Evaluation of Radiotherapy of Tumors in the Pineal Region by Ventriculographic Studies with Iodized Oil*

JIRO SUZUKI, M.D., AND SHIGEAKI HORI, M.D.
Division of Neurosurgery, Institute of Brain Diseases, Tohoku University
School of Medicine, Sendai, Japan

In the treatment of tumors in the pineal region, radiotherapy is often used following some shunting operation because the pinealoma, the most common type of pineal tumor, is highly sensitive to irradiation. Although several statistical and histological evaluations of radiotherapy for pineal tumors have appeared, the objective confirmation of its effectiveness during the course of irradiation has seldom been reported.

Material and Methods
The authors evaluated the effect of irradiation on pineal tumors by conducting consecutive iodine oil ventriculographic studies. Radiopaque oil was instilled into the third ventricle after ventriculostomy, and roentgenographic appearances of pineal tumors were checked before, during, and after radiotherapy. This method enabled us to evaluate the effect of irradiation in vivo; it was found that the reaction of each pineal tumor to radiation was different.

Five out of eight clinically diagnosed pineal region tumors treated with ventriculostomy and radiotherapy were followed by Myodil ventriculography (MVG). Although all five cases showed disturbance of consciousness, symptoms of increased intracranial pressure, and specific symptoms of pineal tumors, the diagnosis was confirmed by pneumoventriculography (PVG) and MVG (Table 1). After PVG, about 2 ml of Myodil were instilled through a polyethylene catheter introduced into the anterior horn of the lateral ventricle for continuous ventricular drainage. This enabled us to study the size and shape of the pineal tumor and the nature of any obstruction of the aqueduct of Sylvius. The administration of Myodil was limited to only one occasion before radiotherapy, except for one case in which a second instillation was carried out 7 months afterwards; the original Myodil had become firmly attached to the wall of the lateral ventricle.

After 1 to 14 days of continuous ventricular drainage, ventriculostomy was performed in all cases. Radiotherapy was then given as soon as possible. Shimazu RT-2000 type Co-60 apparatus was used for radiotherapy. With 75 cm of SFD and $6 \times 6 \text{ cm}^2$ to $8 \times 10 \text{ cm}^2$ of irradiation field size (one on the right and one the left), an initial dose of 50 to 150 r, maintenance dose of 125 to 200 r, and total focal dose of 3475 to 6200 r were given within the span of 5 to 9 weeks. In one case an additional dose of 4350 r after an interval of 13 months was given.

Although Myodil flowed out through a shunting catheter in some cases, embolic complications in the lung or brain did not occur.

Case Reports
Case 1. For 15 months before admission this 25-year-old man complained of general malaise, diplopia, and disturbance of memory. He had been married 3 months prior to his hospital visit, but soon he could not have satisfactory sexual intercourse. Because of easy fatigability he was often absent from his work, and he developed chills and low degree of fever. Two weeks prior to admission intermittent occipital headache and vomiting developed and slow movement and a staggering gait.

Examination. On June 24, 1965, the patient was found to have an apathetic facial expression, slow response to questions, paralysis of vertical gaze, left abducens nerve paralysis, right mydriasis, bilateral absolute
pupil paralysis, and papilledema. He also had a severe hearing loss on the right, reduction of right vestibular function, and marked bilateral cerebellar symptoms so that he was unable to walk without assistance. Blood pressure, hematologic and urologic studies, and the amount of daily urinary hormone excretion were all within normal limits. X-ray studies revealed calcification of the pineal body in the plain skull film, elevation of the bilateral cerebral veins in the carotid angiogram, and symmetrical enlargement of both the lateral and third ventricles in the PVG. The MVG showed a round tumor mass protruding from the pineal area into the third ventricle (Fig. 1 left).

Treatment. A shunting procedure was performed; 10 days later the patient was slightly improved and on the 15th day cobalt-60 irradiation therapy was started. During the course of the radiotherapy, the patient recovered his ability to walk without assistance and showed remarkable improvement in auditory and vestibular function. The size of the pineal tumor in the MVG reduced gradually. Irradiation was discontinued at a total dose of 4750 r over a 5-week period, and the patient was discharged from the hospital. The tumor continued to reduce and 6 months later the tumor shadow had disappeared; by 13 months the obstructed cerebral aqueduct had opened and radio-opaque oil descended into the spinal canal (Fig. 1 right).

