Could different treatment approaches in acromegaly influence life expectancy? A comparative study between Bulgaria and Campania (Italy)

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Abstract

Background: Mortality in acromegaly strictly depends on optimal control of GH and IGF1 levels. Modern medical therapy with somatostatin analogs (SSAs) and GH receptor antagonists (GHRAs) is not available in many countries due to funding restrictions. This retrospective, comparative, cohort study investigated the impact of different treatment modalities on disease control (GH and IGF1) and mortality in acromegaly patients.

Methods: Two cohorts of patients with acromegaly from Bulgaria ($n=407$) and Campania, Italy ($n=220$), were compared, and mortality rates were evaluated during a 10-year period (1999–2008).

Results: The major difference in treatment approach between cohorts was the higher utilization of SSAs and GHRAs in Italy, leading to a decreased requirement for radiotherapy. Significantly more Italian than Bulgarian patients had achieved disease control (50.1 vs 39.1%, $P=0.005$) at the last follow-up. Compared with the general population, the Bulgarian cohort had a decreased life expectancy with a standardized mortality ratio (SMR) of 2.0 (95% CI 1.54–2.47) that was restored to normal in patients with disease control – SMR 1.25 (95% CI 0.68–1.81). Irradiated patients had a higher cerebrovascular mortality – SMR 7.15 (95% CI 2.92–11.37). Internal analysis revealed an independent role of age at diagnosis and last GH value on all-cause mortality and radiotherapy on cerebrovascular mortality. Normal survival rates were observed in the Italian cohort: SMR 0.66 (95% CI 0.27–1.36).

Conclusions: Suboptimal biochemical control was associated with a higher mortality in the Bulgarian cohort. Modern treatment options that induce a strict biochemical control and reduce the necessity of radiotherapy might influence the life expectancy. Other factors, possibly management of comorbidities, could contribute to survival rates.

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Introduction

Acromegaly is a rare disease with an estimated annual incidence of 3–4 cases/million population and a prevalence of 40–90 cases/million population (1, 2). More recent data (3, 4) have reported a higher prevalence of one case out of 8000–11 000 individuals. Typically, chronic growth hormone (GH) excess is caused by benign

pituitary adenoma. Owing to its indolent and insidious nature, diagnosis of acromegaly is often delayed for years (5). Approximately 60% of deaths are due to cardiovascular disease, 25% are due to respiratory disease, and 15% are due to malignancies. When patients have cardiac disease or diabetes mellitus at diagnosis, it is reported that

mortality occurs within 15 years in almost all patients with cardiac disease and only 20% of patients with diabetes would survive for 20 years (6). A GH value of $<2.5 \mu\text{g/l}$ (measured by RIA and probably $<1 \mu\text{g/l}$ measured by modern sensitive immunoassays) and insulin-like growth factor 1 (IGF1) levels normalized for age constitute the most predictive survival index (7). Thus, optimal control of GH and IGF1 is mandatory to ensure normal life expectancy in patients.

Treatment options currently available include surgery, medical therapy such as dopamine agonists (DAs), somatostatin analogs (SSAs), and GH receptor antagonists (GHRAs), and irradiation (8). While surgery and irradiation are used worldwide, modern medical therapies (i.e. SSAs and GHRAs) are not available in all countries due to their high cost. In Italy, SSAs have been available since 1988 and GHRAs were introduced in 2004. In Bulgaria, due to funding restrictions, none of these drugs were routinely available until 2008. As such, patients with acromegaly in Bulgaria and Italy may show difference in control of acromegaly and mortality as poor biochemical control due to lack of treatment options may lead to an earlier death.

Patients and methods

Study design

This was a retrospective, comparative, cohort study. Bulgaria and Campania region in Italy have a similar population of 7364.570 and 5864.662 inhabitants respectively (<http://www.nsi.bg/census2011/index.php>; <http://www.comuni-italiani.it/15/index.htm>). The Departments of Endocrinology in Sofia and Naples are both national referral centers for acromegaly; therefore, the comparison is considered as reliable. However, it should be stated that the Sofia center is the only one dedicated to pituitary diseases in Bulgaria while although the Naples center is well recognized, it is not the only one available, and therefore a greater actual number of more severe cases in the Naples series cannot be ruled out.

Inclusion criteria

Mortality in both centers was evaluated between January 1st 1999 and December 31st 2008. We included all consecutive patients who were alive by the end of 2008 or deceased during the upper period of time. Acromegaly was diagnosed during the period of 1955–2008. All patients were residents of Bulgaria or the Campania

region. The patients followed up in the University Hospital Federico II of Naples from Jan 1st 1997 were included in a registry approved by the Ethical Committee (no. 60/97). Recently, a Bulgarian database including all patients with acromegaly was created and also approved by the local ethical committee (9).

Patients were treated as lost to follow-up in both centers if their last visit has occurred before 2006 (unless deceased). Information regarding these subjects was obtained from local physicians in Campania, whereas in Bulgaria, patients were invited via mail and/or telephone to attend the clinic.

