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## MALIGNANT PINEAL PARENCHYMAL TUMORS IN ADULT PATIENTS: PATTERNS OF CARE AND PROGNOSTIC FACTORS

**OBJECTIVE:** The aim of our study was to analyze patterns of care and to identify prognostic factors in patients at least 18 years of age who received radiotherapy for malignant pineal parenchymal tumors.

**METHODS:** In a multicenter, retrospective study, we analyzed data for 37 previously published cases and 64 patients treated at the participating institutions.

**RESULTS:** A total of 56 patients received postoperative radiotherapy, and 45 patients received primary radiotherapy. Chemotherapy was administered to 34 patients. The median follow-up period was 38 months, and median overall survival was 100 months. The variables that significantly influenced overall survival were the extent of disease (localized versus disseminated;  $P = 0.0002$ ), differentiation (pineal parenchymal tumor of intermediate differentiation versus pineoblastoma;  $P = 0.001$ ), and residual disease ( $\geq 50\%$  versus  $< 50\%$  reduction in size;  $P < 0.0001$ ). In a multivariate analysis, the parameters turned out to be independent risk factors. The median survival in patients with local or spinal failure was 15 months. Local control was better in older patients ( $\geq 32$  yr versus  $< 32$  yr;  $P = 0.02$ ). Spinal control was more successful in patients with pineal parenchymal tumors of intermediate differentiation than it was in patients with pineoblastomas ( $P = 0.03$ ). Nine of 45 treatment failures occurred later than 5 years after treatment.

**CONCLUSION:** Stage, histological characteristics, and response are independent risk factors in adults with malignant pineal parenchymal tumors. Late relapses are common.

**KEY WORDS:** Multivariate analysis, Neurosurgery, Pineoblastoma, Prognosis, Radiotherapy

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The pineal gland is host to a spectrum of neoplasms. Those neoplasms that are considered to derive from or to differentiate toward pineal parenchymal cells are rare and account for just 0.1 to 0.3% of all histologically verified intracranial tumors (11). The typical pineal parenchymal tumor (PPT) in adults is the pineocytoma (PC). The tumor is well defined, and complete excision usually yields long-term control. In contrast, pineoblastomas (PBs) and PPTs of intermediate differentiation (PPTIDs) are extremely rare in adults, and little is known regarding their clinical course and patient outcome. To date, the single publication that focused on this topic reported 11 new patients and 10 previously published cases (9). The aim of our multicenter, retrospective study was to add a de-

scription of a substantial number of new patients with histologically proven PB or PPTID to the previously published cases, to analyze patterns of care, and to identify patient- and tumor-related prognostic factors. Because of the retrospective nature of our study, it does not focus on the prognostic impact of treatment-related variables.

### PATIENTS AND METHODS

#### Patient Selection

Inclusion criteria were defined as histologically verified PB or PPTID, patient age at least 18 years, primary or postoperative radiotherapy, known survival, and known status (i.e., dead, alive) at last follow-up. We searched

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MEDLINE for reports published in 1975 or later that contained the terms *pineoblastoma*, *pineal region tumors*, and *primitive neuroectodermal tumors*. Only publications that provided individual patient data were considered (Group A; n = 37), and the data from these publications are compiled in Table 1 (2, 3, 5, 6, 10, 16, 17, 20, 21, 26–28, 30, 32, 35–38, 44–47).

If reports published in 1990 or later included adult patients with PB or PPTID, but the inclusion criteria were incomplete, the authors were contacted by postal mail or fax and were asked to provide the missing information. Three authors answered our questionnaire (6, 16, 35). Individuals at the four participating institutions in our study (University Hospital, Freiburg, Germany; Center de Radiothérapie, Nice, France, for the national French registry; Mayo Clinic, Scottsdale, AZ; and University of California, San Francisco, San Francisco, CA) reviewed their institutions' archives for the records of adult patients with PB or PPTID. Data from individual patients in some cases had been published previously (9, 15). For these patients, data on relapse and survival were updated. Other cases had been published previously without individual patient data (25, 42, 43). For these patients, data are presented in this article for the first time. Furthermore, all institutions added new and previously unpublished cases to our study data (Group B; n = 64) (Table 2). An aggregate total of 101 patients, comprising previously published cases and cases culled from the archives of the four participating institutions, met the study's inclusion criteria.

### Extent of Disease

Patients were entered into the analysis as having disseminated disease if the magnetic resonance imaging (MRI) studies revealed tumor, the patient's cerebrospinal fluid (CSF) tested positive for tumor cells, or both the MRI and CSF examinations were indicative of tumor dissemination. Patients in whom these examinations were negative were regarded as having localized disease. Patients from whom imaging studies were not obtained were not analyzed with regard to this variable.

### Histological Characteristics (Type of Tumor)

The histopathological diagnoses for the Group A patients were entered into the analysis as published. For Group B patients, the tumor specimens were reviewed by local neuropathologists. The American patients (Patients 77–101) were histologically classified as described by Schild et al. (43). The French patients (Patients 49–76) were classified according to the method of Jouvét et al. (23), with two different tumor grades for PPTID. The German patients (Patients 38–48) were classified according to World Health Organization (WHO) criteria (31).

### Residual Disease after Initial Treatment (Response)

No residual disease after initial treatment was defined as the complete resolution of all lesions as visualized on computed tomographic or MRI scans. Minor residual disease after

initial treatment was defined as at least a 50% decrease in tumor size. Major residual disease after initial treatment was defined as less than a 50% reduction in size, any increase in tumor size, or any appearance of new tumor sites. Patients who did not undergo post-therapeutic imaging were not analyzed with regard to this variable. These terms have the same basic meaning as complete response, partial response, and stable or progressive disease, but the latter terms normally are used to describe the effects of chemotherapy only. We chose to use the phrase *residual disease after initial treatment* to make clear that, in the context of this study, *treatment* means any therapeutic intervention (i.e., radiotherapy, surgery, chemotherapy) for newly diagnosed malignant PPT.

### Treatment Failure

Treatment failures were recorded by site, including the pineal region, the spine, and extraneural sites. Failure included the recurrence or the progression of disease in sites identified as having active disease at presentation or the occurrence of a relapse in a site that was free of disease at presentation. The time until treatment failure was determined on the basis of the date on which radiological or biopsy confirmation of relapse at one of these sites occurred.

### Statistics

Overall survival was defined as the time from diagnosis or first treatment until death. Progression-free survival was defined as the time from diagnosis or first treatment until 1) the progression or the recurrence of disease or 2) death. Local control was defined as the time from diagnosis or first treatment until the progression or the recurrence of disease in the pineal region. Spinal control was defined as the time from diagnosis or first treatment until the progression or the recurrence of disease in the spine. The Kaplan-Meier method was used to estimate overall survival, progression-free survival, local control, and spinal control (24). The log-rank test was used to test for statistically significant differences (29). All variables that were calculated as  $P < 0.1$  in the univariate analysis were included in multivariate analysis using the Cox model (i.e., proportional hazards) (12).

## RESULTS

The median follow-up period was 38 months (range, 3–246 mo; 25% quartile, 18 mo; 75% quartile, 69 mo). At the time of the last follow-up examination, 38 patients had died, and 63 patients were still alive. The median overall survival was 100 months (75, 62, and 41% at 3-, 5-, and 10-yr follow-up, respectively) (Fig. 1). Nine patients lived longer than 10 years after the diagnosis of malignant PPT. The results of the univariate analyses are listed in Table 3.

