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ORIGINAL ARTICLE

# Progression of pituitary tumours: impact of GH secretory status and long-term GH replacement therapy

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## Abstract

**Background** Most patients treated for hypothalamic–pituitary tumours develop GH deficiency. Long-term GH replacement treatment in adults with a previous history of hypothalamic–pituitary tumour could represent a concern about increasing the risk of tumour enlargement or recurrence.

**Purpose** To assess the progression risk of hypothalamic–pituitary tumours according to the GH secretory status (normal GH secretion, non-treated and treated GH deficiency). and determine the predictors of neoplasm recurrence.

**Methods** We retrospectively reviewed 309 patients with tumours of the hypothalamic–pituitary region (294 subjects underwent neurosurgery while 81 radiotherapy) who were followed for 9.9 ± 8.3 years.

**Results** Out of 309 patients, 200 were affected by severe GH deficiency; 90 of these underwent GH therapy. The tumour progression rate did not differ among GH-sufficient, not-treated and treated GH-deficient patients (16.5%, 16.4%. and 10.0%, respectively). In a multivariate analysis, previous radiotherapy (HR 0.12, CI 0.03–0.52, $p < 0.005$) and residual tumour (HR 8.20, CI 2.38–28.29, $p < 0.001$) were independent predictors of recurrence. After controlling for multiple covariates, the tumour recurrence risk in GH-sufficient and GH-treated patients was similar to that observed in not-treated GH-deficient patients.

**Conclusions** With limitations of retrospective analysis, GH therapy is not associated with an increased progression rate of tumours of the hypotalamic–pituitary region during long follow-up, thus supporting the long-term safety of GH treatment. The only predictors of tumour recurrence appear to be the presence of residual disease and the lack of radiotherapy.

**Keywords** GH deficiency · GH replacement · Pituitary tumours · Recurrence · Progression

## Introduction

Pituitary tumours and their treatments are the main causes of acquired hypopituitarism and severe GH deficiency (GHD) in adults, which occurs in up to 80% of patients in the postoperative phase [1].

The GHD syndrome in adults has been recognized since the early 1990s [2]. It includes adverse effects on body composition, bone mineral density, cardiovascular performance, psychological well-being, and quality of life [2–4]. GH replacement therapy has been shown to improve most of these abnormalities [5–7]. While the safety of GH replacement therapy in short-term clinical trials is without doubt, there are still unanswered questions on the long-term. Particularly, there is concern over the mitogenic activity of GH that could increase the rate of tumour recurrence or enlargement in patients with or without residual tumour.

The evidence linking GH to cancer gets progressively weaker when moving from in vitro to in vivo animal models, epidemiological studies, and clinical studies on GH-treated patients. The 2016 position paper from the European Society of Paediatric Endocrinology, the Growth Hormone Research Society, and the Pediatric Endocrine Society stated that the data concerning the neoplastic risk during GH therapy in GH-deficient adults are insufficient to draw any conclusions in this regard [8].

Only a few studies have been published on the long-term effects of GH replacement therapy on pituitary adenoma recurrence or enlargement [9–21]. Limited data cannot

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provide strong evidence on the long-term safety of GH therapy in patients with previous tumours of the hypothalamic–pituitary region [20]. In other studies, the issue of GH replacement safety in patients with or without pituitary residual tumour remained unresolved, due to methodological limitations (a few number of enrolled patients [9–13, 15, 16, 18], heterogeneous diagnoses [11–15], low usage of magnetic resonance imaging (MRI) at follow-up [13, 15, 18], a relatively short observation time [9–15, 19, 20], lack of comparable untreated patients [11–13, 19], inadequate adjustment for potential confounding factors like radiotherapy [11, 13, 15, 16]).

In order to explore the long-term safety of GH replacement therapy, we retrospectively reviewed data from patients followed for hypothalamic–pituitary tumours at our clinic. Our aim was to assess whether GH replacement therapy is associated with an increased risk of tumour progression during long follow-up and determine the predictors of neoplasm recurrence.

