 7 mos.	2 4

Table 2 (4).

Pat. No. & Name	Age	Primary site Stage	Site, Local condition	Previous treatment	Date	Method of applica- tion, $\mu\text{g}/\text{active}$ length (cm) $\times$ number of sources	Dose rate, Time, Total neutron dose	Local and side effects, Survival time	Early effect score 2 mos.	Late effect score 3 mos. later
CARCINOMA OF THE ESOPHAGUS, continued from page 379										
18 K.K.	62	Same as F above T2N XM0	Thoracic esophagus	Ext. irradiation 6000 rad/23F/6w in Jun. 1975.	Aug. '75	Intracanalicular: 2 tandems containing $3 \times 0.48 \mu\text{g}$ cells each (boost therapy)	1.6-3 rad/h 39h/4F/7w 117 rad	Recurred after 3 mos. Second intravesophageal irrad. Died 14 mos. later.	1	3
31 K.S.	55	Same as M above T2N XM0	Thoracic esophagus	Ext. irradiation 5000 rad/25F/6w in Mar. 1976.	May '76	Intracanalicular: 2 tandems containing $3 \times 0.52 \mu\text{g}$ cells each (boost therapy)	1.6-3 rad/h 52 h/2F/5w 156 rad	Ineffective. Died 3 mos. later	3	5
25 T.K.	71	Same as M above T2N XM0	Thoracic esophagus	Ext. irradiation 5400 rad/27F/5.5w in Nov. 1975.	Jan. '76	Intracanalicular: 2 tandems containing $3 \times 0.52 \mu\text{g}$ cells each (boost therapy)	1.6-3 rad/h 71h/3F/12w 213 rad	Ineffective. Died 10 mos. later	2	4
35 S.U.	65	Same as M above T2N XM0	Same as above	Ext. irradiation 6000 rad/20F/7w in Jun. 1976.	Aug. '76	Intracanalicular: 5.1 $\mu\text{g}$ (in total) (boost therapy)	8-15 rad/h at a point of 1.0-0.5 cm from center of the tube 125 h 10000-18700rad	Ineffective. Died 10 mos. later.	2	3
39 K.K.	76	Same as M above T2N XM0	Same as above	Ext. irradiation 6020 rad/29F/7w in Sept. and Oct. 1976.	Jan. '77	Intracanalicular; Same as above	8-15 rad/h 17 h 116-255 rad	Ineffective. Died 7 mos. later	2	3

## CARCINOMA OF THE CERVIX UTERI

9	54	Uterine cervix	Vaginal stump	Radical operation in 1972. Vaginal stump recurrence in 1974.	Mar. '75	Intracavitory surface mold: a) First course 19.8 $\mu\text{g}$ (in total)	12 rad/h 41 h 492 rad	Ineffective. Died of cancer 1.9 yrs later.	3	3
T.T.		T2N <sub>1</sub> M <sub>0</sub>	Recurrence	Treated by Radium.	Apr. '75	b) Second course 13.6 $\mu\text{g}$ (in total)	9.4 rad/h 12 h 113 rad			
Sq. c. ca.					May '75	Volume implant (left parametrium) 1.53 $\mu\text{g}/3.0 \times 5$	15 rad/h 144 h 2160 rad			
11	50	Uterine cervix	Cervix and parametria	Linac X-ray and intracavitory Co-60 $\gamma$ -ray irradiation in May 1974. Intracavitory Co-60 $\gamma$ -ray irradiation for recurrence in Nov. 1974.	May '75	Intracavitory application: 1.44 $\mu\text{g}/3 \text{ cm} \times 5$ , 0.75 $\mu\text{g}/1.5 \times 5$ for tandem, 0.61 $\mu\text{g}$ cell $\times$ 6 for copostat	3 rad/h 75 h 225 rad	Ineffective. Parametritis continued. Died of cancer 8 mos. later.	5	5
J.Y.		T3bN <sub>1</sub> M <sub>0</sub>	Recurrence		Vol. implant (both parametria) by after-loading technique: 0.6 $\mu\text{g}$ cell $\times$ 6, 1.44 $\mu\text{g}/3 \text{ cm} \times 5$ , 0.74 $\mu\text{g}/1.5 \times 5$	5 rad/h 192 h 960 rad				
A.M.	65	Uterine cervix	Endometrium and cervix	Linac X-ray and intracavitory Ra irradiation in 1970. Intracavitory cecum irradiation in Jan. 1975.	Nov. '75	Intracavitory application: 1.28 $\mu\text{g}/3.0 \text{ cm} \times 5$ , 0.66 $\mu\text{g}/1.5 \text{ cm} \times 5$ for tandem, 0.55 $\mu\text{g}$ cell $\times$ 6 for copostat	3 rad/h (point A) 6 rad/h to the target area, 96 h/4F/2w 576 rad	Tumor regressed markedly. Recurred after 5 mos.	1	1
		Well diff. Adenoca.			Jul. '76	Same as above	10 rad/h to the target area, 96 h/4F/8w 960 rad	Tumor regressed again but recurred. Further course of $^{223}\text{Ra}$ treatment. Living with cancer more than 2 yrs.		

