

Pediatric Pituitary Adenoma: Case Series, Review of the Literature, and a Skull Base Treatment Paradigm

Avital Perry¹ Christopher Salvatore Graffeo¹ Christopher Marcellino¹ Bruce E. Pollock¹
Nicholas M. Wetjen¹ Fredric B. Meyer¹

¹ Department of Neurologic Surgery, Mayo Clinic, Rochester Minnesota, United States

Address for correspondence Fredric B. Meyer, MD, Department of Neurologic Surgery – Mayo Clinic, 200 First St SW, Rochester, MN 55905, United States (e-mail: Meyer.Fredric@mayo.edu).

J Neurol Surg B 2018;79:91–114.

Abstract

Background Pediatric pituitary adenoma is a rare skull base neoplasm, accounting for 3% of all intracranial neoplasms in children and 5% of pituitary adenomas. Compared with pituitary tumors in adults, secreting tumors predominate and longer disease trajectories are expected due to the patient age resulting in a natural history and treatment paradigm that is complex and controversial.

Objectives The aims of this study were to describe a large, single-institution series of pediatric pituitary adenomas with extensive long-term follow-up and to conduct a systematic review examining outcomes after pituitary adenoma surgery in the pediatric population.

Methods The study cohort was compiled by searching institutional pathology and operative reports using diagnosis and site codes for pituitary and sellar pathology, from 1956 to 2016. Systematic review of the English language literature since 1970 was conducted using PubMed, MEDLINE, Embase, and Google Scholar.

Results Thirty-nine surgically managed pediatric pituitary adenomas were identified, including 15 prolactinomas, 14 corticotrophs, 7 somatotrophs, and 4 non-secreting adenomas. All patients underwent transsphenoidal resection (TSR) as the initial surgical treatment. Surgical cure was achieved in 18 (46%); 21 experienced recurrent/persistent disease, with secondary treatments including repeat surgery in 10, radiation in 14, adjuvant pharmacotherapy in 11, and bilateral adrenalectomy in 3. At the last follow-up (median 87 months, range 3–581), nine remained with recurrent/persistent disease (23%).

Thirty-seven publications reporting surgical series of pediatric pituitary adenomas were included, containing 1,284 patients. Adrenocorticotrophic hormone (ACTH)-secreting tumors were most prevalent (43%), followed by prolactin (PRL)-secreting (37%), growth hormone (GH)-secreting (12%), and nonsecreting (7%). Surgical cure was reported in 65%. Complications included pituitary insufficiency (23%), permanent visual dysfunction (6%), chronic diabetes insipidus (DI) (3%), and postoperative cerebrospinal fluid (CSF) leak (4%). Mean follow-up was 63 months (range 0–240), with recurrent/persistent disease reported in 18% at the time of last follow-up.

Keywords

- pediatric pituitary adenoma
- transsphenoidal surgery
- radiotherapy
- stereotactic radiosurgery
- hypopituitarism

Conclusion Pediatric pituitary adenomas are diverse and challenging tumors with complexities far beyond those encountered in the management of routine adult pituitary disease, including nuanced decision-making, a technically demanding operative environment, high propensity for recurrence, and the potentially serious consequences of hypopituitarism with respect to fertility and growth potential in a pediatric population. Optimal treatment requires a high degree of individualization, and patients are most likely to benefit from consolidated, multidisciplinary care in highly experienced centers.

Introduction

Pediatric pituitary adenoma is a rare disease, representing 3% of all intracranial neoplasms in children, and ~5% of all pituitary adenomas.^{1–5} As compared with the adult disease, pituitary adenoma in children is predominantly comprised of secreting tumors, with prolactin (PRL), adrenocorticotrophic hormone (ACTH), and growth hormone (GH) secreting tumors observed most frequently.^{4–11} This contrast is most likely attributable to the slow progression of non-secreting tumors, which theoretically may not grow sufficiently in early life to induce symptoms. A combination of advances in our understanding of the underlying disease; on-going developments in radiation and endoscopic technology, and techniques; and shifting attitudes regarding the goals-of-care have cumulatively resulted in a highly nuanced clinical landscape.

Due to the combined rarity and complexity of the disease, pediatric pituitary adenoma has been infrequently studied, and recommendations regarding its optimal management are disparate, debated, and based on relatively poor evidence. Correspondingly, our objective was to report our own experience with these challenging tumors, systematically review the preceding literature, and assemble our findings into a treatment algorithm salient to the clinical practice of pediatric skull base surgery.

Methods

Patient Search, Inclusion Criteria, and Clinical Endpoints

The study cohort was compiled by searching institutional pathology and operative reports using diagnosis and site codes for pituitary and sellar pathology, from 1956 to 2016; positive results in patients aged 25 years and younger at time of treatment were cross-referenced with operative reports and surgical databases to confirm that patients underwent neurosurgical treatment at our institution for pituitary adenoma. Patients over 18 years at the time of diagnosis were excluded. Included patients underwent retrospective chart review to capture relevant clinical outcomes (–Tables 1–3). Given the complexities of pituitary adenoma care and the challenges of definitively identifying periods of true disease remission, in our series and review of the literature, we grouped all failures of primary surgical therapy as a single entity we refer to as *recurrent or persistent disease*,

Table 1 Overview of the study cohort

	<i>n</i> = 39
Age at time of diagnosis (years)	15 (8–18)
Age at time of first operation (years)	16 (9–22)
General neurologic symptoms or focal deficits	
Headache	26 (67%)
Visual disturbance	14 (36%)
Cranial neuropathy	5 (13%)
Depression	5 (13%)
Seizure	2 (5%)
Diplopia	1 (3%)
Stroke	1 (3%)
Vertigo	1 (3%)
Nonspecific symptoms of pituitary dysfunction	
Arrested growth	6 (15%)
Hypothyroidism	6 (15%)
Apoplexy	4 (10%)
Pubertal delay	3 (8%)
Polyuria	1 (3%)
Symptoms suggesting hyperprolactinemia	
Amenorrhea ^a	11 (28%)
Galactorrhea	7 (18%)
Symptoms suggesting hypercortisolemia	
Obesity/weight gain	16 (41%)
Acne	12 (31%)
Hirsutism	11 (28%)
Moon facies	10 (26%)
Striae	6 (15%)
Buffalo hump	5 (13%)
Easy bruising	5 (13%)
Muscle weakness	4 (10%)
Acanthosis nigricans	2 (5%)
Pathologic fracture	1 (3%)

Table 1 (Continued)

	<i>n</i> = 39
Symptoms suggesting hypersomatotropinemia	
Precocious growth	5 (13%)
Acromegaly/gigantism	4 (10%)
Maximum tumor diameter on pre-operative imaging (mm; median (range))	11 (1–40)
Biochemical and pathologic diagnosis	
Prolactin secreting	15 (39%)
ACTH secreting	14 (36%)
GH secreting	7 (18%)
Non-secreting	6 (15%)
Pluri-hormonal	4 (10%)
Atypical features	5 (13%)
Crooke's hyaline change	4 (10%) ^b
Underlying genetic conditions	
Multiple endocrine neoplasia type 1	1 (3%)
McCune–Albright syndrome	1 (3%)

Abbreviations: ACTH; adrenocorticotrophic hormone; GH, growth hormone.

^aPercentage of female patients only.

^bPercentage of ACTH-secreting adenomas.

which we defined as any symptomatic, biochemical, or radiographic evidence of disease at any time following the first operation. Among patients who were identified as having recurrent or persistent disease, we documented disease cure only where explicit evidence confirmed that a patient was symptom-free, off tumor-suppressive pharmacotherapy, and with resolution of any previously documented biochemical and/or radiographic disease.

Systematic Review

A search of the English language literature since 1970 was conducted using PubMed, MEDLINE, Embase, and Google Scholar. Keywords and MeSH terms included “pituitar*” or “hypophys*” in combination with “child*,” “pediatr*,” “paediatr*,” or “adolesc*” and “adenoma” (►Fig. 1). Initial results after deduplication yielded 57 unique English language publications; bibliographies were screened for additional references potentially warranting inclusion, and all abstracts were independently reviewed by two authors to confirm that inclusion criteria were met (defined as case series of biochemically, radiographically, or pathologically confirmed pituitary adenoma reporting extractable treatment and outcomes data); instances of disagreement were secondarily re-reviewed and discussed for final adjudication. Thirty-seven eligible publications were identified, 11 of which reported patients *treated up to 20 years-of-age*, rather than *diagnosed up to 18 years-of-age*, which were deemed a comparable population and included to maximize

Table 2 Surgical management and outcomes

	<i>n</i> = 39
History of preoperative pharmacotherapy	13 (33%)
Microscopic TSR	37 (95%)
Endoscopic endonasal TSR	2 (5%)
Gross total resection	18 (46%)
Disease cured with TSR alone	18 (46%)
Recurrent/persistent disease after initial TSR	21 (54%)
Any repeat operation	10 (26%)
Any postoperative radiation	14 (36%)
Any postoperative pharmacotherapy	11 (28%)
Bilateral adrenalectomy	3 (21%) ^a
Treatment complications	
Chronic postoperative pituitary insufficiency	26 (67%)
Postoperative CSF leak	3 (8%)
Permanent postoperative visual dysfunction	1 (3%)
Chronic diabetes insipidus	1 (3%)
Radiation necrosis	1 (3%)
Radiation-induced optic neuropathy	1 (3%)
Radiation-induced abducens palsy	1 (3%)
Meningitis	1 (3%)
Total clinical follow-up (mo.; median (range))	87 (3–581)
Recurrent/persistent disease at last follow-up	9 (23%)
Mortalities	0 (0%)

Abbreviations: ACTH, adrenocorticotrophic hormone; TSR, transsphenoidal resection.

^aPercentage of ACTH-secreting adenomas.

yield. All 37 publications were reviewed in detail; relevant clinical outcomes were again captured (►Tables 4–5).

Results

Overview of the Study Cohort

Thirty-nine pediatric pituitary adenoma patients at our institution were identified; median ages at times of diagnosis and surgery were 15 and 16 years, respectively (ranges 8–18 and 9–22, respectively). Symptoms at the time of presentation were diverse and heterogeneous, with the most common complaints including headache (67%), obesity/weight gain (41%), visual disturbance (36%), acne (31%), amenorrhea (28%), hirsutism (28%), and moon facies (26%; ►Table 1). Median maximum tumor diameter on preoperative imaging was 11 mm (range 1–40 mm). Among 39 adenomas, biochemical and pathologic analyses diagnosed 15 prolactinomas

Table 3 Detailed treatment courses in recurrent or persistent disease

	<i>n</i> = 21 ^a
Successfully treated recurrent/persistent tumors (after failed primary TSR)	12 (57%)
Repeat TSR alone, cured at last follow-up	3 (14%)
SRS alone (one patient underwent two treatments), cured at last follow-up ^b	4 (19%)
Repeat TSR followed by SRS, cured at last follow-up	3 (14%)
Repeat TSR followed by PBRT, cured at last follow-up	1 (5%)
Repeat TSR, BAX, and EBRT, cured at last follow-up	1 (5%)
Unsuccessfully treated recurrent/persistent tumors (after failed primary TSR)	9 (43%)
Pharmacotherapy alone, persistent disease at last follow-up	4 (19%)
EBRT alone, persistent disease at last follow-up ^b	1 (5%)
SRS alone, persistent disease at last follow-up ^b	1 (5%)
Repeat TSR, BAX, and SRS, persistent disease at last follow-up	1 (5%)
EBRT, multiple TSRs, and craniotomy, persistent disease at last follow-up ^b	1 (5%)
Multiple TSRs and craniotomies; BAX; multiple SRS and EBRT treatments; persistent disease at last follow-up	1 (5%)

Abbreviations: BAX, bilateral adrenalectomy; EBRT, external beam radiotherapy; PBRT, proton beam radiotherapy; SRS, stereotactic radiosurgery; TSR, transphenoidal resection.

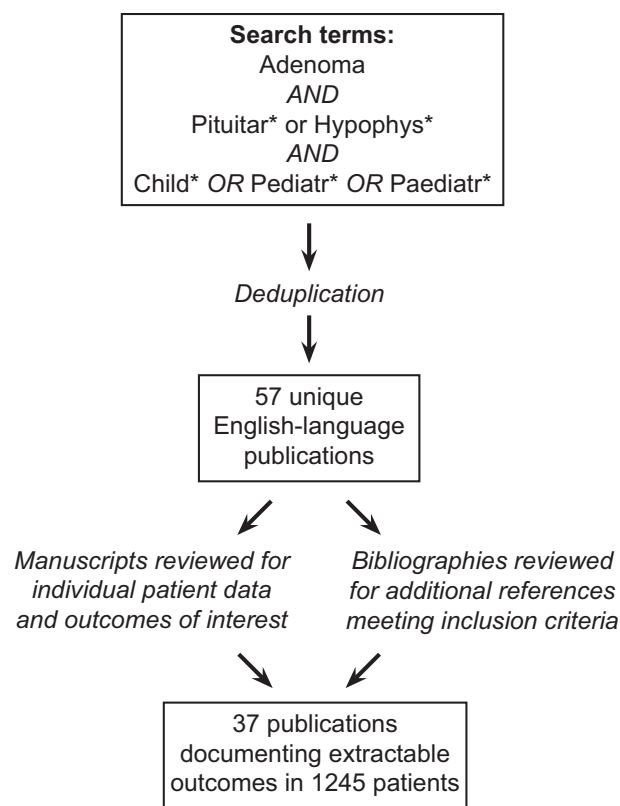
^aPercentages of patients with recurrent/persistent disease after first TSR.

^bPatients with atypical features on pathology (*n* = 5).

(39%), 14 corticotrophs (36%), 7 somatotrophs (18%), and 4 non-secreting adenomas (10%). Four tumors were plurihormonal (10%): three were positive for PRL and GH (8%), and one was positive for ACTH and GH (3%). Five tumors demonstrated atypical pathologic features (13%), and four ACTH-secreting tumors contained Crooke's hyaline change (29%). Underlying genetic conditions were present in one patient with multiple endocrine neoplasia type 1 (MEN-1) and one with McCune-Albright syndrome.

Surgical Management and Outcomes

An initial trial of at least one pharmacologic agent was attempted in 13 (33%) patients, typically with bromocriptine or cabergoline, as well as one trial each of pergolide, octreotide, and pegvisomant (►Table 2). Transphenoidal resection (TSR) was then attempted in 39 (100%) patients, 37 (95%) via either a sublabial, transphenoidal, or transnasal transphenoidal microsurgical technique and 2 (5%) using a purely endoscopic endonasal approach (EEA). A primary surgical cure was obtained in 18 patients, in all of whom gross total resection (GTR) was achieved (46%).

**Fig. 1** Schematic depicting search strategy for systematic literature review

Twenty-one patients experienced recurrent or progressive disease postoperatively. Repeat surgery was undertaken in 10 (26%), radiation of any modality was used in 14 (36%), 11 received pharmacotherapy (28%), and 3 underwent bilateral adrenalectomy (31% of ACTH-secreting tumors). Cumulatively, 39 patients underwent a total of 55 TSRs, 7 craniotomies, 13 stereotactic radiosurgeries (SRS), 5 courses of external beam radiotherapy (EBRT), 1 proton beam radiotherapy (PBRT), and 3 bilateral adrenalectomies (BAX). Detailed treatment courses are outlined in ►Table 3. Atypical pathologic features were significantly associated with recurrent or persistent disease ($p = 0.05$).

