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Radiotherapy for papillary tumor of the pineal region: A systematic review of the literature

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ABSTRACT

Papillary tumor of the pineal region (PTPR) is a rare neuroepithelial brain tumor, characterized by a high risk of local recurrence (greater than 70 % at 6 years). The aim of our study was to review the available literature on radiotherapy for PTPR in order to evaluate timings, schedules, outcomes and toxicities of this treatment modality. In our review, 72.4 % (84) of the patients diagnosed with PTPR received radiation therapy. There is heterogeneity in the dose prescription, ranging from 45 Gy (25 × 1.8 Gy) to 60 Gy (30 × 2 Gy) for 3D Conformal Radiation Therapy and from 12 Gy to 36 Gy for Stereotactic Radiosurgery. Being considered as a grade II or III tumor, PTPR should receive higher total radiation dose in the adjuvant setting. Our analysis showed a very limited treatment-related toxicity with an expected 10-y OS of 72.5 %. At 5-years from the diagnosis, about 60 % of the patients experienced a local recurrence, whereas at 10 years the rate is higher than 80 %. In the literature, conflicting data about radiotherapy for PTPR are reported, in particular regarding disease progression. Although radiotherapy represents a fundamental treatment in the management of PTPR, prospective studies are required to better define its impact on overall survival and progression-free survival.

1. Introduction

Papillary tumor of the pineal region is a rare neuroepithelial brain tumor, first included in the 2007 WHO classification of tumors of the Central Nervous System, where it was defined as a Grade II or III, due to its potential malignant behavior and frequent local recurrences [23]. Tumors of the pineal region account for approximately 0.5–1 % of primary central nervous system (CNS) tumors, and can affect both children and adults. Diagnoses occur primarily in adults in their thirties, with no difference in rate between the sexes [12]. From the histological point of view, PTPR presents as an epithelial-like tumor with papillary architecture and solid areas. Papillary areas are made of a fibrovascular core surrounded by multi-layered cuboidal to columnar epithelioid cells. Perivascular pseudorosettes and canals are often described [11]. Symptoms are typically related to obstructive hydrocephalus secondary to compression of the cerebral aqueduct.

The optimal treatment for PTPR remains controversial. The role of surgery, radiotherapy, and chemotherapy is not well codified. The majority of cases are treated with attempted gross partial or total resection [26]. Radiotherapy could play an important role especially in the adjuvant setting, due to the high percentage of local recurrences.

The aim of our study was to review the available literature on radiotherapy for PTPR, in order to evaluate timings, schedules, outcomes and toxicities of this treatment modality.

2. Materials and methods

We searched for articles reporting on oncologic outcome and

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toxicity of patients affected by PTPR and treated with radiotherapy. A PubMed, Scopus and Clinical key literature search was conducted using the Preferred Reporting Items and Meta-Analyses (PRISMA) [24]. We identified articles published within the last 15 years up to the first of January 2018, using Medline search with the following selection criteria: English language, full papers, PTPR treated with radiotherapy, oncologic and toxicity data available. We performed a literature search using the following medical subject heading (MeSH) terms and free text words: pineal tumors, pineal region tumors, pineal parenchymal tumors, papillary tumor of the pineal region, radiotherapy, conformal radiotherapy, stereotactic radiotherapy, radiosurgery and stereotactic ablative radiotherapy. When multiple publications from the same Centre were available, the most recent one was selected.

All studies identified using the above described search strategy were screened for inclusion in the review using the eligibility criteria. A manual cross-reference search of the eligible papers was performed to identify additional relevant articles.

The initial decision for potential inclusion of the studies was based on titles and abstracts screened by the two authors (A.L. and C.B.). After that, two other reviewers verified independently and unblinded the full version of each article. Disagreements were resolved through team discussion until a consensus was reached. The following information were abstracted from all primary reports: primary author, reference, year of publication, number of patients, patient population, age, sex, tumor size, immunohistological and imaging findings, number of patients treated with radiotherapy for PTPR, study design, intent and schedule of radiotherapy, oncologic outcome (progression-free survival [PFS], overall survival [OS]), and toxicity.

3. Results

We identified a total of 34 relevant articles, 26 of which contained case reports of patients diagnosed with PTPR. More specifically, we analyzed data of 22 case reports and 4 retrospective studies. Data were summarized in evidence tables and described in the text. The flowchart of the systematic review is reported in Fig. 1.

