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Postoperative use of somatostatin analogs and mortality in patients with acromegaly

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Abstract

Objective: To assess the effect of somatostatin analogs (SSAs) on mortality in relation to disease control of acromegaly after pituitary surgery.

Design: A retrospective study in two large tertiary referral centers in The Netherlands.

Methods: Overall, 319 patients with acromegaly in whom pituitary surgery was performed as primary therapy between January 1980 and July 2017 were included. Postoperative treatment with SSA was prescribed to 174 (55%) patients because of persistent or recurrent disease. Disease control at last visit was assessed by IGF1 standard deviation score (SDS). Adequate disease control was defined as IGF1 SDS ≤2. Univariate determinants of mortality and standardized mortality ratios (SMRs) were calculated for groups with and without SSA at any moment postoperatively and at last visit.

Results: In total, 27 deaths were observed. In univariate analysis, determinants of mortality were inadequate disease control (relative risk (RR): 3.41, $P = 0.005$), surgery by craniotomy (RR: 3.53, $P = 0.013$) and glucocorticoid substitution (RR: 2.11, $P = 0.047$). There was a strong trend toward increased mortality for patients who used SSA (RR: 2.01, $P = 0.067$) and/or dopamine agonists (RR: 2.54, $P = 0.052$) at last visit. The SMR of patients with adequate disease control who used SSA at any moment postoperatively (1.07, $P = 0.785$) and at last visit (1.19; $P = 0.600$) was not increased. Insufficiently controlled patients had a significantly raised SMR (3.92, $P = 0.006$).

Conclusions: Postoperative use of SSA is not associated with increased mortality in patients with acromegaly who attain adequate disease control. In contrast, inadequate disease control, primary surgery by craniotomy and glucocorticoid substitution are associated with increased mortality.

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Introduction

Acromegaly is a rare condition characterized by growth hormone (GH) excess, resulting in the overproduction of insulin-like growth factor 1 (IGF1). As a consequence, patients with acromegaly have a reduced life expectancy (1, 2) and suffer from multimorbidity (3, 4). Acromegaly is almost always caused by a pituitary adenoma.

The main treatment goals in acromegaly are to decrease mortality (5, 6) and morbidity (7, 8) through control of GH and IGF1 hypersecretion, reduction or stabilization of pituitary tumor size and prevention of disease recurrence. Trans-sphenoidal surgery (TSS) is currently regarded as the primary treatment of choice for most GH-secreting pituitary adenomas. However,

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postoperative remission is not achieved in 10–25% of microadenomas and 30–55% of macroadenomas (9, 10), necessitating additional treatment. Treatment options applied in the postoperative treatment of acromegaly are repeated surgery, radiotherapy (RT), somatostatin analogs (SSAs), dopamine agonists (DAs) and GH receptor antagonists (GHRAs).

Since their introduction in the 1980s, SSAs have become the main form of medical therapy for acromegaly. SSAs bind to somatostatin receptors, thereby suppressing the secretion of GH, reducing somatotroph cell mass and blocking the synthesis of IGF1 in the liver (11, 12). Treatment with SSA after surgery and/or RT has been found to result in IGF1 normalization in 42–68% of patients (13, 14). However, quality of life is impaired in association with the need for prolonged postoperative therapy by SSA in patients with acromegaly (15).

Although SSAs have been widely used over nearly four decades, hardly any data exist on their effects on mortality in acromegaly. Bogazzi *et al*. compared the primary use of SSA with pituitary adenomectomy and found that patients treated with SSA have a higher risk of death than patients treated with primary surgery (16). However, a proper comparison between groups was difficult due to bias in treatment selection. Patients who received SSA as primary therapy had a longer disease duration, older age and more diabetes. A recent study in a nationwide cohort in Sweden included 151 patients who received medical treatment for acromegaly since 2005 of whom 119 (79%) received SSA. It recorded an SMR of 2.03 among medically treated patients, 0.98 among patients treated with both medication and surgery and 0.45 among those only treated with surgery (17). No data are available on the effects of postoperative use of SSA on mortality in patients with acromegaly who are not cured by surgery.

