Pineal Parenchymal Tumors

Management with Interstitial Iodine-125 Radiosurgery

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Purpose: To evaluate the efficacy of interstitial radiosurgery (IRS) for pineal parenchymal tumors (PPTs).
Patients and Methods: 18 consecutively admitted patients (twelve male and six female, age range 6–68 years, median age 34 years) with PPTs (eight pineocytomas, ten malignant PPTs) were treated at the authors' institution with IRS using stereotactically guided iodine-125 seed implantation (^{125}I-IRS) as either primary or salvage therapy. The cumulative tumor surface dose ranged from 40 to 64 Gy. Adjuvant radiotherapy of the whole brain or the craniospine was done in patients with grade III and grade IV PPT. The median follow-up period was 57.4 months (range 6–134 months).
Results: Overall actuarial 5- and 8-year survival rates after IRS were 100% and 86% for pineocytomas, and the overall actuarial 5-year survival rate was 78% for high-grade PPTs. Follow-up magnetic resonance imaging showed complete remission in 72% (13/18) and partial remission in 28% (5/18) of the cases. One patient developed an out-of-field relapse 4 years after partial remission of a pineocytoma, which had already been treated with IRS. There was no treatment-related mortality. Treatment-related morbidity occurred in two patients only.
Conclusion: This study indicates that stereotactic ^{125}I-IRS for the management of PPTs is quite efficient and safe. Due to the low rate of side effects, IRS may develop into an attractive alternative to microsurgery in de novo diagnosed pineocytomas. In malignant PPTs, IRS may be routinely applied in a multimodality treatment schedule supplementary to conventional irradiation.

Key Words: Brachytherapy · Interstitial radiosurgery · Pineal parenchymal tumors · Pineoblastoma · Pineocytoma · Stereotactic iodine-125 seed implantation

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Pinealisparenchymtumoren. Behandlung durch interstitielle Radiochirurgie mittels Jod-125

Ziel: Die Wirksamkeit der stereotaktischen interstitiellen Radiochirurgie (IRS) zur Behandlung von Pinealisparenchymtumoren (PPTs) wurde analysiert.
Patienten und Methodik: 18 Patienten (zwölf männlich und sechs weiblich, Alter 6–68 Jahre, medianes Alter 34 Jahre) mit einem PPT (acht Pineozytome, zehn maligne PPTs) wurden in der Klinik der Autoren durch eine stereotaktisch geführte interstitielle Radiochirurgie mittels Implantation von Jod-125-Seeds (^{125}I-IRS) behandelt. Die Behandlung erfolgte entweder als Primär- oder als Salvage-Therapie. Die kumulative Tumoroberflächendosis variierte von 40 bis 64 Gy. Adjuvante Ganzhirnbestrahlung oder Bestrahlung der Wirbelsäule wurde bei den Patienten mit malignen PPTs durchgeführt. Die mediane Nachbeobachtungszeit betrug 57,4 Monate (6–134 Monate).
Ergebnisse: Die 5- und 8-Jahres-Überlebensraten nach IRS für Pineozytome betrugen 100% bzw. 86%, und die 5-Jahres-Überlebensrate nach IRS für die höhergradigen PPTs lag bei 78%. Eine komplette Remission wurde in 72% der Fälle (13/18) und eine partielle Remission in 28% der Fälle (5/18) erzielt. Ein Patient entwickelte 4 Jahre nach partieller Remission eines Pineozytoms ein „out-of-field"-Rezidiv. Dieses Rezidiv wurde ebenfalls mittels stereotaktisch geführter IRS behandelt. Es wurde keine behandlungsbedingte Mortalität beobachtet. Eine behandlungsbedingte Morbidität trat bei zwei Patienten auf.
Schlussfolgerung: Die Studie zeigt, dass die Behandlung von PPTs durch stereotaktisch geführte ^{125}I-IRS sicher und effektiv ist. Aufgrund der geringen Nebenwirkungen kann sich diese Behandlung zu einer guten Alternative zur Mikrochirurgie bei de novo

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diagnostizierten Pineozytomen entwickeln. Bei malignen PPTs kann diese Methode als Ergänzung in ein multimodales Behandlungskonzept einbezogen werden.