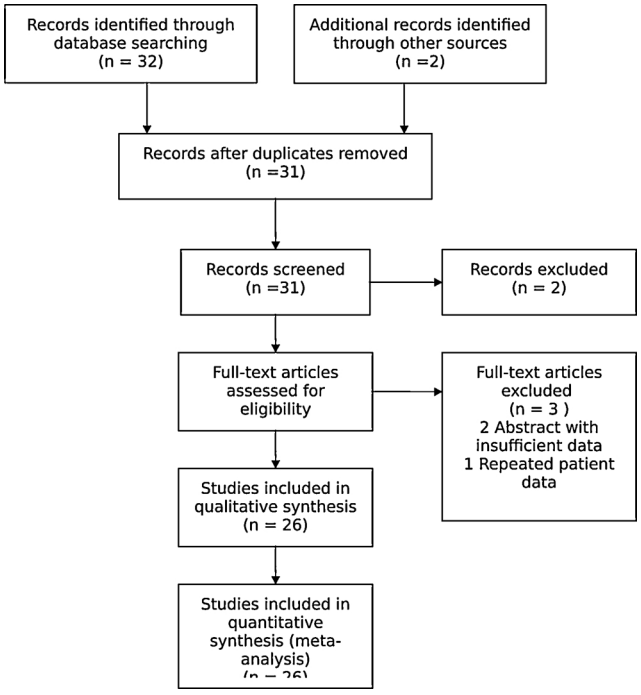

Fig. 1. PRISMA flow diagram.

3.1. Patients characteristics

222 patients from 26 studies [1–5,7–10,15–20,25–32,34,36,37] were collected (Table 1). We extrapolated and analyzed the data of patients diagnosed with PTPR, for a total amount of 116 patients. The age of onset of PTPR ranged from 5 years to 66 years (median 32 years). A slight female predominance was described (56 women versus 52 men). The most common initial symptom was headaches, which affected 83 % of patients, followed by visual disturbances in 67 %, primarily blurred vision and diplopia, and gait disturbances in 41.7 %. Tumor size ranged from 5 mm to 50 mm, with a mean value of 25.5 mm (Table 1).

3.2. Imaging findings

MRI was commonly reported to be the most frequently used diagnostic investigation at disease onset, revealing mixed solid and cystic masses with typically heterogeneous contrast enhancement [1,7–9,15,18,25,27,28,30–32,34]. MRI was used at diagnosis in all studies (not reported in the series by Fevre-Montagne). In the majority of cases, the authors reported intrinsic T1-weighted hyper-intensity of the examined mass [4,10,19,20,27,37]. Other reports described minimal to intermediate signal intensities on T1-weighted MRI and hyper-intensity on T2-weighted imaging [2,5,8,25]. Clear delimitation and necrotic areas were less common features. This tumor was associated with the presence of hydrocephalus in 47 of 69 patients [1,2,4,5,7–9,15–20,25,27,31,32,34,36,37]. During follow-up, all patients underwent scheduled MRI (Table 2).

3.3. Immunohistochemical findings

The immunohistochemical (IHC) profile of PTPR has been analyzed in 21 out of 26 studies [1–4,7,8,10,15,18–20,25,27–32,34,36]. The most common feature of papillary tumor immunophenotype is the strong reactivity for a broad spectrum of cytokeratins, especially CK18 (81.1 %), CK8 (75 %) and Cam5.2 (85.7 %). On the contrary, CK7, CK20 and CK5/6 are predominantly negative or weakly expressed. Strong staining of neuron-specific enolase (NSE), S-100 and vimentin is observed in 77 %, 74 % and 76.3 % of patients, respectively. Moreover, neural cell adhesion molecule (CD56/N-CAM) showed 100 % of positivity. Microtubule-associated protein 2 (MAP2) is strongly positive in the majority of the patients (89 %).

3.4. Management and outcomes

Surgical procedures were reported in 107 patients. In the majority of the patients (82.3 %) an effort has been made to perform a resection, including 61 gross total resections and 27 subtotal resections [1,3–5,7–10,15,17–19,25,27,28,30,31,36,37]. Nineteen patients (17.7 %) underwent diagnostic biopsy only [5,9,10,20,27,29,32,34].

Of the 116 patients affected by PTPR, 84 received radiotherapy (59 in the adjuvant setting, 24 as a definitive treatment, and 1 as a salvage). Focal irradiation was performed in 72.5 % of cases, radiosurgery in 17.7 % of the cases and a combination of whole brain or craniospinal irradiation plus a boost was done in 9.8 % of cases. Three-dimensional conformal radiotherapy was the most frequent treatment technique, with a schedule of 1.8 – 2 Gy per fraction to a total dose ranging from 50.4–60 Gy (Table 3). SRS was adopted in 17 patients, both in the definitive and adjuvant setting, and it was generally performed in a single fraction using Gamma Knife (dose range 12 – 36 Gy).

We evaluated data about systemic treatment in 81 cases: 15 (18.5 %) patients received adjuvant chemotherapy. The chemotherapy regimens that have been used included various combinations of cisplatin, etoposide, nimustine, ifosfamide, vincristine and temozolomide [9,15,25,28,32,36,37].

Toxicity was almost absent, however, Fauchon et al. [9] reported

Table 1
Patients' characteristics.

