J Neurooncol (2010) 100:105–111
DOI 10.1007/s11060-010-0145-5

CLINICAL STUDY - PATIENT STUDY

Late mortality in pediatric patients with craniopharyngioma

Johannes Visser · Juliette Hukin · Michael Sargent · Paul Steinbok · Karen Goddard · Chris Fryer

Received: 15 September 2009 / Accepted: 15 February 2010 / Published online: 4 March 2010

Abstract Ten year survival rates for patients with craniopharyngioma vary from 24 to 100%. A review of the database of all children diagnosed with craniopharyngioma in British Columbia (BC) revealed that several patients died >10 years after diagnosis. This retrospective study investigates the causes and timing of deaths and reports the overall survival in this population based group of patients. A chart review was conducted on all patients aged <17 years, diagnosed in BC with craniopharyngioma between 1967 and 2003. Imaging studies were reviewed by a neuroradiologist. All deaths in the province are reported to a central agency, which allowed identification of patients who died after being lost to clinical follow up. Forty-one patients were identified with nine deaths (aged 11.9–36.9 years). The four patients who died more than 10 years after diagnosis represent 23% of the 17 patients followed for more than 10 years. Three died more than 20 years after diagnosis. The known causes of death were progressive disease (1), uncontrolled diabetes insipidus (1), panhypopituitarism with multi-organ failure (1), pontine infarction (1) and middle cerebral artery infarction in a patient with Moyamoya disease secondary to radiotherapy (1). Two deaths appeared to be seizure related and 1 occurred after orthopedic surgery and remains unexplained. One patient died due to liver failure of unknown etiology. The 10 year overall survival (OS) was 84.1% (95% CI 71.2, 97.1) and the 20 year OS 76.5% (95% CI 58.1, 94.9). Patients remain at risk of premature death more than 10 years after diagnosis. The cause specific late mortality was multifactorial but was rarely due to disease progression. New approaches to craniopharyngioma treatment and life long follow up of cases are required.

Keywords Craniopharyngioma · Survival · Causes of death

J. Visser
Children's Hospital, Leicester Royal Infirmary, Leicester LE1 5WW, UK

J. Hukin (✉)
Division of Neurology and Oncology, British Columbia Children's Hospital, 4480 Oak St, Vancouver V6H 3V4, Canada
e-mail: jhukin@cw.bc.ca

M. Sargent
Department of Radiology, British Columbia Children's Hospital, 4480 Oak St, Vancouver V6H 3V4, Canada

P. Steinbok
Division of Neurosurgery, British Columbia Children's Hospital, 4480 Oak St, Vancouver V6H 3V4, Canada

K. Goddard
Department of Radiation Oncology, British Columbia Cancer Agency, 600 W. 10th Ave, Vancouver V5Z 4E6, Canada

C. Fryer
Division of Oncology, British Columbia Children's Hospital, 4480 Oak St, Vancouver V6H 3V4, Canada

Introduction

Craniopharyngioma is a neoplasm of the pituitary region and represents 4.2% of childhood primary central nervous system tumors in the United States, with a peak incidence between 5 and 14 years [1]. Despite being histologically benign, this tumor often has a malignant course due to its location and tendency to infiltrate surrounding structures. Patients often have evidence of visual loss, hypopituitarism, cognitive dysfunction, morbid obesity and hydrocephalus, due to the tumor's close proximity to the optic pathway, the hypothalamic–pituitary unit and the cerebrospinal fluid drainage system. These disorders may be present at diagnosis, arise after treatment or become apparent at the time of

disease progression. The available treatment modalities of surgery, radiotherapy, intra-cystic radio-/chemotherapy and combinations of these, all have serious potential side-effects. Treatment is not always curative and may contribute to morbidity and mortality [2–6].

Background and rationale

Ten year overall survival rates for craniopharyngioma patients are often reported and vary from 24 to 100% [7]. Twenty year survival rates are seldom reported and range from 78 to 92% [3, 8, 9]. All pediatric patients aged <17 years diagnosed with craniopharyngioma in British Columbia (BC), Canada are treated in Vancouver at British Columbia's Children's Hospital (BCCH) and the British Columbia Cancer Agency (BCCA). BCCH is the only pediatric tertiary care facility in the province, serving a population of 4.2 million people. A review of the database of all children diagnosed with craniopharyngioma in BC revealed that several patients died >10 years after diagnosis. This retrospective study investigates the causes and timing of deaths and reports the overall survival in a population-based group of patients.

