Published in final edited form as:

World Neurosurg. 2018 January ; 109: 487–496.e1. doi:10.1016/j.wneu.2017.09.164.

Physiologic Growth Hormone Replacement Therapy and Craniopharyngioma Recurrence in Pediatric Patients: A Meta-Analysis

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Abstract

Objective—A systematic review and meta-analysis were conducted to examine the effect of growth hormone replacement therapy (GHRT) on the recurrence of craniopharyngioma in children.

Methods—PubMed, EMBASE, and Cochrane databases were searched through April 2017 for studies that evaluated the effect of GHRT on the recurrence of pediatric craniopharyngioma. Pooled effect estimates were calculated using fixed- and random-effects models.

Results—Ten studies (n=3,487 patients) met all inclusion criteria, including 2 retrospective cohorts and 8 case series. Overall, 3,436 pediatric patients were treated with GHRT after surgery and 51 were not. Using the fixed effect model, the overall craniopharyngioma recurrence rate was lower among children who were treated by GHRT (10.9%; 95% CI: 9.80%; 12.1%; $I^2=89.1\%$; P-for heterogeneity <0.01; n=10 groups) compared to those who were not (35.2%; 95% CI: 23.1%; 49.6%; $I^2=61.7\%$; P-for heterogeneity=0.11; n=3); the p-value comparing the two groups was <0.01. Among patients who were treated with GHRT, subgroup analysis revealed that there was a higher craniopharyngioma recurrence prevalence among studies conducted outside the USA (p<0.01), single center studies (p<0.01), lower impact factor studies (p=0.03), or studies with a lower quality rating (p=0.01). Using the random-effects model, results were not materially different except for when stratifying by GHRT, impact factor, or study quality; this led to non-

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Disclosures: The authors have nothing to disclose.

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significant differences. Both Begg's rank correlation test ($p=0.7$) and Egger's linear regression test ($p=0.06$) indicated no publication bias.

Conclusions—This meta-analysis demonstrated a lower recurrence rate of craniopharyngioma among children treated with GHRT than those who were not.

Keywords

growth hormone; craniopharyngioma; recurrence; pediatrics; growth hormone replacement therapy

Introduction

Craniopharyngiomas are histologically benign neuroepithelial tumors found near the pituitary gland that are observed most commonly in children between the ages of 5 and 10. [1] These tumors may cause compression of adjacent neural structures of the brain and impact the normal functioning of the pituitary gland's growth hormone-producing tissue. Growth hormone deficiency stands out as the most common endocrinological disturbance that occurs as a result of a craniopharyngioma.[2]

Growth hormone deficiency results from the destruction of the normal functioning of the pituitary and hypothalamic tissues,[3] which can stem from mass effect, surgical manipulation, or radiosurgery. Pediatric growth hormone deficiency (PGHD) occurs when the body is unable to produce enough growth hormone, or when end-organs are unable to respond to growth hormone normally.[4] Low levels of growth hormone in the body of a child may have significant effects on the child's long-term growth and well-being. Growth Hormone Replacement Therapy (GHRT) involves the use of somatotropin, a growth hormone of recombinant DNA origin, to replace the body's natural pituitary-derived growth hormone.

An important concern for clinicians caring for children who have undergone resection of craniopharyngioma is whether GHRT contributes to the recurrence of these tumors. A conclusive study exclusively analyzing the effect of GHRT on the recurrence of pediatric craniopharyngiomas has yet to be conducted, and the issue remains somewhat of a clinical dilemma. Therefore, we sought to undertake a systematic review and meta-analysis to analyze whether physiologic GHRT increases the risk of craniopharyngioma recurrence among the pediatric population.

Materials and Methods

Literature search

The search for related articles was conducted using PubMed, EMBASE, and Cochrane Library from their creation date through April 23, 2017 for studies evaluating the effect of GHRT on the recurrence of pediatric craniopharyngiomas. The search strategy joined several search terms for growth hormone (e.g., growth hormone, somatotrophic hormone, and Hormone Replacement Therapy), and craniopharyngioma (e.g., pediatric craniopharyngioma, craniopharyngioma*) (Appendix 1).

