Chapter 5

Tumor recurrence or regrowth in adults with nonfunctioning pituitary adenomas using GH replacement therapy

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Abstract

Context
Growth hormone replacement therapy (GH-RT) is a widely accepted treatment in growth hormone deficient (GHD) adults with nonfunctioning pituitary adenomas (NFPAs). However, some concerns have been raised about the safety of GH-RT, because of its potentially stimulating effect on tumor growth.

Objective
The aim of this study was to evaluate tumor progression in NFPA patients using GH-RT.

Design, Setting, and Patients
From the Dutch National Registry of Growth Hormone Treatment in Adults, a nationwide surveillance study in severe GHD adults (1998 - 2009), all NFPA patients with ≥ 30 days of GH-RT were selected (n = 783). Data were retrospectively collected from the start of GH-RT in adulthood (baseline).

Main Outcome Measure
Tumor progression, including tumor recurrence after complete remission at baseline and regrowth of residual tumor.

Results
Tumor progression developed in 12.1% of the patients after a median time of 2.2 (0.1 - 14.9) years. Prior radiotherapy decreased tumor progression risk compared to no radiotherapy (hazard ratio [HR] = 0.16, 95% confidence interval [CI], 0.09 - 0.26). Analysis in 577 patients with available baseline imaging data showed that residual tumor at baseline increased tumor progression risk compared to no residual tumor (HR = 4.5, 95% CI, 2.4 - 8.2).

Conclusions
The findings in this large study were in line with those reported in literature and provide further evidence that GH-RT does not appear to increase tumor progression risk in NFPA patients. Although only long-term randomized controlled trials will be able to draw firm conclusions, our data support the current view that GH-RT is safe in NFPA patients.
Introduction

Clinically nonfunctioning pituitary adenomas (NFPAs) are relatively common benign tumors of the anterior pituitary gland. These tumors frequently present with symptoms and signs of tumor mass effects on adjacent structures due to the absence of features of pituitary hormone hypersecretion.

The treatment of choice for NFPAs usually is transsphenoidal surgery. The main goals of surgery include complete removal or debulking of the tumor and relieve of tumor mass effects on surrounding structures. Pituitary radiotherapy is an additional treatment option, which may be considered for instance after incomplete surgical resection. After surgery alone, reported rates of tumor recurrence or enlargement range between 6% and 46%. After radiotherapy, recurrence rates of approximately 10% or less have been reported, indicating that adjuvant radiotherapy may improve local tumor control.

The treatment of a NFPA or the effects of the tumor itself often result in the development of hypopituitarism, including growth hormone deficiency (GHD). The presence of GHD has been reported in up to 85% of NFPA patients. Adult GHD is, amongst others, associated with adverse changes in cardiovascular risk factors, body composition, bone mineral density, and quality of life. Because growth hormone replacement therapy (GH-RT) has shown beneficial effects on most of these features, many adult GHD patients are nowadays treated with GH-RT. However, some concerns have been raised about the safety of GH-RT in patients with a NFPA, because of the possible stimulating effect of growth hormone (GH) on tumor recurrence or regrowth. Basic research indicates that GH and insulin-like growth factor 1 (IGF-1), through regulation of cell proliferation and apoptosis, may be involved in tumor development and growth. In addition, acromegaly, characterized by elevated GH and IGF-1 concentrations, has been associated with an increased risk of colonic neoplasia. Some epidemiological studies, although not all, suggest that even high-normal IGF-1 concentrations within the age- and gender-adjusted reference range may increase the risk of prostate, colorectal or breast cancer. Studies investigating tumor regrowth or recurrence in pituitary adenoma (PA) patients using GH-RT are relatively scarce in literature. Interpretation and comparison of these studies is difficult due to differences in defining tumor growth, follow-up times and study populations; for example, some studies included patients with various types of PAs. Despite these limitations, reported data so far seem to be reassuring with regard to effect of GH-RT on tumor regrowth or recurrence, but with the caveat that larger, long-term follow-up studies are needed. To date, essentially three studies have assessed the influence of GH-RT on tumor growth in NFPA patients specifically.
In these studies, tumor regrowth or recurrence did not seem to be affected by GH-RT. However, study population sizes were relatively small.

