Phosphorus-32 Therapy of Cystic Grade IV Astrocytomas: Technique and Preliminary Application

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Instillation of [^{32}P]chromic phosphate to cystic brain tumors was performed in six patients. Three patients had craniopharyngioma, two had Grade IV astrocytoma and one had Grade II astrocytoma. The cyst volumes ranged from 2 to 44 cc. A calculated dose of 20,000 rad was delivered to the cyst wall. The [^{32}P]chromic phosphate dose given to achieve this dose ranged from 0.11 mCi to 2.5 mCi. Radionuclide leakage was not detected in either the central nervous system or the reticuloendothelial system by bremsstrahlung scanning. Stereotactic instillation was done in some cases, others had indwelling catheters. The frequency of cyst fluid aspiration in the three patients with craniopharyngioma decreased postinstillation. In the two patients with Grade IV astrocytoma, reductions in both the CT documented cyst size as well as the frequency of cyst aspiration were noted. We conclude that [^{32}P]chromic phosphate installation by stereotactic or indwelling catheter method is a safe and helpful procedure in the management of cystic brain tumors.

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Intracavitary radionuclide instillation offers an alternative method for delivering to a focal area in the brain relatively larger radiation doses in comparison to external radiation therapy. In addition, the potential for decreasing the incidence of radionecrosis of the brain with limited field or focal irradiation cannot be overemphasized (*1*). Hochberg and Pruitt have noted that the limiting factor in survival of patients with glioblastomas is local recurrence. Ninety percent of patients in their study who had recurrence showed recurrence within or close to the primary site (*2*).

We report a method and short-term results of treatment of cystic brain tumors including two patients with Grade IV astrocytoma. Intracavitary instillation of phosphorus-32 (^{32}P) chromic phosphate was done in 11 instances in six patients. Instillation of the radionuclide was done stereotactically in most instances, was simple to perform and was associated with no harmful side effects. Although the period of follow-up is still short, we are encouraged by the ease of administration of the radionuclide, the potential for delivering high doses to a focal area of the brain, the safety of this method, and the ability to decrease cyst fluid accumulation.

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MATERIALS AND METHODS

This study was approved by the University of Michigan Hospitals Institutional Review Committee for Experimentation of Human Subjects.

A complete history and physical examination was done in all patients. Particular points in the history regarding previous cranial surgery or radiation therapy and chemotherapy were specifically sought for during the initial evaluation. A baseline computed tomographic (CT) scan, neuro-ophthalmologic, visual field, endocrine, and routine laboratory examinations were obtained. Review of all radiographic, ophthalmologic, and histologic data from previous hospitalizations was done on all patients.

Stereotactic localization of the target cyst was done in a standard manner (*3, 4*). Briefly, after routine cranial preparation, the patient was brought to the Operating Room for attach-

ment of the stereotactic frame to the scalp. The stereotactic frame was placed after administration of a local anaesthetic. After completion of this attachment the patient was brought to the Neuroradiology Suite where CT guided coordinates were determined. The patient was then brought back to the Operating Room where a trephine hole was made in the appropriate region for access to the cyst. Upon completion of this procedure, the stereotactic needle was passed into the cyst. Cyst fluid was then aspirated. Correct needle positioning in the cyst was denoted by aspiration of a yellowish, thick "motor oil" fluid.

The physical dimensions of the target cyst were determined by radiographic and volumetric methods. Radiographically, the size of the cyst was determined by obtaining the largest measurable diameter in the CT images. In the usual instance the diameter of the cyst is proportional to the cyst volume (*5*). However, the presence of a septated cyst with an isodense septae will result in an error in the estimation of the ^{32}P dosage. In addition, overdosage to the loculated cavity within the cyst and undertreatment of the adjacent tumor may result. To prevent this dosimetric pitfall a second, and volumetric method was used. Injection was made of a known volume of technetium-99m sulfur colloid ([^{99m}Tc]SC) with known activity, followed by withdrawal of an equal volume and measurement of the activity of the fluid withdrawn. In all instances, barbotage and multiple aspirations were made to assure homogeneous radionuclide mixing. Cyst volumes were estimated using the formula:

$$\text{V cyst} \approx \frac{\text{A instilled} \times \text{V instilled}}{\text{A recovered}},$$

where V = volume (ml); A = activity (μCi).