Table 2 (5).

Pat. No. & Name Sex	Age	Primary site Stage, Histology	Site, Local condition	Previous treatment	Date	Method of applica- tion, $\mu\text{g}/\text{active}$ length (cm) $\times$ number of sources	Dose rate, Time, Total neutron dose	Local and side effects, Survival time	Early effect score 2 mos. later	Late effect score 3 mos. later
CARCINOMA OF THE CERVIX UTERI, continued from page 381										
22 F.Y.	65	Uterine cervix T1bNXM0 Well diff. Adenoa.	Primary	No treatment	Nov. '75	Intracavitory applica- tion: 1.28 $\mu\text{g}/3.0 \text{ cm} \times 5$ , 0.66 $\mu\text{g}/1.5 \text{ cm} \times 5$ for tandem, 0.55 $\mu\text{g cell} \times 6$ for copostat	3 rad/h (point A) 144h/6F/4w	Well controlled. Living without disease for more than 2 yrs.	1	1
23 F.N.	42	Uterine cervix T3bNXM0 Well diff. Adenoa.	Primary	No treatment	Nov. '75	Same as above	3 rad/h (point A) 144 h/6 F/4 w 432 rad	Reurred 6 mos. later. Salvaged by operation.	1	3
24 K.S.	62	Uterine cervix T3bNXM0 Well diff. Adenoa.	Primary	No treatment	Jan. '76	Same as above	Same as above	Well controlled. Solitary pulmonary metastasis was removed by operation 1 yr. later. Local recurrence occurred 1.5 yrs. later.	1	1
38 T.M.	62	Uterine cervix T2bNXM0 Sq. c. ca.	Cervix Recurrence	Ext. linac X-ray and intracavitory Co-60 $\gamma$ -ray irradiation in Jan. 1973. Recur- rence in 1976.	Jan. '77	Intracavitory applica- tion: 0.92 $\mu\text{g}/3 \text{ cm} \times 5$ , 0.50 $\mu\text{g}/1.5 \text{ cm} \times 5$ for tandem, 0.4 $\mu\text{g cell} \times 6$ for copostat	3 rad/h (point A) 120h/5F/3m 460 rad	Reurred 2 mos. later. Second $^{223}\text{Ra}$ treatment started in Aug. 1977.	4	—

40	57	Uterine cervix	Cervix and corpus	Ext. mixed beam ir- radiation (X: 2380 rad/13F/30d + n: 640 rad/8F/30d to the whole pelvis, then X: 340 rad/2F/5d + n: 240 rad/3F/10d with central shielding) and intracavitory Co-60 γ-ray 1800 rad/3F/ 10d to point A at NIRS in Jun. 1976. Recurrence in Feb. 1977.	Mar. Intracavitory appli- cation: '77 0.86 μg/3.0 cm × 5, 0.50 μg/1.5 cm × 5 for tandem, 0.7 μg cell × 7 for corpositat	3 rad/h (point A) 72h/3F/2w 216 rad Ineffective.	Recurrent 3 mos. later. Given $^{223}\text{Cf}$ irradiation by remote controlled afterloading technique in Jul. 1977.	2 4
48	59	Uterine corpus	Vaginal stump	Incomplete hys- terectomy in Jul. 1975. Whole pelvis linac X-ray irradia- tion followed by intracavitory Ra treatment in Mar. 1977. Recurrence in Jun. 1977.	Aug. Intracavitory irradia- '77 tion by remote afterloading: 12.5 μg tube × 2, mold: 0.65 μg cell × 10	6 rad/h at 1 cm depth 16h/2F/3w 6 rad/h at 1 cm depth 30sh/5F/3m 1920 rad	Marked mucositis Recurrence 5 mos. later.	1 1
44	63	Uterine cervix	Vaginal stump	Operated 30 yrs. ago for uterine cervix cancer. Recurrence in 1976. Ext. linac X-ray and intra- cavitory Co-60 γ-ray irradiation in Jul., Oct. 1976 and Mar. 1977.	Jul. Intracavitory irradia- '77 tion by remote afterloading: 12.8 μg tube × 2	6 rad/h at 1 cm depth 31h/5F/3w 186 rad	Recurrent 3 mos. later. Intracavitory $^{223}\text{Cf}$ surface mold irradiation was given in Nov. 1977.	2 4

