

Evaluation of Factors Affecting Outcome in Growth Hormone–Secreting Pituitary Adenomas

Amit Padwal¹ Jagath Lal Gangadharan¹ Dwarakanath Srinivas¹ Sampath Somanna¹

¹Department of Neurosurgery, National Institute of Mental Health and Neuro Sciences, Bengaluru, India

Address for correspondence Dwarakanath Srinivas, MBBS, MS, MCH, Faculty Block, Neurocenter, National Institute of Mental Health and Neuro Sciences, Bengaluru 560029, Karnataka, India (e-mail: dwarakaneuro@yahoo.com).

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Abstract

Introduction Management of functioning pituitary adenomas is challenging as they can present with features of an intracranial mass, systemic effects, or a combination of both. In this series, one of the largest in available literature from our country, we have analyzed our experience with surgical management of growth hormone (GH)-secreting pituitary adenomas and factors influencing their hormonal remission.

Materials and Methods The data of all functional pituitary adenomas operated at our institute from January 2002 to December 2011 were obtained from the case files of these patients. This was studied for various clinical-radiologic features, management stratagems, and clinical and hormonal outcomes.

Results Ninety-three patients of GH-secreting pituitary adenomas with a mean age of 32.7 years were included in the study. Fifty-three (57%) patients had headache at presentation; 46 (49%) had visual complaints, whereas menstrual irregularity was seen in majority of females. Mean GH level was 52.05 ng/mL. Fifty (53%) patients had invasive adenoma; 32 had cavernous sinus extension. Among 80 patients with hormonal follow-up, 43 (53.75%) achieved remission of GH level < 5 ng/mL.

Conclusion In this series, one of the largest of its kind, the main factors influencing unfavorable outcome include macroadenomas, invasiveness, high basal GH > 45 ng/mL levels, and mixed adenomas.

Keywords

- ▶ pituitary adenomas
- ▶ invasive adenoma
- ▶ growth hormone–secreting adenomas
- ▶ acromegaly

Introduction

Functioning or hormonally active pituitary adenomas present a special challenge as they can present either with features of an intracranial mass, endocrinologic features, or both. Predicting outcome in these tumors is of extreme clinical importance in guiding the intensity of clinical, radiologic, and hormonal follow-up and the need for adjuvant therapy after surgical resection. At present three therapeutic options are available: neurosurgery, radiotherapy/ radiosurgery, and pharmacotherapy, whose relative role is, though still subject of active debate, complementary. In this series, one of the largest in

available literature from our country, we analyze our experience with surgical management of growth hormone (GH)–secreting pituitary adenomas and also review the available literature.

Materials and Methods

This retrospective analysis was conducted on cases of functional pituitary adenomas operated at our institute from January 2002 to December 2011. The data of all operated pituitary adenomas were obtained from the case files of these patients, which were collected from medical records

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department. This was studied for various clinical-radiologic features, management stratagems, and clinical and hormonal outcomes. The cases of residual/recurrent pituitary adenomas operated elsewhere ($n = 6$) and referred to us for gamma knife radiosurgery or reexplorations were also included, but these cases were not considered for calculating remission and recurrence rates as none of these patients had enough follow-up and postoperative hormonal evaluation. Patients with functional adenoma who were on medical management and did not undergo any surgical intervention at our institute were also excluded from the study.

Diagnostic Criteria

Acromegaly was diagnosed on the basis of typical clinical features and elevated fasting plasma GH levels and not suppressible to less than 2 ng/mL during an oral glucose tolerance testing (OGTT) with 75 g glucose. We did not include plasma insulin-like growth factor 1 (IGF-1) levels as many of our patients could not afford the cost of the test.

Radiologic Features

Tumors were classified into macroadenomas (> 10 mm) or microadenomas (< 10 mm) on the basis of magnetic resonance imaging (MRI). They were further classified as per Wilson-Hardy classification to define stage and grade of adenoma. The evidence of carotid encasement in MRI scan defined invasion of cavernous sinus.