At last clinical follow-up, disease cure had been achieved in 30 (77%) patients including 12 (31%) who had been treated for recurrent or persistent disease, while 9 (25%) remained with recurrent or persistent disease (►Table 2). Complications from any treatment included 26 patients with chronic pituitary insufficiency requiring supplementation of at least one hormone (67%), three cases (8%) of postoperative cerebrospinal fluid (CSF) leak, and one case (3%) each of permanent visual dysfunction, chronic diabetes insipidus (DI), radiation necrosis, radiation-induced optic neuropathy, radiation-induced abducens palsy, or meningitis. Median total clinical follow up was 87 months (range 3–581). There were no mortalities in our series; however, one patient has initiated palliative care and is anticipated to expire due to primary disease.

Table 4 Systematic review of surgical series of pediatric pituitary adenoma: clinical presentation and initial surgical management

First author	Year	n	Age range (y)	Non-secreting	ACTH secreting	PRL secreting	GH secreting	Plurihormonal	Prior RT failed	Prior Rx failed	Primary TSR	Primary TCR	GTR	Disease cured with surgery alone
Richmond	1978	25	5–17	–	4 (16%)	8 (32%)	4 (16%)	–	0 (0%)	0 (0%)	23 (92%)	2 (8%)	17 (68%)	2 (23%)
Fraioli	1983	9	11–15	1 (11%)	1 (11%)	4 (22%)	4 (22%)	2 (22%)	0 (0%)	2 (22%)	9 (100%)	3 (33%)	2 (22%)	13 (89%)
Styne	1984	15	7–13	0 (0%)	15 (100%)	2 (13%)	0 (0%)	5 (33%)	0 (0%)	0 (0%)	15 (100%)	0 (0%)	–	13 (87%)
Fahlbusch	1986	14	<18	–	–	–	–	–	–	–	–	–	–	9 (64%)
Laws	1987	76	7–19	1 (1%)	22 (29%)	43 (57%)	9 (12%)	0 (0%)	–	–	76 (100%)	0 (0%)	76 (100%)	–
Ludecke	1987	26	1–18	0 (0%)	11 (42%)	8 (31%)	7 (23)	0 (0%)	0 (0%)	4 (15%)	26 (100%)	0 (0%)	–	19 (73%)
Maira	1990	52	7–20	19 (37%)	3 (6%)	22 (42%)	8 (15%)	0 (0%)	–	–	51 (98%)	1 (2%)	–	47 (90%)
Haddad	1991	16	7–17	0 (0%)	5 (31%)	13 (81%)	0 (0%)	0 (0%)	0 (0%)	9 (56%)	16 (100%)	0 (0%)	–	7 (44%)
Dyer	1994	66	<16	4 (6%)	36 (55%)	18 (27%)	8 (12%)	0 (0%)	–	–	66 (100%)	0 (0%)	–	56 (85%)
Kane	1994	56	7–18	–	–	–	–	–	0 (0%)	3 (5%)	56 (100%)	0 (0%)	–	19 (34%)
Magiakou	1994	50	4–20	0 (0%)	50 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	–	49 (98%)	0 (0%)	–	47 (94%)
Partington	1994	36	7–17	2 (6%)	16 (44%)	15 (42%)	3 (8%)	9 (25%)	0 (0%)	–	36 (100%)	0 (0%)	32 (89%)	21 (58%)
Leinung	1995	22	<19	0 (0%)	22 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	22 (100%)	0 (0%)	–	10 (45%)
Minder-mann	1995	136	0–19	4 (3%)	48 (35%)	72 (53%)	12 (9%)	17 (29%)	2 (1%)	11 (8%)	136 (100%)	0 (0%)	–	–
Weber	1995	9	7–17	0 (0%)	9 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9 (100%)	0 (0%)	–	6 (67%)
Devoe	1997	35	6–18	0 (0%)	35 (100%)	0 (0%)	0 (0%)	0 (0%)	–	–	35 (100%)	0 (0%)	–	27 (77%)
Massoud	1997	21	8–17	2 (10%)	14 (67%)	1 (5%)	2 (10%)	0 (0%)	1 (5%)	1 (5%)	21 (100%)	0 (0%)	–	16 (76%)
Abe	1998	5	12–18	5 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (80%)	1 (20%)	4 (80%)	4 (80%)
Artese	1998	47	14–20	2 (4%)	3 (6%)	34 (72%)	9 (17%)	0 (0%)	0 (0%)	16 (34%)	43 (91%)	5 (9%)	–	40 (85%)
Dissanevate	1998	4	14–16	0 (0%)	0 (0%)	4 (100%)	0 (0%)	0 (0%)	0 (0%)	3 (75%)	4 (100%)	0 (0%)	–	0 (0%)
Abe	1999	15	0–19	0 (0%)	0 (0%)	0 (0%)	15 (100%)	0 (0%)	0 (0%)	0 (0%)	15 (100%)	0 (0%)	9 (60%)	7 (47%)
Kunwar	1999	150	0–19	4 (3%)	54 (36%)	78 (52%)	12 (8%)	0 (0%)	–	–	150 (100%)	0 (0%)	–	–
Fideleff	2000	15	<19	0 (0%)	0 (0%)	15 (100%)	0 (0%)	0 (0%)	0 (0%)	12 (80%)	–	–	–	7 (47%)

(Continued)

Table 4 (Continued)

First author	Year	n	Age range (y)	Non-secreting	ACTH secreting	PRL secreting	GH secreting	Plurihormonal	Prior RT failed	Prior Rx failed	Primary TSR	Primary TCR	GTR	Disease cured with surgery alone
Tamura	2000	32	9–18	5 (16%)	6 (19%)	12 (38%)	4 (13%)	0 (0%)	0 (0%)	–	30 (94%)	2 (6%)	–	25 (78%)
Nishio	2001	5	10–17	3 (60%)	0 (0%)	1 (20%)	1 (20%)	0 (0%)	0 (0%)	1 (20%)	2 (40%)	3 (60%)	3 (60%)	3 (60%)
Abe	2002	14	14–17	0 (0%)	0 (0%)	14 (100%)	0 (0%)	0 (0%)	0 (0%)	12 (86%)	14 (100%)	0 (0%)	10 (71%)	6 (43%)
Cannavo	2003	27	10–17	8 (30%)	2 (7%)	14 (52%)	3 (11%)	0 (0%)	0 (0%)	11 (41%)	20 (74%)	7 (26%)	–	8 (30%)
Storr	2003	18	6–17	0 (0%)	18 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	18 (100%)	0 (0%)	–	11 (61%)
Kanter	2005	33	5–19	0 (0%)	33 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	33 (100%)	0 (0%)	–	22 (67%)
Das	2007	10	12–17	0 (0%)	10 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9 (90%)	1 (10%)	–	4 (40%)
Mehrazin	2007	21	1–18	2 (10%)	8 (38%)	7 (33%)	4 (19%)	0 (0%)	0 (0%)	0 (0%)	13 (62%)	8 (38%)	–	9 (43%)
Webb	2008	20	5–18	1 (5%)	5 (25%)	5 (25%)	11 (55%)	2 (10%)	–	–	20 (100%)	0 (0%)	12 (60%)	11 (55%)
Locatelli	2010	12	13 ^a	3 (25%)	6 (50%)	3 (25%)	0 (0%)	0 (0%)	–	–	12 (100%)	0 (0%)	12 (100%)	11 (92%)
Oliveira	2010	15	6–18	0 (0%)	15 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	15 (100%)	0 (0%)	13 (87%)	8 (53%)
Tarapore	2011	34	9–18	2 (6%)	10 (29%)	21 (62%)	1 (3%)	0 (0%)	0 (0%)	10 (29%)	34 (100%)	0 (0%)	26 (76%)	28 (82%)
Shah	2011	48	9–19	0 (0%)	48 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	48 (100%)	0 (0%)	–	25 (52%)
Zhan	2015	56	10–18	15 (27%)	6 (11%)	15 (27%)	20 (36%)	0 (0%)	0 (0%)	0 (0%)	56 (100%)	0 (0%)	49 (88%)	28 (50%)
Perry	2017	39	8–18	6 (15%)	14 (36%)	15 (39%)	7 (18%)	4 (10%)	0 (0%)	13 (33%)	39 (100%)	0 (0%)	18 (46%)	18 (46%)
Summary	2017	1284	0–20	7% (89/1189)	43% (529/1228)	37% (444/1214)	12% (114/1214)	3% (114/1284)	<1% (3/911)	14% (108/793)	98% (1225/1255)	3% (33/1255)	78% (283/361)	65% (603/922)

Abbreviations: ACTH, adrenocorticotrophic hormone; GH, growth hormone; GTR, gross total resection; PRL, prolactin; RT, radiotherapy; Rx, pharmacotherapy; TCR, transcranial resection; TSR, transsphenoidal resection.

^aMean age reported

Table 5 Systematic review of surgical series of pediatric pituitary adenoma: recurrence, complications, outcome, and follow-up

First author	Year	N	Recurrent/ persistent disease after initial operation	Any repeat surgery ^b	Any post- operative RT ^b	Any post- operative Rx ^b	BAX ^a	Chronic post- operative pituitary insuffi- ciency	Perma- nent visual dysfunc- tion	Chronic diabetes insipidus	Post- operative CSF leak	Recurrent/ persistent disease at last follow- up	Median follow-up (mo.) ^c
Richmond ^c	1978	25	2 (8%)	–	–	–	0 (0%)	10 (40%)	0 (0%)	1 (4%)	1 (4%)	–	14 ^c
Fraioli	1983	9	1 (11%)	–	–	–	–	6 (67%)	1 (11%)	1 (11%)	1 (11%)	1 (11%)	48
Styne	1984	15	2 (13%)	1 (50%)	–	–	0 (0%)	7 (47%)	–	2 (13%)	–	0 (0%)	32
Fahlbusch	1986	14	5 (36%)	4 (80%)	–	–	–	–	–	–	–	5 (36%)	–
Laws	1987	76	–	–	–	–	–	–	–	–	–	–	–
Ludecke	1987	26	7 (27%)	7 (100%)	5 (71%)	–	0 (0%)	1 (4%)	0 (0%)	–	1 (4%)	–	–
Maira	1990	52	5 (10%)	4 (80%)	1 (20%)	0 (0%)	–	–	–	–	–	0 (0%)	12–108
Haddad ^c	1991	16	9 (56%)	3 (33%)	2 (22%)	4 (44%)	–	2 (12%)	–	–	–	6 (38%)	55 ^c
Dyer	1994	66	10 (15%)	6 (60%)	6 (60%)	6 (60%)	1 (2%)	4 (5%)	–	1 (2%)	1 (2%)	6 (9%)	6–168
Kane	1994	56	37 (66%)	3 (8%)	21 (57%)	19 (51%)	–	6 (10%)	1 (2%)	0 (0%)	1 (2%)	23 (41%)	84
Magiakou ^c	1994	50	3 (6%)	3 (100%)	0 (0%)	0 (0%)	–	7 (19%)	–	0 (0%)	–	0 (0%)	22 ^c
Partington	1994	36	15 (42%)	2 (13%)	4 (27%)	5 (33%)	–	14 (39%)	0 (0%)	1 (3%)	0 (0%)	3 (8%)	60
Leinung	1995	22	12 (55%)	6 (50%)	0 (0%)	0 (0%)	3 (14%)	5 (23%)	–	0 (0%)	–	12 (55%)	80
Mindermann ^c	1995	136	–	14 (64%)	22 (100%)	–	3 (6%)	–	–	–	–	–	24 ^c
Weber	1995	9	3 (33%)	0 (0%)	3 (100%)	0 (0%)	–	4 (44%)	–	3 (33%)	–	0 (0%)	24–128
Devoe ^c	1997	35	8 (23%)	8 (100%)	0 (0%)	–	4 (11%)	5 (14%)	–	0 (0%)	–	2 (6%)	86 ^c
Massoud	1997	21	5 (24%)	3 (60%)	2 (40%)	0 (0%)	1 (7%)	10 (48%)	–	1 (5%)	2 (10%)	0 (0%)	96
Abe ^c	1998	5	1 (20%)	0 (0%)	1 (100%)	0 (0%)	–	4 (80%)	1 (20%)	0 (0%)	–	1 (20%)	132
Artese	1998	47	7 (15%)	0 (0%)	3 (43%)	4 (57%)	–	–	–	1	1	6 (13%)	–
Dissaneevate	1998	4	4 (100%)	0 (0%)	3 (75%)	2 (50%)	–	2 (50%)	1 (25%)	1 (25%)	–	4 (100%)	–
Abe ^c	1999	15	8 (53%)	0 (0%)	4 (50%)	8 (100%)	–	6 (33%)	0 (0%)	3 (20%)	0 (0%)	2 (13%)	74 ^c
Kunwar	1999	150	–	–	–	–	–	–	–	–	–	–	–
Fideleff	2000	15	8 (53%)	0 (0%)	0 (0%)	5 (63%)	–	3 (20%)	–	0 (0%)	–	–	–
Tamura	2000	32	7 (22%)	0 (0%)	8 (100%)	3 (43%)	–	2 (6%)	–	–	–	–	–
Nishio ^c	2001	5	2 (40%)	0 (0%)	2 (100%)	2 (100%)	–	2 (40%)	0 (0%)	–	–	1 (20%)	53 ^c
Abe	2002	14	5 (57%)	0 (0%)	7 (88%)	8 (100%)	–	3 (21%)	1 (7%)	–	1 (7%)	1 (7%)	72 ^c

(Continued)

Table 5 (Continued)

First author	Year	N	Recurrent/ persistent disease after initial operation	Any repeat surgery ^b	Any post- operative RT ^b	Any post- operative Rx ^b	BAX ^a	Chronic post- operative pituitary insuffi- ciency	Perma- nent visual dysfunc- tion	Chronic diabetes insipidus	Post- operative CSF leak	Recurrent/ persistent disease at last follow- up	Median follow-up (mo.) ^c
Cannavo	2003	27	19 (70%)	0 (0%)	8 (42%)	2 (11%)	–	9 (33%)	13 (48%)	4 (15%)	–	17 (63%)	60
Storri ^c	2003	18	7 (39%)	0 (0%)	7 (100%)	7 (100%)	–	–	–	–	–	0 (0%)	83 ^c
Kanter	2005	33	11 (33%)	3 (37%)	0 (0%)	0 (0%)	2 (6%)	10 (30%)	1 (3%)	1 (3%)	0 (0%)	3 (9%)	44
Das	2007	10	6 (60%)	1 (17%)	4 (67%)	0 (0%)	2 (20%)	–	–	0 (0%)	2 (20%)	1 (10%)	82
Mehrazin	2007	21	12 (57%)	1 (8%)	8 (67%)	10 (83%)	1 (13%)	1 (5%)	1 (5%)	0 (0%)	3 (14%)	11 (52%)	–
Webb ^c	2008	20	9 (45%)	6 (67%)	2 (22%)	0 (0%)	–	–	–	–	–	2 (10%)	50 ^c
Locatelli ^c	2010	12	1 (8%)	1 (100%)	0 (0%)	0 (0%)	–	1 (8%)	–	0 (0%)	1 (8%)	0 (0%)	–
Oliveira	2010	15	7 (47%)	0 (0%)	4 (57%)	2 (29%)	4 (27%)	4 (27%)	–	1 (7%)	–	4 (27%)	139 ^c
Tarapore	2011	34	6 (18%)	0 (0%)	9 (150%)	6 (100%)	1 (10%)	8 (24%)	1 (3%)	–	0 (0%)	3 (9%)	18
Shah ^c	2011	48	17 (35%)	1 (4%)	8 (35%)	6 (26%)	4 (8%)	–	–	0 (0%)	5 (10%)	17 (35%)	59 ^c
Zhan ^c	2015	56	28 (50%)	0 (0%)	0 (0%)	0 (0%)	–	4 (7%)	2 (4%)	1 (2%)	2 (4%)	–	52 ^c
Perry	2017	39	21 (54%)	10 (48%)	14 (67%)	11 (52%)	3 (%)	26 (67%)	1 (3%)	1 (3%)	2 (5%)	9 (23%)	87 (3–581)
Summary	2017	1284	35% (319/922)	8% (87/1024)	16% (157/995)	14% (110/798)	5% (28/554)	23% (116/713)	6% (24/405)	3% (23/691)	4% (24/583)	18% (140/768)	64

Abbreviations: ACTH, adrenocorticotrophic hormone; BAX, bilateral adrenalectomy; CSF, cerebrospinal fluid; RT, radiotherapy; Rx, pharmacotherapy.

