Pituitary Tumor Registry: A Novel Clinical Resource*

MARLYS R. DRANGE, NICOLE R. FRAM, VIVIEN HERMAN-BONERT, AND SHLOMO MELMED

Cedars-Sinai Research Institute, University of California-Los Angeles School of Medicine, Los Angeles, California 90048

ABSTRACT

Pituitary adenomas result in clinical sequelae and accelerated mortality due to central mass effects or pituitary hormone hypersecretion and/or insufficiency. The low annual incidence and prolonged natural history of these rare tumors has hindered efforts to evaluate long-term clinical outcomes. Care of these patients is often provided by larger tertiary specialist referral centers. A novel evidence-based computerized pituitary tumor registry was developed to systematically evaluate epidemiological, biochemical, and clinical outcome data. Retrospective registration of 371 patients (99 clinically nonfunctioning tumors (CNFTs), 176 acromegalics, and 96 prolactinomas) with radiological, biochemical, and clinical evidence of pituitary tumors was performed. Analysis of this primarily specialist-referred population revealed a female predominance among CNFT (60%) and prolactinoma (69%) patients. Males had a significantly greater frequency of macroadenomas than females for CNFTs (92% vs. 68%) and for prolactinomas (74% vs. 40%). Males with prolactinomas also had higher mean pretreatment serum PRL levels (1206 vs. 219 ng/mL). Concurrent hyperprolactinemia was present in CNFT (47%) and acromegaly (33%) patients. Radiographic cure, defined as absence of visualized tumor, was achieved in 21% of CNFTs, 34% of acromegalics, and 21% of prolactinomas. Biochemical remission, defined by normalization of hormonal tumor markers, was observed in 35% of acromegaly and 39% of prolactinoma patients in the registry, thus reflecting the tertiary referral patterns. Nine premature deaths (patients aged ≤65 yr) occurred in the acromegaly subpopulation, whereas no premature deaths were encountered in nonacromegalic patients.

In conclusion, this unique and comprehensive pituitary tumor registry enables identification of diagnostic and prognostic markers and evaluation of long-term clinical outcomes. Prospectively, this registry will improve therapeutic guidelines and cost-effective pituitary tumor management. (J Clin Endocrinol Metab 85: 168–174, 2000)

SILENT PITUITARY microadenomas are identified in approximately 11% of autopsy specimens (1). However, symptomatic pituitary tumors are rarely encountered clinically. Based on a study of the Olmstead County population from 1970–1980, the estimated mean annual incidence of pituitary tumors ranges from 0.5 to 7.4 per 100,000 persons depending on age and sex (2), with the highest incidence occurring in women aged 15–44 y. Tumors of pituitary origin are usually slow-growing, benign, monoclonal neoplasms, yet are associated with significant morbidity and premature mortality. Pituitary adenomas come to clinical attention due to mass effects resulting from impingement on local structures or manifestations of pituitary hormone excess or insufficiency (3–7).

These tumors are classified according to their cell type of origin. Each cell type produces specific hormone products under tightly regulated hypothalamic and peripheral control. The hormone-secreting cells may give rise to functional pituitary tumors that hypersecrete one or more hormones including PRL, GH, ACTH, and, rarely, FSH, LH, or TSH. Pituitary tumors with no identifiable clinical hypersecretory syndrome are termed clinically nonfunctioning tumors (CNFTs) because the majority of these tumors are, in fact, of gonadotroph cell origin and actually express, albeit inefficiently, FSH, LH, or their free subunits (6).

Compared with other neoplasms, pituitary adenomas tend to occur in younger patients. Successful management aimed at normalization of hormonal excess or deficiency, decompression of vital structures, and prevention of tumor recurrence often requires lifelong treatment and follow-up. The relatively low annual incidence of pituitary adenoma diagnosis and long natural history of these tumors have hampered efforts to evaluate remote clinical outcomes in significant numbers of patients. Moreover, the various tumor types must be evaluated separately because each has a unique frequency, pathology, therapeutic regimen, and long-term outcome. Reliable tumor type-specific epidemiological information is sparse or nonexistent.

We, therefore, developed a novel evidence-based computerized pituitary tumor registry to collect comprehensive demographic, therapeutic, and clinical outcome information on patients harboring pituitary mass lesions of all types. Our clinic is primarily a tertiary resource for specialist referrals. This data acquisition and evaluation tool provides epidemiological, biochemical, and outcome data for pituitary tumor patients to define features of prognostic significance. The goal of the Pituitary Tumor Registry is improvement of early identification of these patients, tumor management strategies, and long-term outcome. To illustrate the utility of this unique tumor registry, we describe a number of retrospective analyses for the three most common pituitary tumor types: CNFT, acromegaly, and prolactinoma.
Subjects and Methods

Human subjects

Patient participation was approved by the Cedars-Sinai Medical Center and Los Angeles County/University of Southern California Institutional Review Boards.