Method

Children diagnosed with craniopharyngioma tumors before the age of 17 years in BC between 1967 and 2003, were identified using the neuro-oncology and neurosurgical databases. A retrospective chart review of the tertiary oncology charts of the identified patients was conducted. All deaths in BC are reported to a central agency, which allowed identification of patients who died after being lost to clinical follow up. A neuroradiologist (M.S.) reviewed the imaging studies. Descriptive data analysis was used. A Kaplan–Meier curve was used to summarize the overall survival (OS) [10]. Tumor resection (total or subtotal), radiotherapy and intracystic bleomycin were considered definitive treatment modalities. Tumor cysts and hydrocephalus were often drained as an interim measure and these procedures were not considered definitive treatments.

Results

Demographics

Between 1967 and 2003 there were 43 cases of craniopharyngioma among 988 brain tumors in the neurooncology data base (4.35%). Two patients identified in the database were not included since they were diagnosed and initially treated outside of BC. Forty-one children fulfilled the study criteria. This adds an additional 12 BC patients diagnosed between 1967 and 1981, to the 29 patients who were included in a previous report focusing on presenting features, treatment and long term deficits in patients diagnosed between 1982 and 2003 [11]. The median age at diagnosis was 9.4 years (0.6–16.8). Nineteen patients were male and 22 female.

Therapy

The definitive treatment modalities used during primary treatment are summarized in Table 1. Surgery was used as the only primary treatment modality in 14 patients and combined with radiation in a further 15 patients. Four patients were initially treated with radiation only and eight with bleomycin only.

Seventeen patients (41%) required one or more secondary treatments. In some cases the same treatment modality (surgical resection/intracystic bleomycin) was employed more than once but ultimately 32 patients (78%) were treated with more than one modality. Twenty-six had a surgical resection and radiation, one had a surgical resection and intracystic bleomycin, and five had a surgical resection, radiation and bleomycin. The remaining nine patients (22%) required only one modality namely surgical resection (3), radiation (3) or bleomycin (3).

The total of 108 (median three per patient) surgical procedures consisted of 13 gross total resections (GTR), 32 subtotal resections (STR), 37 procedures related to cyst drainage, 20 procedures related to hydrocephalus drainage, two tumor biopsies and four procedures related to post-operative complications.

Radiation was used in 34/41 (83%) patients and the radiation dose ranged between 45 and 57 Gy (median 50 Gy). Protons were used in four cases.

Survival

The median follow-up was 8.71 years (0.9–25.6 years). Twenty-two patients developed progressive disease and nine patients are known to have died. The 10 year and 20 year overall survival (OS) were 84.1% (95% CI 71.2,

Table 1 Definitive treatment modalities used as primary treatment

Treatment modality	Number of patients (% of total) $n = 41$
Gross total resection only	10 (24.4%)
Subtotal resection only	4 (9.5%)
Radiotherapy only	4 (9.5%)
Bleomycin only	8 (19.5%)
Subtotal resection + radiotherapy	15 (36.6%)

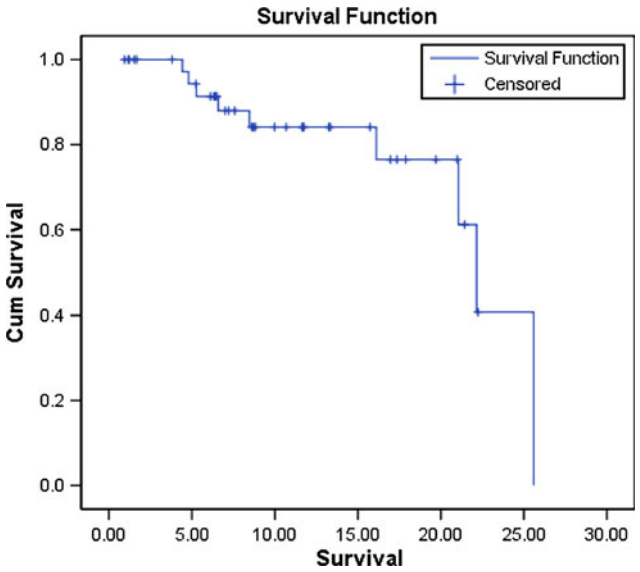

Fig. 1 Overall survival

97.1) and 76.5% (95% CI 58.1, 94.9), respectively (Fig. 1). At conclusion of the study the age of the 32 survivors ranged from 8 to 33 years.