Study Eligibility

Studies were included in the current meta-analysis if they met the following criteria: 1) studies of recurrence of craniopharyngiomas in pediatric patients who did or did not receive GHRT; 2) studies with patient populations ranging from newborn to 18 who have been diagnosed with craniopharyngiomas; 3) studies that included 5 or more patients; 4) measurable outcome was recurrence or non-recurrence of craniopharyngioma; 5) intervention was GHRT. Articles that did not meet the inclusion criteria, were not in English, or did not report recurrence were excluded. Titles and abstracts were screened and selected for the full-text evaluation if it met the inclusion criteria. This screening was performed independently in duplicate. Discrepancies were resolved by consulting a senior author (HZ).

Data Extraction

The following data were extracted from the selected studies, when available: Participants characteristics (age, sex); intervention characteristics (surgery type; GHRT, dose, frequency); study characteristics (authors, publication year, journal impact factor, center, continent, sample size, and study design); and outcome results (number of recurrences in each group, total number). In studies where the median and range were given instead of the mean, the mean was then estimated.[5] The data extraction was performed independently in duplicate. Discrepancies were resolved by consulting a senior author (HZ).

Statistical Analysis

Comprehensive Meta-Analysis (CMA) version 3 (Biostat, Englewood, NJ, USA) was used to perform the data analysis. The overall recurrence prevalence estimate and its 95% confidence intervals among craniopharyngioma patients with or without GHRT was obtained by using the fixed-effect model, which only accounted for the within study variance. In addition, variation between and within studies was evaluated for comparison using a random-effects model.[6] The individual and summary estimates were visualized using forest plots. Cochran's Q test ($p < 0.10$) and I^2 were used to evaluate the heterogeneity among studies. An I^2 was considered high if its value was $> 50\%$. Sub-group analyses by categorical covariates such as growth hormone replacement therapy (GHRT; no GHRT), continent (studies in the US; outside the US), international journal impact factor (median value of 3.7; > 3.7), Newcastle-Ottawa Scale (NOS) (median value of 3; > 3) and center (single; multiple) were used to explore potential sources of heterogeneity. Covariates such as age range, surgery type, treatment duration, length of follow-up, and timing of initiation of GHRT after surgery were not always specified and hence were not used to assess for heterogeneity. Funnel plots, Egger's linear regression test, and Begg's and Mazumdar rank correlation test were used to assess potential publication bias at the p -value of < 0.05 level of significance. The number of missing studies in a meta-analysis was evaluated by the trim and fill method if publication bias was indicated.

Quality Assessments

The nature of the available studies was non-comparative. So, we modified the Newcastle-Ottawa scale to assess the quality of included studies by removing the comparability criteria. [7] The selection and outcome criteria were used to assess the quality of the study. Studies

with a score ≤ 3 (median value) were considered low quality; while those with a score >3 were considered high quality.

Results

The original search resulted in 1200 English articles (427 from PubMed, 764 from Embase and 9 from the Cochrane Library). Ninety articles remained for full text screening after removal of duplicates and papers that did not meet the inclusion criteria based on title and abstract screening. The full-text review resulted in 80 excluded articles (Figure 1).

A total of 10 studies (2 retrospective cohorts and 8 case series) with 3487 patients were available for final analysis. Characteristics of the 10 studies are shown in Table 1.[8–17] The total number of participants per study ranged from 5 to 1038. Overall, 3,436 pediatric patients were treated with GHRT after surgery and 51 were not (age 1.3–17.8 yrs; 57%–84% male). Surgical approach, when reported, was either subfrontal alone (5 patients) or transnasal-transphenoidal (13 patients). The frequency of GH replacement therapy was either daily (69 patients), weekly (739 patients), 3 times/week (18 patients), or 6 times/week (488 patients). GHRT duration ranged between 1.9 and 6.4 years, and the average time of GH initiation after diagnosis was 2.2–2.7 years. Six studies were conducted in the United States (US) and 4 studies outside the US. Study quality yielded an average score of 3 ranging from 2 to 6. The international journal impact factor yielded an average of 3.84 ranging from 1.00 to 9.39.

Using the fixed effect model, the overall craniopharyngioma recurrence rate was lower among children who were treated by GHRT (10.9%; 95% CI: 9.80%; 12.1%; $I^2=89.1\%$; P-for heterogeneity <0.01 ; $n=10$ groups) compared to those who were not (35.2%; 95% CI: 23.1%; 49.6%; $I^2=61.7\%$; P-for heterogeneity=0.11; $n=3$); the p-value comparing the two groups was <0.01 (Figure 2).