Since many patients with acromegaly use SSA postoperatively for control of persistent disease, it is important that these mortality risks are clarified.

Therefore, we aimed to assess the effect of SSA on mortality in relation to disease control in patients surgically treated for acromegaly in two large tertiary neurosurgical referral centers.

Patients and methods

Study population

Data of 319 patients who received pituitary surgery as primary treatment for acromegaly were retrospectively studied. Surgery was performed between January 1980 and July 2017 in the University Medical Center of Groningen (UMCG) and the Radboud University Medical Center of Nijmegen (Radboudumc), which are large tertiary referral centers for patients with pituitary pathology. Study enrollment procedures are shown in the Supplementary Figure 1 (see section on supplementary data given at the end of this article).

Data on baseline demographic characteristics (age, sex, life expectancy), tumor size at diagnosis, date and type of surgery, outcome of surgery (remission or persistent disease) and serum IGF1 concentrations at last visit were collected. In addition, data on the postoperative application of RT and SSA, and the use of SSA, DA, GHRA and hormonal substitution therapy at last visit were collected. Data on disease control at last visit in relation to applied treatment regimens are shown in Figure 1. Date and cause of death were obtained from hospital or general practice records.

The diagnosis of acromegaly was based on biochemical criteria valid at the time of diagnosis i.e. failure of GH suppression to less than 1 µg/L during an oral glucose tolerance test and since 1998, when IGF1 measurements became routinely available, an elevation of the age- and sex-corrected IGF1 SDS of >2 (above the upper limit of normal) (18, 19). The diagnosis was confirmed by histopathological examination of tissue obtained during surgery; a somatotropinoma was found in all patients.

Thirty-four patients (of whom 22 (65%) used SSA postoperatively) were included before March 1989, when short-acting SSA was introduced for the treatment of acromegaly in the Netherlands. Thirty-nine patients (of whom 25 (64%) used SSA postoperatively) were included who were operated between March 1989 and December 1995, the latter marking the time point at which long-acting SSA became available.

Primary pituitary surgery was followed by a second surgical procedure in 42 (13%) patients (25 (14%) in the UMCG, 17 (12%) in the Radboudumc) and by a third surgical procedure in three patients (all in the UMCG) when a large tumor remnant accessible for surgery persisted or in case of recurrent disease.

RT was given postoperatively to patients with evidence of persistent or recurrent GH overproduction. It was administered in a daily dosage of 1.8–2.0 Gy, resulting in a total dose of 45–50 Gy, using a two-field opposed lateral technique or a three-, four-, or five-field technique. All radiation treatment fields were applied daily, five times per week, with an overall duration of 35 days. In the time period 1963–1990, the radiation dose to the tumor was prescribed at the tumor encompassing isodose. From 1991