### Patient Characteristics

Forty-eight patients were men, and 53 patients were women. Their median age was 32 years (range, 18–77 yr; 25%

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TABLE 1. Adult patients with malignant pineal parenchymal tumors<sup>a</sup>

Patient no.	Series (ref. no.)	Sex/age (yr)	Stage	Imaging (loc/spin)	CSF	Shunt	Surgery	RTC (Gy)	RTS (Gy)
1	Neuwelt et al., 1979 (36)	F/23	Loc	CT /no	NA	Yes	No	40.0	No
2	Neuwelt et al., 1979 (36)	F/38	Loc	CT /no	—	Yes	GTR	50.0	34.0
3	Borit et al., 1980 (5)	F/34	NA	VG /no	NA	No	STR	50.0	30.0
4	Jooma and Kendall, 1983 (21)	F/23	Loc	CT /no	NA	No	Res	Postop RT, no details	
5	Lesnick et al., 1985 (27)	F/43	Loc	CT /no	—	No	GTR	39.6	36.0
6	Uematsu et al., 1988 (46)	F/23	Loc	VG /no	NA	Yes	Bio	45.0	No
7	Jacobs and Rosenberg, 1989 (20)	F/20	Loc	CT /no	NA	Yes	Res	Postop RT, no details	
8	Vaquero et al., 1992 (47)	F/48	Loc	CT /no	No	No	Res	40.0	10.0
9	Linggood and Chapman, 1992 (28)	M/35	Loc	NA/NA	—	No	Bio	50.0	30.0
10	Linggood and Chapman 1992 (28)	M/30	Loc	NA/NA	—	Yes	Bio	40.0	30.0
11	Fuller et al., 1993 (17)	M/25	Loc	CT /no	NA	NA	STR	30.6	30.6
12	Fuller et al., 1993 (17)	M/22	Loc	CT /no	NA	NA	STR	No	No
13	Mena et al., 1995 (31)	M/18	Loc	CT /no	NA	No	STR	50.75	Yes
14	Mena et al., 1995 (31)	M/66	Loc	CT /no	NA	NA	Res	50.4	No
15	Patil et al., 1995 (37)	F/20	Loc	MRI /no	—	Yes	Bio	45.6	36.8
16	Matsumoto et al., 1995 (30)	F/36	Loc	MRI /MRI	—	Yes	Bio	0	0
17	Tada et al., 1996 (44)	F/36	Loc	MRI /no	NA	Yes	Bio → Res	Neoadjuvant: 40.0, no target volume	
18	Ashley et al., 1996 (2)	F/23	Dis	MRI /MRI+	—	NA	Bio	Yes	Yes
19	Ashley et al., 1996 (2)	M/23	Loc	MRI /MRI	—	NA	STR	Yes	Yes
20	Ashley et al., 1996 (2)	M/19	Loc	MRI /MRI	—	NA	STR	Yes	Yes
21	Ashley et al., 1996 (2)	M/21	Loc	MRI /MRI	—	NA	STR	Yes	Yes
22	Ashley et al., 1996 (2)	F/22	Loc	MRI /MRI	—	NA	STR	Yes	Yes
23	Ashley et al., 1996 (2)	M/21	Loc	MRI /MRI	—	NA	STR	Yes	Yes
24	Brockmeyer et al., 1997 (6)	M/23	Loc	MRI /MRI	—	No	GTR	Yes	Yes
25	Kurisaka et al., 1998 (26)	F/29	Loc	MRI /no	NA	No	STR	0	0
26	Kurisaka et al., 1998 (26)	M/41	Loc	MRI /no	NA	No	STR	0	0
27	Fujita et al., 1999 (16)	M/19	Loc	MRI /MRI	—	Yes	Bio	30.0	30.0
28	Paulino and Melian, 1999 (38)	M/32	Loc	MRI /MRI	—	NA	STR	Yes	Yes
29	Tsumanuma et al., 1999 (45)	F/73	Loc	NA /NA	NA	No	GTR	0	0
30	Tsumanuma et al., 1999 (45)	F/31	Loc	NA /NA	NA	No	Bio	0	0
31	Tsumanuma et al., 1999 (45)	M/57	Loc	NA /NA	NA	No	GTR	Yes	Yes
32	Barlas et al., 2000 (3)	M/31	Loc	MRI /MRI	—	Yes	Bio	36.0	36.0
33	Barlas et al., 2000 (3)	M/21	Loc	MRI /MRI	—	Yes	Bio	36.0	36.0
34	Barlas et al., 2000 (3)	F/36	Loc	MRI /MRI	—	Yes <sup>b</sup>	Bio	36.0	36.0
35	Nakamura et al., 2000 (35)	F/51	Loc <sup>b</sup>	MRI /no	— <sup>b</sup>	No <sup>b</sup>	STR <sup>b</sup>	40.0 <sup>b</sup>	0 <sup>b</sup>
36	Nakamura et al., 2000 (35)	M/49	Loc	MRI /no	—	Yes	STR	0	0
37	Charafe-Jauffret et al., 2001 (10)	M/26	Loc	MRI /no	NA	Yes	STR	20.0	36.0

<sup>a</sup> Loc, localized disease; spin, spinal; CSF, cerebrospinal fluid (examination); RTC, total dose radiotherapy to the cranium; RTS, total dose radiotherapy to the spine; RTP, total dose radiotherapy to the pineal region; CTx, chemotherapy; Resp, response; CT, computed tomography; NA, not available; RT, radiotherapy; +, dead; —, cerebrospinal fluid free from tumor cells; GTR, gross total resection; NED, no evidence of disease; VG, ventriculography; STR, subtotal resection; Res, resection (extent not specified); Postop, postoperative; CR, complete response; Bio, biopsy; mets, metastasis; dis., prog., disease progression; MRI, magnetic resonance imaging; PPTID, pineal parenchymal tumor of intermediate differentiation (pineoblastoma all others); <sup>125</sup>I, iodine-125 seed; VP16, etoposide; Cis, cisplatin; HU, hydroxyurea; <sup>192</sup>I, seed/afterloading; PR, partial response; CaP, carboplatin; CP, cyclophosphamide; Eto, etoposide; Vin, vinblastine; Ifo, ifosfamide; cer, cerebral; RS, radiosurgery; MRI+, magnetic resonance imaging with evidence of spinal dissemination.

<sup>b</sup> Personal communication.

quartile, 23 yr; 75% quartile, 42 yr). Age and sex were not of prognostic importance (median overall survival of male patients, 86 mo, versus median survival of female patients, 116 mo,  $P = 0.55$ ; median survival in patients  $\leq 32$  yr, 100 mo, versus median survival in patients  $> 32$  yr, 86 mo,  $P = 0.85$ ). When analyzed as a continuous variable, patient age did not determine overall survival ( $P = 0.91$ ). It was associated with

degree of malignancy, however. The diagnosis of PB was made in 90% of patients younger than 23 years of age, in 69% of patients 23 to 42 years of age, and in 58% of patients 42 years of age or older ( $P = 0.003$ ). No age correlation was observed within either the PB group or the PPTID group when these groups were analyzed separately. No patient had a history of retinoblastoma.

