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ORIGINAL ARTICLE

# Growth hormone therapy and risk of recurrence/progression in intracranial tumors: a meta-analysis

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**Abstract** Growth hormone deficiency is common in intracranial tumors, which is usually treated with surgery and radiotherapy. A number of previous studies have investigated the relationship between the growth hormone replacement therapy (GHRT) and risk of tumor recurrence/progression; however, the evidence remains controversial. We conducted a meta-analysis of published studies to estimate the potential relation between GHRT and intracranial tumors recurrence/progression. Three comprehensive databases, PUBMED, EMBASE, and Cochrane Library, were researched with no limitations, covering all published studies till the end of July, 2014. Reference lists from identified studies were also screened for additional database. The summary relative risks (RR) and 95 % confidence intervals (CI) were calculated by fixed-effects models for estimation. Fifteen eligible studies, involving more than 2232 cases and 3606 controls, were included in our meta-analysis. The results indicated that intracranial tumors recurrence/progression was not associated with GHRT (RR 0.48, 95 % CI 0.39–0.56), and for children, the pooled RR was 0.44 and 95 % CI was 0.34–0.54. In subgroup analysis, risks of recurrence/progression were decreased for craniopharyngioma, medulloblastoma, astrocytoma, glioma, but not for pituitary adenomas, and non-functioning pituitary adenoma (NFPA), ependymoma. Results from our analysis indicate that GHRT decreases the risk of recurrence/progression in children with intracranial tumors, craniopharyngioma, medulloblastoma, astrocytoma, or glioma. However, GHRT for pituitary adenomas, NFPA, and ependymoma was not associated with the recurrence/progression of the tumors. GH replacement seems safe from the aspect of risk of tumor progression.

**Keywords** Intracranial tumors · Growth hormone · Risk · Recurrence · Meta-analysis

## Introduction

Surgical resection, radiotherapy, and chemotherapy are currently some of the most efficient treatment methods for brain tumors [1]. However, complications resulting from the management of the tumor are serious, such as growth hormone deficiency (GHD). GHD is often found in tumors post-irradiation or tumors related to sella turcica, such as pituitary adenomas and craniopharyngioma. Growth hormone (GH) plays a significant role in metabolism. It regulated fuel homeostasis and promotes growth through glycometabolism, lipid metabolism, and protein anabolism [2]. Thus, continued exogenous GH infusion is considered in GHD patients, especially those having a disorder of metabolism or a low quality of life.

The safety of GHRT in tumor management remains controversial. Three hundred sixty one children, enrolled in the Childhood Cancer Survivor Study, were treated with GH. The rate ratio of GHRT survivors developing a second neoplasm, as compared to no-GHRT survivors, was 2.15 (95 % CI 1.3–3.5) [3]. Furthermore, in patients with prolonged critical illness, high doses of GH are associated with increased morbidity and mortality [4]. However, recent

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studies have demonstrated that long-term GH use in hypopituitarism may be considered safe in patients with central nervous system (CNS) tumors [5–7]. However, the role of GHRT toward the progression of CNS tumor in patients remained poorly understood. Therefore, we conducted a meta-analysis of published observational studies to validate the role of GH in intracranial tumors.

## Materials and methods

### Research strategy

Reviewers (LS and CMS) performed a systematic literature search independently from three databases, PUBMED, EMBASE, and Cochrane Library for published studies without limitations. Reviewers used the following terms as research strategy: ([MeSH] "brain neoplasms" or "intracranial tumors" or "seller tumors" or "brain tumors") and ([MeSH] "growth hormone" or "growth hormone deficiency*" or "growth hormone replacement therapy" or "GH replacement therapy" or "GHRT"), and ([MeSH] "recurrence" or "recurrence" or "progression" or "enlargement"). No limitations were imposed. A manual search of identified articles' references was performed for additional studies.

### Study selection

The studies were selected using the following criteria: (1) case–control study or cohort design; (2) intracranial tumors treated with growth hormone; (3) relationship between GHRT and recurrence/progression of intracranial tumors was assessed; (4) values of RRs and the corresponding 95 % CIs or sufficient data were estimated; and (5) study with largest sample size or the most recent study in meta-analysis if the same study population was published several times was chosen.