Schlüsselwörter: Brachytherapie · Interstitielle Radiochirurgie · Pinealisparenchymtumoren · Pineoblastome · Pineozytome · Stereotaktische Jod-125-Seed-Implantation

Introduction

Pineal region tumors (PRTs) are a very heterogeneous group comprising four main categories: germ cell tumors, pineal parenchymal cell tumors (PPTs), glial cell tumors, and other miscellaneous tumors and cysts. PRTs are rare and account for < 1% of the primary brain tumors in Western countries, and for 2.2–8% of intracranial tumors in countries of northeastern Asia [5]. After germinomas, PPTs are the second most common pineal tumors in adults and represent 30% of all PRTs [13, 19]. In the World Health Organization (WHO) classification from 2007 [23], PPTs are divided into pineocytoma WHO grade I (PC), PPT with intermediate differentiation WHO grade II–III (PTTimd), and pineoblastoma WHO grade IV (PB).

According to the Brain Tumor Registry of Japan [1], pineocytomas mostly develop in adults. Only 12% of the patients in the registry were children (age at diagnosis: < 15 years). By contrast, pineoblastomas were recognized more often in children (51% of the patients in this registry).

PPTs usually cause an occlusive hydrocephalus by obstruction of the cerebral aqueduct, as well as Parinaud's syndrome due to tectal compression.

Pineocytomas and pineoblastomas share the same anatomic region, but differ in biological behavior, metastatic potential and therapeutic requirements. Also the prognosis of the patients differs with respect to the tumor type.

Table 1. Patient characteristics regarding histology, extent of resection, additional treatment prior to interstitial radiosurgery (IRS), extent of disease at the time of IRS, and additional treatment after IRS. F: female; M: male; PB: pineoblastoma; PC: pineocytoma; PPTimd: PPT with intermediate differentiation WHO grade III; RT: radiotherapy; WHO: World Health Organization.

Tabelle 1. Patientencharakteristika, bezogen auf Histologie, Ausmaß der Resektion, zusätzliche Therapie vor interstitieller Radiochirurgie (IRS), Erkrankungsstatus zum Zeitpunkt der Behandlung sowie zusätzliche Behandlung nach IRS. F: weiblich; M: männlich; PB: Pineoblastom; PC: Pineozytom; PPTimd: PPT mit intermediärer Differenzierung WHO-Grad III; RT: Radiotherapie; WHO: Weltgesundheitsorganisation.

Patient #	Age (years)/ gender	Histology	Extent of resection	Additional treatment prior to IRS	Extent of disease at time of IRS	Additional treatment after IRS
1	6/M	PB	Craniotomy (partial)	RT (whole brain and spine), chemotherapy	No seeding	Chemotherapy
2	39/M	PC	Biopsy	No	No seeding	No
3	26/F	PC	Biopsy	No	No seeding	No
4	48/F	PC	Biopsy	No	No seeding	No
5	46/M	PC	Craniotomy (partial)[a]	No	No seeding	No
6	30/M	PC	Biopsy	No	No seeding	No
7	24/M	PC	Craniotomy (subtotal)	RT (whole brain and spine)	No seeding	No
8	15/F	PC	Biopsy	No	No seeding	No
9	48/F	PB	Craniotomy (subtotal)	RT (whole brain and spine)	Recurrent tumor in cerebellum, extracranial tumor controlled	Chemotherapy
10	12/M	PB	Craniotomy (partial)	No	No seeding	RT (whole brain and spine), chemotherapy
11	50/F	PC	Biopsy	No	No seeding	No
12	60/M	PTTimd	Biopsy	No	No seeding	RT (whole brain)
13	11/M	PB	Craniotomy (partial)	Chemotherapy	No seeding	RT (whole brain and spine)
14	65/M	PB	Biopsy	No	Seeding (spine)	RT (whole brain and spine)
15	36/M	PB	Biopsy	No	No seeding	RT (whole brain and spine)
16	42/M	PB	Biopsy	No	Seeding (spine)	RT (whole brain and spine)
17	68/F	PTTimd	Biopsy	No	No seeding	RT (whole brain)
18	32/M	PTTimd	Biopsy	No	No seeding	RT (focal)

[a]Patient # 5 underwent three craniotomies due to primary or recurrent tumor

Table 2. Patients and implant characteristics.

Tabelle 2. Patienten- und Implantationscharakteristika.

