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MINI REVIEW

Excess mortality after craniopharyngioma treatment: are we making progress?

Nidan Qiao[1,2]

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Abstract

Purpose Craniopharyngioma is associated with an increased risk of mortality even after surgical, radiotherapeutic and hormone supplementations. Previous studies using different designs showed a possible trend of decreasing mortality in recent years. This review summarises studies reporting standardised mortality ratio (SMR) after craniopharyngioma treatment, as well as the bias and confounding in these studies to plan further researches.

Methods PubMed and Embase was searched for manuscripts published before October 2018 using medical subject heading terms ("craniopharyngioma" or "hypopituitarism" and "mortality").

Results Eight studies reported SMR after craniopharyngioma treatment, with a total of 2802 patients. The subgroup meta-analysis using random effects model was conducted to pool the SMR, which was 6.2 (95% CI 4.1–9.4) before 2010 and 2.9 (95% CI 2.2–3.8) after 2010 (subgroup test $p < 0.01$), respectively. Misclassification (one study) and selection bias (six studies) either inflated or deflated the result. The trend of increasing survival rate over the time was observed in studies without reporting SMR. Female patients, childhood-onset disease, hydrocephalus, tumour recurrence, body mass index and panhypopituitarism were identified as the important risk factors for excess mortality.

Conclusions Though bias and confounding existed across studies, the decreasing SMR and increasing survival rate over the time was in favour of a real signal. It is necessary to launch studies to further investigate the morality and risk factors after multidisciplinary treatment of craniopharyngioma in a hospital-based manner, using the modern statistical method to adjust for bias and confounding.

Keywords Craniopharyngioma · Mortality · Survival · Hypopituitarism

Introduction

Craniopharyngioma is an intracranial neoplasm located in the hypothalamic-pituitary region. The tumour processes close relationship to vital structures such as the pituitary gland, pituitary stalk, hypothalamus, and optic chiasm. Patients usually develop hypopituitarism, diabetes insipidus, and visual loss due to tumour compression [1, 2]. Craniopharyngiomas are generally treated with neurosurgery (transcranial or transsphenoidal approach). If uncompleted resected, radiotherapy was recommended to prevent further progress of the residue tumours [3]. The pre-existing endocrine symptoms will not recover in the majority of the patients. Newly developed hypopituitarism, diabetes insipidus and hypothalamic obesity will occur due to surgical injury or radiotherapeutic effect [4, 5]. In previous studies, most of the patients maintain hypopituitarism and almost half of the patients maintain panhypopituitarism after treatment [6, 7]. If not treated appropriately or even treated adequately, hypopituitarism may serve as a risk of increased mortality in the long run [8]. Tumour recurrence, delayed complications after cranial irradiation, second or multiple surgeries, and drug-related adverse events may also attribute to the high mortality risk.

Currently, the state-of-the-art surgical management of craniopharyngioma is now turning to multimodal treatment strategies (combining surgery and radiotherapy) with extensive postoperative follow-up and rehabilitation aimed to limit mortality and morbidity [1, 2, 9]. In recent years, the application of endoscopy in treating craniopharyngioma has

✉ Nidan Qiao
nidan_qiao@hms.harvard.edu

[1] Department of Neurosurgery, Huashan Hospital, Shanghai, China

[2] Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA

gained considerable popularity [4, 10]. The endoscopic technique provides a panoramic surgical view with increased illumination of the anatomic structures and allows for a close-up visual examination of the pituitary stalk and hypothalamus. Tumours extended to supersellar region or third ventricle can now be handled using endoscopic technique [11, 12]. Modern radiotherapy includes proton beam therapy and gamma knife therapy, which may offer a more protective option to adjacent tissues [13, 14]. Multidisciplinary teams including neurosurgery, radiosurgery, endocrinology, neurology, and paediatrics are emerging across the world for long-term pharmacological, neurosurgical, and radiotherapeutic management [2, 15].

A recent meta-analysis showed that standardised mortality ratio (SMR) in acromegaly normalised with biochemical control of the disease with the more frequent use of somatostatin analogues as adjuvant therapy, and comparing with studies published before 2008, SMR decreased in the last decade [16]. Though craniopharyngioma is a different entity to growth hormone-secreting pituitary adenoma, it is still possible that mortality in patients with craniopharyngioma operated on recently might be smaller than that in patients operated on decades ago. Though data from published studies using different designs to investigate SMR after craniopharyngioma can be used to support the aforementioned hypothesis, it is still necessary to launch an observational study to estimate the SMR after endoscopic surgery and multidisciplinary treatment. This review summarises SMR of patients after craniopharyngioma treatment, potential risk factors, as well as the bias and confounding in these studies.