The aim of the present study, therefore, was to evaluate tumor regrowth or recurrence in a large cohort of NFPA patients with GH-RT, using data from the Dutch National Registry of Growth Hormone Treatment in Adults, a nationwide long-term surveillance study in severe GHD adult patients.

Subjects and methods

Study population

In 1998, the Dutch National Registry of Growth Hormone Treatment in Adults was initiated by the Dutch Ministry of Health to gain more insight into the long-term efficacy, safety and costs of GH-RT in GHD adults. From that time on, reimbursement of GH-RT costs was only granted after approval of the diagnosis of severe GHD by an independent board of endocrinologists as well as inclusion of anonymized patient data into the registry. All patients were informed by their attending physician. Severe GHD was diagnosed according to the Growth Hormone Research Society consensus guidelines. Data collection, patient characteristics, and test procedures have previously been described in more detail. Until data closure in 2009, 2891 severe GHD adults were registered.

For the present study, all severely GHD patients with a (treated) NFPA (n = 893) were selected. Patients with < 30 days of GH-RT were excluded (n = 110). Compared to those included in the study (n = 783), excluded patients had a similar age at entry into the registry (p = 0.27), gender (p = 0.69), and onset of GHD (p = 1.00). Patients who were lost to follow-up, who died, or who stopped GH-RT were censored in the analyses. Tumor progression leading to discontinuation of GH-RT was included in the analyses.

Measurements

The data of all registered patients were collected (bi-) annually from medical records by specially trained monitors from the start of enrollment in the registry. When GH-RT had already been started before the first monitor visit, data were retrospectively retrieved. The anonymized collected data were checked for accuracy both before and after entry into the database. In 10% of the patients, data were collected twice by different monitors as an internal quality control.

Persons-years of treatment with GH-RT were calculated from the date of commencement with GH-RT in adulthood (baseline) until the date of last follow-up,
discontinuation of GH-RT, or death. The GH dose was titrated on an individual basis by the attending physician with the purpose of achieving and maintaining age- and gender-specific normalized IGF-1 SD scores. Changes in GH dosage were recorded, and the mean dose per patient was calculated as the cumulative dosage divided by the sum of GH-RT days.

The diagnosis of NFPA, made at the discretion of the attending physician, was verified at entry into the database, according to the collected data. Data regarding the treatment of the NFPA, such as number, type and timing of surgical procedures and radiotherapy, were collected. Other pituitary hormone deficiencies in addition to GHD were identified through recorded deficiencies and hormonal replacement therapies, based on diagnostic tests performed by the attending physicians, at the start of registration and during follow-up. These deficiencies were adequately substituted when appropriate. Smoking status and alcohol use were also recorded from the start of entry into the registry.

Data concerning relevant medical history, NFPA treatment, neuroradiological imaging and adverse events were searched and recorded thoroughly and coded for, amongst others, tumor progression. The definition of tumor progression included tumor recurrence in patients without detectable tumor at baseline as well as tumor regrowth in patients with detectable residual tumor at baseline, irrespective of the extent or clinical consequence of the tumor progression. The date of tumor progression was the date of the first recorded event. Cause and date of death were retrieved from medical records and death certificates from the Dutch Central Bureau of Statistics, as described previously.

Statistical analysis
Continuous variables were expressed as either mean (SD) or median (range), whereas categorical variables were expressed as number (percentage). The student’s t-test was used to compare normally distributed continuous variables, whereas the Mann-Whitney test was used for skewed variables. Categorical variables were compared with the Chi-square or Fisher’s exact test.

