Pineal tumours in the north of England 1968–93

S Bailey, R Skinner, H H Lucraft, R H Perry, N Todd, A D J Pearson

Abstract

The records of 38 patients under 25 years of age presenting with pineal tumours between 1968 and 1993, identified from the Northern Region Children's and Young Adults' Malignant Disease Registry, were analysed retrospectively with regards to clinical presentation, diagnostic approach, treatment strategy, and outcome. The overall five year survival was 45%. Fifteen patients had a histological diagnosis: six with germinomas, three with teratomas, three with astrocytomas, and three with pinealoblastomas. One patient had a definitive diagnosis of teratoma made on the basis of raised tumour markers (α fetoprotein). Treatment consisted of surgery (87%) (ventriculoperitoneal or atrial shunt and/or biopsy), and/or radiotherapy (82%), and/or chemotherapy (26%). Those patients with a tissue diagnosis appeared to have a more favourable outcome, especially after 1976 when treatment was determined by tumour type (five year survival for those with a tissue diagnosis was 91% *v* 51% for those without, 95% confidence intervals 74 to 100% and 26 to 75%).

This study suggests that tissue diagnosis allows more appropriate treatment to be delivered for children with pineal tumours resulting in improved survival. Referral to a centre with neurosurgery, radiotherapy, neuropathology, and paediatric oncology collaboration is essential.

(*Arch Dis Child* 1996;75:181–185)

Keywords: pineal tumours, germinoma, teratoma, astrocytoma.

Department of Child Health, University of Newcastle upon Tyne
S Bailey
R Skinner
A D J Pearson

Northern Centre for Cancer Treatment, Newcastle upon Tyne
H H Lucraft

Newcastle General Hospital, Newcastle upon Tyne
R H Perry
N Todd

Correspondence to:
Dr S Bailey, Sir James Spence Institute of Child Health, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP.

Accepted 7 February 1996

Tumours of the pineal region comprise 3–11% of childhood brain tumours.[1 2] There are three main groups: germ cell tumours (germinomas and teratomas), tumours of pineal cell origin (pinealocytomas and pinealoblastomas), and astrocytomas. Germinomas are the most common, making up 50–60% of all pineal tumours.[1–5]

Until the mid-1970s biopsy of pineal tumours was rarely undertaken due to the high mortality and morbidity of the procedure, reported mortality being in the region of 33% for biopsy alone and 60% for biopsy and subtotal resection.[6–8] Since this time use of perioperative steroids, increasing experience with the operating microscope, and latterly with the use of computed tomography guided stereotactic biopsy has decreased the risks of biopsy, with current experience suggesting a 0–2% mortality and 10% morbidity.[4 9]

Since germinomas are the commonest pineal tumour in children and young adults,[1–5] until recently the majority of pineal tumours were treated either with a trial of cranial irradiation to the tumour site, with those responding proceeding to have a full course of cranial or craniospinal irradiation,[1 10] or alternatively with treament based on presumed tumour type. More recently, treatment has been applied more rationally as a result of the greater diagnostic accuracy from histology or tumour markers (α fetoprotein and β human chorionic gonadotrophin). At the same time, several improvements in chemotherapy and radiotherapy regimens have occurred.[2 11 12] Radiotherapy is the primary treatment for astrocytomas and pinealocytomas. Pinealoblastomas (primitive neuroectodermal tumour, PNET) are chemosensitive and radiosensitive. The possible benefit of chemotherapy in improving cure is currently being assessed by an international study (United Kingdom Children's Cancer Study Group (UKCCSG)/ International Society of Paediatric Oncology (SIOP) PNET StudyIII). Germinomas are highly responsive to radiotherapy, and although the tumours are chemosensitive it is yet to be proved that cure rates are as high as treatment with radiotherapy. In a proposed international study teratomas are to be treated with chemotherapy and radiotherapy as the outlook after treatment with radiotherapy alone is poor.

This report documents the clinical presentation of pineal tumours in children and young adults between 1968 and 1993 in a population based cohort from the north of England, and the evolution of diagnostic approaches, treatment strategies, and outcome during this period.

Patients and methods

PATIENTS

Thirty eight patients under 25 years of age at diagnosis with pineal tumours in the north of England between 1968 and 1993 were identified from the Northern Region Children's and Young Adults' Malignant Disease Registry. Data were collected retrospectively from medical and radiotherapy notes. In one patient (diagnosed in 1976) minimal details only of clinical presentation and treatment were available and therefore this patient was included only in survival calculations.