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TABLE 1. Continued

RTP (Gy)	CTx	Resp	Relapse (site/time[mo]/therapy)	Survival		Comments (original patient no., year of treatment)
				Mo	Status	
55.0	No	NA	Spin/10/RT	11	+	(4), died of spinal metastases, diagnosed at autopsy
50.0	No	NA	No	6	Alive	(5), NED, 1972–1978
50.0	No	NA	Spin/12/RT	24	+	(8), died of tumor, 1967
	No	NA	No	18	Alive	(21), NED
55.6	No	CR	No	16	Alive	(2), NED
45.0	No	PR	Loc/53/RT Loc/72/RT Loc/84/no	100	+	Died of tumor, autopsy, spin mets, 1974
	No	NA	Femur/18/surgery	18	Alive	
50.0	No	NA	Dis. prog., no details	84	+	Died of tumor, 1970–1990
50.0	No	NA	Dis. prog., no details	27	+	Died of tumor, 1972–1985
55.0	No	NA	No	72	Alive	NED
54.0	No	NA	Spin/10/NA	14	Alive	(3), alive with disease, 1948–1988
55.8	No	NA	Loc/12/NA	19	Alive	(12), alive with disease
50.75	No	NA	Spin/36/CT	58	+	(9), 1970–1990
50.4	No	NA	No	46	Alive	(3), NED, PPTID
40 ( <sup>125</sup> I) + 53.1	VP16, Cis, HU	CR	No	18	Alive	NED
36 ( <sup>192</sup> Ir)	No	PR	No	8	Alive	(2), NED, 1993, PPTID
40 ( <sup>192</sup> Ir)	CaP, VP16	PR				
Yes	CP	NA	No	32	Alive	(1), NED
Yes	CP	NA	No	20	Alive	(2), NED
Yes	CP	NA	No	16	Alive	(3), NED
Yes	CP	NA	No	28	Alive	(4), NED
Yes	CP	NA	No	14	Alive	(5), NED
Yes	CP	NA	No	24	Alive	(6), NED
Yes	Cis/Eto	CR	No	100 <sup>b</sup>	Alive <sup>b</sup>	NED, 1993
20.0 RS	Cis/Vin	PR	No	35	Alive	(3), NED, PPTID
30	CaP/Ifo	CR	No	67	Alive	(4), NED, PPTID
54.0	Ifo/CaP/Eto <sup>b</sup>	CR	No <sup>b</sup>	36 <sup>b</sup>	Alive <sup>b</sup>	NED, 1998 <sup>b</sup>
Yes	No	NA	No	61	Alive	(4), 1977–1996
Yes	No	CR	No	20	Alive	(6), NED, PPTID
Yes	No	CR	Loc/62/RT Loc/spin/110/RT/CT	168	+	(7), died of tumor, PPTID
Yes	No	CR	No	21	Alive	(8), NED, PPTID
50.4	No	CR	Loc/24/ <sup>125</sup> I Loc/13/ <sup>125</sup> I Loc/cer/spin/RT/CT	70	Alive	(1), alive with disease, 1991–1996
50.4	No	CR	Loc/18/ <sup>125</sup> I Loc/27/ <sup>125</sup> I	57	Alive	(2), NED
50.4	No	CR	No	51	Alive	(3), NED
60 <sup>b</sup>	No <sup>b</sup>	NA	Dis. prog., no details <sup>b</sup>	16 <sup>b</sup>	+ <sup>b</sup>	(2), 1998 <sup>b</sup>
60	No	NA	Spin/NA	12	+	(3), died of tumor
20.0	No	NA	Spin/sacrum/96/surgery + CT Spin/108/CT	108	Alive	(1), alive with disease

Extent of Disease

Pineal tumors were diagnosed on the basis of computed tomography and MRI in 29 and 63 patients, respectively. Four patients who were treated before 1970 underwent air encephalography or ventriculography. In five Group A patients, no information on imaging of the pineal region was available. The neuraxis was staged in 50 patients at the time of diagnosis by spinal MRI (n = 45) or by myelography (n = 5). The MRI scans in seven patients were positive for either focal lesions or widespread leptomeningeal metastases. In six patients, the CSF, which was obtained by either lumbar puncture or ventricular sampling for cytological examination, contained tumor cells.

Two patients (Patients 73 and 90) had tumor cells in the CSF but had normal myelograms or MRI scans. Two other patients (Patients 84 and 89) had no evidence of tumor cells in the CSF, but their MRI scans revealed spinal metastases. In one patient (Patient 93) who had clinical evidence of disease dissemination, the cytological examination of the ventricular CSF and MRI of the spine revealed no abnormalities.

The extent of disease at first diagnosis could be assessed in 51 patients. Thirteen patients presented with disseminated disease. Patients with PPTID were more likely than patients with PB to present with localized disease (76 versus 90%); however, this difference was not statistically significant (P =

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TABLE 2. Adult patients with malignant pineal parenchymal tumors, new cases<sup>a</sup>