Kaplan-Meier survival curves were used to describe the progression-free survival. Cox proportional hazard analysis was used to evaluate the risk of developing tumor progression in patients who had received prior radiotherapy compared with those who had not received prior radiotherapy and in patients with residual tumor at baseline compared with patients without residual tumor at baseline, respectively. In all analyses, time was measured from start of GH-RT in adulthood until the date of first tumor progression, last follow-up, or death, whichever occurred first. Assumptions of proportional hazards were tested by log-minus-log plots and interaction terms. To
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Adjust for the potentially confounding effects of age at baseline and gender, these variables were included in the Cox proportional hazard models. Other potentially confounding variables, including age at NFPA diagnosis, extension of pituitary deficiency (isolated GHD or multiple pituitary hormone deficiencies), pituitary surgery, radiotherapy and history of tumor progression were examined by adding them separately to the age- and gender-adjusted models. Variables that gave a change in the regression coefficient of > 10% were included in the model. All continuous variables were individually checked for linearity with the outcome variable and, in case of nonlinearity, divided in categories. Potential effect modification by gender was examined by adding an interaction term to the age- and gender-adjusted model. In case of a p-value < 0.10, analyses were stratified for gender.

All statistical analyses were performed using the statistical software package IBM SPSS Statistics version 20 (SPSS Inc). Two-sided p-values of ≤ 0.05 were considered significant.

Results

Baseline characteristics

Severe GHD was diagnosed with a GH stimulation test in 702 (89.7%) of the 783 patients included in the study (54.8% insulin tolerance test, 23.4% GH-releasing hormone [GHRH]/arginine test, 13.4% arginine test, 8.0% GHRH test, 0.4% other). In 75 (9.6%) patients, the diagnosis was based on IGF-1 concentrations ≤ 2 SD in combination with two or more additional pituitary hormone deficiencies. In the remaining cases, either retesting was considered unnecessary because of childhood onset GHD due to evident hypothalamic pituitary disease (n = 2 [0.3%]) or the diagnostic procedure was unknown (n = 4 [0.5%]).

Characteristics of the total study population and of patients with and without tumor progression during follow-up are shown in table 1. In operated patients, the surgical approach was transsphenoidal in 580 (79.9%) of the cases, transcranial in 118 (16.3%), and unknown in 28 (3.8%). Most irradiated patients (66.7%) were treated with conventional radiotherapy, whereas a minority (5.9%) received stereotactic radiotherapy. In the remaining cases (30%), the method used was unknown.

In 596 (76.1%) patients, baseline pituitary imaging data were available (table 2). Compared to those with baseline imaging data, patients without baseline imaging data had a similar age at baseline (p = 0.22), gender (p = 0.84), occurrence of tumor progression (p = 0.14) and duration of GH-RT (p = 0.10).
<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of all patients and of patients with and without tumor progression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>All patients</strong></td>
</tr>
<tr>
<td>No. of patients</td>
<td>783</td>
</tr>
<tr>
<td>Age at baseline, years (mean, SD)</td>
<td>54.8 (11.6)</td>
</tr>
<tr>
<td>Age at NFPA diagnosis, years (mean, SD)</td>
<td>48.0 (13.2)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>478 (61.0)</td>
</tr>
<tr>
<td>Females</td>
<td>305 (39.0)</td>
</tr>
<tr>
<td>Extension of pituitary insufficiency, IGHD</td>
<td></td>
</tr>
<tr>
<td>ACTH insufficiency</td>
<td>601 (76.8)</td>
</tr>
<tr>
<td>TSH insufficiency</td>
<td>627 (80.1)</td>
</tr>
<tr>
<td>LH/FSH insufficiency</td>
<td>636 (81.2)</td>
</tr>
<tr>
<td>ADH insufficiency</td>
<td>105 (13.4)</td>
</tr>
<tr>
<td>PRL insufficiency</td>
<td>5 (0.6)</td>
</tr>
<tr>
<td>≥ 3 other pituitary hormone deficits</td>
<td>487 (62.2)</td>
</tr>
<tr>
<td>Pituitary surgery</td>
<td>726 (92.8)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>390 (50.2)</td>
</tr>
<tr>
<td>If radiotherapy, then postoperative radiotherapy</td>
<td>386 (99.0)</td>
</tr>
<tr>
<td>Radiotherapy dose, Gy (mean, SD)</td>
<td>46.2 (5.9)</td>
</tr>
<tr>
<td>Time between NFPA treatment and start GH-RT, years (median, range)</td>
<td>3.6 (-1.6 to 46.0)</td>
</tr>
<tr>
<td>Onset of GHD, childhood onset</td>
<td>5 (0.6)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>184 (28.0)</td>
</tr>
<tr>
<td>Former</td>
<td>168 (25.6)</td>
</tr>
<tr>
<td>No</td>
<td>304 (46.5)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>246 (46.5)</td>
</tr>
</tbody>
</table>
### Table 1 (continued)