	Pineocytoma	Malignant PPT	All patients
Patients (n)	8	10	18
Median age (range [years])	30 (14–50)	39 (6–68)	34 (6–68)
Male/female ratio	4/4	8/2	12/6
Diagnosis made by			
• stereotactic biopsy	6	6	12
• open biopsy/cytoreduction	2	4	6
Implantation after diagnosis			
• Primary therapy	6	6	12
• Salvage therapy	2	4	6
125-iodine implants permanent/ temporary (range)	7/1 (42 days)	4/6 (42–140 days)	11/7 (42–140 days)
Median initial dose rate (Gy/day)			0.74 (0.57–1.44)
Range surface dose (Gy)	48–65	40–55	40–65
Median volume (cm^3)	1.8	7.7	6
Median number of seeds (range)	2 (2–6)	4 (1–7)	3 (1–7)
Median number of catheters (range)	1 (1–3)	2 (1–3)	1 (1–3)
Adjuvant external-beam irradiation (n patients)	0	8, simultaneous	8
Adjuvant chemotherapy (n patients)	0	3	3

The management of these tumors remains unclear. The literature recommends a variety of treatment approaches, regardless of the disease stage, ranging from surgery or external irradiation alone to combined treatment with surgery, radiotherapy or chemotherapy [5, 6, 18, 24, 26, 33]. Moreover, a number of techniques are recommended, from stereotactic biopsy to complete tumor resection for surgery, and from radiosurgery to craniospinal irradiation for radiotherapy [5, 14, 16, 22, 24, 32].

It was the objective of this retrospective study to determine the efficacy and safety of interstitial radiosurgery (IRS) using stereotactically guided iodine-125 seed implantation (^{125}I-IRS) for PPT as either primary or salvage therapy.

Patients and Methods

Patients

Between April 1992 and December 2003, 18 consecutively admitted patients with PPTs were treated at our institution. All patients (male/female ratio 12/6, median age 34 years, range 6–68 years) had a follow-up of at least 6 months and were considered for the following evaluation.

The cohort presented here included four children aged 6, 11, 12, and 15 years. 14/18 patients exhibited hydrocephalus, two with tectal compression and two with unspecific symptoms. A ventriculoperitoneal shunt was placed in 9/14 patients with hydrocephalus to relieve obstruction of cerebrospinal fluid (CSF) flow. Prior to IRS, 6/18 patients underwent primary open surgery. The remaining twelve patients had had stereotactic biopsies for histological diagnosis validation. 4/6 patients of the open surgery group underwent an adjuvant treatment consisting of external-beam irradiation (two patients: one with a PC, one with a PB), chemotherapy (one patient with a PB) and combined radiochemotherapy (one patient with a PB).

