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Long-Term Mortality after Transsphenoidal Surgery and Adjunctive Therapy for Acromegaly*

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ABSTRACT

To analyze the long term outcome after multimodality therapy for acromegaly, a retrospective review was performed on 162 patients who underwent transsphenoidal surgery at Massachusetts General Hospital between 1978 and 1996. The surgical cure rate for microadenomas was 91%, that for macroadenomas was 48%, and it was 57% overall. The surgical cure rate was significantly dependent on tumor size, but was not dependent on age or sex. An improvement in the surgical cure rate was noted over the course of the review, from 45% before 1987 to 73% since 1991. Long term follow-up was obtained in 99% of U.S. residents (149 of 151), with a mean follow-up period of 7.8 yr. Adjuvant radiation and/or pharmacological therapy was given to 61 patients. Of the entire group, 83% (124 of 149) were in biochemical remission as determined by normalization of serum insulin-like growth factor I levels or by GH suppression after oral glucose tolerance testing at last contact or at death. The recurrence rate was 6% at 10 yr and 10% at 15 yr after surgery in those patients who initially met the criteria for surgical cure. The 10-yr survival rate was 88%, and there were 12 deaths at postoperative intervals of 2–12 yr, with the most common cause of death being cardiovascular disease. A Cox proportional hazards model showed that patient-years with persistent disease carried a 3.5-fold [95% confidence interval (CI), 1.0–12; $P = 0.02$] relative mortality risk compared to those patient-years in remission. A Poisson person-years regression analysis showed no significant difference in survival between those 86 patients cured at operation and an age- and sex-matched sample from the U.S. population [standardized mortality ratio (SMR), 0.84; 95% CI, 0.3–2.2; $P = 0.35$]. A similar analysis on the entire group of 149 patients showed no significant difference in survival from that in a control sample (SMR, 1.16; 95% CI, 0.66–2.0; $P = 0.3$). Mortality risk for patient-years with persistent active disease after unsuccessful treatment *vs.* that in the U.S. population sample remained increased (SMR, 1.8; 95% CI, 0.9–3.6; $P = .05$). This analysis suggests that the decreased survival previously reported to be associated with acromegaly can be normalized by successful surgical and adjunctive therapy. (*J Clin Endocrinol Metab* **83:** 3419–3426, 1998)

THE CURRENT management of acromegaly has become truly multidisciplinary, with contributions from endocrinology, neurosurgery, and radiation oncology. The long term results of this approach are not yet documented in the literature, with separate reports of surgical treatment, radiation therapy, and pharmacological management. Outcome studies for these different treatments describe relative remission rates, but do not focus on long term mortality and morbidity. Previous studies, therefore, may not accurately reflect long term mortality in patients treated with current multimodality therapy. Although a number of natural history studies have focused on the overall increase in mortality associated with acromegaly (1–6), these studies have analyzed heterogeneous patient groups in terms of both the treatment used and the degree of disease control and have combined treated and untreated patients. To determine the long term outcome and mortality in patients treated with combined multimodal therapy, we have reviewed the records of 162 patients with acromegaly who underwent transsphenoidal surgery at Massachusetts General Hospital (MGH) as their primary therapy, followed by adjuvant external beam radiation and/or medical management if necessary. We report that those patients who were surgically cured or placed in remission by adjuvant treatment have a mortality risk not significantly different from that of a sample based on U.S. population data, suggesting that our current multimodality therapeutic regimen appears to normalize the increased mortality associated with acromegaly.

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Subjects and Methods

Patient population

A retrospective chart review was performed on 162 patients who underwent transsphenoidal surgery for acromegaly at the MGH between 1978–1996. Eleven patients were foreign nationals; these cases were excluded from long term outcome analysis because comparative mortality risk was determined on the basis of U.S. population statistics. An attempt was made to contact all 151 remaining patients for a follow-up questionnaire, which addressed surgical and disease-related morbidity, current remission status, need for additional therapy or hormone replacement, and ongoing disability. Follow-up was obtained for 149 of 151 patients (99%). Two U.S. nationals could not be contacted for long term follow-up; one is assumed to be alive on the basis of retirement records, but remission status could not be determined. Both of these patients are considered lost to follow-up for the mortality and recurrence analyses, but are included in surgical remission data, as are the 11 foreign nationals. Mortality and cause of death were confirmed by contact with the patient's family or physician or by death certificate.