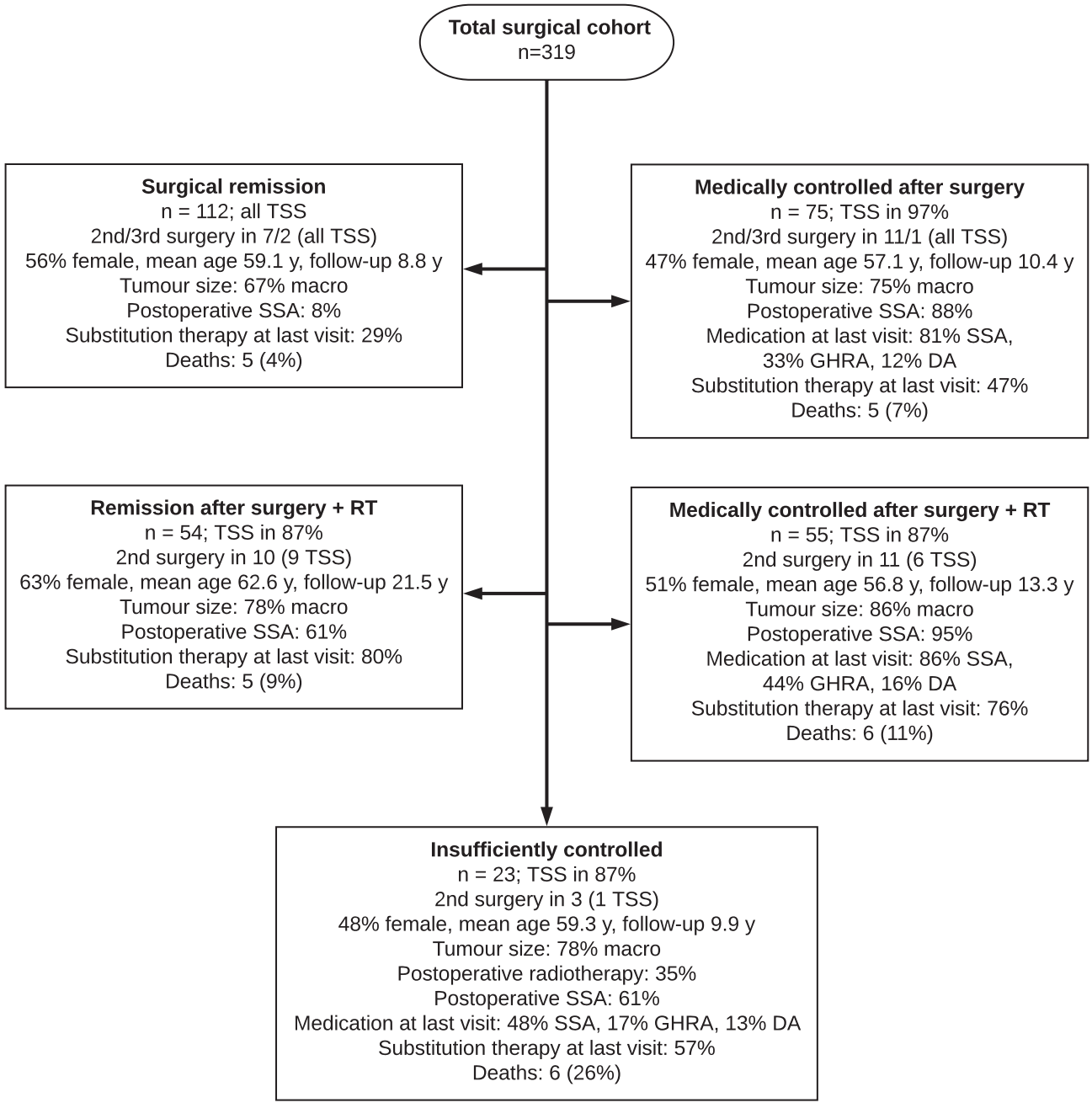

Figure 1
Disease control at last visit and applied treatment regimens.

onward, it was prescribed at a central point in the tumor, according to the recommendations of the International Commission on Radiation Units and Measurements. One patient underwent gamma knife radiosurgery.

SSAs were frequently prescribed for the purpose of preoperative disease control and postoperatively in case of persistent or recurrent disease, according to international guidelines for acromegaly management (20).

The study was approved by the Medical Ethics Review Board of the UMCG. The study fulfilled all requirements for patient anonymity and was in agreement with regulations of our University Hospital for publication of patient data as well as with the Dutch Civil Code (Article 458 on use of data for scientific research).

Laboratory assays

Since 2013, IGF1 concentrations were measured with the IDS-iSYS assay (last IGF1 in 84% of patients) in the UMCG and with a chemiluminescence IGF1 immunoassay on a Liaison analyzer by Diasorin (85% of patients) in the Radboudumc.

Prior assays in use during the study period in the UMCG were a radioimmunoassay (RIA) of the Nichols Institute of Diagnostics, San-Juan Capistrano, CA, USA before 2002 (21), the Nichols Advantage assay from 2002 to February 2006, the Immulite 2500 (Siemens) assay from 2006 to November 2011 and the Immulite 2000 (Siemens) assay from 2011 to April 2013.

Prior assays in use during the study period in the Radboudumc were an in-house RIA traceable to the NIBSC 91/554 standard (22) before December 2009, the Immulite 2500 (Siemens) assay from December 2009 to March 2012 and the Immulite 2000XPI (Siemens) assay from March 2012 to January 2013.

