Doubled mortality rate in irradiated patients reoperated for regrowth of a macroadenoma of the pituitary gland

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Abstract

Background: Reduced life expectancy has been shown in patients with hypopituitarism, mainly caused by cardiovascular diseases. A major cause of hypopituitarism is pituitary adenomas, and radiotherapy may be employed as a treatment modality to reduce the post-operative regrowth rate of these tumours. Recently, we showed that in patients with craniopharyngiomas, tumour regrowth foreshadowed a fourfold risk increase for death. For patients with pituitary adenomas, the impact of regrowth on life expectancy is, however, not known.

Objective: To assess the impact of a reoperation due to a regrowth of a pituitary macroadenoma on mortality, taking into account other candidate prognostic factors.

Design and patients: In 281 patients with operated and irradiated macroadenomas, excluding acromegaly and Cushing’s disease, 35 patients had a regrowth (median follow-up 16.6 years). Possible risk factors for tumour regrowth were investigated by Cox regression models.

Results: For tumour regrowth, age, calendar time at primary surgery, gender and extension of tumour growth had no statistically significant impact. For younger patients, the proportion of regrowths was higher, but after age-stratified Cox regression analysis only regrowth was shown to have a significant impact on mortality, with a more than doubled mortality risk for patients with tumour regrowth as compared with the non-regrowing tumour patients (hazard ratio = 2.24, P < 0.001). This finding was corroborated by cohort analyses using the general population as an external comparison group.

Conclusion: Among patients with irradiated pituitary macroadenomas, excluding acromegaly and Cushing’s disease, a doubled mortality rate was observed for those reoperated for tumour regrowth as compared with patients with non-regrowing tumours.

European Journal of Endocrinology 150 497–502

Introduction

Reduced life expectancy has been shown in patients with hypopituitarism on conventional hormone treatment but with unsubstituted growth hormone (GH) deficiency (1–4). This increase in mortality is mainly caused by cardiovascular diseases (1, 3, 4). A major cause of hypopituitarism is pituitary adenomas, which are treated with surgery, radiotherapy, and medical therapy (5–7). Radiotherapy may be employed as a treatment modality to reduce the regrowth rate of incompletely resected non-secreting adenomas and in secreting pituitary tumours where hormonal control cannot be achieved with surgery and medical therapy. Nevertheless, among those patients that have survived 10 years after radiotherapy combined with limited surgery, about 7% of the adenomas had a regrowth (8).

Recently, we showed that tumour regrowth in patients with craniopharyngiomas foreshadowed a fourfold risk increase for death (9). For patients with pituitary adenomas, the impact of regrowth on life expectancy is, however, not known.

The main aim of the present study was to assess the impact of regrowth of pituitary adenomas on mortality, taking into account other candidate prognostic factors such as age at primary surgery, gender, calendar time of surgery and tumour extension. The study was based on a cohort of patients with operated and irradiated pituitary macroadenomas; patients with acromegaly and Cushing’s disease were excluded.

Patients and methods

Patient cohort and follow-up

During the period 1946–1988, 477 subjects were operated on for a pituitary tumour at the Department of Neurosurgery, Lund University Hospital. We excluded...
133 patients for various reasons, including acromegaly \((n = 27)\), Cushing’s disease \((n = 6)\), death during the first postoperative month \((n = 20)\), missing records or not fully identified \((n = 21)\), died before the start of the Swedish cause-of-death register in 1952 \((n = 6)\), not fully evaluated with respect to hormone status \((n = 40)\), or GH treatment in childhood \((n = 13)\). Of the remaining 344 subjects, 42 patients with the diagnosis of craniopharyngioma and 21 non-irradiated patients were excluded. Thus, the final cohort comprised 281 patients who had a median time of follow-up of 16.6 years (range 0.2–47.4 years). Sixty-five percent of the cohort subjects were males.

Based on pathological diagnosis, the vast majority of the pituitary tumours were regarded as chromophobic adenomas \((n = 276)\). Five tumours were diagnosed as gonadotrophic adenomas.

All tumours were macroadenomas, with suprasellar extension and protrusion into the third ventricle in 72\% \((n = 202)\), suprasellar extension but no protrusion in 20\% \((n = 55)\), or a not exactly defined extension of the tumour in 8\% \((n = 24)\) of patients. Transcranial operations had been performed in 96\% of the patients and in the remainder the operations were transspenoidal. Radiotherapy was given postoperatively within six months in all but seven patients in whom the irradiation was given preoperatively. Pituitary insufficiency was defined as insufficiency in at least one axis of the anterior lobe, and within six months after surgery pituitary insufficiency was diagnosed in 73.5\%, within one year in 78.5\%, within two years in 84.3\%, and within five years in 89\% of patients.