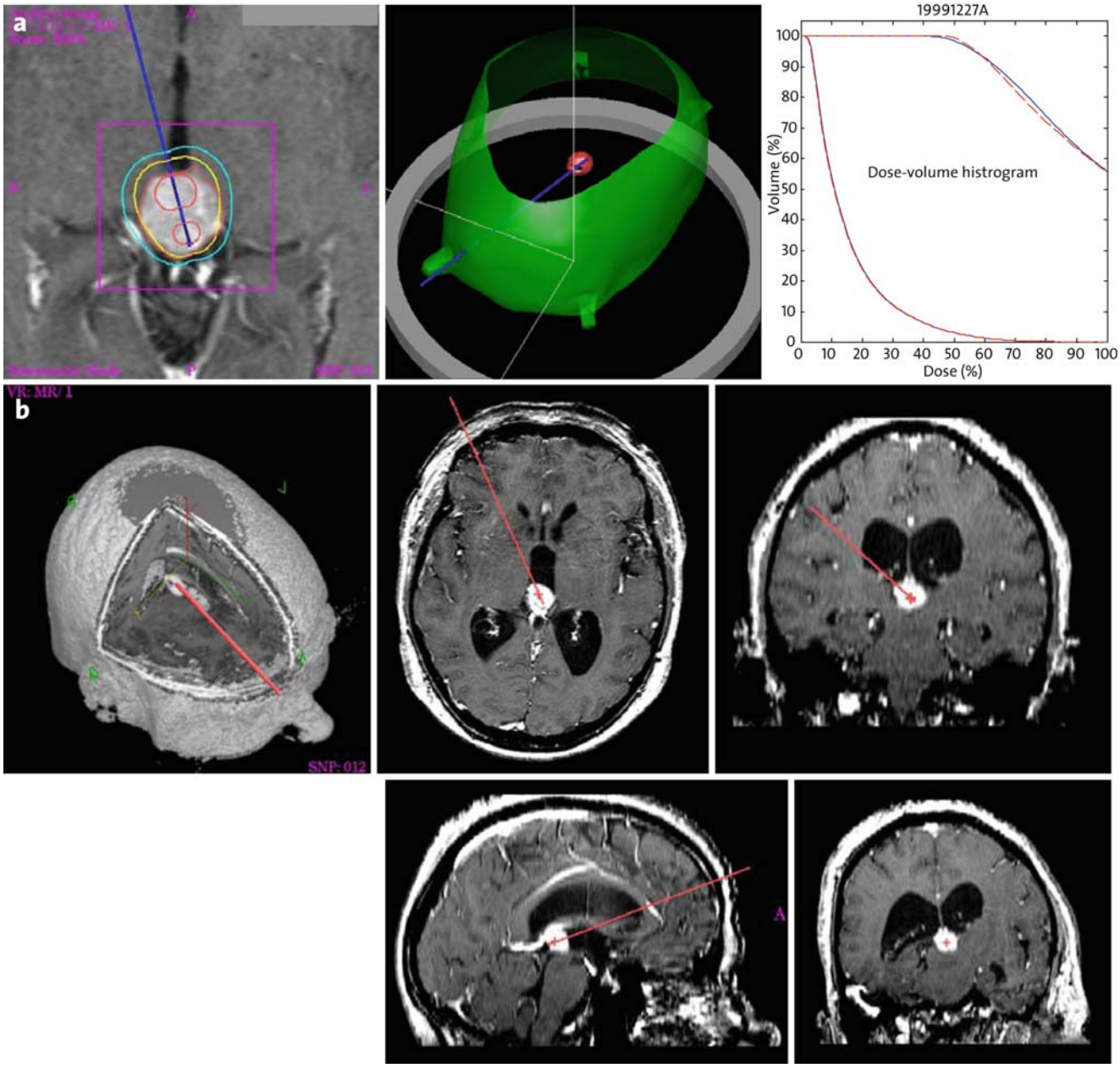
Neuroimaging prior to stereotactic biopsy and ^{125}I-IRS, respectively, showed a mass in the pineal region in all cases, except in one pineoblastoma patient with a distant recurrence adjacent to the 4th ventricle. At the time of IRS, only two patients, who underwent primary stereotactic biopsy, showed evidence of spinal seeding on staging magnetic resonance imaging (MRI) scans (two patients with a pineoblastoma). Table 1 details the patients with their respective histology, extent of resection, additional treatment prior to IRS, extent of disease at the time of IRS, and additional treatment after IRS.

All patients were treated with IRS using computed tomography (CT) and MRI as a basis for stereotactic planning and guiding ^{125}I seed implantation as either primary (n = 12) or salvage (n = 6) therapy. IRS was indicated in patients with a well-circumscribed tumor showing a diameter ≤ 4 cm on CT and/or MR images. The median tumor volume was 6 cm^3 (mean 7.8 cm^3, range 0.4–28.1 cm^3), and the median time between diagnosis and IRS was 3.3 months (range 0–114 months).

According to our treatment schedule for gliomas [21, 36], pineocytomas and PPTs with intermediate differentiation received permanent implants. Pineoblastomas and recurrent PPTs after radiotherapy underwent temporary implantation (range 42–140 days). An adjuvant fractionated radiotherapy was applied in patients with PTT with intermediate differentiation (brain, range 25–36 Gy, 1.8 Gy/day) and in patients with pineoblastoma (craniospine, 36 Gy, 1.8 Gy/day, with a 50-Gy boost in spinal metastatic disease). Young pineoblastoma patients were also treated by systemic chemotherapy as displayed in Tables 1 and 2.

Technical Data

^{125}I seeds (Amersham Buchler GmbH & Co KG, Braunschweig, Germany) were used in both permanent and temporary implants. In patients receiving permanent implants, a cumulative tumor surface dose of 40–65 Gy was applied at a median initial dose rate of 0.74 Gy/day (mean 0.67 Gy/day, range 0.46–0.74 Gy/day). In temporary implants, 40–50 Gy were given at a median initial dose rate of 0.75 Gy/day (mean 0.92 Gy/day, range 0.57–1.44 Gy/day, Table 2). The biopsy and implantation were done under general anesthesia, using a modified Riechert-Mundinger stereotactic frame [35]. Stereotactic three-dimensional treatment planning was done



Figures 1a and 1b. Precise treatment planning: dose plan (a; red line: tumor border; yellow and green lines: 50-Gy and 30-Gy isodose) and trajectory plan (b).

