

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

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## 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.<sup>1–5</sup> As compared with the adult disease, pituitary adenoma in children is predominantly comprised of secreting tumors, with prolactin (PRL), adrenocorticotropic hormone (ACTH), and growth hormone (GH) secreting tumors observed most frequently.<sup>4–11</sup> 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 <sup>a</sup>	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)

	n = 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%) <sup>b</sup>
Underlying genetic conditions	
Multiple endocrine neoplasia type 1	1 (3%)
McCune–Albright syndrome	1 (3%)

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

<sup>a</sup>Percentage of female patients only.

<sup>b</sup>Percentage 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

	n = 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%) <sup>a</sup>
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.

<sup>a</sup>Percentage 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

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**Table 3** Detailed treatment courses in recurrent or persistent disease

	<i>n</i> = 21 <sup>a</sup>
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 <sup>b</sup>	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 <sup>b</sup>	1 (5%)
SRS alone, persistent disease at last follow-up <sup>b</sup>	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 <sup>b</sup>	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.

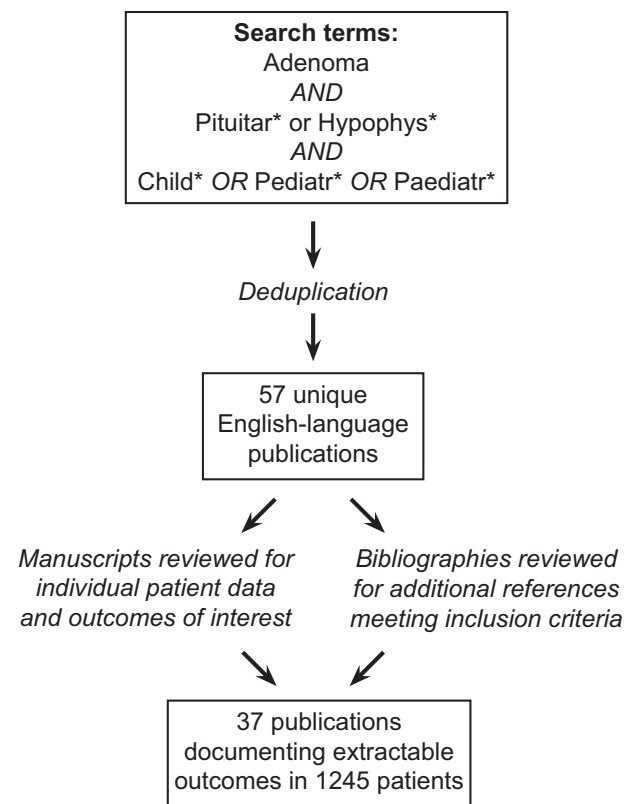
<sup>a</sup>Percentages of patients with recurrent/persistent disease after first TSR.

<sup>b</sup>Patients 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%)
Dissaneevate	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 <sup>a</sup>	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.

<sup>a</sup>Mean 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 <sup>b</sup>	Any post- operative RT <sup>b</sup>	Any post- operative Rx <sup>b</sup>	BAX <sup>a</sup>	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.) <sup>c</sup>
Richmond <sup>c</sup>	1978	25	2 (8%)	-	-	-	0 (0%)	10 (40%)	0 (0%)	1 (4%)	1 (4%)	-	14 <sup>c</sup>
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 <sup>c</sup>	1991	16	9 (56%)	3 (33%)	2 (22%)	4 (44%)	-	2 (12%)	-	-	-	6 (38%)	55 <sup>c</sup>
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 <sup>c</sup>	1994	50	3 (6%)	3 (100%)	0 (0%)	0 (0%)	-	7 (19%)	-	0 (0%)	-	0 (0%)	22 <sup>c</sup>
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 <sup>c</sup>	1995	136	-	14 (64%)	22 (100%)	-	3 (6%)	-	-	-	-	-	24 <sup>c</sup>
Weber	1995	9	3 (33%)	0 (0%)	3 (100%)	0 (0%)	-	4 (44%)	-	3 (33%)	-	0 (0%)	24-128
Devoe <sup>c</sup>	1997	35	8 (23%)	8 (100%)	0 (0%)	-	4 (11%)	5 (14%)	-	0 (0%)	-	2 (6%)	86 <sup>c</sup>
Massoud	1997	21	5 (24%)	3 (60%)	2 (40%)	0 (0%)	1 (7%)	10 (48%)	-	1 (5%)	2 (10%)	0 (0%)	96
Abe <sup>c</sup>	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 <sup>c</sup>	1999	15	8 (53%)	0 (0%)	4 (50%)	8 (100%)	-	6 (33%)	0 (0%)	3 (20%)	0 (0%)	2 (13%)	74 <sup>c</sup>
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 <sup>c</sup>	2001	5	2 (40%)	0 (0%)	2 (100%)	2 (100%)	-	2 (40%)	0 (0%)	-	-	1 (20%)	53 <sup>c</sup>
Abe	2002	14	5 (57%)	0 (0%)	7 (88%)	8 (100%)	-	3 (21%)	1 (7%)	-	1 (7%)	1 (7%)	72 <sup>c</sup>