Remission Criteria

Biochemical remission was defined as postoperative serum GH value < 5 ng/mL in immediate postoperative period (within 72 hours) as well as on follow-up.

Statistical Analysis

Statistical analysis was done using SPSS 15 (SPSS Inc., Chicago, Illinois, United States). Descriptive statistics were given for continuous variables with mean and standard deviation.

Categorical variables were given with frequency and percentage. Association between two variables was tested using chi-square test.

Results

There were a total of 645 patients with pituitary adenomas who were operated at our institute from January 2002 to December 2011; 122 (19%) of them were functional pituitary adenomas. Among them, 93 (14%) were GH-secreting pituitary adenomas, 14 (2%) were prolactinomas, and remaining 15 (2%) were adrenocorticotrophic hormone (ACTH)-secreting pituitary adenomas.

Demography: Among 93 patients, 51 patients were males and 42 were females. Their age ranged from 13 to 60 years. About 77% of the patients were younger than 40 years. The mean age was 32.71 ± 10.16 years.

Clinical presentation: All patients presented with endocrinologic manifestations. In females, the most common endocrinologic manifestation was menstrual disturbance. Forty-six (49%) patients presented with visual complaints, and most common visual problem identified was bitemporal hemianopia in 34 (73%) patients. Uncommon presentations included pituitary apoplexy in four patients and trigeminal nerve involvement due to cavernous sinus invasion. Details are given in ►Fig. 1.

Hormonal evaluation: The mean GH level was 52.05 ng/mL (range: 6–701 ng/mL). About half the patients had serum GH values ≥ 40 ng/mL. Associated hypothyroidism was present in 13 patients and hyperthyroidism in 6. Hyperprolactinemia was observed in 26 (28%) patients. Six patients had serum prolactin value > 200 ng/mL. One patient had value between 100 and 200 ng/mL whereas the remaining 19 patients had value 100 ng/mL probably due to a stalk effect.

Radiology: Patients were divided into Wilson-Hardy grade based on MRI findings (►Table 1). Only one patient had a microadenoma whereas the rest had macroadenomas. Among

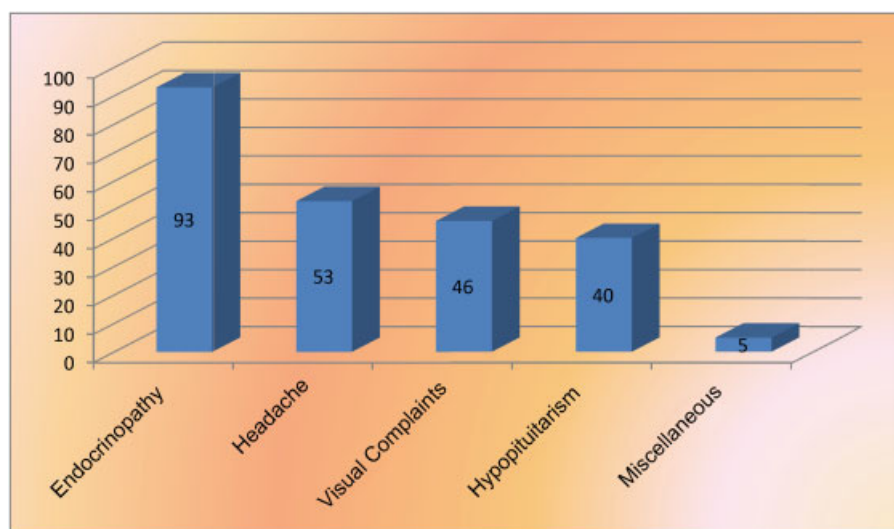


Fig. 1 Clinical features at presentation.

Table 1 Wilson-Hardy grading of GH-secreting pituitary adenomas

Wilson-Hardy grade		No. of patients	%
I (n = 1)		1	1.1
II (n = 55)	0	8	8.6
	A	7	7.5
	B	23	24.7
	C	4	4.3
	D	4	4.3
	E	9	9.7
III (n = 13)	0	1	1.1
	B	4	4.3
	C	1	1.1
	D	1	1.1
	E	6	6.5
IV (n = 24)	B	2	2.2
	C	3	3.2
	D	2	2.2
	E	17	18.3
Total		93	100.0

Abbreviation: GH, growth hormone.