In both centers, results were corrected for inter-method biases to enable the continuous use of reference values (23).

For each IGF1 assay, reference values were derived from healthy subjects. For the purpose of uniform reporting, IGF1 results are expressed as age- and sex-corrected standard deviation scores (SDS). Adequate disease control was defined as an age-normalized serum IGF1 value (IGF1 SDS ≤2), consistent with one of the two main biochemical target goals for management of acromegaly as defined by the Endocrine Society (24). The other therapeutic goal of a random GH <1.0 µg/L (or a nadir serum GH level <1.0 µg/L within 2 h after 75 g of oral glucose in patients with a random GH greater than 1 µg/L) could unfortunately not be used to assess disease control in this study, since postoperative GH values were not available for a sufficient number of patients.

In analysis of IGF1 SDS, only those scores were analyzed that were measured at least 3 months after surgery. In patients who used SSA postoperatively, IGF1 scores were used that were measured at least 3 months after initiation of SSA therapy. In patients in whom SSA had been successfully withdrawn, IGF1 scores were used that were measured at least 3 months after withdrawal of the medication, consistent with clinical guidelines regarding reliability of IGF1 measurements (18, 24).

Statistical analysis

To answer the question whether current treatment with SSA for acromegaly has a (potentially reversible) effect on mortality risk, mortality in patients who used SSA at last visit was compared to mortality in patients who did not use SSA at last visit. To answer the question whether postoperative treatment with SSA for acromegaly affects life expectancy, mortality in patients who used SSA at any moment postoperatively was compared to mortality in patients who did not use SSA at any moment postoperatively. All groups were compared to an age- and sex-related reference population according to the standardized mortality ratio (SMR). SMR is a ratio between observed and expected numbers of deaths. The expected deaths were calculated using the yearly published survival tables of the Dutch population (CBS) accounting for year of birth and sex (http://www.cbs.nl). The mid-P exact test using Miettinen's modification (25) was used for the calculation of SMR confidence intervals (http://www.openepi.com).

There is an inverse correlation between age and life expectancy. Therefore, in analysis of life expectancy, the age at start of follow-up must be considered. In log-rank tests, this problem is usually solved by using age as an independent risk factor. However, because age is related to other risk factors, it is unclear to what extent this correction for age is related to life expectancy and to what extent it is related to the other risk factors. To avoid this methodological bias, age at pituitary surgery was transformed to median life expectancy using the CBS tables and compared with the Mann–Whitney *U* test. Both left and right censoring were applied to correct for attained age at start and end of follow-up. Log-rank tests can be performed without objection this way (26).

Differences were assessed with Fisher's exact test for categorical variables and unpaired *t* tests for continuous variables. When continuous variables were not normally

distributed, a Mann–Whitney *U* test was performed. Data are expressed as mean ± S.D., median (interquartile range) or percentages when appropriate. Two-tail *P*-values <0.05 were considered significant. SPSS 23 and Excel 2010 were used for data analysis.

Results

Study population

A total number of 319 patients (175 from the UMCG and 144 from the Radboudumc) was included in the analysis. Characteristics of the study population are shown in Table 1. Compared to patients who never used SSA (n=145), patients who used SSA at any moment postoperatively (n=174) were younger at time of surgery and at last visit, more often had a macroadenoma, were less frequently operated via the transsphenoidal approach, more often received RT, had more pituitary hormonal deficiencies for which they received substitution and more often received GHRAs and DAs at last visit. Total duration of follow-up was 3887 patient years with 2287 years in the SSA group and 1600 years in the non-SSA group. IGF1 SDS was not different between groups, both in absolute values and for the proportion of patients with adequate disease control (IGF1 SDS ≤2).

Comparison between centers

The patient groups from the UMCG and the Radboudumc were comparable on characteristics like sex, age at diagnosis, tumor size, type of surgery and most forms of substitution of pituitary deficiencies. Differences between centers were that patients from the UMCG had longer follow-up time and received postoperative RT more frequently. At last visit, they received glucocorticoid substitution more frequently and SSA less frequently and had significantly better disease control (Supplementary Table 1).

