Treatment of cystic craniopharyngiomas with yttrium-90 colloid solution.

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The authors analyzed long-term follow-up data to assess the value of intracavitary irradiation with stereotactically implanted beta-emitting radioisotope ^{90}Y -silicate colloid for the treatment of craniopharyngiomas. Fifty-seven craniopharyngiomas in 42 patients were selected for retrospective analysis. The yttrium-90 was implanted intracavitally, using computerized tomography-guided and three-dimensional stereotactic treatment planning. The cumulative dose aimed at the inner surface of the cyst wall was 300 Gy.

An average of 75% shrinkage of the initial cyst volume was observed. In 18 cases the reduction was more than 91%, and the cyst disappeared totally in 11 cases.

A 50% decrease in cyst volume was usually apparent between the 2nd and 4th months. A 70% decrease in cyst volume was seen by the 5th and 6th months and an 80% reduction by the 7th and 8th months. Cysts that were unchanged remained so throughout the observation period. The time course of volume reduction could be expressed mathematically by the formula of $0.73 \times e^{-0.62 \times T} + 0.27$, where "e" is the basic number of natural logarithm and "T" is the time expressed in months. Mean survival duration after intracavitary irradiation was 9.4 years.

The shrinkage of the cyst was a consequence of fibrosis of the wall, as seen on histopathological examination. The neuroophthalmological prognosis was favorable only when the optic disc was normal or nearly normal at the time of the treatment. In the presence of preexisting optic atrophy, visual deterioration proved to be irreversible. The long-term results support the view that intracavitary ^{90}Y -irradiation is a noninvasive and very effective method of treatment for craniopharyngioma cysts. Because of the 1.1 mm half-life decay of beta irradiation, it cannot influence the solid part of the tumor; therefore, the best result can be expected in solitary cysts.

Key Words * yttrium-90 silicate colloid * cystic craniopharyngioma * cyst * intracavitary/intracavitary irradiation * intracavitary/intracavitary brachytherapy * intracavitary/intracavitary radiosurgery

The sheer number of methods for treating craniopharyngiomas (surgical extirpation, aspiration of cyst fluid, shunt operations, external irradiation and radiosurgery, general and intracystic chemotherapy, hormone substitution, intracavitary irradiation, and combinations of the above) indicates that none of the existing treatments is the exclusive modality of choice, and even the phrase "multi-modality management of craniopharyngiomas" is misleading because there is yet no satisfactory state-of-the-art treatment.

In the present study we analyze our results with the intracavitary implantation of ^{90}Y -silicate colloid (Amersham, England) and ^{90}Y -citrate colloid (CIS, France) following partial tumor resection, usually through a frontotemporal craniotomy. The procedure devised by Leksell,[26,27] Wycis,[53] and further developed by Backlund[1-3,42] has been used by us since 1975. The aim of the present study is to assess the volume changes in the treated cysts, the time course of volume reduction, and the ophthalmological signs.

CLINICAL MATERIAL AND METHODS

From December 1975 to July 1994 we performed 60 yttrium-90 implantations into craniopharyngioma cysts in 45 patients. We treated mostly recurrent cysts, following one or repeated surgical procedures, and we analyzed the data of 57 procedures in 42 patients. Preliminary data of parts of this study have been published previously.[16-19,46,47] The median age of patients was 24.3 years (range 4-66 years.). There were 14 female and 28 male patients. The first patient was treated 20 years ago and the most recent patient had a follow-up period of 18 months. Forty patients had operations prior to yttrium-90 implantation, whereas in two cases, yttrium-90 implantation was the primary treatment.