Among patients who were treated with GHRT, subgroup analysis revealed that there were differences in craniopharyngioma recurrence prevalence among studies of different subgroups, including those conducted inside versus outside the USA: $p<0.01$; (outside the USA: 16.3%, 4 studies, which had a higher prevalence than the US studies: 9.40%; 6 studies) (Figure 3); by center type: $p<0.01$; (single center: 32.5%, 6 studies, which had a higher prevalence than the multiple center studies: 9.60%; 4 studies) (Figure 4); by impact factor: $p=0.03$; (studies with impact factor <3.7 : 10.7%, 4 studies, which had a higher prevalence than the studies with impact factor ≥ 3.7 : 7.50%; 4 studies) (Figure 5); and by Newcastle-Ottawa scale: $p=0.01$; (studies with NOS ≤ 3 : 11.0%, 6 studies, which had a higher prevalence than the studies with NOS >3 : 7.40%; 2 studies) (Figure 6). Meta-regression by length of follow-up revealed that studies with longer follow-up after treatment initiation had higher craniopharyngioma recurrence rates ($p<0.01$). Using the random-effects model, results were not materially different from the fixed effect model except for when stratifying by GHRT, impact factor, or NOS; these led to non-significant differences.

Funnel plot visually showed a slight asymmetry; however, both Begg's rank correlation test ($p=0.71$) and Egger's linear regression test ($p=0.06$) indicated no publication bias. After

conducting the trim and fill method to correct for any potential publication bias, the overall imputed fixed effect estimate of 10.0% (9.03%; 11.1%) did not materially change from 11.5% (95% CI: 10.3%; 12.8%) (Figure 7).

Discussion

Contrary to the belief of some practitioners, our current meta-analysis indicated that physiologic GHRT correlated with a lower risk of tumor recurrence/progression when compared to patients who did not receive GHRT therapy. There has been no sufficient evidence to indicate that GH therapy promoted intracranial tumor progression.[18–20] Patients with intracranial tumors, particularly those arising in the sellar or suprasellar regions, commonly have endocrine derangements. Growth hormone deficiency (GHD) has been reported variably in 54–100 percent of pediatric and adult patients with craniopharyngiomas.[21–24] Although GHD usually exists at diagnosis, surgery and radiotherapy adversely affect the function of pituitary gland through direct tissue damage and can aggravate growth hormone deficiency. Growth hormone replacement therapy (GHRT) is the only available goal-directed treatment for patients with GHD.

Growth hormone stimulates a biochemical cascade resulting in the production of IGF-1 and other mediators. Both growth hormone and IGF-1 have well-established mitogenic and antiapoptotic properties.[25–27] Therefore, these agents have previously been proposed to play a considerable role in carcinogenesis and tumor growth, with several groups demonstrating an association between serum IGF-1 levels and prostate, breast, and colon cancer risks.[28–30] In addition, the increased risk of developing certain malignancies as a result of elevated GH are consistent with observations in patients with acromegaly who have elevated levels of circulating GH and IGF-1. However, these patients have higher than normal physiological levels of GH, whereas correct treatment with GHRT involves the use of only physiological doses of GH.[31,32]

Not surprisingly, safety concerns have been raised regarding growth hormone replacement therapy in patients with craniopharyngiomas and its role in recurrence rates. Although growth hormone is essential for normal growth and development, especially in children, its use remains controversial.

Although we did not include studies that mixed adults with pediatric patients or that focused on other interventions aside from GHRT, some of these findings were notably similar. For instance, Karavitaki et al. analyzed the outcomes of pediatric and adult patients with craniopharyngiomas from 1964 to 2005. Thirty-two pediatric and adult patients received GHRT for a mean period of 6.3 ± 4.6 years and were followed for a mean duration of 10.8 ± 9.2 years, and outcomes were compared to a cohort of 53 patients who had not received GHRT. Tumor recurrence was observed in 4 patients treated with GH, while 22 cases observed in the untreated group. Following the adjustment for potential confounding variables, Karavitaki et al. demonstrated that GHRT was not associated with an increased risk of recurrence ($p=0.06$; hazard ratio=0.309).[21] Another study of 108 pediatric patients with brain tumors that was included in this meta-analysis, 31 (28.7%) of which were craniopharyngiomas, also demonstrated no association between GHRT and tumor

recurrence. Eleven of 22 (50%) GH-treated and 4 of 7 (57.1%) non GH-treated patients had tumor recurrence.[16]