There were 25 males (ratio 1.9:1). The median age at diagnosis was 13.3 years with a range from 1.8–24.3 years. Median duration of follow up for survivors was 7.0 years with a range of 1.5–17.1 years.

Table 1 Clinical characteristics on presentation (n=37)*

	No (%)
Raised intracranial pressure	34 (92)
Visual signs	26 (70)
Parinaud's syndrome	18 (51)
Abnormal neurology	8 (22)
Ataxia	7 (19)
Cranial diabetes insipidus	6 (16)
Endocrine abnormalaties	5 (14)

* Parinaud's syndrome, n=35.

Table 2 Summary of treatment received

	No (%)
Surgery alone	3 (8)
Surgery + radiotherapy	22 (58)
Radiotherapy alone	1 (3)
Surgery + radiotherapy + chemotherapy	8 (21)
Chemotherapy alone	2 (5)
No treatment	2 (5)
Surgery	
Number	33 (87)
Biopsy	15 (37)
Shunt	32 (84)
Debulking	5 (13)
Radiotherapy*	
Number	31 (82)
Craniospinal + boost	7/25 (28)
Craniospinal	3/25 (12)
Cranial	2/25 (8)
Local	13/25 (52)
Chemotherapy	
Number	10 (26)
Primary	5 (13)
Salvage	5 (13)

* Details unknown in six patients.

CLINICAL PRESENTATION

Clinical presentation and signs are shown in table 1. 'Abnormal neurology' was defined as pyramidal or cranial nerve signs (other than those involving the eye) at presentation. 'Cranial diabetes insipidus' was defined as clinically significant polydipsia and polyuria together with biochemical results suggestive of the diagnosis (high serum sodium concentration, high serum osmolality). 'Endocrine abnormalities' were defined as documented derangements of cortisol and thyroid hormone requiring replacement treatment. 'Visual signs' included diplopia, cranial nerve palsies, and ptosis. Parinaud's abnormality (failure of upward gaze, pupillary dilatation, and diminution of pupillary light reflex) was considered as a separate entity. One patient had a pre-existing ventriculoperitoneal shunt inserted soon after birth for congenital hydrocephalus. This child presented with a tumour at 1.3 years of age raising the possibility that the hydrocephalus may have been an early unrecognised manifestation of the tumour.

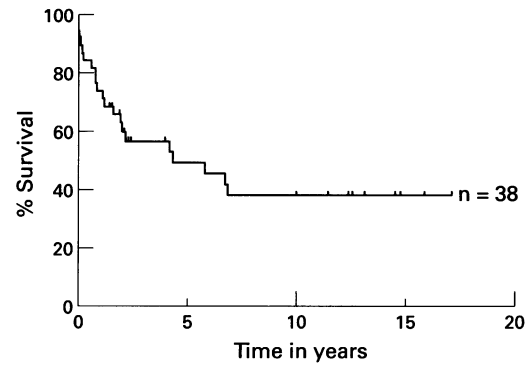

Figure 1 Overall survival.

INVESTIGATIONS

Diagnosis of a pineal tumour was made on central nervous system imaging which included computed tomography (26 patients), air ventriculograms (11 patients), and cerebral angiography (one patient). Magnetic resonance imaging was used for clarification of anatomical location in four patients.

Histopathology was reviewed and verified by a neuropathologist (RHP).

The tissue diagnosis of the tumour was confirmed by initial biopsy in 14 patients, six with germinomas (43%), three with astrocytomas (21%), three with teratomas (21%), and two with pinealoblastomas (14%). One patient had a raised serum α fetoprotein concentration (837 U/ml) and was treated for teratoma, although no biopsy was performed. One patient with pinealoblastoma had the diagnosis made at postmortem examination. After 1989 all six patients had either an initial biopsy (five patients) or raised tumour markers (one patient). The median age at presentation of those with germinomas was 14.4 years, for teratomas it was 14.1 years, pinealoblastomas 6.4 years, and astrocytomas 8.2 years.

