Present Status of Treatment of Malignant Neoplasms by ^{252}Cf Brachytherapy

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悪性腫瘍に対する ^{252}Cf 小線源治療の現時点における評価

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1976年より1983年6月までに352例の悪性腫瘍が ^{252}Cf 小線源によって治療された．うち，子宮頸癌は99例（腟高度浸潤を含めると101例）であった．皮膚，扁桃，舌，口底，歯肉，尿道などには組織内照射が有効であった．子宮頸癌に対する腔内照射は，腔内照射を先行させ，外部照射（光子）はあとで行う方法がよく（71/76, Table 3），逆のスケジュールでは不良（7/23, Table 3）であった．腔内照射を最初に行うことは低酸素状態の癌細胞の多い時期に照射することであり，速中性子線効果が強く出るためである．粘膜悪性黒色腫，悪性glioma にも有効であったが，食道，肺癌には効果が少なかった．

自験例に諸家の報告をあわせてみると，^{252}Cf は初回治療例に対しては153/172（89%），Table 3,（但し，外部照射（光子）先行群は除く）で，再発例に対しては77%の完全消失（CR）率が得られている．再発例は10cm 以下でないと効が少い．

子宮頸癌治療による直腸障害は初期のトライアル群で3/59，5年生存者29例のうちでは第1度のものが1例のみ（Table 5）で軽度であった．

Summary

This report reviews experience and reported observations for ^{252}Cf treatment of advanced cancers in a variety of sites. Good local tumor response was observed for interstitial ^{252}Cf (NT-only) or early ^{252}Cf combined with high dose photon therapy. The least effectiveness was observed with high dose photon therapy followed by ^{252}Cf. Early implant therapy was developed in Lexington to direct anti-hypoxic therapy against tumor hypoxia when the maximum amount of hypoxic tumor was present. Treatment of bulky, localized primary tumors of advanced stage led to long term local control and cure for selected categories of cancer for 2—5 years or more. Treatment of recurrent or metastatic tumors led to frequent local tumor clearance but failures were frequent from distant and further metastatic spread. Most primary tumors of the female genital tract, skin, tonsil, tongue, floor of mouth, alveolar ridge, urethra and mucosal melanoma responded well. Surprisingly, malignant glioma responded well by dramatically improved performance status of patients with

hemispheric brain tumors implanted with ^{252}Cf. Metastatic, persistent or recurrent tumors of the oral cavity, neck lymphadenopathy, breast and rectum also responded well. Only the esophagus and lung tumors have been reported to respond poorly to ^{252}Cf boost therapy. The overall tumor clearance rate for primary tumors was approximately 90% and for recurrent tumors was approximately 77%, but was best for the smaller, lower stage primary tumors about 4—10 cm in diameter. Five year cures for primary low stage cervix tumors was 80—90%, and 37% for advanced stages in the earliest experience.

Introduction

After the initial preparation of Californium by Seaborg and associates[1], further developments and interest in the isotope did not emerge until it was found that ^{252}Cf spontaneously emitted fast neutrons with a near fission spectrum of energies. In 1965, Shlea and Stoddard[2] postulated that ^{252}Cf could be used for clinical radiotherapy. This led to early clinical trials, but after the early exploratory studies[3][4][5], all the U.S. and European centers gave up the trials because they regarded its use as hazardous with excessive risks to personnel, physicians, and environment without a corresponding advantage for cancer therapy. Since the early trials involved very few patients, it is of interest to examine the evidence and experience accumulated since then and to reassess those preliminary conclusions. Interestingly, extensive research has been carried out independently in three widely separated locales in very different parts of the world[5][7][8][9]. This is similar to the early work with ^{226}Ra which was done in Paris, Stockholm and Manchester. The corresponding sites for clinical studies of ^{252}Cf have been in Lexington (U.S.A.), Tokyo (Japan) and the USSR, mostly in Obinsk. The largest experience of approximately 390 cases has been carried out in Lexington, Kentucky. It is the purpose of this paper to review the clinical responses of all reported cases in order to assess the potential usefulness of ^{252}Cf for clinical cancer therapy.