Study	No of pts (total)	Age (median)	Sex	Tumor Size (median,mm)	Clinical signs
Shibahara 2004 [32]	1	29	F	30	Headache
Kern 2006 [17]	1	19	F	NA	Headache, nausea, vomiting, gait disturbance
Fevre-Montagne 2006 [10]	31	29	14 M ; 17 F	25	NA
Dagnew 2007 [7]	3	44	F	23	Headache, gait disturbance, visual loss
Boco 2008 [1]	1	33	M	35	Headache, horizontal nystagmus, dyplopia
Buffenoir 2008 [2]	1	13	M	31	Headache, asthenia, upper limb tremor
Inoue 2008 [15]	1	43	M	25	Vertigo, papilledema, Parinaud sign.
Santarius 2008 [30]	1	33	M	6	Headache, blurred vision
Cerase 2009 [4]	1	56	F	NA	Acute dizziness
Varikatt 2009 [34]	1	21	F	NA	Headache
Yano 2009 [36]	1	17	M	30	Headache, visual disturbances
Sharma 2009 [31]	3	27	2 M ; 1 F	NA	Headache, visual disturbances, ataxia
Nakamura 2009 [25]	1	11	M	NA	Cranial hypertension
Cardenas 2010 [3]	1	47	M	21	Dizziness, drowsiness
Epari 2011 [8]	3	39	2 M ; 1 F	22	Headache, dyplopia, convulsions
Poulgrain 2011 [27]	2	25-42	1 M ; 1 F	20-25	Headache, gait disturbance
Rickard 2011 [28]	2	36-48	1 M ; 1 F	18-21	Headache, gait disturbance, blurring of vision
Lorenzetti 2011 [20]	1	42	F	30	Body paralysis of upward
Patel 2011 [26]	1	23	M	NA	Headache, facial numbness
Yianni 2011 [37]	44	NA	NA	NA	NA
Fauchon 2013 [9]	44	29	21 M ; 23 F	25	Cranial hypertension, hydrocephalus
Riis 2013 [29]	1	20	M	NA	Cranial hypertension
Koziarski 2014 [18]	2	37-45	1 M ; 1 F	22-49	Blurred vision, headache, ataxia
Chatterjee 2015 [5]	3	33	1 M ; 2 F	24	Headache, gait disturbance, visual disturbance
Iorio-Morin 2017 [16]	70	36	NA	NA	Headache, hydrocephalus
Lancia 2017 [19]	1	27	F	24	Blurred vision, diplopia headache

M = male; F = female; NA = not available; CT = computer tomography; MRI = magnetic resonance.

that 2 patients developed Grade 3 Parinaud's syndrome and motor deficit. Moreover, Rickard et al. [28] registered in their case report a grade 2 fatigue in both patients (Table 4).

The mean and median follow-up period was 3.7 years and 5.6 months respectively (range 12–218 months). Yano et al. [36] reported the longest survival time, which was 218 months in a patient who developed multiple recurrences and underwent three different RT treatment during his follow-up (Table 4). Half of the patients (50 %) developed recurrences, most of which were local [5,10,27,36].

Table 2
Imaging characteristics.

Study	No of pts (total)	Image method at diagnosis	MRI characteristics	Hydrocephalus	Image method at FU
Shibahara 2004 [32]	1	CT, MRI	Mixed cystic and solid, heterogeneous enhancement	Y	MRI
Kern 2006 [18]	1	MRI	Cystic tumor	N	MRI
Fevre-Montagne 2006 [11]	31	NA	Hyperintense on T1w, not contrast enhancing	NA	MRI
Dagnew 2007 [17]	3	MRI	Partially cystic mass, heterogeneous enhancement	Y	MRI
Boco 2008 [1]	1	MRI	Mixed cystic and necrotic, heterogeneous enhancement	Y	MRI
Buffenoir 2008 [2]	1	CT, MRI	Mixed solid and cystic tumor, minimally enhancing tumor on T1w	Y	MRI
Inoue 2008 [16]	1	CT, MRI	Mixed cystic and solid, contrast enhancing T2w revealed a hyperintense area	Y	MRI
Santarius 2008 [30]	1	CT, MRI	Multi-cystic tumor with enhancing component	N	MRI
Cerase 2009 [4 u]	1	MRI	High homogeneous signal on T1w inhomogeneous on T2w	Y	MRI
Varikatt 2009 [34]	1	MRI	Contrast enhancing	Y	MRI
Yano 2009 [36]	1	MRI	Homogeneous enhancement	N	MRI
Sharma 2009 [31]	3	MRI	Contrast enhancing	Y	MRI
Nakamura 2009 [25]	1	CT, MRI	Heterogeneous contrast enhancement, hyperintensity on T2w and isointense on T1w.	Y	MRI
Cardenas 2010 [3]	1	MRI	NA	N	MRI
Epari 2011 [9]	3	MRI	Mixed cystic and solid, contrast enanchement, hypointense in T1w and T2w	Y	MRI
Poulgrain 2011 [27]	2	CT, MRI	Mixed cystic and solid, heterogeneous enhancement, hyperintensity on T1w, solid component isointense on T2w	N	MRI
Rickard 2011 [28]	2	MRI	Mixed cystic and solid, heterogeneous enhancement	Y	MRI
Lorenzetti 2011 [21]	1	CT, MRI	Contrast enhancing, hyperintense on T1w and T2w	N	MRI
Patel 2011 [26]	1	CT, MRI	Hyperintense on T1w, not contrast enhancing	N	MRI
Yianni 2011 [37]	44	MRI	NA	NA	MRI
Fauchon 2013 [10]	44	CT, MRI	Contrast enhancing	Y (31 pts)	MRI
Riis 2013 [29]	1	MRI	NA	N	MRI
Koziarski 2014 [19]	2	MRI	Contrast enhancing	N	MRI
Chatterjee 2015 [5]	3	MRI	Hypointense without contrast enhancement, solid; (1) Mixed cystic and solid, heterogeneous enhancement	N	MRI
Iorio-Morin 2017 [17]	70	MRI	NA	Y (53 pts)	MRI
Lancia 2017 [20]	1	MRI	Lobulated mass, hyperintense on T1w	N	MRI

