



**TITLE: Diagnosis and Treatment of Pineal Gland Cysts: A Review of the Clinical Effectiveness and Guidelines**

**DATE:** 16 February 2012

## **CONTEXT AND POLICY ISSUES**

Pineal gland cysts are benign, fluid-filled mass on the pineal gland and are often asymptomatic.<sup>1,2</sup> While the majority are asymptomatic, the cyst can compress adjacent brain structures resulting in clinical symptoms including headache, blurred vision, vertigo and vomiting.<sup>3</sup> Magnetic resonance imaging (MRI) studies have indicated that the prevalence of pineal cysts is between 1.5% and 11%.<sup>3</sup> However, autopsy studies report that the prevalence may be as high as 40%, suggesting the need for more sensitive imaging techniques.<sup>3,4</sup> A 2007 study of healthy adults reported a prevalence of 23% using high resolution MRI, so a gap between cysts identified by imaging and those confirmed in autopsy studies remains.<sup>3</sup>

Different MRI techniques, as well as computed tomography (CT) scanning and ultrasonography have all been employed to detect pineal gland cysts.<sup>5,6</sup>

Management of pineal gland cysts remains controversial due to the large proportion of asymptomatic cysts and the lack of current clinical practice guidelines. Surgical interventions have been used to remove the cyst and resolve symptoms.<sup>3,7</sup> These approaches include both endoscopic surgery and craniotomy, which involves removal of a portion of the skull. Preferred interventions and long term outcomes remain unclear.

The purpose of this report is to review the clinical evidence and clinical practice guidelines regarding the diagnosis and treatment of pineal gland cysts.

## **RESEARCH QUESTIONS**

1. What is the diagnostic accuracy of tests for patients with pineal gland cysts?
2. What is the clinical effectiveness of treatments for patients with pineal gland cysts?
3. What are the evidence-based guidelines and recommendations for the diagnosis and treatment of pineal gland cysts?

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## KEY MESSAGE

Limited evidence suggests that true fast imaging with steady state precession (trueFISP) MRI techniques result in a higher rate of detection of pineal cysts and fewer unconfirmed diagnoses compared with other MRI methods. No controlled trials of treatment interventions were identified; evidence on treatment is mainly found in case reports. No evidence-based guidelines for the diagnosis and treatment of pineal gland cysts were identified.

## METHODS

### Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, EMBASE, The Cochrane Library (2012, Issue 1), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2002 and February 7, 2012.

### Selection Criteria and Methods

One reviewer screened titles and abstracts of the retrieved publications to select articles for full-text review. A second reviewer evaluated the full-text publications for the final article selection according to selection criteria presented in Table 1.

**Table 1: Selection Criteria**

<b>Population</b>	Individuals with a pineal gland cyst
<b>Intervention</b>	Diagnostic tests, treatments
<b>Comparator</b>	Any
<b>Outcomes</b>	Diagnostic accuracy, clinical effectiveness, guidelines and recommendations
<b>Study Designs</b>	Health technology assessments, systematic reviews and meta-analyses, randomized controlled trials (RCTs), non-randomized studies, case reports and case series, evidence-based guidelines.

### Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications or included in a selected systematic review, included populations with mixed indications, or were published prior to 2002.

### Critical Appraisal of Individual Studies

The methodological quality of included studies on detecting pineal gland cysts was performed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool.<sup>8</sup> Detailed checklist results are not presented. Instead, strengths and limitations of each included study are summarized and described. No evidence-based guidelines were identified for critical appraisal.

A formal quality assessment of case reports was not conducted since these study designs are considered to be inferior quality. The quality of these studies will be discussed with other limitations.