For this review, the tumors are divided into two categories, i.e. 1) Primary tumors, where neutron brachytherapy (NT) was the initial and major mode of definitive therapy, and 2) Recurrent tumors, where NT was only done after surgical or radiotherapy had already failed. The clinical experience in successfully clearing the tumor site and the associated complication frequency with NT treatment is reviewed. The tumor clearance frequency is emphasized and is the frequency with which complete tumor regression (CR) was achieved. 100% tumor regression indicates highly effective tumor destruction which with primary tumors can lead to long term tumor control. For recurrent tumors, tumor clearance usually represents a temporary arrest of local tumor progression.

Method of Treatment

Three types of NT treatments have been used: 1) neutron brachytherapy alone (NT-only),[3][4][5][7]; 2) photon or neutron beam therapy followed by NT[3][4][7]; and 3) early NT followed by photon therapy[10][11]. The early NT schedule devised in Lexington[10] represented a novel approach where NT, which is effective against hypoxic tumor[10][12] was directed at, and applied when the tumor was large, bulky and presumed to be maximally hypoxic. Since this concept was tested and developed in Lexington, the reviewed clinical experiences were carried out in largely one center[11]. The other major ^{252}Cf therapy experiences were at the Japan Cancer Institute Hospital (JCIH)[7], Keio[8] and in the USSR at Obinsk, Kiev and Moscow[13]. The balance of the cases, representing only a small number, were done at the Oxford Hospital[4], M.D. Anderson Hospital (MDAH)[3], Memorial Sloan Kettering Cancer Center (MSKCC)[5] and by the U.S. Radiation Therapy Oncology Group (RTOG)[14]. Several types of therapy were utilized:

- *Type 1 therapy was NT-Only.* It involved the implantation of ^{252}Cf sources into tumors with treatment to estimated therapeutic levels with NT alone.
- *Type 2 therapy was Photon therapy followed by NT (boost treatment).* This was given using large photon doses with ^{60}Co, linear accelerators or other x- or gamma ray radiation machines. In a few cases, neutron

beam therapy was used first followed by NT implantation therapy. Boost therapy is directed at the residual tumor core (and hypoxia).

• *Type 3 therapy: NT followed by Photon therapy.* This concept was devised and studied in Lexington and utilized ^{252}Cf before external photon therapy or very early in the treatment course. NT was given early to treat hypoxia of tumors at a time when tumor bulk and hypoxia were maximal.

NT often delivered partial therapeutic dose and the balance was given with high doses of photon therapy.

The relationship $D_{req} = RBE_n \cdot D_n + RBE_{gamma} \cdot D_{gamma}$ represents a means of understanding the studied treatment doses where req = rad equivalent, RBE_n = radiobiological effectiveness for the neutron component of dose, D_n, $RBE_{gamma} = 1.0$ and D_{gamma} = gamma dose. The important component is the neutron dose and that which is responsible for the unique efficacy of ^{252}Cf in clearing hypoxic tumors. The RBE is also high for neutron radiation. Many different values for RBE have been used by the different investigators and vary from 2—7.5. This paper will not attempt to review all those values used for RBE_n (see Maruyama *et al.*[6]) I will focus instead on the clinical observations which have resulted form the application of ^{252}Cf for clinical cancer therapy.

This report will focus on the endpoint of tumor clearance, which as noted elsewhere represents total or subtotal tumor destruction and dissolution. In an effort to understand this endpoint, Maruyama and Muir developed a logistic tumor regression model[15] to desctibe various parameters of tumor clearance. These included lag time for response, clearance frequency, half tumor clearance period (TCP_{50}), clearance rate, tumor regrowth time, and local control frequency.