NA = not available; CT = computer tomography; MRI = magnetic resonance; FU = follow-up; T1w = T1 weighted; T2w = T2 weighted Y = yes;N = no.

Table 3
Treatment characteristics.

Study	N of pts with PTPR	Type of surgery (no. of pts)	N pts treated with RT for PTPR	Intent of radiotherapy (no. of pts)	RT technique (no. of pts)	Linac/GK	Dose (dose per fraction)	chemotherapy
Shibahara 2004 [32]	1	Biopsy	1	Adjuvant	3DCRT	Linac	50.4 Gy (28 × 1.8 Gy)	Adjuvant
Kern 2006 [17]	1	Partial resect.	1	Adjuvant	NA	NA	NA	No
Fevre-Montagne 2006 [10]	31	Biopsy (4), partial resect. (6), gross tumor resect. (21)	15	Definitive (6), adjuvant (9)	NA	NA	NA	NA
Dagnew 2007 [7]	3	Partial resect.	3	Adjuvant	3DCRT (1); SRS (2)	Linac/GK	30 Gy (10 × 3 Gy); 15 Gy (1 × 15 Gy)	No
Boco 2008 [1]	1	Gross tumor resect.	1	Adjuvant	NA	NA	NA	No
Buffenoir 2008 [2]	1	Gross tumor resect.	1	Adjuvant	3DCRT	Linac	54 Gy (30 × 1.8 Gy)	No
Inoue 2008 [15]	1	Gross tumor resect.	1	Adjuvant	3DCRT	Linac	24 + 30 Gy (12/15 × 2 Gy)	Adjuvant
Santarius 2008 [30]	1	Partial resect.	1	Salvage	3DCRT	Linac	55 Gy (33 × 1.6 Gy)	No
Cerase 2009 [4]	1	Gross tumor resect.	1	Adjuvant	3DCRT	Linac	45 Gy (25 × 1.8 Gy)	No
Varikatt 2009 [34]	1	Biopsy	1	Definitive	NA	NA	NA	No
Yano 2009 [36]	1	Biopsy, partial resection	1	Adjuvant	(1 st) 3DCRT + SRS ; (2nd) SRS; (3rd) 3DCRT	Linac/GK	(1 st)30 Gy + 20 Gy; (2nd) 20 Gy; (3rd) 14 Gy	Adjuvant
Sharma 2009 [31]	3	Gross tumor resect. (2), partial resection (1)	3	Adjuvant	NA	NA	NA	NA
Nakamura 2009 [25]	1	Gross tumor resect.	1	Adjuvant	3DCRT	Linac	50.4 Gy (28 × 1.8 Gy)	Adjuvant
Cardenas 2010 [3]	1	Ventricolostomy	1	Definitive	SRS	GK	NA	??
Epari 2011 [8]	3	Gross tumor resect.	3	Adjuvant]]	3DCRT	Linac	45 Gy (25 × 1.8 Gy)	No
Poulgrain 2011 [27]	2	Biopsy (1), partial resection (1)	2	Adjuvant	3DCRT	Linac	50.4 Gy/54 Gy (28/30 × 1.8 Gy)	No
Rickard 2011 [28]	2	Gross tumor resect.	2	Adjuvant	3DCRT	Linac	45 Gy/54 Gy (25/30 × 1.8 Gy)	Adjuvant
Lorenzetti 2011 [20]	1	Partial resect.	1	Adjuvant	3DCRT	Linac	54 Gy (27 × 2 Gy)	Adjuvant
Patel 2011 [26]	1	Biopsy	1	Definitive	3DCRT	Linac	50.4 Gy (28 × 1.8 Gy)	No
Yianni 2011 [37]	2	NA	2	Definitive	SRS	GK	15 Gy (1 × 15 Gy)	NA
Fauchon 2013 [9]	44	Biopsy (6), partial resect. (12), gross tumor resect. (26)	28	Definitive (6), adjuvant (22)	3DCRT (26); SRS (2)	Linac/GK	Range: 12 − 60 Gy	Adjuvant (in 8 pts)
Riis 2013 [29]	1	Biopsy	1	Definitive	SRS	GK	12 Gy (1 × 12 Gy)	No
Koziarski 2014 [18]	2	Gross tumor resect.	2	Adjuvant	SRS	GK	NA	No
Chatterjee 2015 [5]	3	Biopsy (2), partial resection (1)	3	Adjuvant	3DCRT	Linac	45 Gy (25 × 1.8 Gy)	No
Iorio-Morin 2017 [16]	6	NA	6	Definitive	SRS	GK	Range 26.6 − 36 Gy (single fract.)	No
Lancia 2017 [19]	1	Partial resect.	1	Adjuvant	3DCRT	Linac	59.4 Gy (33 × 1.8 Gy)	No

NA = not available; RT = radiotherapy GK = gammaknife;Linac = linear accelerator; 3DCRT = 3D conformal radiotherapy; SRS = stereotactic radiosurgery; Gy = Gray.