## Materials and methods

We retrospectively reviewed data from 309 (152 men, 157 women) out of 1842 patients with a history of tumours of the hypothalamic–pituitary region followed at our Center since 1982 (when the Neuroendocrine Unit was opened at our Center) to 2015 (end of data collection for the present study). We excluded pituitary adenomas under medical treatments like dopamine agonists, somatostatin analogues, and GH antagonist (792 patients), and ACTH secreting pituitary adenomas treated with bilateral adrenalectomy (8 patients) because of the confounding effect of these treatments on the tumor expansion risk. It was impossible to retrieve the radiographic follow-up in 308 patients and the hormonal data in 388 patients. Other causes of exclusion (37 subjects) were lack of informed consent or death at the time of enrollment. Out of the 309 included patients, 217 underwent neurosurgery (NS) only, 4 radiotherapy (RT) only, 77 NS plus RT. Eleven patients with expansive lesions of the hypothalamic–pituitary region never treated with NS or RT were included. Mean follow-up period was 9.9 ± 8.3 years (range 0.4-54 years). As per GHD guidelines [5, 22, 23], GHRH+ arginine test using the BMI cut-offs (GH peak ≤ 11.0 µg/l, ≤8.0 µg/l, and ≤4.0 µg/l in lean, overweight, and obese subjects, respectively) and/or insulin tolerance test (ITT) using a GH peak ≤ 3.0 µg/l were used as validated stimulatory tests for the diagnosis of GHD.

One hundred and nine patients (35.3%) were GH-sufficient (GHS) while 200 affected by severe GHD; out of the total 309 subjects, 110 (35.6%) were not GH replaced (GHNT) while 90 (29.1%) were on GH replacement therapy (GHT), with a mean GH dose of 1.74 ± 1.33 mg/week (range: 0.35–8.4 mg/week) at the last follow-up visit. GHT were based on GH dose titration against the serum IGF-I levels, maintained between the median and the age-related upper limit of normal.

**Table 1** Patients' clinical characteristics

| | Number (%) |
|---|---|
| Patients number | 309 |
| Gender | |
| Male | 152 (49.2%) |
| Female | 157 (50.8%) |
| Age at diagnosis (mean ± SD, years) | 47.2 ± 17.7 |
| Histology | |
| Pituitary adenomas[a] | 239 (77.4%) |
| Craniopharyngiomas or Rathke's cystic lesions | 46 (14.9%) |
| Meningiomas | 10 (3.2%) |
| Other pituitary lesions | 14 (4.5%) |
| Follow-up (mean ± SD, years) | 9.9 ± 8.3 |
| Treatment | |
| NS | 217 (70.2%) |
| RT | 4 (1.3%) |
| NS + RT | 77 (24.9%) |
| None | 11 (3.6%) |
| GHD | |
| Yes | 200 (64.7%) |
| No | 109 (35.3%) |
| GH treatment | |
| Yes | 90 (45.0%) |
| No | 110 (55.0%) |

*NS* neurosurgery, *RT* radiotherapy, *GHD* GH deficiency

[a]Clinically non-functioning pituitary adenoma and gonadotrophinoma = 161 patients; ACTH secretory or ACTH immunohistochemically positive pituitary adenoma = 36 patients; GH secretory or GH immunohistochemically positive pituitary adenoma = 27 patients; PRL secretory or PRL immunohistochemically positive pituitary adenoma = 12 patients; TSH secretory or TSH immunohistochemically positive pituitary adenoma = 3 patients

The percentage of patients who had zero, one, two, three, or four pituitary hormone deficiencies other than GH was 25.2%, 14.5%, 12.9%, 34.3%, and 12.9% respectively. If necessary, patients received thyroxine, sex steroids, and glucocorticoids replacement.

Patients' clinical characteristics are reported in Table 1.

Serial MRI surveillance was performed to detect any recurrence.

Tumour progression was radiologically defined as new onset of a detectable tumour after total removal or regrowth of a pre-existing residual tumour, irrespective of the extent and clinical consequence of the progression. Recurrence and residual tumour enlargement were considered together as end-point for analysis of association with other tumoural characteristics.