Patient no.	Series (ref. no.)	Sex/age (yr)	Stage	Imaging (loc/spin)	CSF	Shunt	Surgery	RTC (Gy)	RTS (Gy)
38	Present study, 2001	F/19	Loc	MRI /MRI	NA	No	Bio	36.0	36.0
39	Present study, 2001	F/49	Loc	CT /no	—	Yes	Bio	36.0	36.0
40	Present study, 2001	M/60	Loc	CT /no	NA	Yes	Bio	0	0
41	Present study, 2001	F/44	Loc	MRI /no	—	Yes	Bio	36.0	36.0
42	Present study, 2001	F/57	Dis	MRI /MRI+	NA	No	Bio	21.6	19.2
43	Present study, 2001	F/30	Loc	CT /no	NA	Yes	Bio	34.2	34.2
44	Present study, 2001	M/35	Loc	MRI /MRI	NA	Yes	Bio	36.0	36.0
45	Present study, 2001	M/21	Dis	MRI /MRI+	Yes	No	Bio	50.0	50.0
46	Present study, 2001	M/35	Loc	MRI /MRI	NA	Yes	Bio	35.2	35.2
47	Present study, 2001	F/31	Loc	MRI /no	—	Yes	Bio	39.0	36.0
48	Present study, 2001	F/25	Loc	MRI /MRI	NA	Yes	Bio	36.0	36.0
49	Fauchon et al., 2001 (15)	F/35	Loc	MRI /no	—	Yes	GTR	0	0
50	Fauchon et al., 2001 (15)	M/37	Loc	CT /no	—	Yes	STR	20.0	0
51	Fauchon et al., 2001 (15)	F/32	Loc	MRI /no	—	No	Bio	0	0
52	Fauchon et al., 2001 (15)	F/52	Loc	CT /MRI	—	Yes	Bio	26.5	0
53	Fauchon et al., 2001 (15)	M/31	Loc	MRI /MRI	—	Yes	Bio	36.0	36.0
54	Fauchon et al., 2001 (15)	M/64	Loc	MRI /no	—	Yes	GTR	0	0
55	Fauchon et al., 2001 (15)	F/34	Loc	MRI /no	—	Yes	Bio	36.0	0
56	Fauchon et al., 2001 (15)	F/45	Loc	CT /no	—	No	Bio	0	0
57	Fauchon et al., 2001 (15)	M/42	Loc	MRI /no	—	Yes	Bio	36.0	36.0
58	Fauchon et al., 2001 (15)	F/23	Loc	CT /no	—	No	STR	30.0	0
59	Fauchon et al., 2001 (15)	F/34	Loc	MRI /no	—	Yes	STR	0	0
60	Fauchon et al., 2001 (15)	F/33	Loc	CT /no	—	Yes	NA	0	0
61	Fauchon et al., 2001 (15)	F/33	Loc	CT /no	—	No	Bio	0	0
62	Fauchon et al., 2001 (15)	F/32	Loc	MRI /MRI	—	Yes	Bio	0	0
63	Fauchon et al., 2001 (15)	M/22	Loc	CT /no	—	Yes	STR	36.0	36.0
64	Fauchon et al., 2001 (15)	F/19	Loc	MRI /MRI	—	Yes	STR	38.0	36.0
65	Fauchon et al., 2001 (15)	M/26	Loc	MRI /no	—	Yes	GTR	35.0	30.0
66	Fauchon et al., 2001 (15)	M/34	Dis	MRI /no	Yes	Yes	STR	40.0	0
67	Fauchon et al., 2001 (15)	M/24	Loc	MRI /MRI	—	Yes	STR	40.0	30.0
68	Fauchon et al., 2001 (15)	M/18	Loc	MRI /no	—	Yes	Bio	36.0	38.6
69	Fauchon et al., 2001 (15)	F/64	Loc	CT /no	—	Yes	Bio	0	0
70	Fauchon et al., 2001 (15)	M/44	Loc	MRI /MRI	—	Yes	GTR	36.0	36.0
71	Fauchon et al., 2001 (15)	F/33	Loc	CT /no	—	Yes	STR	29.0	29.0
72	Fauchon et al., 2001 (15)	F/24	Loc	MRI /no	—	Yes	STR	0	0
73	Fauchon et al., 2001 (15)	F/30	Dis	MRI /MRI	Yes	Yes	STR	20.0	0
74	Fauchon et al., 2001 (15)	F/18	Loc	CT /MRI	—	Yes	Bio	19.8	0
75	Fauchon et al., 2001 (15)	F/20	Loc	CT /no	—	Yes	GTR	0	0
76	Fauchon et al., 2001 (15)	M/44	Loc	MRI /MRI	—	Yes	Bio	40.0	36.0
77	Schild et al., 2001 (42,43)	M/26	Loc	VG /no	NA	NA	Bio	0	0
78	Schild et al., 2001 (42,43)	M/19	Loc	VG /no	NA	NA	Bio	0	0
79	Schild et al., 2001 (42,43)	F/66	Loc	MRI /MG	—	NA	Bio	0	0
80	Schild et al., 2001 (42,43)	F/38	Loc	CT /MRI	—	NA	GTR	54.0	0
81	Schild et al., 2001 (42,43)	F/55	Loc	CT /MG	—	NA	STR	36.0	36.0
82	Schild et al., 2001 (42,43)	M/77	Loc	MRI /no	NA	NA	Bio	50.4	0
83	Schild et al., 2001 (42,43)	M/46	Loc	CT /MG	—	NA	GTR	30.6	0
84	Schild et al., 2001 (42,43)	M/22	Dis	CT /MRI+	—	NA	Bio	36.6	36.6
85	Schild et al., 2001 (42,43)	F/30	Loc	CT /MG	—	NA	GTR	30.6	30.6
86	Schild et al., 2001 (42,43)	M/26	Dis	MRI /MRI+	NA	NA	Bio	45.0	36.0
87	Schild et al., 2001 (42,43)	F/18	Loc	MRI /MRI	—	NA	STR	36.0	36.0
88	Schild et al., 2001 (42,43)	F/25	Loc	MRI /MRI	—	NA	STR	36.0	36.0
89	Chang et al., 1995 (9)	F/30	Dis	MRI /MRI+	—	No	STR	41.4	45.0
90	Chang et al., 1995 (9)	F/31	Dis	MRI /MRI	Yes	Yes	STR	24.0	24.0
91	Chang et al., 1995 (9)	M/39	Dis	MRI /MRI	Yes	Yes	STR	24.0	24.0
92	Chang et al., 1995 (9)	M/40	Dis	MRI /MRI+	—	Yes	Bio	55.7	54.0
93	Chang et al., 1995 (9)	M/25	Dis	MRI /MRI	—	Yes	STR	30.6	30.6
94	Chang et al., 1995 (9)	M/27	Loc	MRI /MRI	—	Yes	GTR	35.0	35.0
95	Chang et al., 1995 (9)	F/55	Loc	MRI /MRI	—	Yes	STR	30.0	30.0
96	Chang et al., 1995 (9)	M/59	Loc	MRI /MRI	—	Yes	STR	30.0	30.0
97	Chang et al., 1995 (9)	M/34	Loc	MRI /MRI	—	Yes	STR	42.0	30.0
98	Chang et al., 1995 (9)	M/56	Loc	MRI /MRI	—	No	STR	30.0	30.0
99	Chang et al., 2001	F/42	Loc	MRI /MRI	—	Yes	GTR	36.0	36.0
100	Chang et al., 2001	M/32	Loc	MRI /MRI	—	Yes	Bio	36.0	36.0
101	Chang et al., 2001	F/35	Dis	MRI /MRI	Yes	Yes	Bio	36.0	36.0

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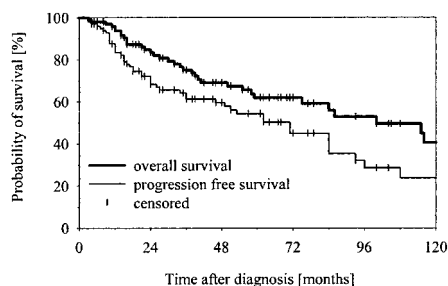
TABLE 2. Continued

RTP (Gy)	CTX	Resp	Relapse (site/time[mo]/therapy)	Survival		Comments (original patient no., year of treatment)
				Mo	Status	
66.0	Cis/CU/Vi	NA	No	24	Alive	NED, 1999
50.0	No	CR	No	125	Alive	NED, 1991
56.0	No	NA	No	3	+	Died of pneumonia, 1997
60.0	No	CR	No	38	Alive	PPTID, NED, 1998
21.6	No	PD	Spin/3/no	4	+	1996
55.0	No	SD	Loc/10/no	16	+	Died of tumor, 1991
57.6	No	NA	Dis. prog., no details	14	+	1999
54.0	Yes	SD	No	15	Alive	Alive with disease, 2000
55.2	No	CR	No	61	Alive	NED, 1994
53	No	NA	Loc/4/CT	12	+	1995
56.0	No	NA	Loc/6/RS Spin/8/CT	15	+	Died of tumor, autopsy, 1997
50.0	No	CR	No	151	Alive	PPTID2, 1984
52.0	No	PD	Spin/84/CT	125	+	PPTID2, 1982
63.0	No	CR	No	104	Alive	PPTID2, 1988
57.0	No	SD	No	135	Alive	PPTID2, 1990
56.0	No	PD	Loc/84/CT Spin/96/CT	115	+	PPTID2, 1991
50.0	No	CR	No	42	Alive	PPTID2, 1991
52.0	No	SD	No	62	Alive	PPTID2, 1993
25.0 RS	No	CR	No	8	Alive	PPTID2, 1996
54.0	VP16/Cis	PD	Loc/62	71	Alive	PPTID2, 1991
45.0	No	CR	No	246	Alive	PPTID2, 1975
Yes	No	PR	No	5	Alive	PPTID2, 1999
50.0	No	PD	Spin/12/CT	32	+	PPTID2, 1977
50.0	No	PR	Loc/93/CT	141	Alive	PPTID3, 1987
24.0 RS	VP16/D/F	PR	Loc/51/CT/RS Loc/78/surgery/RS	105	Alive	PPTID3, 1992
54.0	VP16/Cis	PD	Spin/15/CT	25	+	PPTID3, 1993
54.0	No	CR	No	5	Alive	PPTID3, 1994
50.0	M7	PD	Loc/71	75	+	PPTID3, 1985
60.0	M7	PD	Spin/71/CT	86	+	PPTID3, 1984
50.0	No	PD	Spin/26/CT	39	+	PPTID3, 1988
54.0	MTX i.th.	PD	Spin/sacrum 15/CT	38	+	PPTID3, 1993
18.0 RS	No	PD	No	21	+	PPTID3, 1995
60.0	No	CR	No	27	Alive	PPTID3, 1999
54.0	No	SD	No	39	Alive	PPTID3, 1993
45.0	No	PD	Spin/10	16	+	1980
46.0	No	PD	Spin/46/CT	116	+	1986
56.0	M7	PR	No	4	Alive	1988
60.0	No	CR	No	22	Alive	1995
54.0	VP16/CaP	CR	No	21	Alive	1998
35.0	No	NA	Loc/24/RT	50	+	Died of tumor autopsy loc + spin rec., 1960
49.0	No	NA	Loc/108/no	142	+	Died of tumor autopsy loc + spin rec., 1967
54.0	No	NA	No	79	Alive	NED, 1988
54.0	No	NA	No	57	Alive	NED, 1989
55.8	No	NA	No	128	Alive	NED, 1985
54.0	No	NA	No	34	+	NED, 1991
59.4	No	NA	No	93	Alive	NED, 1988
60.0	Yes	NA	Loc/spin/24/CT	41	+	Died of tumor, 1991
55.8	No	NA	Spin/36/no	40	+	Died of tumor, 1990
49.5	Yes	NA	No	68	Alive	NED, 1991
55.6	No	NA	No	48	Alive	NED, 1991
54.0	Yes	NA	No	45	Alive	NED, 1991
59.4	Lo, Cis, Vi	PD	Loc/8/CT	9	+	(1), 1975-1992
55.0	Lo, Pro, Vi, D, Th		Loc/spin/15/RT/CT	35	+	(2)
54.0	Lo, Pro, Vi, D, Th	PR	Loc/spin/49/RT/CT	59	+	(3)
71.7	Lo, Cis, Vi	PD	Spin/9/CT	14	+	(4)
54.0	No	PR	Spin/10/NA	30	+	(5), dis, clinically diagnosed
55.0	No	CR	No	62	Alive	(7), NED, 1990
72.0	Lo, Cis, Vi	PR	Loc (PET)/17/RS	55	Alive	(9), alive with disease, 1992
72.0	Lo, Cis, Vi	PR	No	64	Alive	(11), NED, 1992
72.0	No	CR	No	62	Alive	(8), PPTID, NED, 1991
72.0	Lo, Cis, Vi	PR	NA/21/NA	55	+	(10), PPTID, NED, 1991
54.0	CU, Cis, Vi	CR	No	11	Alive	2000
54.0 + RS	No	PR	No	77	Alive	1995
55.8	Cy, VP16	SD	Loc/7/RS Loc/15/BT, CT Spin/17/RT, CT Lung/20/RT, CT	22	Dead	1999

