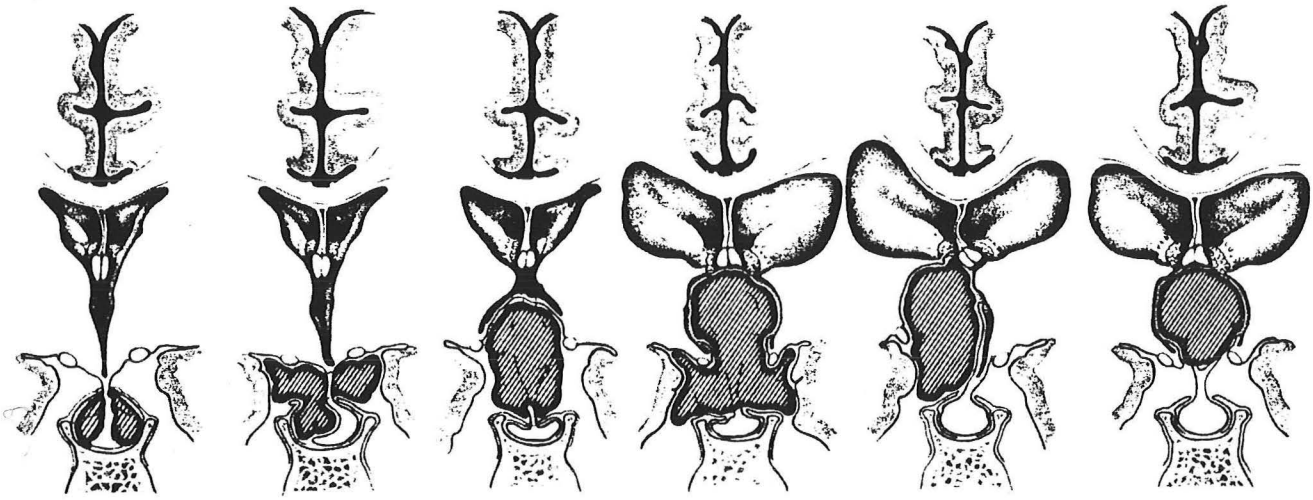
CRANIOPHARYNGIOMAS



Michael J. McPhaul, M.D.
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Genesis

The derivation of craniopharyngioma has been the subject of much speculation. The theories of their genesis can be summarized along two lines as shown in Table I.

Table I

Theories of the Derivation of Craniopharyngiomas

1) Derived from the embryonic remnants of Rathke's pouch.

2) Derived from "metaplasia" of the epithelium of the anterior hypophysis.

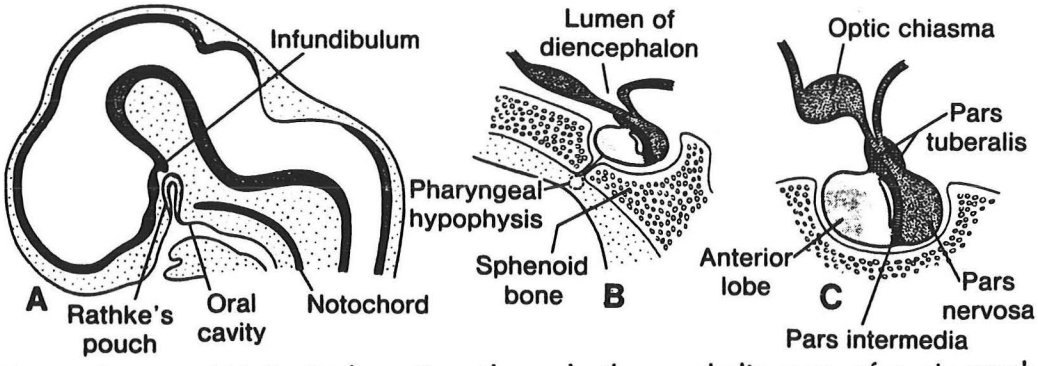


Figure 1. (*A*) Sagittal section through the cephalic part of a six-week embryo, showing Rathke's pouch as a dorsal outpocketing of the oral cavity, and the infundibulum as a thickening in the floor of the diencephalon. (*B* and *C*) Sagittal sections through the developing hypophysis in the 11th and 16th weeks of development, respectively. Note the formation of the pars tuberalis, encircling the stalk of the pars nervosa. Sometimes a remnant of Rathke's pouch is found in the pharynx. It is known as a pharyngeal hypophysis.

The idea that these tumors are derived embryologically comes from the appreciation of the embryogenesis of the pituitary gland. This gland is composed of two sections: the neurohypophysis is derived from neural tissue and the anterior portion is derived from an invagination of pharyngeal ectodermal. As the formation of these structures proceeds, the attachment with the pharynx degenerates. It has been suggested that embryonic cells that do not involute during this process would remain as "nests" of cells scattered along and around the path covered by this migration pathway. This led to the idea, first proposed in 1904 by Erdheim (1), that neoplastic transformation of these cell islands is responsible for the appearance of craniopharyngiomas.

A prediction of this proposed etiology is that the presence of these "nests" of cells in humans should in some way parallel the

frequency of craniopharyngioma. It does not. In a postmortem study of >1300 pituitary glands, no "nests" were detected in 78 patients younger than 10 years of age, despite the fact that the peak of onset of childhood craniopharyngioma is 10-12 years of age. By contrast, such nests of squamous-like cells were found in 30% of patients 50-70 years old. The results of this study would tend to suggest that the genesis of craniopharyngioma may involve the alteration ("metaplasia") of the cells comprising the nature ectodermally- derived segments of the anterior pituitary (2-4).

It is conceivable that these two origins are both correct. As will become evident in subsequent discussion, some authors have suggested that the craniopharyngiomas occurring in adults and in children have different derivation and clinical behavior.

Before leaving the topic of etiology, it is interesting to note that virtually no attention has been directed at possible genetic etiology of craniopharyngiomas. All of the literature regarding the categorization of craniopharyngiomas has focussed on the histological categorization of the tumor: adamantimous, squamous, etc. No studies pertaining to the pathogenesis of these tumors exist and only a single paper examined the karyotypes of a handful of craniopharyngioma specimens. This analysis indicated a very complicated and bizarre karyotype in one of the three samples examined (5).