Timing of deaths

The timing (time since diagnosis and the age at time of death) and causes of death are summarized in Table 2. Of the nine patients who have died, five died within 10 years, one between 10 and 20 years and three, more than 20 years since diagnosis. The four patients who died more than 10 years after diagnosis represent 23% of the 17 patients followed for more than 10 years.

Causes of death

In four cases the cause of death was clear: progressive disease (1), uncontrolled diabetes insipidus (1), panhypopituitarism with multi-organ failure (1) and a massive middle cerebral artery infarct secondary to radiation induced Moyamoya disease (1). The cause of death was less clear in the other five cases. One patient with panhypopituitarism developed epilepsy shortly after a total resection and died due to a seizure 8 years after the diagnosis and surgery (no further information regarding the circumstances of his death was available). The post operative complications in this case included status epilepticus, frontal and cerebellar hemorrhages, spastic quadriplegia, shunt infections and a subdural hygroma which required shunting. The last CT scan of the brain was done 3 years before death and showed no evidence of disease progression. One patient with diabetes insipidus following complete resection of the tumor was found dead at home. At autopsy there was no evidence of viable craniopharyngioma tissue. There was some evidence of possible viral meningitis but the cause of death remains unclear. It was postulated that the patient may have had a seizure resulting in positional asphyxia. One patient presented with clinical features of a devastating pontine infarction and died a couple of days later due to bronchopneumonia (no brain imaging done). One death occured within hours after unrelated orthopedic surgery despite apparent adequate steroid support. The cause of death was not established. One patient died due to liver failure of unknown etiology.

Relationship between deaths and the characteristics of the disease and treatment

Information on the disease and its treatment obtained from the tertiary oncology charts of patients and the results of the neuroradiology review were evaluated in relation to deaths. The amount of available clinical information however varied greatly between patients (more information available on the most recent cases) and only 32/41 cases had imaging available for review (4/9 of those who died). The combination of incomplete clinical information and small patient numbers jeopardized attempts to identify risk factors associated with the disease.

More detailed information was available on the treatment. The definitive primary treatment modality used in the group of survivors were compared with the primary treatment used in patients who died. No particular pattern emerged. Primary treatment in the group of survivors included seven gross total resections (22%), one subtotal resection (3%), four radiotherapy (12%), 13 subtotal resection + radiotherapy (41%) and seven Bleomycin (22%). In the group who died the primary definitive treatment included three gross total resections (33%), three subtotal resections (33%), 0 radiotherapy, two subtotal resection + radiotherapy (22%) and one Bleomycin (11%). When all treatment (primary and subsequent treatments) are considered the number of different treatments/treatment combinations increases to seven and in the face of the relatively small patient numbers no relationship between any particular treatment or combination of treatments and deaths could be detected. The total number of surgical procedures per patient ranged from 1 to 12 (median = 2) in survivors and from 1 to 4 (median = 3) in those who died. Twenty-eight percent (9/32) of survivors and 44% (4/9) of patients who died required a ventriculoperitoneal shunt or an external ventricular drain as part of their primary treatment.

During the 37 years covered by this review there were major advances in surgical technique and radiotherapy. Many of these advances were incremental as newer technologies became available. This retrospective chart review did not capture detailed information on surgical and/or

Table 2 Causes and timing of deaths

$N = 9$	Years since diagnosis	Age (years)	Cause of death
1	4	11.9	Unexplained post-operative death (unrelated orthopedic surgery)
2	4	19.6	Presumed positional asphyxia related to seizure
3	5	12.5	Middle cerebral artery infarct due to Moyamoya disease caused by radiotherapy
4	6	23.3	Tumor progression (invading surrounding structures, brain edema)
5	8	12.3	Seizure related
6	16	27.8	Uncontrolled diabetes insipidus
7	21	26.1	Liver failure (no further information available)
8	22	36.9	Pontine infarction followed by bronchopneumonia
9	25	35	Panhypopituitarism resulting in multiorgan failure

radiotherapy technique in every patient. Available information does however reveal that a wide range of radiotherapy techniques including parallel opposed pairs, three fields, stereotactic and proton therapy were used. To further investigate the possible impact of improvements in the modalities used to treat craniopharyngiomas over time, the study period between 1967 and 2003 were divided into three 10-year periods followed by a final 7-year period. Fifty percent (2/4) of patients diagnosed in the period 1967–1976 died, 31% (5/16) diagnosed in period 1977–1986 died, 25% (2/8) diagnosed in the period 1987–1996 died and none (0/13) diagnosed between 1997 and 2003 died.