<sup>a</sup> Loc, localized disease; spin, spinal; CSF, cerebrospinal fluid (examination); RTC, total dose radiotherapy to the cranium; RTS, total dose radiotherapy to the spine; RTP, total dose radiotherapy to the pineal region; CTx, chemotherapy; Resp, response; MRI, magnetic resonance imaging; Bio, biopsy; Cis, cisplatin; CU, CCNU; Vi, vincristine; NA, not available; NED, no evidence of disease; CT, computed tomography; —, cerebrospinal fluid free from tumor cells; CR, complete response; +, dead; PPTID, pineal parenchymal tumor of intermediate differentiation (pineoblastoma all others); PD, progressive disease; SD, stable disease; dis, disseminated disease; dis. prog., disease progression; RS, radiosurgery; GTR, gross total resection; VP16, etoposide; STR, subtotal resection; PR, partial response; D, dibromodulcitol; F, fluorouracil; M7, 8 drugs in 1 day; MTX, methotrexate; i.th., intrathecal; CaP, carboplatin; VG, ventriculography; RT, radiotherapy; rec., recurrence; MG, myelography; Lo, lomustine; Pro, procarbazine; Th, 6-thioguanine; Cy, Cytosan; PET, positron emission tomography; MRI+, magnetic resonance imaging with evidence of spinal dissemination; Yes (in CSF column), presence of tumor cells in CSF.

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0.21). Overall survival in patients with localized disease was 94, 81, and 54% at 3, 5, and 10 years, respectively (Fig. 2). For patients with disseminated disease, the prognosis was even worse: their median survival was 35 months (50, 30, and 0% at 3-, 5-, and 10-yr follow-up, respectively;  $P = 0.0002$ ). Three patients who were initially staged positive lived longer than 3 years.



**FIGURE 1.** Graph illustrating overall and progression-free survival.

### Histological Characteristics (Type of Tumor)

Sixty-four patients were diagnosed with PB, and 37 patients had PPTID. The median overall survival for patients with PPTID was 165 months (89, 80, and 72% at 3-, 5-, and 10-yr follow-up, respectively) (Fig. 3). Patients with PB fared significantly worse: their median overall survival was 77 months (72, 51, and 23% at 3-, 5-, and 10-yr follow-up, respectively;  $P = 0.001$ ).

### Initial Therapy

#### Surgery

Fifty-six patients underwent resection, and biopsy samples were obtained from 44 patients. In one patient (Patient 1), treatment was initiated without histological analysis; this patient's diagnosis was confirmed at autopsy. Fifty-seven patients underwent shunting for hydrocephalus.

#### Radiotherapy

Fifty-six patients received postoperative radiotherapy, and 45 patients received primary radiotherapy. Five different target volume concepts were identified: 1) spine plus cranium plus pineal boost ( $n = 56$ ), 2) spine plus cranium ( $n = 5$ ), 3) cranium plus pineal boost ( $n = 12$ ), 4) cranium ( $n = 4$ ), and 5) pineal ( $n = 22$ ). In two patients, no information with regard to the treated volume was available. In 80 patients who underwent fractionated radiotherapy (median follow-up, 44 mo), the total dose administered to the pineal region was known (median dose, 54 Gy; dose range, 20–75 Gy; 25% quartile, 50 Gy; 75% quartile, 56 Gy). In three patients, interstitial brachytherapy was used (median follow-up period, 18 mo), either alone or in combination with external beam radiotherapy. Patil et al. (37) stereotactically placed two  $^{125}\text{I}$  permanent seeds into the tumor (total dose, 40 Gy in 8 d), followed by hyperfractionated radiotherapy (total dose, 53.1 Gy; Patient 15). Tada et al. (44) inserted  $^{192}\text{Ir}$  seeds (total dose, 40 Gy in 8 d) and added external beam radiotherapy (total dose, 40 Gy; Patient 17). Matsumoto et al. (30) administered interstitial brachytherapy with  $^{192}\text{Ir}$  as the sole treatment modality (total dose, 36 Gy in 5 d; Patient 16). LINAC or gamma knife radiosurgery was performed in five patients (Patients 25, 56, 62,

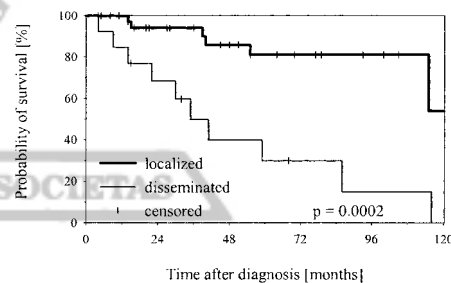
Variable	No. of patients	OS	<i>P</i> value
Age (yr)			
$\leq 32$	53	100	
$> 32$	48	86	0.85
Sex			
Male	48	86	
Female	53	116	0.55
Extent of disease			
Localized	38	Not reached	
Disseminated	13	35	0.0002
Histology			
PPTID	37	165	
PB	64	77	0.001
Residual disease after treatment			
No/minor	41	168	
Major	21	39	$< 0.0001$

<sup>a</sup> OS, overall survival (median); PB, pineoblastoma; PPTID, pineal parenchymal tumor of intermediate differentiation.

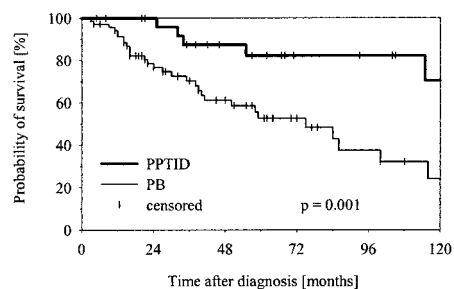
69, and 100). The median follow-up period was 35 months. The single dose administered ranged from 18 to 25 Gy, followed by fractionated radiotherapy in one patient (total dose, 54 Gy; Patient 100). Sixty-four patients received radiotherapy of the spine. In 37 patients, the spine was not irradiated. In 52 patients, the spinal radiation dose was known, with a median of 36 Gy (range, 10–54 Gy).