(Continued)



**Table 5** (Continued)

First author	Year	N	Recurrent/persistent disease after initial operation	Any repeat surgery <sup>b</sup>	Any post-operative RT <sup>b</sup>	Any post-operative Rx <sup>b</sup>	BAX <sup>a</sup>	Chronic post-operative pituitary insufficiency	Permanent visual dysfunction	Chronic diabetes insipidus	Post-operative CSF leak	Recurrent/persistent disease at last follow-up	Median follow-up (mo.) <sup>c</sup>
Cannavo	2003	27	19 (70%)	0 (0%)	8 (42%)	2 (11%)	-	9 (33%)	13 (48%)	4 (15%)	-	17 (63%)	60
Storr <sup>c</sup>	2003	18	7 (39%)	0 (0%)	7 (100%)	7 (100%)	-	-	-	-	-	0 (0%)	83 <sup>c</sup>
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 <sup>c</sup>	2008	20	9 (45%)	6 (67%)	2 (22%)	0 (0%)	-	-	-	-	-	2 (10%)	50 <sup>c</sup>
Locatelli <sup>c</sup>	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 <sup>c</sup>
Tarapore	2011	34	6 (18%)	0 (0%)	9 (150%)	6 (100%)	1 (10%)	8 (24%)	1 (3%)	-	0 (0%)	3 (9%)	18
Shah <sup>c</sup>	2011	48	17 (35%)	1 (4%)	8 (35%)	6 (26%)	4 (8%)	-	-	0 (0%)	5 (10%)	17 (35%)	59 <sup>c</sup>
Zhan <sup>c</sup>	2015	56	28 (50%)	0 (0%)	0 (0%)	0 (0%)	-	4 (7%)	2 (4%)	1 (2%)	2 (4%)	-	52 <sup>c</sup>
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.

<sup>a</sup>Percentages of ACTH-secreting adenomas.

<sup>b</sup>Percentages of recurrent tumors.

<sup>c</sup>Mean 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 cm<sup>3</sup> 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 cm<sup>3</sup>, 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.<sup>12,13</sup> 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.<sup>2,12–16</sup> 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.<sup>2,16–19</sup>

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%).<sup>20</sup> 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.<sup>21,22</sup> 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).<sup>23,24</sup> 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).<sup>25,26</sup> 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.<sup>2,10,27–29</sup> 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.<sup>2,6,7,30</sup> The overall prevalence of pituitary adenoma may be increased among female children up to 2:1, due to the marked prolactinoma predominance in girls.<sup>2,4,9,10,27,28,31</sup> Sporadic pituitary adenomas have been documented to harbor a wide range of mutations involving common tumor suppressor or oncogenes, including *GNAS*, *PTTG*, *HMG2A*, and *FGFR-4*.<sup>28,32,33</sup> 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.<sup>28,34</sup>

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.<sup>28,35</sup> The syndrome arises in patients who inherit a single mutated allele of the *menin* tumor suppressor gene, and subsequently acquire a “second hit.”<sup>36–39</sup> Individuals bearing the *menin* mutation have a 30 to 40% lifetime risk of pituitary adenoma; ~60% of which secrete PRL and 20% GH.<sup>40</sup>

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.<sup>28,41,42</sup> 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, lentiginos, 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.<sup>28,43,44</sup> 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.<sup>28,44–46</sup>