TREATMENT

Three modalities of treatment were used (table 2). Four patients died before treatment was started. Treatment modalities varied over the time period studied, in particular biopsy of the tumour and radiation techniques. Initially only local radiotherapy was delivered. Administration of chemotherapy has occurred in a more

Table 3 Description of chemotherapy

Patient No	Chemotherapy*	Indication	Outcome
1	Vincristine + CCNU	Teratoma, poor radiotherapy response	Died
2	Carboplatin	Local recurrence (pinealoma)	Died
3	BEP	Increase in size despite radiotherapy	Died
4	Carboplatin	Presumed pinealoblastoma, before radiotherapy	Died
5	VAC, JEB + methotrexate	Seedlings in spine, 2 years after diagnosis	Died
6	Etoposide + cisplatin	After radiotherapy, germinoma	Alive
7	ECOMB	Teratoma, primary treatment	Alive
8	Vincristine, carboplatin, etoposide, cycloposphamide	Pinealoblastoma, before radiotherapy	Alive
9	JEB	Teratoma, before radiotherapy	Alive
10	JEB	Germinoma, peritoneal relapse	Alive

CCNU = lomustine; BEP = bleomycin, etoposide, cisplatin; VAC = vincristine, actinomycin D, cycloposphamide; JEB = carboplatin, etoposide, bleomycin; ECOMB = etoposide, carboplatin, vincristine, methotrexate (intratheral + intravenous), bleomycin.

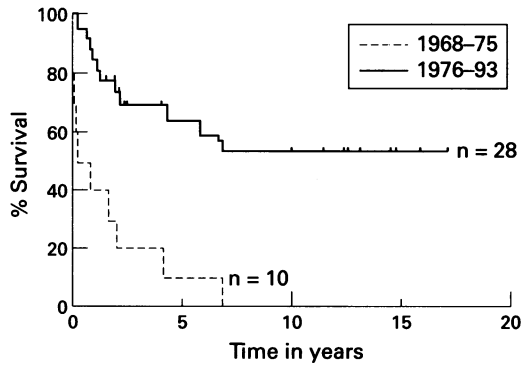

Figure 2 Survival by year of diagnosis.

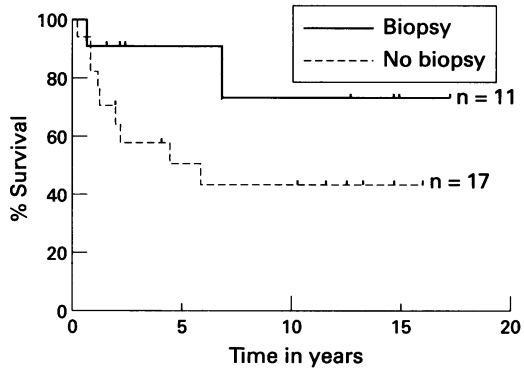

Figure 3 Biopsy compared with no biopsy (1976–93).

controlled manner according to international protocols in the late 1980s and early 1990s.

(A) Surgery

Thirty three patients had surgery (87%) of whom 32 (84%) had a ventricular shunt (atrial or peritoneal). Fourteen patients (37%) had an initial biopsy. Five patients had partial debulking of their tumour; none had a total resection. There was no mortality associated with biopsy of the tumour.

(B) Radiotherapy

Thirty one patients received radiotherapy (82%). Details of 25 patients were available: 13 received local cranial irradiation only, seven received craniospinal irradiation with a pineal boost, three received craniospinal irradiation without a pineal boost, and two whole cranial irradiation only. The patients received betweeen 2500 and 5200 rads in 20–30 fractions over four to six weeks. Before 1976 the majority of patients received only local cranial irradiation irrespective of presumed tumour type.

(C) Chemotherapy

Ten patients received chemotherapy (26%), all but one presenting after 1984 (see table 3). Five patients received chemotherapy as primary treatment, three due to recurrence of the tumour and two after a poor response to radiotherapy.

Treatment was given in varying combinations (table 2). Fifty eight per cent of patients received a combination of surgery (mainly for a cerebrospinal fluid diversion) and radiotherapy.

Results

Twenty two of the patients died (58%) (fig 1); one death occurred as a result of suicide 14.7 years after diagnosis (disease free at death). One patient died during replacement of a ventriculoperitoneal shunt 6.74 years after diagnosis (disease free at death). Median time to death from diagnosis was 1.0 years (range 0.01–6.9 years) and the median age at diagnosis for those who died was 13.8 years. Four