Local control was achieved in one case of recurrent rectal carcinoma in the perineal region (Case 4).

### 3. Overall results:

It is pointed out that good local control of score 1 was achieved in 23 out of 44 cases as summarized in Table 4.

No significant complication was encountered except in one case (Case 33), which developed deep ulceration in the mouth floor after irradiation of 710 rad of neutron. This dose was considered not to be excessive, however.

The relationship between delivered neutron dose ranging from 500 to 2800 rad to the tumor and local response is shown in Fig. 1. Neutron dose of more than 600 rad was necessary to eradicate the disease as reported.<sup>3)4)5)6)</sup> No severe mucosal damage was observed even when the delivered dose exceeded 1500 rad except above one case.

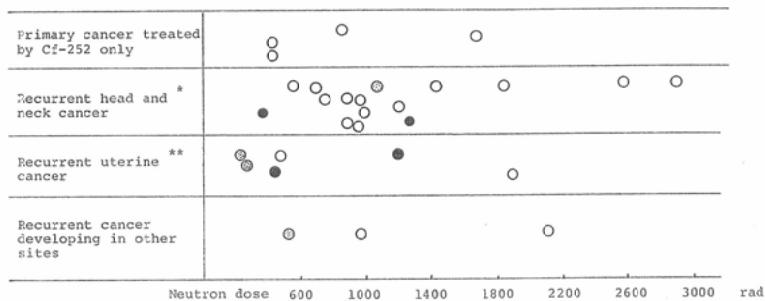


Fig. 1. Relationship between neutron dose and local tumor response by early effect score.  
 (○ score 1, □ score 2-3, ■ score 4-5)

Boost therapy cases are excluded.

\*One case of unknown delivered dose and one case dying of other causes are excluded.

\*\*One case of unknown delivered dose is excluded.

Case Report

Some of the first 10 cases, which had been treated from March 1974 to March 1975, were presented in detail in the first report.<sup>1)2)</sup> The following interesting cases are added from the remaining 34 cases.

**Case 7.** N.M., 51 year old female, carcinoma of the tongue, Recurrent case, squamous cell carcinoma

Radium needle implantation was made for the T2N0M0 tongue cancer in 1970, which recurred in September 1974. Operation was refused. Single plane implantation was made for 168 hours in the left lateral border of the tongue as shown in Fig. 2. Thirteen  $^{252}\text{Cf}$  needles were used, consisting of 3 needles of 1.75 ug/3.0 cm, 5 needles of 0.86 ug/3.0 cm and 5 needles of 0.87 ug/1.5 cm. Dose distribution is shown in Fig. 2. A neutron dose of more than 1800 rad was delivered to the tumor. Severe mucositis which was observed is considered to be due to relatively high dose and large volume irradiation, but no ulceration developed. The patient has been in good health without any symptoms for more than 3 years.