Endocrine evaluation

All patients exhibited classic signs and symptoms of acromegaly, with endocrine diagnosis confirmed by elevated baseline GH levels associated with failure of GH suppression to less than 2 ng/mL after oral glucose loading (OGTT), or an elevated serum insulin-like growth factor I (IGF-I) level. For patients early in the series when IGF-I assays and GH suppression studies were not available, diagnoses were made by the presence of the clinical syndrome associated with an elevation in baseline GH levels to greater than 5 ng/mL. The analysis of postoperative cure was complicated by the changes in criteria for the diagnosis of acromegaly that occurred over the course of the review. The surgical cure rates reported here were based on postoperative serum IGF-I levels in 82% of cases, on GH suppression after OGTT in 7.5% of cases, and on random GH levels in 10.5% of cases (Table 1). Although a GH level below 5 ng/mL was the accepted criteria for cure in clinical use during the early years of this review, for the purposes of our study we have imposed a stricter standard of a GH level below 2.5 ng/mL in those patients for whom no more recent data are available (7). By this criterion, none of the 10.5% of patients analyzed by random GH levels are considered cured. No independent attempt was made to reassess pituitary insufficiency, and the need for long term postoperative adrenal and thyroid replacement was determined on the basis of medication lists provided by the patient. Gonadal steroid replacement was reported for men, but not for women, given the variable indications for their use in females. Current remission status for patients not cured by the surgical procedure was determined by review of their most recent endocrine data; disease recurrence after initial surgical cure, however, was determined on the basis of patient report and not by independent reassessment of their current IGF-I levels.

Treatment protocol

All 162 patients underwent transsphenoidal surgery at MGH, although 17 patients had undergone previous therapy before their surgery here. Adjuvant treatment for those patients not surgically cured was individualized on the basis of the site and size of residual tumor, the magnitude of persistent GH and IGF-I elevation, and patient medical condition and preference.

Human studies

Chart review and patient contact were approved by the Subcommittee on Human Studies of MGH.

Statistical analysis

To analyze the relationship between cure after transsphenoidal surgery and clinical variables, a multivariate logistic regression analysis was used (8). Kaplan-Meier product-limit estimation with 95% confidence intervals and Cox multivariate regression were used to analyze survival experience in the cohort (9). For multivariate Cox analysis, a step-up model-building procedure was used, with a threshold P value of 0.05 for entry into the model. A time-dependent covariate was used to analyze the difference in mortality between time spent in remission *vs.* time spent with active disease. For comparison between survival in the patient cohort and that in an age- and sex-adjusted sample from the United States population, the person-years Poisson regression method was used to calculate a standardized mortality ratio, with 95% confidence intervals (CIs) (10, 11). For graphic display, the Kaplan-Meier estimate of survival in the patient cohort is shown together with the conditional survival estimate for an age- and sex-matched sample from the U.S. population calculated using Verheul's conditional survival method (12). Statistical significance for the standardized mortality ratios was determined using the one-tailed test, both because acromegaly is unlikely to prolong survival and to allow comparison with previous studies, which also have reported one-sided significance tests (2). All other tests of significance were reported as two-tailed. Statistical computations were performed using S-PLUS software (version 3.3, MathSoft, Seattle, WA).

Results

Between 1979–1996, 162 patients underwent transsphenoidal surgery for acromegaly. The mean age was 44 yr (median, 41 yr; range, 20–78 yr), with a male/female ratio of 1:1.2.

Cure of acromegaly after transsphenoidal surgery

The combined surgical cure rate for all tumors regardless of previous treatment or tumor size was 57% (92 of 162). The majority of tumors (129 of 162; 80%) were macroadenomas (tumor diameter, >1 cm), whereas 20% (33 of 162) were microadenomas (tumor diameter, <1 cm). The surgical cure rate was highly dependent on the size of the tumor at presentation; in microadenomas, the cure rate was 91% (30 of 33), whereas in macroadenomas, the cure rate was 48% (62 of 129). Of the 162 patients, 145 (90%) were newly diagnosed and had had no prior treatment. Ten percent (17 of 162) of patients had undergone other therapy before their surgery here. Of the 11 patients with previous transsphenoidal surgery, 8 (73%) were cured by a second procedure at MGH. Two patients had undergone previous craniotomy, and neither had normalization of IGF-I levels after a transsphenoidal operation, whereas only 1 of the 4 who had failed previous radiation therapy achieved surgical remission.