^aPercentages of ACTH-secreting adenomas.^bPercentages of recurrent tumors.^cMean follow-up reported; range shown if neither median nor mean reported.

Primary Stereotactic Radiosurgery

In addition to the 39 patients described above, we separately identified 2 pediatric patients with pituitary adenoma who were treated with primary SRS, rather than TSR. In the former case, an 18-year-old with prolactinoma strongly desired to minimize risk of infertility, correspondingly refused surgery, and was offered SRS as an alternative. The treatment plan consisted of 25 Gy delivered to the 50% isodose line, to a treatment volume of 2.2 cm³ for a maximum dose of 50 Gy. A biochemical cure was documented within 18 months, no permanent hormonal replacement therapies were required, and the patient was able to conceive as intended without fertility treatments. No recurrence has been documented in 7 years of clinical follow-up. The second patient had underlying McCune–Albright syndrome with severe fibrous dysplasia of the skull base and a radiographic adenoma that was considered GH producing by laboratory criteria, which obliterated the sphenoid sinus, precluding TSR. Correspondingly, SRS was offered, with a treatment plan of 20 Gy to the 60% isodose line to a total volume of 1.3 cm³, with a maximum dose of 33.3 Gy. The patient has remained symptom free off pharmacotherapy for over 5 years of follow-up, with minimal persistent supranormal elevation of insulin-like growth factor-1 (IGF-1) and normal GH.

Systematic Review

Literature search identified 37 English language publications reporting surgical series of pediatric pituitary adenomas meeting inclusion criteria with extractable by-patient data on the outcomes of interest, spanning 1978 to 2015 (► **Table 4**). Together with the present series, 1,284 patients have been reported with pediatric pituitary adenoma. ACTH-secreting tumors were most frequently reported (43%), followed by PRL-secreting (37%), GH-secreting (12%), and nonsecreting (7%); plurihormonal tumors were reported in 3%. Less than 1% of all tumors were radiated prior to TSR ($n = 3$), while 14% had been trialed on at least one medication. TSR was the approach of choice in 98% of patients. Extent-of-resection was only documented in 28% of cases; among those, GTR was reported in 78%. Disease was cured with primary surgery in 65%.

The remaining 35% were reported as having recurrent or persistent disease after the initial operation (► **Table 5**). Treatment paradigms were very heterogeneous, follow-up in many prior series was short, and adjuvant therapy was incompletely documented in many manuscripts; notwithstanding, among those patients with recurrent or persistent disease, at least 8% underwent repeat surgery, 16% were radiated, and 14% received postoperative pharmacotherapy. Reported complications included postoperative pituitary insufficiency requiring pharmacologic supplementation in 23%, permanent visual dysfunction in 6%, chronic DI in 3%, and postoperative CSF leak in 4%. Follow-up data was inconsistently reported, but approximate mean follow-up was 63 months (range 0–240, excluding present series). At the time of last follow-up, 18% had recurrent or persistent disease.

Discussion Part One: Lessons from the Study Cohort and Literature Review

In setting the stage for our broader survey of the topic, we reviewed our surgical series of 39 pediatric pituitary adenomas, as well as the preceding literature documenting related cohorts. Several key observations stood out, which collectively reaffirmed the disease's intrinsic challenges.

In our series and literature review, the rates of recurrent or persistent disease after primary surgery were 54% and 35%, respectively, which reflect a two- to three-fold increase from large adult series that have approximated recurrence rates for nonfunctioning, PRL-secreting, ACTH-secreting, and GH-secreting tumors at 16%, 13%, 12%, and 1.3%, respectively.^{12,13} However, our findings are consistent with previous pediatric reviews, which have suggested that secretory pituitary disease is more difficult to control and prone to recurrence in children, particularly Cushing disease, which is estimated to have a 40% 10-year recurrence rate in children—although this conclusion has not been universally reproduced.^{2,12–16} Of note, the higher recurrence rate noted in the study cohort most likely reflects the observed differences in follow-up, as well as a potential underlying reporting bias, given the established tendency for studies to under-report true long-term recurrence rates—particularly in Cushing's disease.^{2,16–19}

In the setting of tumor recurrence, adults also appear to be more easily managed than children are. In adults, repeat surgery is an effective first-line treatment for recurrent or persistent tumor without cavernous sinus involvement, and prior series have documented a biochemical cure in up to 57% of secreting tumors after a second TSR, which is a marked improvement compared with our pediatric results (30%).²⁰ By extension, the clinical trajectories in recurrent or persistent disease have the potential to be quite discouraging in children, with only 7 (33%) of 21 patients reaching a cure after a single treatment for recurrence, and 8 (38%) of 21 patients requiring treatment with at least three different modalities beyond primary TSR.

The pediatric pituitary adenoma population is also especially vulnerable to hypopituitarism, due in large part to the high incidence of recurrence and multi-modality treatments.^{21,22} Although most complications in the present study were rare and comparable to those associated with adult disease, permanent pituitary replacement therapy was required in 67% of our patients, as compared with 2 to 27% in major preceding adult reviews (and up to 55% in isolated series).^{23,24} This contrast is in spite of the fact that hypopituitarism is strongly associated with tumor size, but pediatric tumors are more likely to be microadenomas, with a median maximum tumor diameter of 11 mm in the study cohort (range 1–40 mm).^{25,26} Although our literature review documented a lower overall rate at 23% (range 4–80%), this difference again most likely reflects our increased follow-up time, as well as the higher fraction of recurrent or progressive tumors in our cohort (54% in the study cohort, versus 35% overall), or potentially under-reporting in the literature. Regardless, the possibility that two-thirds of pediatric

patients may suffer some degree of endocrine deficiency has dramatic implications, especially with respect to growth and development and fertility.^{2,10,27–29} With this in mind, we turn to an overview of the key concepts in pediatric pituitary adenoma management.

Discussion, Part Two: Key Concepts in Pediatric Pituitary Adenoma Management

Epidemiology and Genetics

Approximately 3 to 9% of pituitary adenomas occur in children, which corresponds to 3% of all pediatric intracranial neoplasms.^{2,6,7,30} The overall prevalence of pituitary adenoma may be increased among female children up to 2:1, due to the marked prolactinoma predominance in girls.^{2,4,9,10,27,28,31} Sporadic pituitary adenomas have been documented to harbor a wide range of mutations involving common tumor suppressor or oncogenes, including *GNAS*, *PTTG*, *HMG2A*, and *FGFR4*.^{28,32,33} Although clear correlations between disease phenotype and underlying genetic abnormalities remain incompletely understood, several interesting relationships have been characterized—most prominently, the 40% prevalence of *GNAS*-activating mutations in somatotrophic tumors.^{28,34}

Associations with genetic syndromes are rare, but potentially an important consideration in younger patients with pituitary adenoma. MEN-1 is the most common such association and has been reported to present with pituitary adenoma in children as young as 5 years.^{28,35} The syndrome arises in patients who inherit a single mutated allele of the *menin* tumor suppressor gene, and subsequently acquire a “second hit.”^{36–39} Individuals bearing the *menin* mutation have a 30 to 40% lifetime risk of pituitary adenoma; ~60% of which secrete PRL and 20% GH.⁴⁰

A second important association is the McCune–Albright syndrome, in which a non-heritable postzygotic activating *GNAS* mutation yields a range of endocrinologic derangements, café au lait spots, and polyostotic fibrous dysplasia.^{28,41,42} Correspondingly, pituitary surgery can be prohibitively challenging, and when undertaken, may require extensive drilling to effectively create the entire transsphenoidal working corridor. Correspondingly, SRS may be the preferred first-line treatment for these children, as in our case, described above.

Carney complex is a very rare autosomal dominant disorder characterized by endocrine hyperactivity, myxomas, lentigines, schwannomas, and adenomas, which is caused by an inactivating mutation of the *PKARIA* gene in 60% of patients, though the underlying mechanism in the remaining families is incompletely understood.^{28,43,44} Interestingly, Carney complex patients frequently present with non-pituitary Cushing’s syndrome due to primary adrenocortical neoplasms and then subsequently develop GH-secreting pituitary adenomas, which are characteristically slow-growing and difficult to identify on imaging.^{28,44–46}

Familial isolated pituitary adenomas (FIPA) is a term used to describe families with two or more first degree relatives developing pituitary adenomas that are negative for *menin*

or *PRKARIA* mutations.²⁸ Of the 211 families described, ~20% harbor an inactivating heterozygous germline mutation of the tumor suppressor gene *AIP*.^{47–49} No definitive trends have been established regarding disease features within these patients, which may reflect the low disease penetrance. Although PRL- and GH-secreting tumors predominate, the full range of pituitary pathologies has been described.

Clinical Presentation

Pediatric pituitary adenoma presentation varies by hormonal subtype, each of which can be loosely grouped by the relative onset of symptoms. Non-secreting tumors are the least common, as they rarely have time for sufficient growth to produce symptoms while the patient remains in childhood. Correspondingly, when they do appear, these tumors generally occur in post-pubescent individuals, who are best approached and treated as young adults.^{4,8,10}

GH-secreting tumors are uncommon, often present in pre-pubertal children and infants, and preferentially arise in males at a 2:1 incidence with precipitous growth, acromegaly, or headaches—although pubertal arrest or primary amenorrhea may be rare presentations of a GH-secreting adenoma masquerading as a microprolactinoma.^{4,6} ACTH-secreting tumors occur slightly later in childhood, with peak incidence at the onset of puberty, and an overall 3:1 female predominance.^{4,6,14,50} Classic symptoms of hyperadrenocorticism are prototypical and range from Cushingoid appearance to growth arrest, weight gain, amenorrhea, mental status changes, hypertension, and hyperglycemia.^{14,15}

Most prior reviews and textbooks have reported PRL-secreting tumors as the most common pediatric pituitary adenomas; the vast majority of which come to clinical attention during puberty, with a 5:1 female predominance.^{4,51} Primary and secondary amenorrhea account for three-quarters of their presentations, while male children present with growth arrest, delayed puberty, or galactorrhea.^{4,52,53} Interestingly, although PRL-secreting tumors are more common overall, as our series and review demonstrate, ACTH-secreting tumors are the largest fraction of tumors that are surgically treated.^{4,27,51,54,55} This potentially attributable to a publication bias, particularly since there has been so much academic interest within the neurosurgical and endocrinologic communities regarding pediatric Cushing disease.^{14,15,56,57} More likely, this trend reflects the responsiveness of prolactinomas to pharmacotherapy and the general bias against early surgery in the pediatric population.^{28,53,58}

In contrast to adults, children rarely present with focal neurologic signs.^{2,5,55} Visual dysfunction is a hallmark of the nonfunctioning macroadenomas that dominate adult disease, but occurs in fewer than 10% children—although Webb et al documented 60% in one study of 20 children, which was also notable for a higher than average incidence of macroadenoma.^{2,3,5,55} As Webb’s cohort demonstrates, this difference can be attributed to the predominance of secreting tumors among children, who are also thought to be more physically and psychosocially sensitized to the effects of hyperprolactinemia.^{51,52,55}

Preoperative Endocrinologic Evaluation

As in adults, preoperative assessment in children incorporates diagnostic and confirmatory biochemical studies, as well as focused neuroimaging, and formal neuro-ophthalmologic examination with visual field testing. Serum studies panel of anterior pituitary hormones including PRL, ACTH, GH, TSH, LH, and FSH is requisite, both to screen for secondary subclinical abnormalities and to evaluate for possible preoperative pituitary insufficiency.

Laboratory evaluation for prolactinoma begins with a simple serum PRL assay, and although reliable reference ranges have not been definitely established in children, 5 to 25 ng/mL in girls and 5 to 15 ng/mL in boys are generally considered normal, with a peak in puberty.⁵⁸ Supranormal PRL levels below 100 ng/mL may be attributable to the so-called “stalk effect,” in which a macroadenoma compresses the pituitary infundibulum, decreasing tonic dopaminergic inhibition of PRL and producing the mild abnormality.^{29,59} A normal or mildly supranormal PRL with severe symptoms should raise suspicion for the high-dose “hook effect,” especially in the setting of a large tumor. This laboratory phenomenon occurs due to an enzyme-linked immunosorbent assay (ELISA) technique that depends on two-site binding (capture and signal antibodies) for a positive result, which becomes saturated in the presence of extremely high serum PRL concentrations, “hooking” the measured value downward.^{60–63} Above 100 ng/mL, prolactinoma is relatively assured and certain above 200 ng/mL—although results below these thresholds do not exclude the possibility of a true, secreting prolactinoma.^{53,58}

Although serum GH concentration can be readily measured, it is subject to normal diurnal variations and is influenced by a wide swath of physiologic activities including exercise, stress, fasting states, and sleep, potentially resulting in a normal range from 0.5 to 30 ng/mL in a single day.^{64–66} Correspondingly, IGF-1 has been developed as a surrogate marker that reflects the overall physiologic mean GH value during the preceding 24 to 48 hour period.⁶⁷ However, given that both GH and IGF-1 fluctuate with age and are physiologically elevated during adolescence and puberty, multiple measurements of both values are recommended in equivocal cases.⁶ In parallel, the oral glucose tolerance test (OGTT) is a highly specific confirmatory test, in which patients drink a 75 g glucose load; GH suppression to <1 ng/mL within 2 hours of ingestion indicates a normal response, whereas value >2 ng/mL is considered diagnostic, and 1 to 2 ng/mL is strongly suggestive of acromegaly.⁶⁸

Cushing's disease is suggested by hypercortisolism with elevated serum ACTH levels: concentrations from 5 to 20 pg/mL are highly consistent with an ACTH-dependent process and >20 pg/mL are diagnostic.^{69–71} Ectopic ACTH production must subsequently be ruled out, typically using a combination of high-dose dexamethasone suppression (HDDS) and corticotropin-releasing hormone (CRH) stimulation tests.⁷² In true Cushing's disease, overnight administration of oral high-dose dexamethasone will reduce 8 am cortisol to <5 mcg/dL (or below 50% of baseline), while intravenous injection of CRH results in a marked increase

in both ACTH and cortisol within 45 minutes—an effect that can be potentiated by pre-treating with vasopressin, although that is rarely required in children (positive test thresholds are specific to the center and protocol).^{73,74} Ectopic ACTH generally does not respond to either agent. Positive results on both HDDS and CRH is highly specific for Cushing's disease, and a positive CRH test coupled with an unambiguous adenoma on pituitary magnetic resonance imaging (MRI) is considered diagnostic; however, absent positive imaging and conflicting results between HDDS and CRH may prompt inferior petrosal sinus sampling (IPSS) for diagnosis and lateralization.