Olsson et al. conducted a case-control study to assess the risk of tumor recurrence in patients with craniopharyngiomas on long-term GHRT.[33] Fifty-six pediatric and adult patients were included, with a mean duration of GHRT of 13.6 ± 5.0 years, and 70 patients who had not received GHRT. All patients were followed for a mean duration of 13.4 ± 7.8 years with MRI or CT studies. During the observation period, recurrence occurred in 16 percent of patients treated with GHRT and in 43 percent of patients not receiving GHRT. The 10-year tumor progression-free survival rate amounted to 88 percent in the group of patients receiving GHRT and 57 percent in the group not receiving GH, respectively. Furthermore, Cox regression analysis demonstrated that these changes were influenced by initial radiation therapy and absence of residual tumor after primary treatment, and no association was found between tumor progression and GHRT. Interestingly, there was also no significant difference in the serum IGF-1 level ($p=0.35$) between patients with and without tumor recurrence. [33]³⁴

A US-based prospective observational study was performed by Hartman et al. to evaluate the safety of GHRT among adult patients with GHD.[34] The authors compared the adverse event rates, including tumor recurrence, between GH-treated and non GH-treated groups. Tumor recurrence was reported in 8 of 211 (3.8%) patients in the GH-treated group and 2 of 36 (5.6%) patients in the non GH-treated group. Although the mean follow-up period in this study was only 2.3 ± 1.3 years, there was no evidence of increased tumor recurrence with GHRT ($p<0.82$).[34] Similarly, a meta-analysis by Shen et al. analyzed 15 studies evaluating the risk of recurrence in patients with intracranial tumors.[35] Four of 15 studies estimated the recurrence risk in patients with craniopharyngiomas on GHRT. The combined relative risks for GHRT was 0.43 (95 % CI 0.28–0.67; p for heterogeneity=0.225) and the results showed that the use of growth hormone was associated with a decreased risk of tumor recurrence or progression in children with craniopharyngiomas.[35]

Recently, a multicenter, observational, surveillance study was published, the aim of which was to determine the recurrence rates in pediatric patients with craniopharyngiomas postoperatively treated with their recombinant human GH (rhGh) products.[17] Seven hundred thirty nine pediatric patients enrolled in the study, with an average dose of rhGH 0.253 ± 0.07 mg/kg/wk and a median follow-up of 4.3 years (range 0.7–6.4 years). The study had several limitations, including lack of data concerning differences in adjuvant therapy, extent of initial tumor removal and MRI surveillance frequency among these patients, and the fact that GHRT initiation was a year from primary treatment. However, the reported recurrence rate during this relatively short period of follow-up was 6.8 percent, which is even lower than most of previously reported rates. These authors demonstrated that despite the limitations in their study, long-term GH administration did not affect the progression-free survival rate in patients with craniopharyngiomas.[17]

Two other retrospective non-controlled studies included in our analysis have drawn similar conclusions analyzing the Kabi International Growth Study Database (KIGS).[15,10] Darendeliler et al. analyzed 1038 patients with craniopharyngiomas receiving GHRT, and

found that tumor recurrence was observed in 121 (11.7%) cases. Authors have compared their results with other published reports and found no significant association between GHRT and tumor recurrence rates. Further analysis of recurrence-free survival rates referring to the duration from diagnosis to GHRT have shown no significant differences among patients who started GHRT in the first year between 1 and 3 years, 3 and 5 years, and 5 years after diagnosis.[15,10]

In addition to the aforementioned studies, several additional authors, of which one was included in this meta-analysis, [9] reported non-statistically significant, if any, associations between tumor recurrence and GHRT.[9,36–38] Clinicians and surgeons could use these results as a resource for a direct discussion with patients about the safety of using GHRT after brain surgery for craniopharyngioma.