Effect of clinical variables on surgical cure rate

Over the 19 yr encompassed by this series, the surgical cure rate has improved. Before 1987, the overall cure rate regardless of tumor size was 45%, whereas from 1991–1996, it was 73%. There has been a steady increase in cure rate over the course of the study, accompanied by an increase in the

TABLE 1A. Criteria for cure in 162 patients after transsphenoidal surgery

Criteria for cure	Patients analyzed	Reported as cured	Reported as uncured
Serum IGF-I levels	133	85	48
GH suppression <2 ng/mL by OGTT	12	7	5
Random GH <2.5 ng/mL	17	0	17
Total [no. (%)]	162	92 (57)	70 (43)

1B. Criteria for remission in 61 patients requiring adjuvant therapy

Criteria for remission	Patients analyzed	In remission	Not in remission
Serum IGF-I levels	60	42	18
GH suppression <2 ng/mL by OGTT	1	1	0
Random GH <2.5 ng/mL	0	0	0
Total [no. (%)]	61	43 (70)	18 (30)

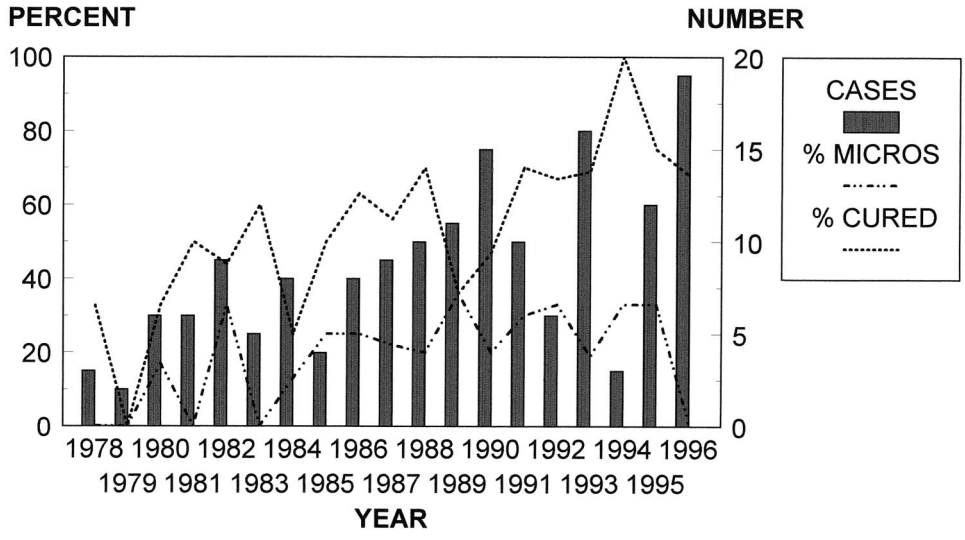

FIG. 1. The percent surgical cure per yr is shown as function of operative year, with the percentage of cases presenting as microadenomas.

total number of cases per yr and the percentage of those cases presenting as microadenomas (Fig. 1). A multivariate logistic regression analysis was performed to determine the effect of clinical variables, including tumor size, patient age, sex, and date of surgery, on surgical cure rate. Age and sex were not significant predictors of surgical cure. The odds of cure were 3.3-fold higher for patients with microadenomas than for those with macroadenomas ($P < 0.001$). The surgical cure rate improved at a rate of 1.11/yr ($P < 0.001$). The odds of cure at the conclusion of the series (1996) were 7.6-fold greater than those at the beginning of the series (1978), and this effect was independent of tumor size. A 1.8-fold relative increase in the odds of a tumor presenting as a microadenoma was noted over the course of the study, but this trend did not reach statistical significance.

Treatment of recurrent disease

Of the 149 patients with long term follow-up, 86 (58%) were cured by transsphenoidal operation. Five patients (5 of 86; 6%), 2 with microadenomas and 3 with macroadenomas, developed recurrent disease by biochemical criteria, with a mean time to recurrence of 5 yr. A Kaplan-Meier analysis presenting fractional remission as a function of postoperative interval is shown in Fig. 2; the recurrence rate was 4% at 5 yr (95% CI, 0–8%), 6% at 10 yr (95% CI, 0–13%), and 10% at 15 yr after surgery (95% CI, 0–19%). Four of these 5 recurrences were from the group of patients initially thought to be cured by IGF-I criteria. Repeat transsphenoidal surgery was performed in 3 of the 5 patients. One patient was in remission after reoperation, whereas the other 2 required adjuvant therapy; all are currently in remission. The fourth patient was treated medically and is also in remission. The fifth patient died without further therapy.

Complications

Surgical mortality and morbidity. There was no perioperative mortality in this series. Two patients required reoperation for repair of cerebrospinal fluid rhinorrhea (2 of 162; 1.2%), and 1 developed postoperative meningitis. One patient returned 1 week after surgery with severe epistaxis and required embolization of sphenopalatine arterial branches. One patient suffered a perioperative intraparenchymal hemorrhage from a cavernous angioma in the frontal lobe, unrelated to the transsphenoidal surgical approach. Five patients (3%) reported severe intermittent sinusitis; 1 was found to be colonized with aspergillus on exploration for sinus drainage.

