Pineal and suprasellar germinomas

Results of radiation treatment

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The results of radiation treatment of 52 patients with a tumor in the pineal region or a suprasellar germinoma are analyzed. The overall 5-year survival rate was 59%. Ten patients in whom initial biopsy confirmed pineal germinoma were all alive 2 to 121 months from diagnosis, although two developed meningeal seeding at 2 and 7 months. Twelve of 15 patients 25 years old or younger with an unbiopsied tumor in the pineal region were alive 12 to 225 months after irradiation, with a 5-year survival rate of 81%. In comparison only five of 16 patients older than 25 years with a pineal region tumor survived, a 5-year survival rate of 37%. This marked age dependence in survival rates was attributed to a high proportion of germinomas in the younger patients and gliomas in the older patients.

KEY WORDS • germinoma • pineal tumor • suprasellar tumor • radiation

UNTIL recently, tumors in the pineal region were treated most often by relief of increased intracranial pressure with a shunt and irradiation, without a tissue diagnosis. Classically there has been a high operative mortality rate of 30% to 50% associated with biopsy or resection at this site. A high proportion of these patients responded very well to radiation treatment and 50% to 80% were alive 5 years later. However, surgical procedures in the pineal region are now practical, with an operative mortality rate of less than 5%. Cysts and benign teratomas may therefore be cured by total excision alone, but malignant tumors cannot be excised radically and require irradiation after biopsy, or partial or subtotal excision. This major change in surgical practice has allowed us to evaluate tumor-specific radiation treatment results for the first time.

The timing of this review was determined by our developing concern that meningeal seeding may be more frequent following surgical intervention at the primary site than with irradiation.

Clinical Materials and Methods

We have reviewed the records of 52 consecutive patients of all ages registered at the Princess Margaret Hospital, Toronto, during an 18-year interval, 1958 to 1976, in whom prior investigation had demonstrated a tumor in the pineal region or a tissue diagnosis of suprasellar germinoma had been made. All but one of these patients underwent radiation treatment at the Princess Margaret Hospital as part of their primary management. None
FIG. 1. Age and sex distribution of 52 patients with pineal region tumors or suprasellar germinomas.

FIG. 2. Tissue diagnosis of pineal region tumors is related to age and year of diagnosis. The upper graph summarizes 26 patients seen between 1958 and 1969, the lower graph shows data from 20 patients seen between 1970 and 1976.

had received previous radiation or specific systemic treatment other than Decadron. Initial radiological and surgical investigation was undertaken at one of the University of Toronto teaching hospitals in 51 of these patients. The patients lived in metropolitan Toronto or certain parts of northern Ontario, a population base of 2.5 to 3.0 million. The Princess Margaret Hospital contains the only radiation oncology unit serving this population. The patients were selected only insofar as following diagnosis, the neurosurgeon considered that radiation treatment was indicated.

<table>
<thead>
<tr>
<th>Tissue Diagnosis</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>pineal</td>
<td></td>
</tr>
<tr>
<td>germinoma</td>
<td>11*</td>
</tr>
<tr>
<td>malignant teratoma</td>
<td>2*</td>
</tr>
<tr>
<td>nonmalignant teratoma</td>
<td>1</td>
</tr>
<tr>
<td>pineoblastoma</td>
<td>1</td>
</tr>
<tr>
<td>primitive neuroectodermal tumor</td>
<td>1</td>
</tr>
<tr>
<td>astrocytoma</td>
<td>2*</td>
</tr>
<tr>
<td>glioblastoma multiforme</td>
<td>1*</td>
</tr>
<tr>
<td>no diagnosis</td>
<td>27</td>
</tr>
<tr>
<td>suprasellar</td>
<td></td>
</tr>
<tr>
<td>ectopic germinoma</td>
<td>6</td>
</tr>
</tbody>
</table>

*Indicates one patient in whom the diagnosis was made at the time of relapse or autopsy.

Summary of Cases

Age, Sex, and Tissue Diagnosis

A marked peak in incidence of these tumors occurred in the second decade of age. Of the 52 patients, 21 were in the age range of 10 to 19 years. Thirty-seven were aged 25 years old or younger, and in this group males outnumbered females by a ratio of 27:10, compared to 9:6 in patients over the age of 25 years (Fig. 1). Before 1970, biopsies were performed before irradiation in only three of 26 patients with a tumor in the pineal region. Since 1970, 12 of 20 patients have had biopsies performed. Twelve of 16 patients 25 years old or younger had a tissue diagnosis and one of the remaining four patients was explored surgically (Fig. 2).