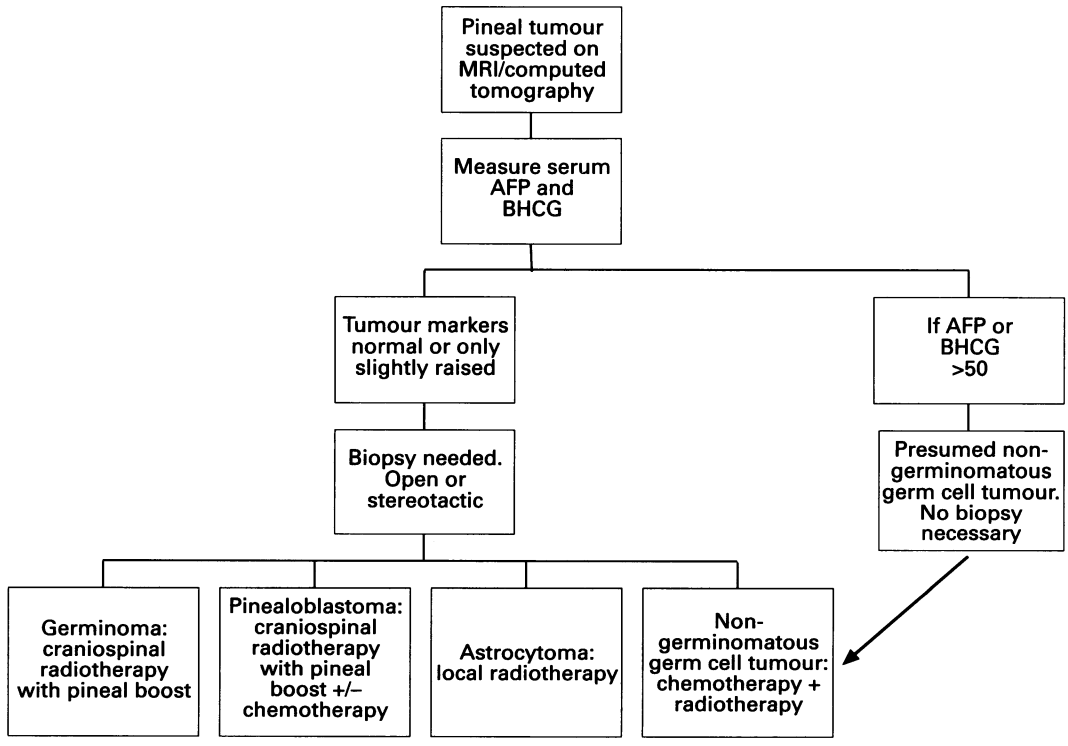

Figure 4 Investigation of pineal tumours (AFP = α fetoprotein; BHCG = β human chorionic gonadotrophin).

(20%) deaths occurred within a month of diagnosis.

Data from before and after 1976 were analysed separately as radiotherapy regimens were changed, no longer did all patients receive local pineal irradiation irrespective of diagnosis, those who did not have astrocytomas received craniospinal irradiation with a boost to the pineal region. From 1968 until 1975 none of 10 patients survived whereas from 1976 until 1993 17 of 28 survived (61%) (fig 2). From 1976 onwards the five year survival of those having a tissue diagnosis or raised serum markers was 91% (95% confidence interval (CI) 74 to 100%) compared with 51% (95% CI 26 to 75%) in those without a tissue diagnosis (p=0.05) (fig 3).

Of the 15 children with either an initial tissue diagnosis (14) or raised serum markers (one), five of six with germinomas (83%), one of two with pinealoblastoma, two of three with astrocytoma, and two of four with teratomas survived.

Nine patients had a documented recurrence; five had a local and four had a distant recurrence; spinal seedlings (two), recurrent tumour in the posterior fossa (one), and peritoneal relapse secondary to seeding via a ventriculoperitoneal shunt (one). Only the last mentioned patient remains alive 1.5 years after diagnosis of the initial tumour. The majority of patients with relapse had initially received only local or inadequate radiotherapy by current standards.

Six patients (16%) had evidence of cranial diabetes insipidus and five (13%) had evidence of panhypopituitarism at presentation. After completion of treatment seven patients (19%) had persistent cranial diabetes insipidus and eight (22%) documented panhypopituitarism. Two patients (5%) had isolated growth hormone deficiency after treatment.

Discussion

The histology of pineal tumours varies. The different tumour types have different therapeutic requirements. For instance spinal seedlings are rare in slow growing astrocytomas and therefore craniospinal irradiation is not indicated but neuroectodermal and germinomatous tumours have a high incidence of spinal seedlings and require generalised neuroradiation. Non-germinomatous tumours respond poorly to radiotherapy, yet there have been very encouraging results with chemotherapy.