Abbildungen 1a und 1b. Behandlungsplan: Dosisplanung (a; rote Linie: Tumorgrenzen; gelbe und grüne Linien: 50-Gy- und 30-Gy-Isodose) und Zugangsplanung (b).

using STP 3.5 (until February 1996 with STP 2; Leibinger, Freiburg, Germany) in cooperation with a medical physicist. Entry points and targets of the catheters were determined taking both, the optimum dose distribution and the safest trajectory into account. The therapeutic isodose curve was prescribed to the surface of the tumor defined on MRI and stereotactic CT (Figure 1).

During autoclavation of the seeds, the stereotactic device was built up and the burr hole was made. An outer nylon catheter (outside diameter 2.0 mm; BEST Industries, Inc., Springfield, VA, USA) was placed stereotactically and loaded with an inner catheter where the ^{125}I seeds had been placed. After verification by orthogonal X-ray, both catheters were fixed in the burr hole and the skin stitched [36].

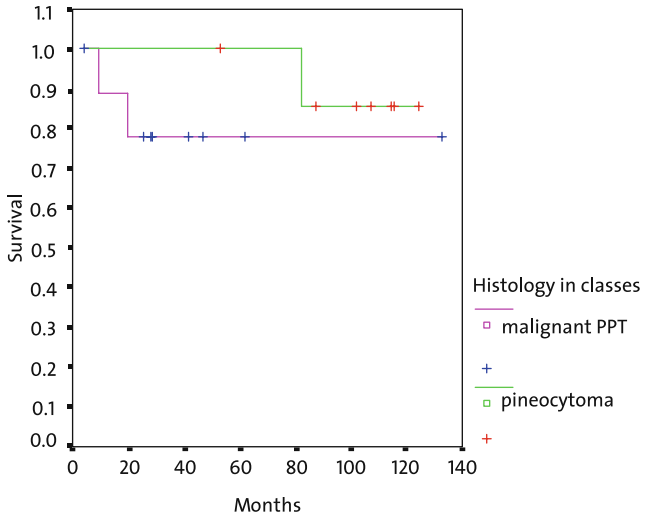
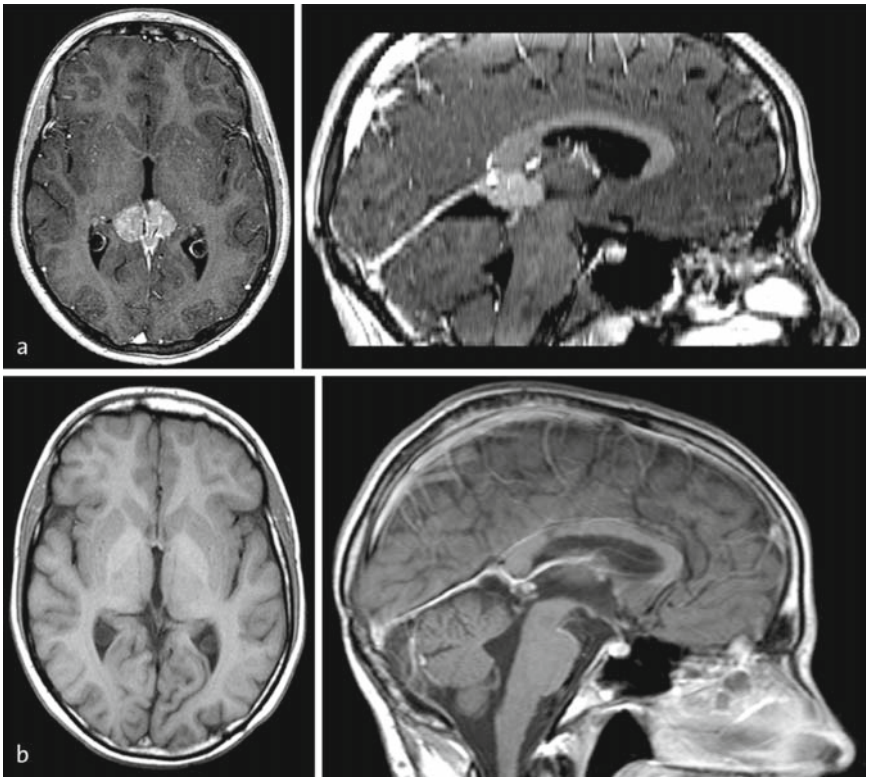


Figure 2. Kaplan-Meier overall survival curves for all 18 PPT patients (eight pineocytomas, three grade III PPTs, seven pineoblastomas) treated with stereotactic ^{125}I-IRS.