<table>
<thead>
<tr>
<th>Medical history</th>
<th>All patients</th>
<th>No tumor progression</th>
<th>Tumor progression</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor progression</td>
<td>120 (15.6)</td>
<td>106 (15.6)</td>
<td>14 (15.4)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

NFPA, nonfunctioning pituitary adenoma; IGHD, isolated growth hormone deficiency; ACTH, adrenocorticotropic hormone; TSH, thyrotrophin; LH, luteinizing hormone; FSH, follicle-stimulating hormone; ADH, antidiuretic hormone; PRL, prolactin; Gy, gray; GH-RT, growth hormone replacement therapy; GHD, growth hormone deficiency

Variables are presented as number (percentage) unless stated otherwise.

<sup>a</sup> Continuous variables were tested with either the Student’s t-test or the Mann-Whitney U-test. Categorical variables were examined with the Chi-square or Fisher’s exact test.

<sup>b-d</sup> Missing subjects: <sup>b</sup>n=1; <sup>c</sup>n=6; <sup>d</sup>n=97

<sup>e</sup> Time from surgery or primary radiotherapy for the nonfunctioning pituitary adenoma or first confirming of the nonfunctioning pituitary adenoma on pituitary imaging when no surgery or radiotherapy was initiated until start of growth hormone replacement therapy.

<sup>f-h</sup> Missing subjects: <sup>f</sup>n=127; <sup>g</sup>n=254; <sup>h</sup>n=14
Tumor progression in NFPA patients using GH-RT

Table 2 | Baseline radiological nonfunctioning pituitary adenoma characteristics of all patients and of patients with and without tumor progression

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>No tumor progression</th>
<th>Tumor progression</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline scan available</td>
<td>596 (76.1%)</td>
<td>518 (75.3%)</td>
<td>78 (82.1%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Type of scan, MRI&lt;sup&gt;b&lt;/sup&gt;</td>
<td>560 (94.8%)</td>
<td>487 (94.9%)</td>
<td>73 (93.6%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Residual tumor at baseline&lt;sup&gt;c&lt;/sup&gt;</td>
<td>363 (62.9%)</td>
<td>298 (59.7%)</td>
<td>65 (83.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumor size, macroadenoma&lt;sup&gt;d&lt;/sup&gt;</td>
<td>289 (83.3%)</td>
<td>233 (82.0%)</td>
<td>56 (88.9%)</td>
<td>0.19</td>
</tr>
<tr>
<td>If macroadenoma: extrasellar extension&lt;sup&gt;e&lt;/sup&gt;</td>
<td>223 (82.6%)</td>
<td>181 (83.4%)</td>
<td>42 (79.2%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Suprasellar extension&lt;sup&gt;f&lt;/sup&gt;</td>
<td>147 (67.1%)</td>
<td>119 (67.2%)</td>
<td>28 (66.7%)</td>
<td>0.94</td>
</tr>
<tr>
<td>Involvement optic chiasm&lt;sup&gt;g&lt;/sup&gt;</td>
<td>44 (20.3%)</td>
<td>36 (20.6%)</td>
<td>8 (19.0%)</td>
<td>0.83</td>
</tr>
<tr>
<td>Parasellar extension&lt;sup&gt;h&lt;/sup&gt;</td>
<td>130 (59.4%)</td>
<td>105 (59.0%)</td>
<td>25 (61.0%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Infraellar extension&lt;sup&gt;i&lt;/sup&gt;</td>
<td>24 (10.8%)</td>
<td>17 (9.4%)</td>
<td>7 (16.7%)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