Limitations and strengths

Our study was limited to English language reports, which could lead to a publication analysis bias. However, no statistically significant publication bias was found. Moreover, GHRT treatment duration was only provided in three out of 10 studies, and ranged between 1 and 5 years. Timing of GHRT after surgery was only provided in 3 out of 10 studies and it was therefore impossible to assess whether results varied by these covariates. Furthermore, data regarding longer term consequences were not available; although length of follow-up was provided in 6 out of 10 studies and ranged between 3.9 and 12.6 years, it was defined differently across studies (e.g., time since completion of tumor treatment;[9] time after initiation of GH therapy;[17] or time since presentation).[12] Other covariates, such as extent of initial tumor removal, perioperative medical treatment modalities, and radiation, were not available in all studies; therefore, it is highly suggested for authors to report such relevant information in future studies with longer follow-up. Because these covariates varied randomly in both groups, however, this type of non-differential misclassification bias would have driven the results towards the null. Additionally, the number of patients in the non-GHRT is small as compared to the GHRT group; nevertheless, this weighted average of three studies still gave a more powerful recurrence prevalence estimate than the results of one study alone. Additionally, the magnitude of the difference in recurrence rate between the two groups was statistically and clinically significant (11% vs. 35%) and both confidence intervals did not overlap (10%–12%) vs. (23%–50%). Finally, the I^2 value for heterogeneity remained high in most of the categories, even after stratification; this could be due to variance in true rates rather than sampling error or residual confounding.

Despite these limitations, our study had much strength. We were able to assess many potential confounders and explore them as a source of heterogeneity using meta-regression and subgroup analyses. We also corrected for the potential publication bias. We presented both fixed and random effect models.

Conclusion

The current meta-analysis demonstrates that GHRT use was not associated with the recurrence of craniopharyngioma for the observed treatment duration period of 1–5 years.

Long-term studies are still needed to fully assess the lifetime treatment risk of GHRT on patients with surgically treated craniopharyngioma.

Acknowledgments

Funding

National Institutes of Health (NIH) Training Grant T32 CA 009001 (DJC).

Glossary

CMA	Comprehensive Meta-Analysis
CT	computed tomography
GHRT	growth hormone replacement therapy
MRI	magnetic resonance imaging
NOS	Newcastle-Ottawa Scale
PGHD	pediatric growth hormone deficiency
US	United States

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Appendix 1

Our Medline search strategy using MeSH terms and [tw] keywords

("Growth Hormone"[Mesh] OR growth hormone*[tw] OR hGH[tw] OR "STH"[tw] OR somatotrophic hormone*[tw] OR "somatotrophin"[TW] OR somatotrophic hormone*[tw] OR "somatotropin"[tw] OR "Hormone Replacement Therapy"[Mesh] OR Hormone Replacement*[tw]) AND ("Craniopharyngioma"[Mesh] OR Craniopharyngioma*[tw])

OR “craniopharyngiomata”[tw] OR pediatric craniopharyngioma[tw]) = **427 papers as of 04/23/17**

Our Embase search strategy using Emtree keywords

(Exp Growth hormone/OR exp human growth hormone/OR growth hormone.tw. OR somatotrophic hormone.tw. OR somatotrophic hormone.tw. OR pituitary growth hormone.tw. OR somatotropin*.tw. OR somatotropin*.tw. OR growth hormone replacement therapy.tw. OR ghrt.tw. OR hormone replacement therapy.tw. OR GH replacement therapy.tw. OR hormone substitution.tw. OR growth hormone treatment.tw. OR recombinant growth hormone.tw.) AND (craniopharyngioma/OR craniopharyngioma*.tw. OR craniopharyngeoma*.tw. OR craniopharyngiomata.tw. OR pediatric craniopharyngioma*.tw.) = **764 papers as of 04/23/17**

Our Cochrane search strategy

“growth hormone”:ti,ab,kw OR “somatotrophic hormone”:ti,ab,kw OR pituitary growth hormone:ti,ab,kw OR somatotropin:ti,ab,kw OR hormone substitution AND “craniopharyngioma”:ti,ab,kw OR craniopharyngiomas OR craniopharyngiomata And pediatrics:ti,ab,kw OR “pediatric” OR child OR children and child* AND hormone replacement therapy:ti,ab,kw = **9 papers as of 04/23/17**

Figure 1.

Figure 2.