Clinical Results of ^{252}Cf for Tumor Therapy

From a review of existing reports, it is possible to assess efficacy of ^{252}Cf in tumor radiotherapy of advanced primary or recurrent radioresistant tumors. From published reports, sufficient detail has been published to assess its effectiveness in achieving local tumor response based upon reports by the Lexington group[10][11][15][16][17], the JCIH group[7], the Oxford group[4], the MDAH group[3], and the MSKCC group[5]. Additional reports from Keio[8], a case report from the American Oncologic Hospital and the U.S. RTOG[14] were useful. Vtyurin[9] reported treating 248 cases of which 103 are described by site, i.e. oral cavity, lower lip, skin and abdomen, and 66 as primary and 37 as persistent or recurrent, but without details on treatment. Vtyurin[13] has prepared a review covering the early clinical experience in the USSR. The largest single experience with primary tumors has been accumulated by Maruyama at the University of Kentucky Medical Center in Lexington, U.S.A. and their results have resurrected interest in neutron brachytherapy. All other

Table 1 Approximate number of patients treated with ^{252}Cf**

Autor	Patient number	Country	Reference
Maruyama, 1983	352*	(Lexington)U.S.A.	17)*
Vtyurin, 1982	248	(Obinsk)USSR	13)
Tsuya *et al.*, 1979, (Sugiyama & Kaneta 1983)	44 (117)†	Japan	7)
Yamashita *et al.* 1982	32 (100)°	Japan	8)
Paine *et al.*, 1974	21	England	4)
Castro *et al.*, 1973	19	(MDAH)U.S.A.	3)
Vallejo *et al.*, 1980	10	(MSKCC)U.S.A.	5)
Others	Small number (~904)	USA and USSR	14)

*This number is 389 through February 1984
†Gann No Rinsho 29: 702, (1983)
°Private Communication
**Updated February 1984

series have tested mostly metastatic lymph node disease or persistent or recurrent tumors where only palliative results would be expected and in fact was observed. From the data in Table 1, over 904 patients have been treated throughout the world with ^{252}Cf.

Dose response was studied by Seydel[14] who reviewed studies of metastatic tumor in lymph node response with ^{252}Cf dose. At 490—645 cGy 2/9 or 22% of tumors responded; with 670—775 cGy, 5/9 or 55% responded; with doses of 805—900 cGy, 9/12 or 75% responded; with doses of 1100—2855 cGy, the frequency of tumor clearance did not increase but the frequency of complications did. Since the equivalent biological doses for NT-only can be estimated by an RBE $\cong$ 6, the dose-response data reported can be judged to be similar to that observed for equivalent photon doses (RBE for skin and hypoxic tumors are $\cong$ 5—7).

In the various series, many recurrent or persistent tumors and terminal patients who lived ony a short time were treated. Those tumors were usually treated with NT-only or with delayed implants. Those treated with NT-only implants achieved complete regression (CR) response about 80% of the time. When photon therapy preceded the NT (i.e. delayed boost implant therapy) it appears that CR response was achieved only approximately 40% of the time. When conventional photon brachytherapy preceded photon radiotherapy no similar increase in effectiveness was observed[11].

For cervix cancers, NT-only implants cleared cancers 83% of the time and in 100% of the adequately treated patients at JCIH[7] (Table 2). Where whole pelvis radiation was not added, recurrence from lateral pelvic extension of disease can be expected due to the limited range of the ^{252}Cf neutrons (i.e. about 2—3 cm)[18]. In Kiev, USSR, Pozmonov *et al.*[13] found more rapid response of exophytic tumor with ^{252}Cf compared to ^{60}Co. Vtyurin reported that Abdullaev at Kiev had observed 82% dissolution of cervix and uterine cancers[13]. The best results have been reported from Lexington[10][11] where 90—94% cleared using early NT.