Because the reduction in tumor size was slow, it was thought that this tumor was less radiosensitive; therefore, an additional 4350 r over a 5-week period was given 13 months later. At the present time, after an interval of 22 months, his sexual potency has improved; he is well and fit for work in spite of slight emotional instability, right mydriasis, and a sluggish light reflex.

Case 2. This 19-year-old school girl had long been the smallest in her class. She had developed amenorrhea and gradual weight loss for 14 months prior to admission, with headache, anorexia, and vomiting for 6 months. Three months prior to admission, she had lost consciousness after bathing and was admitted to a local hospital unable to walk. She was treated for Simmonds’ disease with adrenocortical steroids and improved for a short period, but 1 month before admission the vomiting and headache returned. Because she had become lethargic and developed papilledema, she was transferred to our hospital on October 13, 1965.

Examination. The patient appeared to

### Table 1

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs) &amp; Sex</th>
<th>Duration of Illness (mos)</th>
<th>Treatment*</th>
<th>Co-60 Irradiation</th>
<th>Results</th>
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<tr>
<td>1</td>
<td>25 M</td>
<td>15</td>
<td>VCD VAS</td>
<td>1st Irradiation</td>
<td>Well and working 22 months after discharge.</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>2 8×10</td>
<td>150 to 200 5 4750</td>
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<tr>
<td></td>
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<td>2nd Irradiation</td>
<td>Died 1 week later. Autopsy revealed a pineal mass without tumor cells.</td>
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<td></td>
<td>2 8×9</td>
<td>150 to 175 5 4350</td>
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<tr>
<td>2</td>
<td>19 F</td>
<td>14</td>
<td>VCD VAS</td>
<td>2 7×8</td>
<td>Teratoma was removed 2 months later. Died during postoperative period.</td>
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<td></td>
<td></td>
<td>50 to 175 6 3475</td>
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<td>3</td>
<td>11 M</td>
<td>2</td>
<td>VCD VAS</td>
<td>3 two 7×7 &amp; 6×8</td>
<td>Well and attending school 15 months after discharge.</td>
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<td>50 to 125 9 5525</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>14 M</td>
<td>5</td>
<td>VCD VAS</td>
<td>2 8×8</td>
<td>Well and attending school 8 months after discharge. Tumor shadow still remains.</td>
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<td>150 5 4050</td>
<td></td>
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<tr>
<td>5</td>
<td>15 M</td>
<td>6</td>
<td>VAS</td>
<td>2 6×6</td>
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<td>50 to 150 7 6200</td>
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* VCD Ventricular Continuous Drainage. VAS Ventriculoatrial shunting.
have a small physical frame, 146 cm in height and 28.5 kg in body weight. She was markedly cachectic. The color of the skin was purple, the pubic hair thin, the left pupil slightly mydriatic. There was horizontal nystagmus to the left and marked bilateral papilledema, but no paralysis of vertical gaze. Pupillary light reflexes and visual fields were normal. There was a slight tremor in the tongue and fingers of both hands. Abdominal reflexes were absent bilaterally. Tendon reflex of the legs was hyperactive. No pathological reflex was noted. The blood pressure was 102/60 mm Hg, red blood cells 3.96 million per cu mm, hemoglobin 90%, and white blood cells 6700 per cu mm. Serum electrolytes, blood sugar, urinalysis, and basal metabolic rate were all normal. Estrogen was excreted normally in the daily urine, but 17 ketosteroids and 17 hydroxycorticosteroids were low, 0.17 and 0.6 mg respectively. In the skull films, there was slight widening of the cranial sutures but the sella turcica appeared normal and there was no shadow of calcification. In the PVG, there was dilatation of both lateral ventricles and the third ventricle, plus a distinct filling defect posterior to the third ventricle. In the MVG, the contour of a pineal tumor was clear and only a small part of the entrance to the cerebral aqueduct was seen (Fig. 2 left).