Postoperative hormone replacement

Five of the 104 patients (5%) who did not receive postoperative adjuvant radiation therapy required adrenal steroid replacement therapy. Six patients (6%) required new postoperative replacement of thyroid hormone, and 3 males (6%) required testosterone replacement. In contrast, 52% of the 45 patients who underwent radiation therapy (4 preoperatively) required at least 1 form of hormone replacement: 33% received adrenal steroid replacement, 38% required thyroid hormone, and 31% of males received testosterone. There were 2 cases of permanent diabetes insipidus (2 of 149; 1.3%).

Multimodal therapy for long term disease control

Long term follow-up was obtained in 149 of the 151 U.S. patients (99%), with a mean follow-up of 7.8 yr (range, 1–19 yr; median, 7 yr; Table 2). There were 1162 total patient-years of follow-up, with 422 total patient-years of active disease.

Of these 149 patients, 83% (124 of 149) were in remission at last contact or at time of death. Eighty-one (54%) remained surgically cured without recurrence, 61 (40%) received adjuvant therapy, 5 (3%) died without additional treatment (1 with recurrent disease), and 2 (1.0%) are under observation with intermittently elevated IGF-I levels. The remission criteria for adjuvant therapy are shown in Table 1B, and the results of this treatment are shown in Table 3. Forty-five patients received radiation (including 4 who had failed this therapy preoperatively), usually in conjunction with medical treatment, and 16 were managed medically. Of the 45 patients treated with radiation, 19 (42%) are currently in remission or were at the time of death without additional

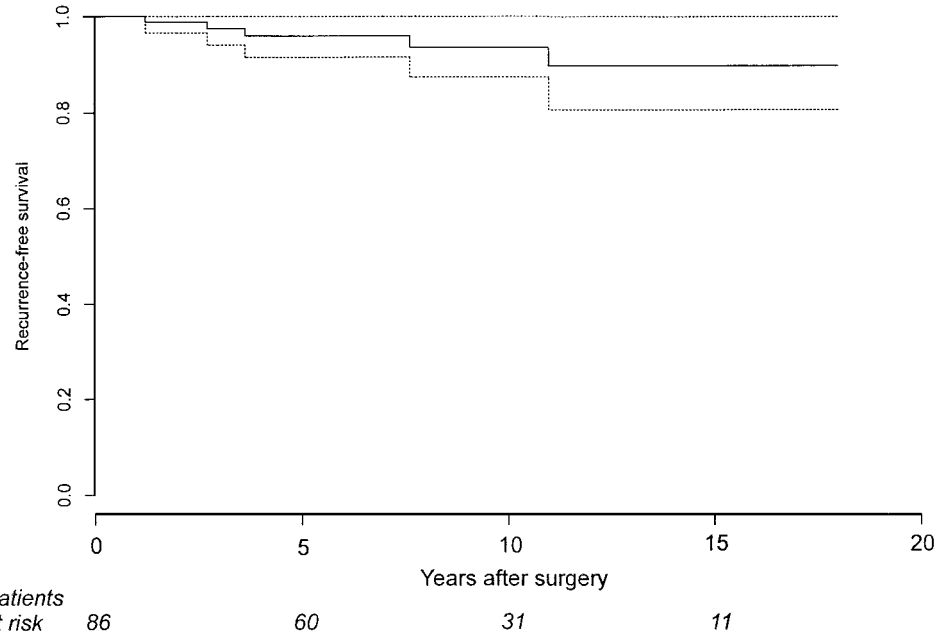

FIG. 2. Kaplan-Meier plot showing recurrence-free survival in 86 patients with long term follow-up who were placed in remission after transsphenoidal surgery. *Dotted lines* indicate the 95% confidence limits.

TABLE 2. Age distribution, follow-up interval, and deaths by age

Age at operation (yr)	No. of patients	Mean follow-up (yr)	Deaths (observed)
<20	1	9.2	0
21–30	30	9.1	1
31–40	38	7.4	0
41–50	33	7.6	2
51–60	27	7.3	0
61–70	13	8	3
>71	7	6.9	6
Total	149	7.8	12

treatment, with a mean time to remission of 6.7 yr after radiation therapy. Twenty-three patients (23 of 45; 51%) are receiving concurrent somatostatin analogues (17 patients), dopamine agonists (5 patients), or both (1 patient) in addition to having been irradiated. Three of these patients died with active disease despite radiation. Of the 16 patients treated solely with medical therapy, 14 of 16 (88%) now are in remission (1 patient has refused radiation despite failure of octreotide, and 1 patient maintained on bromocriptine has minimally elevated IGF-I levels). Somatostatin analogs, with or without dopamine agonists, have been used in 30 patients overall (including both those 18 patients treated with radiation and 12 treated with medication alone); IGF-I levels have normalized in 63%. In those 15 patients who remain alive but not in remission, the reasons for treatment failure are varied. Eight patients are true treatment failures; they have persistently elevated serum IGF-I levels despite surgery, radiation, and maximal octreotide dosage. One patient has elevated serum IGF-I levels with maximal octreotide treatment, but has refused radiation; 4 patients have marginally elevated IGF-I levels with bromocriptine treatment (3 after x-ray therapy), and 2 patients have recently begun octreotide therapy and are not yet at the optimal dose.