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.<sup>28</sup> Of the 211 families described, ~20% harbor an inactivating heterozygous germline mutation of the tumor suppressor gene *AIP*.<sup>47–49</sup> 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.<sup>4,8,10</sup>

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.<sup>4,6</sup> ACTH-secreting tumors occur slightly later in childhood, with peak incidence at the onset of puberty, and an overall 3:1 female predominance.<sup>4,6,14,50</sup> Classic symptoms of hyperadrenocorticism are prototypical and range from Cushingoid appearance to growth arrest, weight gain, amenorrhea, mental status changes, hypertension, and hyperglycemia.<sup>14,15</sup>

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.<sup>4,51</sup> Primary and secondary amenorrhea account for three-quarters of their presentations, while male children present with growth arrest, delayed puberty, or galactorrhea.<sup>4,52,53</sup> 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.<sup>4,27,51,54,55</sup> 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.<sup>14,15,56,57</sup> More likely, this trend reflects the responsiveness of prolactinomas to pharmacotherapy and the general bias against early surgery in the pediatric population.<sup>28,53,58</sup>

In contrast to adults, children rarely present with focal neurologic signs.<sup>2,5,55</sup> 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.<sup>2,3,5,55</sup> 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.<sup>51,52,55</sup>

### 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.<sup>58</sup> 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.<sup>29,59</sup> 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.<sup>60–63</sup> 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.<sup>53,58</sup>

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.<sup>64–66</sup> 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.<sup>67</sup> 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.<sup>6</sup> 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.<sup>68</sup>

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.<sup>69–71</sup> 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.<sup>72</sup> 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

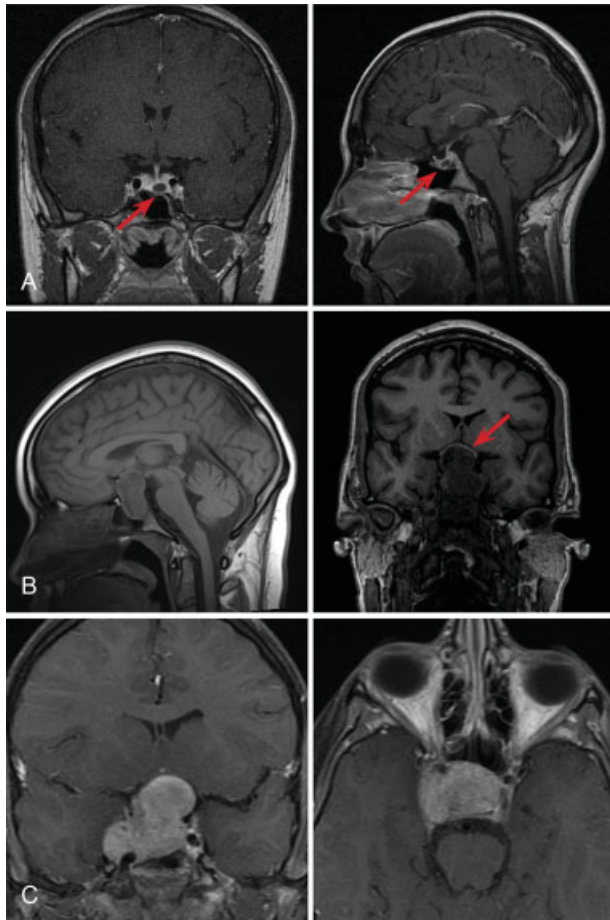
in both ACTH and cortisol within 45 minutes—an effect that can be potentiated by pre-treating with vasopressin, although that is rarely required in children (positive test thresholds are specific to the center and protocol).<sup>73,74</sup> Ectopic ACTH generally does not respond to either agent. Positive 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.<sup>75</sup> These results can be further elevated to 95 to 100% sensitivity and specificity by administering CRH and using a diagnostic threshold >3.<sup>76</sup> 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.<sup>77–79</sup> 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%.<sup>14,76,80,81</sup>

### 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.<sup>10,82,83</sup> 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.<sup>28</sup>

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.<sup>83,84</sup> 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.<sup>83,85</sup> 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.<sup>86</sup>

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.<sup>87–90</sup> 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.<sup>91–93</sup> Of note, female patients desiring fertility should be preferentially placed on bromocriptine, as it had a more well-characterized safety profile.<sup>94–98</sup>