A comprehensive search of medical subject heading terms ("craniopharyngioma" or "hypopituitarism" and "mortality") using PubMed and EMBASE was conducted to identify relevant studies. Reference lists from studies and systematic reviews identified were manually searched to identify additional eligible studies. The outcome of interest was SMR, which was calculated as the ratio of the observed to the expected number of events (death) encountered during the study period. The expected number of events was obtained from the general population according to different studies.

Mortality in patients with craniopharyngioma

Eight studies reporting SMR after craniopharyngioma treatment were identified, with a total of 2802 patients. Publication information, baseline patient characteristics and outcomes are summarised in Table 1.

Bulow et al. [17] first published a study in 1998 and brought out the concept of excess mortality in patients after

Table 1 Studies reporting SMR after craniopharyngioma treatment

Study	Year	Study location	Study period	Sample size	Women	Age	CO	Follow-up duration (median)	SMR [95% CI]	O/E	SMR in subgroups [95% CI]
Bulow [17]	1998	Lund, Sweden	1951–1988	60	40.0%	31.7	43.3%	12.5	5.6 [3.7–8.2]	27/4.8	Women: 11.4 [4.9–22.5] Men: 4.8 [2.9–7.8]
Tomlinson [18]	2001	West Midlands, UK	Before 2000	118	49.3%[a]	45.7[a]	11.4%[a]	NA	8.7 [5.5–13.9]	31/3.6	Respiratory: 22.1 [10.5–46.3] CV: 19.4 [8.1–46.7]
Pereira [19]	2005	Leiden, Netherlands	1965–2002	54	55.6%	31.0	22.2%	10.0	2.9 [1.4–5.0]	10/3.5	Women: 3.80 [1.5–7.2] Men: 1.8 [0.3–4.6]
Crowley [20]	2009	Dublin, UK	1980–2008	70	44.3%	32.8[b]	34.3%	8.0	8.8 5.4–13.3]	21/2.4	Women: 10.5 [5.0–19.3] Men: 7.6 [3.8–13.5]
van Bunderen [21]	2011	Netherlands	1985–2009	300	48.7%[a]	43.5[a]	21.9%[a]	6.1[a]	3.1 [1.8–5.4]	13/4.1	NA
Olsson [22]	2015	Sweden	1997–2011	307	50.8%	35.0	34.5%	9.0	3.8 [2.9–5.0]	54/14.1	Women: 4.9 [3.2–7.2] Men: 3.2 [2.2–4.7] CO: 17.0 [6.3–37] AO: 3.5 [2.6–4.6]
Yuen [23]	2017	28 countries	1994–2012	1669	46.9%	25.3	44.6%	5.3	2.2 [1.8–2.8]	88/39.4	CO: 2.9 [1.9–4.3] AO: 2.1 [1.6–2.7]
Wijnen [24]	2018	Rotterdam, Netherlands & Gothenburg, Sweden	1987–2014	224	46.8%	29.0	50.0%	13.0	2.7 [2.0–3.8]	34/12.4	Women: 5.3 [3.3–8.4] Men: 1.8 [1.1–2.9] CO: 9.0 [5.3–15.6] AO: 1.9[1.2–2.9]

SMR standardised mortality ratio, *O/E* observed/expected, *CO* childhood-onset, *AO* adulthood-onset, *CV* cerebrovascular, *NA* not applicable, *CI* confidence interval

[a]Data from the whole cohort not only including craniopharyngioma

[b]Data reconstructed form figure of age distribution

Table 2 Potential bias and confounding in studies reporting SMR after craniopharyngioma treatment

Study	Year	Study type	Bias and the consequences			Confounding and the consequences
			Misclassification	Selection bias		
				Inclusion	Lost to follow-up	
Bulow [17]	1998	Hospital-based	No	Yes, *deflation*	Yes, *deflation*	No adequate treatment, high immediate mortality, *inflation*
Tomlinson [18]	2001	Database	Possible	Yes, *deflation and inflation*[a]	Not mentioned, possible	No adequate treatment, *inflation*
Pereira [19]	2005	Hospital-based	No	No	No	Long study period, *deflation or inflation*
Crowley [20]	2009	Hospital-based	No	No	No	undetermined
van Bunderen [21]	2011	National registry	Possible	Yes, *deflation*	Yes, *deflation*	undetermined
Olsson [22]	2015	National registry	Yes, *deflation or inflation*[b]	Yes, *deflation*	No	undetermined
Yuen [23]	2017	Database	Possible	Yes, *deflation*	Not mentioned, possible	undetermined
Wijnen [24]	2018	Hospital-based	No	Yes, *deflation*	Not mentioned, possible	undetermined