TABLE 3. Adjuvant therapy for residual/recurrent disease after unsuccessful transsphenoidal surgery

	Remission	Not in remission	Total
XRT			
A. With no other current therapy	19[a]	3[b]	22
B. Currently on octreotide	7	10	17
C. Currently on bromocriptine	2	3	5
D. Both Octreotide/bromocriptine	1	0	1
Total XRT	29	16	45
Medical therapy alone			
A. Currently on octreotide	9	1	10
B. Currently on bromocriptine	3	1	4
C. Both octreotide/bromocriptine	2	0	2
Total medical therapy	14	2	16
Total adjuvant treatment	43	18	61
Combined treatment [no. (%)]	124 (83)[c]	25 (17)[d]	149 (100)

[a] Two of 19 patients have died.
[b] All three patients have died.
[c] Includes 81 patients with long term surgical remission plus 43 patients in remission after adjuvant treatment.
[d] Includes 18 patients with active disease despite adjuvant therapy (three of whom have died), five patients who died without additional treatment, and two patients currently being followed without adjuvant therapy.

Long term mortality after transsphenoidal surgery

Long term survival data were available for 149 of the 151 patients residing in the U.S. (99%). There were 12 deaths in this group at postoperative intervals of 2–12 yr (median, 8.5 yr); no patient died during the perioperative period. Four deaths occurred in the 124 patients who achieved remission, whereas the remaining 8 deaths were in the 25 patients with persistent acromegaly. Patients who died were more likely to have active disease (odds ratio, 14; 95% CI, 3–69; $P < 0.001$).

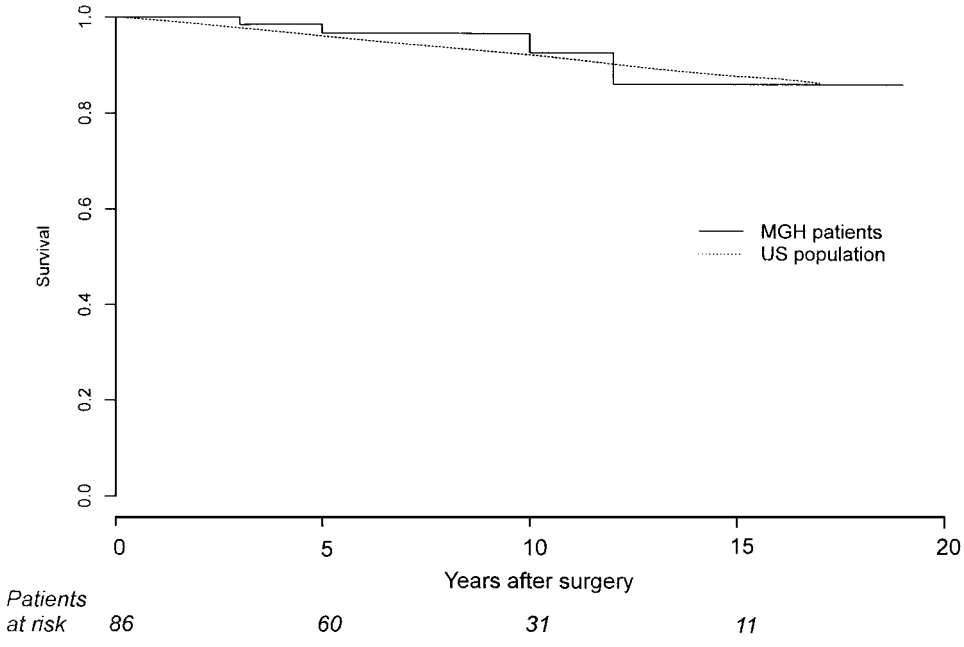

FIG. 3. Poisson person-years regression model showing survival after curative transsphenoidal surgery in 86 patients. The *dotted line* indicates the expected survival for an age- and sex-matched sample from the U.S. population. There is no significant difference in survival (SMR, 0.84; 95% CI, 0.3–2.2; $P = 0.35$).