93 patients, 50 (53%) had invasive adenoma whereas remaining 43 had noninvasive adenoma (►Fig. 2). Among the patients with invasive adenoma, 32 (34%) had adenomas invading the cavernous sinus.

Management: Two patients received preoperative medical management elsewhere. One patient had received somatostatin analogue and other received dopamine agonist. All 93 patients underwent surgery, with the endonasal transsphenoidal route used in 87 patients (►Figs. 3, 4).

Outcome and complications: Of 93 patients, 18 (19%) patients had postoperative cerebrospinal fluid (CSF) leaks. All

CSF leaks were initially managed with lumbar drain placement. Four patients required reexploration and sellar floor reconstruction. Among these 18 patients, 8 had meningitis, which was managed with appropriate antibiotics. None of the patients without CSF leak developed meningitis; thus CSF leak was a significant risk factor for postoperative meningitis ($p < 0.05$). Fifteen (16%) patients had postoperative diabetes insipidus, of whom only three patients needed long-term hormonal supplementation. One patient had intraoperative internal carotid artery (ICA) injury for which she underwent craniotomy and trap ligation of ICA. Rest of her postoperative period was uneventful and she was discharged without any fresh focal neurologic deficit. Two patients had

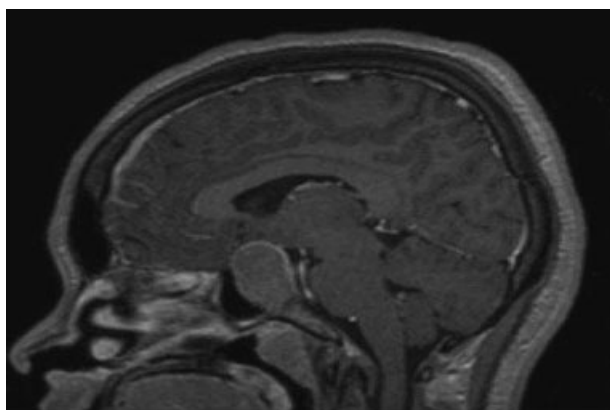


Fig. 2 Preoperative magnetic resonance imaging (MRI) T1 sagittal with gadolinium contrast showing GH-secreting pituitary adenoma stage IIB.

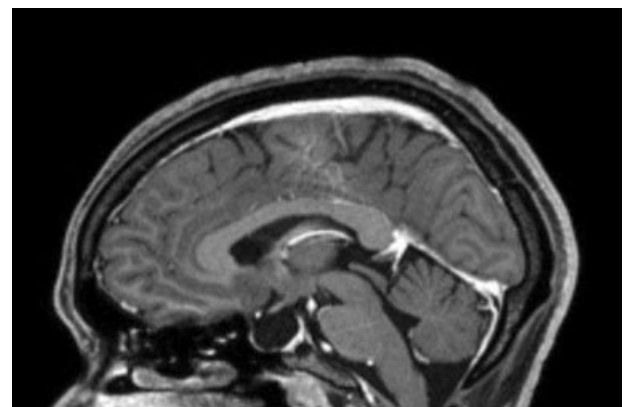


Fig. 3 Postoperative MRI T1 sagittal with gadolinium contrast at follow-up showing complete decompression.