Patient population

Hospital chart review was performed by two physicians who also directly supervised data entry by a data analyst of tertiary referral patients seen at the Cedars-Sinai Medical Center and at the Los Angeles County Hospital from 1982–1999. When appropriate, physicians or patients were contacted for information. To date, 404 patients [99 CNFT, 176 acromegaly (GH-secreting), 96 prolactinoma, 18 Cushing’s (ACTH-secreting), and 15 other nonpituitary intrasellar tumors] have been registered. Further analysis of patients bearing Cushing’s and other intrasellar masses was not undertaken due to the paucity of these tumor types in the registry. Patients included in the pituitary tumor registry had clinical, biochemical, and radiological evidence of an intrasellar mass lesion. All types and classes of tumors were included, and there were no exclusion criteria. Tumor type was determined by hormonal biochemical profile and clinical presentation. Immunohistochemical confirmation was not always available, either because the patient had not undergone surgical excision of the tumor, immunohistochemistry had not been performed at the time of pathological evaluation of the tumor tissue, or pathology reports were not available. Ethnic distribution of registered patients was 69% Caucasian, 19% Hispanic, 8% Asian, and 4% African American. Males accounted for 41% and females accounted for 59% of patients. Patient ages ranged from 8–89 y.

Pituitary tumor registry computer program

The computer software Access 97 (Microsoft Corporation, 1996) was used for development of the registry program. Selection of specific data for registry inclusion was based on review of the current literature regarding prognostic factors for aggressive pituitary tumors and unfavorable clinical outcomes. Factors known to have prognostic significance, those with potential significance, but with insufficient confirmatory information, and possible confounding factors were also included. Data collection worksheets that paralleled the computer program and flow sheets for tracking laboratory results or medication changes were designed using Powerpoint 97 (Microsoft Corporation, 1996). These worksheets were developed to achieve maximum data ascertainment, standardized responses, and to create an efficient, user-friendly system for detailed data collection. To maintain patient confidentiality, data were entered using an arbitrarily assigned identification number. Only individuals registered as principal or coinvestigators had access to identifying information.

Definitions

Tumor size was determined by radiographic analysis. Tumors less than 10 mm in greatest dimension were considered microadenomas and tumors greater than or equal to 10 mm were considered macroadenomas. Hypogonadal symptoms included complaints of diminished libido, oligo- or amenorrhea, infertility, or erectile dysfunction. All laboratory values were interpreted based on the reporting laboratory’s normal range, unless stated otherwise. Concurrent hyperprolactinemia was defined as PRL elevation (upper limits of normal ranged from 14.7–30 μg/L depending on laboratory) in a patient diagnosed with either CNFT or acromegaly. Hypogonadotrophic hypogonadism was diagnosed when estradiol or testosterone levels were low in the presence of inappropriately normal or low FSH and/or LH levels. Hypopituitarism included deficiency of the GH (evoked GH <3 ng/mL), gonadotropin (FSH/LH), thyroid (abnormal thyroid hormone levels with inappropriate TSH levels), adrenal (blunted cortrosyn responses) axes, and/or panhypopituitarism. Radiographic cure was defined as the absence of visualized tumor tissue on magnetic resonance (MRI), sensitivity more than 2 mm, or computed tomography imaging (if MRI scans were not available). Biochemical control of prolactinoma was defined as normalized serum PRL levels. Biochemical remission of acromegaly was defined by the strict criteria of both a normalized insulin-like growth factor-I (IGF-I) for age and sex and a glucose- (or somatostatin analog-) suppressed GH value less than or equal to 2 μg/L.

Statistical analysis

Patient groups were generally compared by Fisher’s two-tailed exact test. Gender predominance was determined by comparison to an expected rate of 50% using Yates corrected χ2 analysis. Because the distribution of pretreatment PRL levels was skewed, the data were log-transformed before application of the two-sample t test and the geometric mean are reported. Standardized mortality ratio (SMR) was computed by standard methods as described previously (7). Diagnosis date and death date or date of last contact were entered as the dates of study entry and exit, respectively. Death rates were obtained for males and females using the “all races” rates in the National Vital Statistics Report [1998, 47(13):11].