Abbildung 2. Gesamtüberleben nach Kaplan-Meier aller 18 PPT-Patienten (acht Pineozytome, drei PPTs Grad III, sieben Pineoblastome), welche mittels stereotaktisch geführter ^{125}I-IRS behandelt wurden.



Figures 3a and 3b. Follow-up MRI of an 11-year-old boy with a pineoblastoma prior to IRS (a) and complete tumor remission 5 years after IRS (b).

Abbildungen 3a und 3b. Verlaufs-MRT des Schädels eines 11-jährigen Jungen mit einem Pineoblastom vor IRS (a) und kompletter Remission 5 Jahre nach Behandlung (b).

Follow-Up

After IRS, clinical follow-up data were obtained from the patients and the referring physicians for a median period of 57.4 months (mean 66 months, range 6–134 months). MRI for patients with pineocytomas was requested at 6-month intervals during the first 2 years and at 1-year intervals thereafter. In patients with malignant PPTs, MRI was scheduled for 3-month intervals during the 1st year and for 6-month intervals thereafter. The median radiographic follow-up was 52.4 months (range 6–12 months). Tumor response was classified according to the MacDonald criteria [25].

Results

All of the 30 stereotactically guided procedures (19 ^{125}I seed implantations and eleven biopsies) were performed without perioperative complications.

Pineocytoma Group (n = 8 Patients)

After a median clinical follow-up of 105 months (range 6–124 months), 50% of the patients (n = 4) were free of symptoms. In the remaining four patients (50%), the symptoms improved or remained stable. There was no treatment-related morbidity or mortality in this group. MR images (median follow-up of 87 months) showed a complete remission in 50% of the patients and a partial remission in the remaining 50% (Figures 4a and 4b). One patient with a recurrent pineocytoma after surgery and fractionated radiotherapy was treated with temporary IRS; 4 years after partial remission, he showed an out-of-field recurrence, necessitating a second IRS, with a local tumor control for 3 years. This patient committed suicide.

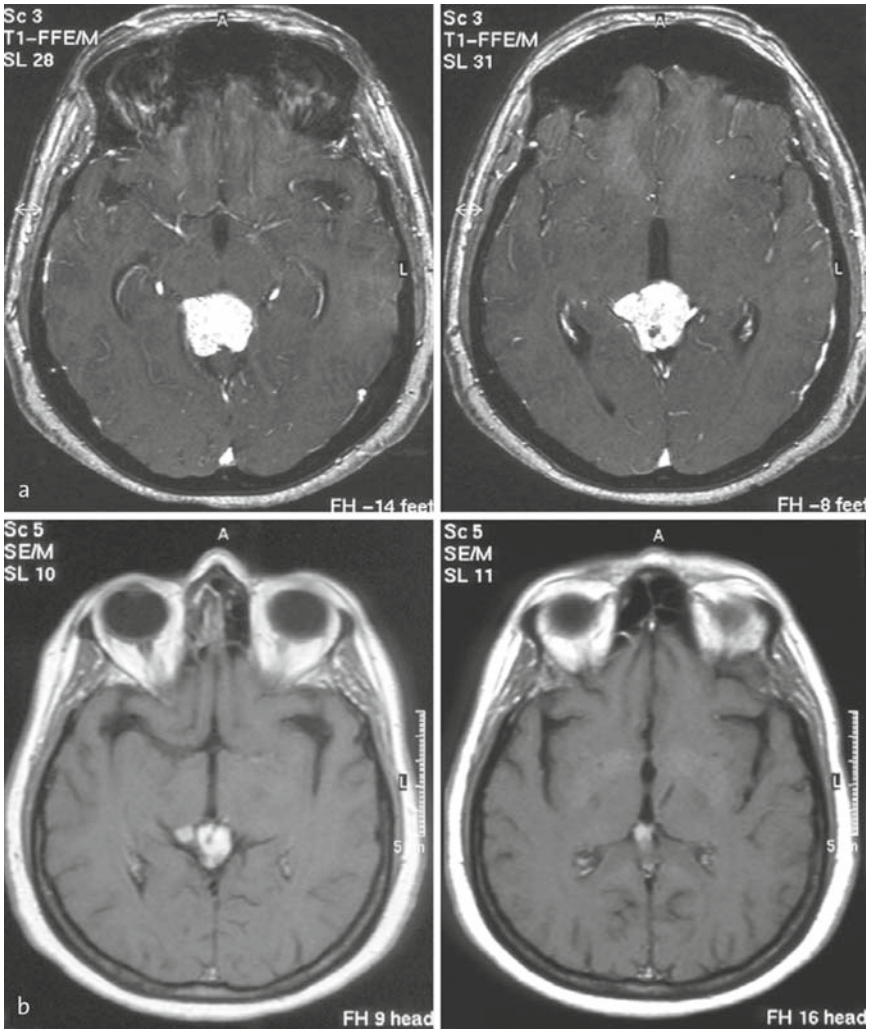
The actuarial overall 5- and 8-year survival rates after IRS for patients with pineocytoma were 100% and 86%, respectively. The Kaplan-Meier curve in Figure 2 shows the overall survival rates.