## SUMMARY OF EVIDENCE

### Quantity of Research Available

The literature search yielded 89 citations. Upon screening titles and abstracts, 76 citations were excluded and 13 potentially relevant articles were retrieved for full-text review. No potentially relevant reports were identified through grey literature searching. Of the 13 potentially relevant reports, one did not meet the inclusion criteria. The study selection process is outlined in a PRISMA flowchart (Appendix 1). Four non-randomized studies<sup>1,4,9,10</sup> and 8 case reports<sup>2,6,11-16</sup> describing a total of 39 patients were included in this review. No health technology assessments, systematic reviews, RCTs, or evidence-based guidelines were identified. Characteristics of the included non-randomized studies are described in Appendix 2.

### Summary of Study Characteristics

#### *Country of origin*

Two non-randomized studies<sup>4,9</sup> were conducted in Germany and two<sup>1,10</sup> were performed in Croatia. The German studies had sample sizes of 54<sup>9</sup> and 111.<sup>4</sup> Both Croatian studies<sup>1,10</sup> included 60 participants. Of the 39 cases described in eight publications, 24 occurred in India,<sup>6</sup> seven in Belgium,<sup>16</sup> four in Germany,<sup>2,13</sup> two in the United States,<sup>12,15</sup> and one each in Italy<sup>11</sup> and Japan.<sup>14</sup>

#### *Population*

One non-randomized study<sup>4</sup> included only adults, and one<sup>9</sup> focused on a pediatric population. Two non-randomized studies included both adults and children.<sup>1,10</sup> Of these four studies two<sup>1,10</sup> included participants without pineal cysts as a control group. Fourteen of the same patients were included in the analysis of both studies.<sup>1,10</sup> Among case reports, 11 patients were adults and four were children.<sup>2,11-16</sup> One case series of 24 patients did not report individual ages, but included both adults and children.<sup>6</sup>

#### *Interventions and comparators*

Two non-randomized studies<sup>4,9</sup> compared trueFISP with other magnetic resonance imaging (MRI) techniques (T1-weighted spin echo [T1-SE], T2 weighted turbo spin echo [T2-TSE] and fluid attenuated inversion recovery [FLAIR]) for detection of pineal gland cysts. Two studies compared transcranial sonography (TCS) with MRI; a group of 14 patients was included in both studies.<sup>1,10</sup> One case report described an instance of pineal cyst detection by TCS.<sup>13</sup> The remainder used computed tomography imaging and/or MRI.

#### *Outcomes*

Three studies reported interrater variability<sup>1,9,10</sup> and one reported intrarater variability<sup>9</sup> of cyst measurement (size and volume) on individual devices.<sup>9</sup> Two reported the variability in cyst or gland measurement between devices; there was an overlap of 14 participants for these two

studies.<sup>1,10</sup> Two studies described the detection frequency and rate of diagnostic uncertainty between different detection techniques.<sup>4,9</sup>

Among case reports, seven publications described the results of different surgical interventions for resolution of symptoms caused by pineal gland cysts.<sup>2,6,11,12,14-16</sup>

### Summary of Critical Appraisal

Individual study strengths and limitations are summarized in Appendix 3.

Methodological quality of the included non-randomized studies was generally good. Selection criteria for study participation was explicitly described in three publications<sup>1,4,9</sup> and all studies<sup>1,4,9,10</sup> described index and reference tests in sufficient detail to permit replication. Three included studies reported uninterpretable results.<sup>4,9,10</sup> The time between index and reference tests was described in three studies.<sup>1,9,10</sup> In all three cases, the time between tests was three months or less, and unlikely to result in a change in clinical condition. One study<sup>4</sup> did not describe the interval between tests. Key limitations in two studies were lack of description of statistical significance of findings<sup>4,9</sup> and lack of clarity whether results from different tests were interpreted independently from one another.<sup>4,9</sup> A subset of 14 patients was included in the analysis of two included studies.<sup>1,10</sup> Formal appraisal of case reports and case series was not performed due to the inferior quality of this type of evidence.

### Summary of Findings

Details of individual study findings are presented in Appendix 4.