Treatment. A shunting procedure was performed. Consciousness as well as appetite improved although diabetes insipidus became prominent. On the 13th day after shunting, irradiation was started with supplement of pitressin tannate in oil and prednisolone. Irradiation therapy improved her general condition; body weight increased to 40 kg, ability to walk returned, and papilledema gradually disappeared.

After 2 weeks of irradiation, the patient complained of headache and vomiting, but they disappeared with an increase in prednisolone dosage. From the 4th week, however, she again developed general malaise, anorexia in addition to fever. Six weeks later these symptoms became worse and white cell count decreased to 3000, so irradiation was discontinued at 3475 r. At that time Myodil was not seen in the ventricles but was found in the spinal canal (Fig. 2 right). The patient deteriorated rapidly, developed a fever of 41°C, and died 1 week later.

**Fig. 1. Case 1. Left:** Myodil ventriculography before irradiation shows contour of a pineal tumor. 
**Right:** 13 months after irradiation with 4750 r Myodil has now descended into the spinal canal.
Fig. 2. Case 2. Left: Myodil ventriculography before irradiation shows outline of a pineal tumor. Right: Myodil has descended into the spinal canal after irradiation with 3475 r.

Fig. 3. Case 2. Autopsy revealed a mass in the pineal region but cerebral aqueduct was patent.
Postmortem examination. At autopsy it was found that, although the cerebral aqueduct was patent, there was a brownish yellow mass (1.7 X 0.6 X 1.8 cm) in the pineal region (Fig. 3). Microscopically this mass consisted of tissue debris; no tumor cells or normal pineal tissue were discovered (Fig. 4 left). Tumor cells were not found in either the ventricular wall or other places, but in the irradiated field some ependyma of the lateral ventricle were missing, and the same area was covered with a thin red-blood-cell layer (Fig. 4 right).

Case 3. After 2 months of severe frontalgia and diplopia and 1 month of frequent vomiting, this 11-year-old boy was admitted to a hospital. After spinal puncture, he became lethargic and incontinent; after PVG he became comatose and was transferred to our hospital on December 6, 1965.

Examination. An emergency shunting operation improved his consciousness. However, left hemiplegia, vertical gaze and conjugation paralysis, right abducens nerve paralysis, horizontal nystagmus to the right, right mydriasis, and bilateral tardy light reflex were noted; there was no noticeable papilledema. X-ray films showed deviation to the right. The PVG revealed symmetrical dilatation of both lateral ventricles, but there was no air in the third ventricle. Injected Myodil disclosed only a small part of the third ventricle adjacent to the foramen of Monro, and this made us suspect that a tumor was occupying most of the third ventricle (Fig. 5 a).

On the 6th day after shunting, irradiation therapy was begun. On the 8th day urinary incontinence improved, verbal response returned gradually, and the gait became normal. After 5525 r of irradiation over a 9-week period, the patient was discharged from the hospital and returned to school. During this period the small third ventricular area which had been visualized in the MVG enlarged, and it became clear that irradiation had reduced the size of the tumor mass (Fig. 5 b, c, and d). However, it did not become small enough to provide patency of the cerebral aqueduct, so surgical removal was carried out.

Operation. Craniotomy (Dandy’s technique) revealed a tumor the size of a hen’s egg in the pineal region, which was very hard and firmly attached to the surrounding tissue. It was removed piecemeal with scissors, and then totally removed; however, the patient died from postoperative bleeding 3 days later. Histologically the tumor was an almost completely scarred teratoma.

Case 4. For about 5 months this 14-year-old boy complained of diplopia and occipital
headache, with a further development of vomiting, vertigo, left tinnitus, bilateral hand tremor, bilateral loss of visual acuity, and inability to walk. One month before admission he had had a convulsive seizure and his consciousness became cloudy. He was admitted to our hospital February 28, 1966.

Examination. Stupor, ptosis of the left eyelid, left abducens nerve paralysis, and bilateral papilledema with no other ocular disturbance were noted on admission. There were also a decrease in the strength of the legs, left hemihypesthesia, right cerebellar symptoms, and tendon hyperreflexia of the legs. In the PVG there was a marked dilata
tion of the lateral and third ventricles, and in the MVG a tumor shadow posterior to the third ventricle and an obstruction of the cerebral aqueduct were noted.