The severity of the endocrine deficiencies as well as the level of replacement therapy and supportive care may have an impact on survival. Multiple endocrinopathies were common at last follow up (26/28 in the 1982–2003 cohort) but the severity/treatment of this complication was seldom documented in the oncology charts. The majority (6/9) of deaths occurred during adulthood and the endocrine management of these patients in BC is undertaken by primary care and medical teams based in other institutions. Researchers did not have access to these charts as part of this retrospective review. To further investigate the possible impact of improvements in endocrine and supportive care over time, the era in which deaths occurred were considered. During the first 10 year period (1967–1976) 0/4 of the patients at risk died (0%), during the second 10 year period (1977–1986) 1/20 of the patients at risk died (5%), during the third 10 year period (1987–1996) 6/27 of the patients at risk died (22%) and during the most recent period 7-year period (1997–2003) 2/34 (6%) of the patients at risk died.

Discussion

Demographics

This is a report of a population based pediatric craniopharyngioma cohort treated within the context of one neuro-oncology team. The proportion that craniopharyngioma represent of all intracranial tumors (4.35%) is similar to published data. The median age at diagnosis of 9.4 years is within the range 5–14 years reported in the literature [1]. In this cohort the number of males (19) and females (22) affected were similar. This is consistent with the data from several population-based registries which demonstrated no gender difference [1, 12].

Therapy

In the absence of randomized controlled trials, management of childhood craniopharyngioma remains controversial and complex. More than one modality of treatment may be required to achieve control of the disease at diagnosis or a second/third modality may need to be introduced at the time of disease progression. In a report on the outcome of a radical surgical excision approach, Poretti et al. report that only 3/25 (12%) were treated with more than one modality [13]. A more conservative surgical approach results in the more common use of radiotherapy as a second modality and Merchant et al. report that with this approach 23/30 (77%) required treatment with more than one modality [14].

In this cohort 78% of patients were exposed to more than one treatment modality. The majority of patients were therefore not only at risk of the effects of the disease but also at risk of the effects of two or more of surgery, radiotherapy and intracystic bleomycin. Concern about the negative impact of radiotherapy on the developing brain is reflected in the fact that, although 82.9% of patients received radiotherapy, only 36.6% of patients received it as part of their primary treatment.

Survival

This study reports long-term survival in an unselected, population-based cohort over a 35 year period. The long period covered by the study allows the reporting of 10 year and 20 year OS.

The 10 year OS of 84.1% compares favorably with the wide range reported (24–100%) [7]. The 20 year OS of 76.5% is only marginally lower than the 10 year OS which reflects the fact that only one patient died between 10 and 20 years after diagnosis. Only six patients were at risk for more than 20 years. Three of these patients died, including the patient at risk for the longest period (25.6 years). This results in an unstable survival curve beyond 20 years and do not allow for the reporting of a survival rate for a longer time interval. Premature deaths, more than 20 years after diagnosis, may however lead to much lower survival rates at longer follow up intervals.

Twenty year OS have been reported in a pediatric (78%) and mixed pediatric and adult (92%) craniopharyngioma cohorts who all received radiotherapy [3, 8]. Karavitaki et al. reported a 95% OS at 5, 10, 20 years and an 80% OS at 30 years in an unselected pediatric craniopharyngioma cohort of 42 patients [9]. Premature deaths therefore also occurred in this group of patients between 20 and 30 years after diagnosis. The causes of these deaths are not described in detail.

Timing of deaths

Late deaths can only be accurately reported in patient cohorts followed for decades or in areas with very accurate tumor registries and death notification systems. Data from the UK national register for childhood tumors reveals that 10 craniopharyngioma patients diagnosed before 1971 died due to treatment related causes more than 5 years after diagnosis(6–10 years: six deaths; 11–20 years: one death; 21–30 years: three deaths) but do not comment on any deaths due to disease progression or unrelated deaths [15]. The distribution of deaths over time, beyond 5 years since diagnosis, is however similar to the experience in this cohort.

Causes of deaths

Due to the retrospective nature of the study it proved difficult to obtain accurate information about the cause of death in every case. This has also been the experience of other investigators [16]. It is however clear that most (8/9) patients died in the absence of evidence of disease progression. Endocrine dysfunction and radiation induced cerebrovascular effects caused almost half of the deaths (4/9) and may have contributed to a further three (two seizures and one unexplained post operative death).