#### *Detection*

One study<sup>9</sup> found the variability of pineal cyst volume measurements using trueFISP was low both with repeated observations by the same user and between different observers. Similarly, two studies<sup>1,10</sup> found that there was no significant difference in pineal gland and cyst size measurements made by different observers using TCS. Two studies<sup>4,9</sup> found that trueFISP detected pineal gland cysts with higher frequency and a lower rate of uncertain diagnosis compared with other MRI techniques, though the statistical significance of these findings was not reported. Two studies<sup>1,10</sup> found no significant difference in pineal cyst or pineal gland size when comparing measurements using TCS with MRI measurements, however there was an overlap of 14 patients included in both studies. Case reports describe detection of pineal gland cysts with MRI, computed tomography scanning, and transcranial ultrasonography.

#### *Treatment*

Treatment of symptomatic pineal gland cysts was reported in 38 cases described in seven articles.<sup>2,6,11,12,14-16</sup> Cysts were successfully removed and symptoms resolved using a variety of different surgical approaches. Infratentorial supracerebellar approaches resulted in resolution of symptoms in three cases.<sup>2</sup> Two cases of cyst removal by suboccipital craniotomy by an infratentorial supracerebellar approach did not resolve symptoms and patients continued to experience headaches.<sup>16</sup> One case of left paramedian craniotomy using a transcallosal transchoroidal approach was reported, with the patient remaining asymptomatic at 18 months follow-up.<sup>15</sup> Neuroendoscopy (burr hole or biportal access) was used in seven cases.<sup>11,12,14,16</sup> Symptoms were successfully resolved in all cases, however one case required a second

endoscopic surgery.<sup>14</sup> One case series reported treatment with infratentorial supracerebellar (20 cases), interhemispheric posterior parietooccipital (three cases) or both surgeries (one case).<sup>6</sup> In one of three patients experiencing seizures, the seizures continued. One patient experienced asymptomatic regrowth. Six patients presented with impaired vision (three of these had severe visual defects). One patient with bilateral blindness did not have any visual recovery and three patients experience improved vision. It was not reported which outcomes were related to which surgical approach.

### **Limitations**

There is a lack of high quality evidence regarding detection and treatment of pineal gland cysts. Information on surgical interventions is found mainly in case reports which limit the ability to draw conclusions about comparative effectiveness or safety of these techniques. Furthermore, the surgical procedures used are not always clearly described, and whether endoscopy or craniotomy was used is not always apparent. Pineal gland cysts may be asymptomatic, and detection studies are limited by the lack of description regarding whether detected cysts are associated with clinical symptoms. Additionally, these studies are limited by the lack of a true gold standard for diagnosis and detection. While different detection techniques may detect cysts with varying frequency, it remains unclear how many cysts go undetected. No guidelines for the diagnosis or treatment of pineal gland cysts were identified. Furthermore, none of the identified studies or case reports were from Canada, and may not reflect the technologies and interventions commonly in use in a Canadian healthcare context.

### **CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING**

Both TCS and trueFISP methods for cyst detection showed good reliability and low variability between measurements. Cyst and gland sizes determined with TCS showed no significant difference from measurements made by 2T MRI, however this finding is limited by the fact that both studies on TCS included many of the same patients. Use of the trueFISP method resulted in a higher cyst detection rate and fewer uncertain findings compared with other MRI techniques. TCS and trueFISP may be viable alternatives to other MRI detection methods, however these findings should be interpreted with caution as the identified evidence is limited in both volume and quality. Different surgical approaches for pineal gland cyst treatment were identified in case reports, however the limited nature of this evidence limits the ability to draw conclusions regarding their safety, cost, or efficacy. No evidence-based clinical practice guidelines were identified by the literature search. Best practice for the diagnosis and treatment of pineal gland cysts remains to be determined and would benefit from larger comparative clinical studies.