In this test, the bilateral inferior petrosal dural venous sinuses are endovascularly canalized and sampled. ACTH values from centrally drawn samples are then compared with ones from the peripheral blood, and an ACTH gradient >2 is diagnostic of Cushing's disease, with a 95% sensitivity and 93% specificity.⁷⁵ These results can be further elevated to 95 to 100% sensitivity and specificity by administering CRH and using a diagnostic threshold >3.⁷⁶ However, minor proximal misplacement of the catheter may yield a false negative, and although the rate of serious complications is quite low, rare cerebrovascular accidents or cranial nerve palsies have been reported, and the logistics of completing the procedure in children are potentially complex.^{77–79} Correspondingly, our practice has been to avoid subjecting children to this intervention whenever possible (it was required in 1 of 14 ACTH-secreting tumors in the study cohort). Finally, although IPSS is a potentially powerful diagnostic tool in patients with equivocal biochemistry, its use as a lateralization technique to guide hemi-hypophysectomy is more controversial. Several studies have reported successful localization resulting in biochemical cure in 71 to 74% of patients; however, others have failed to reproduce this result or improve significantly on the baseline odds of 50%.^{14,76,80,81}

Imaging and Ophthalmologic Assessment

Contrast-enhanced MRI with thin (1–3 mm) coronal slices through the sella is the bedrock of pituitary adenoma imaging and provides essential information for diagnosis and surgical planning (→ Fig. 2). Arbitrarily, pituitary adenomas have been traditionally separated into micro- and macroadenomas using the 10-mm maximum diameter threshold, although both are commonly seen in children, microadenomas predominate, given the predominance of secreting lesions.^{10,82,83} Prolactinomas are the exception to this principle and have a more expansive growth pattern that predisposes to macroadenoma formation—particularly in young males—as well as a tendency to present in older children who are more likely to harbor larger tumors.²⁸

On routine sequences, adenomas are frequently appreciable on pre-contrast T1-weighted images as well demarcated hypointense regions when compared with normal gland—a differentiation that is augmented by the normal gland's robust gadolinium-uptake on contrast-enhanced scans. Contrast-enhanced images are particularly important in the assessment of ACTH-secreting microadenomas, which are typically the smallest lesions and the most likely to

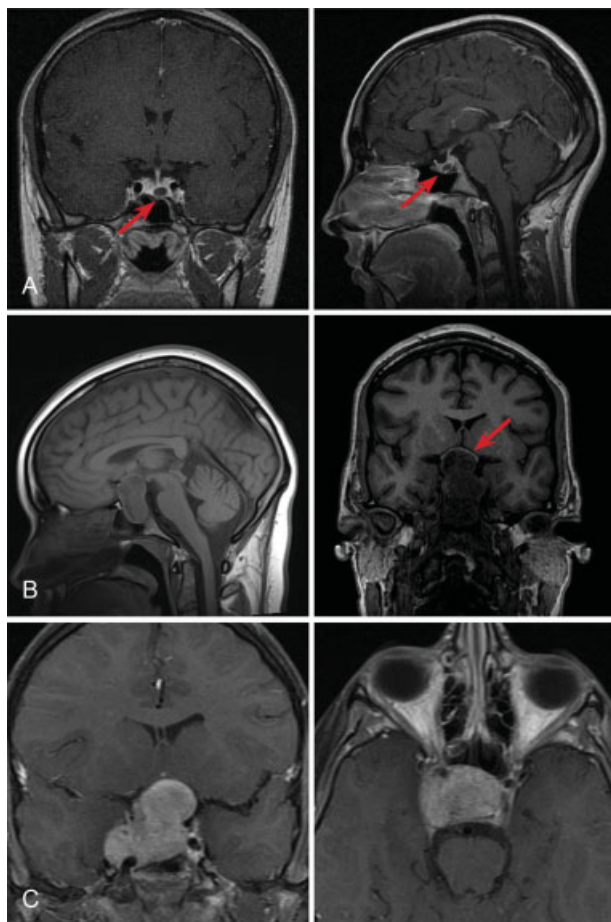


Fig. 2 Gadolinium-enhanced T1-weighted MRI of the brain in the coronal and sagittal planes (A and B) demonstrates a hypo-enhancing eccentric left sellar masses (red arrows) surrounded by briskly enhancing normal hypophyseal tissue, characteristic of pituitary microadenoma. Pre-contrast sagittal T1-weighted and coronal MPRAGE images (B) demonstrate a large, well-circumscribed, sellar mass with surrounding benign bony remodeling, significant superior displacement of the optic chiasm (red arrow), and internal heterogeneity, consistent with a partially hemorrhagic pituitary macroadenoma. Gadolinium-enhanced T1-weighted coronal and axial images (C) demonstrate a large, vividly enhancing sellar mass, with invasion of the bilateral cavernous sinuses, encasement of the internal carotid arteries, and significant suprasellar and middle fossa extension, suggestive of an aggressive pituitary macroadenoma. MPRAGE, magnetization prepared rapid acquisition gradient echo; MRI, magnetic resonance imaging.

enhance.^{83,84} Dynamic MR techniques rely on rapidly repeated scans, which capture the wash-in and wash-out of contrast to demonstrate a time-dependent pattern of early gland enhancement, followed by delayed adenoma enhancement, optimizing visualization of the lesion.

While microadenomas may be difficult to identify, macroadenomas are self-evident lesions that fill and frequently expand the sella or invade the cavernous sinuses and are much more likely to demonstrate internal heterogeneity due to hemorrhage or necrosis—especially if bromocriptine therapy was previously attempted.^{83,85} Although not universally necessary, non-contrast head computed tomography (CT) is an important adjunct in atypical lesions where craniophar-

angioma or meningioma is on the differential. In these circumstances, calcification or hyperostosis favors an alternative diagnosis, while a purely intrasellar lesion with benign bony expansion is more likely to indicate adenoma.⁸⁶

Although visual dysfunction is uncommon in children due to the low incidence of macroadenoma, ophthalmologic evaluation with visual field testing is recommended where possible. The purpose is two-fold: first, awareness and articulation of subtle visual symptoms is less reliable in children; and second, it provides formal documentation of the patient's preoperative baseline.

Medical Management and The Role of Deferred Surgery

Although TSR is the preferred first-line treatment for most pituitary tumors, prolactinomas warrant a trial of medical management with dopamine agonists before a surgical intervention is considered. Cabergoline is typically more effective and better tolerated than its pharmacologic predecessor bromocriptine, with stable biochemical remission documented in 70% of macroadenomas and 80 to 90% of microadenomas.^{87–90} Cabergoline also has the advantages of a once- or twice-weekly 0.25 to 2 mg dose formulation and decreased incidence of major adverse events including hemorrhage and spontaneous CSF leak—although intolerable side effects remain the chief etiology of treatment failure.^{91–93} Of note, female patients desiring fertility should be preferentially placed on bromocriptine, as it had a more well-characterized safety profile.^{94–98}

In some individuals, medical monotherapy may provide a sustained cure.⁹⁹ Colao et al reported 64 to 69% sustained remission at 5 years after a 2-year treatment period with cabergoline, a marked improvement over 7 to 38% described previously after cessation of bromocriptine.^{99–106} Still other new data on pergolide, lisuride, and quinagolide have demonstrated comparable or superior efficacy to cabergoline with respect to biochemical remission and tumor regression; however, each is still awaiting the Food and Drug Administration approval, particularly with respect to the potential risk of valve disease in association with chronic exposure to these agents.^{29,107–109} These findings are promising; however, given the elevated risk of recurrence in younger patients, extrapolations to the pediatric population are guarded.

While the majority of patients with prolactinoma will benefit from an initial trial of medical management, particularly in the pediatric population, there are several relative indications for early surgical intervention, including acute visual loss or cranial nerve palsy.^{29,110,111} As these sequelae typically occur in large, invasive macroadenomas, a surgical cure may not be obtained, but decompression relieves mass effect, and tumor cytoreduction will potentiate response to anti-dopaminergic therapy.^{112,113} Multi-modal therapy is often required in these patients, in particular SRS, to treat cavernous sinus disease, but TSR is almost always preferred route for acute decompression of the optic apparatus.²⁹ Similarly, patients who have a very low probability of tumor control with pharmacotherapy may benefit from

initial surgical treatment, as dopamine agonists may increase tumor fibrosis, predisposing to a more challenging resection.¹¹⁴

By contrast, the somatostatin analog octreotide has been shown to biochemically normalize GH hypersecretion in up to 55% of adults and induce a degree of radiographic tumor remission in 25 to 70%, but has not been shown to provide a durable disease cure, and the potential risks of life-long therapy in children are not established.^{115–117} Some prior studies have demonstrated improved surgical cure rates after octreotide pretreatment; however, this has not been consistently reproduced, and neither a dose–response relationship nor an ideal duration-of-pretreatment is established.^{118–120} Correspondingly, we do not recommend the first-line medical therapy for most children with GH-secreting pituitary adenomas.¹¹⁷

Transsphenoidal Surgery, Skull Base Techniques, and Special Consideration in Pediatrics

TSR is the preferred treatment for pituitary adenoma in the overwhelming majority of circumstances, particularly given that most are limited to the sellar or midline suprasellar regions.^{5,11,121,122} Sellar microadenomas predominate in the pediatric population, making a large fraction potentially amendable to primary TSR; however, sphenoid sinus pneumatization has the potential to limit the operative corridor. Although first observed as early as 6 months in some children, the pneumatization process predominantly occurs during years 3 to 7, and the completion may take until the child is 9 to 12.^{123–125}

In some patients with partial pneumatization, the midline sphenoid bone can potentially be removed with a high-speed drill to provide access to the sella, which is often preferable to a transcranial approach for small, intrasellar lesions.^{8,56,126} Radiology-based anatomic studies have described approximate drilling distances by age group, which can be correlated with preoperative imaging (ideally, a stereotactic CT scan).^{127,128} Of note, even among the youngest children studied, clival inter-carotid distances never prohibited transsphenoidal surgery. However, pedicled nasoseptal flaps are difficult to raise in patients aged <10 years and questionable in patients 10 to 13 years, potentially limiting reconstructive options if an elevated risk of CSF leak is anticipated.¹²⁹ Finally, even modern endoscopic instruments may still be very large for safe, efficient use in smaller nares; correspondingly, a sublabial approach may be preferred in up to 39%.¹³⁰ Additionally, image guidance may be extremely helpful to guide the drilling necessary to better establish a transsphenoidal corridor.

A related technical question is centered on the comparison between microscopic and endoscopic techniques for pediatric pituitary tumor resection. In the adult population, this question has been interrogated for pituitary adenoma as well as a wide range of other midline cranial base neoplasms, with generally equivocal findings. Results have varied widely between centers and surgeons, and EEA is generally accepted as a non-inferior alternative to microsurgery. Most reports suggest EEA has improved rates of GTR and improvement of

visual function and decreased rates of pituitary insufficiency but there has been concern of a higher rate of carotid artery injury.^{131–138} Few prospective trials comparing EEA and microsurgery have been completed, with five meeting criteria for inclusion in a recent meta-analysis.^{139–145} Although the overall evidence level and data quality were quite low, the study concluded that EEA is associated with significantly lower complication rates, but not biochemical cure, as compared with microscopic TSR. Further prospective study is clearly required to answer this question more definitively, particularly in children.

Neither prospective studies have compared the techniques in children, nor has any retrospective study specifically taken up the EEA question in pediatric pituitary adenoma. Massimi et al reviewed a 31-patient series comparing 14 sublabial microsurgical and 17 EEA operations in a mixed population of pediatric neoplasms that included adenomas, but with a majority of craniopharyngiomas.¹⁴⁶ Mean ages were comparable at 11.4 and 10.2 years, and there were no significant differences between the groups preoperatively. Tumor control and complication rates were not significantly different, although EEA was associated with fewer pediatric intensive care unit (PICU) admission, shorter hospitalizations, and lower pain scores. Rigante et al reported another mixed series comparing 11 sublabial microsurgical and 10 EEA operations from the same group, with comparable results.¹⁴⁷ In addition to these direct comparisons, several other authors have published self-referencing series juxtaposing newer endoscopic results to prior microsurgical series, most of which have concluded that extent-of-resection, pituitary insufficiency, and CSF leak are stable, but not significantly improved after EEA.^{126,136,148,149}

Advocates of EEA in the pediatric population suggest that it is associated with decreased trauma to the anterior nasopharynx (no nasal speculum) and a faster, less morbid recovery.¹⁵⁰ Opponents highlight longer operative times, the theoretically increased risk of carotid injury, and the need for a wider corridor, potentially mandating more extensive drilling of incompletely pneumatized sinuses. EEA was previously thought to risk disruption of the craniofacial growth plates, predisposing to deformity; although rational, this hypothesis has been disproven, with no cases of delayed disfigurement identified in the several large series publishing the first long-term perspectives on EEA in children.^{48,126,148,151}

A final consideration regarding EEA for pediatric pituitary adenoma is the finding that, in individual surgeons and the neurosurgical community at large, adoption of EEA has a clear learning curve, with significantly worse outcomes anticipated during the earliest phase.^{152–156} Given the scarcity of pediatric tumors requiring TSR, the significant morbidity associated with a poor surgical outcome, and the relative youth of the approach—particularly as compared with the depth of experience among more senior practitioners of transsphenoidal microsurgery—we recommend that treatment for pediatric pituitary tumors be concentrated in centers-of-excellence and eschew the use of EEA by inexperienced surgeons.

Although uncommon in children, significant suprasellar tumor extension beyond the midline corridor and into the Sylvian fissure presents an important indication for transcranial or combined approaches.^{157,158} In many of these tumors, pituitary function is already severely compromised; therefore, the endocrine risks of accessing the sella laterally are less pronounced. However, a prefixed chiasm may present a daunting obstacle; therefore, in such cases, a pterional approach is typically preferred, as it allows the shortest and most direct possible transcranial trajectory to the sub- and retrochiasmatic spaces.¹⁵⁹ By contrast, in patients with a postfixed chiasm and significant tumor between the optic nerves or extending anterior to the tuberculum sellae, a subfrontal or transbasal approach may warrant consideration—including the unilateral subfrontal, which minimizes risk to the frontal sinus or olfactory system.

For especially large, expansive tumors and recurrences that extend along the sellar and parasellar axes, anterolateral approaches can be expanded via orbitozygomatic or orbital-optic osteotomies, allowing greater access with minimized frontal lobe retraction.^{159,160} Less frequently indicated are transpetrosal or transcavernous approaches; however, they may prove useful in cases of large, invasive pituitary adenoma with significant extension throughout the retrochiasmatic, interpeduncular, or prepontine spaces. Rarely, remarkably aggressive tumors are reported with widespread posterior fossa involvement, and these lateral skull base techniques are requisite for debulking.^{161,162}

Focused Review of Pathologic Features

The pathologic classification of pituitary tumors is extensive, and based on a combination of features including hormonal content, cell type, and ultrastructural morphology, which collectively outline 18 specific adenoma subtypes as of the 2004 World Health Organization (WHO) guidelines.^{163–166} Each adenoma subtype has predictable biologic patterns of behavior, with implications in terms of capacity for recurrence, overall prognosis, and response to treatment. Although these patterns have been derived from adult populations, the dominant pathologies are in parallel among children, with granulated PRL cell adenoma, densely granulated growth hormone cell adenoma, and densely granulated corticotroph adenoma comprising 27.0%, 7.1%, and 9.6%, respectively of all pituitary tumors, and therefore the overwhelming majority of secreting adenomas.^{163,165,166} Characteristic corticotroph-type tumors show diffuse adenoma cells, with loss of typical reticulated nesting, and diffuse ACTH positive staining (►Fig. 3A–C).

