8 Meningiomas and Meningeal Tumors

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8.1 Definition

Meningiomas are tumors arising from the arachnoidal coverings of the brain [64]. They are responsible for the vast majority of meningeal tumors and occur anywhere on the brain surface including the skull base and rarely also in the ventricular system.

Other than meningiomas, hemangiopericytomas and meningeal sarcomas belong to the group of mesenchymal, non-meningothelial tumors [4]. As with every other tissue, metastases and lymphoma can also occur in the meninges.

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8.2 Epidemiology

Epidemiological data for most tumors of the central nervous system are difficult to obtain as cancer registries tend to be regional or at best national as in the Scandinavian countries [16]. A very comprehensive source is the statistical report published by CBTRUS (Central Brain Tumor Registry of the United States) of which the latest 2017 edition covers the data collection time of 2010–2014 [60].

Meningiomas show a rising incidence with age. In unselected autopsy series, 2.7% of the male and 6.2% of the female population over the age of 80 have meningiomas which up to that point were undiscovered. The reported incidence is variable between different investigations but disregarding the changing proportions from the growing incidence of cerebral metastases with better oncological therapies; one can assume that meningiomas are responsible for about 15% of all male intracranial tumors and 30% of the females. Meningiomas make up 36.8% of the gross total of adult tumors of the CNS [60]. Not considering the autoptic cases, the numbers which are reported on a population base vary between 1.6 and 5.5 per 100,000. CBTRUS reports an age-adjusted incidence rate of 8.41 per 100,000 of the US standard population and 0.25 for the age group up to 19 years demonstrating the relation to age [60] . As a rule the tumors are reported to be 1.5–3 times more frequent in

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Table 8.1 Meningiomas in an unselected departmental series over 10 years ($N = 679$)[a]

Location	*n*	Histology[b]	*n*	Age	*n*
Convexity	291				
Skull base	153				
Posterior fossa/tentorium	93				
Orbit	28				
Ventricular	5				
		Meningiotheliomatous	250		
		Fibrillary	142		
		Transitional	163		
				0–30 years	35
				31–50 years	190
				51–70 years	361
				71–90 years	93

[a]Courtesy of P. Emami, Dept. of Neurosurgery UKE
[b]The three most frequent histological subtypes

females. In the 2010–2014 period, the rate given by CBTRUS is 4.86 for males and 11.01 for females showing an increase over the years which however may be a reflection of broader availability of and access to diagnostic procedures as well as a reflection of an aging population with growing life expectancy. Peak incidence is the sixth decade in life (median age at diagnosis at CBTRUS is 66 years). Pediatric meningiomas are very rare making up 6.7% in the age group between 0 and 19 years in this report [60] with others putting the number as 2% of all tumors in that population [62].

There does not seem to be any association with race or any geographical preference which cannot be explained with access to medical care or pattern of reporting.

An unselected 10-year series from the university department of neurosurgery in Hamburg reflects these demographics with a female/male ratio of 507:172 (2.9:1) (Table 8.1).

8.3 Molecular Genetics

The majority of patients who suffer from neurofibromatosis type 2 (NF2) develop meningiomas [46, 48, 73]. In sporadic meningiomas *NF2* gene mutations are detectable in up to 60% and thus represent the most frequent gene alteration. The *NF2* tumor suppressor gene is located on chromosome arm 22q, and mutations in one allele are typically associated with either monosomy 22 or large deletions involving the other allele. Absent or strongly reduced immunoreactivity of the NF2 gene product merlin (schwannomin) has also been demonstrated in meningiomas. Merlin belongs to the 4.1 family of structural proteins that link the cytoskeleton to proteins of the cytoplasmic membrane. Recently, another member of this family, the 4.1B/DAL-1 protein, has been implicated in meningioma pathogenesis. 4.1B/DAL-1 expression is lost in 70–80% of meningiomas. No mutations were detected in the *4.1B/DAL-1* gene which is located on chromosome arm 18p. However, loss of heterozygosity (LOH) involving the *4.1B/DAL-1* region on 18p was identified in 70% of meningiomas [45].