Dosimetry

The desired dose to the wall of the target cyst was estimated to be 20,000 rad. Previous studies have shown that an absorbed dose to the cyst wall exceeding 10k rad but not exceeding 40k rad is optimal for the purposes of cyst wall irradiation (*6, 7*). The activity of [^{32}P]chromic phosphate to be injected to the cyst to deliver this dose was determined by a formula based on the beta-dose calculations derived by Loevinger et al. (*8*). This calculation assumed complete and homogeneous mixing of the radionuclide in the cyst and a spheroid or ellipsoid configuration of the target cyst. Assuming that the target dose is 20,000 rad, the half-life of ^{32}P at 14.3 days and mean energy of beta disintegration at 0.69 MeV the Loevinger formula can be simplified to:

$$\text{ACT} = \frac{27.47V}{f},$$

where ACT — is the activity to be injected (μCi); V — volume of the cyst (ml); f — volume dependent dosimetric factor, increasing from 0–5.0 with increasing diameter of a spherical cyst.

Table 1 is a nomogram for the estimation of ^{32}P activity for a range of target cyst volumes and cyst diameters.

In Patient 4, a 246 μCi of [^{99m}Tc]SC was instilled to the cyst. The recovered activity, after repeated barbotaging, mixing and aspirating an equal volume instilled, was 10.25 Ci. If the above formula is used and a 3% decay of [^{99m}Tc]SC is subtracted from the original dose, an estimated 23-ml cyst volume is obtained. Table 1 shows that the [^{32}P]chromic phosphate dose needed to give 20,000 rad to the cyst wall is 1.4 mCi for a 23-ml volume cyst (Table 2).

After determination of the target cyst volume, the 1.4 mCi [^{32}P]chromic phosphate was instilled in a similar fashion as the [^{99m}Tc]SC when the cyst volume was determined. Figure 1 is a schematic representation of the stereotactic method used in this study.

To determine possible leakage of the radionuclide outside of the target cyst, bremsstrahlung scanning of the target cyst was done at daily intervals up to at least the third post-operation day. The same scanning methods were used over the liver and upper abdomen since any leakage of the chromic phosphate would likely be taken up by the reticuloendothelial system (RES). External counting of blood and urine was done at periodic intervals postinstillation. Each sample was assayed using a two-window technique. A wider window was set at 5–1,700 keV, a narrower one at 50–1,700 keV. Duplicate samples were used in each assay. A distilled water blank was used to measure background activity. In addition, routine laboratory examinations were also done at the periodic levels postinstillation.

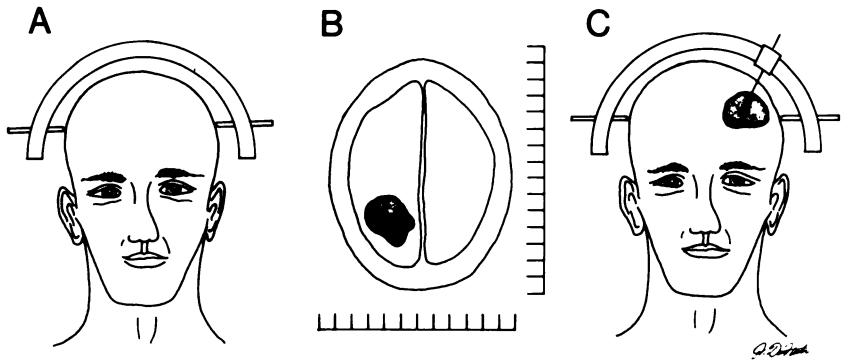
TABLE 1
Nomogram for Calculating ^{32}P Dose (μCi) to Achieve Target 20,000 rad to Cyst Wall*