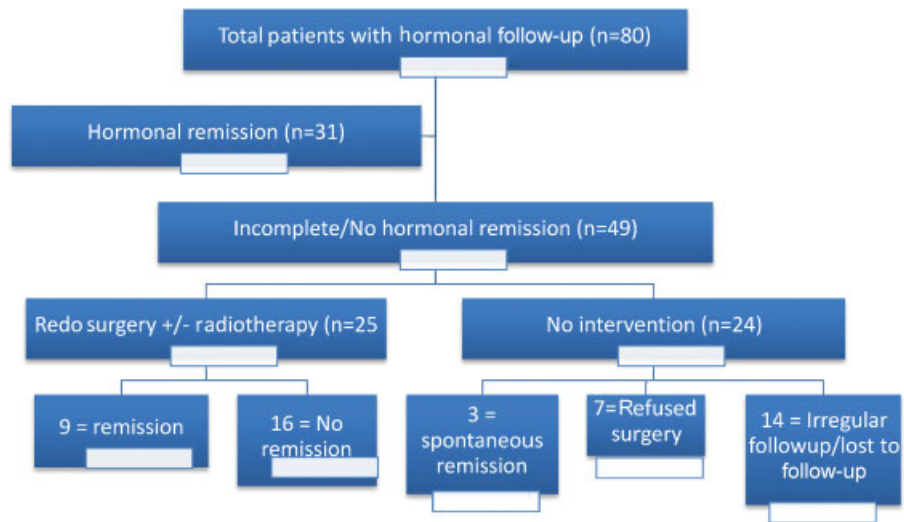


Fig. 4 Management of patients: flowchart.

intraoperative cavernous sinus injury (probably due a lateral trajectory) and they developed postoperative hemiparesis. Visual deterioration was observed in two patients. Two patients expired postoperatively: one due to sudden cardiac arrest whereas the second expired due to meningitis.

Follow-up: The follow-up period ranged from 6 weeks to 7 years with the mean follow-up being 15.07 months.

Clinical: The patients, who had achieved endocrinologic remission, had subjective improvement in their endocrinologic manifestations.

- **Hormonal:** Eighty patients had hormonal follow-up, of whom 31 patients had postoperative GH value < 5 ng/mL, thus achieving immediate postoperative remission. Of the remaining 49 patients, 25 underwent reintervention in an attempt to achieve remission. Among these 25 patients, 9 (36%) achieved remission following second intervention. The details are given in ►Table 2. Among the remaining patients, 16 had hormonal follow-up. Three (12%) patients had serum GH levels < 10 ng/mL, one (4%)

had GH level 10 to 20 ng/mL, whereas 12 had values > 20 ng/mL.

- There were 21 patients who did not achieve remission and did not undergo second intervention were analyzed. Among these, seven (33%) had serum GH levels < 10 ng/mL. As these patients improved symptomatically, they refused second intervention. Eight (38%) patients had serum GH level 10 to 20 ng/mL whereas the remaining six (29%) had serum GH level > 20 ng/mL. Three patients who did not undergo any reintervention achieved remission spontaneously during follow-up. Thus among 80 patients, 43 (53.75%) achieved biochemical remission. Ten (12.5%) patients achieved almost complete biochemical remission. This coupled with their significant clinical improvement made them refuse a second surgery (►Fig. 4).
- **Radiologic:** Among 93 patients, 52 (56%) patients had follow-up MRI. Among 42 patients who achieved remission, 35 had follow-up MRI and 4 had only follow-up computed tomographic (CT) imaging. Among these

Table 2 Correlation between cavernous sinus invasion and remission

Cavernous sinus invasion	Total no. of patients	Final remission		Total
		Yes	No	
No	Total no.	32	22	54
	% without invasion	59.3%	40.7%	100.0%
	% within final remission	76.2%	57.9%	67.5%
Yes	Total no.	10	16	26
	% with invasion	38.5%	61.5%	100.0%
	% within final remission	23.8%	42.1%	32.5%
Total		42	38	80
		52.5%	47.5%	100.0%
		100.0%	100.0%	100.0%