Craniopharyngioma recurrence prevalence for growth hormone replacement therapy (Yes) or no GHRT (No). The forest plot represents the craniopharyngioma recurrence prevalence (95% CI) after GHRT (Yes) or no GHRT (No) among patients with craniopharyngioma. Solid squares represent the point estimate of each study; horizontal lines denote 95% CIs; and the diamond represents the pooled estimate of the intervention effect. The size of the solid squares is proportional to the weight of the study. The overall “fixed” prevalence was 11.5% (95% CI: 10.3%; 12.8%) ($I^2=89.0\%$; p -heterogeneity<0.01); the fixed pooled prevalence was 10.9% (95% CI: 9.80%; 12.1%) for GHRT ($I^2=89.1\%$; p -heterogeneity<0.01; 10 studies) and 35.2% (95% CI: 23.1%; 49.6%) for no GHRT ($I^2=61.7\%$; p -heterogeneity=0.11; 3 studies); P -value comparing the two groups was <0.01 using the fixed effect model and =0.07 using the random effect model.

Figure 3.

Craniopharyngioma recurrence prevalence by continent for studies in the USA or outside the USA within the GHRT group: Forest plot. Solid squares represent the point estimate of each study; horizontal lines denote 95% CIs; and the diamond represents the pooled estimate of the intervention effect. The size of the solid squares is proportional to the weight of the study. The overall “fixed” prevalence was 10.9% (95% CI: 9.80%; 12.1%) for GHRT ($I^2=89.1\%$; p -heterogeneity <0.01 ; 10 studies). The fixed pooled prevalence was 16.3% (95% CI: 13.3%; 19.8%) for studies outside the US ($I^2=92.3\%$; p -heterogeneity <0.01 ; 4 studies) and 9.40% (95% CI: 8.20%; 10.7%) for the US studies ($I^2=78.9\%$; p -heterogeneity <0.01 ; 6 studies); P -value comparing the two groups was <0.01 using both the fixed and random effect models.

Figure 4.

Craniopharyngioma recurrence prevalence by center (multiple vs. single) within the GHRT group: Forest plot. Solid squares represent the point estimate of each study; horizontal lines denote 95% CIs; and the diamond represents the pooled estimate of the intervention effect. The size of the solid squares is proportional to the weight of the study. The overall “fixed” prevalence was 10.9% (95% CI: 9.80%; 12.1%) for GHRT ($I^2=89.1\%$; p -heterogeneity <0.01 ; 10 studies). The fixed pooled prevalence was 9.60% (95% CI: 8.50%; 10.7%) for multiple center studies ($I^2=84.5\%$; p -heterogeneity <0.01 ; 4 studies) and 32.5% (95% CI: 24.6%; 41.7%) for single center studies ($I^2=56.2\%$; p -heterogeneity $=0.04$; 6 studies); P -value comparing the two groups was <0.01 using both the fixed and random effect models.

Figure 5.

Craniopharyngioma recurrence prevalence by international journal impact factor (<3.7; 3.7) within the GHRT group: Forest plot. Solid squares represent the point estimate of each study; horizontal lines denote 95% CIs; and the diamond represents the pooled estimate of the intervention effect. The size of the solid squares is proportional to the weight of the study. The overall “fixed” prevalence was 10.9% (95% CI: 9.80%; 12.1%) for GHRT ($I^2=89.1\%$; p -heterogeneity<0.01; 10 studies). The fixed pooled prevalence was 10.7% (95% CI: 9.50%; 12.1%) for studies with impact factor <3.7 ($I^2=92.0\%$; p -heterogeneity<0.01; 4 studies) and 7.50% (95% CI: 5.60%; 10.0%) for studies with impact factor ≥ 3.7 ($I^2=67.4\%$; p -heterogeneity=0.03; 4 studies); 2 studies were conference abstracts and did not have an impact factor. P-value comparing the two groups was 0.03 using the fixed effect model and 0.60 using the random effect model.

Figure 6.

Craniopharyngioma recurrence prevalence by the Newcastle-Ottawa scale (NOS: ≤3; >3) within the GHRT group: Forest plot. Solid squares represent the point estimate of each study; horizontal lines denote 95% CIs; and the diamond represents the pooled estimate of the intervention effect. The size of the solid squares is proportional to the weight of the study. The overall “fixed” prevalence was 10.9% (95% CI: 9.80%; 12.1%) for GHRT ($I^2=89.1\%$; p -heterogeneity<0.01; 10 studies). The fixed pooled prevalence was 11.0% (95% CI: 9.70%; 12.4%) for studies with NOS ≤3 ($I^2=86.1\%$; p -heterogeneity<0.01; 6 studies) and 7.40% (95% CI: 5.70%; 9.60%) for studies with NOS >3 ($I^2=88.4\%$; p -heterogeneity<0.01; 2 studies); 2 studies were conference abstracts and did not have an NOS. P-value comparing the two groups was 0.01 using the fixed effect model and 0.80 using the random effect model.