Two interesting pathologic subtypes were observed at high rates among our patients: Crooke's cell adenoma and atypical adenoma. In ACTH-secreting tumors, pathologic accumulation of perinuclear cytokeratin within the suppressed normal gland cells is a common and clinically insignificant feature termed Crooke's hyaline change. However, when these changes are observed within adenoma cells, the diagnosis of a Crooke's cell adenoma is made, which is an aggressive but benign variant carrying a 60% risk of recurrence and 24% chance of multiple recurrence.¹⁶⁷ Character-

istic pathologic features include faint perinuclear ACTH staining with correspondingly strong CAM5.2 staining (►Fig. 3D–F). Among the four patients diagnosed with Crooke's cell adenoma in our cohort, two were cured at primary TSR, one had two recurrences requiring repeat TSR followed by PBRT before a biochemical cure was established, and the final patient remained severely symptomatic in spite of multi-modality treatment including EBRT, multiple repeat TSRs, and a craniotomy, highlighting the potential for these tumors to be remarkably aggressive, particularly in recurrence-prone pediatric patients.

Atypical pituitary adenoma is defined by the presence of mitoses, Ki-67 index >3%, and nuclear p53 staining with nuclear pleomorphism (►Fig. 3G).^{168,169} Adult series have approximated 3 to 15% incidence, as compared with the very rare 0.2% prevalence of pituitary carcinoma, with no clear correlation established between specific atypical features and disease phenotype.^{165,166,170,171} In our series, we encountered five atypical adenomas (13%); all had complex histories requiring multi-modality treatment, and only one was ultimately cured. Taken together with the lack of reliable pathologic predictors of clinical behavior, we recommend close follow-up of all atypical lesions and prompt, aggressive treatment of any recurrence.

Management of Progression or Recurrence

Encouragingly, a significant fraction of pediatric pituitary adenomas do quite well following initial resection, with our own series and the literature review documenting a surgical cure in 46% and 65%, respectively. Notwithstanding, recurrent or persistent disease is a common, potentially morbid, and frequently often multiply occurring management challenge in pediatric patients.

The best choice for second-line therapy is very dependent on the characteristics of the recurrence and the patient. In patients with an anatomically accessible lesion, repeat surgery is typically offered, particularly if there was a period of apparent disease remission following the initial resection. Successful treatment with a second operation was observed in 14% of our patients and up to 57% in prior series of secreting tumors in adults.^{20,172} However, many patients fail repeat surgery, and a large fraction have recurrent or progressive disease due to cavernous sinus involvement, which requires consideration of alternative modalities.

Pharmacotherapy is frequently trialed if repeat surgery is failed or not offered; however, patients with prolactinoma and many with GH-secreting lesions will have failed preoperative medical therapy and are unlikely to achieve durable symptomatic or biochemical disease control. Additionally, as recurrence indicates a more aggressive disease phenotype, treatment with the goal of a definitive cure is recommended. A specific exception is made for pre- or peripubertal children without severe symptoms, in whom temporizing with medication to delay radiation may be recommended—particularly if they are cabergoline- or octreotide-naïve. Combination therapies may also be effective, for example the addition of cabergoline or the GH receptor agonist pegvisomant to octreotide, which has been shown to be act synergistically in controlling recurrent

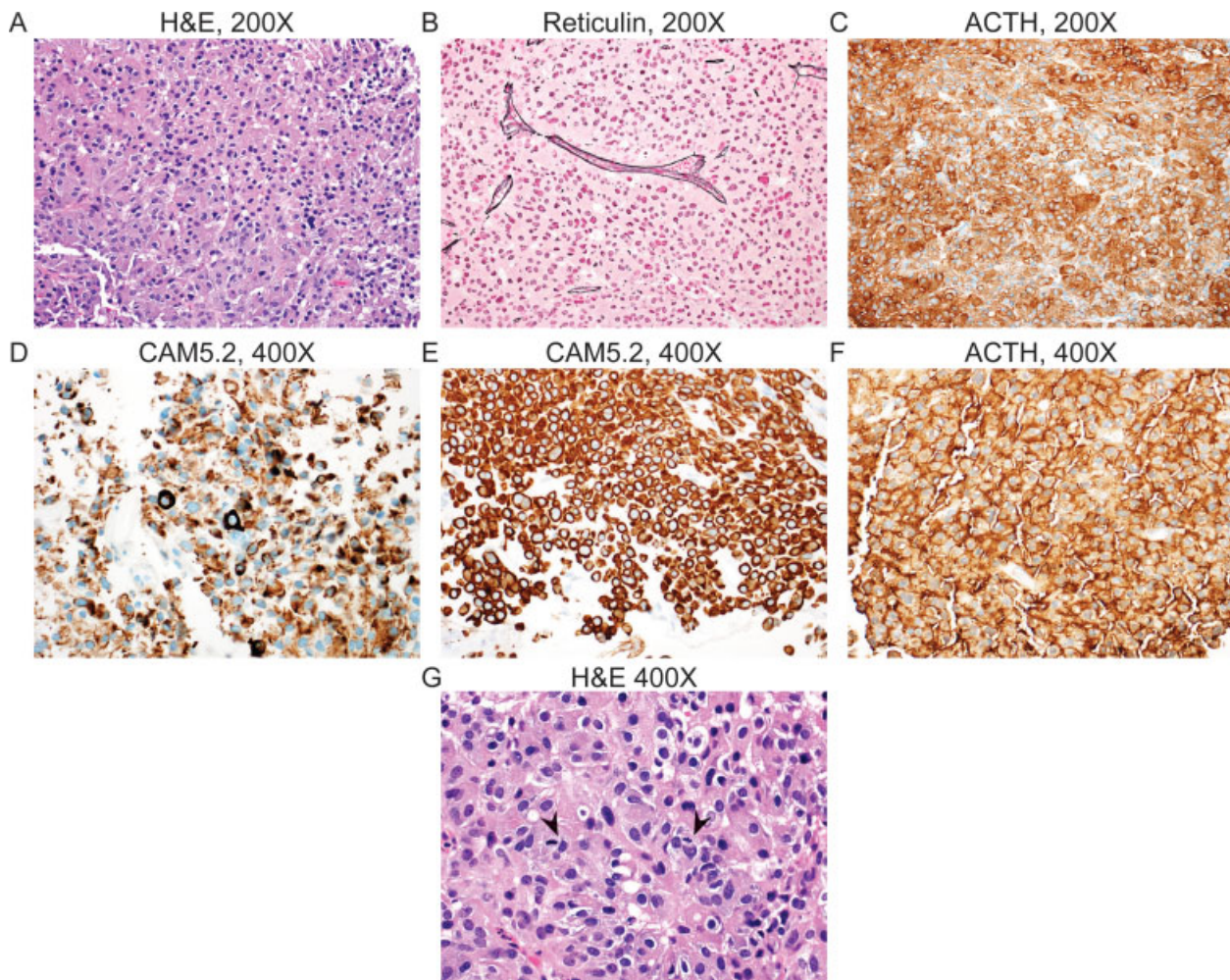


Fig. 3 Histopathologic photomicrographs demonstrating a corticotroph-type tumor with typical features including diffuse adenoma cells (A, H&E, 200X), loss of typical reticulated nesting (B, Reticulin, 200X), and diffusely positive immunohistochemical staining for ACTH (C, ACTH, 200X). Crooke's cell adenoma, with characteristic strongly positive perinuclear CAM5.2 staining (D and E, CAM5.2, 400X), and a corresponding haloing of perinuclear ACTH positivity (F, ACTH, 400X). Atypical pituitary adenoma, demonstrating two mitoses (arrowheads) in a high-powered field (G, H&E, 400X). ACTH, adrenocorticotropic hormone; H&E, hematoxylin and eosin.

GH-secreting adenomas in adults.^{116,117} Of note, all anti-tumor medications should be discontinued prior to radiation if at all possible, as dopamine and somatostatin antagonist appear to confer a radio-protective effect on tumor cells.^{173–175}

In adults, non-operative pituitary recurrences respond quite favorably to radiation—in particular, SRS. Prior series have reported treatment success in 97% of nonsecreting tumors and 45 to 93% secreting adenomas, with Pollock estimating an overall success rate of durable biochemical cure in at least 60% of recurrent secreting tumors.^{174–180} Hypopituitarism is the most common complication, with 10 to 12% of adults requiring chronic hormonal supplementation after SRS.^{16,48,181,182}

Data on pediatric pituitary radiotherapy is more limited, due to its infrequent use; as our literature review demonstrates, radiation of any modality was reported in only 16% of children with recurrent or persistent disease. This reflects a general attitude of reluctance given the pronounced risk of hypopituitarism, as well as the more general (but still rare) complications of radiation in a young population with benign

disease. GH deficiency in particular has been reported in up to 86 to 100% of pediatric patients after radiation, with rare reports describing symptomatic post-radiation deficiencies in the full range of anterior pituitary hormones.^{16,183} Although this can be managed with supplementation, most patients still do not reach mid-parental target height.^{57,184,185} Complications notwithstanding, our own results and those studies that have specifically reported outcomes in pediatric secretory disease have demonstrated compelling efficacy, with local control rates of 64 to 100% after recurrence across all modalities and tumor subtypes.^{14,16,130}

No study has yet compared EBRT and SRS in pediatric pituitary adenoma. Thoren et al reported a landmark series on SRS as primary treatment for pediatric Cushing's disease in 1986; eight patients were treated, of whom seven were cured, while one went on to BAX for persistent disease, and all eight required chronic pituitary supplementation.¹⁸³ In our series, 5 (36%) of 14 recurrences treated with radiation failed; however, when stratified by modality, 7 (70%) of 10 SRS and 1 (100%) PBRT patient were ultimately cured, as

compared with 1 (25%) of 4 EBRT treatments. Based on the available data and our clinical experience, we recommend SRS over EBRT in patients with symptomatic recurrences refractory to medical treatment whose tumors have 3-mm margin between the optic nerve and the lesion, and a treatment volume $<3\text{ cm}^3$. This disposition is further augmented by extrapolations from the adult population and data on pediatric radiation in malignant disease, which suggest a significantly increased long-term risk of cognitive impairment or the development of a radiation-induced neoplasm following EBRT, as well as faster remission of endocrine symptoms after SRS.^{16,130,179,182,186–188}

Large tumors abutting the optic nerve may still be managed using SRS and careful dose planning keeping the maximum optic nerve point dose <10 to 12 Gy ; however, this may reduce the chance for biochemical cure in a hormone-producing tumor, as these usually require at least 20 Gy marginal doses. Alternatively, some centers recommend fractionated SRS, IMRT, or EBRT, supported by varying degrees of evidence.^{48,181,182} Overall experience with PBRT for pediatric pituitary adenoma remains quite limited at present; however, preliminary adult series have reported post-radiation hypopituitarism in as few as 30% of patients with comparable local control to SRS, suggesting that it may become an important alternative modality as access expands and costs decline.^{182,186,189,190} With respect to the broader clinical picture, patients undergoing radiation are recommended to discontinue any pituitary-suppressive pharmacotherapies for 2 to 4 weeks, to promote tumor cell division and therefore radiosensitivity.

Although ACTH-secreting adenomas are often radiosensitive, severe Cushing's disease has the potential to be both disabling and treatment resistant. BAX provides durable correction of symptomatic hypercortisolemia and was previously considered a preferable alternative to radiation in children. However, the treatment requires lifelong hormonal supplementation, and the decrease in negative feedback on adenoma cells resulting from the BAX may lead to a rapid and dangerous adenoma growth known as Nelson–Salassa syndrome, which is thought to be more prevalent and aggressive among younger patients.¹⁹¹ Correspondingly, radiation is recommended prior to BAX in most pediatric cases, reserving BAX for those cases that fail both repeat surgery and radiation. If BAX is required for rapid correction of severe hypercortisolemia, prophylactic SRS may be offered concurrently, which has been shown to significantly decrease the risk of Nelson–Salassa syndrome in adults.¹⁹² However, given our previous finding that a subset of Nelson–Salassa patients experience an indolent natural history, waiting for tumor growth following BAX is our preferred approach, in radiation-naïve children.^{191,192}

Rarely, atypical pituitary adenomas, carcinomas, or instances of Nelson–Salassa syndrome may be refractory to multi-modality treatments, as in two of our patients. Trials of chemotherapeutic agents in pituitary disease have been disappointing, but nevertheless they represent a potential last line of defense.¹⁷⁰ Temozolomide, a well-tolerated deoxyribonucleic acid (DNA)-alkylating agent that is widely used

in glioma treatment, has demonstrated better efficacy than preceding chemotherapeutic regimens, with an overall clinical or radiographic response rate of 60 to 69%.^{170,193–197} Newer targeted therapies are also undergoing active investigation as second-line, concomitant, or alternative agents in aggressive pituitary adenoma, including the anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibody bevacizumab, mammalian target of rapamycin (mTOR) inhibitor everolimus, and epidermal growth factor receptor (EGFR)2 inhibitor lapatinib.^{198–201} At present, data are very limited even in the adult population, and the risk–benefit calculus of trialing any chemotherapy in a child will be determined on an individualized basis—although by this point in the natural history, patients have usually aged beyond the elevated risks of pediatric care.

Major Complications and their Management

Although a broad range of complications has been documented after pituitary adenoma treatment, most are rare occurrences, with pituitary insufficiency, DI, and CSF leak comprising the majority of significant treatment consequence. As described above, symptomatic deficiencies of anterior pituitary hormones are the most frequent complications of both surgery and radiation, with chronic pharmacologic supplementation required in $\sim 25\%$ after surgery, 10% after radiation, and up to two-thirds complex patients with extended follow-up, as in the study own cohort. GH deficiency is the most common, with significant implications in children with respect to overall growth potential, as well as onset and duration of puberty. Thyroid and corticotropin deficiencies occur less frequently, but management with supplementation is uncomplicated and rarely morbid; gonadotropin deficiency is rare in the absence of panhypopituitarism, but may require treatment for secondary infertility.^{6,202} In women with prolactinomas who retain normal gonadotropin function, inducing biochemical remission using bromocriptine is generally sufficient to promote normal fertilization; however, conception and obstetric care for women with refractory disease is potentially complex and may require an experienced reproductive endocrinologist.^{203,204}

Though typically transient, DI nevertheless has the potential to be a major management challenge and potentially life threatening in its most serious iterations. Macroadenomas, invasive or aggressive lesions, and patients presenting with subclinical sodium derangements at baseline are at especially high risk, but in all patients an elevated index of suspicion is warranted if postoperative urine output is brisk.^{145,148,205} Pediatric resuscitation goals vary by age and weight, but core treatment principles include early administration of oral or subcutaneous desmopressin acetate (DDAVP), urine replacement with half-normal saline, and serial serum sodium checks.²⁰⁶ Most patients recover in hours-to-days; however, some undergo poly-phasic cycles of polyuria and antidiuresis, while $\sim 3\%$ develop stable euvolemic disease requiring chronic DDAVP.⁵⁴

Postoperative CSF leak has been estimated in 3 to 8% of pediatric TSR cases and been reported in up to 20% in some individual series, with significant risk factors including tumors

vulnerability of these children to both treatment and disease morbidity. Complicating matters further, this vulnerability to major, life-altering endocrine dysfunction, such as infertility or growth arrest, may exert its own confounding influence on treatment patterns and disease natural history. By way of example, many studies have concluded that children are at higher risk of adenoma recurrence, yet it remains unknown whether this is attributable to a true phenotypic difference in disease aggressiveness or a reflection of a subtly more conservative treatment paradigm and almost impossible to discern retrospectively.

Notwithstanding, based on the available data, we have observed that most patients respond well to surgery and experience a swift and uncomplicated recovery; however, recurrent or persistent disease appears to be more frequent in children than in adults and may be more difficult to manage and marked by serial recurrences requiring multimodality therapy. Ultimately, the plan of care must be tailored to the individual patient and tumor; however, we have consolidated our overarching strategy, and standard practices are consolidated into a treatment algorithm that can be adapted to the demands of specific cases (→Fig. 4).