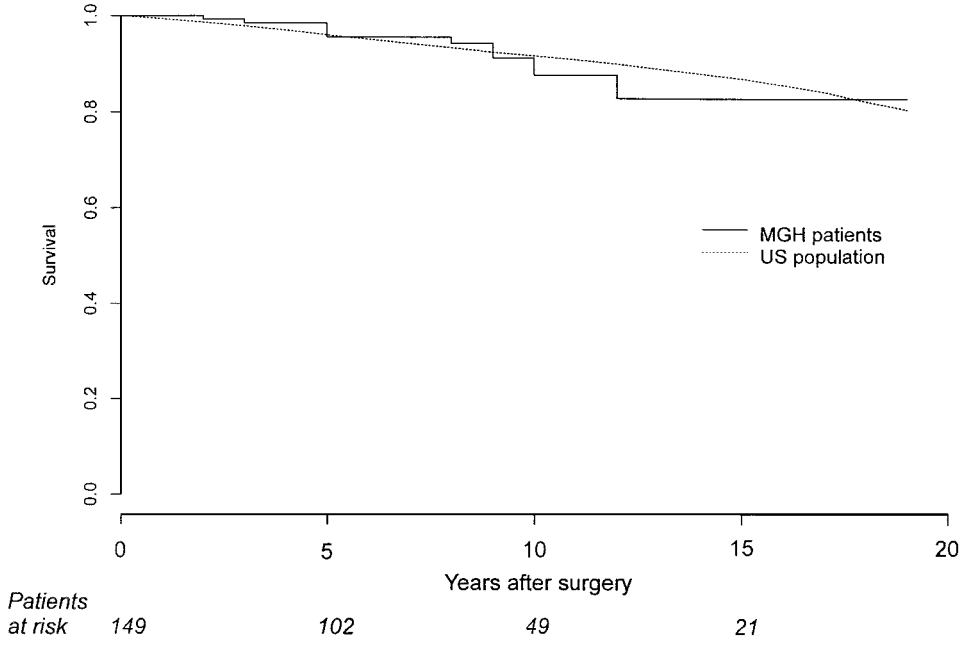

FIG. 4. Poisson person-years regression model showing survival after transsphenoidal surgery in 149 patients with acromegaly, of whom 83% are in remission. The *dotted line* indicates the expected survival for an age- and sex-matched sample from the U.S. population. There is no significant difference in survival (SMR, 1.16; 95% CI, 0.66–2.0; $P = 0.3$).

The primary cause of death was cardiovascular (5 cases), followed by malignancy (4 cases: leukemia, prostate, astrocytoma, and adenoid cystic carcinoma), and respiratory (1 case). The cause of death was unknown in 2 patients.

A person-years Poisson regression analysis was performed to determine the relative mortality risk between those 86 patients cured by transsphenoidal surgery and an age- and sex-matched sample from the U.S. population (Fig. 3). There is no significant difference between the survival curves (standardized mortality ratio (SMR), 0.84; 95% CI, 0.3–2.2; $P = 0.35$). A survival analysis was similarly performed to compare mortality rates in the entire group of 149 patients with treated acromegaly to an age- and sex-matched control population, with the point of entry into the analysis as the date of transsphenoidal surgery (Fig. 4). The survival curve again shows no significant difference from the control population (SMR, 1.16; 95% CI, 0.66–2.0; $P = 0.3$). The 5-, 10-, and 15-yr survival rates are 96% (95% CI, 92–99.5), 88% (95% CI, 80–96), and 83% (95% CI, 74–93), respectively. To determine whether there was an isolated adverse effect from persistently elevated IGF-I levels after unsuccessful treatment, the mortality risk for patients who failed transsphenoidal surgery was compared to that of the general population over the interval that their IGF-I levels remained elevated. This interval represents the patient-years at risk with persistent disease while awaiting the beneficial effects of radiation, often before octreotide was available, or in those cases refractory to all therapy. Pa-

tients were considered at risk only for those postoperative years during which they had active disease, and patients were censored at the date of biochemical remission or the date of the last follow-up if no adjunctive treatment was successful. The standardized mortality ratio (observed/expected deaths) for this group was 1.8 (95% CI, 0.9–3.6; $P = 0.05$).

A Cox proportional hazards model was used to analyze the relative mortality risk for patient-years in remission *vs.* those with persistent active disease. In a univariate analysis, age was a significant predictor of mortality ($P < 0.001$); uncorrected for age, a patient-year with active disease carried a 4.1-fold (95% CI, 1.2–14; $P = 0.02$) relative increase in mortality risk as opposed to a patient-year in remission. In a multivariate analysis adjusting for age, the mortality risk for a year spent with active disease increased 3.5-fold (95% CI, 1.0–12; $P = 0.04$). The survival plot for a 45-yr-old patient with acromegaly comparing remission with persistent disease is shown in Fig. 5.