### Data extraction and methodological assessment

The following data were independently extracted from of the participants involved in the study: surname of the first reviewer, publication year and country of literature, age at diagnosis of subjects in the study, numbers of case and control groups, follow-up and GH therapy years, methods of recurrence/progression diagnosis, and study quality. Methodological quality was evaluated standardly by two observers using the Newcastle-Ottawa Scale (NOS) criteria [8]. NOS included three steps: (1) subject selection, 0–4; (2) comparability of subject, 0–2; and (3) clinical outcome, 0–3. The NOS scores ranged from zero to nine. A score of six or more indicated a good quality; otherwise, the study is deemed to have relatively lower quality. All the disagreements were resolved carefully by two reviewers through discussion.

### Statistical analysis

The STATA software (Version 12.0, Stata Corporation, College Station, TX, USA) was used for the analysis. RR values and the corresponding 95 % CI were used to estimate the relationship between GHRT and risk of recurrence/progression in intracranial tumors with GHD. Heterogeneity, in the analysis, was evaluated by the Q statistic and $I^2$ statistic [9, 10]. Heterogeneity was tentatively assigned with the values corresponding to middle heterogeneity and notable heterogeneity: $I^2$ values <30 and >50 % [9]. $p > 0.1$ for the Q statistic or $I^2 < 50$ % for the $I^2$ statistic were considered statistically insignificant [10]. If heterogeneity was indicated, random-effect model was used; otherwise, fixed-effect model was employed [11]. Moreover, subgroup analyses were performed to explore potential factors for heterogeneity. In order to assess the stability of each study for the overall estimation, sensitivity and publication bias analyses were conducted as described previously [11]. For the best possible information available, more than one method for bias was conducted for assessment, for example Egger's test and Begg's funnel plot [12, 13]. Briefly, sensitivity analysis was employed to assess the impact of individual study on the overall estimation.

## Results

### Literature search and study characteristics

Figure 1 summarizes the flow chart of literature search and selection. A total of 524 articles were selected for identification. Fifteen studies, published from 1985 to 2013, were selected in the meta-analysis. Of the 15 studies, six were carried out from UK, three from USA, two from Germany, two from Sweden, one from Norway, and one from Canada. Additional characteristics of the included studies are shown in Table 1. As shown in table, seven of the selected studies obtained seven or more scores, which indicated that the study quality was relatively higher [5–7, 14–22]; whereas, other studies with relatively lesser scores were considered of lower quality [23–25].

### Correlation of GHRT- and GH-deficient intracranial tumors

Different types of GH-deficient intracranial tumors were researched in the studies. As shown in forest plots, the pooled RR for GHRT versus no-GHRT was 0.48 (95 % CI

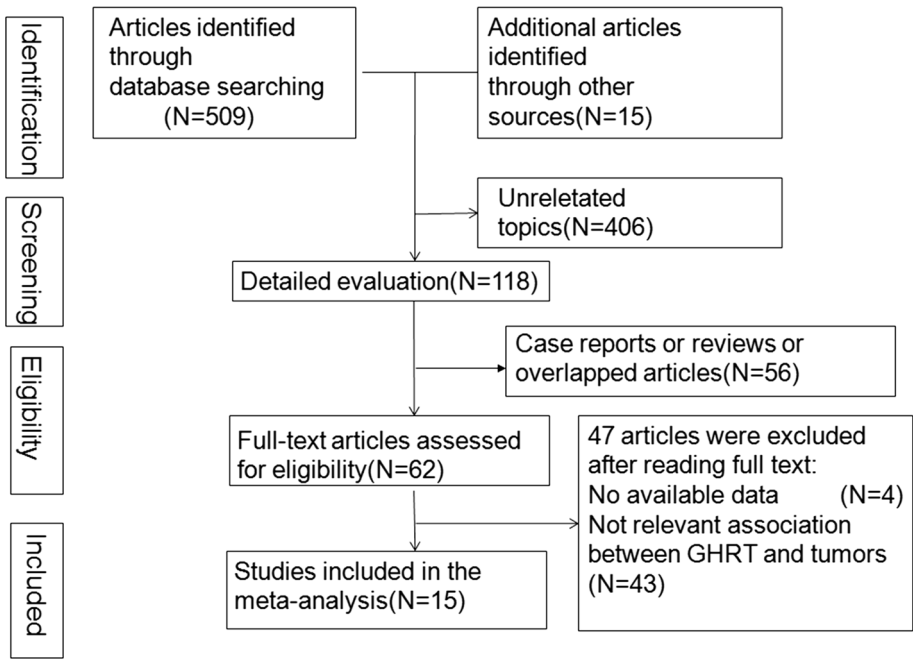


**Fig. 1** Flow chart of literature selection

0.39–0.56; $I^2 = 14.7$ %, $p$ for heterogeneity = 0.285) for all types of GH-deficient intracranial tumors (Fig. 2).