Subjects

A total of 407 patients treated at the Clinical Center of Endocrinology and Gerontology, Medical University – Sofia, Bulgaria, and 220 treated at Naples Federico II University Hospital, Italy, were included in the study. Bulgarian patients diagnosed before 1979 were irradiated as a first line of treatment, whereas subjects diagnosed later were primarily operated. Unsuccessful surgical intervention was a criterion for treatment with DAs. If medical therapy was inefficient, patients were reoperated or irradiated following medical counsel. In the case of irradiation, most of the patients have been treated with DAs until the effect of radiotherapy was set in. Treatment throughout the study was as follows: primary radiotherapy $n=20$ patients, of whom seven were additionally treated with DAs; primary DAs, $n=12$ patients; one surgical intervention, $n=126$ patients; one surgery + radiotherapy, $n=7$ patients, one surgery + DAs, $n=68$ patients; one surgery + radiotherapy + DAs, $n=21$ patients; two or more surgical interventions, $n=16$ patients; two or more surgeries + radiotherapy, $n=11$ patients; two surgeries + DAs, $n=32$ patients; and two or more surgeries + radiotherapy + DAs, $n=49$ patients. In Italy, a number of recent papers have described the treatment protocols (10, 11, 12, 13). During the study, 190 of the Bulgarian and 27 of the Italian patients were lost to follow-up and all of them had data relating to life/death status obtained from the civil registration and administrative services of both countries. Both baseline and follow-up GH and IGF1 samples were taken in the fasting state during routine hospital or outpatient assessment. Control of acromegaly in both centers after 1999 was defined as a basal GH level of $<2.5 \text{ ng/ml}$ and/or a GH level of $<1 \text{ ng/ml}$ during oral glucose tolerance test (OGTT) and normal age-adjusted IGF1 values (14). (When only one marker was present, remission was determined using it.) Both centers routinely

used CT/MRI to assess the pituitary adenoma size. However, while Italy switched from CT to MRI at the beginning of the 1990s itself, this change was made during the mid-1990s in Bulgaria, which might constitute a bias in the precise assessment of the adenoma size between both cohorts. The date and cause of death were determined from general practice and hospital records, or from death certificates.

Diagnoses of hypertension and diabetes mellitus were set up according to internationally accepted criteria at the time of their diagnoses or as current use of an antihypertensive or a glucose-lowering drug was present. Blood pressure and carbohydrate metabolism were evaluated at each visit in both centers but patients' compliance to therapy has not been considered for the purpose of this study. Comorbidities represent the cumulative data captured over the entire follow-up period. The analysis of comorbidities was performed at the time of the last visit.

Laboratory methods

In the Naples laboratory, GH levels were assessed using modern IRMA or immunoenzymatic methods (sensitivity from 0.2 to 0.05 $\mu\text{g/l}$). Serum IGF1 was measured by IRMA following ethanol extraction; normal ranges have been reported previously (15, 16). The assay sensitivity was 0.8 $\mu\text{g/l}$. In Bulgaria, serum GH levels from 1992 onwards were determined by a solid-phase two-site fluorometric assay based on a direct sandwich technique with two monoclonal antibodies directed against two different epitopes of the human GH molecule (DELFI; Perkin Elmer Life and Analytical Sciences, Wallac Oy, Finland). The sensitivity of this assay was <0.03 mIU/l. Until 1992, GH hormone values were measured by RIA. A conversion factor of two was used to transform the mIU/l units to $\mu\text{g/l}$. IGF1 levels were routinely assessed in the clinic from 1999 onwards. Serum IGF1 was measured using an IRMA following acid-alcohol extraction (Immunotech; Beckman Coulter Co., Marseille, France). The assay sensitivity was <0.26 nmol/l. Differences in IGF1 assay data were resolved using data transformation in the upper limit of normal (ULN) range (ULN=1).

Disturbances in any of the other pituitary axes were proven by appropriate biochemical tests or evidence of replacement therapy.

Statistical analysis

Results are expressed as mean $\pm$ s.d. or as median (range) in normally and non-normally distributed data respectively.

Continuous data were analyzed using Student's *t*-test, the Mann-Whitney *U* test when appropriate, and ANOVA analysis of more than two groups, while categorical data were analyzed using the χ^2 test. Possible predictors of mortality were studied only in the Bulgarian cohort due to the small number of deaths in the Italian one. For this purpose, Cox regression analysis was used adjusted for age and sex, as the number of females was twice more than that of males. In order to assess their independent predictive power, significant or near-to-significant variables in the univariate analysis were applied in a multivariate Cox regression analysis. All statistical analyses were performed using SPSS for Windows version 16.0 (SPSS, Inc.). The mortality of both cohorts was compared with the general population using the standardized mortality ratio (SMR), based on reference mortality data adjusted for age, sex, calendar year, and region of residence, obtained from the statistical institutes of Bulgaria and Campania. The expected number was estimated by multiplying age-, sex-, and calendar period-specific death rates in the general population by the person-years at risk accumulated within the age-, sex-, and calendar period-specific strata corresponding to the patient cohort. Exact 95% CIs and *P* values were obtained using the normal approximation in which the s.e.m. of the natural logarithm of the SMR is one divided by the square root of the observed number of deaths for the CIs and the expected number of deaths for the *P* value. Exact CIs were constructed and Poisson approximation for *P* values was used when the observed number of deaths was <100 . A *P* value of <0.05 was considered statistically significant (17).