The cohort was followed from the date of the first operation until the date of death, emigration or December 31 1998, whichever occurred first. Through a linkage with the national Swedish cause-of-death register, specific causes of death occurring in the cohort from 1952 to 1998 were recorded. During the follow-up, 35 patients had a regrowth which resulted in a reoperation. As a clinical routine assessment, all patients harbouring macroadenomas had regular ophthalmological follow-ups. Thus, regrowth was either detected through the new appearance of visual deterioration or with more pronounced deterioration of visual acuity or visual field defects together with confirmatory radiological imaging \((n = 24)\), or by routine assessment with radiological imaging giving evidence of an increase in pituitary tumour size \((n = 5)\), even without symptoms from the tumour mass. In 6 patients this exact information was missing. Due to the retrospective study design and the very long follow-up period, there were no homogenous routines for surveillance imaging. However, computerized tomographies were performed since the 1970s and magnetic resonance imaging (MRI) since the 1980s. It is possible, however, that some patients had a regrowth without a reoperation, as regular scanning was not performed. The present study revealed a cumulative incidence of regrowth of 12.5\% for a median follow-up of 16.6 years.

Furthermore, in all but four cases an operation record was available that confirmed a tumour regrowth. A reoperation that occurred within 6 months of the first operation was considered as a complication of the first operation and not a regrowth. Five patients were reoperated within one month, but no patients were reoperated 1–6 months after the first operation. In 23 of the 25 reoperated and later deceased patients, the medical records were available and, apart from two cases of eye-muscle paresis, no postoperative complications as e.g. seizures that required treatment with anti-epileptic drugs, were recorded.

### Radiation dosimetry

During the first two decades of the inclusion period, all 111 patients were treated with four fields of 200kV X-rays. A median dose of 40 Gy (range 30–52), with \(\leq 2\) Gy per fraction, was given. During 1969 to 1988, all 163 patients were treated with either Cobalt-60 or high energy X-rays (6 MV–33 MV) with a two- or three-field technique. With this radiation technique, a median dose of 42 Gy (range 36–60), with \(\leq 2\) Gy per fraction was given. For those seven patients that had been irradiated before 1946, no dosimetric data were available. Six patients, of whom five were among the 25 deceased patients with a regrowing tumour, had been irradiated twice (Table 1).

### Statistical methods

Gender, age (five-year groups), and calendar-year specific mortality rates for the general population of Southern Sweden were used for calculation of standardized mortality ratios (SMRs). The corresponding 95% confidence intervals (CIs) for SMRs were calculated by treating the observed number as a Poisson variable, or a normal variable if the observed value was greater than 15 (10).

The effects of candidate prognostic factors besides age at primary surgery, i.e. gender, calendar time of primary surgery, extension of the tumour at first operation, and tumour regrowth on postoperative survival, were analyzed by Cox regression (10, 11). Tumour regrowth was treated as a time-dependent factor, i.e. a person remained in the risk set for the no regrowth group until the time that the regrowth occurred, and then entered the risk set for the regrowth group.