In general terms, prolactinomas are treated on cabergoline, while other adenomas and prolactinomas failing medical therapy or presenting with significant neurologic symptoms are offered surgery. Recurrent or persistent tumors are offered repeat surgery where anatomically feasible. Those recurrences not amenable to surgery may be successfully temporized with medications—particularly in prepubescent patients with mild symptoms—but the majority of these patients will ultimately require radiation, typically via single-fraction SRS. Cases of severe Cushing's disease may ultimately necessitate BAX, while extremely aggressive adenomas and carcinomas are potentially candidates for chemotherapy, with the caveat that these highly complex cases will inevitably require the most tailored and potentially unconventional treatment plans. Taken together, the study cohort and literature review inform our perspective on this challenging entity, but perhaps most importantly, they highlight the need for better evidence, and the development of an adaptive framework for translating the study of a rare and highly variable disease into rational, individualized patient care.

Previous Presentations

Components of this work were presented or submitted as abstracts at the NASBS 2016 and CNS 2017.

Conflicts of interest

None.

Acknowledgment

The authors would like to thank Dr. Aditya Raghunathan for his expert input and provision of histopathologic photomicrographs.

References

- Espay AJ, Azzarelli B, Williams LS, Bodensteiner JB. Recurrence in pituitary adenomas in childhood and adolescence. *J Child Neurol* 2001;16(05):364–367
- Kane LA, Leinung MC, Scheithauer BW, et al. Pituitary adenomas in childhood and adolescence. *J Clin Endocrinol Metab* 1994;79(04):1135–1140
- Maira G, Anile C. Pituitary adenomas in childhood and adolescence. *Can J Neurol Sci* 1990;17(01):83–87
- Mindermann T, Wilson CB. Pediatric pituitary adenomas. *Neurosurgery* 1995;36(02):259–268, discussion 269
- Partington MD, Davis DH, Laws ER Jr, Scheithauer BW. Pituitary adenomas in childhood and adolescence. Results of transsphenoidal surgery. *J Neurosurg* 1994;80(02):209–216
- Abe T, Tara LA, Lüdecke DK. Growth hormone-secreting pituitary adenomas in childhood and adolescence: features and results of transnasal surgery. *Neurosurgery* 1999;45(01):1–10
- Artese R, D'Osvaldo DH, Molocznik I, et al. Pituitary tumors in adolescent patients. *Neurol Res* 1998;20(05):415–417
- Dyer EH, Civit T, Visot A, Delalande O, Derome P. Transsphenoidal surgery for pituitary adenomas in children. *Neurosurgery* 1994;34(02):207–212, discussion 212
- Kunwar S, Wilson CB. Pediatric pituitary adenomas. *J Clin Endocrinol Metab* 1999;84(12):4385–4389
- Lafferty AR, Chrousos GP. Pituitary tumors in children and adolescents. *J Clin Endocrinol Metab* 1999;84(12):4317–4323
- Massoud AF, Powell M, Williams RA, Hindmarsh PC, Brook CG. Transsphenoidal surgery for pituitary tumours. *Arch Dis Child* 1997;76(05):398–404
- Jane J, Thapar K, Laws E. Pituitary tumors: functioning and nonfunctioning. *Youmans Neurological Surgery*. Philadelphia, PA: Elsevier Saunders; 2011:1476–1510
- Jane JA Jr, Laws ER Jr. The surgical management of pituitary adenomas in a series of 3,093 patients. *J Am Coll Surg* 2001;193(06):651–659
- Joshi SM, Hewitt RJ, Storr HL, et al. Cushing's disease in children and adolescents: 20 years of experience in a single neurosurgical center. *Neurosurgery* 2005;57(02):281–285, discussion 281–285
- Shah NS, George J, Acharya SV, et al. Cushing disease in children and adolescents: twenty years' experience in a tertiary care center in India. *Endocr Pract* 2011;17(03):369–376
- Storr HL, Plowman PN, Carroll PV, et al. Clinical and endocrine responses to pituitary radiotherapy in pediatric Cushing's disease: an effective second-line treatment. *J Clin Endocrinol Metab* 2003;88(01):34–37
- Atkinson AB, Kennedy A, Wiggam MI, McCance DR, Sheridan B. Long-term remission rates after pituitary surgery for Cushing's disease: the need for long-term surveillance. *Clin Endocrinol (Oxf)* 2005;63(05):549–559
- Bochicchio D, Losa M, Buchfelder M. Factors influencing the immediate and late outcome of Cushing's disease treated by transsphenoidal surgery: a retrospective study by the European Cushing's Disease Survey Group. *J Clin Endocrinol Metab* 1995;80(11):3114–3120
- Rees DA, Hanna FW, Davies JS, Mills RG, Vafidis J, Scanlon MF. Long-term follow-up results of transsphenoidal surgery for Cushing's disease in a single centre using strict criteria for remission. *Clin Endocrinol (Oxf)* 2002;56(04):541–551
- Benveniste RJ, King WA, Walsh J, Lee JS, Delman BN, Post KD. Repeated transsphenoidal surgery to treat recurrent or residual pituitary adenoma. *J Neurosurg* 2005;102(06):1004–1012
- Friedman RB, Oldfield EH, Nieman LK, et al. Repeat transsphenoidal surgery for Cushing's disease. *J Neurosurg* 1989;71(04):520–527
- Patil CG, Veeravagu A, Prevedello DM, Katznelson L, Vance ML, Laws ER Jr. Outcomes after repeat transsphenoidal surgery for recurrent Cushing's disease. *Neurosurgery* 2008;63(02):266–270, discussion 270–271
- Baskin DS, Boggan JE, Wilson CB. Transsphenoidal microsurgical removal of growth hormone-secreting pituitary adenomas. A review of 137 cases. *J Neurosurg* 1982;56(05):634–641

- 24 Sudhakar N, Ray A, Vafidis JA. Complications after trans-sphenoidal surgery: our experience and a review of the literature. *Br J Neurosurg* 2004;18(05):507–512
- 25 Fatemi N, Dusick JR, Mattozo C, et al. Pituitary hormonal loss and recovery after transsphenoidal adenoma removal. *Neurosurgery* 2008;63(04):709–718, discussion 718–719
- 26 Nomikos P, Ladar C, Fahlbusch R, Buchfelder M. Impact of primary surgery on pituitary function in patients with non-functioning pituitary adenomas – a study on 721 patients. *Acta Neurochir (Wien)* 2004;146(01):27–35
- 27 Katavetin P, Cheunsuchon P, Swearingen B, Hedley-Whyte ET, Misra M, Levitsky LL. Review: Pituitary adenomas in children and adolescents. *J Pediatr Endocrinol Metab* 2010;23(05):427–431
- 28 Keil MF, Stratakis CA. Pituitary tumors in childhood: update of diagnosis, treatment and molecular genetics. *Expert Rev Neurother* 2008;8(04):563–574
- 29 Liu JK, Couldwell WT. Contemporary management of prolactinomas. *Neurosurg Focus* 2004;16(04):E2
- 30 Faglia G, Spada A. Genesis of pituitary adenomas: state of the art. *J Neurooncol* 2001;54(02):95–110
- 31 Nishio S, Morioka T, Suzuki S, Takeshita I, Fukui M, Iwaki T. Pituitary tumours in adolescence: clinical behaviour and neuroimaging features of seven cases. *J Clin Neurosci* 2001;8(03):231–234
- 32 Alexander JM, Biller BM, Bikkal H, Zervas NT, Arnold A, Klibanski A. Clinically nonfunctioning pituitary tumors are monoclonal in origin. *J Clin Invest* 1990;86(01):336–340
- 33 Spada A, Mantovani G, Lania A. Pathogenesis of prolactinomas. *Pituitary* 2005;8(01):7–15
- 34 Heaney AP, Melmed S. Molecular targets in pituitary tumours. *Nat Rev Cancer* 2004;4(04):285–295
- 35 Stratakis CA, Schussheim DH, Freedman SM, et al. Pituitary macroadenoma in a 5-year-old: an early expression of multiple endocrine neoplasia type 1. *J Clin Endocrinol Metab* 2000;85(12):4776–4780
- 36 Marx SJ, Agarwal SK, Kester MB, et al. Multiple endocrine neoplasia type 1: clinical and genetic features of the hereditary endocrine neoplasias. *Recent Prog Horm Res* 1999;54:397–438, discussion 438–439
- 37 Spada A. Genetic aspects of pituitary tumors. *J Pediatr Endocrinol Metab* 2001;14(Suppl 5):1213–1216, discussion 1261–1262
- 38 Thakker RV, Bouloux P, Wooding C, et al. Association of parathyroid tumors in multiple endocrine neoplasia type 1 with loss of alleles on chromosome 11. *N Engl J Med* 1989;321(04):218–224
- 39 Vergès B, Boureille F, Goudet P, et al. Pituitary disease in MEN type 1 (MEN1): data from the France-Belgium MEN1 multicenter study. *J Clin Endocrinol Metab* 2002;87(02):457–465
- 40 Asa SL, Ezzat S. The pathogenesis of pituitary tumours. *Nat Rev Cancer* 2002;2(11):836–849
- 41 Akintoye SO, Chebli C, Booher S, et al. Characterization of gsp-mediated growth hormone excess in the context of McCune-Albright syndrome. *J Clin Endocrinol Metab* 2002;87(11):5104–5112
- 42 Koch G, Tiwisina T. [Contribution to the heredity of acromegaly and hyperostosis generalisata with pachyderma (chromophobe hypophysis adenoma in father and son)]. *Arztl Forsch* 1959;13:489–504
- 43 Boikos SA, Stratakis CA. Carney complex: pathology and molecular genetics. *Neuroendocrinology* 2006;83(3–4):189–199
- 44 Boikos SA, Stratakis CA. Pituitary pathology in patients with Carney Complex: growth-hormone producing hyperplasia or tumors and their association with other abnormalities. *Pituitary* 2006;9(03):203–209
- 45 Kurtkaya-Yapici O, Scheithauer BW, Carney JA, et al. Pituitary adenoma in Carney complex: an immunohistochemical, ultrastructural, and immunoelectron microscopic study. *Ultrastruct Pathol* 2002;26(06):345–353
- 46 Pack SD, Kirschner LS, Pak E, Zhuang Z, Carney JA, Stratakis CA. Genetic and histologic studies of somatotrophic pituitary tumors in patients with the “complex of spotty skin pigmentation, myxomas, endocrine overactivity and schwannomas” (Carney complex). *J Clin Endocrinol Metab* 2000;85(10):3860–3865
- 47 Beckers A, Aaltonen LA, Daly AF, Karhu A. Familial isolated pituitary adenomas (FIPA) and the pituitary adenoma predisposition due to mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene. *Endocr Rev* 2013;34(02):239–277
- 48 Guaraldi F, Storr HL, Ghizzoni L, Ghigo E, Savage MO. Paediatric pituitary adenomas: a decade of change. *Horm Res Paediatr* 2014;81(03):145–155
- 49 Tichomirowa MA, Barlier A, Daly AF, et al. High prevalence of AIP gene mutations following focused screening in young patients with sporadic pituitary macroadenomas. *Eur J Endocrinol* 2011;165(04):509–515
- 50 Fraioli B, Ferrante L, Celli P. Pituitary adenomas with onset during puberty. Features and treatment. *J Neurosurg* 1983;59(04):590–595
- 51 Cannavò S, Venturino M, Curtò L, et al. Clinical presentation and outcome of pituitary adenomas in teenagers. *Clin Endocrinol (Oxf)* 2003;58(04):519–527
- 52 Dissanevate P, Warne GL. Hyperprolactinaemia and pituitary adenomas in adolescence. *J Pediatr Endocrinol Metab* 1998;11(04):531–541
- 53 Fideleff HL, Boquete HR, Sequera A, Suárez M, Sobrado P, Giaccio A. Peripubertal prolactinomas: clinical presentation and long-term outcome with different therapeutic approaches. *J Pediatr Endocrinol Metab* 2000;13(03):261–267
- 54 Albright AL, Pollack IF, Andelson PD. Principles and Practice of Pediatric Neurosurgery. New York, NY:Thieme;2015
- 55 Webb C, Prayson RA. Pediatric pituitary adenomas. *Arch Pathol Lab Med* 2008;132(01):77–80
- 56 Oliveira RS, Castro Md, Antonini SR, Martinelli CE Jr, Moreira AC, Machado HR. Surgical management of pediatric Cushing's disease: an analysis of 15 consecutive cases at a specialized neurosurgical center. *Arq Bras Endocrinol Metabol* 2010;54(01):17–23
- 57 Styne DM, Grumbach MM, Kaplan SL, Wilson CB, Conte FA. Treatment of Cushing's disease in childhood and adolescence by transsphenoidal microadenectomy. *N Engl J Med* 1984;310(14):889–893
- 58 Abe T, Lüdecke DK. Transnasal surgery for prolactin-secreting pituitary adenomas in childhood and adolescence. *Surg Neurol* 2002;57(06):369–378, discussion 378–379
- 59 Arafah BM, Neik KE, Gold RS, Selman WR. Dynamics of prolactin secretion in patients with hypopituitarism and pituitary macroadenomas. *J Clin Endocrinol Metab* 1995;80(12):3507–3512
- 60 Barkan AL, Chandler WF. Giant pituitary prolactinoma with falsely low serum prolactin: the pitfall of the “high-dose hook effect”: case report. *Neurosurgery* 1998;42(04):913–915, discussion 915–916
- 61 Comtois R, Robert F, Hardy J. Immunoradiometric assays may miss high prolactin levels. *Ann Intern Med* 1993;119(02):173
- 62 Fleseriu M, Lee M, Pineyro MM, et al. Giant invasive pituitary prolactinoma with falsely low serum prolactin: the significance of ‘hook effect’. *J Neurooncol* 2006;79(01):41–43
- 63 Frieze TW, Mong DP, Koops MK. “Hook effect” in prolactinomas: case report and review of literature. *Endocr Pract* 2002;8(04):296–303
- 64 Chapman IM, Hartman ML, Straume M, Johnson ML, Veldhuis JD, Thorner MO. Enhanced sensitivity growth hormone (GH) chemiluminescence assay reveals lower postglucose nadir GH concentrations in men than women. *J Clin Endocrinol Metab* 1994;78(06):1312–1319
- 65 Iranmanesh A, Grisso B, Veldhuis JD. Low basal and persistent pulsatile growth hormone secretion are revealed in normal and