### GHRT and risk of tumor recurrence/progression in children

Seven studies supported the available information on the risk of tumor recurrence/progression in children treated with GH. The pooled RR was 0.44 (95 % CI 0.34–0.54; $I^2 = 0.0$ %, $p$ for heterogeneity = 0.680) (Fig. 3). Figure 3 represents the information on infants and older children.

### Subgroup analysis

*GHRT for craniopharyngioma*

A total of four studies [7, 21, 22, 26] in our meta-analysis estimated the risk of craniopharyngioma. Figure 4 shows the forest plots for craniopharyngioma recurrence/progression in individuals with and without GHRT. The combined RR for GH use was 0.43 (95 % CI 0.28–0.67; $I^2 = 31.2$ %, $p$ for heterogeneity = 0.225).

*GHRT for pituitary adenomas*

Four studies [5, 19, 20, 22] assessed the relationship between GHRT and risk of recurrence/progression in pituitary adenomas. The cumulative estimated risk associated with GH use was 0.85 (95 % CI 0.65–1.11; $I^2 = 16.6$ %, $p$ for heterogeneity = 0.309). For NPFA, the risk was 0.93 (95 % CI 0.70–1.25; $I^2 = 0.0$ %, $p$ for heterogeneity = 0.403) (Fig. 4).

*GHRT for brain tumors*

As shown in Fig. 5, the combined RR for medulloblastoma was 0.27 (95 % CI 0.17–0.42; $I^2 = 3.7$ %, $p$ for heterogeneity = 0.374). RRs for ependymoma and astrocytoma were 0.87 (95 % CI 0.52–1.47; $I^2 = 0.0$ %, $p$ for heterogeneity = 0.536) and 0.51 (95 % CI 0.29–0.93; $I^2 = 0.0$ %, $p$ for heterogeneity = 0.675), respectively. Ependymoma and astrocytoma were part of glioma, and the pooled RR for glioma was 0.64 (95 % CI 0.45–0.90; $I^2 = 22.8$ %, $p$ for heterogeneity = 0.274).

### Sensitivity analysis and publication bias

For sensitivity analysis, we left out each of the studies, in turn, to investigate the influence of a single study on the overall risk estimation. In Fig. 6, the corresponding RRs for GHRT versus no-GHRT were not significantly altered. The Begg's funnel plot showed that the RR values were symmetrical. The results from the Egger's test suggested that there was no pronounced publication bias ($p$ for Egger's test of all types of intracranial tumors, and tumors in children were 0.453 and 0.121, respectively).

## Discussion

While hypothalamus and pituitary axis were blocked or broken because of tumor, surgical resection, radiotherapy, and GHD occurred with serious clinical symptoms, such as increased morbidity. GH was injected to balance the endocrine system. However, infused GH raised the serum