Table 4
Follow-up and Outcomes.

Study	Image method at FU	Median follow-up	OS [rate] at the end of FU	PFS [years]	Toxicity (y/n)	Toxicity grade
Shibahara 2004 [32]	MRI	1 y	100 %	1 y	N	0
Kern 2006 [17]	MRI	1.8 y	100 %	1.8 y	N	0
Fevre-Montagne 2006 [10]	NA	4.2 y (mean)	Estimated 5 y: 73 %	Estimated 5 y: 27 %	NA	NA
Dagnew 2007 [7]	MRI	4.8 y	100 %	4.8 y	N	0
Boco 2008 [1]	MRI	2.2 y	100 %	2.2 y	N	0
Buffenoir 2008 [2]	MRI	2 y	100 %	2 y	N	0
Inoue 2008 [15]	MRI	1 y	100 %	1 y	N	0
Santarius 2008 [30]	MRI	7 y	100 %	7 y	N	0
Cerase 2009 [4]	MRI	2.4 y	100 %	2.4 y	N	0
Varikatt 2009 [34]	MRI	11.2 y	100 %	11 y	N	0
Yano 2009 [36]	MRI	18.2 y	100 %	9 y	N	0
Sharma 2009 [31]	MRI	1.3 y	100 %	1.3 y	N	0
Nakamura 2009 [25]	MRI	15 y	100 %	15 y	N	0
Cardenas 2010 [3]	MRI	10 y	100 %	10 y	N	0
Epari 2011 [8]	MRI	2.7 y	100 %	2.7 y	N	0
Poulgrain 2011 [27]	MRI	1.8 y	100 %	1.9 y	N	0
Rickard 2011 [28]	MRI	1.3 y	100 %	1.3 y	Y	G2 (fatigue)
Lorenzetti 2011 [20]	MRI	9 y	100 %	9 y	N	0
Patel 2011 [26]	MRI	2 y	100 %	2 y	N	0
Yianni 2011 [37]	MRI	5 y	NA	NA	NA	NA
Fauchon 2013 [9]	MRI	5.2 y	88.5 % (GTR), 75 % (PR), 50 % (B)	Median: 4.8 y	Y	G3 (Parinaud syndr., motor deficit)
Riis 2013 [29]	MRI	5 y	100 %	5 y	N	0
Koziarski 2014 [18]	MRI	9 y; 2 y	100 %	9 y; 2 y	N	0
Chatterjee 2015 [5]	MRI	3.75 y	100 %	8.2 y	N	0
Iorio-Morin 2017 [16]	MRI	11.6 y	100 %	11.6 y	NA	NA
Lancia 2017 [19]	MRI	3.4 y	100 %	3.4 y	N	0

NA = not available; G grade; MRI = magnetic resonance; FU = follow-uP; y = year; Y = yes;N = no.

4. Discussion

Pineal tumors correspond to less than 1 % and 3–8 % of brain tumors in adults and children, respectively. Computed tomography and MRI concur in the precise definition of the shape, size and location of these lesions. More specifically, MRI can provide anatomical details, which can be crucial in the distinction between benign and malignant tumors, and can help discriminating between true pineal masses and parapineal invasion of the gland [33]. The development of MRI has therefore improved the identification of abnormal pineal enlargements, while it can still be difficult to distinguish small masses because of the similar signal intensity with that of the gland itself.

Despite being so rare, we can recognize a wide spectrum of different cancers arising in the pineal gland or in its close proximity. In the WHO 2016 classification, PTPR is one of the 4 different nosographic entities in the group of the pineal region tumors. From the pathological point of view, PTPR are well-circumscribed with low infiltrative margins. The single cells have abundant clear to eosinophilic cytoplasm with round to oval nuclei. A “signet-ring” appearance is occasionally observed. Mitotic figures are usually scarce as areas of diffuse pleomorphism and necrosis but tumor variability has been reported in literature [10]. In particular, a more pronounced proliferative index seem to be associated to younger patients. Immunohistochemically, PTPR is characterized by diffuse positivity for cytokeratins. Moreover, the neoplastic cells express vimentin, S100 and NSE. Sometimes, neuroendocrine markers as chromogranin A and synaptophysin are detected, whereas CD56 is usually strongly expressed. According to 2016 WHO Classification of CNS tumors, papillary tumors of the pineal region are considered as grade II or III [14]. Nevertheless, definitive histological criteria are not still recognized. The most important features seem to be mitotic activity count and proliferative index evaluated by ki-67 expression. In 2006, Fevre-Montange et al. [10] observed that tumors with more than 5 mitoses per 10 high power fields had a higher probability of recurrence and progression. Heim et al. [13] in 2014 suggested that patients with 3 or more mitoses per 10 high power fields and with more than 10 % of ki-67 proliferative index had a worse prognosis.