**Table 2** Differences among the three groups of patients according to GH secretory status

| | GHS ($N=109$) | GHT ($N=90$) | GHNT ($N=110$) | $p$-value |
|---|---|---|---|---|
| Age at diagnosis (years), mean ± SD | 50.2 ± 15.5 | 40.8 ± 18.5 | 51.8 ± 16.2 | 0.0002 |
| Gender (F) (%) | 65.1 | 46.7 | 40 | 0.001 |
| Histology | | | | |
| Pituitary adenomas (%) | 80.7 | 66.7 | 82.7 | 0.018 |
| Craniopharyngiomas or Rathke's cystic lesions (%) | 11.9 | 26.7 | 8.2 | |
| Dimension at diagnosis[a] (cm), mean ± SD | 2.4 ± 1.5 | 2.5 ± 2.3 | 3.4 ± 4.4 | 0.002 |
| Diameter at diagnosis ≥ 1 cm (%) | 89.6 | 87.5 | 94.5 | 0.20 |
| Neurosurgery (%) | 92.7 | 97.0 | 95.5 | 0.22 |
| Radiotherapy (%) | 11.0 | 35.6 | 33.6 | 0.0001 |
| Tumour rest at baseline (%) | 53.2 | 43.3 | 64.6 | 0.011 |
| Ki-67[b], mean ± SD | 3.7 ± 3.2 | 3.6 ± 2.4 | 3.0 ± 2.6 | 0.44 |
| No other pituitary deficits besides the possible GHD (%) | 57.4 | 5.6 | 10.0 | 0.0001 |
| 3 or 4 pituitary deficits besides the possible GHD (%) | 11.1 | 78.9 | 56.4 | |
| IGF-I SDS[c], mean ± SD | 0.05 ± 1.37 | −0.02 ± 0.90 | −0.99 ± 0.76 | 0.0001 |
| Time of GH replacement therapy[d] (months), mean ± SD | N.A. | 96.4 ± 50.7 | N.A. | |
| Follow-up (months), mean ± SD | 83.2 ± 70.6 | 178.1 ± 111.5 | 106.9 ± 92.1 | 0.0001 |
| Tumour progression (%) | 16.5 | 10.0 | 16.4 | 0.33 |

*GHS* GH-sufficient patients, *GHT* GH-deficient patients on GH replacement therapy, *GHNT* GH-deficient patients not on GH replacement therapy

[a]Analysis conducted on 233 patients

[b]Analysis conducted on 90 patients

[c]Analysis conducted on 220 patients

[d]Analysis conducted only in GHT patients

For the present analysis, the date of the last available MRI was recorded as the last visit and the date of tumour recurrence was the date of the first recorded event.

Written informed consent was obtained from all the patients. The study was approved by the Ethics Committee at the University of Turin Hospital, Italy.

## Biochemical methods

Serum GH levels (μg/l) were measured in duplicate by IRMA method (hGH-CTK IRMA, DIASORIN Biomedica, Saluggia, Italy). The sensitivity of the assay was 0.04 μg/l. The inter- and intra-assay coefficients of variation (CV) were 8.6–12.3% and 4.2–6.2%, respectively. Serum IGF-I levels (μg/l) were measured in duplicate by RIA method (DIAsource ImmunoAssays, Belgium) after acid–ethanol extraction to avoid interference by binding proteins. The sensitivity of the method was 0.3 μg/l. The inter- and intra-assay CV were 10–12.6% and 3.8–13.9%, respectively.

## Statistical methods

All variables measured are presented as mean ± SD. Comparisons between different groups of GH secretory status (GHS, GHT, GHNT) were performed using Student's $t$-test or $\chi^2$ test.

Kaplan–Meier survival curves were obtained for each group to describe the cumulative incidence of tumour progression. The log-rank test was used to compare survival times between subgroups.

The Cox proportional hazards model was used to analyse the impact of the confounding variables on tumour's recurrence/expansion in univariate and multivariate analysis.