Results

Characteristics of patients

Table 1 summarizes all patients' characteristics and presents comparison between both cohorts. Owing to the introduction of IGF1 assay from 1999 onwards in the Bulgarian center, the analysis of IGF1 values of Bulgarian patients was performed only in those having available data at diagnosis: 13.8% compared with 83.6% of the Italian patients. IGF1 values at the last follow-up were available in 58.2 and 85.4% of the Bulgarian and Italian patients respectively.

Treatment

The most important difference in the treatment approach between both cohorts was the availability of SSAs and

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Table 1 Patients' characteristics.

	Bulgaria	Campania (Italy)	P (exact two-tailed)
<i>n</i>	407	220	
Females	268 (65.8)	112 (50.9)	<0.001
Mean age at diagnosis (years)	41.8 ± 11.34	43.1 ± 13.32	0.22
Median baseline GH levels (μg/l)	21.5 (0.3–100.0)	23.0 (0.5–370)	0.23
Median baseline IGF1 levels (ULN)	2.7 (0.72–7.26)	2.0 (0.5–6.37)	0.001
	(<i>n</i> = 56)	(<i>n</i> = 184)	
Duration from diagnosis	13.73 ± 8.6	11.24 ± 7.34	<0.001
Years between symptoms and treatment	9.3 ± 5.4	8.6 ± 6.96	0.176
Number of deceased patients	71	7	<0.001
Tumor size			
Macroadenomas, <i>n</i> (%)	291/400 (72.5)	175 (79.6)	0.16
Comorbidities			
Hypertension, <i>n</i> (%)	229/398 (57.5)	71 (32.3)	<0.001
Diabetes, <i>n</i> (%)	106/393 (27)	47 (25.9)	0.144
Cancer, <i>n</i> (%)	26 (6.3)	10 (4.5)	0.375
Mean follow-up (years)	9.9 ± 8.5	8.3 ± 6.2	0.014
Median final GH levels (μg/l)	3.33 (0.05–50.0)	1.9 (0.1–63.0)	<0.001
Median final IGF1 levels (ULN)	0.94 (0.05–5.06)	0.74 (0.1–4.69)	0.006
	(<i>n</i> = 237)	(<i>n</i> = 188)	
Treatment throughout the study period			
Surgery, <i>n</i> (%)	329 (80.8)	158 (71.8)	0.012
Radiotherapy, <i>n</i> (%)	106 (26)	34 (15.5)	0.003
Somatostatin analogs (SSAs), <i>n</i> (%)	32 (7.8)	140 (63.6)	<0.001
Dopamine agonists (DAs), <i>n</i> (%)	184 (45.2)	87 (39.5)	0.205
GH receptor antagonist, <i>n</i> (%)	0	28 (12.7)	<0.001
Hypopituitarism			
Hypopituitarism of at least one axis, <i>n</i> (%)	87/356 (24.4)	43 (19.5)	0.182
Panhypopituitarism, <i>n</i> (%)	33/356 (9.3)	9 (4.1)	0.021
Hypogonadism, <i>n</i> (%)	144/280 (51.4)	53 (24.1)	<0.001
Hypothyroidism, <i>n</i> (%)	64/354 (18.7)	28 (12.7)	0.102
Hypoadrenalism, <i>n</i> (%)	42/355 (11.8)	27 (12.3)	0.89

GHRAs. SSAs were used in Bulgaria during a clinical trial for a short period of time and none of the patients were under such treatment by the time of the last visit. Therefore, surgical interventions and radiotherapy were more frequently performed in Bulgaria due to insufficient funding for the respective medications (Table 1). Besides, the use of radiotherapy (telegammatherapy) in Bulgaria remained relatively high over the years. The mean total dose $\pm$ s.d. was 45.3 ± 7.6 Gy. Only few patients had radiosurgery (gamma knife) that was performed out of the country. On the other hand, the use of radiotherapy in the Italian cohort sharply decreased after the introduction of SSAs in clinical practice, and conventional radioablation has been replaced by radiosurgery in most of the patients requiring radiotherapy. The use of DAs before the introduction of SSAs in clinical practice was comparable between the Campania and Bulgaria cohorts (39.5 vs 45.2%; Table 1). However, this practice changed over time, such that administration of DAs decreased in 16% (*n* = 35) of the Italian patients, the majority of whom used DAs in combination with SSAs or GHRAs, while it was still

followed in the Bulgarian cohort. Moreover, it was documented that Bulgarian patients had a higher frequency of hypogonadism and total hypopituitarism.