**Table 1** Characteristics of studies included in the meta-analysis

| References | Ages (years) | Cases/controls | Follow-up period (years) | GH therapy period (years) | Recurrence/ progress diagnosis | Intracranial tumor types | Study quality |
|---|---|---|---|---|---|---|---|
| Arslanian et al. [23], USA | NR (C) | 8/24 | 5.5 | NR | CT | Craniopharyngioma, germinoma, medulloblastoma, glioma, dermoid, retinoblastoma, metastatic rhabdomyosarcoma, chromophobe adenomas | 6 |
| Clayton et al. [24], Norway | 10.8 ± 2.2 | 13/21 | NR | NR | NR | Medulloblastoma, glioma | 6 |
| Ogilvy-Stuart et al. [25], UK | <14.4 | 47/160 | 5.1 | NR | NR | Medulloblastoma, glioma | 6 |
| Swerdlow et al. [14], UK | <16 | 179/910 | 6.4[a]<br>4.5[b] | NR | NR | Medulloblastoma, glioma, others | 8 |
| Packer et al. [15], Canada | <15 | 545 | 5 | NR | NR | Medulloblastoma | 7 |
| Sklar et al. [16], USA | <17.2 | 172/1489 | 6.2 | 4.6 | NR | Medulloblastoma, glioma | 8 |
| Hatrick et al. [17], UK | NR | 47/28 | NR | 3.4 | CT MRI | Pituitary tumors, craniopharyngioma, meningioma | 7 |
| Karavitaki et al. [18], UK | 17.6 ± 14.3[a]<br>38.8 ± 16.8[b] | 32/53 | 10.8 ± 9.2[a]<br>8.3 ± 8.8[b] | 6.3 ± 4.6 | CT MRI | Craniopharyngioma | 8 |
| Buchfelder et al. [19], Germany | NR | 55/55 | 5 | 8.2 ± 6.7 | MRI | Pituitary adenomas | 8 |
| Olsson et al. [20], Sweden | 49.6 ± 12.8[a]<br>51.6 ± 12.0[b] | 121/114 | 9.9 ± 3.9<br>10.1 ± 4.4 | 10 ± 4 | CT MRI | Pituitary adenomas | 7 |
| Arnold et al. [5], UK | 53.7 ± 14.6[a]<br>56.2 ± 14.0[b] | 23/107 | 6.8 ± 4.2 | 4.6 ± 2.5 | CT MRI | Pituitary adenomas | 7 |
| Rohrer et al. [21], Germany | <17.5 | 44/59 | 7.5[a]<br>4.5[b] | NR | NR | Craniopharyngioma, medulloblastoma, ependymoma | 8 |
| Mackenzie et al. [6], UK | 33[a]<br>29[b] | 110/110 | 14.5[a]<br>15[b] | 8[a]<br>NR[b] | CT MRI | Pituitary adenomas, craniopharyngioma, intracranial neoplasm | 7 |
| Olsson et al. [7], Sweden | 25.1 ± 16.4[a]<br>32.3 ± 16.9[b] | 56/70 | 13.6 ± 5.0[a]<br>13.4 ± 7.8[b] | 13.6 ± 5.0 | CT MRI | Craniopharyngioma | 7 |
| Hartman et al. [22], USA | NR | 1309/339 | 2.3 ± 1.4[a]<br>2.3 ± 1.6[b] | 0.5–1 | NR | Pituitary adenomas, craniopharyngioma. others | 6 |

*CT* computed tomography, *F* female, *MRI* magnetic resonance imaging, *M* male, *NR* not reported

[a] Case group

[b] Control group

concentration of insulin-like growth factors-1 (IGF-1), which stimulated cell proliferation and inhibited apoptosis [27].

In the analysis of association between GHRT and GH-deficient intracranial tumors, results have indicated that GHRT was correlated with a decrease risk of tumor recurrence/progression. In the subgroup analyses, decreased risks were also obtained from craniopharyngioma, medulloblastoma, astrocytoma, and glioma. Irrelevant risks of tumor recurrence/progression were acquired from pituitary adenomas, NFPA, and ependymoma. However, the fluctuation in serum levels of GH and IGF-1 was observed in neoplastic disease, which might affect tumor progression [28]. In addition, Renehan et al. conducted a