#### Chemotherapy

Chemotherapy was administered to 34 patients. Various treatment regimens were used. With regard to the timing of surgery, radiotherapy, and chemotherapy, we identified four different concepts: 1) surgery followed by chemotherapy followed by radiotherapy,



**FIGURE 2.** Graph illustrating overall survival according to extent of disease at diagnosis.



**FIGURE 3.** Graph illustrating overall survival according to histological characteristics.

2) surgery followed by chemotherapy plus radiotherapy, 3) surgery followed by radiotherapy followed by chemotherapy, and 4) surgery followed by chemotherapy followed by radiotherapy followed by chemotherapy. Drugs that were administered are listed in *Tables 1* and *2*. Ashley et al. (2) treated patients with high-dose cyclophosphamide as a single agent. In all other instances, chemotherapy included a combination of two (6, 44) to eight drugs (15). Chemotherapy was administered to all but three patients who presented with disseminated disease at their initial diagnosis. Patients with PB were significantly more likely than patients with PPTID to be treated with chemotherapy ( $P = 0.05$ ).

### Residual Disease after Initial Treatment (Response)

Twenty-seven patients had no residual disease, 14 patients had minor residual disease, and 21 patients had major residual disease. The overall survival of patients with no residual disease was 100% at 10 years. The median overall survival time was 100 months in patients with minor residual disease (81, 60, and 40% at 3-, 5-, and 10-yr follow-up, respectively) (*Fig. 4*). The median overall survival time was 39 months in patients with major residual disease (55, 45, and 15% at 3-, 5-, and 10-yr follow-up, respectively;  $P < 0.0001$ ). In 8 of 27 patients, primary radiotherapy resulted in complete disappearance of all visible tumor; these patients did not undergo resection or chemotherapy.

### Progression-free Survival and Time to Progression

The median progression-free survival time was 71 months (61, 54, and 24% at 3-, 5-, and 10-yr follow-up, respectively) (*Fig. 1*). The median progression-free survival time was significantly shorter in patients with disseminated disease than in those with localized disease (median progression-free survival time in patients with localized disease was not reached; median progression-free survival time in patients with disseminated disease was 24 mo). The median progression-free survival time was also significantly shorter in patients with PB versus PPTID (median progression-free survival time in patients with PPTID, 93 mo, as compared with patients with PB, 46 mo). For patients whose therapy failed, the median time to disease progression was 21 months. Patients whose therapy failed within 21 months after diagnosis had a median overall survival time of 24 months (24, 12, and 12% at 3-, 5-, and 10-yr follow-up, respectively). Patients whose therapy failed more than 21 months after diagnosis had a median overall survival time of 100 months (100, 68, and 33% at 3-, 5-, and 10-yr follow-up, respectively;  $P < 0.0001$ ).

### Treatment Failure

Fifty-six patients did not experience relapse. In 14 patients, tumor control was achieved by primary radiotherapy; these patients did not undergo resection or chemotherapy. In 18 patients, the pineal region was the site of first relapse. Seventeen patients had relapses that were limited to the spine. In three patients, the first failure occurred in both the pineal region and the spine.

Treatment failure occurred outside the central nervous system in three patients (Patients 7, 37, and 68). These patients had histologically proven metastases of the sacrum (Patient 68), the trochanter of the right femur (Patient 7), and the T8 vertebral body (Patient 37) that were identified 15 months, 18 months, and 8 years, respectively, after being diagnosed with PB. In four patients (Patients 8, 9, 35, and 43), tumor progression was reported, but no details regarding the site of relapse were provided.

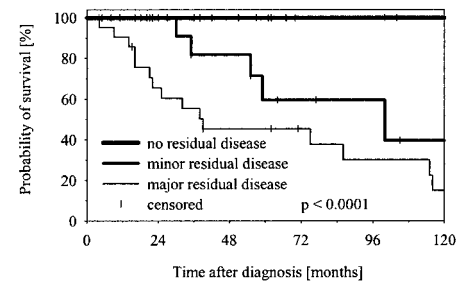
The median overall survival time of patients who failed locally or in the spine was 15 months (23, 5, and 0% at 3-, 5-, and 10-yr follow-up, respectively). The prognosis in this group was determined by histological characteristics (median survival time of patients with PPTID who failed locally or in the spine, 23 mo, as compared with 12 mo for patients with PB who failed locally or in the spine;  $P = 0.09$ ) and the extent of residual disease after primary treatment (median survival time of patients with no or minor residual disease who failed locally or in the spine, 39 mo, as compared with 13 mo for patients with major residual disease;  $P = 0.003$ ). Patients who responded well to therapy had a significantly greater chance than their nonresponding counterparts of remaining disease-free: 73% of patients with no or minor residual disease did not experience treatment failure, whereas 76% of patients with major residual disease experienced failure ( $P = 0.0002$ ).

### Local Control

Local control was achieved in 86, 79, and 53% of patients at 3-, 5-, and 10-year follow-up, respectively. Age, sex, and histological characteristics were evaluated for their influence on local control. Patients who were age 32 years or older demonstrated better local control than did patients who were younger than 32 years of age (95, 90, and 72% versus 78, 69, and 37% at 3-, 5-, and 10-yr follow-up, respectively;  $P = 0.02$ ). Each extra year of age reduced the relative risk (RR) of the failure of local control by 4% ( $P = 0.06$ ).

### Spinal Control

Spinal control was achieved in 81, 77, and 64% of patients at 3-, 5-, and 10-year follow-up, respectively. Age, sex, and histological characteristics were evaluated regarding their influence on spinal control. Spinal control was significantly greater in patients with PPTID than in patients with PB (93, 92, and 81% versus 74, 69, and 50% at 3-, 5-, and 10-yr follow-up, respectively;  $P = 0.04$ ). Patients with PPTID had a 0.55 RR of



**FIGURE 4.** Graph illustrating overall survival according to residual disease.

spinal failure as compared with patients who had PB ( $P = 0.03$ ).

### Multivariate Analysis (End Point Overall Survival)

The first multivariate analysis was restricted to pretreatment variables that were of prognostic importance in the univariate analysis (e.g., stage and histological characteristics) ( $n = 51$ ) (Table 4). Variables for stage and histological characteristics were independent risk factors. The RR of dying was 0.61 for patients with PPTID as compared with patients with PB and 0.69 for patients with localized disease as compared with patients with disseminated disease ( $P = 0.01$  and  $P = 0.04$ , respectively). In the second multivariate analysis, we added residual disease as a posttreatment variable (Table 4). In this model, residual disease was the most important risk factor. The RR was 0.48 for patients with no or minor residual disease as compared with patients who had major residual disease ( $P = 0.001$ ).

## DISCUSSION

Malignant PPT is very rare in adult patients. Few clinical data are available in the literature regarding adults with malignant PPT; these patients are generally included in series with children or with patients who have other pineal region tumors (i.e., germinomas). To date, only a single publication that included 10 adult patients with malignant PPT focused on this topic (9). The heterogeneity of management also renders the interpretation of published data more difficult. Currently, these patients are treated according to pediatric protocols or according to modalities chosen by the treating physician. The spectrum ranges from localized radiotherapy to the pineal region (26, 30, 35, 45) to radical resection, craniospinal radiotherapy, and multidrug chemotherapy (6, 9, 15, 42).