We also performed a Cox regression analysis to examine possible prognostic impact of age at primary surgery, gender, calendar time of primary surgery, and tumour extension on first tumour regrowth. Prognostic factors that showed a tendency of effect \((P < 0.20)\) in the univariate analyses were considered further in the multivariate analysis. The Cox regression
Table 1 Information on 25 deceased patients operated and irradiated for a regrowing pituitary macroadenoma during the period 1946-1988.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Number of re-operations</th>
<th>Irradiated twice</th>
<th>Time between last operation and death</th>
<th>Underlying causes of death</th>
<th>Contributing causes of death</th>
<th>Autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>2</td>
<td>No</td>
<td>22 yrs, 10 months</td>
<td>Myocardial infarction</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>M</td>
<td>1</td>
<td>No</td>
<td>2 months</td>
<td>Pneumonia</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>M</td>
<td>3</td>
<td>No</td>
<td>1 yr, 9 months</td>
<td>Pituitary tumour</td>
<td>Pituitary adenoma</td>
<td>No</td>
</tr>
<tr>
<td>M</td>
<td>1</td>
<td>No</td>
<td>9 yrs, 8 months</td>
<td>Pneumonia</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>M</td>
<td>1</td>
<td>Yes</td>
<td>9 yrs, 2 months</td>
<td>Pulmonary embolism</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>M</td>
<td>2</td>
<td>No</td>
<td>1 yr</td>
<td>Pituitary adenoma</td>
<td>Cerebral infarction</td>
<td>Yes</td>
</tr>
<tr>
<td>F</td>
<td>1</td>
<td>No</td>
<td>5 yrs, 6 months</td>
<td>Fibrosis myocardi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>2</td>
<td>No</td>
<td>10 months</td>
<td>Pituitary tumour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>1</td>
<td>No</td>
<td>30 yrs, 3 months</td>
<td>Pulmonary embolism</td>
<td>Pituitary adenoma, acuticus neurinoma</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>2</td>
<td>No</td>
<td>5 months</td>
<td>Pneumonia</td>
<td>Astrocitoma, pituitary adenoma, pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>1</td>
<td>No</td>
<td>1 month</td>
<td>Encephalomalacia</td>
<td>Hypertension</td>
<td>Yes</td>
</tr>
<tr>
<td>F</td>
<td>2</td>
<td>Yes</td>
<td>1 month</td>
<td>Pulmonary oedema</td>
<td>Pulmonary embolism</td>
<td>Yes</td>
</tr>
<tr>
<td>M</td>
<td>2</td>
<td>Yes</td>
<td>1 yr, 10 months</td>
<td>Pituitary tumour</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>M</td>
<td>1</td>
<td>No</td>
<td>9 yrs, 10 months</td>
<td>Cardiosclerosis and cardiac hypertrophy</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>M</td>
<td>5</td>
<td>Yes</td>
<td>1 yr, 3 months</td>
<td>Pneumonia</td>
<td>Cerebrovascular diseases, pituitary adenoma</td>
<td>No</td>
</tr>
<tr>
<td>F</td>
<td>2</td>
<td>No</td>
<td>11 yrs, 4 months</td>
<td>Pituitary tumour</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>M</td>
<td>2</td>
<td>No</td>
<td>10 yrs</td>
<td>Myocardial infarction</td>
<td>Cardiosclerosis</td>
<td>Yes</td>
</tr>
<tr>
<td>M</td>
<td>2</td>
<td>No</td>
<td>1 yr, 3 months</td>
<td>Pituitary tumour</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>M</td>
<td>1</td>
<td>Yes</td>
<td>19 yrs, 7 months</td>
<td>Pulmonary embolism</td>
<td>Pituitary tumour, cerebral infarction</td>
<td>No</td>
</tr>
<tr>
<td>F</td>
<td>1</td>
<td>No</td>
<td>6 yrs, 10 months</td>
<td>Astrocytoma</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>F</td>
<td>1</td>
<td>No</td>
<td>28 yrs, 5 months</td>
<td>Pneumonia</td>
<td>Cerebrovascular disease</td>
<td>No</td>
</tr>
<tr>
<td>M</td>
<td>1</td>
<td>No</td>
<td>15 yrs, 2 months</td>
<td>Status post myocardial infarction</td>
<td>Cardiosclerosis</td>
<td>Yes</td>
</tr>
<tr>
<td>F</td>
<td>1</td>
<td>No</td>
<td>1 yr, 5 months</td>
<td>Myocardial infarction</td>
<td>Cardiosclerosis</td>
<td>No</td>
</tr>
<tr>
<td>M</td>
<td>1</td>
<td>No</td>
<td>2 yrs, 4 months</td>
<td>MEN I</td>
<td>Myocardial infarction</td>
<td>Yes</td>
</tr>
<tr>
<td>M</td>
<td>1</td>
<td>No</td>
<td>10 yrs, 7 months</td>
<td>Colon cancer</td>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>

yr, year; yrs, years.
analyses were performed using the computer package SPSS 10.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Risk factors for tumour regrowth

Thirty-five patients had regrowths; ten of them were reoperated more than once. For younger patients the proportion of regrowths was higher (Table 2) due to the fact that the risk for intercurrent death is always lower at a younger age. In older age groups, fewer will survive for a long time, which will limit the number of long time periods between the first and second operation. As a consequence, younger patients have a longer median interval between operations.

Age at primary surgery had, however, no prognostic impact on tumour regrowth ($P = 0.4$). Twice as many of the patients with suprasellar extension and protrusion into the third ventricle experienced a regrowth compared with those with suprasellar extension but without such protrusion, but the discrepancy was not statistically significant ($P = 0.17$). None of the two other candidate prognostic factors turned out to have a statistically significant effect (gender, $P = 0.9$; calendar time of primary surgery, $P = 0.25$).