PPT with Intermediate Differentiation and Pineoblastomas (n = 10)

The median clinical follow-up was 28.3 months (range 6 months to 11.1 years). Of the ten patients, two were free of symptoms after IRS, and five (50%) showed improved or stable clinical status. The remaining three patients developed the following complaints: in one patient, a 68-year-old female, double vision and gaze palsy occurred. The second patient, a 6-year-old boy, who had had previous surgery, polychemotherapy, craniospinal radiotherapy and IRS for a distant

recurrence adjacent to the 4th ventricle, exhibited slowed motor output and deficient cognitive functions. The third patient, a 65-year-old male, experienced remarkable deterioration of cognitive functions 2 years after IRS. Concomitantly, MRI displayed substantial global brain atrophy 2 years after conformal IRS and external-beam irradiation.

With a median follow-up of 28 months (range 6–112 months), MR images showed complete local remission in 90% of cases and partial remission in 10% (Figures 3a and 3b). Two patients with an initially seeding pineoblastoma showed complete local remission but tumor spread 4 and 20 months, respectively, after IRS: in one patient two metastases occurred in the right cerebellopontine angle and in the left cavernous sinus, which were treated with linac radiosurgery and chemotherapy. The second patient with early spinal progressive disease was treated with further chemotherapy and died 20 months after IRS. One patient died 6 months after IRS for unknown reasons (no autopsy was available). In this group, we did not observe treatment-related mortality. The overall actuarial 5-year survival rates after IRS were 78% (Figure 2).



Figures 4a and 4b. MRI of a 50-year-old female patient with pineocytoma before IRS (a) and 5 years later (b).

Abbildungen 4a und 4b. MRT des Schädels einer 50-jährigen Patientin mit einem Pineozytom vor IRS (a) und 5 Jahre später (b).

Discussion

The current results show the considerable safety and efficacy of ^{125}I-IRS for the treatment of patients with pineocytoma, PPT with intermediate differentiation, or pineoblastoma. In the pineocytoma group (n = 8), the overall actuarial 5- and 8-year survival rates were 100% and 86%, respectively. With a comparably high median follow-up of > 7 years, all patients showed either complete tumor remission (50%) or partial remission (50%). The local tumor control rate (complete and partial remission) was 100%. Only one patient showed an out-of-field recurrence 4 years after partial remission. Four of eight patients (50%) were free of symptoms after IRS, and another four showed improved or stable clinical status.

Also the high-grade PPTs (PTTimd and PB, n = 10) responded to IRS resulting in a high overall actuarial 5-year survival rate (78%). With a median follow-up of 28 months, a high local tumor control rate of 100% (90% complete and 10% partial remission) was yielded. In both groups, there was neither acute morbidity nor mortality related to treatment. In three patients, late morbidity occurred after combined IRS and external-beam irradiation. In case of the third patient (6-year-old boy treated with surgery, polychemotherapy and craniospinal radiotherapy prior to IRS) who developed a slowed motor output and deficient cognitive functions, we assume that the deficits are not related to IRS due to the location of the implants in the cerebellum.

Interstitial brachytherapy for the treatment of malignant diseases is well established [7, 12, 27, 28, 30, 34, 37, 38] but reports in the literature addressing interstitial irradiation of these tumors using stereotactic ^{125}I seed implantation are rare. Taken together, they amount to three pineoblastoma cases [4, 29] and four patients with pineocytoma [22]. As a consequence, the data analyzed here represent the largest series of a single institution.

Patil et al. [29] reported on one case that was treated with a schedule combining IRS, radiotherapy and chemotherapy. Follow-up MRI showed complete remission 18 months after treatment. In the second pineoblastoma study, a life prolongation of two patients treated with IRS for recurrent tumor was described [4]. The pineocytoma patients (n = 4) had a median follow-up of 41 months, and a local tumor control rate of 100% [22]. In all three studies, no treatment-related side effects were reported.