- hyposomatotropic men studied with a new ultrasensitive chemiluminescence assay. *J Clin Endocrinol Metab* 1994;78(03):526–535
- 66 Ribeiro-Oliveira A Jr, Barkan A. The changing face of acromegaly—advances in diagnosis and treatment. *Nat Rev Endocrinol* 2012;8(10):605–611
 - 67 Stoffel-Wagner B, Springer W, Bidlingmaier F, Klingmüller D. A comparison of different methods for diagnosing acromegaly. *Clin Endocrinol (Oxf)* 1997;46(05):531–537
 - 68 Carmichael JD, Bonert VS, Mirocha JM, Melmed S. The utility of oral glucose tolerance testing for diagnosis and assessment of treatment outcomes in 166 patients with acromegaly. *J Clin Endocrinol Metab* 2009;94(02):523–527
 - 69 Katznelson L, Bogan JS, Trob JR, et al. Biochemical assessment of Cushing's disease in patients with corticotroph macroadenomas. *J Clin Endocrinol Metab* 1998;83(05):1619–1623
 - 70 Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. *Endocr Rev* 1998;19(05):647–672
 - 71 Woo YS, Isidori AM, Wat WZ, et al. Clinical and biochemical characteristics of adrenocorticotropin-secreting macroadenomas. *J Clin Endocrinol Metab* 2005;90(08):4963–4969
 - 72 Grossman AB, Howlett TA, Perry L, et al. CRF in the differential diagnosis of Cushing's syndrome: a comparison with the dexamethasone suppression test. *Clin Endocrinol (Oxf)* 1988;29(02):167–178
 - 73 Dickstein G, DeBold CR, Gaitan D, et al. Plasma corticotropin and cortisol responses to ovine corticotropin-releasing hormone (CRH), arginine vasopressin (AVP), CRH plus AVP, and CRH plus metyrapone in patients with Cushing's disease. *J Clin Endocrinol Metab* 1996;81(08):2934–2941
 - 74 Orth DN, DeBold CR, DeCherney GS, et al. Pituitary microadenomas causing Cushing's disease respond to corticotropin-releasing factor. *J Clin Endocrinol Metab* 1982;55(05):1017–1019
 - 75 Kaltsas GA, Giannulis MG, Newell-Price JD, et al. A critical analysis of the value of simultaneous inferior petrosal sinus sampling in Cushing's disease and the occult ectopic adrenocorticotropin syndrome. *J Clin Endocrinol Metab* 1999;84(02):487–492
 - 76 Oldfield EH, Doppman JL, Nieman LK, et al. Petrosal sinus sampling with and without corticotropin-releasing hormone for the differential diagnosis of Cushing's syndrome. *N Engl J Med* 1991;325(13):897–905
 - 77 Gandhi CD, Meyer SA, Patel AB, Johnson DM, Post KD. Neurologic complications of inferior petrosal sinus sampling. *AJNR Am J Neuroradiol* 2008;29(04):760–765
 - 78 Lefournier V, Gatta B, Martinie M, et al. One transient neurological complication (sixth nerve palsy) in 166 consecutive inferior petrosal sinus samplings for the etiological diagnosis of Cushing's syndrome. *J Clin Endocrinol Metab* 1999;84(09):3401–3402
 - 79 Miller DL, Doppman JL, Peterman SB, Nieman LK, Oldfield EH, Chang R. Neurologic complications of petrosal sinus sampling. *Radiology* 1992;185(01):143–147
 - 80 López J, Barceló B, Lucas T, et al. Petrosal sinus sampling for diagnosis of Cushing's disease: evidence of false negative results. *Clin Endocrinol (Oxf)* 1996;45(02):147–156
 - 81 Tabarin A, Greselle JF, San-Galli F, et al. Usefulness of the corticotropin-releasing hormone test during bilateral inferior petrosal sinus sampling for the diagnosis of Cushing's disease. *J Clin Endocrinol Metab* 1991;73(01):53–59
 - 82 Tien RD, Kucharczyk J, Bessette J, Middleton M. MR imaging of the pituitary gland in infants and children: changes in size, shape, and MR signal with growth and development. *AJR Am J Roentgenol* 1992;158(05):1151–1154
 - 83 Yousem DM, Grossman RI. *Neuroradiology: The Requisites*. 3rd ed. Philadelphia, PA: Mosby/Elsevier; 2010
 - 84 Batista D, Courkoutsakis NA, Oldfield EH, et al. Detection of adrenocorticotropin-secreting pituitary adenomas by magnetic resonance imaging in children and adolescents with cushing disease. *J Clin Endocrinol Metab* 2005;90(09):5134–5140
 - 85 Yousem DM, Arrington JA, Zinreich SJ, Kumar AJ, Bryan RN. Pituitary adenomas: possible role of bromocriptine in intratumoral hemorrhage. *Radiology* 1989;170(1 Pt 1):239–243
 - 86 Zimmerman RA. Imaging of intrasellar, suprasellar, and parasellar tumors. *Semin Roentgenol* 1990;25(02):174–197
 - 87 Casanueva FF, Molitch ME, Schlechte JA, et al. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. *Clin Endocrinol (Oxf)* 2006;65(02):265–273
 - 88 dos Santos Nunes V, El Dib R, Boguszewski CL, Nogueira CR. Cabergoline versus bromocriptine in the treatment of hyperprolactinemia: a systematic review of randomized controlled trials and meta-analysis. *Pituitary* 2011;14(03):259–265
 - 89 Molitch ME, Elton RL, Blackwell RE, et al. Bromocriptine as primary therapy for prolactin-secreting macroadenomas: results of a prospective multicenter study. *J Clin Endocrinol Metab* 1985;60(04):698–705
 - 90 Webster J, Piscitelli G, Polli A, Ferrari CI, Ismail I, Scanlon MF; Cabergoline Comparative Study Group. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. *N Engl J Med* 1994;331(14):904–909
 - 91 De Bellis A, Colao A, Savoia A, et al. Effect of long-term cabergoline therapy on the immunological pattern and pituitary function of patients with idiopathic hyperprolactinaemia positive for antipituitary antibodies. *Clin Endocrinol (Oxf)* 2008;69(02):285–291
 - 92 Perry A, Graffeo CS, Copeland WR III, et al. Delayed Cerebrospinal Fluid rhinorrhea after gamma knife radiosurgery with or without preceding transsphenoidal resection for pituitary pathology. *World Neurosurg* 2017;100:201–207
 - 93 Schlechte JA, Sherman BM, Chapler FK, VanGilder J. Long term follow-up of women with surgically treated prolactin-secreting pituitary tumors. *J Clin Endocrinol Metab* 1986;62(06):1296–1301
 - 94 Molitch ME. Management of prolactinomas during pregnancy. *J Reprod Med* 1999;44(12, Suppl):1121–1126
 - 95 Molitch ME. Pregnancy and the hyperprolactinemic woman. *N Engl J Med* 1985;312(21):1364–1370
 - 96 Schlechte JA. Clinical practice. Prolactinoma. *N Engl J Med* 2003;349(21):2035–2041
 - 97 Skrabanek P, McDonald D, Meagher D, et al. Clinical course and outcome of thirty-five pregnancies in infertile hyperprolactinemic women. *Fertil Steril* 1980;33(04):391–395
 - 98 Weiss MH. Medical and surgical management of functional pituitary tumors. *Clin Neurosurg* 1981;28:374–383
 - 99 Colao A, Di Sarno A, Cappabianca P, Di Somma C, Pivonello R, Lombardi G. Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. *N Engl J Med* 2003;349(21):2023–2033
 - 100 Johnston DG, Hall K, Kendall-Taylor P, Patrick D, Watson M, Cook DB. Effect of dopamine agonist withdrawal after long-term therapy in prolactinomas. Studies with high-definition computerized tomography. *Lancet* 1984;2(8396):187–192
 - 101 Liuzzi A, Dallabonzana D, Oppizzi G, et al. Low doses of dopamine agonists in the long-term treatment of macroprolactinomas. *N Engl J Med* 1985;313(11):656–659
 - 102 van 't Verlaet JW, Croughs RJ. Withdrawal of bromocriptine after long-term therapy for macroprolactinomas; effect on plasma prolactin and tumour size. *Clin Endocrinol (Oxf)* 1991;34(03):175–178
 - 103 Wang C, Lam KS, Ma JT, Chan T, Liu MY, Yeung RT. Long-term treatment of hyperprolactinaemia with bromocriptine: effect of drug withdrawal. *Clin Endocrinol (Oxf)* 1987;27(03):363–371
 - 104 Warfield A, Finkel DM, Schatz NJ, Savino PJ, Snyder PJ. Bromocriptine treatment of prolactin-secreting pituitary adenomas may restore pituitary function. *Ann Intern Med* 1984;101(06):783–785

- 105 Wu ZR, Zhang Y, Cai L, et al. Long-term clinical outcomes of invasive giant prolactinomas after a mean ten-year followup. *Int J Endocrinol* 2016;2016:8580750
- 106 Zárte A, Canales ES, Cano C, Pilonieta CJ. Follow-up of patients with prolactinomas after discontinuation of long-term therapy with bromocriptine. *Acta Endocrinol (Copenh)* 1983;104(02):139–142
- 107 Orrego JJ, Chandler WF, Barkan AL. Pergolide as primary therapy for macroprolactinomas. *Pituitary* 2000;3(04):251–256
- 108 Webster J. Cabergoline and quinagolide therapy for prolactinomas. *Clin Endocrinol (Oxf)* 2000;53(05):549–550
- 109 Webster J. A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. *Drug Saf* 1996;14(04):228–238
- 110 Amar AP, Couldwell WT, Chen JC, Weiss MH. Predictive value of serum prolactin levels measured immediately after transsphenoidal surgery. *J Neurosurg* 2002;97(02):307–314
- 111 Tyrrell JB, Lamborn KR, Hannegan LT, Applebury CB, Wilson CB. Transsphenoidal microsurgical therapy of prolactinomas: initial outcomes and long-term results. *Neurosurgery* 1999;44(02):254–261, discussion 261–263
- 112 Thorner MO. Prolactinoma. *West J Med* 1983;139(05):703–705
- 113 Vance ML, Thorner MO. Prolactinomas. *Endocrinol Metab Clin North Am* 1987;16(03):731–753
- 114 Bevan JS, Webster J, Burke CW, Scanlon MF. Dopamine agonists and pituitary tumor shrinkage. *Endocr Rev* 1992;13(02):220–240
- 115 Abe T, Lüdecke DK. Effects of preoperative octreotide treatment on different subtypes of 90 GH-secreting pituitary adenomas and outcome in one surgical centre. *Eur J Endocrinol* 2001;145(02):137–145
- 116 Fleseriu M, Hoffman AR, Katznelson L; AACE Neuroendocrine and Pituitary Scientific Committee. Pituitary scientific C: American Association of Clinical Endocrinologists and American College of Endocrinology Disease State clinical review: management of acromegaly patients: what is the role of pre-operative medical therapy? *Endocr Pract* 2015;21(06):668–673
- 117 Katznelson L, Atkinson JL, Cook DM, Ezzat SZ, Hamrahian AH, Miller KK; American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly—2011 update. *Endocr Pract* 2011;17(Suppl 4):1–44
- 118 Carlsen SM, Lund-Johansen M, Schreiner T, et al; Preoperative Octreotide Treatment of Acromegaly study group. Preoperative octreotide treatment in newly diagnosed acromegalic patients with macroadenomas increases cure short-term postoperative rates: a prospective, randomized trial. *J Clin Endocrinol Metab* 2008;93(08):2984–2990
- 119 Losa M, Mortini P, Urbaz L, Ribotto P, Castrignanó T, Giovanelli M. Presurgical treatment with somatostatin analogs in patients with acromegaly: effects on the remission and complication rates. *J Neurosurg* 2006;104(06):899–906
- 120 Mao ZG, Zhu YH, Tang HL, et al. Preoperative lanreotide treatment in acromegalic patients with macroadenomas increases short-term postoperative cure rates: a prospective, randomised trial. *Eur J Endocrinol* 2010;162(04):661–666
- 121 Laws ER, Scheithauer BW, Groover RV. Pituitary adenomas in childhood and adolescence. *Prog Exp Tumor Res* 1987;30:359–361
- 122 Tarapore PE, Sughrue ME, Blevins L, Auguste KI, Gupta N, Kunwar S. Microscopic endonasal transsphenoidal pituitary adenomectomy in the pediatric population. *J Neurosurg Pediatr* 2011;7(05):501–509
- 123 Fujioka M, Young LW. The sphenoidal sinuses: radiographic patterns of normal development and abnormal findings in infants and children. *Radiology* 1978;129(01):133
- 124 Jang YJ, Kim SC. Pneumatization of the sphenoid sinus in children evaluated by magnetic resonance imaging. *Am J Rhinol* 2000;14(03):181–185
- 125 Szolar D, Preidler K, Ranner G, et al. Magnetic resonance assessment of age-related development of the sphenoid sinus. *Br J Radiol* 1994;67(797):431–435
- 126 Locatelli D, Massimi L, Rigante M, et al. Endoscopic endonasal transsphenoidal surgery for sellar tumors in children. *Int J Pediatr Otorhinolaryngol* 2010;74(11):1298–1302
- 127 Banu MA, Rathman A, Patel KS, et al. Corridor-based endonasal endoscopic surgery for pediatric skull base pathology with detailed radioanatomic measurements. *Neurosurgery* 2014;10(Suppl 2):273–293, discussion 293
- 128 Tatreau JR, Patel MR, Shah RN, et al. Anatomical considerations for endoscopic endonasal skull base surgery in pediatric patients. *Laryngoscope* 2010;120(09):1730–1737
- 129 Shah RN, Surowitz JB, Patel MR, et al. Endoscopic pedicled nasoseptal flap reconstruction for pediatric skull base defects. *Laryngoscope* 2009;119(06):1067–1075
- 130 Kanter AS, Diallo AO, Jane JA Jr, et al. Single-center experience with pediatric Cushing's disease. *J Neurosurg* 2005;103(5, Suppl) 413–420
- 131 Berker M, Hazer DB, Yücel T, et al. Complications of endoscopic surgery of the pituitary adenomas: analysis of 570 patients and review of the literature. *Pituitary* 2012;15(03):288–300
- 132 Bokhari AR, Davies MA, Diamond T. Endoscopic transsphenoidal pituitary surgery: a single surgeon experience and the learning curve. *Br J Neurosurg* 2013;27(01):44–49
- 133 Cappabianca P, Alfieri A, de Divitiis E. Endoscopic endonasal transsphenoidal approach to the sella: towards functional endoscopic pituitary surgery (FEPs). *Minim Invasive Neurosurg* 1998;41(02):66–73
- 134 Charalampaki P, Ayyad A, Kockro RA, Perneczky A. Surgical complications after endoscopic transsphenoidal pituitary surgery. *J Clin Neurosci* 2009;16(06):786–789
- 135 Halvorsen H, Ramm-Petersen J, Josefsen R, et al. Surgical complications after transsphenoidal microscopic and endoscopic surgery for pituitary adenoma: a consecutive series of 506 procedures. *Acta Neurochir (Wien)* 2014;156(03):441–449
- 136 Kassam AB, Prevedello DM, Carrau RL, et al. Endoscopic endonasal skull base surgery: analysis of complications in the authors' initial 800 patients. *J Neurosurg* 2011;114(06):1544–1568
- 137 Prevedello DM, Doglietto F, Jane JA Jr, Jagannathan J, Han J, Laws ER Jr. History of endoscopic skull base surgery: its evolution and current reality. *J Neurosurg* 2007;107(01):206–213
- 138 Yano S, Hide T, Shinojima N. Efficacy and complications of endoscopic skull base surgery for giant pituitary adenomas. *World Neurosurg* 2017;99:533–542
- 139 Bastos RV, Silva CM, Tagliarini JV, et al. Endoscopic versus microscopic transsphenoidal surgery in the treatment of pituitary tumors: systematic review and meta-analysis of randomized and non-randomized controlled trials. *Arch Endocrinol Metab* 2016;60(05):411–419
- 140 Cho DY, Liao WR. Comparison of endonasal endoscopic surgery and sublabial microsurgery for prolactinomas. *Surg Neurol* 2002;58(06):371–375, discussion 375–376
- 141 Enseñat J, Quesada JL, Aparicio J, et al. Comparación del abordaje transfenoidal microquirúrgico frente al abordaje endonasal transfenoidal endoscópico. Estudio prospectivo de 50 pacientes. *Neurocirugía (Astur)* 2009;20(04):335–344, discussion 344–345
- 142 Jain AK, Gupta AK, Pathak A, Bhansali A, Bapuraj JR. Excision of pituitary adenomas: randomized comparison of surgical modalities. *Br J Neurosurg* 2007;21(04):328–331
- 143 Kahilogullari G, Beton S, Al-Beyati ES, et al. Olfactory functions after transsphenoidal pituitary surgery: endoscopic versus microscopic approach. *Laryngoscope* 2013;123(09):2112–2119
- 144 Little AS, Chapple K, Jahnke H, White WL. Comparative inpatient resource utilization for patients undergoing endoscopic or microscopic transsphenoidal surgery for pituitary lesions. *J Neurosurg* 2014;121(01):84–90