In the context of excluding patients unable to identify or lost to follow-up, the excluded or censored patients will make the result be more favorable to the experimental group (here, decreasing the mortality of the craniopharyngioma cohort), thus deflating the SMR. On the other hand, including only patients with certain conditions (say, hypopituitarism) or the existence of confounding (no adequate medical treatment) will make the result be less favorable to the experimental group (here, increasing the mortality of the craniopharyngioma cohort), thus inflating the SMR

SMR standardised mortality ratio

[a]Two kind of selection bias

[b]Misclassification of the diagnosis can either deflation or inflation the result

the treatment of craniopharyngioma. They chose the control population from where the patients were recruited to avoid regional differences, and the reported SMR was 5.6 (95% CI 3.7–8.2). Selection bias existed due to the excluded nine patients with missing records or incomplete identification. Though detailed surgical treatment and radiotherapy was mentioned in the study, there was little information on postoperative medical treatment and only three adults had a limited period for growth hormone substitution. They also found a relatively high immediate postoperative mortality (13%) caused by surgical complications Table 2.

In the first decade of the millennium, three studies reporting SMR came out. Tomlinson et al.'s study [18] was based on a hypopituitarism database, which included a subgroup of patients with craniopharyngioma (12%). The common problem of using a database lies in the survivor bias: only patients who are alive could have entered the database. When calculating the SMR, it requires the assumption that events (deaths) after craniopharyngioma treatment should be equally distributed over the time. We can infer from some publications [17, 19] that a lot of events happen within the first year after surgery or radiosurgery. As a result, this selection bias may deflate the actual SMR. On the contrary, another selection bias of this study led the result in the opposite direction: the database only included patients with hypopituitarism, which itself is a risk factor for high mortality. Another study published in the similar period was conducted by Pereira et al. [19] in a hospital-based manner. Fifty-four patients underwent surgery without lost to follow-up. Though the median follow-up period was ten years, the relatively high total follow-up person-years (828 person-years) contributed to the low reported SMR: 2.9. The long study period (37 years) also suggested that the reported SMR might reflect the mixed treatment effect of strategy or technique evolution. The third study in this period was also conducted in a hospital-based manner [20]. Lost to follow-up were covered by contacting family practitioner according to the paper. This paper described demographic distributions within the cohort thoroughly. Though they offered growth hormone replacement to all eligible patients in this study, no survival benefit was observed.

Four studies were published after 2010. van Bunderen et al. [21] used samples with growth hormone deficiency from Dutch registry. Hormone replacement therapy including growth hormone was adequate in the majority of the patients. Possible bias including survivor bias and lost to follow-up. In the craniopharyngioma subgroup, the reported SMR was 3.1 (95% CI 1.8–5.4). Olsson et al. [22] reported a similar SMR in another registry-based study. Possible false classification may occur in any registry-based research, and the false classification rate was around 1 to 3% in this study. Another limitation of the registry-based