Treatment outcomes are summarized in Table 2. Significantly more patients in Campania have achieved normal IGF1 and safe GH levels at the last visit mainly due to the beneficial effect of the medical treatment. As no Bulgarian patient has been treated with SSAs or GHRAs at the last follow-up, we assume that this beneficial effect is related to the greater efficacy of the latter two.

Mortality data

Over the study period, deceased patients were significantly less in Campania (7) than in Bulgaria (71) by absolute numbers ($P < 0.001$) (Fig. 1). Moreover, the observed/expected ratio in Bulgaria was significantly higher compared with the general population, unlike the Italian one: 71/35.4 (95% CI 1.54–2.47; $P < 0.05$) vs 7/10.6 (95% CI 0.27–1.36; $P = \text{NS}$). Male/female ratio was 0.75 and 0.65 ($P = 1.00$) in Campania and Bulgaria respectively; mean

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Table 2 Treatment outcomes at the last visit in Bulgaria and Campania.

	Safe GH levels ^a			IGF1 (ULN) ≤1.0			Remission combined ^b		
	Bulgaria	Italy	P value	Bulgaria	Italy	P value	Bulgaria	Italy	P value
Surgery, n/total (%)	96/165 (58.2)	27/42 (64.2)	0.598	75/108 (69.4)	24/33 (72.7)	0.829	95/165 (57.6)	28/45 (62.2)	0.612
Rö without S, n/total (%)	8/18 (44.4)	2/5 (40)	1.0	2/5 (40)	3/3 (100)	0.196	8/18 (44.4)	2/5 (40)	1.0
S + M, n/total (%)	22/81 (27.2)	42/79 (53.2)	0.001	20/63 (31.7)	51/80 (63.8)	<0.001	14/81 (17.2)	41/84 (48.8)	<0.001
S + Rö, n/total (%)	24/39 (61.5)	11/14 (78.5)	0.333	18/25 (72)	8/10 (80)	1.0	24/41 (58.5)	11/14 (78.5)	0.215
S + Rö + M, n/total (%)	14/42 (33.3)	9/15 (60)	0.124	20/36 (55.6)	11/14 (78.6)	0.197	12/42 (28.6)	8/15 (53.3)	0.117
M only, n/total (%)	2/12 (16.7)	21/45 (46.7)	0.103	2/6 (33.3)	33/45 (73.3)	0.069	4/13 (30.8)	22/47 (46.8)	0.358
Others, n/total (%)	11/47 (23.4)	3/5 (60)	0.114	2/15 (13.3)	2/3 (66.7)	0.108	2/47 (4.3)	0/10 (0)	1.0
Total, n/total (%)	177/404 (43.8)	115/205 (56.1)	0.005	139/258 (53.9)	132/188 (70.2)	0.001	159/407 (39.1)	112/220 (50.9)	0.005

Rö, radiotherapy; M, medical therapy; S, surgery; Others, newly diagnosed patients without further information on treatment or patients without treatment.

^aSafe GH levels were defined as basal GH levels of <2.5 µg/l and/or GH levels of <1 µg/l during OGTT.

^bRemission is defined by both safe GH and normal IGF1 values. If one of the variables was missing, remission was defined by the present one.

age on diagnosis was higher in Campania without reaching statistical significance (53.7 ± 16.6 vs 46.4 ± 11.5 ; $P=0.129$). Mean age of death was similar between both countries: 61.3 ± 13.2 vs 61.9 ± 11.0 ($P=0.885$) for Campania and Bulgaria respectively. In Campania, 3/2.5 (observed/expected) patients died due to cardiovascular causes (one myocardial infarction and two heart failures), 3/5.7 due to neoplasms (uterus and pituitary tumor), and 1/8 due to other causes (nutritional disorder). In Bulgaria, 21/5.9 (observed/expected) patients died due to cerebrovascular causes (coded as stroke in 19 and chronic cerebrovascular disease in two), 31/13.4 patients due to cardiovascular causes (acute myocardial infarction in ten, chronic ischemic heart disease in six, heart failure in five, pulmonary thromboembolism in five, cardiac arrest in four, and cardiomyopathy in one), 12/8.4 patients due to malignant tumors (two cases with lung cancer; two with hepatic cancer; and one with prostate, breast, colic uteri, ovarian, cerebral, pancreatic, and colon cancers, and a melanoma), and 7/8.2 due to other causes (renal infection, COPD, pneumonia, chronic renal failure, diabetes mellitus, disease of the digestive tract, and nontoxic goiter).

As mentioned above, the estimated mortality of the Italian cohort, expressed as SMR, was similar to that of the general population, while Bulgarian patients had two times higher mortality rates compared with the general population. Patients in Bulgaria had significantly increased cerebrovascular and cardiovascular death rates (Table 3). Both irradiated and nonirradiated patients had an increased mortality with a predominance of cerebrovascular causes in irradiated and cardiovascular causes in nonirradiated patients. All-cause and vascular mortalities were restored to normal in patients in remission. However, the interpretation of cerebrovascular mortality in remission should be cautious due to the small number of deaths.