The main treatment options for pineal region tumors are surgery and radiotherapy. Due to its anatomical location and the presence of neurovascular structures, it has been considered traditionally challenging to find the best way to surgically access this region [35]. However, because of the wide range of pineal tumor subtypes, a histologic diagnosis is mandatory for the most appropriate clinical management to be chosen. Generally, a wider resection of the lesion is associated with a better prognosis [9], but a radical surgical intervention can carry potential risk of operative morbidities, especially for invasive tumors. In our review, only 61 (52.6 %) patients received a gross tumor resection, and 27 of these (44 %) underwent adjuvant radiotherapy. These data underline that post-operative local treatment after radical surgery was strongly suggested between the different Institutions [1,2,4,8–10,15,18,25,28,31], considering PTPR strong tendency for local relapse.

Radiation therapy is not only the mainstay of the palliative treatment of brain metastases, but it also plays a pivotal role in the clinical management of most malignant and many benign primary CNS tumors. It can be delivered post-operatively with the aim of decreasing local failure and delay recurrence, as it happens for gliomas, or it can also represent the definitive treatment in more radiosensitive diseases such as Primitive NeuroEctodermical Tumors (PNET) and germ cells tumors. From a radiobiological point of view, the majority of cell populations within CNS behave as "late-responding tissues", due to their low mitotic index and slowly proliferation rate. However, a spectrum of radiation-related toxicity can occur in patients receiving radiotherapy to the brain; these sequalae can be the expression of specific tissues being damaged (i.e. cognitive impairment in the case of white matter injury) or the consequence of vascular damage (i.e. radiation necrosis).

Concerning pineal masses, irradiation following drainage was historically considered the gold standard treatment, since the malignant nature of the majority of such lesions does not make them amenable to complete excision. Large radiation fields have been used in the past in order to prevent microscopic spread of the disease around the ventricular system.

In our review of the literature, 72.4 % (84) of the patients diagnosed

with PTPR received a radiation therapy course as part of their therapeutic strategy, both as a radical treatment or as an adjuvant approach. More specifically, 24 patients underwent a definitive radiation treatment (11 SRS, 13 3DCRT), whereas the remaining 60 received an adjuvant 3D conformal radiotherapy, or less frequently SRS, on the residual macroscopic and/or microscopic tumor. Data on adjuvant chemotherapy are scarce and regimens used in the few available studies included various combinations of drugs.

Adjuvant chemotherapy is based mainly on cisplatinum and etoposide (VP-16) protocols, including carboplatin-VP16-vincristine, temozolomide, and nimustina [9,20,25,28]. Bevacizumab should be considered for inoperable recurrent PTPRs and in those responsive to radiation or standard cytotoxic treatments [6]. The role of multimodality therapy is not well defined. Only few patients received radiotherapy and chemotherapy combined treatment [9,25]; furthermore, the drugs used were different in each study, this does not allow us to draw any conclusions regarding the possible synchronous effect of combination.

One of the most interesting results in our analysis is that a very limited treatment-related toxicity (3.5 % of patients reported a G2/G3 late toxicity, with no iatrogenic endocrine manifestations) has been recorded, with an expected 10-y OS of 72.5 %. At 5-year from the diagnosis, about 60 % of the patients experienced a local recurrence, whereas at 10 years the rate is higher than 80 %. Regarding disease progression, the largest published retrospective study on PTPR [9] showed no correlation between adjuvant radiotherapy and PFS. Nevertheless, a recent systematic review analyzing 127 patients affected by pineal parenchymal tumors demonstrates that adjuvant radiotherapy is a significant prognostic factor for OS [21].

Stereotactic radiosurgery as a definitive treatment for PTPR is considered by some authors [16] equivalent to gross tumor resection concerning survival, with the possibility of being performed again in case of recurrence.

In the literature, few and conflicting data about radiotherapy for PTPR are reported, but analyzing the results of the present review we can try to draw some conclusion. Gross tumor resection is considered the main treatment modality. Different treatment regimens were adopted in terms of doses, fractionations, volumes, radiation technique and timing of treatment. Many authors administered adjuvant radiotherapy because of the high risk of local disease recurrence after surgery. In the majority of the cases, adjuvant radiotherapy was delivered on the operative bed. Radiation therapy, in adjuvant or definitive setting, seems to be safe with a very low toxicity profile. There is heterogeneity in the dose prescription, ranging from 45 Gy (25 × 1.8 Gy) to 60 Gy (30 × 2 Gy) for 3DCRT and from 12 Gy to 36 Gy for SRS. Being considered as a grade II or III tumor, PTPR should receive higher total radiation dose in the adjuvant setting, which may range from 54 Gy to 60 Gy.