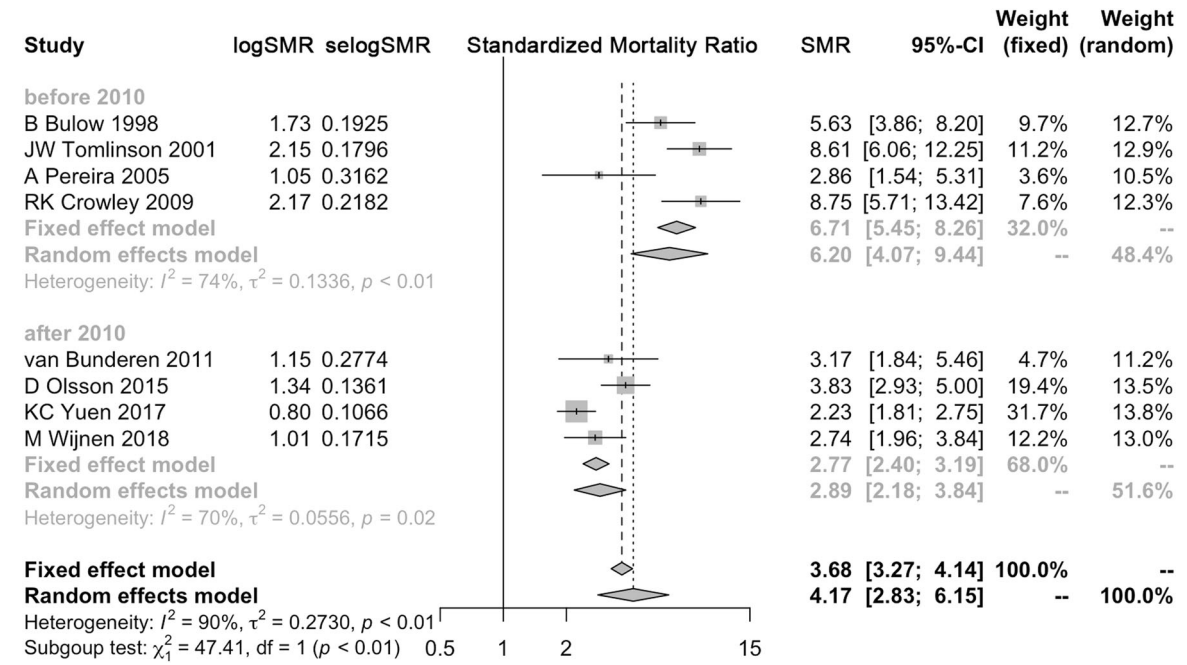

Fig. 1 Subgroup meta-analysis on standardized mortality ratio (SMR) by publication period. Fixed effects model assumes no heterogeneity among studies, while random effects model assumes heterogeneity among studies (more conservative in this case). The subgroup analysis was based on the pooled result in two subgroups (before 2010 versus after 2010) using random effects model

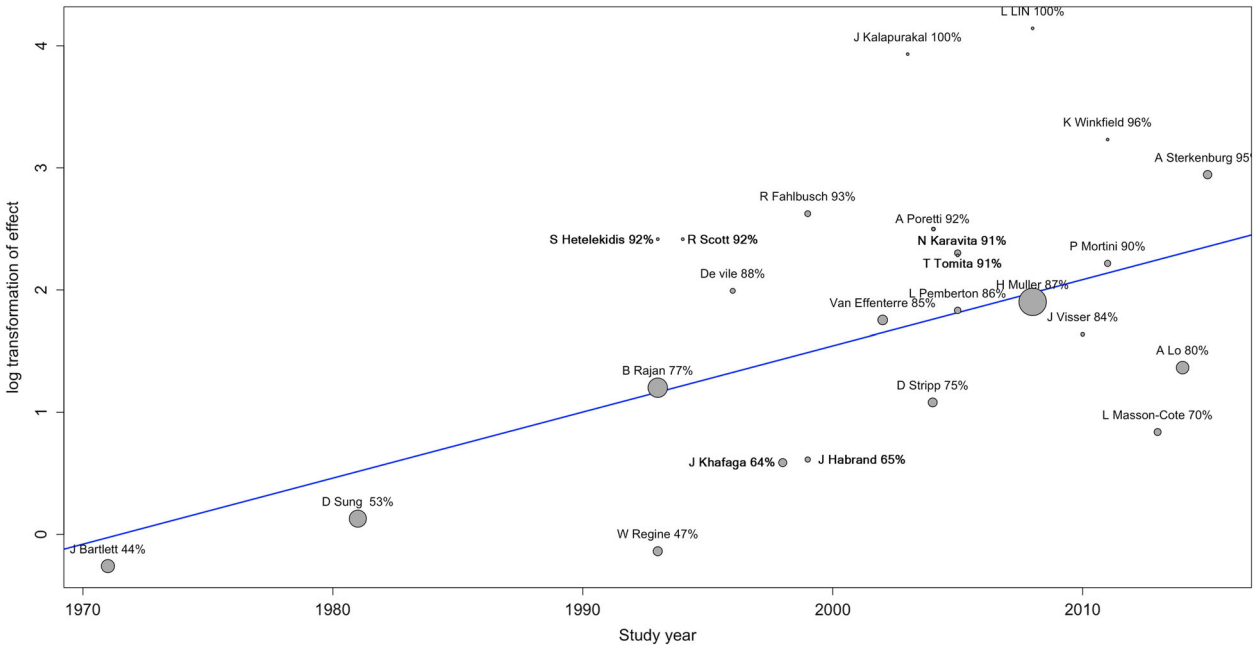

Fig. 2 Ten-year survival rate increases with time ($P < 0.001$). The relationship of 10-year survival rate (log scale) against the publication year was plotted by using "metareg" function in R: x-axis is the publication year and y-axis is log transformed proportion, which equals to log(p/1-p). The actual proportion is labeled beside each study. The size of bubbles is inversely proportional to the variance of the estimated rate

research was that it lacks individual information to infer risk factors. The two most recent studies both reported an SMR less than 3. The study by Yuen et al. [23] extracted data on 1669 patients from KIMS (Pfizer International Metabolic Database). This study was not only a multicentre mortality study but also had the largest sample size up to date. Growth hormone replacement was sufficient in this cohort and reported SMR was 2.2 (95% CI 1.8–2.8). Survivor bias,

observational bias due to frequent visiting doctors and possible lost to follow-up may contribute to the relatively low SMR. The most recent study was conducted by Wijian et al. [24] This study enrolled 224 patients in two countries. Though demographic information was investigated to identify possible risk factors, the analysis was performed without confounding adjustment. Survivor bias also existed in 53 patients (24%) who were treated before and then entered the study.