Treatment. A shunting operation was performed, and irradiation was started 6 days later. The patients’ general condition improved rapidly, and 2 weeks after irradiation with 1950 r he was able to walk without assistance. At that time fluoroscopic studies revealed that Myodil descended from the ventricle to the spinal canal, thereby indicating that the cerebral aqueduct had become patent. After a total dose of 4050 r over a period of 5 weeks the patient was discharged with normal visual acuity; the papilledema and other symptoms had disappeared. At the present time, 15 months later, he is fine and attending school.

Case 5. Six months before admission this 15-year-old boy developed ptosis of the left and then the right eyelid, followed by diplopia. Since then he has complained of occipital headache, palpitation, and general malaise. One month before admission he was unable to sit up. Headache and vomiting became more aggravated.

Examination. On September 14, 1966, the patient was stuporous, with marked eye symptoms including ptosis of both eye lids, vertical gaze paralysis, posterior internuclear ophthalmoplegia, bilateral mydriasis, absolute pupillary paralysis, and papilledema. There were also marked cerebellar symptoms as

Fig. 5. Case 3. Myodil ventriculograph before irradiation (a), and after irradiation (b = 875 r; c = 2825 r; d = 4625 r).
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well as pathological reflexes such as the Babinski. The blood pressure was 96/60, and basal metabolic rate minus 21%; there were no abnormalities in hematologic or urinary examinations. In the skull film there were marked digitations of the skull and flattening of the sella turcica, but no abnormal calcified areas. Carotid angiography revealed slight deviation of the anterior cerebral artery to the right. In the MVG a tumor mass was seen protruding from the pineal region to the third ventricle and producing obstruction of the cerebral aqueduct.

Treatment. A shunting procedure was carried out; radiation therapy was started 5 days later. In 7 weeks 6200 r were given. The patient improved markedly with complete disappearance of cerebellar symptoms and pathological reflexes. Tendon reflexes became normal. Vertical gaze paralysis as well as convergence paralysis improved. Although the patient still had fixed pupils, he was discharged and able to attend school. Follow-up studies with MVG revealed that, in spite of a reduction of the tumor mass, obstruction of the cerebral aqueduct persisted.

Discussion

Whether to treat pineal tumors initially with radical surgery or radiation therapy is not generally agreed. It is also emphasized that at that time that, although pinealomas were relatively well demarcated, they were really malignant with an invasive tendency toward the cerebral parenchyma so that, even after successful resection, postoperative irradiation was indispensable. The general trend of therapy for these tumors, however, appears to be the combination of a shunting operation with radiation therapy. The reason is that the radical operation is difficult, and that pinealomas, which comprise most of the pineal tumors, are sensitive to irradiation. The first successful removal of pinealomas was reported by Peet; the patient survived 31 years, having had postoperative irradiation. In most of the long survivals the patients received either radiation therapy alone or a combination of surgery and postoperative radiation therapy. Moreover, there are few long survivals among those who did not have radiation therapy. These observations leave no doubt about the importance of radiation therapy for this tumor. Radiation therapy is not always successful, however; some cases show no improvement, further aggravation, sudden death, or recurrence. If irradiation is scheduled immediately after a shunting operation without histological studies, the tumor's degree of radiosensitivity is unknown and any given therapy is not predetermined. Because this blind irradiation also exposes less radio-resistant areas such as the hypothalamus and hypophysis determination of the total irradiation dose, duration, and field is very difficult. Different types of tumor have different radiosensitivities, and at the present time it is almost impossible to judge the radiosensitivity in individual cases. The change of symptoms is another indication of the effectiveness of radiation, but it is not always helpful because there are some cases in which the shunting procedure alone brings about improvement.