MRI, magnetic resonance imaging
Variables are presented as number (percentage).
<sup>a</sup> Variables were examined with the Chi-square or Fisher’s exact test.
<sup>b-h</sup> Missing subjects: <sup>b</sup> n=5; <sup>c</sup> n=19; <sup>d</sup> n=16; <sup>e</sup> n=20; <sup>f</sup> n=4; <sup>g</sup> n=6; <sup>h</sup> n=1

Growth hormone replacement therapy

The median follow-up time for the total study population was 5.2 (0.1 - 20.2) years; 5.1 (0.1 - 20.2) years, representing 3981 person-years of GH-RT, for patients without tumor progression and 6.0 (0.7 - 15.2) years, being 4701 treatment-years, for patients with tumor progression (p = 0.10). The median GH dose did not differ between the two groups (0.28 [0.06 - 1.3] vs. 0.26 [0.04 - 0.8] mg per day).

Tumor progression

Tumor progression developed in 95 (12.1%) patients after a median follow-up of 2.2 (0.1 - 14.9) years. Most patients (92.6%) had undergone NFPA treatment before the progression occurred; 69 (72.6%) had undergone pituitary surgery alone, whereas 19 (20%) had received surgery and postoperative radiotherapy. Median time between prior treatment and tumor progression was 5.1 (0.9 - 23.2) years.

After tumor progression, 17 (17.9%) patients were treated with surgery alone, 36 (37.9%) with radiotherapy alone, and 10 (10.5%) with surgery and postoperative radiotherapy, whereas in 32 (33.7%) patients close monitoring was deemed adequate. In 20 (21.1%) patients, GH-RT was stopped because of the tumor progression, whereas in 16 (16.8%) patients it was temporarily discontinued for a median duration of 15.4 (0.5 - 53.4) months.
Progression-free survival and comparison of subgroups

The progression-free survival of the total study population is shown in figure 1. Of all patients, 399 (51.4%) had received radiotherapy as part of the prior tumor treatment (in six patients it was unknown whether they had received radiotherapy). Tumor progression occurred in 19 (4.8%) of these patients, whereas in the patients without prior radiotherapy tumor progression occurred in 76 (20.1%). Cox proportional hazard
analysis demonstrated that patients who had received prior radiotherapy had a decreased risk of developing tumor progression compared with those who had not received prior radiotherapy, also after adjustment for age and gender (hazard ratio [HR] = 0.16, 95% confidence interval [CI], 0.09 - 0.26, p < 0.001). Age at NFPA diagnosis, extension of pituitary deficiency, surgery and history of tumor progression were not found to be relevant confounders. The progression-free survival of patients with and without prior radiotherapy is shown in figure 2.

In 363 (62.6%) of the patients with baseline imaging data, there was evidence of residual adenoma at baseline (table 2). Tumor progression was observed in 65 (17.9%) of these patients, whereas in patients without residual tumor this was observed in 13 (6.1%) cases. Cox proportional hazard analysis in patients with available baseline imaging data showed that patients with residual tumor at baseline had an increased risk of developing tumor progression compared with patients without residual tumor, also after adjustment for age and gender (HR = 3.7, 95% CI, 2.0 - 6.8, p < 0.001). Of the other evaluated potentially confounding variables (age at NFPA diagnosis, extension of pituitary deficiency, surgery, radiotherapy and history of tumor progression), radiotherapy emerged as the only relevant confounder (HR after adjustment for age, gender and radiotherapy = 4.5, 95% CI, 2.4 - 8.2, p < 0.001). The progression-free survival of patients with and without residual tumor is shown in figure 3. Within the subgroup of patients with residual adenoma at baseline, nine (5.4%) patients who had received prior radiotherapy developed tumor progression,
compared to 56 (28.9%) patients who had not received prior radiotherapy (p < 0.001). Within the group of patients without residual tumor at baseline, two (2.1%) patients with prior radiotherapy developed tumor progression vs. 11 (9.3%) patients without prior radiotherapy.