Results

Patient gender and tumor size (Fig. 1)

From 1982 through current (1999), nearly three-quarters of all patients registered harbored macroadenomas (76 of 98 CNFTs, 142 of 168 acromegalies, and 46 of 92 prolactinomas). CNFTs (60%, n = 99, P < 0.05) and prolactinomas (69%, n = 96, P < 0.01) were more frequent in women in contrast to the equal gender distribution for patients with acromegaly (51% male, 49% female, n = 176) in the registry. Males with prolactinomas tended to have larger tumors than females with this tumor type, 74% (n = 27) macroadenomas vs. 40% (n = 65, P < 0.01), and higher mean pretreatment serum PRL levels, 1206 (n = 22) vs. 219 ng/mL (n = 43, P < 0.001). Males with CNFTs also had a significantly greater (P < 0.01) likelihood to have a macroadoma, 92% (n = 38) compared to 68% (n = 60) for females. Distribution of tumor size was equal between men and women with GH-secreting tumors (84% and 85% macroadenomas, respectively).

Diagnostic information and symptoms

The age of patients at the time of diagnosis peaked in the third decade for acromegaly, the fourth decade for prolactinomas, and across the fourth and fifth decades for CNFT (Fig. 2). The mean time delay from reported symptom onset to diagnosis was 3.0 ± 3.9 y for prolactinomas (n = 84) and 1.9 ± 2.9 y for CNFTs (n = 77) compared to 7.2 ± 7.7 y for acromegalies (n = 146). Internists or family physicians (29%) and endocrinologists (24%) were primarily responsible for making the initial diagnosis of pituitary lesions (n = 261). Tumor type-specific distribution of the diagnostic source is illustrated in Table 1. Differences in diagnostic source correlates with the particular symptomatology associated with each tumor type that is listed in Table 2. Patients with CNFTs generally presented with mass-related effects such as headache (48%) and visual deficits (48%). Those with acromegaly most frequently reported features unique to GH excess, such as acral enlargement (86%) and maxillofacial changes (74%). Patients with PRL-secreting tumors presented most commonly with hypogonadal symptoms (70%), galactorrhea (49%), and headache (46%). Since galactorrhea is uncommon in men (8) and only 4% (3/82) of patients in the registry reporting this symptom were male, the incidence of galactorrhea was analyzed separately for female patients. Thirty-two percent (n = 59) of female patients harboring CNFTs, 17% (n = 86) with acromegaly and 68% (n = 66) with pro-
lactinomas, reported galactorrhea as a presenting clinical feature. Not surprisingly, patients complaining of headache more commonly had macroadenomas for GH-secreting tumors (93%, n = 67) and CNFTs (81%, n = 48). In contrast, reports of headache by patients with PRL-secreting tumors (n = 41) were more evenly distributed between small (44%) and large (56%) tumors, suggesting that factors in addition to tumor size-related mass effect may contribute to incidence of headache in patients with prolactinomas. Hypogonadal symptoms were more commonly observed in patients with CNFT microadenomas (34%, n = 35) than GH-secreting tumors of similar size (11%, n = 65).

Concurrent hormonal aberrations (Table 3)

Concurrent hyperprolactinemia was present in 47% (n = 73) of CNFT and 33% (n = 140) of acromegaly patients. Thirty-two percent of CNFTs with hyperprolactinemia were less than 1 cm in size compared to 5% of acromegaly tumors exhibiting concurrent hyperprolactinemia. Partial or complete pituitary hormone insufficiency was present at diagnosis in 44% of CNFT (n = 66), 38% of acromegaly (n = 130), and 71% of prolactinoma patients (n = 80). The gonadal axis (FSH/LH) was affected in nearly all cases (93%, 96%, and...
100%, respectively). Concurrent pretreatment hypogonadotropic hypogonadism was also more likely to occur in patients bearing CNFT microadenomas (26%, n = 27) than GH-secreting microadenomas (4%, n = 46). Indeed, the incidence of hypogonadotropic hypogonadism paralleled that of concurrent hyperprolactinemia in these patients. Hypopituitarism occurred as a treatment complication in 32% (n = 66) of prolactinoma patients. Overall, partial or complete pituitary insufficiency was encountered in 65% of CNFT (n = 66), 63% of acromegaly (n = 124) and 49% of prolactinoma (n = 76) patients following treatment. Persistent diabetes insipidus was present in 14% of CNFT (n = 66), 10% of acromegaly (n = 124) and 3% of prolactinoma (n = 76) patients. Hypopituitarism and diabetes insipidus were consistently associated with large tumors (80%, n = 159, P < 0.001).