Pathology

Classically, craniopharyngioma has been viewed as a spectrum of disease. Grossly, the tumor generally consists of a mass of cystic and partially calcified tissue that betrays its presence by the effects of the mass within the cranium, resulting in visual, endocrine, or mental status changes. In recent years, it has been noted that this spectrum of specimen types may have some relationship to the subsequent clinical behavior of the tumor. Adamson et al (6) reported a series of 93 adult and pediatric patients with craniopharyngiomas. These investigators retrospectively analyzed the histologic features of the tumor and classified it according to microscopic criteria into either adamantinous or squamous papillary types. The former type being characterized by "palisading adamantinous epithelium" and a high frequency of tumoral calcification. The second type was characterized by the absence of calcification, the absence of keratin nodule formation, and the absence of adamantinous epithelium. The age of diagnosis in this series is shown in Figure 2 and indicates that the papillary squamous histologic type is rare in children and adolescents and more common in adulthood. An interesting feature of this study is that the outcome in this group of patients appeared to have a relationship to the type of histology, with squamous papillary tumors having in general a better outcome. It is of interest to note that this latter group

was also found to have a lower incidence of postoperative recurrence.

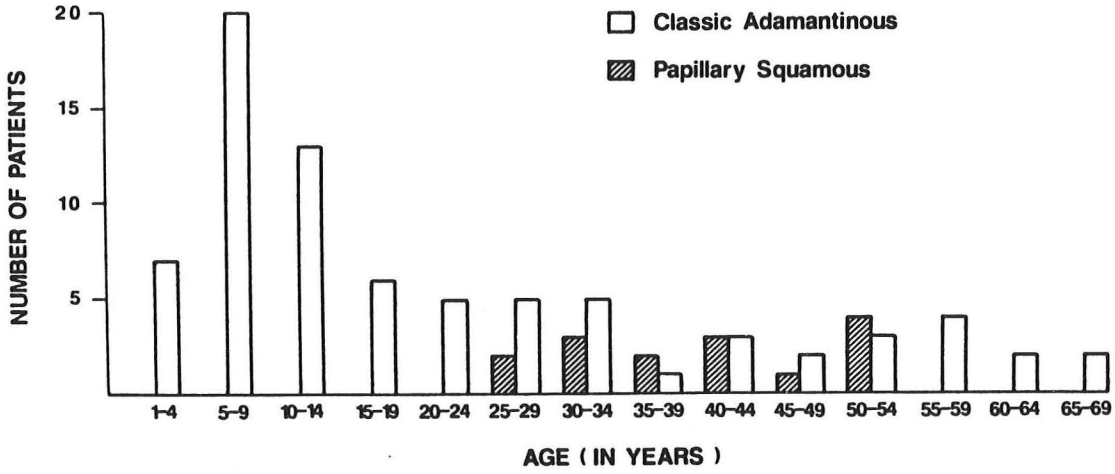


FIG. 2 Age distribution in 93 craniopharyngioma patients, differentiating the adamantinous and squamous varieties.

Incidence/Presentation

Craniopharyngiomas account for approximately 3-4% of intracranial tumors. When broken down according to patient age, they account for a higher proportion of intracranial tumors in children (~10%) than in patients of all ages (~2-3%). The peak age of presentation of patients with craniopharyngiomas is bimodal with a first peak occurring between the ages of 5 and 10, with a second peak occurring much later in adulthood - approximately 60 years of age.

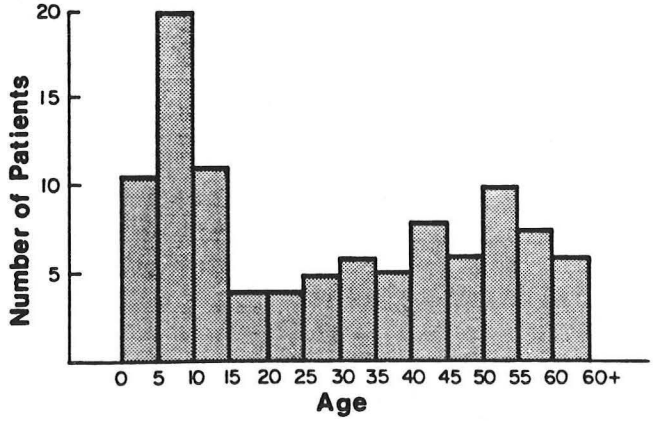


Figure 3. Age distribution in a series of 109 patients with craniopharyngioma. (Data from Sung, D. I. et al.: Treatment results of craniopharyngioma. Cancer, *47*:847–852, 1981.)

The signs and symptoms at presentation in children and adults are quite divergent. This has been attributed by some authors to

the belief that children will suffer dramatic declines in visual function before complaining or before it becomes obvious to those around them that something is wrong. As a result, behavioral changes, endocrine abnormalities (e.g., growth retardation), or overt signs of increased intracranial pressure may be the presenting complaint. By contrast, adults most frequently present with gradual changes in visual activity.