Mortality

A total number of 27 deaths was observed. Patient characteristics, details on treatment and causes of death are shown in Supplementary Table 2. Eleven patients died due to malignancy, four due to cardiac disease, six due to cerebrovascular disease, two due to other causes and in four cases the cause of death could not be established.

Table 1 Characteristics of patients with or without use of SSA at any moment postoperatively. Data are given as absolute numbers (percentage if no values missing) or as median (interquartile range).

	Total patients	Patients with SSA	Patients without SSA	*P* value
Number	319	174 (55)	145 (45)	
Female	171 (54)	86 (49)	85 (59)	0.115
Age*	46.3 (37.5;55.4)	42.9 (34.9;52.8)	49.6 (40.2;57.4)	<0.001
Life expectancy*	38.5 (29.7;47.0)	41.1 (33.1;49.1)	33.5 (26.8;43.3)	<0.001
Age at last visit or death*	59.0 (50.7;67.8)	57.9 (48.9;65.8)	59.7 (52.5;69.9)	0.014
Follow up*	10.7 (4.5;18.1)	11.8 (6.3;20.0)	8.6 (2.6;16.3)	0.008
Micro-/macroadenoma	63/235	22/139	41/96	0.001
TSS/craniotomy	300/18	158/15	142/3	0.013
Postoperative RT	117 (37)	92 (53)	25 (17)	<0.001
Substitution for pituitary deficiencies at last visit				
Any axis	165 (52)	110 (63)	55 (38)	<0.001
Thyroid hormone	101 (32)	69 (40)	32 (22)	0.001
Glucocorticoids	93 (29)	63 (36)	30 (21)	0.002
Sex hormones	79 (25)	59 (34)	20 (14)	<0.001
Antidiuretic hormone	18 (6)	10 (6)	8 (6)	1.000
Growth hormone	6 (2)	4 (2)	2 (1)	0.692
Medication at last visit				
SSA	119 (37)	119 (68)	–	–
GHRA	53 (17)	45 (26)	8 (6)	<0.001
DA	21 (7)	16 (9)	5 (3)	0.043
Disease control at last visit				
IGF1 SDS ≤2	296 (93)	160 (92)	136 (94)	0.665
IGF1 SDS	0.47 (−0.25;1.14)	0.55 (−0.10;1.25)	0.27 (−0.49;1.08)	0.066

*Age, life expectancy and follow-up in years at and from date of primary surgery.
DA, dopamine agonist; GHRA, growth hormone receptor antagonist; IGF1, insulin-like growth factor 1; RT, radiotherapy; SDS, standard deviation score; SSA, somatostatin analog; TSS, transsphenoidal surgery.

Table 2 Univariate log-rank test on associations of baseline characteristics, substitution of pituitary hormonal deficiencies, treatment modalities and metabolic control with mortality.

	Chi-square	*P* value	RR (95% CI)
Sex (female vs male)	0.907	0.341	0.69 (0.33;1.47)
Tumor size (macro- vs microadenoma)	2.39	0.122	0.53 (0.23;1.19)
Surgery type (craniotomy vs TSS)	6.20	**0.013**	3.53 (1.31;9.56)
Postoperative RT	0.36	0.55	0.79 (0.37;1.69)
Hormonal substitution at last visit			
Any axis	0.245	0.62	0.82 (0.38;1.77)
Thyroid hormone substitution	0.41	0.524	0.78 (0.36;1.69)
Glucocorticoid substitution	3.94	**0.047**	2.11 (1.01;4.41)
Antidiuretic hormone substitution	0.05	0.821	1.26 (0.17;9.23)
Medication at last visit			
SSA	3.36	0.067	2.01 (0.95;4.22)
GHRA	0.43	0.514	0.62 (0.15;2.59)
DA	3.79	0.052	2.54 (0.99:6.47)
Use of SSA at any moment postoperatively	1.67	0.196	1.66 (0.77;3.60)
IGF1 SDS >2	7.95	**0.005**	3.41 (1.45;8.00)

DA, dopamine agonists; GHRA, growth hormone receptor antagonists; IGF1, insulin-like growth factor 1; RR, relative risk; RT, radiotherapy; SDS, standard deviation score; SSA, somatostatin analogs; TSS, transsphenoidal surgery.