**Discussion**

GHD frequently occurs in patients with NFPAs, either as a consequence of the treatment of the tumor, the tumor itself, or a combined effect of both. GH-RT has shown positive effects on features associated with adult GHD. However, it has been suggested GH-RT may increase the risk of tumor recurrence or growth, despite mostly reassuring data in literature so far. In the present observational study in a large cohort of NFPA patients using GH-RT, tumor progression developed in 12.1% of the patients after a median of 2.2 (0.1 - 14.9) years after starting GH-RT in adulthood. Radiotherapy as part of prior NFPA treatment significantly decreased the risk of tumor progression. Residual tumor was associated with an increased risk of tumor progression.

Several studies have investigated recurrence or regrowth of PAs after surgery and/or radiotherapy in patients not using GH-RT. In a series of 159 NFPA patients, tumor recurrence or regrowth occurred in 33.5% after a median of 4.1 (1 - 20.7) years following surgery. In two other studies including NFPA patients who had undergone transsphenoidal surgery, recurrence rates were 21% and 32%, respectively. After pituitary radiotherapy, lower recurrences rates have been reported. Gittoes et al. found that only 4 of 63 (6%) postoperatively irradiated NFPA patients developed tumor progression, whereas 27 of 63 (43%) patients who were not postoperatively irradiated developed tumor progression. Likewise, in a cohort of 122 NFPA patients, tumor progression occurred in 4% and 57%, respectively, of patients with and without postoperative radiotherapy. In a series of 411 patients with various types of PAs who had all received radiotherapy, whether or not combined with surgery, only 25 (6%) patients developed tumor progression. The tumor progression rates in the entire cohort and in patients with or without prior radiotherapy of 12.1%, 4.8% and 20.1%, respectively, in the present study, appear to be similar to or lower than those reported by the abovementioned studies. This could indicate that GH-RT may not impose an increased risk of tumor progression in NFPA patients. However, several aspects that may widely vary between studies, such as treatment related factors (e.g. surgical technique, extent of surgery, radiotherapy), study population, tumor characteristics, and follow-up duration have to be taken into account when comparing different studies.
So far only few studies in the literature have explored the possible effect of GH-RT on tumor progression in NFPA patients specifically. Buchfelder et al. compared operated NFPA patients who were either treated with GH-RT or not in a retrospective case-control study of 55 matched pairs. Within a 5-year follow-up period, tumor progression occurred in 29.1% of the treatment group and in 21.8% of the control group ($p = 0.25$). Because data for this study were partly derived from the German KIMS database (Pfizer International Metabolic Database), treated patients were selected from multiple centers with differences in surgical expertise, whereas control patients were selected from one specialized neurosurgical center. Also, no adjustments were made for the proportion of patients in both groups, approximately 20%, who had received postoperative radiotherapy. Arnold et al. assessed the effect of GH-RT on tumor recurrence in 130 NFPA patients who were solely treated with surgery and followed up in a single center. Tumor progression occurred in 35% of 23 patients with GH-RT and in 36% of 107 patients without GH-RT. Further analysis revealed that GH-RT was not a significant predictor of progression after adjustment for several confounders. In another case-control study in NFPA patients using GH-RT ($n = 121$) or not ($n = 114$), the progression-free survival rates were similar in both groups. During an observation period of approximately 10 years, tumor progression was found in 26% of the GH-treated patients and in 32% of the non-GH-treated patients. Although the nonrandomized nature of these studies could have led to bias with regard to the choice for GH-RT, for instance, because patients with larger (residual) tumors may have been less likely to receive GH-RT and the sample sizes were limited, all these studies suggest that GH-RT does not increase tumor progression risk. The observed tumor progression rates in the present study seem to be comparable with or lower than those reported in literature. The rate of 12.1% in our entire study population was lower than those in the treatment and control groups of the three aforementioned studies. This may be due to differences in sample size, whether radiotherapy was administered, or follow-up time. Nevertheless, the results of the present study support data in literature that GH-RT, aiming at restoring physiological IGF-1 concentrations, does not appear to have a negative impact on tumor progression in patients with a NFPA.