Germinoma was diagnosed in nine of 10 initially biopsied patients between the ages of 10 and 25 years inclusive, and in only one of five biopsied patients under the age of 10 years. The other diagnoses were pineoblastoma, primitive neuroectodermal tumor, astrocytoma Grade III, and a possibly malignant teratoma. In only two of the patients older than 25 years was the tissue diagnosis known: one was malignant teratoma and one glioblastoma multiforme. In both, the diagnosis was made at the time of relapse. Overall, 31 of 52 patients had no tissue diagnosis at the time of primary irradiation.
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It is interesting that of the 11 patients with a pineal germinoma proven at any time, all were male and aged 7 through 25 years, whereas of the six additional patients with suprasellar germinoma, aged 10 to 25 years, three were male and three were female. The tissue diagnosis for the series is given in Table 1.

Survival

Overall, the 5- and 10-year crude actuarial survival rates were 59% and 55% (Fig. 3). In the subset of 31 patients with an unbiopsied tumor of the pineal region, survival was markedly age-dependent. The 5-year crude survival rate was 81% for those aged 25 years and under, compared with 37% for the older patients (Fig. 4).

Pineal Germinoma

In 10 patients the diagnosis of germinoma was established before irradiation. Eight of these patients had an initial shunt procedure (ventriculoperitoneal in six, ventriculoatrial in one, and Torkildsen in one); four underwent exploration and biopsy, two had partial excision, and four had subtotal excision of the tumor. All were then transferred to the Princess Margaret Hospital for radiation treatment. All are alive, 2 to 121 months from diagnosis, but two relapsed with meningeal seeding (Fig. 5 and Table 2).

Unbiopsied Pineal Region Tumors

Patients 25 Years or Younger. The data on proven germinomas may be supplemented by the treatment results in young patients with unbiopsied pineal region tumors. In an unknown proportion of these patients, the correct diagnosis would be germinoma. The data in Fig. 2 indicate that most of these patients very likely had a germinoma. The similarity of the survival curves in Figs. 4 and 5 for these
TABLE 2
Survival data of 10 patients with pineal germinoma related to tissue volume
irradiated and site of relapse

<table>
<thead>
<tr>
<th>Volume Irradiated</th>
<th>No. of Cases</th>
<th>Relapse Site</th>
<th>Time (mos)</th>
<th>No. of Survivors</th>
<th>Duration of Follow-up (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>local &amp; cranial</td>
<td>5</td>
<td>cord (1),</td>
<td>2</td>
<td>5</td>
<td>16+, 17+, 38+, 38+, 121+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cord &amp; VII</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>local &amp; craniospinal</td>
<td>5</td>
<td>nerve (1)</td>
<td></td>
<td>5</td>
<td>2+, 4+, 9+, 22+, 23+</td>
</tr>
<tr>
<td>total</td>
<td>10</td>
<td></td>
<td></td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Follow-up data are given in Table 3. Twelve of 15 patients have had no relapse. Two patients relapsed at the primary site late and died at 99 and 125 months, respectively. Late relapse of this degree is not characteristic of germinal tumors at any site. One patient relapsed with meningeal seeding at cord level at 20 months and at that time a tissue diagnosis of germinoma was obtained.

Patients Older than 25 Years. All 16 patients in this age group had shunts placed (Torkildsen shunt in 11); all 16 were irradiated to a local volume around the primary tumor only. Eleven of these patients have had recurrences (Fig. 4). In 10, the recurrence was at the primary site or the patient had no convincing evidence of control of the primary tumor. In one patient who developed meningeal spread, a diagnosis of malignant teratoma was established at the time of first relapse. This patient subsequently died with extensive disease confined to the central nervous system. This response to radiation treatment suggests that the majority of these tumors were adult gliomas arising in the immediate vicinity of the pineal gland, although not necessarily from it.

Suprasellar Germinoma

Five of the six patients with suprasellar germinoma presented with diabetes insipidus. All had a tissue diagnosis before irradiation, but partial excision was undertaken in only three. Tumor was present in the suprasellar region in all; it was also present within the sella in one, in the pineal region in one, and grossly involved the optic nerve in one.

The tissue volume irradiated was local in two, local plus whole brain in three, and local plus craniospinal in one. Following irradiation, two are alive without relapse at 190 and 207 months and four are dead. One patient developed meningeal spread evidenced by cord compression on the second day of elective craniospinal irradiation, and died within 2 months of diagnosis. The three remaining patients died at 3, 10, and 10 months after diagnosis. All four patients who died had major life-threatening defects in their control mechanisms for water and sodium. Hypernatremic coma contributed to or caused death in at least two of these patients. Three underwent autopsy at which no gross tumor was present.