Determinants of mortality

In univariate analysis, the most important determinant of increased mortality was insufficient disease control at last visit, defined as an IGF1 SDS >2 (RR 3.41, $P=0.005$), as shown in Table 2. Surgery by craniotomy and glucocorticoid substitution was also found to be associated with increased mortality. SSA use at any moment postoperatively was not significantly associated with mortality, but there was a strong trend toward increased mortality for patients who used SSA (RR: 2.01, $P=0.067$) and/or DAs (RR: 2.54, $P=0.052$) at last visit.

Standardized mortality ratios

SMRs are shown in Table 3. Patients with adequate disease control at last visit who never used SSA postoperatively had a normal SMR (1.04, $P=0.875$). Patients with adequate disease control who used SSA at any moment postoperatively (1.07, $P=0.785$) and at last visit (1.19; $P=0.600$) also had a normal SMR. Insufficiently controlled patients (IGF1 SDS >2) had a significantly raised SMR (3.92, $P=0.006$), including patients who used SSA at any moment postoperatively (SMR: 7.25, $P<0.001$) and patients who used SSA at last visit (SMR: 7.02, $P=0.003$).

Discussion

In this study, postoperative use of SSA is not associated with increased mortality in patients with acromegaly who attain adequate disease control. In contrast, inadequate disease control, primary surgery by craniotomy and glucocorticoid substitution are associated with increased mortality. These are the first data available on the effects of SSA on mortality in patients who are not cured by pituitary surgery.

Esposito *et al.* recently demonstrated excess mortality in acromegaly in Sweden to have significantly declined over the past decades, coinciding with the

Table 3 Standardized mortality ratios.

Group	Number	Deaths	SMR (95% CI)	*P* value
Patients with adequate disease control (IGF1 SDS ≤2) at last visit never using SSA	136	9	1.04 (0.51;1.90)	0.875
Patients with adequate disease control (IGF1 SDS ≤2) at last visit using SSA at any moment postoperatively	160	12	1.07 (0.58;1.82)	0.785
Patients with adequate disease control (IGF1 SDS ≤2) at last visit using SSA at last visit	108	8	1.19 (0.55;2.25)	0.600
Patients with inadequate disease control (IGF1 SDS > 2) at last visit	23	6	3.92 (1.59;8.16)	0.006
Patients with inadequate disease control (IGF1 SDS >2) at last visit using SSA at any moment postoperatively	14	5	7.25 (2.66;16.1)	<0.001
Patients with inadequate disease control (IGF1 SDS >2) at last visit using SSA at last visit	11	4	7.02 (2.23;16.9)	0.003

IGF1, insulin-like growth factor 1; SDS, standard deviation score; SMR, standardized mortality ratio; SSA, somatostatin analogs.

increasing availability of medical treatment options (17). Additionally, Maione *et al*. found the proportion of patients in the French acromegaly register with adequate disease control to have increased over time (27). Holdaway *et al*. previously found that normalization of serum IGFI for age and sex was associated with normalization of mortality in patients with acromegaly, comparable to mortality in the general population (6). In our study, patients who used SSA postoperatively and attained adequate disease control (IGF1 SDS ≤2) had a normalized SMR. This provides evidence that SSA are an effective form of therapy for acromegaly, that not only provides disease control (13, 28) or reduces tumor size (29, 30), but also reduces the increased mortality caused by the disease. The paradigm of residual peripheral disease activity during use of SSA, i.e. extra-hepatic acromegaly as proposed by Neggers *et al*. (31), could not be found to result in increased mortality in this study.

In a previous study comparing the effect of primary use of SSA with surgical treatment of the disease, medical treatment resulted in a higher risk of death than surgery (RR: 5.52, 95% CI: 1.06–28.77, P=0.043). However, this study had several treatment selection biases, because patients treated with SSA were older, had a longer duration of disease at diagnosis and had higher IGF1 values. They also had more comorbidities making them unsuitable for surgery (16).