In some individuals, medical monotherapy may provide a sustained cure.<sup>99</sup> 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.<sup>99–106</sup> 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.<sup>29,107–109</sup> 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.<sup>29,110,111</sup> 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.<sup>112,113</sup> 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.<sup>29</sup> 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.<sup>114</sup>

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.<sup>115–117</sup> 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.<sup>118–120</sup> Correspondingly, we do not recommend the first-line medical therapy for most children with GH-secreting pituitary adenomas.<sup>117</sup>

### 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.<sup>5,11,121,122</sup> 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.<sup>123–125</sup>

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.<sup>8,56,126</sup> Radiology-based anatomic studies have described approximate drilling distances by age group, which can be correlated with preoperative imaging (ideally, a stereotactic CT scan).<sup>127,128</sup> 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.<sup>129</sup> 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%.<sup>130</sup> 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.<sup>131–138</sup> Few prospective trials comparing EEA and microsurgery have been completed, with five meeting criteria for inclusion in a recent meta-analysis.<sup>139–145</sup> 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.<sup>146</sup> 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.<sup>147</sup> 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.<sup>126,136,148,149</sup>

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.<sup>150</sup> 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.<sup>48,126,148,151</sup>

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.<sup>152–156</sup> 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.<sup>157,158</sup> 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.<sup>159</sup> 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.<sup>159,160</sup> 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.<sup>161,162</sup>

### 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.<sup>163–166</sup> 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.<sup>163,165,166</sup> 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.<sup>167</sup> 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.

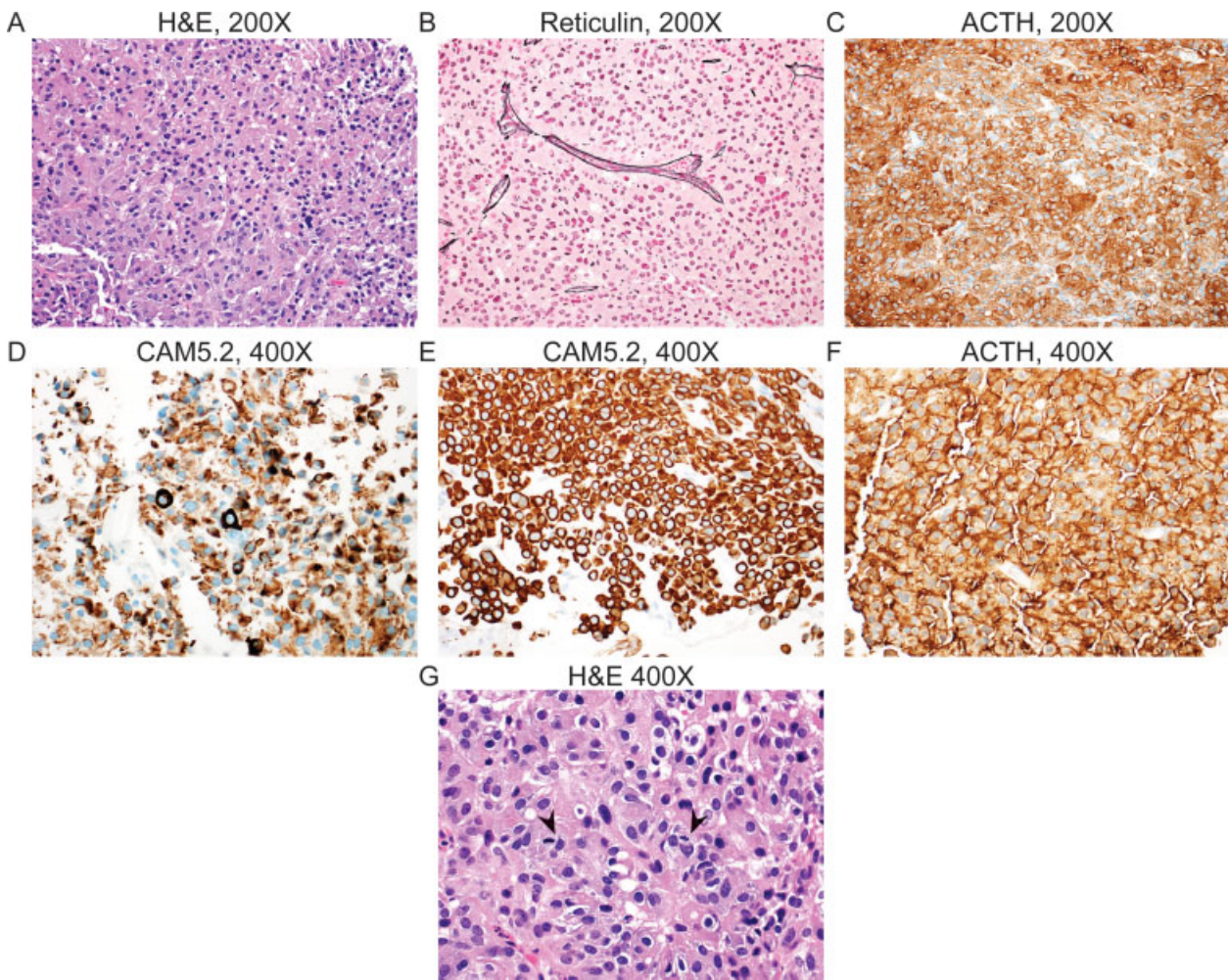
Atypical pituitary adenoma is defined by the presence of mitoses, Ki-67 index >3%, and nuclear p53 staining with nuclear pleomorphism (–Fig. 3G).<sup>168,169</sup> Adult series have approximated 3 to 15% incidence, as compared with the very rare 0.2% prevalence of pituitary carcinoma, with no clear correlation established between specific atypical features and disease phenotype.<sup>165,166,170,171</sup> 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.<sup>20,172</sup> 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 halting 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.<sup>116,117</sup> 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.<sup>173–175</sup>