Fig. 5. Survival (solid line) and relapse-free survival (broken line) of 10 patients with pineal germinomas measured from day of diagnosis.
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**TABLE 3**

Survival data of 15 patients (aged < 25 years) with unbiopsied pineal region tumors related to tissue volume irradiated and site of relapse

<table>
<thead>
<tr>
<th>Volume Irradiated</th>
<th>No of Cases</th>
<th>Relapse</th>
<th>Site</th>
<th>Time (mos)</th>
<th>No. of Survivors</th>
<th>Duration of Follow-up (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>local</td>
<td>10</td>
<td>2</td>
<td>primary (2)</td>
<td>uncertain</td>
<td>8</td>
<td>12, 14, 24, 69, 108, 157, 144, 225, 99, 125</td>
</tr>
<tr>
<td>local &amp; cranial</td>
<td>5</td>
<td>1</td>
<td>cord* (1)</td>
<td>20</td>
<td>4</td>
<td>35, 102, 125, 178, 29</td>
</tr>
<tr>
<td>total</td>
<td>15</td>
<td>3</td>
<td></td>
<td></td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

*Germinoma.

found. It appeared that tumor control by irradiation was as complete as in the pineal germinomas, but that irreversible damage to hypothalamic homeostatic control centers was of such a degree as to be incompatible with prolonged life in some of these patients. These patients will be reported in detail in a later communication.

**Radiation Treatment**

This analysis will be limited to patients with proven pineal or suprasellar germinoma and patients 25 years old or younger with an unbiopsied pineal region tumor. In total, 31 such patients were irradiated (10 with pineal germinoma, six with suprasellar germinoma, and 15 with unbiopsied pineal region tumor).

Only two patients, both unbiopsied, had recurrence at the primary site. Four additional patients developed meningeal seeding (three pineal and one suprasellar germinoma). None of the five patients with a pineal germinoma who received adjuvant craniospinal irradiation has relapsed, although the follow-up period is short (Table 2).

**Tissue Volume Irradiated**

The parameters that describe the tissue volume irradiated, namely field size at the primary site and adjuvant cranial (CR RT) or craniospinal (CS RT) irradiation, are given in Table 4 and related to relapse both at the primary site and in the meninges. It can be

**TABLE 4**

Radiation field size at primary site and use of adjuvant radiation compared with the site of subsequent tumor relapse*

<table>
<thead>
<tr>
<th>Field Size (sq cm)</th>
<th>Total Cases</th>
<th>Adjuvant RT</th>
<th>Primary Site</th>
<th>Cases with Relapse</th>
<th>Meningeal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CR CS Nil</td>
<td></td>
<td>Total Site Adjuvant RT</td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>5</td>
<td>— — 5</td>
<td>2</td>
<td>1 cord CR</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>7</td>
<td>5 1 1</td>
<td>—</td>
<td>2 cord CR</td>
<td></td>
</tr>
<tr>
<td>40-59</td>
<td>2</td>
<td>— 1 1</td>
<td>—</td>
<td>2 cord CS</td>
<td></td>
</tr>
<tr>
<td>60-79</td>
<td>6</td>
<td>3 2 1</td>
<td>—</td>
<td>1 cord + VII CR</td>
<td></td>
</tr>
<tr>
<td>80-99</td>
<td>3</td>
<td>— 2 1</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥100</td>
<td>8</td>
<td>5 — 3</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>31</td>
<td>13 6 12</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

*Analysis includes 31 patients aged < 25 years with pineal and suprasellar germinomas and unbiopsied pineal region tumors. RT = radiation therapy; CR = cranial; CS = craniospinal.
TABLE 5
Primary tumor irradiation dose related to local recurrence*

<table>
<thead>
<tr>
<th>Dose (Rads × 10³)</th>
<th>No. of Cases</th>
<th>Total</th>
<th>Primary Site Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-4.5</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.5-5.0</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.0-5.25</td>
<td>17</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>&gt;5.25</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>31</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*Analysis includes 31 patients aged <25 years with pineal and suprasellar germinomas and unbiopsied pineal region tumors.

seen that only two patients first relapsed at the primary site and that they were treated with the smallest fields (<30 sq cm) and did not receive adjuvant irradiation. We used small field sizes early in this series. Currently, the local field size is 60 to 100 sq cm in nearly all patients.