Table 2　Clearance of tumors in various sites with ^{252}Cf neutron brachytherapy and implant times

Anatomic site	Author	CR/Total	Overall clearance frequency (%)	Duration of implant (hrs.)
CERVIX/VAGINA—Primary tumors				
DELAYED NT	CASTRO	4/5 ┐ 11/28	39	39
PT + NT	MARUYAMA	7/23 ┘		7.5
NT-Only	TSUYA	5/6	83	144
NT + PT	MARUYAMA	49/54 ┐ 73/78	94	7.5
	〃	24/29 ┘		(×1—3)
SKIN, HEAD AND NECK, RECURRENCES AND LYMPH NODE METASTASES				
NT-Only	CASTRO	3/4 ┐		69
	TSUYA	13/19		123
	VALLEJO	8/10 ┘ 33/47	70	144—168
	YAMASHITA	9/14 ┘		〃
PT + NT	CASTRO	1/6	16	48
BREAST RECURRENCE				
NT	PAINE	4/4 ┐ 11/12	92	123.5
PT + NT	〃	7/8 ┘		134
ESOPHAGUS, PRIMARY				
PT + NT	TSUYA	0/7	0	52
MELANOMA, MUCOSAL				
NT	CASTRO/TSUYA	4/4 ┐ 5/5	100	96—121
NT + PT	MARUYAMA	1/1 ┘		7.5

NT=neutron brachytherapy;　PT=photon therapy
Sequence indicates schedule in which used
NT-Only indicates interstitial implant only

Table 3 Reported response frequency of primary tumors to ^{252}Cf or photon + ^{252}Cf in a variety of sites

Anatomics site	Sequence	CR/Total	%	Recurrence reported*	Institution
SKIN					
SCC	PT + NT	1/1			OXFORD
SCC	NT	2/2 — 7/8	88		〃
BCC	NT	3/4			〃
BCC	NT	1/1		1/1	MDAH
TONGUE	PT + NT	0/2	0		〃
TONSIL-OROPHARYNX	NT + PT	7/7	100	3/7	LEXINGTON
LIP	PT + NT	2/2	100	1/2	MDAH
ORAL CAVITY	NT	9/14	67		KEIO
LUNG	PT + NT	0/1	0		JCIH
ESOPHAGUS	PT + NT	1/7	14	1/1	JCIH
ALVEOLAR RIDGE	NT + PT	2/2	100		LEXINGTON
CERVIX					
STABE IB	NT-	3/3	100	2/3	JCIH
STAGE IB-IIB	NT + PT	24/24	100	0	LEXINGTON
STAGE IIB	NT + PT	20/21	95	4	〃
STAGE IIIB	NT + PT	27/31	87	18	〃
STAGE I-IV	PT + NT	7/23	30	16	〃
MUCOSAL MELANOMA					
	NT	2/2			JCIH
	NT + PT	1/1 — 5/5	100		LEXINGTON
	PT + NT	1/1			MDAH
VAGINA					
	PT + NT	4/4 — 9/10	90		MDAH
	NT + PT	5/6			LEXINGTON
FEMALE URETHRA					
	NT + PT	3/3	100		〃
CORPUS CARCINOMA	NT + PT	11/11	100		〃
GLIOBLASTOMA MULTIFORME	NT + PT	9/10	90		〃
			153/172 (89%) excluding delayed NT)		

For explanation of abbreviations, see Table 2

*only noted where author noted whether recurrence occurred

For recurrent head and neck tumors or those of skin, or lymph node metastases, NT-only cleared tumors with the following frequencies: MSKCC 80%, Obinsk 78%, MDAH 75%, JCIH 68% and Keio 67% for an average of 78%. For skin cancers of basal or squamous cell type 88% tumor clearance has been reported (Table 3). All mucosal melanomas reported have been cleared locally by NT[3)7)11)]. For skin melanomas, Vtyurin[13)] noted that 5/5 showed response in 4—6 weeks but 3/5 did not show a CR response. Other USSR investigators such as Kozlova *et al.* and Kiseleva and Kvasov noted only limited response[13)]. The efficacy for clearing tumors using NT-only indicates that a sufficient number of neutrons and gamma rays were emitted by ^{252}Cf to destroy the cancer. Masses from recurrent or metastatic breast cancer at Oxford responded in 100% of treated cases[4)].