Inactivation of the *NF2* and *4.1B/DAL-1* genes occurs with approximately equal frequency in benign (WHO grade I), atypical (WHO grade II), and anaplastic (WHO grade III) meningiomas, suggesting that both represent relatively early events in tumorigenesis. In contrast, several other most likely random genetic alterations have been identified more frequently in the more malignant tumor forms and are therefore believed to be associated with meningioma progression [91]. In the approximate order of their frequency, these alterations are allelic losses on chromosome arms 1p, 14q, 10q, 9p, and 17q. However, with the exception of the *CDKN2A*, $p14^{ARF}$, and *CDKN2B* genes on 9p which display alterations in the majority of malignant meningiomas and spell for particularly shortened survival ([61], no other tumor suppressor genes could consistently be

identified as altered in meningiomas. Recent mutations found in NF2-intact meningiomas affect the AKT1 (involved in PI3K signaling), SMO (Hedgehog activation), KLF4 (transcription factor), and TRAF7 (a ubiquitin ligase) genes [17]. Interestingly these meningiomas were found to be clinically more benign and stable and appeared to have a preference for the medial skull base. Another new mutation affecting the TERT promotor seems to be associated with highly aggressive biological behavior [75].

Gene expression analyses by array-based techniques have been used also in meningioma research and in a series where spinal and cranial meningiomas were compared that way; a distinct set of 35 genes distiguishing between these entities was identified [76], but as such there are no surprising new insights from microarray techniques in the analysis of meningioma.

8.4 Etiology and Prevention

Meningiomas should be considered spontaneous tumors. Very early they have been found to be associated with a complete or partial loss of chromosome 22 [90], but that has so far not provided any clues as for the origin of these tumors. The only established association is with ionizing radiation, and that has been obtained from the large series of immigrants into Palestine in the early 1950s who were regularly irradiated for tinea capitis and then had a much higher than normal incidence of meningiomas with a delay of about 35 years [74]. Likewise has the follow-up from citizens of Hiroshima and Nagasaki who were exposed to the atomic blasts shown that in this population, there was a higher incidence of meningiomas with a very similar delay [65]. The doses producing meningioma with this long delay are to be considered rather low as high doses of therapeutic radiation for neoplasm produces meningiomas with a shorter delay (around 5 years [84]) or rather induces anaplastic gliomas. The indications about the role of diagnostic exposure to radiation are most likely limited to specific dental procedures [49].

As meningiomas occur most frequently in postmenopausal women [85] and meningiomas are known to have high levels of steroid hormone receptors, it has been attempted for a long time to establish a relationship between steroid hormones and the growth of meningiomas [33, 35]. The only vague association comes from the observation that, in some cases, meningiomas which had gone undetected became symptomatic during pregnancy [90] (Fig. 8.1) and even grew so rapidly that they spontaneously hemorrhaged (personal observation). In that context there is a constantly ongoing debate whether women who are known to have a meningioma or have had a meningioma removed should be on hormonal replacement therapy. Currently there does not appear to be a risk in respect to contraceptives, but there is a hint

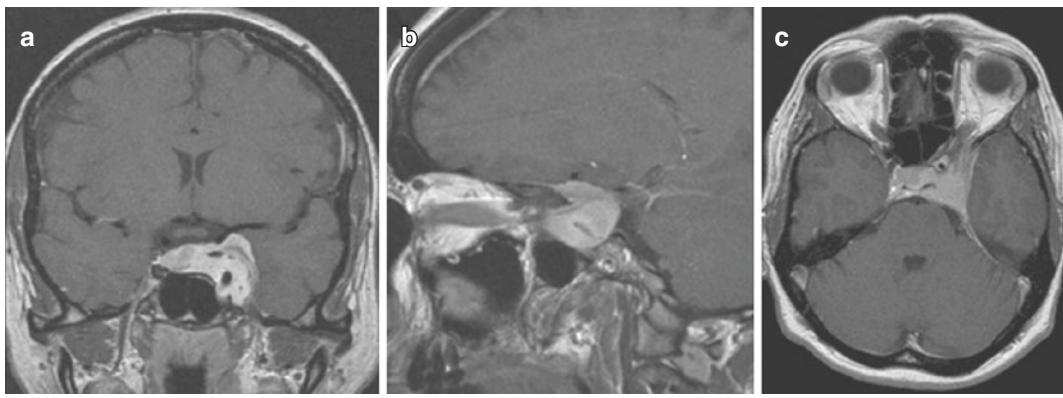

Fig. 8.1 Cavernous sinus meningioma of a 30-year-old woman (**a**–**c**) which during two pregnancies caused transient visual problems on the left eye. Despite extension into the sellar lumen (**a**), there is no endocrine dysfunction. The tumor has been biopsied and is under observation with the option of radiotherapy in case of progressive symptoms