Adjuvant compartmental irradiation was used in all 10 patients with pineal germinoma (CR RT in five and CS RT in five), in four of the patients with suprasellar germinoma (CR RT in three and CS RT in one), and in five of 15 patients with an unbiopsied pineal region tumor (CR RT in five). One of six patients treated with CS RT has relapsed; in this case of suprasellar germinoma, cord compression occurred during the second day of CS RT. Three of 13 patients treated with CR RT first relapsed in the meninges. All had pineal germinoma and relapsed outside the irradiated volume in the spinal cord, although one patient simultaneously developed a seventh nerve palsy of lower motor neuron type. Conversely, none of the 10 patients with an unbiopsied tumor treated by local irradiation alone developed meningeal seeding.

Radiation Dose

These patients received daily radiation treatments, 5 or 6 days a week, at a dose rate of approximately 1000 rads a week to doses appropriate for a glioma. Twenty-two of 31 patients received 5000 rads or more (Table 5). Only one patient received less than 4000 rads (3520 rads, 28 sq cm field, unbiopsied), and is well 225+ months later. The two patients who relapsed at the primary site received 5000 rads, but to a small volume.

The dose employed in adjuvant CR RT and CS RT in 19 patients varied: it was less than 2000 rads in three patients, 2000 to 3000 rads in four patients, 3000 to 4000 rads in 10 patients, and greater than 4000 rads in two patients. Four of these 19 patients relapsed: two in the cord after CR RT, one in the cord on the second day of CS RT, and one simultaneously in the cord and the seventh nerve after CR RT. This last patient could reasonably be regarded as an example of reseeding from the cord to the cerebral meninges.

Discussion

Primary Tumor Control by Irradiation

The primary tumor was controlled by irradiation in all 10 proven cases of pineal germinoma and in the unknown number among the 15 unbiopsied patients aged 25 years or younger. In the latter group, two patients relapsed at the primary site but did so very late and died 99 and 125 months after diagnosis. It is very unlikely that their tumors were germinomas. Thus, we conclude that pineal germinomas are highly curable by irradiation.

Because we have no proven example of a germinoma recurring at the primary site after irradiation, it is not possible to evaluate prognostic factors for control of the primary tumor related either to tumor biology or to treatment. In this series, tumor control was achieved regardless of whether the tumor was unbiopsied, biopsied, or resected. Likewise, we cannot analyze radiation dose or volume at the primary site for the prospect of control. All 10 proven pineal germinomas received a dose close to 5000 rads in 25 fractions to a generous volume around the primary tumor. All 10 patients received elective cranial irradiation and five received spinal irradiation. In our earlier experience with unbiopsied tumors in the pineal region there was a wider dose range to the primary tumor: five of 15 patients received a dose less than 5000 rads. None of the patients who received a lower dose relapsed. Five of these 15 unbiopsied patients received elective CR RT, but none received CS RT. These data suggest that the unbiopsied pineal germinomas were
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probably truly limited to the site of origin and the immediately adjacent tissues.

The radiation dose employed was developed during the years when these tumors were not biopsied and necessarily needed to be high enough to treat a glioma adequately. Similar relatively high doses of radiation have been used with considerable success by all recent authors. However, it is noteworthy that the occasional patient who received a lower radiation dose appeared to do as well. We believe the optimal radiation dose is the minimum dose that will provide close to 100% local control, for although the immediate harmful effects of irradiation on nervous tissue at these dose levels may be subtle, catastrophic effects do occur decades later and are dose-related. The optimum local radiation dose for pineal germinomas is unknown. Its determination should be one important objective of any current investigative program.

The appropriate tissue volume to irradiate is also not clear. A margin of 2 to 3 cm around a pineal region tumor requires radiation fields of $8 \times 8$ cm or larger.

Irradiation of such a restricted volume is usually successful. Eight of our 10 patients aged 25 years or younger, with an unbiopsied pineal region tumor, who were treated by local irradiation, are alive. Cole reported that 14 of 16 unbiopsied patients were still alive; Sano reported approximately 69% of 34 biopsied patients with germinomas in the pineal or suprasellar regions were alive at 5 years.

The irradiation of any larger tissue volume can be justified only as an adjuvant treatment to control occult meningeal seeding.

Meningeal Seeding

Literature review indicated that the risk of meningeal seeding in pineal or suprasellar germinoma was 10% to 15%. Based on this risk factor, the known high-cure rate from local irradiation alone, and the morbidity associated with craniospinal irradiation, most authors have favored some form of local irradiation alone unless there was evidence of local seeding. Of recent authors, only DeGirolami and Schmidek advocated the routine use of elective craniospinal irradiation. Today we can hope to salvage some of the patients who have meningeal seeding by additional radiation and combination chemotherapy as was accomplished in our two patients who remain in complete remission 14+ and 31+ months after meningeal relapse (Table 2), but it is possible that the late effects associated with intensive retreatment programs may be prohibitive.