Following routine neuroradiological and neurosurgical examination of the patient, cyst volume was determined by computerized tomography (CT) (in the early days of the treatment, by cystography or isotope dilution methods).[11,22,32,44] In the cases of cystography the volume has been calculated from the 3 diameters measured after the positive contrast and air cystography by the formula of simple ellipsoidal volume calculation: $4r^3 \cdot \frac{1}{2} \cdot \frac{1}{3} \gg 0.52 \cdot x/2 \cdot y/2 \cdot z/2$. The enlargement factor was taken into consideration. Since 1980 the cyst volume has been calculated by CT volumetric analysis alone. Computerized tomography scanning of cysts was performed (2.5-mm thick slices with table increments of 2 mm). On each slice, the area of cyst was measured in square centimeters. The sum of the area was multiplied by the slice thickness to give the volume in cubic centimeters. The measurement of volume was used for the calculation of radioactivity to be injected. The application was by a technique comparable to the Backlund method.[2,3] The calculations were performed by our own microcomputer program.[16] Our dosimetry was also based on the Loevinger formula,[29] as done by other authors as well.[2,5,21,26,33,35,40,48,52] Implantation of ^{90}Y into the cyst was performed through a frontal burr hole or by transsphenoidal puncture. In the initial cases we used a free-handed technique; however, since 1989 we have applied stereotactic techniques using Leksell and Riechert-Mundinger frames. The mean dose delivered to the cyst wall was 302 Gy. To detect possible leakage of the isotope we performed gamma camera examinations in all cases following implantation, detecting the "Bremsstrahlung." [5] Cyst shrinkage was monitored by repeated CT examinations (by cystography or autopsy during earlier years). The time course of postirradiation relative volume reduction (VR) was analyzed by 88 measurements obtained from CT scanning of cyst volume in 33 patients (Fig. 1). To simplify representation, the initial original cyst volume (OCV) was normalized to 100% in all cases. The curve shows the sequence of the average reduction of the relative cyst volume calculated by linear interpolation of 88 CT volume measurements with a 95% confidence interval. Beyond 9 months we had insufficient data to permit

reliable analysis.

Fig. 1. Graph showing reduction of relative cyst volumes and time course postimplantation using serial CT measurements.

Histopathological examination of the cyst wall after yttrium-90 treatment was performed in seven cases. Material for light and electron microscopy was obtained at operation or autopsy.

RESULTS

In 42 patients selected for retrospective analysis a total of 57 craniopharyngioma cysts were treated with stereotactically applied intracavitary irradiation (STAIR) using yttrium-90. We implanted the yttrium-90 mainly at recurrent cysts after one or more microsurgical operations. Other centers use this method as a primary modality of management.[2,3,39] Additional treatments were performed before and/or after the ⁹⁰Y-STAIR, including resection, aspiration, and shunt placement (Table 1).

We have not observed leakage of yttrium-90 by gamma camera examination in any case.

TABLE 1 ADDITIONAL TREATMENTS BEFORE AND AFTER THE FIRST ⁹⁰ Y-STAIR TREATMENT IN 42 PATIENTS WITH CRANIOPHARYNGIOMA*		
Procedure	Before 1st ⁹⁰ Y Implant	After 1st ⁹⁰ Y Implant
resection	34 (1 resection) 7 (2 resections) 3 (3 resections)	10
aspiration	14	9
shunt	6	5
* Eleven patients received second and third ⁹⁰ Y implants.		

Preoperative Data

The mean OCV preimplantation was 20.4 ml (range 2.7-73 ml). In children the mean OCV preimplantation was smaller than in adults (16 vs. 22 ml, respectively). In the adamantinous and mixed histological types of cysts the mean OCV was less than in the squamous type (13.8 and 19.1 ml, respectively, vs. 22.6 ml).

Neuroophthalmological data before yttrium-90 treatment are presented in Table 2. Visual field defects or impairment of visual acuity were observed in 40 of 42 patients. Patients with no pre- or postoperative defect have been excluded. A unilateral optic nerve lesion was present in seven cases, chiasmal damage in 25, and a lesion of the optic tract in eight. Only five patients had a normal optic disc. Temporal pallor was found in 13 cases, and optic atrophy was documented in 22 patients preoperatively.