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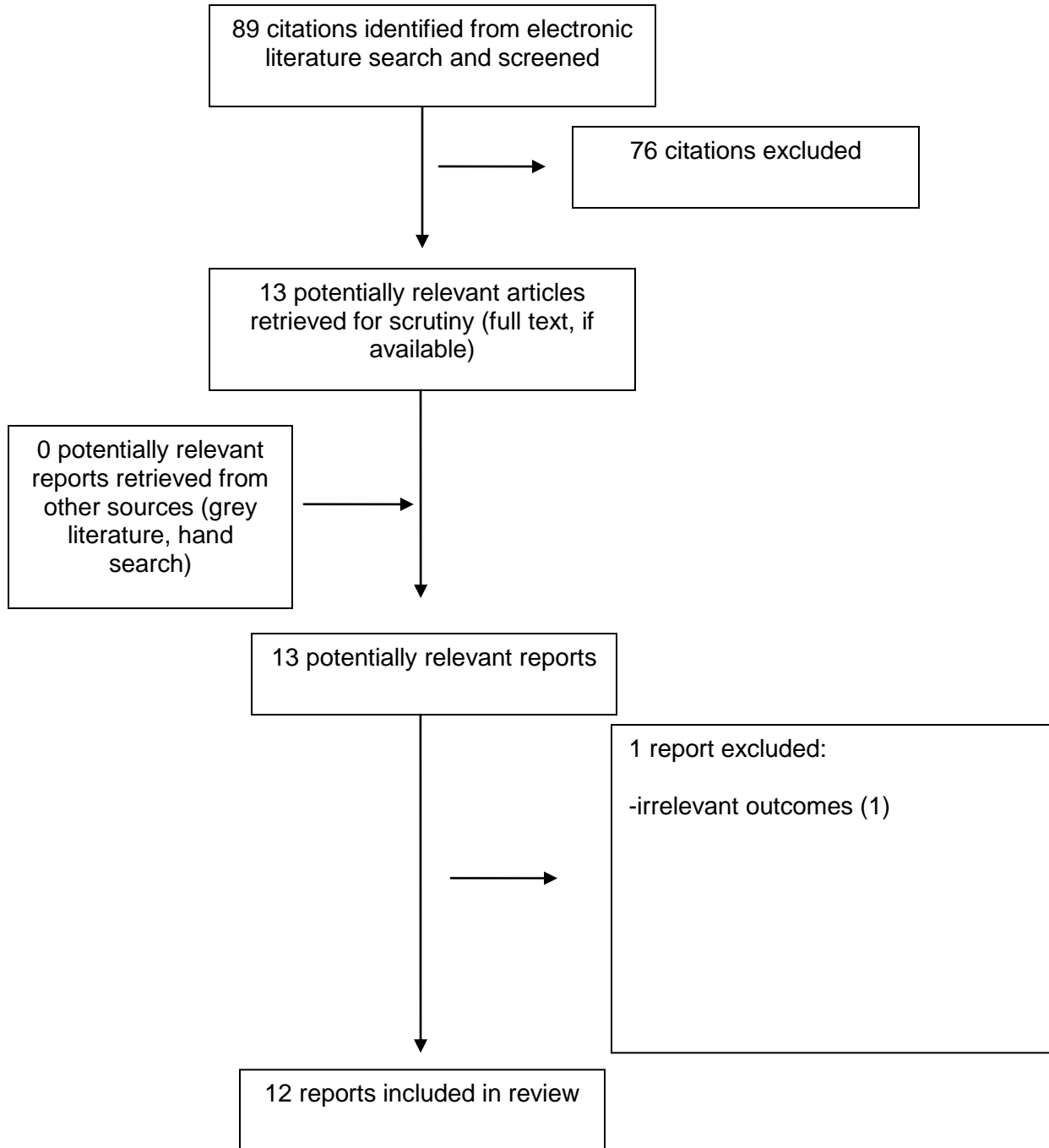
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Appendix 1: Selection of Included Studies