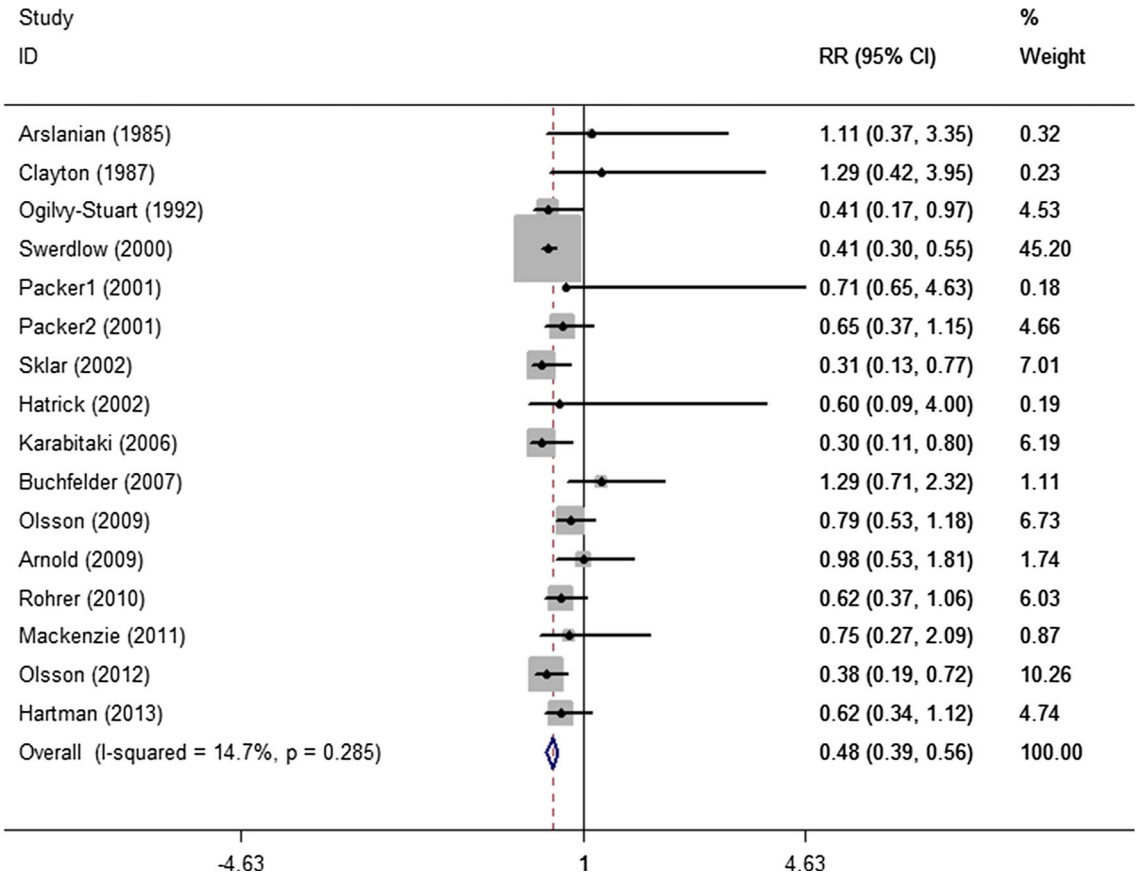


**Fig. 2** Forest plot of GHRT and tumor recurrence/progression in GH-deficient intracranial tumors

meta-regression analysis and demonstrated that high level of IGF-1 contributed to carcinogenesis in prostate, colorectal, and premenopausal breast cancers [29]. However, the results from intracranial tumors treated with GH indicated that GHRT was not associated with increased risk of recurrence/progression. During the period of GH treatment, the dose of GH was adjusted regularly depending on serum level of IGF-1 [5]. Thus, in patients treated with GH, the level of GH was elevated in accordance with the normal reference levels of IGF-1. Berg et al. confirmed that IGF-1 levels were influenced by several factors other than GH [30]. GH was found to induce high levels of IGF-1 in many malignancies [31, 32]. In our meta-analysis, most of tumors were benign. Renehan et al. also demonstrated that high-normal levels of IGF-1 had no influence on postmenopausal and lung cancer [29]. From this inconformity, GH might promote the progression of some of the tumors, but not all. It was undeniable that heterogeneity resulted in varied effects of tumors on same interventions.

More detailed information on age, which was major risk factor for tumors, was taken into consideration. Results have confirmed that GHRT in children decreased the risk of tumor recurrence/progression (RR 0.44, 95 % CI 0.34–0.54). No sufficient evidence from the studies indicated that GH promoted the progression of intracranial tumors [14, 16, 25]. Ergun-Longmire et al. performed a retrospective study with 361 survivors treated with GH, and confirmed that these survivors were easier to trap in second neoplasms (RR 3.21) [3, 16]. Recent studies have reported no statistically significant increase in the risk of occurrence of the CNS subsequent neoplasms with GH exposure [33]. Equivocal conclusion on the issue was addressed by assessing the current resource. CNS tumors are a heterogeneous family of neoplasms that differ in tissue origins, degree of apoptosis, amplification, and invasive potential, especially during prognosis. Segregation of varied tumors and randomized controlled trials would be beneficial to confirm the potential relationship between GH treatment and second neoplasms.