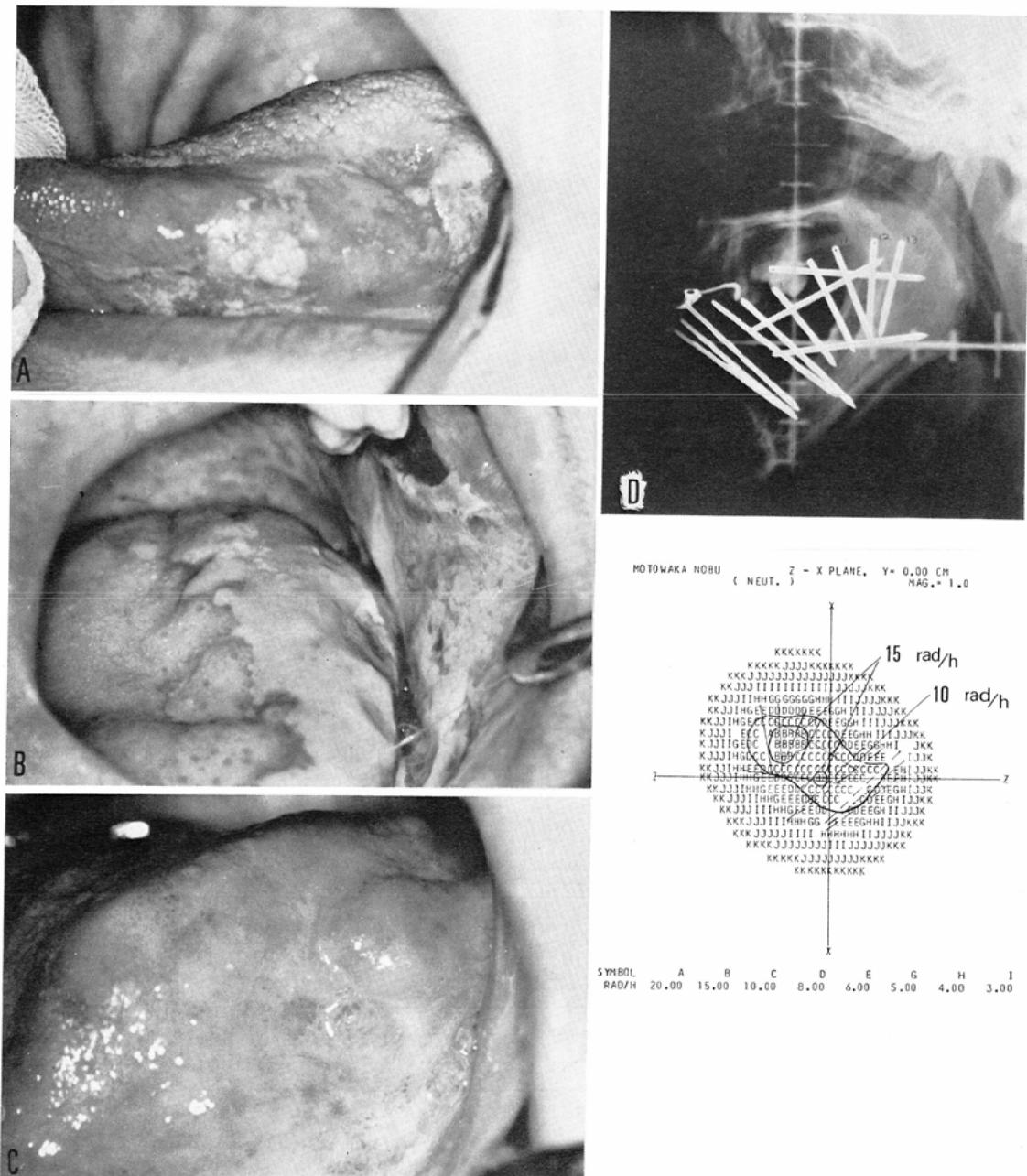


Fig. 2. Case 7. Recurrent tongue cancer. A: Before  $^{252}\text{Cf}$  treatment. Recurrent foci were seen spreading from the anterior to posterior border of the left lateral portion of the tongue. B: 14 days after removal of  $^{252}\text{Cf}$  needles. Marked mucositis was observed. C: One year after treatment. Tongue is cured completely and is soft and smooth. D: Positioning film of the  $^{252}\text{Cf}$  needling. E: Areal dose distribution on the X-Z plane.