Cyst diam. (cm)	Volume (ml)	v	f	^{32}P activity (μCi)
0.2	0.004	0.93	.495	0.22
0.4	0.034	1.85	.455	2.05
0.6	0.11	2.78	.425	7.11
0.8	0.27	3.70	.420	17.66
1.0	0.52	4.63	.420	34.01
1.2	0.91	5.56	.425	58.82
1.4	1.44	6.48	.430	91.99
1.6	2.14	7.41	.435	135.14
1.8	3.05	8.33	.443	189.13
2.0	4.19	9.26	.450	255.78
2.2	5.58	10.19	0.452	339.12
2.4	7.24	11.11	0.455	437.10
2.6	9.20	12.04	0.457	553.01
2.8	11.50	12.96	0.460	686.75
3.0	14.14	13.89	0.462	840.75
3.2	17.16	14.82	0.467	1,009.39
3.4	20.58	15.74	0.470	1,202.84
3.6	24.43	16.67	0.472	1,421.81
3.8	28.73	17.59	0.472	1,672.06
4.0	33.50	18.52	0.475	1,937.36
4.2	38.79	19.45	0.477	2,233.88
4.4	44.60	20.37	0.480	2,552.42
4.6	50.97	21.30	0.480	2,916.97
4.8	57.91	22.22	0.482	3,300.39
5.0	65.45	23.15	0.485	3,707.03

*Nomogram assumes homogenous mixing in cyst and either spheroid or ellipsoid cyst (*12*).

$\text{Act} = \frac{27.47}{\frac{V}{f}}$ V = volume.

FIGURE 1
Schematic representation of stereotactic localization and instillation of [^{32}P]chromic phosphate to cystic Grade IV Astrocytoma in parietal region. Stereotactic frame is attached to skull with local anesthesia (A). Stereotactic coordinates are cross-checked with CT coordinates (B). After cross-checking of coordinates, stereotactic needle is passed into parietal cyst through trephine hole made in appropriate location (C)



Particular attention was paid to the hemogram which is a sensitive index to radiotoxicity to blood forming organs.

Radiation safety precautions were observed throughout the procedures. After performance of the procedure the room was surveyed by a thin window Geiger counter.* Contaminated instruments were double bagged and taken to the designated hot room where they were washed in nonionic detergent. Any instrument which showed significant residual activity was bagged, labeled, and stored in a designated room for radioactivity to decay to background. In all instances, the minimum number of instruments was used.

RESULTS

From June 1983 to August 1984, six patients were entered into the study. Three had histologically proved craniopharyngioma, two had Grade IV astrocytoma and one had Grade II astrocytoma. Table 2 shows their demographic and pertinent clinical information. Four females and two males were entered, their ages ranging from 33–66 yr. The two patients who had Grade IV astrocytoma received whole-brain radiotherapy.

TABLE 2
Demographic and Clinical Information for Six Patients

Patient no.	Age	Sex	Dx	mCi Dose	Vol. cyst (ml)	No. of Tx's*	Previous Tx
1	33	M	CP‡	0.5	17	1	Craniotomy
2	62	F	CP	0.4	7	1	Craniotomy
3	60	F	G IVA§	0.54	44	3	Craniotomy + RT†
				2.5	44		Chemo
				1.6	28		
4	66	F	G IVA	1.4	23	3	Craniotomy + RT
				1.4	23		
				1.4	23		
5	48	F	CP	0.11	2	2	Craniotomy
				0.15	2		
6	43	M	G IIA¶	0.45	8	1	Craniotomy

*Tx = treatment.
†RT = radiation therapy.
‡CP = craniopharyngioma.
§G IVA = Grade IV Astrocytoma.
¶G IIA = Grade II Astrocytoma.

In one patient chemotherapy was also given, in addition to radiotherapy.

In four of six patients, stereotactic instillation of radionuclide was done. One patient had a Rickham reservoir in place for cyst decompression. Direct instillation by way of this reservoir was done. Patient 6 had a pre-existing trephine hole from a prior craniotomy. Without stereotactic guidance a direct [^{32}P]chromic phosphate instillation through this trephine hole to a relatively large and superficial cyst was done. Patient 3 who had Grade IV astrocytoma had three instillations. The first dose which was given stereotactically was deemed too small for the target cyst volume. Subsequent instillations were done through the existing stereotactic trephine hole with no difficulty. The longest interval between two doses was 12 mo in Patient 5.