Appendix 2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics, Sample Size (n)	Index Test	Reference Standard	Clinical Outcomes
Bumb, <sup>9</sup> 2011, Germany	Retrospective cross-section, consecutive patients	Children (age 0 to 17 years) enrolled for cranial MRI between June 2007 and November 2009  Mean age: 5.4 N=54	MRI (trueFISP)	MRI (T1-SE)  MRI (T2-TSE)  MRI (FLAIR)  1.5T scanner used	Intrater variability (cyst volume, trueFISP only)  Interrater variability (cyst volume, trueFISP only)  Detection frequency  Rate of diagnostic uncertainty
Nolte, <sup>4</sup> 2010, Germany	Prospective cross-section, randomly included patients	Adults (age 19 to 86 years) enrolled for cranial MRI  Mean age: 58 N=111	MRI (trueFISP)	MRI (T1-SE)  MRI (T2-TSE)  MRI (FLAIR)  1.5T scanner used	Detection frequency  Rate of diagnostic uncertainty
Budišić, <sup>1</sup> 2008, Croatia*	Case-control study	Patients with MRI detected pineal gland cyst  Mean age: 19.6 n=20  Control patients  Mean age: 29.4 n=40	Trans-cranial sonography (TCS)	2T MRI	Interrater variability (cyst and gland size, TCS only)  Interdevice variability (cyst and gland size)
Budišić, <sup>10</sup> 2008, Croatia*	Case-control study	Patients with MRI detected pineal gland cyst  Mean age: 17.64 n=14 <sup>†</sup>  Control patients  Mean age: 29.37 n=39 <sup>†</sup>	TCS	2T MRI	Interrater variability (cyst and gland size, TCS only)  Interdevice variability (cyst and gland size)

FLAIR = fluid attenuated inversion recovery; MRI = magnetic resonance imaging; T1-SE = T1-weighted spin echo; T2-TSE = T2 weighted turbo spin echo; TCS = trans-cranial sonography; trueFISP = true fast imaging with steady state precession

\*14 reported participants were the same in each report.

<sup>†</sup>Seven additional subjects excluded from the study due to poor insonation (6 cases, 1 control)

### Appendix 3: Summary of Critical Appraisal

First Author, Publication Year, Country	Strengths	Limitations
Bumb, <sup>9</sup> 2011, Germany	<ul style="list-style-type: none"> <li>• Selection criteria explicitly described</li> <li>• Time between tests described and unlikely to result in change in clinical condition</li> <li>• Index and reference tests described in detail to permit replication</li> <li>• All patients received all tests</li> <li>• Interrater variability assessed without knowledge of initial evaluation</li> <li>• Uninterpretable results were reported</li> </ul>	<ul style="list-style-type: none"> <li>• Unclear whether individual test results were interpreted without knowledge of the results of other tests</li> <li>• Statistical significance of some outcomes not described</li> </ul>
Nolte, <sup>4</sup> 2010, Germany	<ul style="list-style-type: none"> <li>• Selection criteria explicitly described</li> <li>• Index and reference tests described in detail to permit replication</li> <li>• All patients received all tests</li> <li>• Results evaluated by two radiologists blinded to patient clinical information</li> <li>• Uninterpretable results were reported</li> </ul>	<ul style="list-style-type: none"> <li>• Period between tests not described</li> <li>• Unclear whether individual test results were interpreted without knowledge of the results of other tests</li> <li>• Statistical significance of some outcomes not described</li> </ul>
Budišić, <sup>1</sup> 2008, Croatia*	<ul style="list-style-type: none"> <li>• Selection criteria explicitly described</li> <li>• Time between tests described and unlikely to result in change in clinical condition</li> <li>• Index and reference tests described in detail to permit replication</li> <li>• Test results evaluated without knowledge of the results of other tests</li> </ul>	<ul style="list-style-type: none"> <li>• Uninterpretable results were not reported</li> </ul>
Budišić, <sup>10</sup> 2008, Croatia*	<ul style="list-style-type: none"> <li>• Index and reference tests described in detail to permit replication</li> <li>• Time between tests described and unlikely to result in change in clinical condition</li> <li>• Test results evaluated without knowledge of the results of other tests</li> <li>• Study withdrawals explained</li> </ul>	<ul style="list-style-type: none"> <li>• Study selection criteria not explicitly described</li> <li>• High study exclusion rate (12%), related to uninterpretable results from the index test</li> </ul>

\*14 reported participants were the same in each report.