Mortality and causes of death among patients with and without tumour regrowth

Twenty-five of the thirty-five patients with regrowth had died during the follow-up period (Table 1), which corresponds to a mortality four times that of the general population (SMR 3.74; 95% CI 2.42–5.53). Eight had died from cardiovascular diseases (SMR 2.53, 95% CI 1.09–4.99) and, more specifically, among the eight, two had died from cerebrovascular diseases (SMR 3.77, 95% CI 0.46–13.6). Among the 246 patients without observed tumour regrowth, 164 had died (SMR 1.71, 95% CI 1.46–5.53), which was about half the mortality rate of patients with tumour regrowth. Seventy-nine patients without tumour regrowth had died from cardiovascular diseases (SMR 1.56, 95% CI 1.24–1.95) and, more specifically, among the 79, 32 had died from cerebrovascular diseases (SMR 3.54, 95% CI 2.42–5.00).

For one of the patients with a regrowing tumour, the pituitary tumour was a part of a multiple endocrine neoplasm (MEN)-I syndrome. Moreover, among the patients with regrowing tumours, one patient died of acromegaly, and two patients had acusticus neurinoma and astrocytoma respectively, as contributing causes of death.

Table 2 Association between age at primary surgery and tumour regrowth in a cohort of 281 patients irradiated and operated for a pituitary macroadenoma.

<table>
<thead>
<tr>
<th>Age at primary surgery (years)</th>
<th>$n_{\text{total}}$</th>
<th>$n$ (proportion)</th>
<th>Median time* (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq 39$</td>
<td>59</td>
<td>11 (19%)</td>
<td>7.0 (0.6–37.3)</td>
</tr>
<tr>
<td>40–49</td>
<td>61</td>
<td>11 (18%)</td>
<td>8.7 (3.5–25.0)</td>
</tr>
<tr>
<td>50–59</td>
<td>78</td>
<td>9 (12%)</td>
<td>3.5 (0.6–23.0)</td>
</tr>
<tr>
<td>60–69</td>
<td>68</td>
<td>3 (4%)</td>
<td>1.9 (0.6–7.3)</td>
</tr>
<tr>
<td>$\geq 70$</td>
<td>15</td>
<td>1 (7%)</td>
<td>2.8</td>
</tr>
</tbody>
</table>

* Time between primary surgery and re-operation (years).

Prognostic factors for postoperative survival

In the univariate analyses, apart from age at primary surgery, only tumour regrowth showed a tendency towards prognostic impact on survival in the total cohort. Because age at primary surgery was related to the proportion of patients with regrowing tumours (Table 2), it was essential to analyze the impact of tumour regrowth in each age group. The prognostic effect of tumour regrowth became significant in the age-stratified Cox regression analysis, with an estimated twofold increased mortality for patients with tumour regrowths as compared with the non-recurrent tumour patients (hazard ratio (HR), 2.24; 95% CI, 1.44–3.48; Table 3). However, there was no indication that the effect (i.e. the HR) varied across the age groups ($P = 0.6$).

Discussion

This is the first study reporting an increased mortality rate in patients with irradiated and re-operated regrowing pituitary macroadenomas, excluding patients with acromegaly and Cushing’s disease, compared with those patients without a regrowth. Other tentative risk factors such as gender, age, calendar time of primary surgery, and type of tumour extension had no significant impact on postoperative survival. It is reassuring that the results from the analyses comprising external comparisons (the general population) and the internal comparisons (survival analysis) were very consistent, showing about a doubled mortality rate among patients with tumour regrowths as compared with patients with pituitary macroadenomas without regrowth.

Thirty-five patients had tumour regrowth resulting in a reoperation during a follow-up from 1946 to 1998. We are confident that these 35 reoperations were due to a tumour regrowth, because reoperations within 6 months after initial surgery were excluded. Furthermore, the operation records verified tumour regrowth in 89% of the cases. In the present study, a regrowth of 12.5% was seen after 16.6 years follow-up. This indicates that the diagnostic accuracy in the present study was not inferior to what has been
observed in a surveillance study with regular scanning, 7% for 15 years (8).