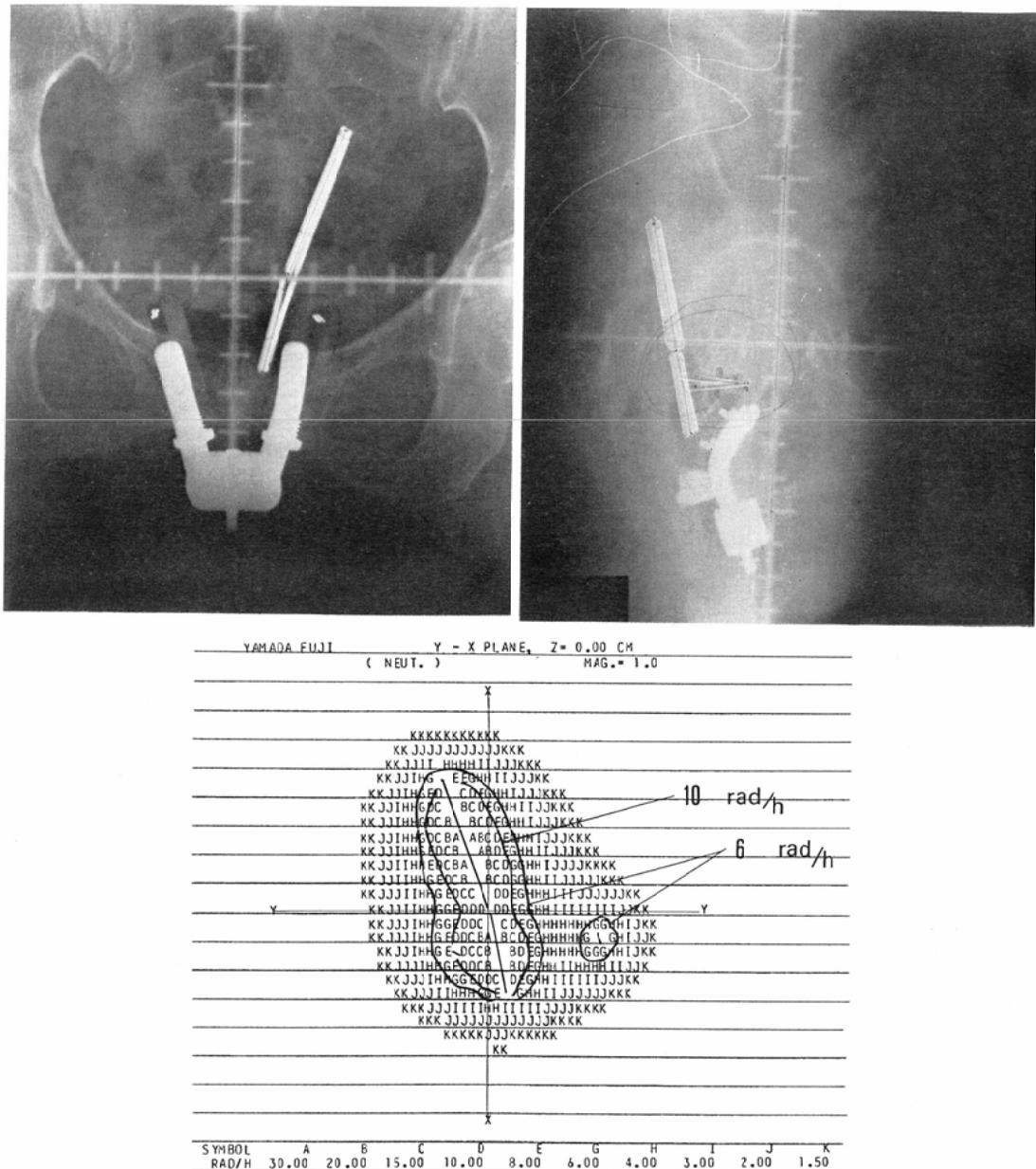


Fig. 3. Case 22. Primary uterine cervix cancer with papillary adenocarcinoma. Positioning films (frontal and lateral) and areal dose distribution on X-Y plane of the intracavitary application of  $^{252}\text{Cf}$  sources.

**Case 8.** T.A., 58 year old male, carcinoma of the lung, T1N0M1b, Primary case, squamous cell carcinoma.

The patient complained of cough and right supraclavicular mass measuring  $4 \times 3 \times 3$  cm in size in September 1974. Chest X-ray showed right hilar mass. External X-irradiation of 6000 rad in 7