Most of our studies included were retrospective in nature. Thus, some of the influencing factors were unavoidable. Additionally, years of follow-up were not equal or were too short. The optimum duration of recurrence/progression was probable beyond the follow-up period. The segregation of varied tumors with enough patients was required. Moreover, selection and publication bias in the

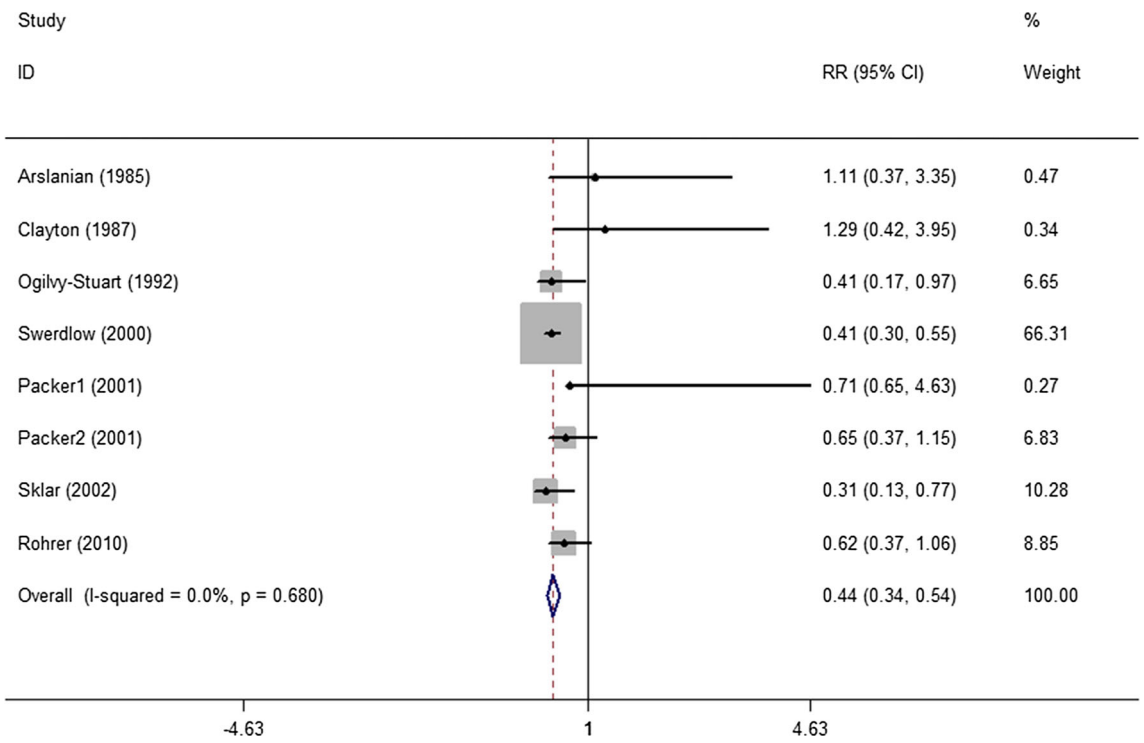


**Fig. 3** Forest plot of GHRT and tumor recurrence/progression in children

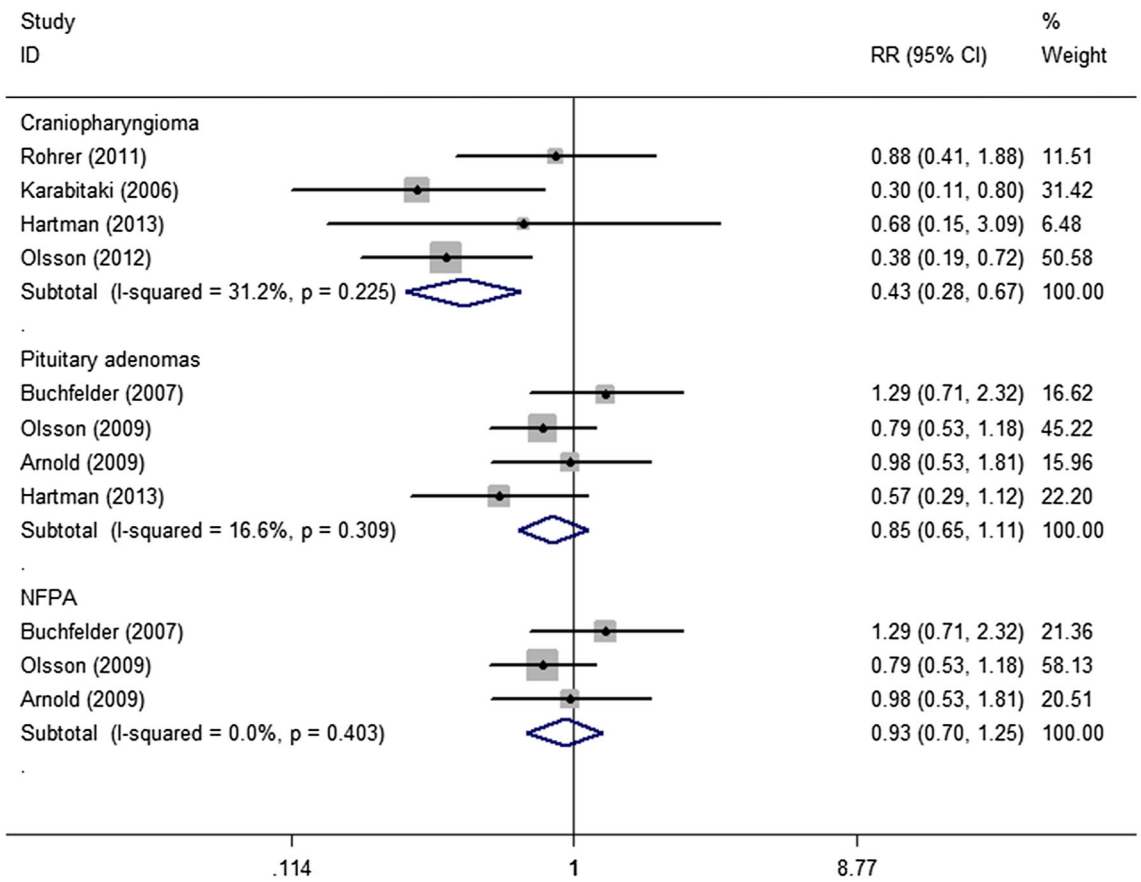


**Fig. 4** Forest plot of GHRT and tumor recurrence/progression in craniopharyngioma, pituitary adenomas, and NFPA

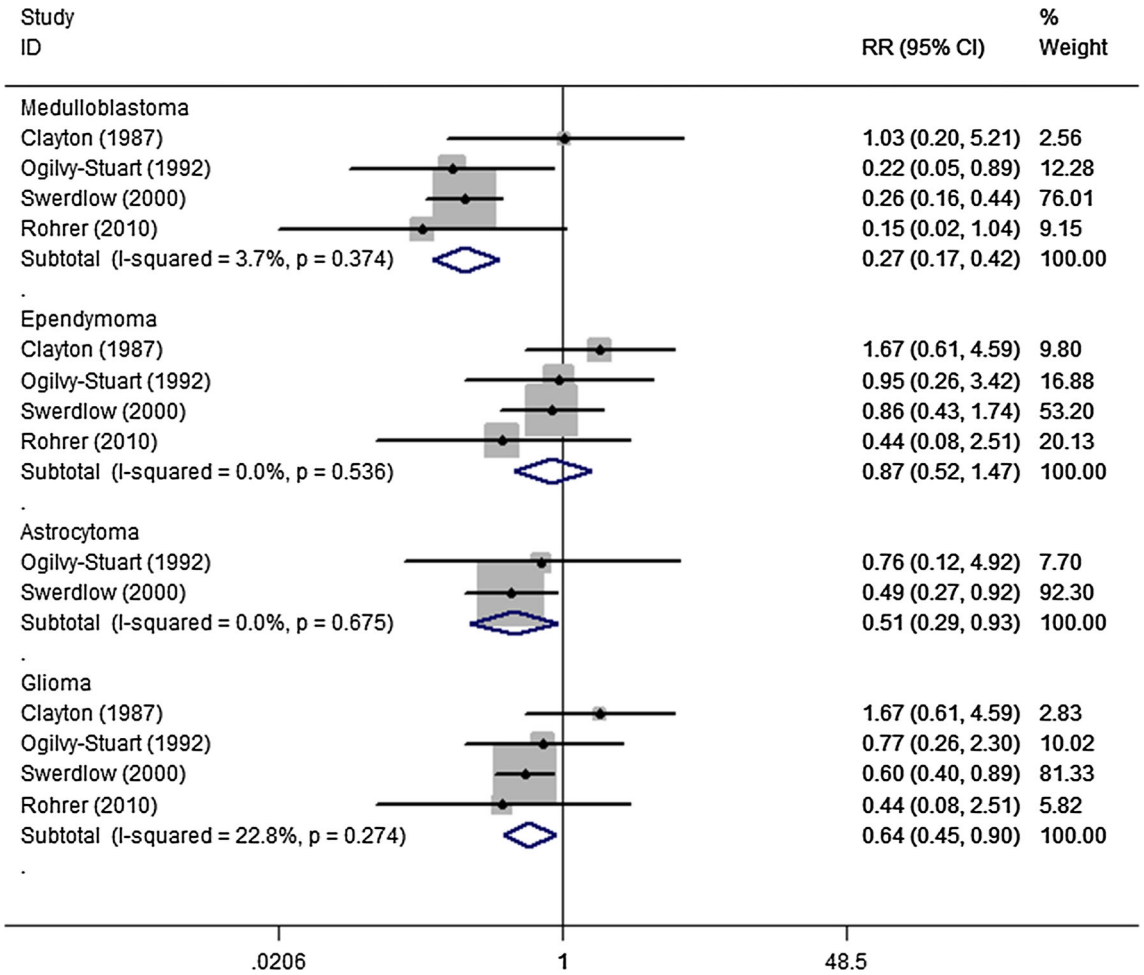


**Fig. 5** Forest plot of GHRT and tumor recurrence/progression in medulloblastoma astrocytoma, and glioma

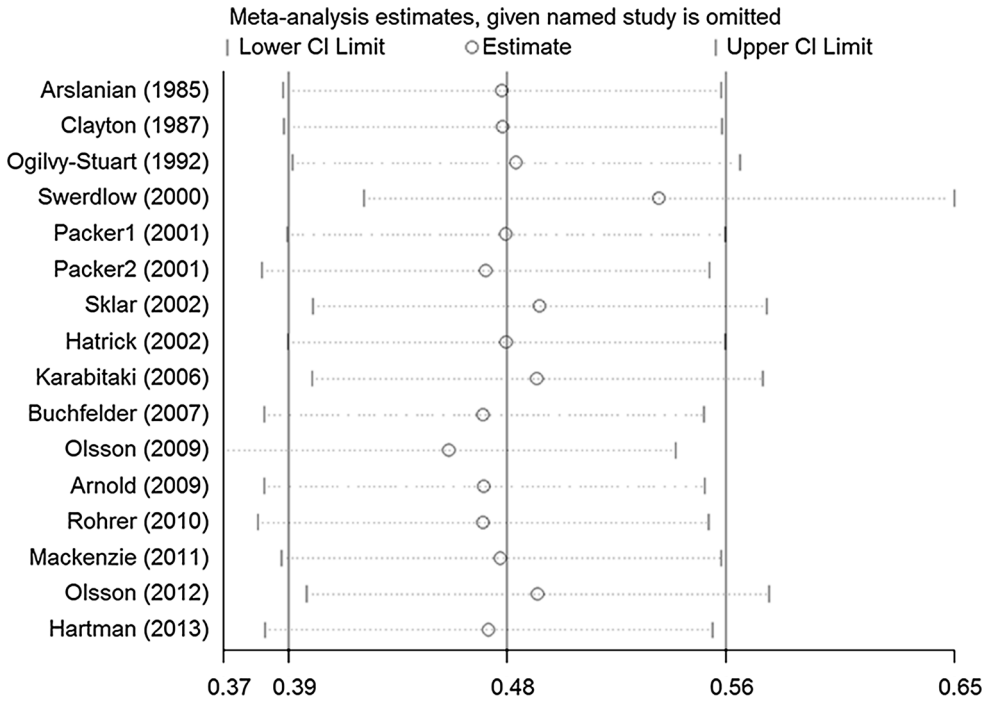


**Fig. 6** Sensitivity analyses for GHRT and no-GHRT for intracranial tumors

meta-analysis because of non-random samples and unpublished literatures.

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**Conflict of interest** The authors have declared that no competing interests exist.



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