Possible risk factors for regrowth were investigated in the present study and there was no impact of gender, calendar year of surgery, or age at surgery. However, there was a non-significant doubled risk for regrowth for the tumours with a protrusion into the third ventricle compared with those without this protrusion. This is in agreement with the finding that patients harbouiring smaller tumours (2–4 cm) have better progression-free survival rates than patients with larger tumours (>4 cm) (12). The question remains as to why patients with regrowing tumours have an increased mortality? We investigated death certificates from all 25 deceased patients with regrowing tumours. Autopsies had been performed in 56% of these cases. One patient had a pituitary tumour as part of the MEN-I syndrome. One patient died from a second cerebral tumour (astrocytoma) and another two patients had a second cerebral tumour as contributing cause of mortality (astrocytoma and acusticus neurinoma respectively). Whether irradiation contributes to an increased risk of second brain tumours is disputed. A crude recent meta-analyses performed on the published cohort studies of patients with irradiated pituitary tumours gives a standardized incidence ratio of 6.1 (95% CI 3.2–10.7) (13). Thus, the results are in favour of an increased risk for second brain tumours in patients treated with irradiation for a pituitary tumour. A caveat to this conclusion is, however, that non-positive studies may not have been published, causing a publication bias, and that non-irradiated cohort studies are still missing. Thus, this question cannot be fully answered at present. Three of the deceased patients with tumour regrowth had prolactinomas treated with bromocriptine. Five patients had been irradiated twice. Re-irradiation of regrowing pituitary adenoma has been accompanied by complications such as temporal lobe injuries and more extended hypopituitarism (14). Fractionated doses of ≤ 2 Gy, as in the present study, seem to be accompanied by less complication (15, 16). Thus, among the patients with regrowing pituitary macroadenomas with fatal outcome there was a subgroup with concomitant diseases. Furthermore, a proportion of subjects suffered from very aggressively growing macroadenomas that in spite of irradiation and dopaminergic treatment or repeated radiotherapy had a regrowth.

All patients harboured macroadenomas, and a vast majority of the tumours were extending into the third ventricle. The extension of the tumour had no significant impact on survival in the present study. These results are in accordance with the previous finding that the extension of the tumour had no impact on the increased cardiovascular mortality seen in hypopituitary patients (1). Almost all patients (96%) had had a transcranial operation. Thus, the impact of operation technique on survival could not be evaluated in the present study. However, a previous study gives no indication of different mortality risks for pituitary tumour patients operated with the transcranial or the transsphenoidal technique (4). Moreover, all deaths during the first post-operative month were excluded from the analyses in order to avoid inclusion of deaths due to surgical complications. Furthermore, among the deceased patients with a regrowing tumour only a few post-operative complications were recorded (two patients with eye-muscle paresis) and none were on treatment with anti-epileptic drugs. It should be emphasized that we have assessed the consequences of a re-operation for tumour regrowth for mortality but the relative impact of probably more directly causative factors such as degree of hypopituitarism or surgical trauma could not be assessed. There was no regular postoperative surveillance testing programme for these patients. The medical records, however, do show that five years postoperatively, 89% had pituitary insufficiency, which is in accordance with previous findings (17). All patients were given adequate conventional hormone treatment, except in five cases that were also treated with GH for a median of 2 years (range 1–4). None of the patients with a regrowing tumour had been treated with GH.

The present cohort was based on a consecutive case series of patients from a well-defined geographical area, and a selection bias could therefore be avoided. Further, not irradiated patients and those with acromegaly and Cushing’s disease were excluded, leaving a rather homogenous cohort of macroadenoma patients operated by the transcranial route. Thus, the patients in this cohort have not been treated according to present therapeutic policies. However, we do not consider this

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**Table 3** Estimated hazard ratios (HR) for death after surgery for pituitary macroadenoma with respect to tumour regrowth, with and without age stratification (<39, 40–49, 50–59, 60–69, and ≥ 70 years at primary surgery).

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>No age stratification</th>
<th>With age stratification</th>
<th>χ²-test for interaction (the likelihood ratio test (10)) between regrowth and age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regrowth (time dependent; yes vs no)</td>
<td>HR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.40 (0.92 – 2.14)</td>
<td>2.24 (1.44 – 3.48)</td>
</tr>
<tr>
<td></td>
<td>P&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.14</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup> 95% confidence interval.
<sup>b</sup> P-value obtained from Wald’s test (10).
<sup>c</sup> Test for interaction (the likelihood ratio test (10)) between regrowth and age gave P = 0.6, i.e. there was no indication that the HR varied between the age groups.
to be a drawback. Without knowledge of the results of previous therapeutic policies, we will not have a baseline allowing us to evaluate newer treatments. Furthermore, it should be born in mind that a long follow-up as in the present study (median 17 years) is needed to evaluate long-term outcomes of specific treatments.

In conclusion, this is the first study reporting a doubled mortality rate for patients with irradiated pituitary macroadenomas, excluding acromegaly and Cushing’s disease, re-operated for tumour regrowth as compared with patients with non-regrowing tumours. Other tentative prognostic factors such as age, gender, calendar time of primary surgery and extension of the tumour had no statistically significant impact on post-operative survival in the Cox regression model.

Acknowledgements

This work was supported by The Swedish Medical Research Council (grant no K 1999-27X013074-01A) and the Medical Faculty, Lund University, Sweden.

References


Received 19 October 2003
Accepted 24 December 2003

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