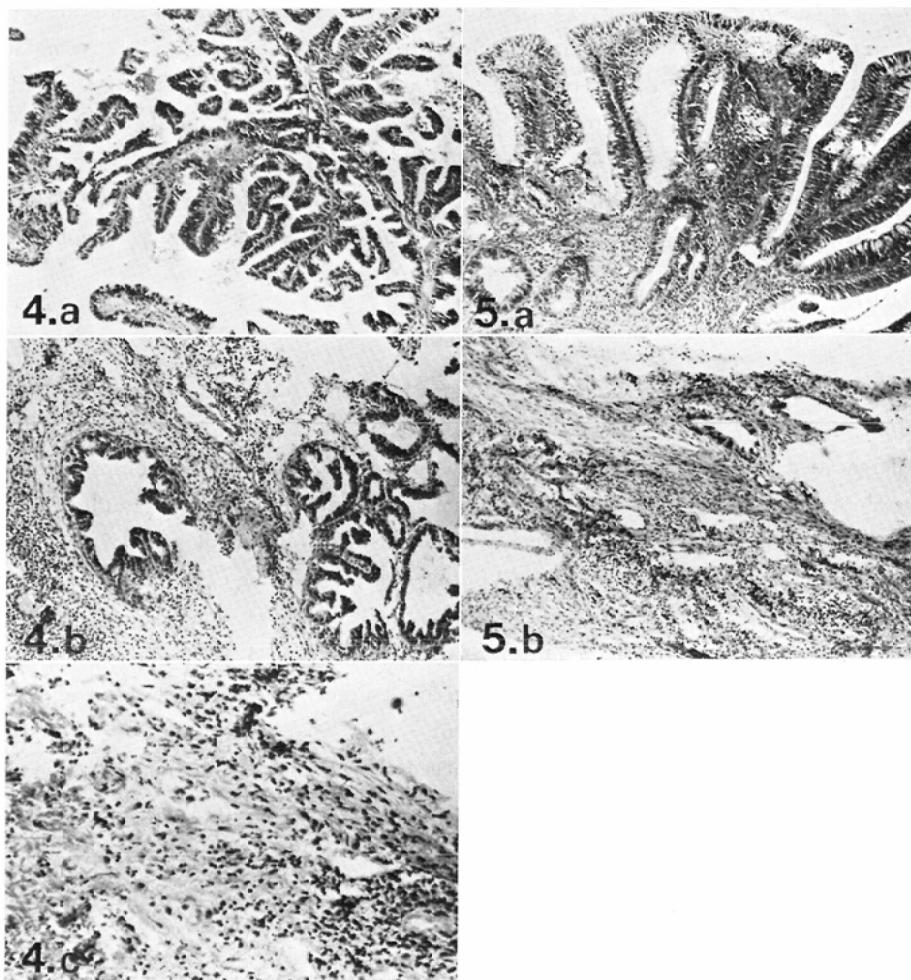


Fig. 4. Case 22. (same patient as described in Fig.3) Papillary adenocarcinoma of the uterine cervix. 4.a: Prior to  $^{252}\text{Cf}$  treatment (H.E.  $\times 500$ ). 4.b: Two days after the 1st session of  $^{252}\text{Cf}$  intracavitary irradiation for 24 hrs. Almost no change was observed. 4.c: Two days after the 3rd session of the treatment. No cancer cells could be seen.

Fig. 5. Case 23. Primary uterine cervix cancer with papillotubular adenocarcinoma. 5. a: Prior to  $^{252}\text{Cf}$  treatment. 5. b: Seven days after the 2nd session of  $^{252}\text{Cf}$  intracavitary irradiation for 24 hrs. Marked radiation effect with tiny degenerative cancer foci can be seen. (Figs. 4 and 5 were provided by the courtesy of Drs. Masubuchi and Kubo, Department of Gynecology, Cancer Institute Hospital)

weeks was given to the primary and supraclavicular tumor. Double plane implantation of  $^{252}\text{Cf}$  needles (0.82 ug/3.0 cm  $\times$  5, 0.84 ug/1.5 cm  $\times$  3) was made in November 1974, because of the poor effect of X-irradiation to the supraclavicular mass. Calculated neutron dose of 500 rad was given in 68 hours. The tumor decreased in size and severe neuralgic pain radiating to the right upper extremity disappeared. The patient has been well without symptoms for more than 2 years and 9 months.

**Case 22.** F.Y., 65 year old female, T1bNXM0, Primary case, carcinoma of the uterine cervix.

$^{252}\text{Cf}$  sources were applied intracavarily in November 1975 as shown in Fig. 3. As no standard sources were available,  $^{252}\text{Cf}$  needles were bundled to make 3 sources; 1 tandem source consisted of 9.7 ug of  $^{252}\text{Cf}$  and 2 corpostat consisted of 1.65 ug of  $^{252}\text{Cf}$ , respectively. Calculated dose distribution shown in Fig. 3 was delivered for 144 hours/6F/6 weeks. External X-irradiation of 4500 rad was delivered to the parametrium using a center splitter. A remarkable response was observed histologically as shown in Fig. 4. The patient has been well for more than 2 years. Another example (Case 23) of marked histological effectiveness is shown in Fig. 5.