- 145 Storr HL, Drake WM, Evanson J, et al. Endonasal endoscopic transsphenoidal pituitary surgery: early experience and outcome in paediatric Cushing's disease. *Clin Endocrinol (Oxf)* 2014;80(02):270–276
- 146 Massimi L, Rigante M, D'Angelo L, et al. Quality of postoperative course in children: endoscopic endonasal surgery versus sublabial microsurgery. *Acta Neurochir (Wien)* 2011;153(04):843–849
- 147 Rigante M, Massimi L, Parrilla C, et al. Endoscopic transsphenoidal approach versus microscopic approach in children. *Int J Pediatr Otorhinolaryngol* 2011;75(09):1132–1136
- 148 Chivukula S, Koutourousiou M, Snyderman CH, Fernandez-Miranda JC, Gardner PA, Tyler-Kabara EC. Endoscopic endonasal skull base surgery in the pediatric population. *J Neurosurg Pediatr* 2013;11(03):227–241
- 149 Zhan R, Xu G, Wiebe TM, Li X. Surgical outcomes of the endoscopic transsphenoidal route to pituitary tumours in paediatric patients >10 years of age: 5 years of experience at a single institute. *Arch Dis Child* 2015;100(08):774–778
- 150 Snyderman CH, Pant H, Carrau RL, Prevedello D, Gardner P, Kassam AB. What are the limits of endoscopic sinus surgery?: the expanded endonasal approach to the skull base. *Keio J Med* 2009;58(03):152–160
- 151 AlQahtani A, Turri-Zanoni M, Dallan I, Battaglia P, Castelnovo P. Endoscopic endonasal resection of sinonasal and skull base malignancies in children: feasibility and outcomes. *Childs Nerv Syst* 2012;28(11):1905–1910
- 152 D'Haens J, Van Rompaey K, Stadnik T, Haentjens P, Poppe K, Velkeniers B. Fully endoscopic transsphenoidal surgery for functioning pituitary adenomas: a retrospective comparison with traditional transsphenoidal microsurgery in the same institution. *Surg Neurol* 2009;72(04):336–340
- 153 Dehdashti AR, Ganna A, Karabatsou K, Gentili F. Pure endoscopic endonasal approach for pituitary adenomas: early surgical results in 200 patients and comparison with previous microsurgical series. *Neurosurgery* 2008;62(05):1006–1015, discussion 1015–1017
- 154 Graffeo CS, Dietrich AR, Grobelny B, et al. A panoramic view of the skull base: systematic review of open and endoscopic endonasal approaches to four tumors. *Pituitary* 2014;17(04):349–356
- 155 Higgins TS, Courtemanche C, Karakla D, et al. Analysis of transnasal endoscopic versus transseptal microscopic approach for excision of pituitary tumors. *Am J Rhinol* 2008;22(06):649–652
- 156 O'Malley BW Jr, Grady MS, Gabel BC, et al. Comparison of endoscopic and microscopic removal of pituitary adenomas: single-surgeon experience and the learning curve. *Neurosurg Focus* 2008;25(06):E10
- 157 Buchfelder M, Kreutzer J. Transcranial surgery for pituitary adenomas. *Pituitary* 2008;11(04):375–384
- 158 Dolenc VV. Transcranial epidural approach to pituitary tumors extending beyond the sella. *Neurosurgery* 1997;41(03):542–550, discussion 551–552
- 159 Couldwell WT. Transsphenoidal and transcranial surgery for pituitary adenomas. *J Neurooncol* 2004;69(1–3):237–256
- 160 Jane JA, Park TS, Pobereskin LH, Winn HR, Butler AB. The supraorbital approach: technical note. *Neurosurgery* 1982;11(04):537–542
- 161 Iwai Y, Hakuba A, Katsuyama J, et al. A case of ectopic large pituitary adenoma. *No Shinkei Geka* 1990;18(01):71–75
- 162 Ohata K, Takami T, Goto T, Hara M. Transpetrosal look-up approach for retrochiasmatic suprasellar tumors. *Skull Base* 2005;15:B-9
- 163 DeLellis RA. *Pathology and Genetics of Tumours of Endocrine Organs*. vol 8. Lyon, France: IARC; 2004
- 164 Figarella-Branger D, Trouillas J. The new WHO classification of human pituitary tumors: comments. *Acta Neuropathol* 2006;111(01):71–72
- 165 Saeger W, Honegger J, Theodoropoulou M, et al. Clinical impact of the current WHO classification of pituitary adenomas. *Endocr Pathol* 2016;27(02):104–114
- 166 Scheithauer BW, Gaffey TA, Lloyd RV, et al. Pathobiology of pituitary adenomas and carcinomas. *Neurosurgery* 2006;59(02):341–353, discussion 341–353
- 167 George DH, Scheithauer BW, Kovacs K, et al. Crooke's cell adenoma of the pituitary: an aggressive variant of corticotroph adenoma. *Am J Surg Pathol* 2003;27(10):1330–1336
- 168 Pernicone PJ, Scheithauer BW, Sebo TJ, et al. Pituitary carcinoma: a clinicopathologic study of 15 cases. *Cancer* 1997;79(04):804–812
- 169 Thapar K, Yamada Y, Scheithauer B, Kovacs K, Yamada S, Stefanescu L. Assessment of mitotic activity in pituitary adenomas and carcinomas. *Endocr Pathol* 1996;7(03):215–221
- 170 Di Ieva A, Rotondo F, Syro LV, Cusimano MD, Kovacs K. Aggressive pituitary adenomas—diagnosis and emerging treatments. *Nat Rev Endocrinol* 2014;10(07):423–435
- 171 Zada G, Woodmansee WW, Ramkissoon S, Amadio J, Nose V, Laws ER Jr. Atypical pituitary adenomas: incidence, clinical characteristics, and implications. *J Neurosurg* 2011;114(02):336–344
- 172 Ram Z, Nieman LK, Cutler GB Jr, Chrousos GP, Doppman JL, Oldfield EH. Early repeat surgery for persistent Cushing's disease. *J Neurosurg* 1994;80(01):37–45
- 173 Landolt AM, Haller D, Lomax N, et al. Octreotide may act as a radioprotective agent in acromegaly. *J Clin Endocrinol Metab* 2000;85(03):1287–1289
- 174 Landolt AM, Haller D, Lomax N, et al. Stereotactic radiosurgery for recurrent surgically treated acromegaly: comparison with fractionated radiotherapy. *J Neurosurg* 1998;88(06):1002–1008
- 175 Pollock BE, Nippoldt TB, Stafford SL, Foote RL, Abboud CF. Results of stereotactic radiosurgery in patients with hormone-producing pituitary adenomas: factors associated with endocrine normalization. *J Neurosurg* 2002;97(03):525–530
- 176 Goffman TE, Dewan R, Arakaki R, Gorden P, Oldfield EH, Glatstein E. Persistent or recurrent acromegaly. Long-term endocrinologic efficacy and neurologic safety of postsurgical radiation therapy. *Cancer* 1992;69(01):271–275
- 177 Pollock BE, Carpenter PC. Stereotactic radiosurgery as an alternative to fractionated radiotherapy for patients with recurrent or residual nonfunctioning pituitary adenomas. *Neurosurgery* 2003;53(05):1086–1091, discussion 1091–1094
- 178 Rutkowski MJ, Flanagan PM, Aghi MK. Update on the management of recurrent Cushing's disease. *Neurosurg Focus* 2015;38(02):E16
- 179 Sheehan JM, Vance ML, Sheehan JP, Ellegala DB, Laws ER Jr. Radiosurgery for Cushing's disease after failed transsphenoidal surgery. *J Neurosurg* 2000;93(05):738–742
- 180 Sheehan JP, Kondziolka D, Flickinger J, Lunsford LD. Radiosurgery for residual or recurrent nonfunctioning pituitary adenoma. *J Neurosurg* 2002;97(5, Suppl):408–414
- 181 Loeffler JS, Shih HA. Radiation therapy in the management of pituitary adenomas. *J Clin Endocrinol Metab* 2011;96(07):1992–2003
- 182 Sheehan JP, Xu Z, Lobo MJ. External beam radiation therapy and stereotactic radiosurgery for pituitary adenomas. *Neurosurg Clin N Am* 2012;23(04):571–586
- 183 Thorén M, Rahn T, Hallengren B, et al. Treatment of Cushing's disease in childhood and adolescence by stereotactic pituitary irradiation. *Acta Paediatr Scand* 1986;75(03):388–395
- 184 Devoe DJ, Miller WL, Conte FA, et al. Long-term outcome in children and adolescents after transsphenoidal surgery for Cushing's disease. *J Clin Endocrinol Metab* 1997;82(10):3196–3202
- 185 Magiakou MA, Mastorakos G, Oldfield EH, Gomez MT, Doppman JL, Cutler GB Jr, et al. Cushing's Syndrome in Children and Adolescents—Presentation, Diagnosis, and Therapy. *N Engl J Med* 1994;331:629–636

- 186 Ding D, Starke RM, Sheehan JP. Treatment paradigms for pituitary adenomas: defining the roles of radiosurgery and radiation therapy. *J Neurooncol* 2014;117(03):445–457
- 187 Estrada J, Boronat M, Mielgo M, et al. The long-term outcome of pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. *N Engl J Med* 1997;336(03):172–177
- 188 Jennings AS, Liddle GW, Orth DN. Results of treating childhood Cushing's disease with pituitary irradiation. *N Engl J Med* 1977;297(18):957–962
- 189 Petit JH, Biller BM, Yock TI, et al. Proton stereotactic radiotherapy for persistent adrenocorticotropin-producing adenomas. *J Clin Endocrinol Metab* 2008;93(02):393–399
- 190 Ronson BB, Schulte RW, Han KP, Loreda LN, Slater JM, Slater JD. Fractionated proton beam irradiation of pituitary adenomas. *Int J Radiat Oncol Biol Phys* 2006;64(02):425–434
- 191 Graffeo CS, Perry A, Carlstrom LP, et al. Characterizing and predicting the Nelson-Salassa syndrome. *J Neurosurg* 2017;127(06):1277–1287
- 192 Pollock BE, Young WF Jr. Stereotactic radiosurgery for patients with ACTH-producing pituitary adenomas after prior adrenalectomy. *Int J Radiat Oncol Biol Phys* 2002;54(03):839–841
- 193 Heaney AP. Clinical review: Pituitary carcinoma: difficult diagnosis and treatment. *J Clin Endocrinol Metab* 2011;96(12):3649–3660
- 194 Losa M, Bogazzi F, Cannavo S, et al. Temozolomide therapy in patients with aggressive pituitary adenomas or carcinomas. *J Neurooncol* 2016;126(03):519–525
- 195 McCormack AI, Wass JA, Grossman AB. Aggressive pituitary tumours: the role of temozolomide and the assessment of MGMT status. *Eur J Clin Invest* 2011;41(10):1133–1148
- 196 Ortiz LD, Syro LV, Scheithauer BW, et al. Temozolomide in aggressive pituitary adenomas and carcinomas. *Clinics (Sao Paulo)* 2012;67(Suppl 1):119–123
- 197 Raverot G, Castinetti F, Jouanneau E, et al. Pituitary carcinomas and aggressive pituitary tumours: merits and pitfalls of temozolomide treatment. *Clin Endocrinol (Oxf)* 2012;76(06):769–775
- 198 Fukuoka H, Cooper O, Ben-Shlomo A, et al. EGFR as a therapeutic target for human, canine, and mouse ACTH-secreting pituitary adenomas. *J Clin Invest* 2011;121(12):4712–4721
- 199 Fukuoka H, Cooper O, Mizutani J, et al. HER2/ErbB2 receptor signaling in rat and human prolactinoma cells: strategy for targeted prolactinoma therapy. *Mol Endocrinol* 2011;25(01):92–103
- 200 Jouanneau E, Wierinckx A, Ducray F, et al. New targeted therapies in pituitary carcinoma resistant to temozolomide. *Pituitary* 2012;15(01):37–43
- 201 Ortiz LD, Syro LV, Scheithauer BW, et al. Anti-VEGF therapy in pituitary carcinoma. *Pituitary* 2012;15(03):445–449
- 202 Katznelson L, Klibanski A. Prolactinomas. *Cancer Treat Res* 1997;89:41–55
- 203 Rasmussen C. Hyperprolactinaemia—a clinical study with special reference to long-term follow-up, treatment with dopamine agonists, and pregnancy. *Ups J Med Sci* 1990;95(01):1–29
- 204 Rasmussen C, Bergh T, Nilius SJ, Wide L. Return of menstruation and normalization of prolactin in hyperprolactinemic women with bromocriptine-induced pregnancy. *Fertil Steril* 1985;44(01):31–34
- 205 Gsponer J, De Tribolet N, Déruaz JP, et al. Diagnosis, treatment, and outcome of pituitary tumors and other abnormal intrasellar masses. Retrospective analysis of 353 patients. *Medicine (Baltimore)* 1999;78(04):236–269
- 206 Hoorn EJ, Zietse R. Water balance disorders after neurosurgery: the triphasic response revisited. *NDT Plus* 2010;3(01):42–44
- 207 Das NK, Lyngdoh BT, Bhakri BK, et al. Surgical management of pediatric Cushing's disease. *Surg Neurol* 2007;67(03):251–257, discussion 257
- 208 Kassam A, Thomas AJ, Snyderman C, et al. Fully endoscopic expanded endonasal approach treating skull base lesions in pediatric patients. *J Neurosurg* 2007;1062, Suppl):75–86
- 209 Tamaskauskas A, Sinkūnas K, Draf W, et al. Management of cerebrospinal fluid leak after surgical removal of pituitary adenomas. *Medicina (Kaunas)* 2008;44(04):302–307
- 210 Garcia-Navarro V, Anand VK, Schwartz TH. Gasket seal closure for extended endonasal endoscopic skull base surgery: efficacy in a large case series. *World Neurosurg* 2013;80(05):563–568
- 211 Kassam AB, Thomas A, Carrau RL, et al. Endoscopic reconstruction of the cranial base using a pedicled nasoseptal flap. *Neurosurgery* 2008;63(01, Suppl 1):ONS44–ONS52, discussion ONS52–ONS53
- 212 Richmond IL, Wilson CB. Pituitary adenomas in childhood and adolescence. *J Neurosurg* 1978;49:163–168
- 213 Fahlbusch R, Buchfelder M, Müller OA. Transsphenoidal surgery for Cushing's disease. *J R Soc Med* 1986;79:262–269
- 214 Lüdecke D, Herrmann H-D, Schulte F. Special problems with neurosurgical treatment of hormone-secreting pituitary adenomas in children. In: Kageyama N, Takakura K, Epstein FJ, Hoffman HJ, Schut L, eds. *Intracranial Tumors in Infancy and Childhood Vol 30*. New York, NY: Karger Publishers; 1987:362–370
- 215 Haddad SF, VanGilder JC, Menezes AH. Pediatric pituitary tumors. *Neurosurgery* 1991;29:509–514
- 216 Leinung MC, Kane LA, Scheithauer BW, Carpenter PC, Laws ER Jr., Zimmerman D. Long term follow-up of transsphenoidal surgery for the treatment of Cushing's disease in childhood. *J Clin Endocrinol Metab* 1995;80:2475–2479
- 217 Abe T, Ludecke DK, Saeger W. Clinically nonsecreting pituitary adenomas in childhood and adolescence. *Neurosurgery* 1998;42:744–750; discussion 750–741