Table 3 Correlation between grade of the tumor and remission

Hardy grade	No. of patients	Final remission		Total
		Yes	No	
0	Total no.	7	0	7
	% within Hardy grade	100.0%	0.0%	100.0%
	% within final remission	16.7%	0.0%	8.8%
A	Total no.	4	3	7
	% within Hardy grade	57.1%	42.9%	100.0%
	% within final remission	9.5%	7.9%	8.8%
B	Total no.	15	11	26
	% within Hardy grade	57.7%	42.3%	100.0%
	% within final remission	35.7%	28.9%	32.5%
C	Total no.	3	4	7
	% within Hardy grade	42.9%	57.1%	100.0%
	% within final remission	7.1%	10.5%	8.8%
D	Total no.	3	4	7
	% within Hardy grade	42.9%	57.1%	100.0%
	% within final remission	7.1%	10.5%	8.8%
E	Total no.	10	16	26
	% within Hardy grade	38.5%	61.5%	100.0%
	% within final remission	23.8%	42.1%	32.5%
Total	Total no.	42	38	80
	% within Hardy grade	52.5%	47.5%	100.0%
	% within final remission	100.0%	100.0%	100.0%

39 patients, significant tumor was seen during follow-up in 30 patients whereas 9 had insignificant residue.

- **Visual:** Of the 46 patients with preoperative visual deficits, 19 (41%) had improvement in visual deficits in follow-up. Visual deterioration was observed in two patients. In one of those patients, preoperative vision was normal whereas in the other, it was worsening of preoperative visual deficit.

Recurrence: Out of 43 patients who achieved remission, only 4 had biochemical recurrence in follow-up (9%).

Correlation between size of the tumor and remission: In our series, only one patient had microadenoma. Postoperative remission was achieved in that patient, but during follow up at 1 year, he had GH value of 11.5 ng/mL suggestive of recurrence. He was reoperated and achieved remission. In Hardy grade 0 adenomas, remission rate was

Table 4 Correlation between preoperative GH level and remission

Preoperative GH level (ng/mL)	No. of patients	Final remission		Total
		Yes	No	
< 40	Total no.	27	11	38
	% within GH level	71.1%	28.9%	100.0%
	% within final remission	64.3%	28.9%	47.5%
≥40	Total no.	15	27	42
	% within GH level	35.7%	64.3%	100.0%
	% within final remission	35.7%	71.1%	52.5%
Total	Total no.	42	38	80
	% within GH level	52.5%	47.5%	100.0%
	% within final remission	100.0%	100.0%	100.0%

Abbreviation: GH, growth hormone.

Table 5 Size, grade, and invasiveness of the adenoma

Study	Microadenoma (%)	Macroadenoma (%)	Intrasellar adenoma (%)	Infra/para/suprasellar adenoma (%)	Noninvasive adenoma (%)	Invasive adenoma (%)
Ross and Wilson ⁶	14	86	79	21	69	31
Minniti et al ¹²	17	83	28	62	–	–
Kruetzer et al ¹³	33	67	46	54	46	54
Present study	1	99	10	90	47	53

100%. In grades A and B adenomas, it was 57%, whereas in grades C and D adenomas remission rate of 43% was observed. In grade E adenomas, remission rate was 38%. There was association between these two variables ($p = 0.09$). In 41 patients with invasive adenomas, remission rate was observed in 13 (31%) patients, whereas 30 patients (76%) remission in noninvasive adenoma group (► **Table 3**). Out of 26 patients with cavernous sinus invasion, only 10 (38.5%) patients achieved remission, whereas out of 54 patients without cavernous sinus invasion, 32 (59.3%) patients achieved remission. Though there is a correlation between these two groups, it was not statistically significant ($p = 0.08$) (► **Table 2**).

Correlation between preoperative GH level and remission: For correlation, patient groups were divided into two groups, based on preoperative serum GH value. Those with serum GH level < 40 ng/mL had remission rate of 71% whereas those with serum GH levels ≥ 40 ng/mL had remission rate of 37%. The difference in these two groups was statistically significant ($p = 0.02$) (► **Table 4**).