In our retrospective study encompassing nearly four decades, no data were available on disease activity before surgery. However, patients who were treated with SSA postoperatively more often had a macroadenoma, also received other forms of medical therapy and postoperative RT more often and had more pituitary hormonal deficiencies for which they received substitution, all implying higher disease activity. This was also reflected by a strong trend toward a higher IGF1 SDS at last visit in patients who used SSA postoperatively compared to patients who did not. In our study, all patients received surgery as primary treatment and therefore the indication for medical treatment was made postoperatively as a consequence of persistent or recurrent disease activity, and not for the purpose of primary treatment as was the case in the study of Bogazzi *et al*. (16). For these reasons, it is plausible that patients who received SSA postoperatively had more aggressive disease, which presumably translated into a strong trend in the univariate log-rank test toward an increased mortality for patients who used SSA at last visit. However, mortality in these patients in terms of SMR was only increased when disease activity at last visit as measured by IGF1 SDS was increased as well.

The retrospective design of this study carries several limitations. Biochemical criteria for the diagnosis of acromegaly have evolved and assays for quantification of GH and IGF1 have greatly improved (32). However, despite differences in assays used between centers and over a study period encompassing nearly four decades, the relationship between inadequate disease control (IGF1 SDS >2) and increased mortality stayed intact, as previously observed by others (5, 6). Only IGF1 concentrations at last visit were analyzed, a method of analysis that may not reflect exposure to both GH and IGF1 excess during all phases of the disease process and has several limitations in predicting mortality (33). Various changes have taken place in the treatment of acromegaly over the decades, including the introduction of the GH receptor antagonist pegvisomant in 2002 (34) and the increasingly restrictive use of RT due to improvements in the surgical and medical treatment of acromegaly.

It can be argued that under the null hypothesis of no effect of SSA on mortality, the mortality in the group of patients using SSA at any moment postoperatively will be lower than the mortality in the group of patients not using SSA, as patients who survive longer have more chance to use SSA. However, this is not the case, since the indication for SSA treatment is of major influence. SSAs were prescribed postoperatively either for control of persistent disease due to incomplete tumor resection or because of disease recurrence. The chance of recurrent disease is obviously higher in patients who survive longer. However, in acromegaly, disease recurrence after complete tumor resection by an experienced neurosurgeon is very uncommon (35). Patients who survive longer do not have a higher chance of incomplete tumor resection. In fact, patients with a decreased survival time due to acromegaly-related death have a higher chance to have an irresectable tumor and therefore have a higher chance to have an indication for postoperative treatment with SSA, as reflected in our patients' baseline characteristics and validating the statistical approach applied in this study.

Of interest is our finding that RT was not associated with increased mortality in this study. We have previously reported this in other pituitary patient cohorts as well (36). These results are in contrast to results reported by others (37, 38). New stereotactic RT techniques provide more precise targeting of the tumor with better control of the radiation dose received by adjacent brain structures. Long-term studies evaluating morbidity and mortality rates after these new techniques are needed in order to evaluate their brain-sparing effects (39).

Surgery by techniques other than transsphenoidal was shown to be associated with increased mortality, reflecting a subgroup of patients treated by older surgical techniques in combination with patients who had a large macroadenoma with probably aggressive disease that was inoperable through the transsphenoidal approach.

Cortisol substitution therapy was found to be associated with increased mortality in this study. This is in agreement with findings reported by Sherlock *et al.* (37). It could be speculated that ACTH deficiency is a surrogate marker for larger GH-producing tumors, that were operated on by craniotomy more frequently and in which adjuvant RT and substitution therapy was indicated more often. However, alternative explanations remain possible, such as the increased incidence of hypocortisolistic crises in this population (40).

In conclusion, in this retrospective study, the primary determinant associated with increased mortality was an IGF1 SDS >2. Mortality was not increased in patients treated postoperatively with SSA who attained adequate disease control. Larger, prospective studies are needed to confirm these effects of SSA on mortality in acromegaly.

Supplementary data
This is linked to the online version of the paper at https://doi.org/10.1530/EJE-18-0166.

Declaration of interest
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