Location

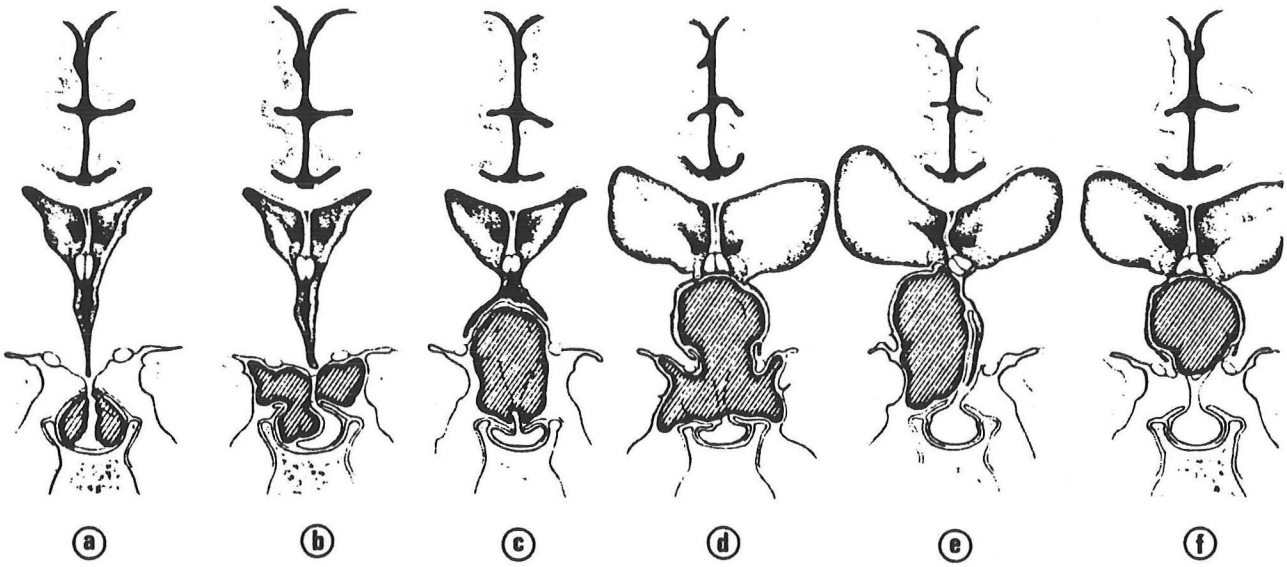


FIG. 4 Diagrammatic representation of the most common locations of craniopharyngiomas. a: Purely intrasellar-infradiaphragmatic; b: intra- and suprasellar, infra- and supradiaphragmatic; c: supradiaphragmatic, parachiasmatic, extraventricular; d: intra- and extraventricular; e: paraventricular in respect to the third ventricle; and f: purely intraventricular.

The most frequent locations of craniopharyngiomas is shown in Figure 4 from an article by Yasargil et al (7). These tumors can be intrasellar, suprasellar, supradiaphragmatic, or even intraventricular. The location and extent of these tumors account for the complications that would most often be associated with these lesions: particularly partial or panhypopituitarism, visual disturbances due to compression of the optic nerves or chiasm, or obstructive hydrocephalus. It is notable that in contrast to pituitary tumors, involvement of the hypothalamus is frequent and a substantial percentage of patients (in some series as many as 20%) have diabetes insipidus preoperatively.

Therapeutic Options

The therapeutic options that are currently employed in most institutions are neurosurgical debulking of the tumor either alone or in combination with radiation therapy. Within each of these avenues, considerable variations are possible. At most centers,

radiation alone or cyst aspiration are not usually employed as single modalities.

The Surgical Treatment of Craniopharyngiomas

Surgical excision represents the focus of therapy in most centers. This is true in both pediatric and adult patients, as the initial complaint frequently demand immediate attention (symptoms of increased intracranial pressure, visual loss).

Table II. *Operative Approaches for Craniopharyngioma*

Approach	Advantages	Disadvantages
Extra-axial Approaches		
Subfrontal	Good visualization of optic nerves and chiasm	Poor visualization of mass within third ventricle
	Good visualization of ipsilateral carotid artery	Poor visualization of undersurface of ipsilateral tract, chiasm
	Below circle of Willis	
Pterional	Shortest distance to parasellar region	Essentially unilateral
	Below circle of Willis	Poor visualization of contralateral optic nerve
	Good visualization of retrosellar region	
Lamina terminalis	Good visualization of anterior third ventricle	Difficult to locate lateral landmarks
	Allows separation of mass from choroid plexus, internal cerebral veins	Highest risk of hypothalamic damage
Transaxial Approaches		
Transsphenoidal	Avoids craniotomy; direct visualization of tumor within sella	Poor visualization of anterior, lateral, or interpeduncular extension of tumor
	Good decompression of undersurface of chiasm	Difficult if both sella and pituitary gland are normal
Transcallosal	Largely extra-axial on medial hemispheric surface	Divides anterior corpus callosum
	Good visualization of both walls of third ventricle	Risk of bilateral fornix damage
	Allows approach to both sides of anterior third ventricular tumor	Difficult to identify landmarks
Transcortical	Ease of landmark identification	Requires hydrocephalus
	Good visualization of ipsilateral foramen of Monro	Poor visualization of third ventricle walls
	Good visualization of anterior and contralateal third ventricle walls	Divides frontal region cortex; possible postoperative seizure disorder

A variety of surgical approaches have been applied. A listing of each of these approaches is summarized in Table II. Each of these approaches has been advocated by one or more groups as general methods or to debulk tumors that present specific problems (e.g., intraventricular tumor). In each case, however, the goal is to permit as clear an exposure of the tumor as possible so as to permit as complete tumor resection as possible. In most cases at our institution, either the transfrontal or transsphenoidal approaches are employed. Unfortunately, the transsphenoidal approach can only be utilized for small tumors located within the sella. The transsubfrontal approach is reserved for the majority of larger tumors in which a more extensive operative field is

required. This route permits good accessibility to the region of the hypothalamus, carotid arteries and suprasellar region.

TABLE III

SURGERY, RADICAL

Series	# Patients	# Recurrences	Population	Comments
Review (8)	92	19%	A&C	
Richmond (20)	8	3	C	
Cabeduzo (21)	13	4	C&A	Avg F/U=6 yrs
Sung (22)	14 children 23 adults		A&C	5YS=100% 10YS=100% 59% 25%
Shapiro (23)	22	5 (23%)	C	Mean F/U = 3.3 yrs
Baskin (24)	7	1 (0)		No reccurrence following second operation in 1 patient
Kang (25A)	TE 2 TE + RT 5	1		50% 5 YS 100% 10 YS
Weiss (26)	19	postop CT+ 4/4 postop CT- 2/14	C	Median F/U=42 mos for those with no recurrence 1 death
Wen (27)	20	?		Many complications; 2 postop deaths 5Ys=80%
Fischer (28)	8 (some rec'd rad Rx as well)	4	C	10YS=7/8 (1 due to "hypothalamic crisis") impact on life assessed
Lichter (29)	8	3	A&C	Avg F/U=4/8 Yrs; extensive postsurgical complications (least w/DI and hypopit)
Yasargil (7)	144 (90 TE)	7%	A&C	21 deaths: 10 early postop infection; 11 shunt infection and endocrine, 3 operative; mixture of 1^{0} and 2^{0} operations; 14 cases got radiation previously. Outcomes graded: adults 73% "good" (39/74 >6y F/U) children 61% "good" (34/70 >60y F/U)

One of the major controversies that has affected the neurosurgical treatment of craniopharyngioma is the extent of surgical debridement that is effected at the time of operation. One of the strongest proponents of so-called "radical surgical resection" of craniopharyngiomas was Donald Matson, who began to attempt to remove all craniopharyngioma tissue either at initial operation or at secondary operations performed for recurrent disease (41). Subsequently, many surgeons have embraced this philosophy and have attempted to treat this disorder by radical excision. A summary of several such series is shown in Table III.