Therapy and clinical outcome

Several treatment modes, including surgery, irradiation, and pharmacotherapy, are currently available for the management of pituitary tumors. Utilization patterns of these individually and as combinations for each tumor type are listed in Table 4. Surgery alone was the most common modality used in the treatment of CNFT (46%, n = 99), and medical treatment with dopamine agonists (either bromocriptine or the newer long-acting agent cabergoline) was the mainstay of prolactinoma therapy (53%, n = 96). In this tertiary patient population, a combination of surgical and medical therapy (40%, n = 176) or all modalities (21%) was used for the management of GH-secreting tumors. Pharmacotherapy with either somatostatin analogs (39%, n = 90), such as octreotide, dopamine agonists (16%), or both (46%) was used as an adjunctive therapy after surgery. Several of the registered patients were also enrolled in clinical trials that used novel sustained-release formulations of somatostatin analogs or GH receptor antagonists.

Radiographic cure was achieved in 21% of CNFTs (n = 58), 34% of GH-secreting tumors (n = 137), and 21% of prolactinomas (n = 72). Biochemical remission, by the stringent criteria defined, was achieved in 35% of ascertainable acromegaly patients (n = 124), whereas biochemical remission resulting in sustained normalization of serum PRL levels was achieved in 39% of prolactinoma patients (n = 94). Further evaluation of the characteristics of cured patients revealed that the majority of biochemically controlled prolactinomas, 62% (n = 37), were less than 1 cm in size. However, 79% (n = 43) of biochemically controlled acromegaly patients and 70% of radiographically-cured tumors (10 of 12 CNFTs, 34 of 44 acromegalies, and 4 of 13 prolactinomas) were microadenomas.

Nine deaths occurred in acromegaly patients aged 40–65 y. These deaths were caused by cardiovascular/cerebrovascular disease, malignancy, respiratory disease, diabetic complications, and suicide (three, two, two, one, and one patient, respectively). No premature deaths were identified for the other tumor types. The computed SMR is 0.85 (confidence interval, 0.42–1.52).

Discussion

The goals of this project are to improve early identification of patients with pituitary tumors, define management strategies, and provide a basis for assessing long-term outcomes. Tumor registries are an important resource for the study of cancer epidemiology, treatment strategies, and long-term clinical outcomes. Thus, we developed a comprehensive computerized tumor registry program for data collection on patients with pituitary/intrasellar mass lesions. Using this prototype database program, retrospective demographic,
clinical, and biochemical presentation, therapeutic and outcome data for the three most common pituitary tumor types—CNFTs, GH-secreting tumors, and prolactinomas—were analyzed. Patients encountered in this study were largely tertiary referrals from other specialists. Thus, the results depict these parameters in a select group of patients who may have more complex disease and do not necessarily reflect characteristics of the overall population.

Results for prolactinomas revealed a female predominance, although male patients had a greater frequency of macroadenomas and higher pretreatment serum PRL levels. The higher hormone levels observed in male patients are most likely a direct reflection of tumor size, as these parameters are generally concordant (9). These findings are consistent with previous studies (10, 11) and in contrast to postmortem studies that indicated an equal distribution of clinically nonsignificant microprolactinomas encountered across adult age groups and between sexes (8). Estrogen is known to stimulate lactotroph proliferation and PRL gene transcription leading to increased PRL synthesis (12, 13).

Taken together, these results suggest that the female sex, perhaps due to estrogen, is associated with tumor promotion, but additional nongender related factors are required to confer tumor aggressiveness or invasiveness.

CNFT diagnosis was also significantly more frequent in women, with men more commonly bearing macroadenomas than their female counterparts. These results are similar to prolactinomas and in contrast to GH-secreting tumors in which both gender and macroadenomas were equally distributed. These observations may reflect gender differences in patient inclination to seek medical attention for hypogonadal symptoms. Conversely, this may reflect a true as yet unexplored gender-based difference in the biologic phenotype of CNFT similar to that observed for prolactinoma.

Analysis of these results demonstrated that clinical onset and diagnosis of the majority of pituitary tumors occurred in young adults. More patients bearing CNFT, as compared to acromegaly and prolactinoma, were diagnosed past 40 yr of age presumably due to the absence of overt clinical manifestations until this slow-growing tumor caused pressure-related effects on local central structures. These data also confirm previous findings that the clinical effects of GH excess present insidiously, such that there was an average of 7.2 y delay between reported time of symptom onset and diagnosis of acromegaly. This figure is comparable to earlier studies that report delays on the order of 7 yr (14, 15) and likely underestimates the actual time lapse. Importantly, these results should challenge the practicing clinician to entertain the diagnosis of acromegaly earlier in the course of this debilitating disease.