To give a clear picture of SMR in these studies, a subgroup meta-analysis using "metagen" function in R (version 3.4.2) was performed to pool SMR by different publication period (before 2010 and after 2010). Using random effects model, the pooled SMR was 6.2 (95% CI 4.1–9.4) before 2010 and 2.9 (95% CI 2.2–3.8) after 2010 (subgroup test $p < 0.01$). The heterogeneity among studies can only be explained by publication year (mete-regression $p = 0.013$). No other sources of the heterogeneity, including sample size, age, female proportion and childhood-onset proportion were observed. As discussed in the introduction, the decreasing SMR may be due to the update of treatment technique or strategy. Publication bias that studies reporting different results from previous researches are more likely to be published cannot be ruled out either.

Risk factors of mortality

Five studies reported increased mortality in female patients compared to male patients with craniopharyngioma [17, 19, 20, 22, 24]. Three studies reported increased mortality in childhood-onset patients compared to adulthood-onset patients [22–24]. The crude mortality rate after surgical or radiotherapeutic treatment of craniopharyngioma seems to be comparable between women and men [20, 22, 24]. The crude mortality rate in child-onset craniopharyngioma was even lower than that in adult-onset craniopharyngioma in some studies [22–24]. The SMR can be approximately calculated by the ratio of crude mortality rate in the cohorts and the crude mortality rate in the general population. AS a result, the SMR will be dependent on the crude mortality in the general population (which is smaller in female than in male and much smaller in child than in adult).

Except for gender and childhood-onset disease, hydrocephalus [24], tumour recurrence [17, 24], body mass index [20, 23] and panhypopituitarism [24] were identified as the important risk factors for excess mortality in patients with craniopharyngioma. But these risk factors were calculated using univariate model without confounding adjusting. Most of historical studies included patients without adequate treatment. It can be argued that adequate treatment maybe one of the key factors to bring down the SMR.

Five studies reported the cause of death after treatment of craniopharyngioma [17, 19, 20, 22, 24]. Cerebrovascular cause, including myocadiac infarction, cerebral infarction, cerebral haemorrhage and pulmonary embolism, was the primary cause of death in these patients: the proportion ranged from 24 to 56%. There is a trend that infection-related death (including pneumonia, sepsis and meningitis) drops in recent studies (30 to 33% in studies before 2010 and 14 to 18% in studies after 2010). The proportion of malignant-related mortality (4–20%) seems to keep constant over the time Fig. 1.

Other studies only reporting survival data

We also searched studies reporting survival rate instead of SMR. Majority of the studies on craniopharyngioma only report survival data without SMR due to lost to follow-up and lack of the data on control general population [7, 25–48]. The reported 5-, 10- or 20-year overall survival was calculated based on the Kaplan–Meier curve. Figure 2 was made by plotting the 10-year survival rate (log transformed rate) against the publication year. The size of bubbles is inversely proportional to the variance of the estimated rate. Though only five studies published after 2010, it can still be inferred from the figure that the survival rate was increasing over time.

Conclusion

Though bias and confounding exist across studies, the decreasing SMR and increasing survival rate over the time are in favour of a real signal. New implementation of surgical instruments for a clear view; delicate surgical procedures and advanced radiotherapeutic techniques to protect adjacent tissues like hypothalamus and pituitary stalk; earlier tumour detection due to more prevalence of the MRI; and standardised postoperative pituitary hormone replacement is the state-of-the-art treatment strategy for craniopharyngioma. It is necessary to further investigate the SMR after multidisciplinary treatment of craniopharyngioma. Due to the survivor bias in registry study (and cannot be adjusted), hospital-based studies are preferred. Lost to follow-up was inevitable in such a design, but the modern statistical method (using inversed probability weighting by creating a pseudo-population given the information of the cohort's baseline characteristics [49]) can be used to adjust for this selection bias. When investigating possible risk factors, multivariate logistic regression model condition on cofounders (or propensity score matching, inversed probability weighting) should be used.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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References