It is considered that accurate histological diagnosis is necessary to offer optimal treatment to individual patients with pineal tumours, as current chemotherapy and radiotherapy protocols are based on tumour type. It has been suggested that this approach has led to an improvement in outcome. [9] The benefit of a histological diagnosis is now generally felt to outweigh the risk of biopsy, especially in the light of the markedly reduced morbidity and mortality of the procedure. In our unit all patients are now biopsied unless markedly raised serum α fetoprotein or β human chorionic gonadotrophin concentrations are detected. The outcome seems to be better if histological diagnosis is obtained (especially in non-germinomatous tumours) but the patient numbers in this study were too small to be statistically significant.

The histological type seems to be important in predicting outcome. Germinomas have the best survival in our study (83% five year survival), a figure comparable with other studies.[10 13] Pinealoblastomas and mixed germ cell tumours seem to have the worst outcome, although with improved chemotherapy and radiotherapy the prognosis for these tumours has improved. Overall the outcome has improved, all patients diagnosed between 1968–75 died whereas from 1976–93 survival was 57%. The overall survival is similar to other studies in children.[4 5] Three major differences have occurred over time: (1) The use of craniospinal irradiation in certain tumour subtypes, (2) greater use of biopsy, and (3) use of chemotherapy and inclusion into national and international protocols (for example the PNET study). There is a proposed international intracranial germ cell tumour protocol about to be opened under the auspices of the UKCCSG.

Eighty four per cent of our patients had cerebrospinal fluid diversion shunts inserted to relieve hydrocephalus and raised intracranial pressure, usually soon after diagnosis. One patient died during replacement of the shunt six years after diagnosis, with no evidence of tumour recurrence. This series seems to demonstrate a higher incidence than other studies of raised intracranial pressure and shunt insertion.[4 14] Cerebrospinal fluid diversions are not without their hazards: in our series one patient died (without evidence of tumour) as a complication of ventriculoperitoneal shunt replacement and another child developed malignant ascites secondary to cerebrospinal fluid seeding via the shunt. In other studies surgical decompression without a shunt was performed in some patients.

In contrast to previous teaching, radioresponsiveness is not a good way to determine tissue diagnosis. Germinomas are the most radiosensitive tumours. However, if there is no or only moderate response, it is not possible to distinguish between astrocytomas (local radiotherapy) and pinealoblastomas (craniospinal irradiation). Biopsy after a test course of radiotherapy may be hazardous, difficult to interpret, and interrupts and hence reduces the effectiveness of the radiotherapy. Radiotherapy should be tailored to tumour type and hence establishing the diagnosis is essential for optimal treatment.

Patients with germinomas typically receive 25.5 Gy to the whole craniospinal axis in 17 fractions with a pineal boost of 19.5 Gy in 13 fractions. Patients with pinealoblastomas receive 30–35 Gy in 20 fractions to the whole craniospinal axis with a pineal boost of 20 Gy in 12 fractions. Patients with astrocytomas receive local treatment to the tumour of 54 Gy in 30 fractions. Until the mid-1970s radiotherapy was less likely to encompass the whole craniospinal axis [10] with a local boost and this

could be responsible for the high recurrence rate in the early patients in this series. One patient was presumed to have an astrocytoma based on response to a test dose of irradiation and hence received local radiotherapy. This patient relapsed with spinal seedlings and at postmortem examination the diagnosis was revised to pinealoblastoma. Appropriate treatment with craniospinal irradiation might have prevented this outcome.

Pinealoblastomas, teratomas, and germinomas are chemosensitive.[9 15] Teratomas have poor survival with radiotherapy but encouraging results with chemotherapy are now reported.[13 15 16] The role of chemotherapy in pinealoblastomas is being evaluated as part of an international study (UKCCSG/SIOP III). The relative value of chemotherapy in germinomas compared with radiotherapy requires further evaluation. No national protocol was available for use in the majority of our patients, but UKCCSG protocols are now available or being planned for all these tumour types. The use of standardised treatment will allow the roles of chemotherapy and radiotherapy to be clarified.

Since 1987 we have used a more rational approach to management (fig 4). If a markedly raised α fetoprotein or β human chorionic gonadotrophin in the serum is present this is taken as diagnostic of a non-germinomatous mixed germ cell tumour. Our approach would be to treat this tumour type with chemotherapy based on the Charing Cross regimen.[17] If the markers are negative then a biopsy is undertaken. Should the biopsy show a low grade astrocytoma then local radiotherapy alone is given. If a high grade astrocytoma is diagnosed then treatment is based on national protocols. In future low grade astrocytomas which have no symptoms and do not appear to be progressing will be initially observed before the start of treatment. Dysgerminomas receive craniospinal irradiation with a boost to the tumour site. Primitive neuroectodermal tumours are randomised on the current SIOP study where radiotherapy and surgery are compared with chemotherapy, radiotherapy, and surgery. Non-germinomatous tumours are initially treated with chemotherapy, those having residual disease undergo surgical removal. In a proposed study, non-germinomatous tumours would initially receive surgery and chemotherapy followed by radiotherapy in thee case of residual disease.