Our study was based on clinical data collected from 101 adult patients with malignant PPT, a sample size large enough to provide new insights into the clinical course of the disease and to allow valid conclusions to be drawn with regard to prognostic factors. Because of methodological limits, we presume that overall survival is overestimated in our series. The

figures presented in the Results should be interpreted cautiously for several reasons. First, the prognosis for patients with malignant brain tumors is usually bad. Cases in which the disease course was favorable are more likely to be reported than are those that led to the expected fatal outcome (46). Therefore, publication bias in the literature must be assumed. Furthermore, we did not include in this study patients in whom radiotherapy was withheld because of early disease progression; because of treatment-associated complications, including death (19); or because adjuvant treatment was considered unnecessary after surgery for relatively benign PPTID (Grade II) (15). In addition, clear-cut diagnostic criteria for PPTID were not defined until recently, which probably resulted in a number of false-positive cases of PB being reported (23). This point is illustrated by the analysis of Fauchon et al. (15), who used stringent diagnostic criteria. In their series, overall survival at 5 years was only 10% in patients with PB, as compared with the 51% overall survival at 5-year follow-up in our series.

### Extent of Disease

In patients who presented with localized disease, median survival was not reached. For patients with disseminated disease, median survival was 35 months ( $P = 0.001$ ). This finding is consistent with the results of the study by Chang et al. (9), who described five adult patients with malignant PPT and positively staged disease who experienced disease progression either focally or in the spine and died 1 to 20 months after tumor recurrence. In contrast, all five patients with negatively staged disease were alive without disease progression after a median of 26 months of follow-up.

One can draw comparisons between the series presented here and medulloblastoma series because these tumors are histologically similar and have a high propensity for central nervous system seeding. In adult patients with medulloblastomas, the prognostic significance of the extent of disease at diagnosis has been clearly established. In the series of Merchant et al. (33), patients with no evidence of disease beyond the primary tumor site had significantly higher 5-year overall (59 versus 30%) and 5-year disease-free (49 versus

TABLE 4. Multivariate analysis, end point overall survival ( $n = 51$ )<sup>a</sup>

Variable	First model		P value	Second model		P value
	RR	95% CI		RR	95% CI	
Extent of disease						
<i>Loc versus dis</i>	0.69	0.48–0.99	0.04	0.81	0.49–1.19	0.26
Histology						
<i>PPTID versus PB</i>	0.61	0.37–0.88	0.01	0.54	0.28–0.97	0.06
Residual disease						
<i>No/minor versus major</i>		Not included		0.48	0.25–0.70	0.001

<sup>a</sup> RR, relative risk; CI, confidence interval; loc, localized disease; dis, disseminated disease; PPTID, pineal parenchymal tumor of intermediate differentiation; PB, pineoblastoma.

29%) survival probability as compared with those with more extensive disease ( $P = 0.02$ ). In a multivariate analysis, metastasis stage was the only prognostic factor that influenced overall and disease-free survival. Other investigators have confirmed these results (1, 7, 40).

Our study demonstrates the prognostic importance of complete staging of the entire neuraxis for adults with malignant PPT. Cytological examinations and neuraxis imaging alone have limited ability to detect dissemination but are complementary. This finding is demonstrated in some cases that had radiographic evidence of tumor spread to the spinal axis and in which the cytological examination was negative. Conversely, some patients with positive cytological examinations had no radiographic evidence of tumor spread.

Many patients included in this study did not undergo complete staging of the spine and thus might have been understaged. If complete staging had been performed in all patients, we presume that disseminated disease would have been diagnosed in more than 13 cases.

### Histological Characteristics (Type of Tumor)

The median overall survival for patients with PPTID was 165 months. Patients with PB had a median survival of 77 months ( $P = 0.001$ ). The clinical and pathological characteristics of PC and PB were outlined by Borit et al. (5), with PB occurring mostly in young people and PCs being typical in adults. This finding is substantiated by our series. Older age was clearly associated with tumors that were less malignant. Similar findings were reported by Fauchon et al. (15); in their study, the mean patient ages were 13, 27, 40, and 47 years in patients with PB, PPTID (Grade III), PPTID (Grade II), and PC, respectively. However, a number of PPTs do not fit precisely into the PC or PB categories and have been termed *pineal parenchymal tumor of intermediate differentiation* (22), *mixed pineocytoma/pineoblastoma* (31), or *pineocytoma with anaplasia* (45). Little is known regarding their clinical behavior.

In a small number of clinicopathological studies, the association of histological features and prognosis of malignant PPT was analyzed (23, 34, 43, 45). Jouvett et al. (23) did the most comprehensive work in this area. On the basis of their study of a series of 66 PPTs that included 11 PCs, 39 mixed or intermediate PPTs, and 16 PBs, they proposed a prognostic classification scheme comprising four grades: Grade I for PC, Grade II for PPT with fewer than six mitoses and positive immunolabeling for neurofilaments, Grade III for PPT with six or more mitoses but without immunostaining for neurofilaments, and Grade IV for PB. Overall survival and event-free survival differed significantly among the groups in their study. Our series corroborates their results: in comparison with patients with PB, patients with PPTID in our series had better median overall survival and better progression-free survival (93 versus 46 mo;  $P = 0.01$ ). PPTID seemed to be less aggressive than PB in our series, as reflected by greater spinal control rates (92 versus 69% at 5-yr follow-up;  $P = 0.04$ ). In the Fauchon et al. (15) series, the mean time to disease progression was 1.3 years for patients with PPTID (Grade III), as compared

with only 0.7 years for patients with PB. The rate of spinal failures increased with tumor grade (PPTID Grade II, 7%; PPTID Grade III, 36%; and PB, 57%).

Our study emphasizes the importance of making a precise histological diagnosis. In addition to the extent of disease, histological findings were an independent prognostic factor in multivariate analysis. Given the rarity of the lesion, malignant PPTs should be subjected to central pathology review. Fauchon et al. (15) considered the histological diagnosis of PPT inappropriate in 10.6% of 281 patients with pineal region tumors after central neuropathology review.

### Residual Disease after Initial Treatment (Response)

The radiosensitivity of pineal region tumors described by the pioneers of neuro-oncology also was observed in our series of adult patients with malignant PPTs, most of whom were treated during the past decade. In 30% of the patients we studied, no residual disease was diagnosed after primary radiotherapy. Currently, tissue specimens that allow an accurate diagnosis can be obtained safely by performing modern microsurgical and stereotactic neurosurgical procedures (13, 25, 41). Tumor shrinkage is definitely no longer "evidence on which to base a diagnosis of pinealoblastoma" (39, p 152).

This study highlights the prognostic impact of residual disease for patients with malignant PPT. Overall survival at 10-year follow-up was 100% in patients with no residual disease. The median overall survival was 100 months in patients with minor residual disease and 39 months in patients with major residual disease ( $P < 0.0001$ ). On the basis of multivariate analysis, residual disease independently predicted overall survival. This variable might help to detect poor-risk patients shortly after the end of therapy. In patients with PB who had localized disease, the rate of ultimate treatment failure was 15% when no residual disease was diagnosed, whereas ultimate treatment failure occurred in more than 50% of patients with major residual tumor in the pineal region.

### Treatment Failure

The median overall survival of patients whose treatment failed was 15 months. The median overall survival was 26 months in patients whose treatment failure occurred in the pineal region, as compared with 12 months in patients whose treatment failure occurred in the spine ( $P = 0.12$ ). Usually, patients with malignant PPT are administered intensive therapy once the diagnosis is made. As a consequence, the available treatment options in the event of recurrence are limited, especially when the spine is affected. Cases such as the one reported by Uematsu et al. (46) (Patient 6 in our study), in which the patient was treated with 45 Gy to the pineal region at first diagnosis, 45 Gy for the first local relapse, and another 20 Gy for the second local relapse, are not the rule but the exception.