Hyperprolactinemia was observed in one third of patients with acromegaly. This finding was not unexpected because GH-secreting (somatotrophs) and PRL-secreting cells (lactotrophs) derive from a common progenitor cell, the mammosomatotroph (16). Moreover, the frequency observed for our patient population is similar to previous reports that indicate approximately 35% of acromegalics patients have concomitant hypersecretion of PRL and GH (17). Alternatively, moderate serum PRL elevation may be due to “stalk section effect” caused by disruption of dopaminergic inhibition of PRL synthesis and secretion. We also observed concurrent PRL elevation in 47% of CNFTs. This frequency is similar to that reported (42–65%) in the few studies addressing this phenomenon (summarized in Ref. 18). Serum PRL elevation in these patients was mild, usually less than 100 μg/L, suggesting that the stalk-section phenomenon is the underlying etiology for concurrent hyperprolactinemia observed in CNFT patients. Stalk-section effect is not specific for large tumors. Smith and Laws (19) found no significant correlation between PRL levels and tumor size, stalk deviation, or degree of stalk compression as assessed by MRI in a series of 44 pathologically confirmed PRL-negative tumors. Indeed, in the results herein, 32% of the CNFTs associated with secondary hyperprolactinemia were microadenomas. Conversely, raised intrasellar pituitary tissue pressure has been associated with hypopituitarism and hyperprolactinemia and may explain these findings (20, 21). Alternatively, some small prolactinomas producing proportionately low PRL levels may have been misclassified as CNFTs. The only definitive way to confirm tumor type is to demonstrate tumor cell PRL production in vitro by PRL immunohistochemical staining. These data demonstrating mild to moderate elevations in serum PRL in CNFTs and acromegaly illustrate the need to routinely obtain an MRI and include a screening IGF-I level to rule out acromegaly, CNFT, and nonpituitary sellar or hypothalamic masses in the evaluation of low-level hyperprolactinemia.

Pituitary insufficiency can be encountered in patients with any size or type of intrasellar mass and, thus, serves as an important diagnostic indicator of a pituitary lesion (3). Hypogonadotropic hypogonadism was a relatively common pretherapeutic finding for all tumor types and corresponds to the frequency of hypogonadal symptoms at presentation. The frequency of hormone deficiency loss generally follows the order GH > FSH/LH > TSH > ACTH (3). These results suggest that an even greater percentage of patients may have been GH deficient. Adequacy of the GH axis was rarely evaluated in the past, but remains to be explored as an additional tumor surveillance marker.

A higher prevalence of hypogonadotrophic hypogonadism was observed in CNFT patients than in those with acromegaly. This difference does not appear to be tumor size-dependent, suggesting that the mechanism is not tumoral destruction of the adjacent gonadotrophs by direct invasion or compression. Similar findings were previously reported by Greenman et al. (22) and Damjanovic et al. (23). Interestingly, we found that the presence of hypogonadism in these patients paralleled that of concurrent hyperprolactinemia. Indeed, hyperprolactinemia may explain the presence of FSH/LH deficiency in these patients because PRL is known to cause hypogonadotrophic hypogonadism by alteration of the gonadotropin secretory pattern (24). Moreover, PRL levels were not evaluated in the studies cited above. An alternative explanation may imply the existence of a common mechanism resulting in concurrent hyperprolactinemia in CNFTs and hypogonadotrophic hypogonadism, perhaps through perturbations of the hypothalamic dopaminergic pathways. The underlying mechanism(s) remain to be elucidated.

Therapeutic outcomes in these patients reflect the fact that
as tertiary referrals most had resistant or complicated disease. Radiographic cure, defined as absence of visualized tumor, was attained in only 21–34% of tumors analyzed. The low rate of apparent tumor eradication (21%) observed for prolactinoma was predictable because the majority of these tumors were treated pharmacologically. Dopamine agonist therapy for prolactinoma generally decreases serum PRL levels, restores the eugonadal state, and decreases tumor mass. Meta-analysis of 271 macroadenomas revealed that 79% of patients showed shrinkage of at least 25% of tumor mass (25). Some microadenomas and a few larger tumors shrink to the point of disappearance, however, the majority of medically-treated prolactinomas do not. Moreover, dopamine-agonist therapy is not curative. Discontinuation of the drug usually results in recurrent hyperprolactinemia and often tumor reexpansion (8). In addition, the patient population included in the registry is primarily tertiary referral based. Indeed, 56% (n = 249) of registered patients were referred by other endocrinologists. Thus, this patient population represents a group with more aggressive disease or disease refractory to standard specialist treatment approaches.