# Results

Stratifying for GH secretory status, there was a significant difference among the three groups in age at diagnosis,

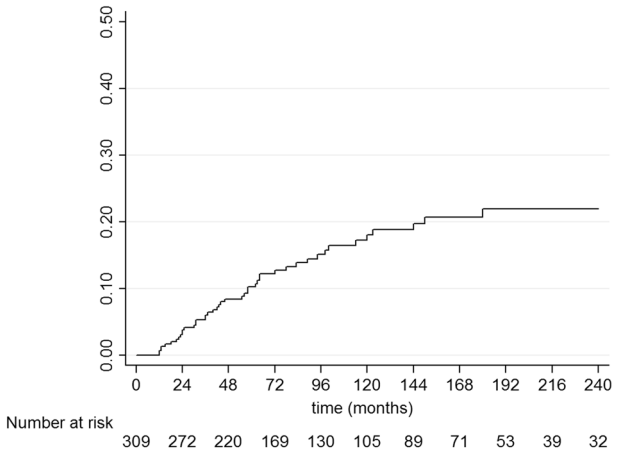


**Fig. 1** Cumulative incidence of tumour progression in 309 patients with history of a tumour of the hypothalamic–pituitary region

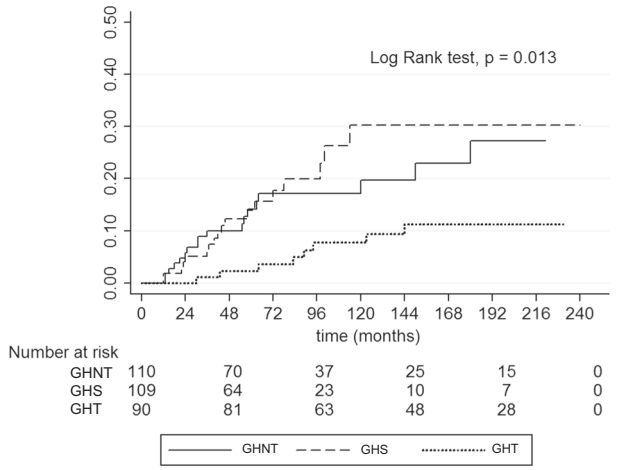


**Fig. 2** Cumulative incidence of tumour progression in 309 patients with history of a tumour of the hypothalamic–pituitary region in function of the GH secretory status (GHNT GH-deficient patients not on GH replacement therapy, GHS GH-sufficient patients, GHT GH-deficient patients on GH replacement therapy)

gender, tumour histology and dimension, residual tumour, previous RT, number of other associated pituitary deficits, IGF-I SDS, and duration of follow-up (Table 2).

Forty-five patients out of 309 (14.6%) developed tumour progression. The cumulative incidence of progression is displayed in Fig. 1. The progression rate was not different between GHNT (16.4%) and GHS (16.5%) and notably was not affected by GH treatment (GHT vs GHNT: 10.0% vs 16.4%) (Table 2). However, when analyzed in function of time, the GH secretory status was significantly associated to progression ($p < 0.013$), showing a lower incidence in GHT. Kaplan–Meier estimates stratified for GH secretory status are reported in Fig. 2. GHT with progression did not differ from GHT without progression in terms of either IGF-I SDS ($0.50 \pm 0.80$ vs $-0.02 \pm 1.12$, $p = 0.82$) or GH dose ($1.59 \pm 0.84$ vs $1.75 \pm 1.37$ mg/week, $p = 0.74$).