Before 1978 treatment was directed by assumption of the tumour type. A similar approach to that outlined above is now used in most units with an apparent improvement in outcome. [1]

It is known that a large number of patients with pineal tumours present with endocrine abnormalities. The current practice in Newcastle is for all patients to have endocrine investigations before and after treatment. Endocrine sequelae in patients with pineal tumours are likely to become increasingly important as more children survive. Cranial diabetes insipidus, if not present at diagnosis, was unlikely to develop subsequently. However other pituitary hormone deficencies appeared as a consequence of radiotherapy.

In conclusion, pineal tumours form a small but important part of paediatric neuro-oncology. These patients need referral to a multidisciplinary team including neurosurgery, radiotherapy, neuropathology, and paediatric oncology specialists, and treatment on one of the recently established protocols. It is important to use histologically guided management in order to optimise the outcome.

We would like to thank Ms L Moore for identifying the patients from the Northern Region Children's and Young Adults' Malignant Disease Registry, Ms V Robson for finding the medical records, Mr S Cotterill for invaluable help with the statistics, and the Leukaemia Research Fund and North of England Children's Cancer Research Fund for financial support.

1 Baumgarner JE, Edwards MSB. Pineal tumours. *Paediatric Neuro-Oncology* 1992; **3:** 853-62 .
2 Hoffman HJ, Yoshida M, Becker LE, *et al.* Experience with pineal region tumours in childhood. Experiences at the Hospital for Sick Children. In: Humphrey RP, ed. *Concepts in paediatric neurosurgery.* Basel: Karger, 1983:360.
3 Bloom HJG. Primary intracranial germ cell tumours. *Clin Oncol (R Coll Radiol)* 1983; **2:** 233-2.
4 Edwards MSB, Hudgins RJ, Wilson CB. Pineal region tumours in children. *J Neurosurg* 1988; **68:** 689-97.
5 Wara WM, Jenkin RDT, Evans A, *et al.* Tumours of the pineal and suprasellar region, Childrens Cancer Study Group treatment results, 1960-1975. *Cancer* 1979; **43:** 698-701.
6 Dandy WE. Operative experience in cases of pineal tumours. *Arch Surg* 1945; **51:** 1-14 .
7 Poppen JL, Marino R. Pinealomas and tumours of posterior portion of the third ventricle. *J Neurosurg* 1968; **28:** 357-64.
8 De Girolami U, Schmidek HH. Clinicopathological study of fifty-three tumours of the pineal region. *J Neurosurg* 1973; **39:** 455-62.
9 Lingood RM, Chapman PH. Pineal tumours. *J Neurooncol* 1992; **12:** 85-91.
10 Dearnaley DP, A'Hern R, Whittaker S,*et al.* Pineal and CNS germ cell tumours, Royal Marsden Hospital experience 1962-1987. *Int J Radiat Oncol Biol Phys* 1990; **18:** 773-81.
11 Packer JP, Sutton LN, Rosenstock JG, *et al.* Pineal region tumours in childhood. *Pediatrics* 1984; **74:** 97-102.
12 Chapman PH, Ongood RM. The management of a pineal area tumour. A recent reappraisal. *Cancer* 1979; **46:** 1253-7.
13 Kiltie AE, Gattamaneni HR. Survival and quality of life of paediatric intracranial germ cell tumour patients treated at the Christie Hospital, 1972-1993. *Med Pediatr Oncol* 1995; **25:** 450-6.
14 Abay EO, Laws ER, Grado GL, *et al.* Pineal tumours in children and adolescents. Treatment by shunting and radiotherapy. *J Neurosurg* 1981; **55:** 889-95.
15 Allen JC, Ho Kim J, Packer R. Neoadjuvant chemotherapy for newly diagnosed germ cell tumours of the central nervous system. *J Neurosurg* 1987; **67:** 65-70.
16 Calaminus G, Bamberg M, Barenzelli MC, *et al.* Intracranial germ cell tumours: a comprehensive update of the European data. *Neuropediatrics* 1994; **25:** 26-32.
17 Smith DB, Newlands ES, Begent RH, *et al.* Optimum management of pineal germ cell tumours. *Clin Oncol (R Coll Radiol)* 1991; **3:** 96-9.