An examination of the data indicates that patients in whom radical excision has been accomplished have an improved prognosis compared with those in whom subtotal resection alone is effected. On the surface, this would seem to leave little doubt that radical resection would be considered the treatment of choice. Counterbalancing this improvement in outlook, however, is the rate of complication(s) that are observed in the patient category labelled "radical." These complications are often of a major nature, such a blindness, hemiparesis, or even death. Another disturbing aspect hidden by a superficial analysis of such series is the manner in which the outcome of such operations are measured. Measurements such as number of recurrences are really too crude. In those series in which operative results are classified as good, poor, or moderate one can appreciate that many such patients are substantially impaired, along with a certain frequency of perioperative death. It should be noted that an aggressive surgical approach does not ensure cure, as even in those patients undergoing radical surgery, a substantial number recur, although this percentage varies widely from series to series.

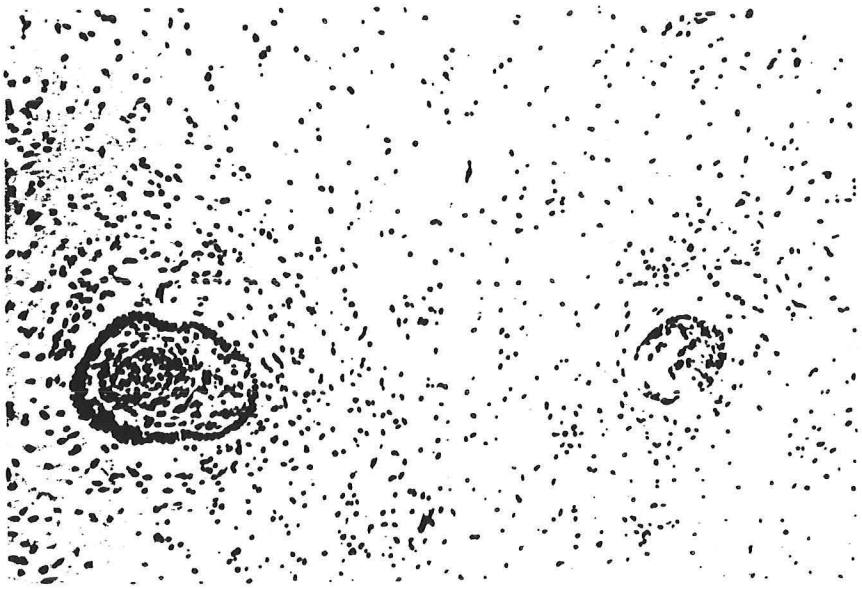


FIG. 5 Finger-like extensions of craniopharyngioma, cut across, lie in a portion of the hypothalamus (surgical specimen).

The difficulties encountered with the surgical resection of this tumor require some explanation. While these tumors are not considered malignant in the sense of tumor metastases and the like, the cellular component of these tumors often infiltrate into the surrounding parenchyma. Thus even though a surgeon may resect all visible tumor, small islands or tumor tissues, such as those depicted in Figure 5, can regrow, resulting in eventual tumor recurrence. The second point is simply the location of the tumor (Figure 6). These tumors are frequently adherent to or insinuated into major structures - particularly problematic are the attachments to the hypothalamus, medial internal carotid arteries,

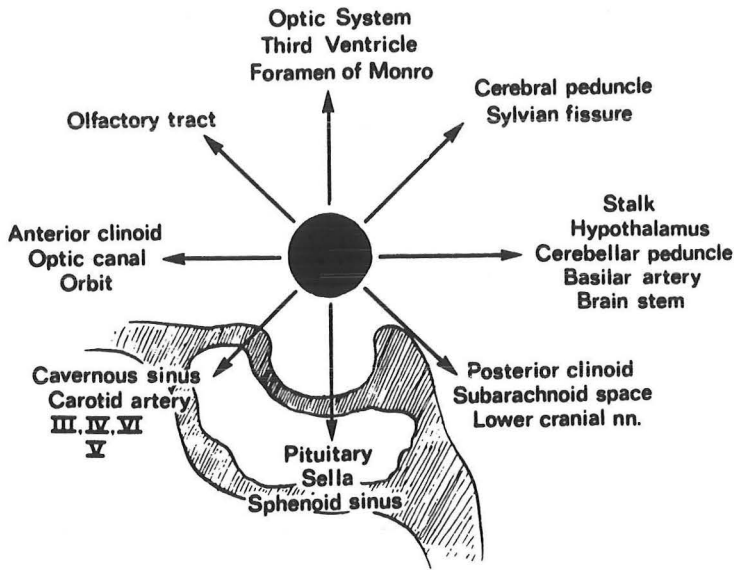


FIG. 6 The parasellar structures which may be involved by craniopharyngiomas.

pituitary stalk, optic chiasm and optic tracts. Attempts to aggressively dissect the tumor segments free from such structures are often responsible for poor operative results seen among survivors of aggressive surgery.

TABLE IV

SURGERY, PARTIAL

Series	# Patients	# Recurrence	POP	Comments
Review (8)	111	75%	A&C	
Richmond (20)	4		C	5YS=50% 10YS=50%
Cabeduzo (21)	14	10	A&C	Mean F/U 6.1 Yrs.; No Qual of Life Assess
Sung (22)	14 Children 23 Adults		C&A	5YS=71% 10YS=52% 37% 31%
Shapiro (23)	9	7	C	Clinically Symptomatic = Recurrence
Kang (25A)	4		C	5YS=3/4 (75%)
Weiss (26)	7	7		(median F/U=12 mos)
Thomsett (30)	11	1		25 mos mean F/U
Lichter (29)	10	5	A&C	3 recurr→Rx with RT; 1 reop 7 alive NED 5 good, 1 fair, 1 poor Complic.: postop death (1) sellar abcess (1); DI (1) hyperphagia (1)
Hoogenhout (31)	11	5/11 (5 yr) 5/7 (10 yr)		3 postop deaths (total) 4 dead of dz 5YS=73% 10YS=43%
Manaka (32)	80 "radical" (21)			5YS-35% 10YS=27% No mention of complications postop deaths excluded from analysis

Given the difficulties inherent in attempts at total resection of the tumor, what can be expected in patients in whom only partial tumor resection is accomplished? Comparisons of this type are somewhat dangerous, as those tumors in which complete resection is accomplished might represent tumors with a fundamentally different biological behavior. This caveat aside, there are two ways to address this issue. The first method was to compare the surgical results of several series (different centers, different surgeons) in a type of "averaging" analysis. A comparison of this type was performed by Amacher (8) and indicates an increased incidence of recurrence in patients receiving subtotal resection as compared to those receiving complete excision. A second approach to answer this question has been utilized by several investigators who have summarized their own experiences, allocating patients to different treatment regimens. A summary of several series (of both types) is shown in Table IV and supports a several-fold increased frequency in patients treated with subtotal resection of the tumor alone compared to the incidence of recurrence following presumed complete resection. This trend is present in virtually all series in which adequate followup is available.