The causes of late treatment related deaths captured in the UK national register for childhood tumors were: Addisonian crisis (7), intracranial venous thrombus (1), cerebroatherosclerosis (1) and bronchopneumonia (1) [15]. The higher proportion of endocrine deaths may reflect suboptimal endocrine management in the past (only patients diagnosed before 1971 were included). A more recent prospective study of pediatric and adult patients with hypopituitarism, revealed that those with underlying craniopharyngioma were much more likely to die prematurely than those with other causes of hypopituitarism: Standardized mortality ratio (SMR) 9.28 (99% CI 5.84–14.75) versus 1.61 (99% CI 1.30–1.99), $P < 0.0001$. The authors suggest that this marked difference may reflect the degree of hypothalamic disruption and the subsequent metabolic abnormalities, including obesity, seen in craniopharyngioma patients. The main causes of death (respiratory and cerebrovascular) did however not differ between those with craniopharyngioma and those with other causes of hypopituitarism [17]. Bülow et al. report the causes of death and standardized mortality ratio in a population based mixed adult and pediatric craniopharyngioma cohort of 60 patients who had undergone surgery between 1951 and 1988. Only 3/27 deaths were reported in the 26 patients <20 years old at diagnosis. The causes of death in this group were septicaemia, pneumonia and cerebral hemorrhage. These deaths all occurred within 4 months of surgery and were considered postoperative complications. The overall mortality rate for the whole group was more than five times higher than that of the general population (SMR 5.55, 95% CI 4.93–22.5). Cause specific SMR's revealed an increased risk of cardiovascular (including cerebrovascular) mortality (SMR 3.21, 95% CI 1.29–6.61). Bivariate analysis revealed that younger patients had a better prognosis in this cohort [18]. In the series we report here, 2/9 deaths were attributed to vascular complications (middle cerebral artery infarct and suspected pontine infarct).

The cause of sudden unexpected deaths are often very difficult to establish. During episodes of infection (and peri-operatively) these are often attributed to inadequate steroid replacement therapy [16]. Prolonged seizures that are not witnessed may also lead to sudden unexplained deaths. Mong et al. reports two cardiac related deaths and 3/12 patients with prolonged QTc (at risk of sudden cardiac death). The possible role and mechanism of cardiac arrhythmia in premature sudden death of craniopharyngioma patients need further investigation [19].

With 26/28 patients in the 1982–2003 British Columbia cohort reported to suffer from multiple endocrinopathies, 84% of the whole 1967–2003 cohort treated with radiotherapy and the majority of patients exposed to more than one intracranial surgical procedure, survivors remain at risk of premature death secondary to endocrine deficiency, acute stroke, acute symptomatic seizures, and less commonly tumor progression.

Relationship between deaths and the characteristics of the disease and treatment

Studying a population-based patient cohort stretching over a 37 year period allowed the researchers to detect and report on the causes of early and late mortality. The long time period covered and the retrospective nature of the study, however contributed to the clinical dataset being incomplete. This limitation, the low incidence of the disease, changes to imaging and treatment techniques and the absence of a standard treatment did not allow for the identification any reliable relationships between deaths and the disease or its treatment.

The era in which patients were originally diagnosed and treated were considered as a possible surrogate marker for the impact of improvements in neurosurgical and radiotherapy techniques over time and the introduction of intracystic Bleomycin in 1994. The proportion of patients diagnosed in sequential time periods who since died, declined gradually and consistently from 50% in the first 10-year period (1967–1976) to 0% in the most recent time period (1997–2003). Although this may suggest a gradual improvement in survival over time in line with improvements in treatment techniques, the long interval between diagnosis and death (median interval of 8 years) and relatively small numbers do not allow for this conclusion to be drawn.

The era in which patients died were considered as a possible surrogate marker of the impact of improvements in endocrine and supportive care over time. The majority of deaths (8/9) however, occurred during the most recent 17 years while only one patient died during the first 20 years. This do not suggest a clear impact of more modern endocrine and supportive care on the number of deaths. The cumulative number of patients at risk during the most recent 17 years (40) is however higher than the during the first 20 years (20) which may mask such an impact.