**Table 3** Univariate analysis of factors affecting tumour progression

| | HR | 95% CI | *p*-value |
|---|---|---|---|
| GH status | | | |
| GHS vs GHNT | 1.20 | 0.62–2.31 | 0.59 |
| GHT vs GHNT | 0.39 | 0.17–0.87 | 0.02 |
| Age at diagnosis (years) | 1.02 | 1.00–1.04 | 0.02 |
| Gender (F) | 0.50 | 0.27–0.94 | 0.003 |
| Histology | | | |
| Pituitary adenomas | 1.15 | 0.58–2.27 | 0.69 |
| Dimension at diagnosis | | | |
| Diameter at diagnosis[a] (cm) | 1.04 | 0.96–1.12 | 0.38 |
| Diameter at diagnosis ≥ 1 cm | 1.32 | 0.41–4.27 | 0.64 |
| Diameter at diagnosis[a] ≥ 3 cm | 2.05 | 1.06–3.97 | 0.003 |
| Neurosurgery | 0.23 | 0.11–0.54 | 0.001 |
| Radiotherapy | 0.29 | 0.12–0.70 | 0.006 |
| Tumour rest at baseline | 6.84 | 2.89–16.19 | 0.000 |
| Ki-67[b] | 1.03 | 0.86–1.23 | 0.77 |
| No. of pituitary deficits | 0.82 | 0.66–1.01 | 0.06 |
| IGF-I SDS[c] | 0.82 | 0.54–1.23 | 0.33 |
| GH dose[d] (mg/week) | 0.89 | 0.51–1.57 | 0.69 |

*GHS* GH-sufficient patients, *GHT* GH-deficient patients on GH replacement therapy, *GHNT* GH-deficient patients not on GH replacement therapy, *HR* hazard ratio, *CI* confidence interval

[a]Analysis conducted on 233 patients

[b]Analysis conducted on 90 patients

[c]Analysis conducted on 220 patients

[d]Analysis conducted only in GHT patients

Univariate analysis of several covariates indicated that age at diagnosis (HR 1.02, CI: 1.00–1.04, $p < 0.02$), tumour diameter greater than 3 cm (HR 2.05, CI: 1.06–3.97, $p < 0.003$), and presence of residual tumour (HR 6.84, CI: 2.89–16.19, $p < 0.000$) were positively associated with progression, while female gender (HR 0.50, CI: 0.27–0.94, $p < 0.003$), previous NS (HR 0.23, CI: 0.11–0.54, $p < 0.001$), and RT (HR 0.29, CI: 0.12–0.70, $p < 0.006$) were negatively associated (Table 3).

In a multivariate analysis, adjusting for multiple confounding factors that correlated with progression, GHT showed a similar tumour progression risk to that observed in GHS and GHNT (Table 4). Independent predictors (positive and negative, respectively) of tumour progression were the presence of tumour rest (HR 8.20, CI: 2.38–28.29, $p < 0.001$) and the previous RT (HR 0.12, CI: 0.03–0.52, $p < 0.005$).

## Discussion

GHD frequently occurs in patients with hypothalamic–pituitary tumours as a consequence of either

**Table 4** Multivariate analysis of factors affecting tumour progression

| | HR | 95% CI | *p*-value |
|---|---|---|---|
| GHS vs GHNT | 1.37 | 0.66–2.83 | 0.399 |
| GHT vs GHNT | 0.58 | 0.21–1.66 | 0.313 |
| Age at diagnosis | 1.00 | 0.98–1.02 | 0.763 |
| Gender (F vs M) | 0.75 | 0.37–1.55 | 0.441 |
| Dimension at baseline (≥3 cm vs <3 cm) | 1.71 | 0.83–3.51 | 0.144 |
| Neurosurgery (yes vs no) | 0.52 | 0.20–1.34 | 0.175 |
| Radiotherapy (yes vs no) | 0.12 | 0.03–0.52 | 0.005 |
| Tumour rest at baseline (yes vs no) | 8.20 | 2.38–28.29 | 0.001 |

Number of subjects: 233

Number of recurrences: 36

Time at risk: 19815 months

LR chi2(8) = 50.42

Log likelihood: −152.16805 Prob > chi2 = 0.0000

*GHS* GH-sufficient patients, *GHT* GH-deficient patients on GH replacement therapy, *GHNT* GH-deficient patients not on GH replacement therapy, *HR* hazard ratio, *CI* confidence interval

the tumour itself, its treatment, or both [1, 5, 22, 23]. GH therapy shows positive effects on clinical features associated with adult GHD [6, 7, 24–26]. However, it has been suggested that GH therapy may increase the risk of tumour recurrence or growth, despite mostly reassuring data available so far [5]. It is noteworthy that the reassuring data on this topic, mostly from the two main post-marketing surveillance databases, are burdened by an absolutely inadequate average duration of follow-up, as these neoplasms are characterized by indolent course [20].