Radiation Therapy and Craniopharyngiomas

The utility of radiation therapy in patients with malignant disease in the central nervous system is unquestioned. In some instances, this modality has dramatically extended the lifespan of patients with previously fatal diseases, such as medulloblastomas. Over the years, however, the application of radiation therapy to these malignant diseases has led to the recognition of several untoward complications of radiotherapy. A critical examination of the side effects of radiation therapy of lesions in the central nervous system is particularly important in conditions characterized as "benign" - that is, those with a relatively indolent natural history. This categorization applies particularly to entities such as the craniopharyngiomas and to pituitary adenomas. In conditions such as these, unless employed in a discriminating fashion, it is conceivable that the risks of radiation might outweigh the benefits gained by the use of radiotherapy (15).

Table V

Cerebral Injury Following Radiotherapy

- Acute
- Early Delayed
- Delayed

(Acute, Early Delayed) — more common following whole brain irradiation

Diffuse injury

Focal necrosis (radionecrosis)

- anterior visual pathway
- hypothalamic-pituitary axis

Cerebrovascular damage

Radiation-induced tumors

Effects on intellectual function

Radiation effects on the CNS: The types of injuries induced by irradiation of the CNS has usually been classified by the timing of onset of symptoms following irradiation. A listing of a representative categorization is shown in Table V. Acute encephalopathy and early delayed encephalopathy, as represent symptom complexes that are most frequently observed after whole brain irradiation or following large doses of irradiation. These will not be discussed further. Instead, the subsequent discussion will focus on the delayed types of injury; specifically focal necrosis, cerebrovascular complications, cognitive deficits, and secondary malignancies following radiotherapy (9-12).

Focal necrosis. This form of radiation induced injury can be observed months to years following radiation therapy. The incidence of this type of complication is generally held to occur with an incidence of 3-5%, although many such estimates include results from earlier series in which doses or dose fractions were in some cases considerably higher.

The etiology of delayed radionecrosis of brain is not settled. Three different theories have been advanced, including direct effects of radiation on brain tissue and an immune response to radiation-induced expressed antigens. A third theory, which has

received the widest support, centers on the vascular changes induced by radiation (11). This effect is discernible upon both large and small vessels. Reports of atherosclerotic-like lesions in large intracranial and extracranial vessels have been described (12). According to this theory, progressive changes in the vasculature induced by radiation ultimately result in infarction of the supplied areas. The greater vascularity of the cortex, is postulated to account for the observation that this type of injury principally affects the white matter, sparing (relatively) the cortical structures. The presence of demyelination and loss of oligodendrocytes is observed in the less affected areas surrounding more severely affected areas of coagulation necrosis.

The onset of this injury is variable, occurring months to several years following radiotherapy, presentation can be indistinguishable from recurrent tumor with a mass-like lesion present in the field(s) previously irradiated. CT and MRI are not helpful as the lesions may show radiographic characteristics (e.g., enhancement) similar to tumor recurrence. Position emission tomography appears to be the only noninvasive method that can accurately discriminate between focal necrosis and recurrent tumor.

Fig 7 NSD values and complications†

NSD (ret)	Series 1‡	Series 2§	Total
<1500	0/16 (0)	0/87 (0)	0/103 (0)
1500–1599	3/22 (13.6)	2/20 (10)	5/42 (11.9)
1600–1699	1/14 (11.8)	3/14 (20)	4/28 (14.3)
>1700	1/3 (33)	0/1 ( )	1/4 (25)

†Nervous tissue damage.
‡Harris and Levine patients.[22]
§Aristizabal and Caldwell patients.

A specific type of radiation-induced necrosis is delayed damage to the anterior visual pathway, following radiation for sellar or parasellar tumors. Such a complication is evidenced by a progressive loss of vision in one or both eyes and can occur months or even years (average 17 months) following therapy. Visual loss is progressive and irreversible. In cases such as this, a careful radiographic and/or surgical examination to exclude the possibility of recurrent tumor is mandatory. This complication is probably the one that is most daunting and gives the physician the most pause when recommending therapeutic options. Early reports suggested that the total dosage of radiation administered determined the frequency with which visual complications occurred. More recent series have focussed on the individual fraction size and the timing (13, 14). Figure 7 is taken from Ref. 14. This information is taken from series of patients treated for pituitary tumors or for craniopharyngiomas. These data suggest that at ret doses <1500 ret no instances of visual impairment occurred in 103 total patients. As the values of NSD increased, the incidence of

visual impairment increased. This information would suggest that conventional megavoltage therapy even of the sella and suprasellar region (i.e., near the optic chiasm), if properly administered and with careful attention to the timing and spacing of the administered dose results in a low incidence of visual complications (on the order of 1% or less).

Although not as well defined pathologically, radiation-induced damage to the hypothalamus likely involves similar mechanisms. The resulting hypopituitarism has received the most attention and has been postulated to result from damage to either the hypothalamus and/or pituitary (52, 53). It is difficult to define the exact incidence of anterior hypopituitarism or diabetes insipidus in all but the more recent series and diabetes insipidus. Panhypopituitarism is present in most patients except those treated by the most conservative surgical procedures. In one series examining patients treated for pituitary adenomas with surgery or surgery combined with radiation, the latter combination produced a higher frequency of hormonal deficiencies. The frequency with which hormonal deficiencies occurred also increased with time following radiation (48). This aspect of patient care demands continued vigilance, particularly for the appearance of secondary adrenal insufficiency.

Effects on Cognitive Function

Much of the early data regarding the outcome of patients treated with radiotherapy focussed on improvements in patient survival. More recent studies have attempted to address the question of whether therapeutic radiation exacts a toll on the intellectual development and function of patients. Studies of intellectual development of children treated with central nervous system irradiation (e.g., for brain tumors or leukemia) suggest that effects on intellectual development are more pronounced when irradiation occurs at young ages, particularly under age 7. Two recent studies (46, 47) suggest that this may be true for patients, including those with craniopharyngiomas, treated at an early age with less extensive radiotherapy. Although these studies included other tumor types in addition to craniopharyngiomas, each study demonstrated a measurable effect on cognitive function using intelligence tests. These changes were most marked in children treated at an early age (<5 years of age). These findings suggest that radiation should be administered cautiously to young children (particularly <5 years of age) with craniopharyngiomas. While similar data on changes in cognitive function in adult patients treated with radiation do not exist, it is of interest that no impairment was evident in the older children (46).