Disability from disease

The employment status of each patient was determined at the time of last follow-up. Of the 114 patients responding to this portion of questionnaire, 87% reported that their work capacity remained the same despite their disease. Only 4 (4 of 82 previously employed; 5%) patients reported ongoing disability: 2 patients had suffered strokes, 1 was disabled from lung cancer, and 1 cause of disability was unreported.

Discussion

We report the long term outcome in 149 patients with acromegaly after transsphenoidal surgery and adjunctive therapy. The overall remission rate was 83%. The observed mortality risk for those patients with persistent disease after unsuccessful treatment was significantly greater than the risk expected for the general population (SMR for this group, 1.8; 95% CI, 0.9–3.6; $P = 0.05$), confirming previous reports (1–6). (There may, in fact, be a selection bias inherent in a surgical series favoring the underestimation of mortality risk, as it is possible that patients too ill to undergo surgery would not be referred and therefore their deaths would not be included in overall disease mortality rates.) In addition, the mortality risk for those patients with active disease was significantly greater than the mortality risk seen in those patients whose disease was in remission (3.5-fold increased risk; 95% CI, 1.0–12; $P = 0.04$). Successful therapy, however, appears to reduce this increased risk. The standardized mortality ratio for those patients cured by transsphenoidal surgery was not significantly different from that in an age- and sex-matched sample based on U.S. population data, demonstrating that surgical cure of acromegaly appears to normalize the increased mortality risk previously reported to be associated with the disease. In addition, the SMR for the entire group after surgery and adjunctive treatment was not significantly different from that for the control sample population, suggesting that successful treatment of acromegaly in a population of patients, as indicated by remission of disease in 83% of the treated group, will reduce the mortality risk to a rate indistinguishable from the control population baseline. This confirms the benefits of aggressive multimodality therapy for acromegaly.

Our results show that patients who died after beginning treatment for acromegaly were more likely to be those with active disease (odds ratio, 14; $P < 0.001$) than were those alive at last contact. This result does not establish that a patient-year with active acromegaly carries a higher mortality risk than time spent in remission. Adjuvant therapy does not induce remission immediately; patients who live longer after treatment begins are increasingly likely to achieve remission as time passes. If some patients die during this period, those who die sooner will be more likely to have high IGF-I levels at last contact than those who live for longer periods, even

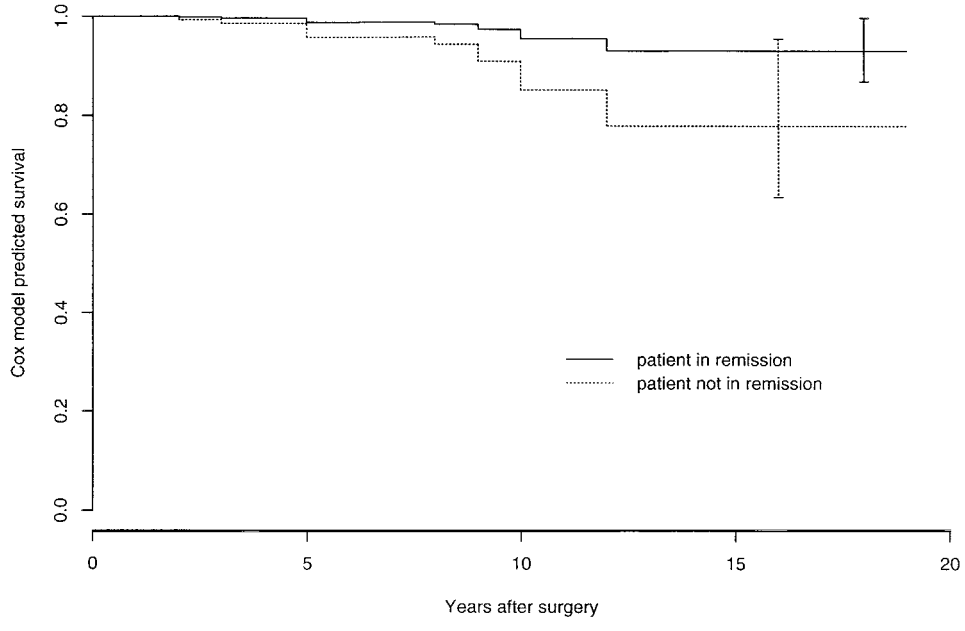

FIG. 5. Projected survival curve for a 45-yr-old patient with acromegaly after transsphenoidal surgery. The *solid line* shows the expected survival for a surgically cured patient. The *dotted line* shows the expected survival for a patient not in remission after surgery. *Error bars* are 90% confidence limits.

if the cause of death is unrelated to acromegaly. This introduces a strong bias into the analysis, suggesting that high IGF-I levels cause death, when the true causal relationship could be that longer life improves the chances of remission at last contact. We used a time-dependent covariate in a Cox proportional hazards model to determine the effect of remission on postoperative survival, because this method avoids the bias introduced when a survival model is stratified by the presence or absence of remission at last patient contact (13–16). This model suggests that a patient-year with active disease compared to a year in remission carries an age-adjusted relative mortality risk of 3.5 ($P = 0.04$).