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.<sup>174–180</sup> Hypopituitarism is the most common complication, with 10 to 12% of adults requiring chronic hormonal supplementation after SRS.<sup>16,48,181,182</sup>

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.<sup>16,183</sup> Although this can be managed with supplementation, most patients still do not reach mid-parental target height.<sup>57,184,185</sup> 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.<sup>14,16,130</sup>

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.<sup>183</sup> 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.<sup>16,130,179,182,186–188</sup>

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  $12 \text{ Gy}$ ; however, this may reduce the chance for biochemical cure in a hormone-producing tumor, as these usually require at least  $20 \text{ Gy}$  marginal doses. Alternatively, some centers recommend fractionated SRS, IMRT, or EBRT, supported by varying degrees of evidence.<sup>48,181,182</sup> 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.<sup>182,186,189,190</sup> 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.<sup>191</sup> 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.<sup>192</sup> 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.<sup>191,192</sup>

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.<sup>170</sup> Temozolomide, a well-tolerated deoxyribonucleic acid (DNA)-alkylating agent that is widely used

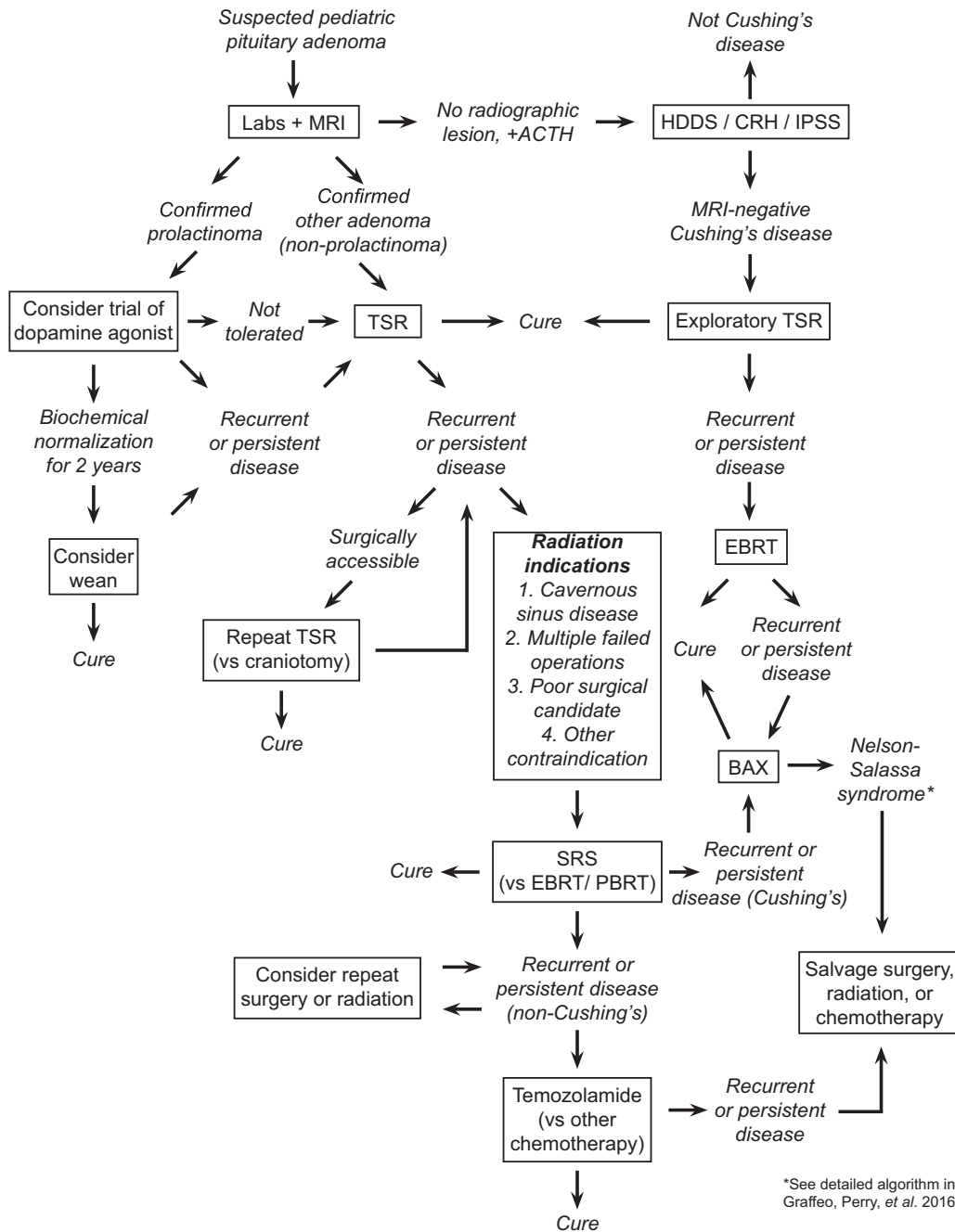
in glioma treatment, has demonstrated better efficacy than preceding chemotherapeutic regimens, with an overall clinical or radiographic response rate of 60 to 69%.<sup>170,193–197</sup> Newer targeted therapies are also undergoing active investigation as second-line, concomitant, or alternative agents 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.<sup>198–201</sup> 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.<sup>6,202</sup> 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.<sup>203,204</sup>