TABLE 2 NEUROOPHTHALMOLOGICAL DATA PRE- AND POST ⁹⁰ Y-STAIR TREATMENT IN PATIENTS WITH CRANIOPHARYNGIOMA					
Signs	No. of Cases				
	Pre-treatment	Posttreatment			
		Complete Recovery	Im-proved	Un-changed	Pro-gression
visual acuity					
5/5-5/12	10	2	1	7	0
5/10-5/50	11	3	3	4	1
<5/50	10	1	1	7	1
blind	9	0	0	9	0
total	40	6	5	27	2
optic disc					
normal	5	2	2	1	0
temporal pallor	13	3	4	6	0
severe pallor or atrophy	22	0	0	20	2
total	40	5	6	27	2
visual field lesions					
unilateral optic nerve	7	3	2	3	0
chiasmal	25	2	3	17	2
optic tract	8	0	0	8	0
total	40	5	5	28	2

Postoperative Results

Cyst Volume Decrease. Following 57 yttrium-90 implantation procedures in 42 patients, shrinkage occurred in 45 cysts. Three cysts did not shrink even after repeated yttrium-90 implantation. The results of ⁹⁰Y-STAIR are unknown for 9 cysts.

After ⁹⁰Y-STAIR the mean OCV was reduced from 20.4 to 3.93 ml (mean 1.5 ml). The total volume of all cysts after ⁹⁰Y-STAIR diminished from 1131.1 to 180.8 ml.

The VR of all cysts is shown in Fig. 2. The VR of the cystic part of the craniopharyngioma was more than 91% in 18 cases (within this group, the cyst disappeared totally in 11 cases). More than a 50% VR occurred in 18 cases, a 20 to 50% reduction in five, and less than 20% in three cysts. The volume did not change in two cysts, minimally increased in one, and the changes could not be determined in nine cases. The overall mean VR in all 48 cysts was 75.02%. The mean reduction in the cyst size was 76.2% in children (aged lt 14 years), 74.5% in adults, 73.2% in females, and 75.9% in males. A 72.4% reduction

was seen in cysts larger than 20 ml, and a 77.1% reduction occurred in smaller cysts. The mean VR was 74.6% in primary and 76.7% in recurrent cysts. Analyzing the histological subtypes, the adamantinous cysts had the best prognosis with an 80.4% VR. In the squamous group the mean VR was 72.4%, whereas it was 48.1% in the mixed type, making this the group with the worst overall prognosis. The VR was more significant (76.2%) in 13 cysts receiving less than 302 Gy compared to those receiving more than 302 Gy, which had a reduction of 69.8%.

Fig. 2. Bar graph showing the frequency distribution of percent of VR. In most cases there was an 80 to 100% permanent VR after irradiation. (The two cysts without VR are not illustrated).

Following the intracavitary irradiation with ⁹⁰Y, the reduction in cyst volume was progressive to 50% between 2 and 4 months, to 70% between 5 and 6 months, and 80% in 7 and 8 months postimplantation with a 95% confidence interval (Fig. 3 continuous curve). The diminished or obliterated cysts did not change their volume over a long observation period.

Fig. 3. Graph showing the time course of VR following ^{90}Y -STAIR. The continuous curve shows the mean of VR based on CT measurements and estimated by our formula (dotted line).

Clinical Outcome

The mean survival time during the 20-year follow-up period (1975-1995) was 9.1 years (minimum 1.5 years, maximum 20 years). The mean survival time of the patients still living was 10.6 years and in the group of deceased patients the survival period was 3.9 years. Actuarial survival rates at 5 and 10 years were 84% and 72%, respectively. Figure 4 shows the Kaplan-Meier survival analysis of our patients. The yttrium-90 was given longer than 5 years ago in 33 cases (78.5%) and longer than 10 years ago in 13 cases (31%).

Fig. 4. Graph showing the Kaplan-Meier survival curves of this multimodality treatment: 5-year survival was achieved in 84% and 10-year survival was achieved in 72% of our cases.

The ^{90}Y -STAIR did not result in significant changes in the neurological symptoms of our patients. There was one perioperative death from meningo ventriculitis 1.5 months after transnasal puncture; two patients died due to unrelated causes several years following treatment (one due to pulmonary embolism, one to cardiac insufficiency); and two patients died due to progression of the solid part of the craniopharyngioma several years after the procedure.

It seems obvious that our clinical results were impeded by the volume of the solid tumor. The average size of the solid part was 7.2 ml (range 0-37 ml). There was no solid tumor at all in six cases. The volume was less than 3 ml in five, 3 to 10 ml in 10, 10 to 20 ml in three, and more than 20 ml in six cases.