Effect of biochemical control and other factors on mortality

Factors predicting mortality in the Bulgarian cohort in univariate Cox regression analysis (adjusted for age and sex) were levels of GH and IGF1 at the last visit, duration of active disease, uncontrolled comorbidities (arterial hypertension, diabetes mellitus, and dyslipidemia), and patients lost to follow-up (Table 4). When these variables were applied in a multivariate analysis, age at diagnosis and last GH value remained as the independent predictors of mortality. IGF1 was excluded from the multivariate

Figure 1

Kaplan-Meier survival analysis in the Bulgarian and the Italian cohorts.

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Table 3 All-cause and cause-specific mortality of the Bulgarian cohort.

	Observed	Expected	SMR	95% CI	P
All-cause	71	35.4	2.00	1.54–2.47	<0.05
All-cause in remission	19	15.2	1.25	0.69–1.81	NS
Cardiovascular	31	13.4	2.31	1.49–3.13	<0.05
Cardiovascular in remission	6	5.7	1.05	0.21–1.89	NS
Cerebrovascular	21	5.9	3.54	2.03–5.06	<0.05
Cerebrovascular in remission	5	2.5	1.98	0.24–3.72	NS
Neoplastic	12	8.4	1.43	0.62–2.24	NS
Other causes	7	8.2	0.85	0.22–1.49	NS
All-cause irradiated	23	8.9	2.59	1.53–3.65	<0.05
Irradiated in remission	7	3.2	2.21	0.57–3.84	NS
Nonirradiated	48	27	1.77	1.27–2.28	<0.05
Nonirradiated in remission	11	11.5	0.96	0.38–1.52	NS
Cerebrovascular in irradiated	11	1.5	7.15	2.92–11.37	<0.05
Cerebrovascular in nonirradiated	10	4.4	2.28	0.87–3.69	NS
Cardiovascular in irradiated	7	3.4	2.08	0.54–3.62	NS
Cardiovascular in nonirradiated	24	10.1	2.38	1.43–3.34	<0.05

analysis due to the small number of deceased patients with available data ($n=14$) and consequently highly unreliable statistical results. A separate multivariate Cox regression model was built using the GH values before irradiation. GH values and age at diagnosis were significant predictors of mortality (hazard ratio (HR) 1.024 (95% CI 1.001–1.047), $P=0.037$ and HR 1.2 (95% CI 1.11–1.30), $P<0.001$), respectively, while lost to follow-up or control of arterial hypertension, diabetes, and dyslipidemia did not show any statistical significance. There was a trend for a higher rate of deaths in patients after unsuccessful surgery, 14.6% (34/233), vs cured patients after operation, 7.3% (7/96), $P=0.097$. However, the Cox model did not show any significant influence of surgical outcome on

mortality. Patients who were followed up regularly had a significantly higher percentage of hypopituitarism compared with patients who were lost to follow-up, 41.8 vs 24.4% respectively. As the actual rate of hypopituitarism by the end of the study period in the latter could not be estimated, the influence of hypopituitarism was studied in only regularly followed-up patients. Patients lost to follow-up were censored in the analysis of all the other variables. After being adjusted for age, none of the deficient axes were associated with higher HRs: hypogonadism HR 1.84 (95% CI 0.46–7.4; $P=0.389$); hypothyroidism HR 5.12 (95% CI 0.66–39.95; $P=0.119$); and hypoadrenalism HR 2.5 (95% CI 0.32–19.42; $P=0.38$). Panhypopituitarism vs no pituitary deficiency was not

Table 4 Effect of biochemical and other factors on mortality in acromegaly patients.

	Univariate sex- and age-adjusted Cox regression analysis			Multivariate Cox regression analysis		
	HR	95% CI	P	HR	95% CI	P
Gender (male)	0.68	0.41–1.13	0.14			
Age at diagnosis (years)	1.10	1.07–1.13	<0.001	1.11	1.08–1.15	<0.001
Last GH ($\mu\text{g/l}$)	1.02	1.01–1.03	<0.001	1.02	1.007–1.03	0.001
Last IGF1 (nmol/l)	1.01	1.01–1.03	<0.001			
GH at diagnosis	1.002	0.99–1.01	0.541			
Adenoma size at diagnosis (macroadenoma)	1.31	0.76–2.26	0.33			
Radiotherapy (yes vs no)	1.51	0.89–2.58	0.128			
Cured after surgery (no vs yes)	1.12	0.48–2.62	0.798			
Hypopituitarism ^a (yes vs no)	2.32	0.68–7.91	0.137			
Hypertension ^b (controlled vs uncontrolled)	2.20	1.27–3.82	0.005	0.87	0.45–1.67	0.673
Diabetes ^b (controlled vs uncontrolled)	3.03	1.54–5.93	0.001	0.79	0.35–1.76	0.557
Dyslipidemia ^b (controlled vs uncontrolled)	1.84	1.06–3.2	0.031	0.695	0.38–1.27	0.237
Lost to follow-up (yes vs no)	2.42	1.31–4.45	0.005	0.99	0.45–2.21	0.983

^aOnly regularly followed-up patients were analyzed.^bControlled includes also patients without hypertension, diabetes, or dyslipidemia, respectively.

associated with a significantly higher mortality ratio (HR 2.002 (95% CI 0.26–15.54); $P=0.51$).