### Discussion

As shown in Table 4, it should be noted that score 1 response was achieved in all 4 radioresistant cases primarily treated by  $^{252}\text{Cf}$  only, which consisted of one case of malignant melanoma and 3 cases of well differentiated papillary adenocarcinoma of uterine cervix. In the boost therapy group, score 1 response was obtained in 1 out of 7 cases of esophageal cancer and in 1 of 3 cases of other cancers.

In the recurrent cases, score 1 response was obtained in 13 out of 18 cases of head and neck cancer including the cases of tongue cancer, in 2 out of 7 cases of uterine cancer, in none of 2 cases of esophageal cancer, in one of 2 cases of skin cancer and in one case of rectal cancer (Table 4).

In total, good local control corresponding to score 1 was achieved in 23 out of 44 cases. In 2 cases it was impossible to score, because one had received surgery prior to application and the other died of intercurrent disease shortly after the treatment.

Intracavitary boost irradiation for esophageal cancer has been unsuccessful, because of the advanced stage of these cases exceeding the indications for this modality of irradiation.

It is concluded that favorable results can be expected in most cases of head and neck cancer, malignant melanoma (primary) and adenocarcinoma of the uterine cervix, which are radioresistant cancers. Interstitial application for tongue and mouth base cancers, either primary or secondary, is considered to be promising, because of the higher control rate and lesser injury to the mandibular bones with no evidence of necrosis, due to lesser neutron absorption than X-ray. Among our cases no case of bony necrosis has been encountered so far. No unusual skin reactions or severe delayed changes has been reported by the American or Europeang group.<sup>3)(4)(5)(6)</sup>

The optimum neutron dose and clinically useful values of RBE remain to be determined in the future for various histological types and local clinical conditions using a larger number of cases.<sup>3)(4)(5)(6)</sup> Tentatively, an RBE value of 6 was adopted in this study.

The foregoing observations were obtained under phase I study between March 1974 and August 1977, and further detailed clinical observation and randomized trial are considered necessary in the future. We feel in view of the overall results that  $^{252}\text{Cf}$  brachytherapy is as good as or considerably better than  $^{226}\text{Ra}$  therapy with higher therapeutic advantage.

In 1977, we designed and constructed a remote afterloading machine so that these sources could be handled safely.<sup>7)</sup> This remotely controlled afterloading machine is provided with three channels connected to  $^{252}\text{Cf}$  tubes for intracavitory use in the uterine cervix. Furthermore, each of the three channels can be used individually according to varying conditions, permitting intracavitory

irradiation for eradicating residual tumors inside the esophagus or bronchus following external irradiation. The details of the machine were reported by Dr. Onai et al<sup>7</sup>. Two cases were treated with the use of this machine as shown in Table 2 (5) (Cases 44 and 48). Clinical experience with <sup>252</sup>Cf seed assemblies for manual afterloading will be described in the next report.

### Summary

This report summarizes our clinical experience at the Cancer Institute Hospital from March 1974 to August 1977 with the use of small sources of Californium-252 on 44 cases consisting of 14 primary and 30 secondary cases. Radioresistant tumors of recurrent tumors developing from irradiated and/or operated scars were submitted to this therapy. Cf-252 needles, seeds and tubes were used as implants, surface molds and intracavitary application for various sites and conditions, either singly or combined with X-ray or <sup>60</sup>Co  $\gamma$  rays. The results can be summarized as follows.

1. Good local control corresponding to score value of 1 was achieved in 23 out of 44 cases, which indicates that further continued clinical trial will be encouraging.
2. Most cases of head and neck cancer, skin cancer, malignant melanoma, papillary adenocarcinoma of the uterine cervix cancer have responded favorably to neutron dose of over 600 rad. On the contrary, carcinoma of the esophagus unfortunately responded poorly to intracavitary boost therapy. This will need further clinical investigation.
3. No severe side effect has been observed so far, suggesting a higher therapeutic advantage than <sup>226</sup>Ra.

### Acknowledgement

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