Interestingly, it has been found that high dose photon therapy done before a delayed NT implant was less effective (Table 2—3). For cervix, both the University of Kentucky and the MDAH observed similar similar response data for primary or recurrent tumors. The results were similar to conventional photon therapy experience[19)]. For primary or recurrent esophagus tumors, JCIH reported a tumor response frequency of 14% (Table 3, 4)[7)]. For recurrent or metastatic lymph node disease, MDAH reported only 16% response[3)]. Oxford noted 67% of metastatic breast disease responded with delayed NT but 100% with NT-only[4)]. This suggests that delayed implant given to masses that have been reduced in size and bulk after high dose photon radiation therapy was less effective in producing tumor control. Beach and Maruyama[20)] postulated a

microdosimetric basis for those observed effects, based upon the relative paucity of the high linear energy transfer events by NT-only without added photon radiation therapy.

The use of early NT followed by photon radiation cleared 94% of primary cervix cancers at Lexington. The significance of tumor clearance becomes evident with later long term control and cure[15]. Tumor clearance after NT was found to be sustained and leads to 5-year disease-free survival and cure[21]. For bulky stage IB-IIB (small) tumors[16] actuarial 5 year cures of 80% were observed and 37% absolute 5-year cures were found for more advanced cancers[16)21]. ^{252}Cf NT was also effective for large oropharyngeal tumors i.e. T4 tonsillar-oropharyngeal primary tumors responded in 100% of treated cases and 67% were long term approximately 2 year survivors or deceased NED of intercurrent disease[22]. 100% of vaginal melanomas and carcinomas responded in the primary site. Corpus carcinoma was remarkably sensitive whether primary or recurrent[23]. 90% of patients with malignant glioblastoma multiforme of the hemisphere of the brain improved in their performance status immediately after brain NT implant therapy and showed decreased size by serial CT scans[24]. Those that were reoperated or rebiopsied showed no residual tumor[25]. Similar results have been reported by Parker *et al.*[25] and Caterall *et al.*[27] for neutron beam therapy. Overall, the tumor response frequency based on all sites and tumors was similar in the U.S.A., Japan, and USSR at the major ^{252}Cf NT therapy projects.

The two important categories of tumors treated were the unfavorable *primary* tumors, where NT represented a treatment aimed at cure, and the other group were *recurrent* tumors. The latter group of tumors had already had radical surgery, heavy conventional radiotherapy or radical surgery and heavy conventional radiotherapy and all these therapies had failed to cure the tumors (i.e. persistent, recurrent or metastatic). The intent of therapy in this group of tumors was *palliative* and to determine whether response occurred. In many of the series, it is likely that there was some selection in the size of tumors treated. The favorable 80% clearance frequency reported suggests that most investigators concentrated on the implantable or smaller tumors. It is difficult to treat massive 10—20 cm tumors with NT implants alone.

In the primary tumor group, it is now clear that not only was CR response achieved but also led to local tumor control and 5-year cures for cervical cancers[16)21]. Thirty-seven percent cures were achieved for high stage disease; 80% cures were achieved for lower stage disease. Thus, cure depended on the type of tumor, the stage of disease at the time of treatment, and it was important that treatment produce tumor response soon after treatment. Unless CR response was observed, less chance for ultimate tumor control and cure was noted. Large and bulky adenocarcinomas and small cell carcinomas of the cervix were found to respond more slowly[11]. From an analysis of the reported experience with cervix cancers (Table 3—4), NT-only cleared 20/26 (77%) of primary cancers; this was reduced to 15/41 (37%) with initial photon radiation and delayed NT; with early NT results were best with 118/131 or 90% of the tumors responding[17]. Complete response for primary tumors could lead to permanent tumor control for low stage disease; for high stage disease, distant metastases or regional failure at sites usually arising 3—5 cm from the sources, i.e. at low dose points, could occur[18]. For many, even in advanced stages, temporary local control was achieved and distant metastases became a prominent failure pattern. Overall, it was found that primary tumors responded with an approximately 89% rate from the reported experience of all clinics (Table 3) when the delayed implant experiences were excluded. The notable exception was the esophagus-lung tumors where tumor response was observed only 13% of the time[7]. Failures in that site may be due to poor scheduling, technically poor implants, or to the basically high virulence of cancers in those sites. Clearly, more research is needed. Vtyurin[13] reported an overall 89/103 (86%) response rate for primary (90%) and recurrent (78%) oral cavity tumors by ^{252}Cf contact therapy. Maruyama *et al.*[24] noted 90% frequency of improvement of at least 3 + in performance status for malignant hemispheric gliomas after NT and radiation[24]. This was in marked contrast to the general experience at Kentucky with photon or chemotherapy and photon radiation reported by Chin *et al.*[28] where the mean survival time was 47—69 weeks, with a steady decline in performance status during and