As SMR for cerebrovascular death was increased in irradiated patients, we have additionally studied the effect of radiotherapy in this subset of the cohort. In a univariate analysis corrected for age and sex, radiotherapy was a negative predictor of survival with a HR of 4.54 (95% CI 1.54–11.68), $P=0.005$. In a multivariate analysis including age at diagnosis, GH values at last visit, lost to follow-up, arterial hypertension, diabetes, and dyslipidemia, irradiation remained an independent predictor of mortality with a HR of 5.75 (95% CI 1.75–19.2) $P=0.004$, together with age at diagnosis with a HR of 1.15 (95% CI 1.08–1.22), $P<0.001$, a trend in the last GH value with a HR of 1.02 (95% CI 0.997–1.04), $P=0.093$, and no statistically significant influence of the other variables.

In order to study the influence of different treatment modalities, patients were divided into three groups: group 1 (treated by surgery, $n=165$); group 2 (treated with adjuvant to surgery medical therapy (DAs), $n=81$), and group 3 (operated and irradiated +/- medical therapy, $n=83$) (Table 5).

Lost to follow-up vs regularly followed-up patients had significantly higher percentages of uncontrolled arterial hypertension (60% (48/80) vs 23.7% (32/135), $P<0.001$), dyslipidemia (83.2% (79/95) vs 63.3% (57/90), $P=0.003$), and comparable control of diabetes (35.9% (14/39) vs 26.6% (17/64), $P=0.378$). Active vs patients in remission had comparable percentages of uncontrolled comorbidities diabetes (31.6% (24/76) vs 25.9% (7/27), $P=0.634$), arterial hypertension (36.5% (46/126) vs 38.2% (34/89), $P=0.886$), and dyslipidemia (68.2% (73/107) vs 80.8% (63/78), $P=0.065$).

Discussion

This was a retrospective, comparative study of two acromegaly cohorts, in Bulgaria and Campania region in Italy, aiming at assessing the mortality during the period of 1999–2008 as related to different treatment modalities and control of acromegaly.

Since the first series of Wright *et al.* (18) in 1970 assessing the mortality, a number of studies have demonstrated that acromegaly is associated with a reduced life expectancy due to cardiovascular, cerebrovascular, respiratory diseases, and malignancy in different proportions (19). In accordance with our results of the Bulgarian cohort, increased vascular mortality has been reported in several studies (20, 21, 22, 23, 24). On the other hand, a tendency toward increased life expectancy has been observed in recent studies (22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34). They suggested that the improved survival rate could be due to more stringent criteria for remission and the introduction of modern and more efficient treatment options, such as SSAs and GHRAs. A recent meta-analysis by Holdaway *et al.* (7) has demonstrated that studies with >30% utilization of SSAs or >70% of remission rates reported normal life expectancy in contrast to higher mortality rates in those with lower percentages of SSA administration and remission rates. In line with these findings, the Campania cohort had a normal life expectancy – an SMR of 0.66 (95% CI 0.27–1.36; $P=0.269$) in agreement with two recent studies concerning mortality among the Italian population (33, 34, 35). Owing to funding restrictions in Bulgaria, SSAs and GHRAs were not available in clinical practice until 2008 and none of the patients were under such

Table 5 Characteristics of patients in the three treatment groups. Significance was assessed using ANOVA analysis in continuous variables and Fisher's exact test in categorical variables.

Variables	Surgery ($n=165$)	S+M ($n=81$)	S+Rö ($n=83$)	P value
Females, n (%)	99 (60)	54 (66.7)	64 (77.1)	0.027
Age at diagnosis (years)	44.1 ± 10.3	39.5 ± 12.9	36.1 ± 10.0	<0.001
Macroadenoma at diagnosis n (%)	95 (61.3)	64 (79)	75 (93.8)	<0.001
Last GH (mIU/l)	12.69 ± 20.55	18.47 ± 22.64	17.75 ± 27.08	0.101
Last IGF1 (nmol/l)	39.2 ± 33.04	56.97 ± 30.76	48.42 ± 42.03	0.006
Duration of follow-up (years)	11.6 ± 7.2	12.6 ± 8.0	16.9 ± 7.3	<0.001
Hypertension (absence or controlled), n (%)	119 (78%)	69 (86.3%)	62 (79%)	0.298
Diabetes (absence or controlled), n (%)	148 (94.2)	71 (87.7)	76 (95.1)	0.159
Dyslipidemia (absence or controlled), n (%)	92 (62.1)	56 (71.8)	45 (58)	0.147
Deceased patients, n (%)	25 (15.2)	6 (7.4)	10 (12)	0.229
Age at death (years)	57.0 ± 9.6	56.0 ± 12.9	57.5 ± 8.6	0.957
Lost to follow-up, n (%)	84 (50.9)	23 (28.4)	26 (31.3)	<0.001

S+M, surgery plus medical treatment; S+Rö, surgery plus radiotherapy +/- medical therapy.