Edson and colleagues reported their concern of the risk of long-term effect on cognition and quality of life after adjuvant radiotherapy mainly related to the young age of diagnosis and treatment (median age of 37 in their cohort). In their retrospective study 2 out of 5 patients treated with radiotherapy presented significant on cognition and the inability to return to their normal ordinary functions [22].

Fauchon et al. revealed very good rates of toxicity in their multicenter retrospective series. Of the 22 patients receiving RT only 2 presented serious adverse events; one had thalamic radionecrosis with diplopia and hypersomnia, while the other one manifested thalamotectal radionecrosis, leading to motor deficiency and Parinaud's syndrome [9].

Finally no toxicity was described at last follow-up in the case reports of some authors [19,26,29].

Very few data are available for chemotherapy; as a matter of fact, this treatment modality was offered to the patients only in 7 studies [9,15,20,25,28,32,36].

The main limitation of the reported studies in our review is their retrospective nature, based on single-institution or pooled experiences. The other limitation is the small number of patients included in each series.

5. Conclusion

To our knowledge, this is the first systematic review about the role of radiotherapy in the management of PTPR, which is a rare disease characterized by a high risk of local recurrence (greater than 70 % at 6 years) [9]. Although radiotherapy represents a fundamental treatment in the management of PTPR, prospective studies are required to better define its impact on overall survival and progression-free survival.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of study formal consent is not required.

Informed consent

This article does not contain any study with human participants performed by any of the authors."

Declaration of Competing Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

References

[1] T. Boco, S. Aalaei, M. Musacchio, R. Byrne, E. Cochran, Papillary tumor of the pineal region, Neuropathology 28 (1) (2008) 87–92.
[2] K. Buffenoir, P. Rigoard, M. Wager, S. Ferrand, A. Coulon, J.L. Blanc, B. Bataille, A. Listrat, Papillary tumor of the pineal region in a child: case report and review of the literature, Childs Nerv. Syst. 24 (3) (2008) 379–384.
[3] R. Cardenas, V. Javalkar, J. Haydel, R. Wadhwa, M. Fowler, B. Scheithauer, A. Nanda, Papillary tumor of pineal region: prolonged control rate after gamma knife radiosurgery - a case report and review of literature, Neurol. India 58 (3) (2010) 471–476.
[4] A. Cerase, I.M. Vallone, G. Di Pietro, G. Oliveri, C. Miracco, C. Venturi, Neuroradiological follow-up of the growth of papillary tumor of the pineal region: a case report, J. Neurooncol. 95 (3) (2009) 433–435.
[5] D. Chatterjee, K. Gupta, N. Kumar, R. Chhabra, B.D. Radotra, Papillary tumor of the pineal region-report of three cases with literature review, Neurol. India 63 (4) (2015) 567–570.
[6] A.L. Cohen, K. Salzman, C. Palmer, R. Jensen, H. Colman, Bevacizumab is effective for recurrent papillary tumor of the pineal region: first report, Case Rep. Oncol. 6 (2013) 434–440.
[7] E. Dagnew, L.A. Langford, F.F. Lang, F. DeMonte, Papillary tumors of the pineal region: case report, Neurosurgery 60 (5) (2007) E953–5 discussion E953-5.
[8] S. Epari, R. Bashyal, S. Malick, T. Gupta, A. Moyadi, S.V. Kane, M. Bal, R. Jalali, Papillary tumor of pineal region: report of three cases and review of literature, Neurol. India 59 (3) (2011) 455–460.
[9] F. Fauchon, M. Hasselblatt, A. Jouvet, et al., Role of surgery, radiotherapy and chemotherapy in papillary tumors of the pineal region: a multicenter study, J. Neurooncol. 112 (2) (2013) 223–231.
[10] M. Fèvre-Montange, M. Hasselblatt, D. Figarella-Branger, et al., Prognosis and histopathologic features in papillary tumors of the pineal region: a retrospective