Discussion

Demography and Clinical Features

In our study, males and females were almost equally affected (51 males and 42 females). Seventy-seven percent patients were young (< 40 years) with a mean age of 32.71 ± 10.16 years. Scacchi et al and Esposito et al observed similar demography in their study.¹ Forty-nine percent patients presented with visual disturbances, which is higher than in available literature. This could be due to the delayed

presentation in our patients. Hypopituitarism was observed in 43% patients and menstrual irregularities were the most common endocrinologic manifestation in females. About 57% patients presented with headache. Holdaway and Rajasooriya,² in their study on epidemiology of acromegaly, noticed that the incidence of visual field defect ranged between 4 and 62% in different series in the literature. The incidence of headache mentioned is between 37 and 87%. Higher incidence of visual disturbances in our study suggests the higher incidence of macroadenomas with significant suprasellar extension. We observed hypopituitarism at presentation in 43% patients. This finding is almost the same as observed by Esposito et al.¹ Four patients had pituitary apoplexy at presentation. Occurrence of apoplexy in GH-secreting pituitary adenoma is rare and reported incidence is 2% of all macroadenomas.^{3,4}

The prevalence is estimated to be 40 to 130 per million inhabitants and is most often diagnosed in middle-aged adults (average age 40 years).^{1,2} Because of the insidious onset and slow progression, acromegaly is frequently diagnosed from 4 to more than 10 years after its onset.¹ Acromegaly reduces life expectancy with the death rate among acromegaly patients being more than twice that of a control population.⁵

Diagnosis

The endocrine criteria include an elevated basal GH level (> 5 ng/mL), insufficient GH suppressibility (> 2 ng/mL) on OGTT, and elevation of serum IGF-1 levels.⁵ Measurement of circulating GH-releasing hormone (GHRH) is the preferred test for the differential diagnosis between GH-secreting pituitary adenoma and ectopic GHRH secretion.. Esposito

Table 6 Remission rates in different series

Author	No. of Patients	Remission rates (%)			Remission criteria
		Total	Microadenoma	Macroadenoma	
Ross and Wilson ⁶	153	56	NA	NA	GH < 5 ng/mL
Losa et al ⁷	29	55	NA	NA	GH < 1 ng/mL on OGTT and normal IGF-1 level
Fahlbusch et al ⁴	222	56	72	49	GH < 2 ng/mL during OGTT
Tindall et al ⁸	91	82	NA	NA	GH < 5 ng/mL and/or normal IGF-1 level

Abbreviations: GH, growth hormone, IGF-1, insulin-like growth factor 1; NA, not applicable; OGTT, oral glucose tolerance testing.

et al¹ observed hypopituitarism in 45% of patients. The average GH level in their series was 32.6 ± 6.1 ng/mL. Ross et al⁶ noticed that approximately 34% patients had preoperative GH level > 50 ng/mL. Six of our patients had increase in serum prolactin level suggestive of common acidophilic origin of both the cell lines.

Correlation between Grade of the Tumor and Remission

Our study had maximum number (99%) of macroadenomas with 90% adenomas having suprasellar or parasellar extension. About 50 (53%) had invasive adenoma similar to the series reported by Kruetzer et al.⁷ Among the patients with invasive adenoma, 32 (34%) had adenomas invading the cavernous sinus, thereby making the total extirpation of tumor difficult. This is in contrast to the other studies, which have a higher incidence of microadenomas and a lesser frequency of invasiveness (►Table 5).

Tumor size and invasion status have a clear influence on surgical outcome. Understandably, remission rates are highest for microadenomas, and they drop significantly for invasive macroadenomas and those with extrasellar extension. Postoperative remission for all macroadenomas varies from 49 to 77%. When remission rates of diffuse (grade II) and invasive (grades III and IV) macroadenomas are separated, outcomes among the latter are considerably less favorable. For grades II, III, and IV tumors, Tindall and coworkers reported remission rates of 60, 23.1, and 0%, respectively.⁸ The radiotherapeutic response of somatotroph adenomas is predictable. GH levels drop to 50% of baseline in the first 2 years and to 75% of baseline after 5 years. The latent interval required to suppress GH levels to < 5 ng/mL is at least 10 years. Radiation therapy also effectively halts tumor progression.⁹