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treatment at the last visit. Bulgarian patients had access only to DAs (bromocriptine and cabergoline) known for their lower efficacy in acromegaly (36, 37). The lack of SSAs and GHRAs and the poorer efficacy of DAs are the most possible explanation for the significantly higher rates of other treatment options, such as neurosurgical interventions and radiotherapy. These differences in the treatment approach resulted in a significantly better biochemical control (safe GH and normal IGF1 levels) of acromegaly in Campania, mainly due to adjuvant medical therapy (Table 2). As expected, the mortality was significantly higher in Bulgarian vs Campania patients when evaluated by absolute numbers (71 vs 7 deceased patients; $P < 0.001$) (Fig. 1) and compared with both general populations (Table 3).

The higher all-cause and vascular mortality in the Bulgarian cohort were restored to normal in patients in remission with an SMR of 1.25 (95% CI 0.69–1.81) for all-cause and SMR of 1.05 (95% CI 0.21–1.89) for cardiovascular deaths. Cerebrovascular death was also without any significant difference with respect to the general population, although SMR was almost two times higher at 1.98 (95% CI 0.24–3.75, $P = \text{NS}$). The latter result should be interpreted with caution, as the number of deaths was relatively small. The beneficial effect of biochemical control on the outcome has been widely investigated. Bates *et al.* (38) were the first to demonstrate that an increased mortality was reduced to normal when GH levels reached $< 2.5 \mu\text{g/l}$. Their observations were supported by numerous further studies (22, 26, 27, 28, 29, 30, 32, 38, 39) with a pooled SMR of 1.1 (0.9–1.4; $P = 0.50$) (7). Some research groups reported even lower GH targets: $2 \mu\text{g/l}$ by Ayuk *et al.* and a further improvement in mortality when GH was reduced to $< 1 \mu\text{g/l}$ (23, 26). Indeed, the last GH value (or post-glucose GH (30)) has been ascertained as a strong predictor of mortality by uni- and multivariate analyses in various surveys (23, 26, 27, 33, 35). In agreement, the last GH value was an independent predictor of mortality in our study as well (Table 4). Mortality rates were restored to levels comparable to the general population when IGF1 values were also below the ULN (25, 26, 30, 39). Although the majority of patients with normal IGF1 values had safe GH levels, the independent role of the growth factor for survival was not demonstrated in such a definite manner (23, 26, 27, 33, 35). A probable explanation for such controversial results could be the relatively smaller number of patients tested for IGF1, methodological difficulties in IGF1 measurements, as well as the lack of own age-adjusted reference values. In the Bulgarian cohort, IGF1 was a

negative predictor of survival in the univariate analysis but due to the small number of deceased patients with available IGF1 values, its role as an independent predictor of mortality could not be reliably studied.

Apart from factors specific for acromegaly, other classical risk factors influencing particularly vascular mortality, such as hypertension, diabetes, and dyslipidemia, might influence the life expectancy. Control of these comorbidities in the Bulgarian cohort significantly improved the survival prognosis according to the univariate Cox model. Only few surveys have demonstrated an independent predictive role of diabetes and/or hypertension (18, 20, 26). Cardiovascular and glucose metabolism alterations are known to be more frequent in patients with acromegaly and dependent on disease control (6). This interrelation could be a possible explanation for the observation that comorbidities have lost their significant influence in multivariate analysis where biochemical status has preserved its dominant role (2, 33, 35, 38). In agreement, in our study, hypertension, diabetes mellitus, and dyslipidemia were not independent predictors of mortality in the multivariate analysis. However, comorbidities could not be neglected, because there are no studies to properly investigate the complex interrelation between their management and outcomes in acromegaly as yet. Furthermore, as acromegaly is a rare disease, the number of censored patients always remains relatively small, which could question the reliability of the statistical results.

With regard to the specific treatment approach, the detrimental effect of radiotherapy has been seriously studied in the last decade (40, 41). Thus far, four studies have presented SMR in irradiated vs nonirradiated patients with acromegaly and all of them have demonstrated significantly increased death rates with respect to radiotherapy, mainly due to higher cerebrovascular death rates (23, 24, 27, 34). Radiotherapy has also been proved to be an independent predictor of mortality (23, 24, 31, 33, 35). In our study, both irradiated and nonirradiated patients had a higher all-cause mortality compared with the general population, with SMRs of 2.59 (95% CI 1.53–3.65) and 1.77 (95% CI 1.27–2.28) respectively. However, telegraphamtherapy was associated with seven times higher cerebrovascular death rate than expected – an SMR of 7.15 (95% CI 2.92–11.37) while other vascular mortalities were not significantly increased (Table 3). Regression analysis revealed similar data – radiotherapy was a strong independent predictor of cerebrovascular mortality. Direct comparison with other studies with regard to the all-cause mortality could be hampered by different

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proportions of death causes and different time periods between irradiation and censoring.