The neuroophthalmological signs in 40 patients, (excluding the two cases with normal pre- and postoperative examinations) are given in Table 2. After yttrium-90 therapy the status of 27 patients did not change. The ophthalmological status improved in 11 patients with thin-walled cysts. Deterioration of vision occurred in two patients: radiation damage was suspected as the cause in one and compression of the optic nerve by the solid part of the tumor in the other. Five patients had transient oculomotor nerve paresis: one occurred at the time of the puncture due to direct injury of the oculomotor nerve, and in the remaining four patients, neuropathy developed during the follow-up period.

Histological Examination

Our previous light and electron microscopy studies of the cyst wall following ^{90}Y -irradiation revealed that the lining epithelial cell layer was damaged and that the cyst wall shrank. Thickened capillary walls

were also seen. We found proliferation of endothelial cells and subendothelial connective tissue with focal calcification and narrowed lumens of small vessels with a large amount of thick collagen bundles showing hyaline degeneration.[46,47]

DISCUSSION

The possibilities and limitations of the intracavitary implantation of radioisotopes into craniopharyngioma cysts have been documented in the last two decades.[3,8,13,17,33] Radioisotopes emitting short-range beta radiation and with a short half-life $\text{Na}^{32}\text{PO}_4$, [27] $\text{Cr}^{32}\text{PO}_4$, [4,9,20,37,40,47-54] $\text{Bi}^{32}\text{PO}_4$, [28] ^{198}Au -colloid, [4,6,12,21,23] $^{90}\text{YCl}_3$, [7] and later with ^{90}Y -silicate colloid [2,3,10,15-19,24,27,34,35,38,44,52] or $^{186}\text{rhenium}$ [34-36,43,48,52] have all been used.

Our results confirm the data previously reported regarding the lasting 74 to 100% decrease in volume following high-energy beta irradiation of cystic craniopharyngiomas.[3,31,34,39,44] In our study the mean value of the decrease of OCV measured by CT was 75.1%. Of the 48 cysts irradiated and afterwards controlled, 61% showed more than an 80% decrease of the OCV, with complete disappearance in 23%. In 27% of the irradiated cysts the VR has been between 40% and 80%. Less than a 40% decrease occurred in 10.6% of the cases. In 6.5% of the cysts shrinkage was not significant, and the mean residual volume was 25% of the OCV. Even these cases of volumetrically poor results, with only arrest of steady increase in cyst size as opposed to an actual decrease, nevertheless proved to be important to the patient.

A number of theoretical explanations for these less successful results can be given. The true reason in a given case will, however, remain only a speculative guess. The cyst may not shrink if the solid or mainly calcified part of the tumor represents its major component or if the cyst is walled in by the sella itself rather than secreting endothelium (the solid parts of the tumor were not influenced by this kind of irradiation because of the 1.1 mm half-life decay of the radiation); or if the yttrium-90 leaks out of the cyst into the subarachnoidal space through the puncture hole. Thus far this has been excluded by gamma camera monitoring; it is doubtful whether this examination is enough to indicate the leakage, and we plan to measure the beta irradiation of the cerebrospinal fluid the day after the operation. The ethylene diamine tetra-acetic acid content of the positive contrast material might also decrease the effect of ^{90}Y in cases where cystography is performed.

Frequently a new cyst or cysts develop later; however, these clinically recurrent cysts in most cases have not originated from the cysts previously irradiated by yttrium-90. Hence "recurrent cysts," defined as those that reappear following initial response to treatment, should be differentiated from "successive cysts," which are actually new cysts that develop in polycystic craniopharyngiomas, usually several years posttreatment. Such successive cysts should be treated with a successive yttrium-90 implantation. However, we believe that multicystic craniopharyngiomas (when at least two or more cysts are present) require separate calculations and puncture. Cyst subtypes do not show significantly different response to treatment; however, small solitary cysts and adamantinous tumors react more to ^{90}Y -STAIR, whereas the "mixed type" consisting of solid portions, the squamous type, and large cysts are less responsive.