multicenter study of 31 cases, J. Neuropathol. Exp. Neurol. 65 (10) (2006) 1004–1011.
[11] M. Fèvre-Montange, A. Vasiljevic, J. Champier, A. Jouvet, Histopathology of tumors of the pineal region, Future Oncol. 6 (5) (2010) 791–809.
[12] M. Fèvre Montange, A. Vasiljevic, J. Champier, A. Jouvet, Papillary tumor of the pineal region: histopathological characterization and review of the literature, Neurochirurgie 61 (2–3) (2015) 138–142.
[13] S. Heim, R. Beschorner, M. Mittelbronn, et al., Increased mitotic and proliferative activity are associated with worse prognosis in papillary tumors of the pineal region, Am. J. Surg. Pathol. 38 (1) (2014) 106–110.
[14] IARC, WHO Classification of Tumours of the Central Nervous System, Revised 4t, World Health Organization, Lyon, France, 2016.
[15] T. Inoue, T. Kumabe, M. Kanamori, Y. Sonoda, M. Watanabe, T. Tominaga, Papillary tumor of the pineal region: a case report, Brain Tumor Pathol. 25 (2) (2008) 85–90.
[16] C. Iorio-Morin, H. Kano, M. Huang, et al., Histology-stratified tumor control and patient survival after stereotactic radiosurgery for pineal region tumors: a report from the international gamma knife research foundation, World Neurosurg. 107 (2017) 974–982.
[17] M. Kern, P. Robbins, G. Lee, P. Watson, Papillary tumor of the pineal region–a new pathological entity, Clin. Neuropathol. 25 (4) (2006) 185–192.
[18] A. Koziarski, B. Grala, E. Skrobowska, Papillary tumor of the pineal region. Report of two cases and literature review, Neurol. Neurochir. Pol. 48 (5) (2014) 356–362.
[19] A. Lancia, G. Ingrosso, R. Santoni, The role of adjuvant radiotherapy in the treatment of papillary tumors of the pineal region: some general considerations and a case report, Klin. Onkol. 30 (6) (2017) 456–459.
[20] M. Lorenzetti, F. Motta, R. Campanella, D. Bauer, A. Assi, C. Arienta, S.M. Gaini, M. Caroli, Adjuvant temozolomide chemotherapy for treatment of papillary tumor of the pineal region, World Neurosurg. 76 (1–2) (2011) 160–163.
[21] S. Mallick, R. Benson, G.K. Rath, Patterns of care and survival outcomes in patients with pineal parenchymal tumor of intermediate differentiation: an individual patient data analysis, Radiother. Oncol. 121 (2) (2016) 204–208.
[22] E.A. Mark, G.N. Fuller, P.K. Allen, N.B. Levine, A.J. Ghia1, A. Mahajan, P.D. Brown, F. DeMonte, J. Li, Outcomes after surgery and radiotherapy for papillary tumor of the pineal region, World Neurosurg. 84 (1) (2015) 76–81 July.
[23] E. Matyja, W. Grajkowska, P. Nauman, W. Bonicki, Histopathological patterns of papillary tumour of the pineal region, Folia Neuropathol. 49 (3) (2011) 181–190.
[24] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, PRISMA Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Ann. Intern. Med. 151 (4) (2009) 264–269 W64.
[25] H. Nakamura, K. Makino, M. Kochi, Y. Nakazato, J. Kuratsu, Successful treatment of neoadjuvant therapy for papillary tumor of the pineal region, Brain Tumor Pathol. 26 (2) (2009) 73–77.
[26] S.K. Patel, K.L. Tomei, L.D. Christiano, A. Baisre, J.K. Liu, Complete regression of papillary tumor of the pineal region after radiation therapy: case report and review of the literature, J. Neurooncol. 107 (2) (2012) 427–434.
[27] K. Poulgrain, R. Gurgo, C. Winter, B. Ong, Q. Lau, Papillary tumour of the pineal region, J. Clin. Neurosci. 18 (8) (2011) 1007–1017.
[28] K.A. Rickard, J.R. Parker, T.W. Vitaz, A.R. Plaga, S. Wagner, J.C. Parker, Papillary tumor of the pineal region: two case studies and a review of the literature, Ann. Clin. Lab. Sci. 41 (2) (2011) 174–181.
[29] P. Riis, A.T.C.J. van Eck, H. Dunker, M. Bergmann, W. Börm, Stereotactic radiosurgery of a papillary tumor of the pineal region: case report and review of the literature, Stereotact. Funct. Neurosurg. 91 (3) (2013) 186–189.
[30] T. Santarius, J.A. Joseph, K.T. Tsang, D.G. O'Donovan, R.W. Kirollos, Papillary tumour of the pineal region, Br. J. Neurosurg. 22 (1) (2008) 116–120.
[31] M.C. Sharma, D. Jain, C. Sarkar, V. Suri, A. Garg, B.S. Sharma, V.S. Mehta, Papillary tumor of the pineal region–a recently described entity: a report of three cases and review of the literature, Clin. Neuropathol. 28 (4) (2009) 295–302.
[32] J. Shibahara, T. Todo, A. Morita, H. Mori, S. Aoki, M. Fukayama, Papillary neuroepithelial tumor of the pineal region. A case report, Acta Neuropathol. 108 (4) (2004) 337–340.
[33] A.G. Solomou, Magnetic resonance imaging of pineal tumors and drop metastases: a review approach, Rare Tumors 9 (3) (2017) 6715.
[34] W. Varikatt, M. Dexter, H. Mahajan, R. Murali, T. Ng, Usefulness of smears in intraoperative diagnosis of newly described entities of CNS, Neuropathology 29 (6) (2009) 641–648.
[35] I. Yamamoto, Pineal region tumor: surgical anatomy and approach, J. Neurooncol. 54 (3) (2001) 263–275.
[36] H. Yano, N. Ohe, N. Nakayama, J. Shinoda, T. Iwama, Clinicopathological features from long-term observation of a papillary tumor of the pineal region (PTPR): a case report, Brain Tumor Pathol. 26 (2) (2009) 83–88.
[37] J. Yianni, J. Rowe, N. Khandanpour, G. Nagy, N. Hoggard, M. Radatz, A. Kemeny, Stereotactic radiosurgery for pineal tumours, Br. J. Neurosurg. 26 (3) (2012) 361–366.