Patients who underwent surgery as the only treatment had a better biochemical profile at the time of the last follow-up; however, the number of deceased patients was similar compared with those treated with medical therapy and/or radiotherapy. Probably, some other factors have influenced the outcome, which we could not study due to the small number of deceased patients in the groups. The relatively low cure rates after surgery (29% overall) could have also been a factor impeding a manifestation of beneficial influence of successful surgery on mortality. With regard to treatment options, a recent survey has shown for the first time a higher death risk in acromegaly patients with diabetes mellitus treated with primary SSAs despite appropriate correction for several covariates (35). Owing to the small number of patients on primary medical therapy (DAs) in the Bulgarian population, its effect on mortality has not been examined.

Tumor expansion and especially time after radiotherapy are associated with an increased risk for hypopituitarism in acromegaly (19). Hypopituitarism has been related to an increased mortality in nonfunctioning pituitary adenomas although its independent role for decreased survival in acromegaly is disputable (40). Most of the studies did not demonstrate association or predictive role of pituitary deficiency in either of the axes (26, 31, 33, 34). In agreement, hypopituitarism was not related to a higher mortality in the Bulgarian cohort. However, the analysis of patients from the West Midland Database showed an increased mortality risk in patients with ACTH deficiency and especially those on higher doses of hydrocortisone (>25 mg daily), explained by mechanisms similar to adrenal deficiency and Cushing's syndrome (24). Patients with hypopituitarism had an increased mortality rate close to significance in a multivariate model with IGF1 in the study by Bogazzi *et al.* (35).

Undoubtedly, the current study has several weak points. The period of evaluation of mortality is shorter than the period of follow-up, which could create a bias in our results. However, acromegaly is a rare disease and evaluation of 10-year mortality since diagnosis would not provide a sufficient number of both alive and deceased patients to draw reliable conclusions. On the other hand, assessment of mortality for a longer period of time could have been hampered by the lack of reliable normative mortality data of the general population or life/death status of all consecutive patients. Inclusion of patient-years before modern treatment in Italy was available could also bias our findings. External analysis (comparison between

the study and general population) and, moreover, comparison between two different study cohorts originating from different general populations has its pitfalls as there could be a number of difficult-to-measure variables. In line with this, Bulgarian and Italian populations have some differences in cardiovascular risk factor burden that should be taken into consideration when speculating over the mortality rates of both cohorts. By the end of the study (2008), the prevalence of hypertension, obesity, and smoking was higher in Bulgaria than in Italy: 51.4 vs 46.1%; 23.7 vs 19.1%; and 34.3 vs 19.6% respectively (www.who.int/nmh/countries/), while the mean total cholesterol and fasting glucose levels were of comparable values. Standardized death rate per 100 000 for diseases of the circulatory system was several times higher in Bulgaria (611.28) than in Italy (173.8) (www.data.euro.who.int/hfad/b/). Furthermore, apart from the treatment approach and treatment outcomes, both patient cohorts had some baseline differences (Table 1). We have tried to overcome the differences between cohorts by performing internal analysis of factors influencing mortality in the Bulgarian cohort. Clearly, the retrospective nature of the study might have biased data collection of comorbidities and this deserves a carefully designed prospective study to better understand the power of individual comorbidity and its treatment on mortality in acromegaly.

Conclusion

This retrospective study compared the mortality rates during the period of 1999–2008 of two acromegaly cohorts followed up for over a 40-year period of time. The more frequent adjuvant medical therapy and especially the use of SSAs and GHRA in Campania, as well as leading to a decreased use of radiotherapy, was the major difference in treatments between both patient populations. The integrated approach resulted in a better disease control of the Italian patients. Bulgarian patients had an increased vascular mortality and, as a result of relatively high use of conventional radiotherapy by modern standards, an increased cerebrovascular death rate. Although both patient cohorts originate from populations with different risk factor backgrounds, disease activity in this study was demonstrated to be a major predictor of mortality. In line with this, we speculate that modern treatment options by reducing hormone levels could increase the life expectancy. Nevertheless, due to the high circulatory death rates of the general population in Bulgaria, the influence of comorbidities, such as hypertension, diabetes, and dyslipidemia, could not be thoroughly neglected. The additional beneficial effect

of comorbidities' management remains to be elucidated in future prospective studies.

Declaration of interest

This study did not receive any financial support. During the study period, A Colao was recipient of unrestricted grants by Ipsen, Italfarmaco, Novartis, and Pfizer for research programs in acromegaly, received lecture fees from Ipsen, Italfarmaco, Novartis, and Pfizer, and has been a member of the Scientific Boards of Novartis and Ipsen. R Pivonello received lecture fees from Novartis. S Zacharieva received lecture fees for lectures on acromegaly from Novartis and Pfizer. None of the other authors have any conflict of interest to disclose.

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