The cyst volumes ranged from 2 to 44 ml. The ^{32}P dosage given to achieve 20,000 rad to the cyst wall ranged from 0.11 mCi to 2.5 mCi. Patient 3 received the highest dose for a cyst volume estimated at 44 cc radiographically and volumetrically. On the third instillation, the ^{32}P dose was decreased to 1.6 mCi because of a reduction of the cyst volume to 28 ml. All patients at the time of this report are alive. The first treatment was done on June 1983 on Patient 1 who at this point has only minor neurologic deficits from the craniopharyngioma. Since the natural history of craniopharyngioma is variable and the interval between the last treatment of Patient 3 (glioblastoma multiforme) and the time of this report is about 8 mo, no meaningful survival or rate of recurrence data has been accumulated at the time of this report.

In all six patients a successful cyst instillation was achieved by either using stereotactic methods or thru an indwelling catheter. There was no instance of radionuclide leakage outside of the target cyst. Bremsstrahlung scans showed focal, loculated activity at the target cyst site (*9*).

Bremsstrahlung scanning of the upper abdomen, liver, and spleen were negative in all instances for any RES activity. No anemia, leukopenia, or thrombocytopenia was noted anytime in this study. Assays of the blood and urine showed no significant activity over background. This finding agrees with that of Boye et al. (*10*) who noted no significant blood activity after instillation of intraperitoneal ^{32}P colloids.

DISCUSSION

The purpose of this study was to determine the feasibility of using stereotactic methods in instilling radionuclide

TABLE 3
Physical Characteristics of Radionuclides Used for Beta Irradiation of Cystic Brain (*11*)

Item	Mean E (MeV)	Max E (MeV)	$T_{1/2}$ (days)	Penetration (mm)	Half-value depth in tissue (mm)
^{186}Re	0.3	0.98	3.8	3.0	—
^{90}Y	0.9	2.2	2.7	11.0	1.1
^{32}P	0.7	1.7	14	7.9	0.8 mm

to cystic brain tumors. European investigators have extensive experience with this mode of therapy including stereotactic procedures in the treatment of craniopharyngiomas and Grade I–III astrocytomas (*5, 11, 12, 13*). We sought to use this technique for the treatment of cystic Grade IV astrocytomas, in the hope of delivering large tumoricidal dose to the cystic regions of the primary site to decrease the rate of cyst fluid accumulation and to shrink the size of the cyst.

Table 3 shows the physical characteristics of the three radionuclides, rhenium-186 (^{186}Re), yttrium-90 (^{90}Y), and ^{32}P which have been used in intracavitary therapy of cystic brain tumors. The advantages of using ^{32}P include its general availability and the greater experience with this radionuclide compared to either ^{90}Y or ^{198}Re. Additionally because it has a lesser tissue penetration, edematogenic effects in normal brain are likely to be less with ^{198}Re than with ^{32}P. At present however, ^{90}Y and ^{198}Re are not generally available in this country. Additionally, cell culture studies of craniopharyngioma cells have shown that a ^{32}P dose of 50 μCi/ml for 48 hr results in irreversible cellular damage (*14*).

This study has shown that stereotactic instillation of [^{32}P]chromic phosphate is a safe procedure. Thus far, we have encountered no instance of leakage of the radionuclide outside of the target cyst. In addition, hematologic and other systemic side effects were not noted in any of our patients. A previous study by Boye et al. has shown that blood and bone marrow activity are minimal even after direct [^{32}P]chromic phosphate instillation to the peritoneal cavity (*10*).

As previously mentioned, all our six patients are alive since treatment. An obvious benefit was noted in terms of the significant prolongation of the interval for repeat cyst decompression. This was also true for Patient No. 4 who had Grade IV astrocytoma. In the other patient with Grade IV astocytoma an objective reduction in cyst size was noted in the postinstillation CT scans. The short interval between treatment and this report precludes a meaningful assessment of the long-term therapeutic benefits of this method at this point.

We conclude that stereotactic instillation of [^{32}P]chromic phosphate to cystic brain tumors carries minimal risk in trained hands. The potential benefits of this form of treatment are the delivery of larger tumoricidal doses to the area of the primary tumor as well as reducing the rate of cyst fluid reaccumulation and reducing the cyst size. Concomittantly, the potential for sparing normal brain tissues from damaging radiation makes [^{32}P]chromic phosphate instillation an attractive alternative to the existing therapy for malignant brain tumors.

FOOTNOTE

*Eberline Instrument Corp., Santa Fe, NM.

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