Secondary Malignancies

There have been many reports of malignancies following cranial irradiation. The latency of the appearance of these tumors is

long, in most series between 10 and 20 years following treatment. Figure 8 (taken from Ref. 15) lists 45 neoplasms occurring in adult patients irradiated for "benign" intracranial tumors, particularly pituitary adenomas, meningiomas, and craniopharyngiomas. While many cases occurred in patients receiving large doses of radiation, a substantial number occurred in patients receiving acceptable cumulative radiation doses. Despite the gravity of these secondary malignancies, this has to be considered an extremely rare complication of radiotherapy.

Fig 8 *Reported cases of radiation-induced second tumors**

Authors & Year	Initial Tumor	Age (yrs),† Sex	Dose (cGy)	Latency (yrs)	Second Tumor
Terry, *et al.*, 1959	pit. adenoma	26, F	15,825	12	fibrosarcoma
	pit. adenoma	42, M	12,000	5	fibrosarcoma
	pit. adenoma	46, F	13,150	8	fibrosarcoma
Jones, 1960	meningioma	33, M	4000	10	astrocytoma
Meredith, *et al.*, 1960	pit. adenoma	51, F	2052	6	osteogenic sarcoma
Newton, *et al.*, 1962	pit. adenoma	39, F	3910	10	fibrosarcoma
Goldberg, *et al.*, 1963	acromegaly	24, F	?	30	anaplastic epidermoid carcinoma
	acromegaly	30, F	2325	15	hemangioendothelioma
	acromegaly	28, F	3940	10	fibrosarcoma
	acromegaly	31, F	4200	20	sarcoma
Wheelock, 1963	pit. eosinophilic adenoma	50, F	?	12	sarcoma
	pit. adenoma	38, F	?	12	fibrosarcoma
Greenhouse, 1964	acromegaly	24, F	4000	6	sarcoma
Waltz & Brownell, 1966	pit. adenoma	42, M	4500	5	sarcoma
	pit. adenoma	38, M	3500	8	sarcoma
Chang & Pool, 1967	pit. adenoma	?	?	27	sarcoma
Sparagana, *et al.*, 1972	pit. adenoma	50, M	10,037	21.25	osteogenic sarcoma
Rubinstein, 1972	pit. adenoma	32, F	?	18	fibrosarcoma
Bogdanowicz & Sachs, 1974	pit. adenoma	16, F	6114	16	meningioma
Tanaka, *et al.*, 1975	oligodendroglioma	17, F	6600	23	meningioma
Waga & Handa, 1976	craniopharyngioma	23, F	5600	12	meningioma
Amine & Sugar, 1976	pit. adenoma	16, F	5100	10	osteogenic sarcoma
Gonzalez-Vitale, *et al.*, 1976	pit. adenoma	26, M	5000	11	malignant fibrous histiocytoma
Powell, *et al.*, 1977	pit. adenoma	52, M	5000	13	fibrosarcoma
Komaki, *et al.*, 1977	craniopharyngioma	22, M	5400	6	glioblastoma
Robinson, 1978	meningioma	36, M	2750	22	astrocytoma
Ahmad & Fayos, 1978	pit. adenoma	56, M	4092	10	fibrosarcoma
Averback, 1978	pit. adenoma	52, F	5400	1	sarcoma, glioblastoma
	meningioma	36, M	5814	1	sarcoma, glioblastoma
Coppeto & Roberts, 1979	acromegaly	46, M	10,000	8	fibrosarcoma
Preissig, *et al.*, 1979	glomus jugulare	43, M	4480	8	anaplastic astrocytoma
Gerlach & Janisch, 1979	pit. adenoma	?	?	?	sarcoma
Shin, *et al.*, 1980	prolactinoma	56, F	5000	3	fibrosarcoma
Martin, *et al.*, 1980	pit. adenoma	18, F	4500	5	fibrosarcoma
Pieterse, *et al.*, 1982	pit. adenoma	48, M	4500	20	sarcoma
Piatt, *et al.*, 1983	pit. adenoma	25, M	4500	10	glioblastoma multiforme
	acromegaly	38, M	4900	14	glioblastoma multiforme
Nagatani, *et al.*, 1984	prolactinoma	?	?	?	fibrosarcoma
Shi, *et al.*, 1984	pit. adenoma	54, M	5000	8	fibrosarcoma
Kolodny & Dluhy, 1985	pit. adenoma	23, M	4000 +2700 (17 yrs later)	19	meningioma
Pages, *et al.*, 1986	pit. adenoma	23, M	5400	27	fibrochondrosarcoma
Marus, *et al.*, 1986	acromegaly	52, F	4500	6	malignant astrocytoma
Zuccarello, *et al.*, 1986	meningioma	32, M	5600	10	glioblastoma
Shapiro, *et al.*, 1989	pit. adenoma	27, M	9500	22	glioblastoma
	optic glioma	25, F	6300	4	glioblastoma

* Pit. = pituitary; ? = unknown.

† Age at treatment of the initial tumor.

TABLE VI

SURGERY AND RADIATION

Series	# Patients	# Recurrences	Population	Comments
Review (8)	138	30%	A&C	
Calvo (33)	18		A&C	11 alive and well, F/U of 7>5 yrs; 11 mean=3 yrs No complications: VF nor RN; 6 patients reop; 6 irradiated after recurrence
Richmond (20)	12		C(1-20ys)	5Ys=88% 10Ys=44%; good quality of life in survivors
Shapiro (23)	29	11 0	C C	limited resection=22 incomplete resection=7
Sung (22)	31		A&C	5YS 10YS Adults ST 11 91 76 MIN 7 67 67 Children ST 6 100 72 MIN 8 87 87 Postop endocrine deficits-prob related to rad; as many as 50%→late appearance of > deficit; no mention of RN or VS deterior. Mean F/U=4Ys
Bloom (34)	73		C	5YS=92 10YS=84 15YS=79 (70-81: 100/96/96 projected)
Fischer (25)	6	1	C	1 death, progressive disease; school perform-endocrine/ psych prob; radical ± RT; SL better
Danoff (35)	10		C(<20ys)	5YS 6/9 (67%) 10YS4/8 (50%)
Kang (25A)	3	0	C	5YS=100%
Wen (20)	8	0	A&C	5YS-100% best early; poorer later in course; FCI=25%, II=50%, III=12.5%, IV=12.5% 3 postoperative deaths; VA and FC=to surg alone (no worse)
Weiss (26)	5	1	C	median F/U=89 mos (44-155 mos) - Value of postop scan