While CT and MRI findings may suggest PPT, they cannot provide definitive diagnosis. Thus, an accurate histological diagnosis of individual tumor is indispensable for accessing the therapeutic strategy. This can be accomplished by stereotactic serial biopsy. Various studies confirmed that a stereotactic biopsy of pineal lesions can be performed safely, has a high diagnostic yield, and facilitates rational treatment planning. Severe morbidity and mortality rates of 0–2.1% and a diagnostic yield rate of 94% were reported [2–3, 22, 31–33]. In our series, stereotactic biopsies were done in twelve patients with a diagnostic yield rate of 100%. There were no perioperative complications with neither the stereotactic biopsies nor ^{125}I seed implantations (n = 30) done at our center. Thus, our results are well comparable with those of most contemporary series.

However, the definitive therapy of these tumors remains controversial and is generally complicated by their anatomic location adjacent to the midbrain and the deep venous system. The literature recommends different treatment schedules regardless of the disease stage, from surgery, external irradiation or radiosurgery alone to combined treatment with surgery, radiotherapy and chemotherapy. Despite the general refinement of microsurgical techniques, operative morbidity and mortality still remain high. Contemporary studies report a surgical mortality rate of 4–7% [1, 5], and the permanent morbidity rate may be as high as 10% [5, 11]. Although complete surgical resection is only feasible in the minority of cases, recurrences are observed more often than expected from the histological diagnosis of this type of tumor.

Another treatment option for PPT patients is external-beam irradiation [17, 20, 24, 33]. Although the efficacy of external-beam irradiation for pineocytoma remains controversial, malignant PPT requires fractionated radiation with a field that includes the ventricular system. A retrospective study on 30 PPT patients (nine pineocytomas, six PPTs with intermediate differentiation, 15 pineoblastomas) revealed that fractionated radiotherapy, applied primarily or as an adjuvant postoperatively, can control the tumor and increase survival. The projected 3- and 5-year survival rates of patients with pineocytomas were 100% and 67%, and 78% and 58% for those with other forms of PPT. Local failure occurred after external-beam irradiation in 1/4 patients with pineocytomas, and 5/15 with high-grade PPTs [33].

In a second, retrospective multicenter study on 111 patients who received radiotherapy for malignant PPTs (56 postoperative radiotherapy, 45 primary radiotherapy), overall survival was significantly influenced by the extent of disease (localized vs. disseminated; $p = 0.0002$), differentiation (PPT of intermediate differentiation vs. pineoblastoma; $p = 0.001$), and residual disease ($\geq 50\%$ vs. $< 50\%$ reduction in size; $p < 0.0001$) [24].

In agreement with the literature, our data show that the extent of disease at diagnosis appears to be an important prognostic factor for pineoblastomas [24, 33]. In our study, 2/3 patients with initially seeding pineoblastoma showed complete local remission, but distant tumor spread became obvious at 4 and 20 months, respectively. Thus, initial staging should include examination of the CSF and an MRI of the spine.

The main advantage of IRS over conventional radiotherapy is the reduction of the radiation dose to surrounding normal brain while augmenting the radiobiological effect on the tumor volume. By reducing the total brain dose, IRS may also play an important role in children with malignant PPT. Compared with the results of external radiotherapy for PPTs; our results demonstrate a significantly higher local tumor control rate (100%) with a quite considerable complete tumor remission of 72% and also an increase of survival.

A further treatment option is systemic chemotherapy, but its benefits after craniospinal irradiation remain unclear [6, 10, 17].

A relatively new therapeutic option for PPT is radiosurgery using gamma knife or linear accelerator [8, 9, 15, 16]. The results of these studies may indicate that radiosurgery is beneficial for local tumor control associated with a lower risk of permanent complications. However, for final conclusions longer follow-up periods are required.

Conclusion

IRS for PPTs has obvious advantages because of its minimal invasiveness, its ability to provide high local tumor control, and its low incidence of treatment-related morbidity. Hence, stereotactic IRS might be an attractive alternative to microsurgery as a safe approach for treating PPT patients, as a primary therapy for small pineocytomas, as salvage therapy after microsurgical decompression of gross symptomatic tumor, and as one arm of a multimodal therapy including conventional irradiation for malignant PPTs (PPTs with intermediate differentiation and pineoblastomas). On the basis of this study, stereotactic management for PPTs can be advocated.

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