1. H.L. Müller, Diagnosis, treatment, clinical course, and prognosis of childhood-onset craniopharyngioma patients. Minerva Endocrinol. **42**(4), 356–375 (2017). https://doi.org/10.23736/S0391-1977.17.02615-3
2. P. Mortini, Craniopharyngiomas: a life-changing tumor. Endocrine **57**(2), 191–192 (2017). https://doi.org/10.1007/s12020-016-1192-2
3. J.A. Jane, E.R. Laws, Craniopharyngioma. Pituitary 9(4), 323–326 (2006). https://doi.org/10.1007/s11102-006-0413-8. (2017) 42 (4):356–375 https://doi.org/10.23736/S0391-1977.17.02615-3
4. L.Z. Leng, J.P. Greenfield, M.M. Souweidane, V.K. Anand, T.H. Schwartz, Endoscopic, endonasal resection of craniopharyngiomas: analysis of outcome including extent of resection, cerebrospinal fluid leak, return to preoperative productivity, and body mass index. Neurosurgery **70**(1), 110–23 (2012). https://doi.org/10.1227/NEU.0b013e31822e8ffc. discussion123–4
5. A. Aggarwal, N. Fersht, M. Brada, Radiotherapy for craniopharyngioma. Pituitary **16**(1), 26–33 (2013). https://doi.org/10.1007/s11102-012-0429-1
6. C. Du, C.-Y. Feng, X.-R. Yuan et al. Microsurgical Management of Craniopharyngiomas via a Unilateral Subfrontal Approach: A Retrospective Study of 177 Continuous Cases. WNEU **90**(C), 454–468 (2016). https://doi.org/10.1016/j.wneu.2016.03.002
7. R. Van Effenterre, A.-L. Boch, Craniopharyngioma in adults and children: a study of 122 surgical cases. J. Neurosurg. **97**(1), 3–11 (2002). https://doi.org/10.3171/jns.2002.97.1.0003.5
8. C. van Bunderen, I. van Nieuwpoort, L. Arwert et al. Does growth hormone replacement therapy reduce mortality in adults with growth hormone deficiency? Data from the Dutch national registry of growth hormone treatment in adults. J. Clin. Endocrinol. Metab. **96**(10), 3151–3159 (2011). https://doi.org/10.1210/jc.2011-1215
9. S.M. Webb, Clinical outcomes of childhood craniopharyngioma: can we do better? Endocrine **62**(1), 1–2 (2018). https://doi.org/10.1007/s12020-018-1654-9
10. M. Koutourousiou, P.A. Gardner, J.C. Fernandez-Miranda, E.C. Tyler-Kabara, E.W. Wang, C.H. Snyderman, Endoscopic endonasal surgery for craniopharyngiomas: surgical outcome in 64 patients. J. Neurosurg. **119**(5), 1194–1207 (2013). https://doi.org/10.3171/2013.6.JNS122259
11. H. Nishioka, N. Fukuhara, M. Yamaguchi-Okada, S. Yamada, Endoscopic Endonasal Surgery for Purely Intrathird Ventricle Craniopharyngioma. WNEU **91**(C), 266–271 (2016). https://doi.org/10.1016/j.wneu.2016.04.042
12. W.C. Jean, Multimodality, Multidirectional Resection of Craniopharyngioma: Versatility in Alternating the Principal and Auxiliary Surgical Corridors and Visualization Modalities. WNEU **102**, 376–382 (2017). https://doi.org/10.1016/j.wneu.2017.03.067
13. M. Losa, V. Pieri, M. Bailo et al. Single fraction and multisession Gamma Knife radiosurgery for craniopharyngioma. Pituitary **21** (5), 499–506 (2018). https://doi.org/10.1007/s11102-018-0903-5
14. T. Ajithkumar, A.-L. Mazhari, M. Stickan-Verfürth et al. Proton Therapy for Craniopharyngioma - An Early Report from a Single European Centre. Clin. Oncol. (R. Coll. Radiol.) **30**(5), 307–316 (2018). https://doi.org/10.1016/j.clon.2018.01.012
15. H.L. Müller, T.E. Merchant, S. Puget, J.-P. Martinez-Barbera, New outlook on the diagnosis, treatment and follow-up of childhood-onset craniopharyngioma. Nat. Publ. Group. **13**(5), 299–312 (2017). https://doi.org/10.1038/nrendo.2016.217