Appendix 4: Summary of Individual Study Findings

First Author, Publication Year, Country	Study Design, Sample Size (n)	Main Findings
Bumb, <sup>9</sup> 2011, Germany	Retrospective cross-section, consecutive pediatric patients  N=54	Intrarater variability (trueFISP): Pearson correlation coefficient 1.00 (P < 0.05)  Interrater variability (trueFISP): Pearson correlation coefficient 0.998 (P < 0.05)  Frequency of Pineal Cysts (P-values not reported): trueFISP: 57.5% T1-SE MRI: 7.4% T2-TSE MRI: 14.8% FLAIR: 13.0%  Percentage of indistinct findings (P-values not reported): trueFISP: 1.9% T1-SE MRI: 24.1% T2-TSE MRI: 18.5% FLAIR: 18.5%
Nolte, <sup>4</sup> 2010, Germany	Prospective cross-section, randomly included patients  N=111	Frequency of Pineal Cysts (P-values not reported): trueFISP: 35.1% T1-SE MRI: 9.0% T2-TSE MRI: 4.5% FLAIR: 9.0%  Percentage of indistinct findings (P-values not reported): trueFISP: 5.4% T1-SE MRI: 17.1% T2-TSE MRI: 11.7% FLAIR: 16.2%
Budišić, <sup>1</sup> 2008, Croatia*	Case-control study  N=60	Interrater variability (one way ANOVA): Cyst size, TCS, case group: P = 0.475 Gland size, TCS, control group: P = 0.473  Interdevice variability (one way ANOVA): Cyst size, TCS first obs. vs. MRI, case group: P = 0.453 Cyst size, TCS second obs. vs. MRI, case group: P = 0.425 Gland size, TCS first obs. vs. MRI, control group: P = 0.497 Gland size, TCS second obs. vs. MRI, control group: P = 0.370
Budišić, <sup>10</sup> 2008, Croatia*	Case-control study N=60*	Interrater variability (one way ANOVA): Cyst size, TCS, case group: P = 0.425 Gland size, TCS, control group: P = 0.373  Interdevice variability (one way ANOVA): Cyst size, TCS first obs. vs. MRI, case group: P = 0.353 Cyst size, TCS second obs. vs. MRI, case group: P = 0.425 Gland size, TCS first obs. vs. MRI, control group: P = 0.497 Gland size, TCS second obs. vs. MRI, control group: P = 0.370

First Author, Publication Year, Country	Study Design, Sample Size (n)	Main Findings
		Seven participants (12%) had uninterpretable results from TCS and were excluded from the analysis
Sarikaya-Seiwert, <sup>2</sup> 2009, Germany	Case report (3 cases)	<p>3 cases of MRI-detected pineal cysts in patients experiencing symptomatic intracystic hemorrhage.</p> <p>All patients made a full recovery after supracerebellar infratentorial excision of the cyst. Occlusive hydrocephalus was demonstrated in 2 cases with hydrocephalus</p> <p>Authors' conclusions: "MR imaging can identify intracystic hemorrhage by a characteristic fluid-fluid interface. [...] microsurgical resection of cysts may be an effective and curative treatment option." (p. 130)</p>
Costa, <sup>11</sup> 2008, Italy	Case report (1 case)	<p>One case of a 39 year old woman with a history of headache and visual disturbance. Pineal gland cyst was detected with MRI.</p> <p>Neuroendoscopic surgery with a biportal technique resulted in complete resolution of headache and papilledema at one-year follow-up.</p> <p>Authors' conclusions: "...the endoscopic approach represents a minimally invasive and safe procedure in the treatment of symptomatic pineal cysts." (p. 231)</p>
Gore, <sup>12</sup> 2008, USA	Case report (1 case)	<p>One case of a 37 year old woman with a history of headaches. MRI revealed a cystic lesion in the pineal region.</p> <p>Nonoperative management was unsuccessful. Headaches were resolved after complete endoscopy supracerebellar infratentorial resection of the cyst.</p> <p>Authors' conclusions: "The endoscopic supracerebellar infratentorial approach [...] is an excellent minimally invasive surgical option for resection or fenestration of symptomatic pineal cysts." (p. 108)</p>
Desai, <sup>6</sup> 2006, India	Case report (24 cases)	<p>24 cases of epidermoid pineal cyst were surgically treated between 1992 and 2003. Primary clinical features were headache (24 patients), ataxia (10 patients), deteriorating vision (9 patients) and giddiness (8 patients). Cysts were identified by computerized tomography and/or MRI.</p> <p>20 cases were treated with a supracerebellar infratentorial approach and 3 with an interhemispheric posterior parietoccipital approach. One case received both interventions. During follow-up, one patient had asymptomatic re-growth of the residual tumour, and one patient with residual tumour continued to experience generalized seizures.</p> <p>Authors' conclusions: "Radical surgery for pineal region</p>