Radiotherapy significantly decreased the risk of tumor progression in the present study. This association was not influenced by potentially confounding variables. Similar findings have been reported by others. Although radiotherapy has positive effects on tumor control, concerns have been raised about long-term side effects such as hypopituitarism and increased risks of cerebrovascular events (CVEs) or secondary intracranial tumors. It has been postulated that GH-RT may enhance this risk of secondary tumors because of the potential mitogenic effects of GH and IGF-1 and
reports of increased risk of secondary tumors in childhood cancer survivors or children treated with GH-RT. However, in other studies, no increased risk of secondary neoplasms in patients receiving GH-RT after central nervous system irradiation nor an association between IGF-1 concentration and the occurrence of malignancies in GH-treated adults were observed. These findings are line with previous reports from our registry. In one study, mortality due to malignancies was not elevated in adults receiving GH-RT compared to the background population. In another study, the occurrence of secondary intracranial tumors did not differ between irradiated and nonirradiated NFPA patients (1.1% vs. 0.6%), but the risk of CVE was increased in irradiated men. Overall, as discussed in a recent review, fatal and nonfatal malignancies do not appear to be more prevalent in GH-treated adults compared to the general population, and also not in previously irradiated patients. Nevertheless, potential side effects of pituitary irradiation should be carefully balanced against benefits.

The presence of residual tumor at baseline significantly increased tumor progression risk in the present study, also after adjustment for potential confounders. This has also been observed by others. Olsson et al. found that tumor progression developed in 37% and 10% of patients using GH-RT with and without residual tumor, respectively, compared to 17.9% and 6.1% in the present study. They suggested that, because the rates in their treatment group, including patients with residual tumor, were comparable with those in the control group and those in literature, GH-RT may also be safely administered in patients with residual tumor. This is in line with the findings in the present study. For instance, in the subgroup of our patients with residual tumor who had not received radiotherapy, 28.9% developed tumor progression, which is comparable with reported ranges, varying between 21% and 57%, in surgically treated, but nonirradiated, NFPA patients not using GH-RT. In addition, Arnold et al. showed that after adjustment for several confounders, including type of tumor removal (partial or complete), GH-RT was not a predictor of recurrence. These combined data indicate that GH-RT may also be initiated in the presence of residual NFPA, although long-term surveillance is recommended.

The present study has both strengths and limitations. The large size of the study population, including only patients with a NFPA and excluding other types of tumors, is one of the major strengths. Due to this large number, comparisons between different subgroups could be made. Furthermore, potentially confounding effects of several factors were evaluated. The follow-up duration was relatively long and similar between patients with and without tumor progression. However, one could argue that the follow-up period might not have been long enough to detect tumor growth in the usually slow-growing NFPA. A limitation of our study is the lack of a control group of untreated GHD patients with a NFPA. However, our findings were compared
with those in literature, thereby taking into account the difficulties of such comparisons. The nonrandomized and retrospective design, inherent to the observational nature of the database, presents another limitation. Unfortunately, performing a prospective randomized study in NFPA patients does not seem feasible due to practical and ethical constraints.

In summary, in this observational study in a large number of NFPA patients using GH-RT, the development of tumor progression was investigated. The findings in this study in combination with those reported in literature, thereby taking into account the presented limitations, indicate that GH-RT does not seem to increase the risk of tumor progression. Although more robust conclusions may only be generated by large randomized prospective studies with long-term follow-up, evidence so far seems reassuring. Data suggest that GH-RT, with regard to tumor progression, may be safely administered to GHD patients with a NFPA.

Acknowledgements

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