16. F. Bolfi, A.F. Neves, C.L. Boguszewski, V.S. Nunes-Nogueira, Mortality in acromegaly decreased in the last decade: a systematic review and meta-analysis. Eur. J. Endocrinol. **179**(1), 59–71 (2018). https://doi.org/10.1530/EJE-18-0255
17. B. Bülow, R. Attewell, L. Hagmar, P. Malmström, C.H. Nordström, E.M. Erfurth, Postoperative prognosis in craniopharyngioma with respect to cardiovascular mortality, survival, and tumor recurrence. J. Clin. Endocrinol. Metab. **83**(11), 3897–3904 (1998). https://doi.org/10.1210/jcem.83.11.5240
18. J.W. Tomlinson, N. Holden, R.K. Hills et al. Association between premature mortality and hypopituitarism. Lancet **357**(9254), 425–431 (2001). https://doi.org/10.1016/S0140-6736(00)04006-X
19. A.M. Pereira, E.M. Schmid, P.J. Schutte et al. High prevalence of long-term cardiovascular, neurological and psychosocial morbidity after treatment for craniopharyngioma. Clin. Endocrinol. **62**(2), 197–204 (2005). https://doi.org/10.1111/j.1365-2265.2004.02196.x
20. R.K. Crowley, O.P. Hamnvik, E.P. O'Sullivan et al. Morbidity and Mortality in Craniopharyngioma Patients after Surgery. *Clin. Endocrinol*. 2010:no–no. https://doi.org/10.1111/j.1365-2265.2010.03838.x.
21. C.C. van Bunderen, I.C. van Nieuwpoort, L.I. Arwert et al. Does Growth Hormone Replacement Therapy Reduce Mortality in Adults with Growth Hormone Deficiency? Data from the Dutch National Registry of Growth Hormone Treatment in Adults. J. Clin. Endocrinol. Metab. **96**(10), 3151–3159 (2011). https://doi.org/10.1210/jc.2011-1215
22. D.S. Olsson, E. Andersson, I.-L. Bryngelsson, A.G. Nilsson, G. Johannsson, Excess Mortality and Morbidity in Patients with Craniopharyngioma, Especially in Patients with Childhood Onset: A Population-Based Study in Sweden. J. Clin. Endocrinol. Metab. **100**(2), 467–474 (2015). https://doi.org/10.1210/jc.2014-3525
23. K.C.J. Yuen, A.F. Mattsson, P. Burman et al. Relative risks of contributing factors to morbidity and mortality in adults with craniopharyngioma on growth hormone replacement. J. Clin. Endocrinol. Metab. **103**(2), 768–777 (2017). https://doi.org/10.1210/jc.2017-01542
24. M. Wijnen, D.S. Olsson, M.M. van den Heuvel-Eibrink et al. Excess morbidity and mortality in patients with craniopharyngioma: a hospital-based retrospective cohort study. Eur. J. Endocrinol. **178**(1), 93–102 (2017). https://doi.org/10.1530/EJE-17-0707
25. J.R. Bartlett, Craniopharyngiomas--a summary of 85 cases. J. Neurol. Neurosurg. Psychiatr. **34**(1), 37–41 (1971)
26. D.I. Sung, Suprasellar tumors in children: a review of clinical manifestations and managements. Cancer **50**(7), 1420–1425 (1982)
27. W.F. Regine, M. Mohiuddin, S. Kramer, Long-term results of pediatric and adult craniopharyngiomas treated with combined surgery and radiation. Radiother. Oncol. **27**(1), 13–21 (1993)
28. S. Hetelekidis, P.D. Barnes, M.L. Tao et al. 20-year experience in childhood craniopharyngioma. Radiat. Oncol. Biol. **27**(2), 189–195 (1993)
29. B. Rajan, S. Ashley, C. Gorman et al. Craniopharyngioma--a long-term results following limited surgery and radiotherapy. Radiother. Oncol. **26**(1), 1–10 (1993)
30. R.M. Scott, S. Hetelekidis, P.D. Barnes, L. Goumnerova, N.J. Tarbell, Surgery, radiation, and combination therapy in the treatment of childhood craniopharyngioma--a 20-year experience.