Figure 7.

Funnel Plot of Standard Error by Logit event rate. The vertical solid line is drawn at the pooled log odds ratio, and the other two lines represent the expected 95% confidence interval for a given standard error. The funnel plot visually shows a slight asymmetry towards the left of the logit of the event rate. However, Both Begg's rank correlation test ($P = 0.71$) and Egger's linear regression test ($P = 0.06$) indicated no publication bias. After conducting the trim and fill to correct for any potential publication bias, the overall imputed fixed effect estimate of 10.0% (9.03%; 11.1%) did not materially change from 11.5% (95% CI: 10.3%; 12.8%).

Table 1

Characteristics of the studies included in the meta-analysis.

Author, Year, [Reference #]	Journal Impact Factor	Continent	Center	Treated arm for GHRT (n/N)	Control arm for no GHRT (n/N)	Age range, years	% Male	Surgery Type	Study Duration/Length of follow-up (mean, years)	Intervention Type (Name, Dose)	Frequency	Route of Admin GH	Timing of initiation of GHRT after surgery	GH treatment duration (years)	NOS
Alev Ozon Z 2015 (abstract) [8]	na	Outside the USA	Single	11/24	na	na	na	Gross total resection	na	GH	na	na	2.7	na	na
Arslian S * 1985 [9]	7.15	USA	Single	4/13	0/5	3.9–17.8	na	Sub-frontal and trans-sphenoidal	1970–1983/5.5	Somatotropin, 0.1 unit/kg.	3x/week	IM/SC	na	na	6
Darendeliler F 2006 [10]	1.67	USA	Multiple	121/1038	na	4.3–14.9	N/A	na	Started: Jan 2004/10.3	Genotropin, 0.17 mg/kg/wk	NA	IM/SC	na	1.9	3
Kanev PM 1991 [11]	3.74	USA	Single	0/5	na	na	na	Sub-frontal	1985 – 1987/na	Protropin, 0.1 mg/kg each, or daily injections of 0.05 mg/kg.	3x/week	SC	na	na	3
Kim KE * 2016 (abstract) [12]	na	Outside the USA	Single	11/47	13/39	1.24–16.65	na	na	1980–2016/10.6	“GHR” 0.103±0.001 (0.08–0.13 u/kg/d)	Daily	na	na	3.64±2.51 (0.6–9.39 years)	na
Moshang T 1995 [13]	9.39	USA	Single	2/19	na	3.5–12.5	84.2	na	1985–1995/na	rhGH	na	na	2.4	na	3
Moshang T 1996 [14]	3.79	USA	Multiple	35/546	na	na	na	na	na	rhGH	na	na	na	na	3
Price DA 1997 [15]	2.48	Outside the USA	Multiple	54/488	na	4.9–14.8	57	na	1988–1996/5	rhGH, mean dose <u>0.49±0.15</u> IU/kg/week (during 1 st year of treatment) or <u>0.48±0.16</u> IU/kg/week (during 1 st 5 years of treatment)	6x/week (range 3–7)	Injection	median 1.56, mean 2.23±1.88	1 or 5	2
Rohrer TR 2010 [16]	1.00	Outside the USA	Single	11/22	4/7	1.3–15.5	65.5	na	na/12.6	hGH, 0.025 mg/kg	Daily	Injection	na	na	2
Smith TR 2016 [17]	1.76	USA	Multiple	50/739	na	<9; 9–13; >13 years	na	na	1986–2005/3.9	hGH Protropin, Nutropin, Nutropin AQ Nutropin Depot 0.253±0.07 mg/kg/wk	Weekly	na	na	na follow-up 4.3yrs (range= 0.7–6.4)	5

GHRT= Growth hormone replacement therapy; hGH= Human growth hormone; rhGH= recombinant human growth hormone; NOS= Newcastle-Ottawa Scale; n= # of events; N=sample size; na= not available.

* Studies with a * indicate retrospective cohort studies; otherwise, case series.