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.<sup>145,148,205</sup> 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.<sup>206</sup> 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.<sup>54</sup>

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



**Fig. 4** Treatment algorithm for pediatric pituitary adenoma. ACTH, adrenocorticotropic hormone; BAX, bilateral adrenalectomy; CRH, corticotropin releasing hormone; EBRT, external beam radiotherapy; HDDS, high-dose dexamethasone suppression; IPSS, inferior petrosal sinus sampling; MRI, magnetic resonance imaging; PBRT, proton beam radiotherapy; SRS, stereotactic radiosurgery; TSR, transsphenoidal resection.

with suprasellar extension, intraoperative CSF leak, or prior treatment with surgery, radiation, or dopamine agonists.<sup>92,136,207–209</sup> General management strategies are comparable to adults, with the specific exception that children younger than 10 to 13 years may not have adequate tissue to support a vascularized nasoseptal flap.<sup>129</sup> Similarly, although lumbar drainage may be attempted as a first-line intervention—potentially in combination with acetazolamide—the procedure may require sedation in children, and the drain itself is more prone to inadvertent removal. Correspondingly, most leaks are better managed via exploration and repair. Simple defects may be adequately treated with abdominal fat graft;

however, larger fistulas or leaks in patients who have been radiated or multiply operated are more likely to be successfully treated with a nasoseptal flap or a comparable autograft, and multi-layer repair is universally recommended.<sup>208–211</sup>

### Conclusion

Pediatric pituitary adenomas are a diverse and remarkably challenging family of tumors; the ideal management of which is subject to a broad range of potentially complicating factors including restrictive anatomy, the predominance of secretory disease, and the potentially heightened

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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 trialed 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.

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