Cabeduzo (21)	16	1	A&C	avg F/U=6.2Ys for those free of disease; no complications with radiation
Lichter (29)	10	2	A&C	operative complic: 3 CN palsies, 1 panhypopit, 1 sellar abcess, 1 CSF leak; 1 hemiparesis; 1 death due to DZ, avg F/U=10Ys; no mention VF; life quality= 7 good - 2 poor
Hoogenhout (31)	9	1/9(5yr F/U)	A&C	3 postop deaths; rad compli= hypopit, surg complic=1) optic nerve damage, 2) hemiparesis, 3) DI, 4) panhypopit, 5) CSF leak; 5YS=100 10YS=100
		2/8(10yr F/U)	A&C	
Manaka (32)	45 "radical"		A&C	No data on quality of life; both histologic types showed better survival; 5YS-89%; 10YS=76%; no info on complications; even higher survival rate when accounting for decade of surgery

Table VI (cont'd)

Radiation as an Adjunctive Measure. The poor results observed in patients with partial resection alone led to the use of radiation therapy as a adjunctive measurement. The results of series examining its utility are tabulated in Table VI. These series are very heterogenous, derived from the experiences of many different surgeons, a substantial range of radiotherapy techniques, and a confusing spectrum of ways in which the results have been tabulated. If one examines only the average rate of recurrence, this is clearly reduced to a level below that observed with partial resection alone. In those series in which it is available, this decrease in recurrence is correlated with a marked improvement in 10 year (or greater) survival rate. Although some early series suggested that the use of radiation therapy "delayed" recurrence, later series seem to suggest that it actually prevents recurrence in a large number of patients treated in this fashion.

If one accepts that radiotherapy at least delays, if not prevents, tumor recurrence, an important consideration is to determine at what cost is this improvement in prognosis purchased. This is a much more difficult question to answer, as the number of possible undesired events/outcomes is several. In many series only the barest of mention is made of the sequelae of surgery and of radiation therapy. In addition, some possible poor outcomes are impossible to define, as the effects (e.g., cognitive function) would not be known except by comparison to the patient himself prior to treatment. Nonetheless, it would appear that the side effects encountered following modern conventional radiotherapy are infrequent. In this regard it is helpful to remember that we are not looking at the desirability of untoward events, but the alternatives of recurrence and/or death. In this light the drawbacks of radiation appear to be more than counterbalanced by

the reduction in morbidity and mortality due to tumor recurrence in patients treated with radiation compared to those that were not treated with radiation. This difference is evident both in 5 and 10 year survival and in the frequency of tumor recurrence.

Radiation Alone

The number of studies (see Table VII) examining the use of radiation alone in the management of craniopharyngiomas is not as extensive as the number examining surgical versus surgical and radiation. However, the results of several series are quite impressive. Long-term survival of 80% or better is presented in many instances. Peri-radiation mortality is low. Disturbing is the occurrence of a glioma in a series of 21 patients. Despite this, in two of the series examining several therapies (20, 28), this treatment group of patients rated the best in terms of performance status and quality of life. The series include both adults and children, although the latter predominate. In one the two largest series (28), significant bias as to treatment mode used may be present, as the analysis was done retrospectively. In the other series (36), however, radiation was the only treatment method used.

Stereotactic Radiation

Two final methods of treatment have developed at the fringes of the craniopharyngioma therapy controversy. Both involve the delivery of radiation to very focussed locations within the tumor. In the first method, radioactive materials are delivered stereotactically into the cystic structures of the tumor. This permits the delivery of large amounts of radiation to the cyst wall causing involution of the cyst. The second has been popularized using the term "gamma knife" or radiosurgery (16, 17, 38, 39). In this method, a large number of individual radioactive sources are focussed from many different directions onto single or multiple targets. The delivery of this dose from so many different orientations spares all but the focus the full effects of the radiation.

Table VII reports two series using methods of this type. The first by Pollack et al provided encouraging results using the instillation of ^{32}P-colloid into the cystic structures. The followup in this series, however, is quite short. More recent updates on this same series (38) indicate that this approach is not without its complications as one patient became blind.

The last series is that reported by Backlund et al (18) from the Karolinska, where many of these stereotactic techniques have been pioneered. This is an impressive series due to the rational approach that they have applied to 42 consecutive (i.e., unselected) patients and the long followup that they were able to

TABLE VII

RADIATION ALONE

Series	# Patients	# Recurrences	Population	Comments
Richmond (20)	8		C (age 1-20)	5YS=100% 10YS=100% ; Quality of life= "good" in all 8; 6/8 hypopit; 2/8-DI (least complications of used options)
Bloom (34)	73		C	5YS=92%, 10YS=84%, 15YS=79%' Quality of survival good; 90% - no serious neurological deficits, vision good or useful in 82%
Wen (27)	3	1	A&C	5YS=100% One required surgery; no complic at 8,12,13 yrs
Fischer (25)	21	1	C	F/U=10 yrs (7-13); 1 glioma (1/21 deaths) quality of life best of treatment options examined: school perform, endocrine, activity level; no mention of VF probs in any group
Flickinger (36)	21	3	A&C	Mean F/U=9.4 Yrs; 3 died with cyst tap or before XRT completed/no comment VFΔ's endocrine Δ's
Danoff (35)	6		C (<20 y/o)	Aspiration and/or biopsy; 5YS=83%, 10YS=83%; 2 patients →hormonal defect; No assessment of VF; 79% group 1 or 2 perf status (lumped with ST + RT)
		STEREOTACTIC RADIATION		
Pollack (37)	9		A&C	Reasonable outcome - 14-45 mos (mean 27); 2 patients had undergone prior ST resection; increased solid component in one→craniotomy; some visual improvement, some endocrine improvement; 1 patient became blind (prior external beam radiation)
Backlund (18)	42 (consecutive)		A&C	4 deaths; F/U 10-23 yrs; no perioperative deaths; visual Δ's only complic→rare; 2 deaths-Addisonian crisis (1); epilepsy (1); pscychosocial; 79% working; 90% good outcome; endocrine: 68% panhypopituitarism but only 35% had DI

present (only are not available). The approach has employed a combination of intracystic injections and radiosurgery. Although the criteria employed are not discussed in detail, in several cases of very large tumors, surgical treatment and/or radiotherapy were employed. The results of this protocol are shown in Fig. 9 and indicate survival of 86% with followup of at least 10 years. Visual field evaluation pre- and postoperative showed dramatic declines in visual acuity in two eyes. In the remaining cases, visual function was preserved or improved. Perhaps the most impressive feature of this study (19) is the assessment by these investigators of the effects of their treatment on the lives of their patients. 79% of patients were gainfully employed and only two of the 31 surviving patients had gross neurological or intellectual deficits.