Table 4 Reported frequency of response for recurrent cancers to ^{252}Cf or photon + ^{252}Cf in a variety of sites

Anatomic site	Sequence	CR/Total	%	Recurred	Institution
SKIN	PT/NBT + NT	2/3	67		JCIH
TONGUE	NT-Only	8/8	100	3	〃
TONSIL	NT + PT	1/1	100	1	LEXINGTON
PAROTID	NT	1/1	100		OXFORD
METASTATIC LYMPH NODES, NECK	NT + PT	1/2			LEXINGTON
	NT	1/1			AOH
	NT	8/10 — 12/18	67		MSKCC
	PT + NT/NT	2/5			MDAH
NECK FROM LARYNX, HYPOPHARYNX	NT	2/4	50		JCIH
MIDDLE EAR, ETHMOID SINUS, HARD PALATE	NBT + NT				
	PT + NT	2/3	67		JCIH
LUNG, METASTASES TO SKIN OR LYMPH NODE	NT	1/2	50		MDAH/JCIH
ESOPHAGUS	PT + NT	0/2	0		JCIH
BREAST METASTASES, SOFT TISSUE	PT + NT, NT	11/12	92		OXFORD
RECTUM	NT	1/1			MDAH
	NT + PT	5/7	75		LEXINGTON
CORPUS CARCINOMA	NT + PT	6/8	75		〃
LIPOSARCOMA	PT + NT	PR 1/1	?		OXFORD
GLIOBLASTOMA MULTIFORME	NT + PT	0/1	0		LEXINGTON
CERVIX-VAGINA	NT, PT + NT	5/7	71 — 7/9	78	JCIH
	NT + PT	2/2	100		LEXINGTON
		67/87	77		
RESPONSE OF TUMORS NOT CLEARLY STATED TO BE PRIMARY OR RECURRENT					
VTYURIN, USSR, ORAL CAVITY		89/103	86		OBINSK
〃 (cited) BREAST, ORAL, SKIN, SOFT TISSUES, VAGINA		7/12	58		MOSCOW
〃 , ABDULLAEV, USSR CERVIX/UTERUS		37/45	82		KIEV

ABBR.: See Table 2
AOH=American Oncologic Hospital; NBT=Neutron beam therapy

after radiotherapy. These response rates which have been observed have not heretofore been reported by radio-oncologists and encourage further research, especially studies focused on advanced *primary* tumor therapy.

The second category of tumor commonly treated in the early experiences were *recurrent* tumors. By a similar analysis (Table 4), the results observed with NT-only noted tumor responses in 41/49 (84%); early NT followed by high dose photon radiation therapy cleared approximately 90%; The least successful schedule was photon therapy followed by delayed NT, and in that schedule, only 7/14 (50%) of the tumors responded. While an overall response frequency of 77% was achieved, almost all will recur locally or distantly or both soon afterwards. Nevertheless, the fact of regular tumor response appears to have been adequately shown. ^{252}Cf is therefore an excellent isotope for local palliative therapy for recurrent tumors. However, repeat local recurrences continue to be a major therapeutic problem. Of the recurrent tumor sites, the oral cavity, head and neck, breast, and GYN tumors were most successfully treated for temporary tumor control. Breast tumors can achieve long tumor control periods because of the variety of effective adjuvant chemotherapeutic and endocrinological therapies available.