Previous retrospective studies have reported decreased survival even in treated groups, although treatment in most of these series was primarily with radiation (1–6). Wright and colleagues observed a nearly 2-fold increase in observed *vs.* expected deaths, although mortality rates were lower in treated patients, primarily after radiotherapy (1). The studies of Alexander *et al.* (5) and Bengtsson *et al.* (6) similarly report decreased survival, with persistent mortality risk even after treatment. Survival in acromegaly, regardless of treatment, was reduced by about 10 yr compared to that in the general population as reported in the series of Rajasoorya *et al.* (4). The benefits of successful therapy were suggested by Bates *et al.* (2), who reported a 2.7-fold increase in observed *vs.* expected mortality overall and showed that the mortality rate normalized in that population whose GH level could be reduced to less than 5 ng/mL. Similar results have recently been reported by Abosch *et al.* (17). The normalization of this increased mortality risk in our series may be related to the beneficial effects of rapidly lowering GH levels with successful transsphenoidal surgery as opposed to awaiting the delayed benefits of radiation therapy. As a correlation has been shown between longer duration of symptoms and decreased survival (4), it is likely that the more rapid correction of serum IGF-I levels seen with transsphenoidal surgery may be contributing to the improvements noted here. In addition, most earlier long term outcome studies emphasized the natural history of acromegaly rather than the efficacy of treatment; it is possible that the administered therapy, although beneficial, may have nonetheless been inadequate.

Current therapeutic strategies for acromegaly include transsphenoidal surgery, radiation therapy or radiosurgery, and medical management with somatostatin analogs or dopamine agonists (18, 19). Transsphenoidal surgery has been employed in the treatment of acromegaly since Cushing's first report in 1909 (20), with multiple surgical series now in the literature (21–31). Cure rates in the more recent series tend to be higher than those from older studies, comparable to the improved surgical outcome noted here. Although this may represent in part a selection bias in publication (successful series are more likely to be submitted), analysis of our data suggests that surgical remission rates have, in fact, improved over time. Contributing factors could include the rapid incorporation of magnetic resonance image scanning into the evaluation of patients with pituitary tumors beginning in the early 1980s; this clearly allowed improved surgical planning and follow-up. Of equal or greater importance, however, have been the advances in endocrine diagnosis of acromegaly, especially with improved GH and serum IGF-I assays. This has led to revised criteria of remission over the years, initially from GH less than 10 ng/mL, to GH less than 5 ng/mL, to GH suppression after OGTT to less than 2 ng/mL, and to normalization of the IGF-I level. These changes make the interpretation of retrospective results such as those presented here more difficult; two of our patients who died were cured by the criterion of GH levels below 5 ng/mL, but not by the criterion of GH levels below 2.5 ng/mL, and categorizing these patients as cured, although historically legitimate, will alter the statistical analysis so that the increased mortality risk with active disease is no longer significant (age-adjusted relative mortality risk, 2.5; $P = 0.12$). The more stringent criteria are also more difficult to meet (and make comparison between surgical series problematic), but they permit the definitive diagnosis of acromegaly to be made at an earlier stage. Surgical results are clearly better with smaller, more accessible, tumors that can be completely removed before bony or cavernous sinus invasion occurs. The incidence of microadenomas in our surgical population appears to be increasing each year, possibly as a result of increased awareness on the part of primary care physicians and endocrinologists, using both improved imaging and biochemical assays for patient screening.

There have also been significant advances in adjunctive therapy. Radiation therapy, as employed in the natural history studies, was primarily fractionated external beam treatment; newer stereotactic radiosurgical techniques may hasten remission. Although the efficacy of radiation therapy has been recently questioned (32), our data show that 42% (19 of 45) of patients who received postoperative radiation therapy have normal IGF-I levels without additional ongoing therapy at a mean follow-up of 6.7 yr after radiation. Medical management, originally restricted to dopamine agonists, has proved increasingly beneficial since the introduction of the somatostatin analogs (33, 34); octreotide, alone or after radiation therapy, has normalized IGF-I levels in 63% (19 of 30) of the patients in this series. As patients with active disease have significantly higher mortality rates than those in remission, and normalization of serum IGF-I levels appears to return the increased mortality risk to the sample population baseline, aggressive multimodality attempts to normalize IGF-I levels are warranted. Although a relatively small number of patients remain refractory to the best available combined therapy, advances in surgical, radiosurgical, and pharmacological therapy may lead to further improvement.

Acknowledgments

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