It must be noted that 9 (20%) of 45 treatment failures occurred more than 5 years after initial treatment (4 in patients with PB and 5 in patients with PPTID), but no treatment

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failure was observed later than 10 years after initial therapy. Late relapse seems to be common in patients with malignant PPT independent of tumor differentiation (46). Similar findings were reported for adult patients with medulloblastoma (4, 8, 14, 18). Survival at 10 years seems to be a reliable indicator of treatment efficacy. Thus, publications regarding PPT that describe results associated with short-term follow-up should be interpreted cautiously.

## CONCLUSIONS

From our data, we draw the following conclusions. The prognosis for adult patients with malignant PPT is determined by tumor differentiation and stage. Complete disappearance of all visible tumor correlated with 100% survival at 10 years. Treatment failure was diagnosed up to 10 years after treatment and had a detrimental effect on prognosis, especially when treatment failure involved the spine. Several fundamental issues regarding the therapeutic management of malignant PPT in adult patients remain to be investigated, such as the prognostic effect of the extent of resection, the radiation dosage to the pineal region and the spine, and the role of chemotherapy. These aspects of the treatment of malignant PPTs in adult patients need to be clarified in future trials, for which this study provides a rational basis.

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## COMMENTS

This retrospective, multicenter study critically analyzes the clinical results and the prognostic factors in patients with malignant, pineal parenchymal tumors (PPTs). A total of 101 patients, including 64 patients who were treated at the participating institutions and 37 previously published cases, were studied. Considering the rarity of these oncotypes, this series is probably the largest ever published (1), and therein lies the importance of the contribution.

Fifty-six of 101 patients underwent postoperative radiation treatment, whereas 45 of 101 were irradiated after bioptic diagnosis. Chemotherapy was administered in one-third of the cases. Local tumor control was much greater in patients who had surgical removal than in those who received radiotherapy after biopsy (relative risk, 0.52), and effective local control in patients with no or minor residual disease had a major influence on survival (relative risk, 0.43). Local tumor control did not translate to better overall survival; instead, exactly the contrary was found (surgically treated patients, 86 mo; biopsy group, 115 mo), which suggests an eventual dominant role of spinal control treatment

failure, although the latter treatment was studied in a minority of the patients (approximately 22-23%). As always in retrospective appraisals, the inclusion criteria, histological classification scheme, therapeutic indications and techniques, and follow-up criteria may not be homogeneous, thus making an appropriate evaluation of the results difficult. However, the overall median survival (100 mo), even if it is overestimated as the authors suggest, and the resulting actuarial survival rate are extremely interesting with regard to malignant tumors that have a high potential for metastasis. Furthermore, the major prognostic variables identified (i.e., oncological staging, histological characteristics, tumor response to therapy) might be relevant in designing future prospective studies.

Finally, the role of the newly defined PPT of intermediate differentiation as a clinicopathological entity might become important. Prospective investigations are under way (1, 3), and, given the widely debated impact of radiochemotherapy in these patients, stratification studies are needed. These studies will better define the real prospects for minimally invasive approaches (2, 3) in a multidisciplinary armamentarium.

**Albino Bricolo**  
**Massimo Gerosa**  
Verona, Italy

1. Chandy MJ, Damaraju SC: Benign tumours of the pineal region: A prospective study from 1983 to 1997. *Br J Neurosurg* 12:228-233, 1998.
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The article is devoted to the important problem of malignant PPTs in adults. These tumors are rare, which makes it difficult to develop principles for their effective treatment. The authors collected unique material consisting of 101 cases (their own multicenter experience as well as cases from the literature). Their meticulous analysis of this material permits me to draw some important conclusions regarding the prognosis for and the principles for treating patients with these tumors.

It is both interesting and important to note that, like that of medulloblastomas, the behavior of malignant PPTs in adults is relatively more benign than it is in children. The authors demonstrate that biopsy in combination with irradiation provides favorable results if no signs of tumor dissemination are found.

My experience in treating 53 patients with malignant PPTs, 39 of whom were adults, permits me to make some comments. In my practice, the results achieved in treating patients with these tumors have not been as good as those presented by the authors, which proves the authors' awareness that, as a rule, favorable results of tumor treatment are most often published, and therefore the data derived from the literature are more optimistic than realistic.

As a main treatment paradigm for patients with malignant PPTs, Lutterbach et al. recommend histological confirmation

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of PPT followed by irradiation. This recommendation is made on the basis of data from the literature regarding more frequent tumor dissemination after direct surgery rather than stereotactic biopsy. The decision regarding the indications for tumor removal (or stereotactic biopsy) followed by irradiation and chemotherapy should be made strictly on an individual basis. In making a decision, it is important to be aware of not only tumor dissemination but also tumor size and the possibility of gross total resection. With large tumors, better results are achieved when the tumor volume is reduced before irradiation.

**Alexander N. Konoyalov**

*Moscow, Russia*

**A**lthough the therapeutic outcome of patients with pineocytomas is quite well known, the fate of adult patients with malignant PPTs, including patients with pineoblastomas (PBs) and PPTs of intermediate differentiation, is almost unknown. Because PPTs are quite rare and because most of them are either pineocytomas or PBs, only a cooperative investigation such as the one described in this study can demonstrate a conclusive result. This multicenter cooperative study demonstrates clearly the factors that influence the prognosis for adult patients with PPTs. It is interesting to note that radiotherapy alone yielded a cure in a substantial number of patients but that the increased radiation dose did not lead to favorable outcome. Further studies are required before the most efficient mode of radiotherapy can be determined.

**Kintomo Takakura**

*Tokyo, Japan*

**M**alignant PPTs in adult patients are rare. Analysis of prognostic variables for these tumors is difficult because the number of patients studied in individual series is small. To overcome this difficulty, the authors combined cases from several institutions and included new patients as well as previously published cases, which yielded 101 cases suitable for their study. Not surprisingly, patients with disseminated disease and tumors with less-differentiated histological characteristics had a less favorable prognosis. This study demonstrates the limitations of histopathological diagnosis, because clinical outcomes varied to a significant degree among patients whose tumors had the same histological characteristics.

The retrospective, multicenter design of this study introduced many variables that can influence the interpretation of the re-

sults. Variations in therapeutic protocols, postoperative staging, radiological methods, pathological processing, and analysis cannot be controlled for in this type of study. The authors have made a credible effort to minimize these limitations, and their pooled case study design may be the only way to analyze rare tumor entities. Such an analysis, although useful for determining the prognostic value of patient- and tumor-related variables, is inappropriate for drawing conclusions regarding the role of therapeutic intervention, as the authors acknowledge. It is interesting that the absence of residual disease correlated with improved prognosis, a finding that might be obvious in patients treated with radio- or chemotherapy but that also implies a benefit of aggressive surgical management.

**Jeffrey N. Bruce**

*New York, New York*

**T**he aim of this multicenter retrospective study was to assemble a substantial number of adult patients with histologically proven PBs or PPTs of intermediate differentiation and to attempt to clarify the clinical course and prognosis of patients with those very rare tumors. A total of 101 patients met the inclusion criteria. The median follow-up period was 38 months. By the time of median follow-up, 38 patients had died, and 63 were still alive. Nine patients lived longer than 10 years after receiving the diagnosis of malignant PPT. Median overall survival for the whole patient group was 100 months.

It is interesting to discover that age and sex are not prognostic factors. Median survival in patients with localized disease was not reached, although median survival was 35 months for patients with disseminated disease. For patients with PPT of intermediate differentiation and those with PBs, the median survival rates were 165 and 77 months, respectively. Because malignant PPTs are rare in adult patients, the publication of this multicenter series is excellent. It provides much information on prognosis and is a substantial contribution to the literature. This article provides an important basis for future research on malignant PPTs in adult patients. As the authors note, however, a number of questions regarding the prognostic impact of the extent of surgical resection, the role of chemotherapy, and the way to administer radiotherapy remain unanswered. I await the publication of new studies on this topic.

**Jacques Brotchi**

*Brussels, Belgium*

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