While the tumor response rates were excellent, advanced stage disease will still fail frequently in regional and distant sites consistent with the poor prognosis of advanced cancer in any site. The control of

large, bulky tumors without regional spread appeared to be distinctly improved in frequency compared to conventional therapies. The frequency of CR response of bulky tumors allows the potential application of other secondary therapies, specifically surgery and chemotherapy. In general, there was need for more effective systemic therapy to control the distant metastatic disease in patients with advanced stage disease.

A comparison of the treatment times shows that the short (Table 1) implant times of ~7.5 hours was as effective in all comparable sites as the longer and more protracted implant times. Similar or improved response data were noted for cervix, vagina, mucosal melanoma, head and neck, brain and tonsillar-oropharyngeal regions. The short implant times developed in Lexington were equal to or usually superior to the longer implant schedules of 40—168 hours used in the other pilot studies. For example, for cervix and vagina tumors, 76% tumor response was observed at institutions which used implant times of 39—144 hours. At Lexington, 73/78 (94%) cleared their tumors with 1—3 implants of approximately 7.5 hours duration, using the early schedule. for the tonsil-oropharyngeal tumors, the 69—168 hour implants cleared 66% of head and neck tumors (Table 2—4), whereas the short duration oral tube implant used in Lexington cleared 100%[21]. Vtyurin[13] noted 86% response of 103 primary and recurrent oral tumors with contact NT. Mucosal melanomas were controlled equally well by short or protracted implant schedules.

The data of Yamashita *et al.*[8] are of considerable interest as they used doses of 100—130 cGy given in 30 minutes 2—3 times per week at a distance of 1 cm, to a dose of 800—1500 cGy. This was followed by 5000-8000 cGy of linac radiation. 13/18 (72%) of treated cervix tumors cleared and in the head and neck region 9/14 (69%) responded. This led to 60% 1—3 year NED survivors. While these results are excellent, it may be that the RBE of ^{252}Cf was reduced by delivering dose at very rapid rates. Low dose rate photon treatment minimizes γ-contribution to the radiation effects and reduces normal tissue effects.

Discussion

In our experience with ^{252}Cf therapy, we focused on the problem of local control for primary tumors, especially those of advanced stage which could not be easily controlled by conventional therapy. ^{252}Cf implantation was therefore combined with large volume, high dose, fractionated radiation to supplement the local implant therapy[11]. For cervix and GYN tumors, such an approach led to tumor cure[16][21][23] when 5000—6000 cGy was added to the NT implant treatment. Our results show that tumor clearance was critically dependent upon the schedule in which ^{252}Cf was used. It was maximally effective when tumors were large and bulky and NT was scheduled early[10]. Effectiveness was lost when NT was delayed until after pelvic high dose photon therapy[10][11]. With the early NT, tumor response frequency was 90+% for bulky tumors and was regularly observed[10][17]. It was important that radiation isodose be matched to tumor size and dimensions on an individualized basis as geographic low dose can lead to marginal recurrences as has been well documented by Tsuya *et al.*[7], Vtyurin[13] and in our unpublished experience.

One of the most important responses produced by ^{252}Cf was rapid complete tumor regression, an observation reported by us for GYN cancers[1]. This response has now been confirmed by Pozmogov *et al.*[15] who estimated a RBE of 12 for clearance of cervix cancers compared to an RBE of two for mucous membrane reactions. Vallejo *et al.*[5] also reported more rapid resolution of metastatic lymph nodes in the neck with a 50% regression time of 20 days vs. 31 days for ^{192}Ir. Vtyurin[13] reports USSR observations of 70—80% responders in 2—3 weeks after ^{252}Cf vs. 6—7 weeks for conventional radiation. The clearance phenomenon was most striking with the use of early NT, for which we have postulated the importance of scheduling neutron therapy before external irradiation therapy[11].