The exact risk of meningeal relapse remains uncertain. The literature primarily reflected pathology reviews or reports in which this complication was under special scrutiny. In autopsy series, the denominator is the total number autopsied, an undefined proportion of these patients, so that the true incidence may be overestimated. Reports drawing attention to this complication likewise tend to overestimate the incidence. Conversely, the literature contained records of many patients who died postoperatively or very early in the follow-up period, before occult meningeal seeding would have had an opportunity to progress to overt meningeal disease. The rarity of this tumor, the absence of sizeable series of patients treated by uniform methods, and the improving survival rate during the last two decades compound the difficulty of reliably estimating the rate of meningeal spread.

It is well established in autopsy series that local seeding in the walls of the third and lateral ventricles is frequent. Spread by way of the cerebrospinal fluid (CSF) seems most likely. Sano recently reported that at diagnosis it is possible to culture tumor cells from the CSF in 60% of patients aged under 15 years old.

For these reasons there may be a place for adjuvant irradiation beyond the local tumor. It has been proposed that such an increased irradiated volume should encompass, at a minimum, the whole ventricular system. Logically, this volume may be increased to include the whole brain or the whole craniospinal axis, but at present there are no data that allow the use of these relative volumes to be evaluated.

In the current era of successful biopsy and resection, it could be that surgical intervention will increase the risk of seeding, as was seen in two of our five patients with a pineal germinoma in whom the spine was not irradiated, compared to none of five in whom craniospinal irradiation was undertaken. Two of us (W.J.K.S. and C.W.K.), therefore,
currently favor routine elective craniospinal irradiation. Conversely, in reporting 34 proven germinomas in the pineal and suprasellar region, Sano\cite{2} did not mention meningeal spread as a problem, and Wara, et al.,\cite{28} found only one local recurrence among six surgically treated patients.

**Gonadal Germinomas**

We believe that an analogy should be made with gonadal germinomas for these are histologically identical tumors in which treatment by resection and irradiation has been very successful. At this institution, in clinical Stage I seminoma of the testis, orchidectomy followed by 2500 rads in 20 fractions to the lymphatic drainage areas in the para-aortic and pelvic regions has been associated with only a 1% risk of first relapse within the irradiated volume in approximately 300 patients. In ovarian dysgerminoma, provided a grossly complete surgical resection had been accomplished, postoperative irradiation to the whole abdomen to a dose of 2500 rads in 20 fractions prevented abdominal relapse in all 11 patients treated at this institution.

In gonadal germinoma, a dose of 2500 rads in 20 fractions is therefore effective in eradicating occult disease. It seems likely that this should also be true for pineal germinoma and is worthy of trial.

**A New Conservatism**

The addition of the computerized tomography (CT) scan to classical ventricular contrast and angiographic studies has enhanced the accuracy of preoperative diagnosis. Simple cysts and benign cystic teratomas may now be diagnosed preoperatively with some assurance, but the differential diagnosis between the solid malignant tumors (germinoma, malignant teratoma, astrocytoma, ependymoma, and the rarer tumors) remains difficult.

A case may be made for a trial of irradiation in those patients likely to have a pineal germinoma.\cite{17,24} If a rapid response is seen on serial CT scans, with disappearance of the tumor in 1 to 3 months, the working diagnosis of germinoma can reasonably be considered to be established.

The germinoma is a very rapidly responding, radiocurable tumor, and if the patients with these tumors can be appropriately selected, the morbidity associated with their surgical treatment can be avoided. Such a strategy assumes that partial or subtotal resection of a germinoma does not contribute to cure, and that there is an appreciable operative morbidity and a high degree of diagnostic accuracy. Should tumor response be delayed, exploration, biopsy, and resection, if possible, would still be indicated. Experience with this new approach is fragmentary and clearly requires extension.

**Conclusions**

Pineal germinoma is a rare tumor in which irradiation will produce a very high local cure rate, but meningeal seeding occurs in a moderate proportion of these patients and is the chief obstacle to cure with minimum morbidity. There are three current important therapeutic questions: 1) What is the optimal radiation dose? 2) Is routine elective cranial or craniospinal irradiation indicated? and 3) Is biopsy and resection of value?

At this time it appears that currently available treatment methods are able to eradicate a pineal germinoma, but if answers to these basic questions are to be obtained and an optimal treatment plan is to evolve rapidly, collaborative endeavor on a national or international scale is necessary.

**Acknowledgments**

Eight of the reported cases were treated by our present or former colleagues in radiation oncology at the Princess Margaret Hospital: C. L. Ash, F. A. Beale, J. M. M. Darte, and M. V. Peters, to whom we are indebted.

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