Fig 9 *Treatment Modalities and Total Outcome.* A. Intracystic isotope (Yttrium-90). B. Stereotactic external single dose irradiation. C. Surgical removal. D. Conventional radiotherapy (linear accelerator).

Modality	N	Alive and well	Death due to tumour	Death, intercurrent disease
A	17	14	–	3
B	4	3	–	1
A and B	4	4	–	–
A and C	4	2	2	–
A and D	1	–	1	–
C	9	8	1	–
D	1	lost for follow-up		
C and D	2	–	2	–
	42	31	6*	4**

* All tumours large/huge, polycystic (Type II), failure rate in 10–23 years perspective: $^{6}/_{42}$ = 14.3%.

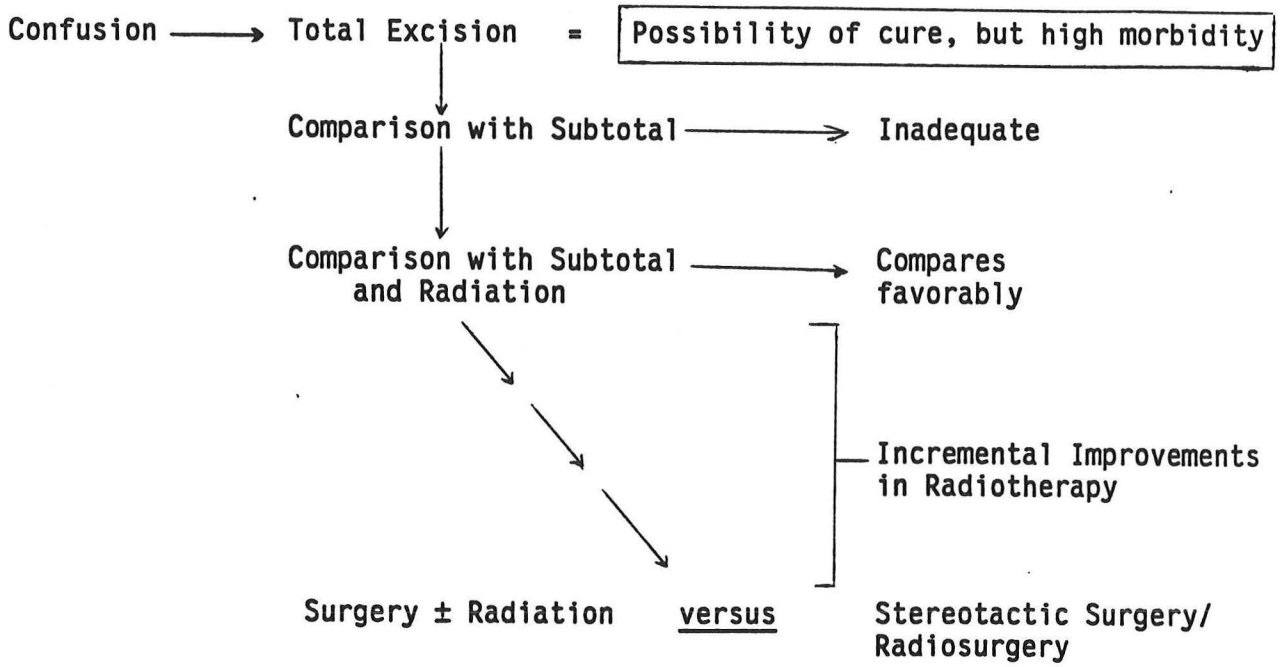
** Autopsy: No recurrent tumour (3), "suprasellar cyst" (1).

MANAGEMENT OF THE PATIENT WITH CRANIOPHARYNGIOMA

Much of the controversy surrounding the management of patients with craniopharyngioma relates to the fact that the tumor is critically situated and is not readily resectable. Equally important, perhaps, is the realization that the therapies are evolving - the series available for analysis today represent work initiated ten or more years ago. In that space of time, technical advances both in the realm of imaging techniques and radiotherapy have further modified the diagnostic and therapeutic possibilities.

Figure 10

Evolution of the Treatment of Craniopharyngioma



This review of the literature permits several conclusions to be reached:

1) When technically feasible, a total excision should be performed. Extreme caution should be exerted in order that this only be attempted in instances where this goal does not place any critical structures at risk.

2) Radiation treatment appears to have a substantial effect on the regrowth of tumors in patients in which subtotal resection is accomplished, using conventional doses (5000-5500 rads) in fractions not to exceed 180-200 rads/dose. These doses appear to carry minimal risk to the visual tracts and to the surrounding brain parenchyma.

3) The exact timing with which radiation must be administered is not clear. In only one series (26) was mention made of the ability to predict recurrence based on the immediate post-op scan. In some series, it has been suggested that radiation in the early post-operative period improved outcome (27), but this trend is not consistent among all series. It would seem reasonable to monitor all patients in which total resection had been believed to be accomplished with serial MRI's or CT's and to administer radiotherapy should any evidence for recurrence become evident. Patients in whom only subtotal excision is accomplished should receive adjunctive radiation treatment.

4) Patients treated surgically to remove craniopharyngiomas will have a high frequency of diabetes insipidus, requiring the administration of ddAVP for life. Most patients will require treatment for deficiencies of one or more anterior pituitary hormones. Those patients receiving radiation therapy, alone or as an adjunctive treatment, who do not demonstrate panhypopituitarism at the outset will need to be closely monitored to detect the appearance of new hormonal deficiencies, particularly thyroid hormone and glucocorticoids. Even in several of the recent large series, one or more patient deaths are attributed to Addisonian crises.

5) It would appear that stereotactic manipulations and irradiation probably have a role in the management of craniopharyngiomas. Further experience with larger numbers of patients will be required to determine whether these methods can supplant the combination of surgery and conventional radiotherapy.

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