Pediatr. Neurosurg. **21**(Suppl 1), 75–81 (1994). https://doi.org/10.1159/000120866
31. C.J. De Vile, D.B. Grant, B.E. Kendall et al. Management of childhood craniopharyngioma: can the morbidity of radical surgery be predicted? J. Neurosurg. **85**(1), 73–81 (1996). https://doi.org/10.3171/jns.1996.85.1.0073
32. Y. Khafaga, D. Jenkin, I. Kanaan, M. Hassounah, M. Shabanah Al, A. Gray, Craniopharyngioma in children. Radiat. Oncol. Biol. **42**(3), 601–606 (1998).
33. R. Fahlbusch, J. Honegger, W. Paulus, W. Huk, M. Buchfelder, Surgical treatment of craniopharyngiomas: experience with 168 patients. J. Neurosurg. **90**(2), 237–250 (1999). https://doi.org/10.3171/jns.1999.90.2.0237
34. J.-L. Habrand, O. Ganry, D. Couanet et al. The role of radiation therapy in the management of craniopharyngioma: a 25-year experience and review of the literature. Radiat. Oncol. Biol. **44**(2), 255–263 (1999)
35. J.A. Kalapurakal, S. Goldman, Y.C. Hsieh, T. Tomita, M.H. Marymont, Clinical outcome in children with craniopharyngioma treated with primary surgery and radiotherapy deferred until relapse. Med. Pediatr. Oncol. **40**(4), 214–218 (2003). https://doi.org/10.1002/mpo.10247
36. D.C.H. Stripp, A. Maity, A.J. Janss et al. Surgery with or without radiation therapy in the management of craniopharyngiomas in children and young adults. Radiat. Oncol. Biol. **58**(3), 714–720 (2004). https://doi.org/10.1016/S0360-3016(03)01570-0
37. A. Poretti, M.A. Grotzer, K. Ribi, E. Schönle, E. Boltshauser, Outcome of craniopharyngioma in children: long-term complications and quality of life. Dev. Med. Child Neurol. **46**(4), 220–229 (2004)
38. N. Karavitaki, C. Brufani, J.T. Warner et al. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. Clin. Endocrinol. **62**(4), 397–409 (2005). https://doi.org/10.1111/j.1365-2265.2005.02231.x
39. T. Tomita, R.M. Bowman, Craniopharyngiomas in children: surgical experience at Children's Memorial Hospital. Childs Nerv. Syst. **21**(8-9), 729–746 (2005). https://doi.org/10.1007/s00381-005-1202-9
40. L.S. Pemberton, M. Dougal, B. Magee, H.R. Gattamaneni, Experience of external beam radiotherapy given adjuvantly or at relapse following surgery for craniopharyngioma. Radiother. Oncol. **77**(1), 99–104 (2005). https://doi.org/10.1016/j.radonc.2005.04.015
41. L.L. Lin, El.I. Naqa, J.R. Leonard et al. Long-term outcome in children treated for craniopharyngioma with and without radiotherapy. J. Neurosurg. Pediatr. **1**(2), 126–130 (2008). https://doi.org/10.3171/PED/2008/1/2/126
42. H.L. Müller, Childhood craniopharyngioma. Recent advances in diagnosis, treatment and follow-up. Horm. Res. **69**(4), 193–202 (2008). https://doi.org/10.1159/000113019
43. J. Visser, J. Hukin, M. Sargent, P. Steinbok, K. Goddard, C. Fryer, Late mortality in pediatric patients with craniopharyngioma. J. Neurooncol. **100**(1), 105–111 (2010). https://doi.org/10.1007/s11060-010-0145-5.3
44. K.M. Winkfield, H.K. Tsai, X. Yao et al. Long-term clinical outcomes following treatment of childhood craniopharyngioma. Pediatr. Blood Cancer **56**(7), 1120–1126 (2011). https://doi.org/10.1002/pbc.22884
45. P. Mortini, M. Losa, G. Pozzobon et al. Neurosurgical treatment of craniopharyngioma in adults and children: early and long-term results in a large case series. J. Neurosurg. **114**(5), 1350–1359 (2011). https://doi.org/10.3171/2010.11.JNS10670
46. L. Masson-Cote, G.L. Masucci, E.G. Atenafu et al. Long-term outcomes for adult craniopharyngioma following radiation therapy. Acta Oncol. **52**(1), 153–158 (2013). https://doi.org/10.3109/0284186X.2012.685525
47. A.C. Lo, A.F. Howard, A. Nichol et al. Long-term outcomes and complications in patients with craniopharyngioma: the British Columbia Cancer Agency experience. Int. J. Radiat. Oncol. Biol. Phys. **88**(5), 1011–1018 (2014). https://doi.org/10.1016/j.ijrobp.2014.01.019
48. A.S. Sterkenburg, A. Hoffmann, U. Gebhardt, M. Warmuth-Metz, A.M.M. Daubenbüchel, H.L. Müller, Survival, hypothalamic obesity, and neuropsychological/psychosocial status after childhood-onset craniopharyngioma: newly reported long-term outcomes. Neuro. Oncol. **17**(7), 1029–1038 (2015). https://doi.org/10.1093/neuonc/nov044
49. M.A. Hernán, J.M. Robins, Per-Protocol Analyses of Pragmatic Trials. N. Engl. J. Med. **377**(14), 1391–1398 (2017). https://doi.org/10.1056/NEJMsm1605385