In our study, we observed a correlation between Hardy grade and final remission. Patients with Hardy grade 0 had remission in 100% cases, in grades A and B it was 57%, and in grades C and D adenomas remission rate was 43%. In grade E adenomas, remission rate was 38%. We observed a correlation between cavernous sinus invasion and remission. Only 38.5% patients with cavernous sinus invasion could achieve remission whereas 59.3% patients without invasion achieved remission. We observed that higher the grade of the tumor, the lesser is the chance of remission. Similarly, we observed a correlation between invasiveness of the tumor and chances of remission. Invasive adenomas had only 31% remission whereas noninvasive adenomas had remission in 74% of cases. Tindall et al⁸ observed the remission rate of 23% in invasive adenomas whereas 60% in noninvasive adenomas. While in patients with cavernous sinus invasion, their remission rate was 0%. Ross and Wilson⁶ observed remission rate of 23% in stage IV tumors whereas it was 57% each for stages III and II. Minniti et al¹⁰ observed the remission rate in microadenomas to be 81%. In invasive adenomas and adenomas with cavernous sinus invasion, remission rate was 38% and 4% respectively. Similarly, Esposito et al¹ observed biochemical remission in 76% of microadenomas and 51% of macroadenomas (►Table 6).¹¹⁻¹⁶ Reduced

biochemical remission in our series can be attributed to the higher number of invasive adenomas.

Correlation between Preoperative Growth Hormone Level and Remission

The mean serum GH level was 52.05 ng/mL. About 50% patients had GH level > 40 ng/mL.

Ross et al⁶ observed the serum GH value of < 50 ng/mL in 66% patients. Also, Esposito et al¹ observed mean GH value to be 32.6 ± 6.1 ng/mL in their series. Minniti et al¹⁰ observed that only 20% patients in their series had GH level > 50 ng/mL. Serum GH levels were higher in our study as compared with other studies, again probably due to delayed presentation in our cohort. Hyperprolactinemia was present in 28% patients in our series, which is slightly lower compared with literature where it ranges from 37 to 38%.^{1,10}

The control of GH- and IGF-1 secretion is the main goal of treatment, as normalization of these two parameters is the most significant determinant of reversing the increased mortality rate of the patients. Because this is a study, which spans a time before the criteria were altered, we have used the older criteria (< 5 ng/mL) for defining remission.

In our series, we observed remission in 37% cases in patients with preoperative serum GH level ≥ 40 ng/mL whereas patients with level < 40 ng/mL had remission in 71% of the cases. The comparison with various series is detailed in ►Tables 5, 6.

Complications

Out of 93 patients, 18 (19%) had postoperative CSF leak. Four patients required reexploration and sellar floor reconstruction. Eight patients had postoperative meningitis. This is in comparison to Ross et al⁷ who mentioned postoperative CSF leak in 5% patients, which required surgical intervention in 2% cases. In their series 2% patients had meningitis whereas carotid injury was noted in 1% patients. Minniti et al¹⁰ observed CSF leak in 4% patients and diabetes insipidus in 8% patients. They observed meningitis in 1% patients and none of the patients had visual deterioration. Esposito et al¹ observed CSF leak in 3% patients whereas diabetes insipidus was noticed in 9% cases. Higher incidence of CSF leak and meningitis in our series could be because of higher number of invasive tumors. Also, CSF leak was a significant ($p < 0.05$) risk factor for infection, and hence all attempts must be made to prevent intraoperative CSF leak.

Conclusion

In this series, one of the largest in available literature from our country, we have examined our experience with surgical management of GH-secreting pituitary adenomas. In this series, one of the largest of its kind, the main factors influencing unfavorable outcome include macroadenomas, invasiveness, high basal GH > 45 ng/mL levels, and mixed adenomas. Though our overall rates of complete remission are slightly lower than available literature, they are comparable with the literature when the cohort characteristics with a

significantly higher proportion of unfavorable prognostic factors are taken into consideration.

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