In the present study including 309 patients followed for hypothalamic–pituitary tumours, the rate of recurrence or enlargement of pituitary neoplasm did not differ between subjects with or without GHD and was not affected by GH therapy. Radiotherapy significantly decreased the risk of tumour progression. Residual tumour was associated with an increased risk of tumour progression.

Growth hormone raises serum concentrations of IGF-I, which not only stimulates cell proliferation but also inhibits apoptosis. It has been recognized that the combination of these mitogenic and antiapoptotic effects can have a profound impact on tumour growth [27, 28]. A number of epidemiologic studies have consistently shown that higher circulating levels of IGF-I, even within the normal range, are associated with an increased risk of several common solid cancers, including breast, prostate, lung, and bowel [29]. On the other hand, the reduction in IGF-I levels has also been shown to reduce the incidence of colorectal tumours [28, 30] and delay the onset of chemically or genetically induced mammary tumours [28, 31]. Animal studies involving manipulation of the GH/IGF-I axis also add compelling support to the epidemiological studies. Transgenic mice overexpressing human growth hormone or IGF-I show an increased incidence of breast cancer [28, 32]. The evidence linking GH to cancer gets progressively weaker when moving from in vitro to in vivo animal models, epidemiological studies, and clinical studies on GH-treated patients. In this perspective, our unadjusted data with Kaplan–Meier estimates showed an even lower incidence of tumour progression in GHT patients. Particularly, the rate of progression of the pituitary tumour did not differ between subjects with and without GHD, while GHT patients showed an unadjusted lower risk of tumour recurrence or remnant enlargement when compared to GHNT. Moreover, IGF-I SDS values were not related to progression of the lesion, and there was not significant difference in IGF-I SDS between GHT patients with and without tumours progression. These last observations indirectly suggest the absence of a relationship between the GH secretory status, GH replacement therapy, and the risk of tumour recurrence or residual tumour enlargement.

Although the non-randomized nature of this and previous studies [9–21] could have led to bias, including the biased allocation to interventions based on baseline patient's characteristics, all these studies suggest that GH therapy does not increase tumour progression risk.

Radiotherapy significantly decreased the risk of tumour progression in the present study, even after adjusting for potential confounders. Similar findings have been reported by other groups [19, 21, 33–35].

The presence of residual tumour at baseline significantly increased tumour progression risk in the present study. This association was not influenced by confounding variables. Similar results have also been observed by others [10, 15, 17, 19].

The limitations of our study include its retrospective and non-randomized nature. To date there have been no randomized placebo-controlled studies of GH treatment on long-term pituitary tumours recurrence. Available data are limited to non-randomized studies such as ours. As previously mentioned, it may be argued that selection bias have been introduced in including subjects into the GH-treated group. In order to minimize this, adjustment for putative prognostic factors was undertaken. Nonetheless, the possibility of GH therapy being offered to subjects whose tumours were considered less aggressive cannot be excluded.

On the other hand, a strength of our study is the long follow-up period, particularly in the GHT group. While having a significantly longer follow-up time compared to GHNT and GHS patients, GHT subjects present an unadjusted lower recurrence risk, suggesting that the lower risk of progression cannot be mediated by a brief follow-up time observed in previous studies [10–15, 19].

Finally, to the best of our knowledge, this is the first study exploring the progression rate of hypothalamic–pituitary tumours based on GH secretory status, thus comparing treated and non-treated GH-deficient patients with GH-sufficient subjects.

In summary, the findings of this retrospective study indicate that neither the GH secretory status nor GH replacement therapy seems to influence the risk of tumour progression, contributing to the evidence for long-term GH therapy safety.

More robust conclusions may only be generated by large randomized prospective studies. Unfortunately, this type of study does not seem feasible due to practical and ethical constraints, especially considering the need for long follow-up periods (>10 years) [36] considering the indolent nature of lesions often associated with GHD. However evidence on GH therapy security so far seems reassuring.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

**Research involving human participants and/or animals** All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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