Intuitively, surgical resection seems more likely to completely eradicate a benign tumor mass, with the caveat that surgical outcome is highly dependent on the skill and expertise of the neurosurgeon. There is little literature available regarding radiographic cure rates for the hormone-secreting pituitary tumor types, as surgical success rates are generally based on biochemical outcome. Abnormal elevation of tumor-specific hormonal products is generally more sensitive than the radiographic visualization of tumor. Indeed, biochemical remission often did not correlate with radiographic cure of patients in the pituitary tumor registry. Surgical cure rates and frequency of radiological evidence for residual tumor posttherapeutically have also been poorly documented for CNFT (18), even though serial radiographic imaging is obligatory due to the lack of a reliable biochemical marker. These results suggest that the majority of CNFTs and GH-secreting tumors were incompletely excised, possibly due to tumor extension to anatomical areas that are less surgically accessible. Conversely, tumor size alone does not reliably predict likelihood for radiographic cure, as 83% of cured CNFTs (n = 12) and 77% of cured acromegaly tumors (n = 44) were macroadenomas.

Less than 40% of patients in the registry bearing functional tumors attained biochemical remission. The published surgical remission rate for acromegaly ranges from 42–88% (summarized in Ref. 26), whereas the remission rate for medical therapy in conjunction with incomplete surgical resection was 40–60% (27–30). Remission rates for dopamine agonist-treated prolactinomas ranged from 60–80% for macroadenomas (31–33) and 70–90% for microadenomas (34). Notably, remission rates encountered in this registry for both tumor types are either at the lowest extreme or less than earlier reports. Several possibilities account for these observations. First, this tertiary-referred patient population represents a group with more aggressive or refractory disease. The high percentage of patients in the registry that required multimodal therapy lends support to this notion. Second, the criteria for remission were more stringent than those used in most reported series, particularly for acromegaly. The majority of acromegaly outcome studies were based on single random GH levels ranging from 2.5–10 μg/L (30). Single serum GH measurements, in the absence of a dynamic suppression test, are not reliable indicators of disease status because GH release is pulsatile. GH concentrations vary from undetectable (in standard assays) about half the daytime to 30 μg/L in normal individuals (35, 36). In acromegaly, basal GH is rarely undetectable and overlaps unacceptably with the normal range (37). Circulating IGF-I levels, which reflect integrated 24-h GH concentrations, are a better indicator of GH hypersecretion. This test coupled with a glucose-suppressed GH is the current recommended strategy for diagnosing and monitoring acromegaly (10).

Prolonged exposure to excessive circulating GH levels is associated with an approximately 3-fold increased mortality rate (15, 38, 39). In contrast, the calculated SMR for the registered acromegaly population did not indicate an increased death rate. Several recent series have confirmed that therapy resulting in biochemical remission of acromegaly normalizes mortality rate to that of the general population (26, 40, 41). Thus, it is possible that the normal mortality rate observed reflects the influence of partially normalized GH levels. Alternatively, the calculated mortality ratio may underestimate the true death rate. First, the current survival status could not be ascertained for 27% of patients, and deceased patients are likely to be lost to follow-up at a greater frequency. Additionally, patients who died before presentation to a tertiary center did not have an opportunity to be included in the calculation. These results demonstrate the importance of successful biochemical control and appropriate long-term management of these patients.

In conclusion, we have developed a novel computerized pituitary tumor registry program designed to collect comprehensive demographic, therapeutic, pathologic, and outcome information on patients harboring these rare tumors and who are referred for tertiary consultation. Specifically, predictors of pituitary tumor recurrence and markers of persistent disease activity may be identified. This tool will be used prospectively to overcome the limitations introduced by the incomplete data ascertainment inherent to retrospective analyses of rare diseases. This registry can be used to improve surveillance protocols and long-term therapeutic outcomes. Moreover, identification of patients with low likelihood for recurrence should reduce the amount of healthcare resources unnecessarily consumed and improve the overall cost-effectiveness of long-term pituitary tumor management.

Acknowledgments

We acknowledge Drs. Martin Weiss and Hyrar Shahiniian for generously allowing us access to their patient records.

References