Due to these difficulties we have sought a diagnostic method that will give objective information about the effectiveness of irradiation in each individual case, making it possible to administer the most appropriate radiation therapy. Diagnostic methods used until now are: 1) consecutive carotid angiography, especially in the venous phase; 2) pneumoventriculography; and 3) observation of the effect of test radiation on biopsied and cultured tumor cells. None of these is satisfactory, however. Compared to these methods, consecutive ventriculographic studies with iodized oil, as we have described elsewhere in this report, has proved simple, helpful diagnostically, and free from complications. In some cases there was apparently a gradual reduction of Myodil in the ventricle unassociated with returning patency of the cerebral aqueduct. In these cases Myodil seemed to have flowed out to the blood stream through the catheter, but it never caused pulmonary or cerebral embolization. In one case Myodil was observed attached firmly to the ventricular wall for a long time, but it never caused any clinical symptoms.
The five cases reported here showed marked improvement, with full development of consciousness and normal gait. In Cases 1, 4, and 5, the patients had no recurrence and have lived a normal life for 22, 15, and 8 months since discharge. In Cases 1 and 5, the MVG revealed a disappearance of the tumor shadow and a reopening of the cerebral aqueduct, suggesting almost complete recovery, but in Case 4 a small tumor shadow remained, requiring strict follow-up of the patient with a consideration of possible reirradiation or surgery.

Because Case 2 had such prominent endocrine symptoms as Simmonds' disease and diabetes insipidus, the initial dose of irradiation was reduced to 50 r and supplemental hormone therapy was administered. Subsequently, her symptoms almost disappeared and a decrease in tumor size and an opening of the cerebral aqueduct were seen in the MVG. But at a dose of 3475 r, symptoms due to probable overdose developed and she died. At autopsy no tumor cells but a mass, which appeared to be a replacement of the tumor, was found in the pineal region. That sufficient irradiation caused a complete disappearance of the tumor located in the field of irradiation is often reported, but this case seems to tell us that, although irradiation is very effective, it can be fatal by damaging important centers in the adjacent area. When patients have endocrine disturbances, especially panhypopituitarism, it is said that they are less resistant to irradiation; one sudden death has been reported and a case of aggravation of panhypopituitarism after a few years' interval. From these experiences it is believed that, to treat this kind of case, avoidance of overdose as well as administration of supplementary hormone therapy is important.

In Case 3, as in other cases, the patients recovered enough to be able to attend school. A considerable reduction in the size of the tumor shadow by radiation therapy was seen in the MVG, but surgery revealed a remnant of teratoma that agreed with MVG findings. There are some reports that irradiation is not effective for teratomas, but since there is a combined form of teratoma of mature type and pinealomas of two cell pattern it is thought that irradiation can be effective for this type of teratoma. Thus, it can be recommended that teratomas be irradiated and followed with MVG, even though irradiation may sometimes cause hardening of tumor remnants, greater adhesion, and future difficulty in performing a radical operation.

In conclusion, when radiation therapy is prescribed, an effort to diagnose the disappearance of the tumor even in cases of clinical improvement should be continued, and if the tumor does not vanish, reirradiation and/or radical operation should be further considered. Rubin and Kramer once said: "The management of the patient does not end with the completion of radiation therapy." We think that this is quite true.

Summary

Five cases of pineal tumors, clinically diagnosed and treated with a shunting operation plus cobalt-60 radiation, have been reported. Consecutive ventriculographic studies with iodized oil (Myodil) were useful as a follow-up procedure to observe the size of the tumor during and after irradiation therapy. Although Myodil appeared to escape slowly from the ventricle into the blood stream through a shunting catheter, it did not cause any untoward complications.

In all five cases Co-60 radiation reduced the size of the demonstrable tumor. Returning patency of the cerebral aqueduct obstruction was confirmed by descent of the Myodil into the spinal canal in three of five cases. In two cases, however, a tumor contour could still be seen in the MVG. We have therefore emphasized that consecutive follow-up is important even after termination of radiation therapy.

Autopsy of one of the two fatal cases revealed complete elimination of the tumor by irradiation but overdose was suspected as the cause of death. Uniform irradiation could be dangerous and thus should be avoided in favor of therapy guided by the response of the specific tumor.

Acknowledgment

Grateful acknowledgment is made to Dr. Nakamichi Goro, Director of the Department of Radiology, Sendai Railway Hospital, for his constant interest and collaboration.
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References