First Author, Publication Year, Country	Study Design, Sample Size (n)	Main Findings
		epidermoid tumors is associated with an excellent immediate postoperative and long-term outcome.” (p. 124)
Harrer, <sup>13</sup> 2005, Germany	Case report (1 case)	A pineal cystic lesion was identified by transcranial ultrasonography in a 25 year old asymptomatic volunteer in an imaging study. The cystic lesion was confirmed by MRI.  Authors’ conclusions: “[T]ranscranial ultrasonography may represent an easy and cost-effective imaging technique for follow up of cystic lesions of the pineal gland” (p. 564)
Kurosaki, <sup>14</sup> 2005, Japan	Case report (1 case)	A 22 year old woman presented with somnolence and upward gaze palsy with headache. Computed tomography revealed a pineal cystic lesion which was confirmed by MRI.  Neuroendoscopic treatment improved symptoms after the second surgery.  Authors’ conclusions: “Neuroendoscopic manipulation is minimally invasive and may be effective for treating pineal lesions [...] careful preoperative diagnosis of the epidermoid cysts based on diffusion-weighted MR imaging is required.” (p. 218)
Patel, <sup>15</sup> 2005, USA	Case report (1 case)	A 29 year old woman presented with severe occipital headache and trouble focusing when reading. T1- and T2-weighted MRI revealed a pineal gland cyst.  The cyst was removed by an anterior transcallosal surgical approach; the patient remained symptom free for the duration of an 18-month follow-up.  Authors’ conclusions: “MRI is requisite for making the diagnosis. Management of pineal cyst apoplexy remains controversial. We believe the most effective approach is surgical resection.” (p. E1066)
Michielsen, <sup>16</sup> 2002, Belgium	Case report (7 cases)	7 cases of symptomatic pineal cyst were evaluated between 1991 and 2000. Primary clinical features was headache (6 patients). Cysts were identified by computerized tomography and/or MRI.  4 cases were treated with neuroendoscopic surgery and 2 with a sub-occipital craniectomy. One case did not receive surgery. All patients undergoing endoscopy were asymptomatic on follow-up. Both patients treated with an infratentorial supracerebellar approach continued to experience headaches.  Authors’ conclusions: “[P]ineal cysts in the presence of obstructive hydrocephalus are a clear indication for endoscopy with a rigid endoscope.” (p. 233)

ANOVA = analysis of variance; FLAIR = fluid attenuated inversion recovery; MRI = magnetic resonance imaging; obs = observer; T1-SE = T1-weighted spin echo; T2-TSE = T2 weighted turbo spin echo; TCS = trans-cranial sonography; trueFISP = true fast imaging with steady state precession; USA = United States of America

\*Seven participants excluded from analysis