The shrinkage of the cyst following ^{90}Y -STAIR or other beta-emitting radioisotopes begins after several months and becomes stable after 6 months to 1 year.[3,13,34,40,42,44,45] From our repeated CT measurements we concluded that the time course of shrinkage of craniopharyngioma cysts following ^{90}Y -STAIR might be expressed mathematically by the formula $0.73 \times e^{-0.62 \times T} + 0.27$, where "e" is the

basic number of natural logarithm and "T" is the time expressed in months. Figure 3 shows the duration of VR following ^{90}Y -STAIR based on CT measurements (continuous curve) and estimated by our formula (dotted line).

Shrinkage of the cyst results in the improvement of both neurological and ophthalmological symptoms. Subsequent surgery, external irradiation, or shunting procedures may also contribute to the results of ^{90}Y -STAIR.

The radiation dose used in previously reported series ranges from 50 to 1000 Gy, and the most accepted value is 200 Gy.[32,40] We have been applying a 302 Gy mean radiation dose to the cyst wall. We plan to lower the radiation dose to 200 Gy or less in cases in which the cyst is adherent to the optic pathways or to hypothalamic structures. Experience from gamma knife radiosurgery indicating that doses more than 8 to 10 Gy may damage optic pathways should be considered when planning the dose in intracavitary treatments. The third, fourth, and fifth cranial nerves exposed to a dose from 4.5 to 30 Gy did not develop signs of neuropathy.[25]

The prognosis was good only when an intact optic disc or slight temporal pallor was seen.[12] Vision improved in 11 of 18 patients with intact optic discs or slight temporal pallor of the discs at the time of treatment. In most cases the lack of the ophthalmological improvement may be explained by the fact that the isotope was implanted at a late stage of the disease. The optic disc in these patients was pale or frankly atrophic. In cases in which the duration of the preoperative visual impairment was less than 1 year, improvement was still possible.[14,39] Any changes of visual function due to treatment usually occurred between 2 weeks and 6 months after yttrium-90 implantation.

The ^{90}Y irradiation prevents cyst fluid formation and will result in shrinkage of the cyst. To analyze the mode of action it is important to know the cause of the cyst formation in craniopharyngiomas. Large cysts may develop due to degenerative changes in the stroma with maturation and accumulation of sloughed-off squamous epithelium.[39] In addition, craniopharyngiomas have special fenestrated capillaries that might enable plasma proteins and fluid to escape more readily into the extravascular spaces. Our immunohistochemical and electron microscopy investigations revealed that the tumors might have a mucus-secreting component.[47]

After beta irradiation with yttrium-90 for 10 days and penetration 3 to 4 mm into the tissues, the lining epithelial layer of the cyst wall is destroyed, and further proliferation of tumor cells is inhibited. In specimens obtained from autopsy, a large amount of collagen fibers with focal hyaline degeneration was present in the cyst wall. Proliferation of the intimal cells and narrowing of small vessel lumens by subendothelial connective tissue occurred as well. Considering that fibrous tissue is more susceptible to shrinkage, the fibrosis induced by radiation with destruction of the squamous epithelium and vascular changes might explain the reduction of cyst volume and diminished fluid secretion after yttrium-90 treatment.[46]

Both the data from the literature and our findings prove that intracavitary instillation improves the rate of survival and quality of life in these difficult cases.

CONCLUSIONS

Our long-term results support the view that intracavitary ^{90}Y irradiation is a minimally invasive and very effective method of treatment for craniopharyngioma cysts. Because of the physical characteristics of

beta irradiation, its effect is limited to the cystic part of the tumor; thus, the best result can be expected in solitary cysts.

During our more than 20-year follow-up period, an average of 75% shrinkage of the initial cyst volume was observed. In 18 cases the reduction was more than 91%, and the cyst disappeared totally in 11 cases. The time course of VR sometimes takes a year and can be expressed mathematically by the formula of $0.73 \times e^{-0.6 \times T} + 0.27$, where "e" is the basic number of natural logarithm and "T" is the time expressed in months. Because of the low operative mortality and morbidity rates, this method is an indispensable contribution to the multimodality treatment of cystic craniopharyngiomas.

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