Conclusion

Patients remain at risk of premature death more than 10 years after diagnosis. Reported survival rates 10 and 20 years after diagnosis may underestimate the true risk of premature death. The cause specific mortality is multifactorial but is rarely due to disease progression. Life-long multidisciplinary follow-up by specialists knowledgeable in the late effects of the disease and its treatment is essential. In the case of pediatric patients who survive into adulthood, arrangements have to be in place to ensure transition to an appropriate adult multidisciplinary team. Prospective multicentre trials, investigating new approaches to craniopharyngioma treatment are required. These studies should ideally include lifelong follow-up to ensure any impact on the causes and risk of late mortality is appreciated.

References

1. Bunin GR, Surawicz TS, Witman PA, Preston-Martin S, Davis F, Bruner JM (1998) The descriptive epidemiology of craniopharyngioma. J Neurosurg 89(suppl. 4):547–551
2. Hoffman HJ, De Silva M, Humphreys RP, Drake JM, Smith ML, Blaser SI (1992) Aggressive surgical management of craniopharyngiomas in children. J Neurosurg 76(suppl. 1):47–52
3. Regine WF, Kramer S (1992) Pediatric craniopharyngiomas: long term results of combined treatment with surgery and radiation. Int J Radiat Oncol Biol Phys 24(suppl. 4):611–617
4. Flickinger JC, Lunsford LD, Singer J, Cano ER, Deutsch M (1990) Megavoltage external beam irradiation of craniopharyngiomas: analysis of tumor control and morbidity. Int J Radiat Oncol Biol Phys 19(suppl. 1):117–122
5. Jiang R, Liu Z, Zhu C (2002) Preliminary exploration of the clinical effect of bleomycin on craniopharyngiomas. Stereotact Funct Neurosurg 78(suppl. 2):84–94
6. Hukin J, Steinbok P, Lafay-Cousin L et al (2007) Intracystic bleomycin therapy for craniopharyngioma in children: the Canadian experience. Cancer 109(suppl. 10):2124–2131
7. Strother DR, Pollack IF, Fisher PG (2002) Tumors of the central nervous system. In: Pizzo PA, Poplack DG et al (eds) Principles and practice of pediatric oncology. Lippincott Williams & Wilkins, Philadelphia, p 803
8. Varlotto JM, Flickinger JC, Kondziolka D, Lunsford LD, Deutsch M (2002) External beam irradiation of craniopharyngiomas: long-term analysis of tumor control and morbidity. Int J Radiat Oncol Biol Phys 54(suppl. 2):492–499
9. Karavitaki N, Brufani C, Warner JT et al (2005) Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. Clin Endocrinol (Oxf) 62(suppl. 4):397–409
10. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457–481
11. Hukin J, Visser J, Sargent M, Goddard K, Fryer C, Steinbok P (2005) Childhood craniopharyngioma: Vancouver experience. Childs Nerv Syst 21(suppl. 8–9):758–765
12. Sorva R, Heiskanen O (1986) Craniopharyngioma in Finland. A study of 123 cases. Acta Neurochir (Wien) 81(suppl. 3–4):85–89
13. Poretti A, Grotzer MA, Ribi K, Schonle E, Boltshauser E (2004) Outcome of craniopharyngioma in children: long-term complications and quality of life. Dev Med Child Neurol 46(suppl. 4):220–229
14. Merchant TE, Kiehna EN, Sanford RA et al (2002) Craniopharyngioma: the St. Jude children's research hospital experience 1984–2001. Int J Radiat Oncol Biol Phys 53(suppl. 3):533–542
15. Hawkins MM, Kingston JE, Kinnier Wilson LM (1990) Late deaths after treatment for childhood cancer. Arch Dis Child 65(suppl. 12):1356–1363
16. Lyen KR, Grant DB (1982) Endocrine function, morbidity, and mortality after surgery for craniopharyngioma. Arch Dis Child 57(suppl. 11):837–841
17. Tomlinson JW, Holden N, Hills RK et al (2001) Association between premature mortality and hypopituitarism. West midlands prospective hypopituitary study group. Lancet 357(suppl. 9254):425–431

18. Bulow B, Attewell R, Hagmar L, Malmstrom P, Nordstrom CH, Erfurth EM (1998) Postoperative prognosis in craniopharyngioma with respect to cardiovascular mortality, survival, and tumor recurrence. J Clin Endocrinol Metab 83(suppl. 11):3897–3904

19. Mong S, Pomeroy SL, Cecchin F, Juraszek A, Alexander ME (2008) Cardiac risk after craniopharyngioma therapy. Pediatr Neurol 38(suppl. 4):256–260