Although advanced primary cervix tumors of even Stage IIIB size can completely respond by these schedules, we have also learned that there can be a radioresistance of these tumors (10—15 cm in diameter) that can lead to tumor persistence, incomplete tumor response and local recurrence. This resistance we have postulated to be non-hypoxically determined[17] since it was not responsive to NT plus the added hypoxic

Table 5 Frequency of reported complications noted for pelvic radiation using Cf-252 or neutron beam

Location		No. patients	Frequency %	Tumor clearance/ Control† Rate (%)			Reference
Cf-252 trials							
Castro *et al.*	MDAH, USA	0/7	0		80%		3
Tsuya *et al.*	JCIH**, Japan	0/7	0		80%		7
Yamashita *et al.*	Keio, Japan	0/18	0		72%		8
Maruyama *et al.** (Preliminary trial)	Lexington, USA	3/59	5		90%		11
Maruyama *et al.* (Surgery and radiation)	Lexington, USA	1/24 (grade 1)	4		100%		16
Maruyama *et al.** (Absolute 5-yr survivors)	Lexington, USA	1/29 (grade 1)	3.8		37%		21
Kiev institute (cited by Vtyurin††)	Kiev, USSR	1/20	5		82%		13
Neutron beam							
Batterman *et al.*	Netherlands	16/47	34		50%		31, 32
Tsunemoto *et al.*	Japan	18/85	21		77%		30
Morales *et al.* mixed beam only		43	20	NBT°	29%		29
+ radiation active implant		16	30+	Boost	63%	59%	
	MDAH, USA			Mixed	81%		
				NBT	35%		
Parker *et al.*	RTOG, USA	10/57	18+	Boost	56%	58%	36
				Mixed	77%		

*NT + fractionated whole pelvis radiation
**JCIH=Japan Cancer Institute Hospital
°NBT=neutron beam therapy
†Cf-252 workers report clearance frequency; Neutron beam worker report control rate
††248 patients have been studied in the USSR

radiosensitizer, metronidazole, given orally, intravenously and intravaginally during the ^{252}Cf implant (unpublished data). The other problem has been that of distant metastases and these have appeared later in spine, paraortic lymph nodes, lung, skin, brain and other remote sites despite local tumor control. While it is extremely important to debulk the primary tumor site, it is also equally important to develop effective secondary therapies, specifically adjuvant chemotherapy to improve the likelihood of cure for the patient.

While the results reviewed here are early results, it appears that excellent local responses of very advanced and radioresistant or even recurrent/persistent/metastatic tumors was observed by the use of ^{252}Cf. Complications were remarkably low for pelvic radiation compared to neutron beam therapy where severe pelvic complicatins were observed with a frequency of approximately 25%[29)~33)]. From published reports, a low frequency of complications[34)37)] of about 5% has been reported (Table 5). In sites other than the pelvis, less data is available. Tsuya *et al.*[7)] noted protracted mucositis of the oral mucosa where NT dose was delivered to previously heavily irradiated tissues in which surgery had also been done. The low frequency of adverse side effects appear to be due to the low energy fast neutron, its limited range in tissue, the rapid fall off in dose with distance from the sources, and the large proportion of gamma dose[18)]. The confined neutron dose in tumor and limited normal tissue dose leads to a high therapeutic gain factor. Thus, the high RBE in hypoxic tumor was greatly amplified by the relatively low RBE in oxygenated normal tissues[34)]. The present results therefore encourage further clinical research into the use of ^{252}Cf for bulky localized cancer therapy. Probably the use of afterloading equipment[8)35)], facilities specifically designed for ^{252}Cf brachytherapy[35)] and use of the short implant schedules[1)] with the addition of high dose fractionated photon radiation therapy[17)] will lead to improved tumor control and 5-year cures[16)17)21)]. The possibility of greater effectiveness of added or concurrent adjuvant therapies may well be improved by initial clearance of large, bulky tumor masses. It is

concluded that favorable results have been observed and can result from ^{252}Cf brachytherapy added to our armamentarium for radioresistant tumor therapy. However, new principles for its application and special equipment and facilities designed for neutron brachytherapy are now needed (e.g. see Onai *et al.*[35]). Further studies are essential to evaluate ^{252}Cf NT's role in modern cancer therapy.

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