of an indication that hormonal replacement therapy may increase the risk for meningioma [18]. As, however, no study has been done up to date in which the use of steroid replacement has been evaluated in a randomized controlled prospective fashion in these patients and likely never will be, the management of these patients will remain in the hands of individually deciding physicians who have to closely observe the patient and decide what is best. More recent studies failed to demonstrate any hormonal clues in women [20] and in men found that estrogen-like dietary components of soy and tofu are somewhat reducing the risk, while a high body mass index is associated with a higher incidence of meningioma [78]. A considerable number of meningiomas express progesterone receptors; however proliferating cells shut down the receptor which explains the failure of anti-progesterone therapies in meningiomas [21].

There is a weak indication that there may be an inherited susceptibility as in one epidemiological study, a first degree relative with a meningioma increases the risk 4.4-fold to also develop such lesion [19].

8.5 Signs and Symptoms

There are no typical signs or symptoms which are unequivocally specific for meningiomas. The clinical symptomatology is basically determined by the location of the lesion, the size, and the impact on its immediate surroundings. For clinical purposes, meningiomas are subspecified according to their site of origin, and this classification allows the description of the most frequent signs associated with the typical locations (Table 8.2).

Table 8.2 Symptoms of meningiomas according to location

Location	Typical symptoms
Convexity	
Frontal	Affective disorders
Parietal	Seizures
	Motor or sensory disorder, hemiparesis
Temporal	Speech disorders, memory impairment
Parasagittal	Seizures
	Motor or sensory disturbance
Olfactory meningioma	Loss of olfaction
	Affective disorders
	Loss of activity
Tuberculum sellae meningioma	Visual field or visual acuity loss
Clinoid process meningioma	Visual field or visual acuity loss
Cavernous sinus meningioma	Diplopia
	Facial pain or numbness
	Ocular venous congestion
Optic sheath meningioma	Loss of vision
Orbital meningioma	Exophthalmos
Sphenoid wing meningioma	
Medial	Loss of vision, diplopia
	Psychomotor seizures
	Schizoaffective disorders
Lateral	Seizures
	Speech problems
Tentorial meningioma	Hydrocephalus, seizures, visual field loss
	Ataxia
Cerebellar meningioma	Ataxia, vertigo, hydrocephalus
Foramen magnum meningioma	Hydrocephalus, symptoms of dorsal, lateral or ventral brain stem compression
Cerebellopontine angle meningioma	Unilateral cranial nerve dysfunction
Petroclival or clivus meningioma	Unilateral or bilateral cranial nerve dysfunction and symptoms of ventral brain stem compression
Ventricular meningioma	Partial hydrocephalus

The direct symptoms also depend very much on the size of the tumor and the growth rate. Large tumors which have grown over many years may have produced only very few symptoms because the surrounding brain had a chance to adapt while slowly becoming displaced (Fig. 8.2). In cases of caudal skull base meningiomas, this may lead to extreme brain stem compression without almost any symptoms (Fig. 8.3) or in the case of perisellar meningiomas absence of endocrinopathies. Meningiomas also differ in their respect for the arachnoidal boundary, independent of size. As arachnoid infiltration is related to edematous brain reaction, tumors respecting the arachnoid tend to be larger because of lack of brain reaction.

Seizures may be a presenting sign and were seen in 22.7% of patients preoperatively in one large series [15]. Seizures are more frequent in the typical ictogenic regions, particularly when lesions extend exophytically into the temporomesial region or the perirolandic area.

There are many ways for meningiomas to also indirectly affect the brain and produce symptoms. Meningiomas at the tentorial edge, be they supra- or infratentorial, can lead to compression of the CSF pathways and thus result in occlusive hydrocephalus as do large meningiomas in the posterior fossa (Fig. 8.4). Meningiomas which produce an extraordinary amount of edema (frequently of the secretory type [10, 55]) cause an indirect mass effect exceeding their own mass severalfold and can cause drowsiness and even loss of consciousness up to the extreme of herniation (Fig. 8.5). Meningiomas occluding a major sinus such as the falcine meningiomas or parasagittal meningiomas or those of the torcular or transverse sinus can cause venous congestion and generalized edema to the extreme of chronic intracranial hypertension with papilloedema and impairment of visual acuity and the development of pseudotumor cerebri especially when the occluded sinus is dominant (Fig. 8.6a, b). It is

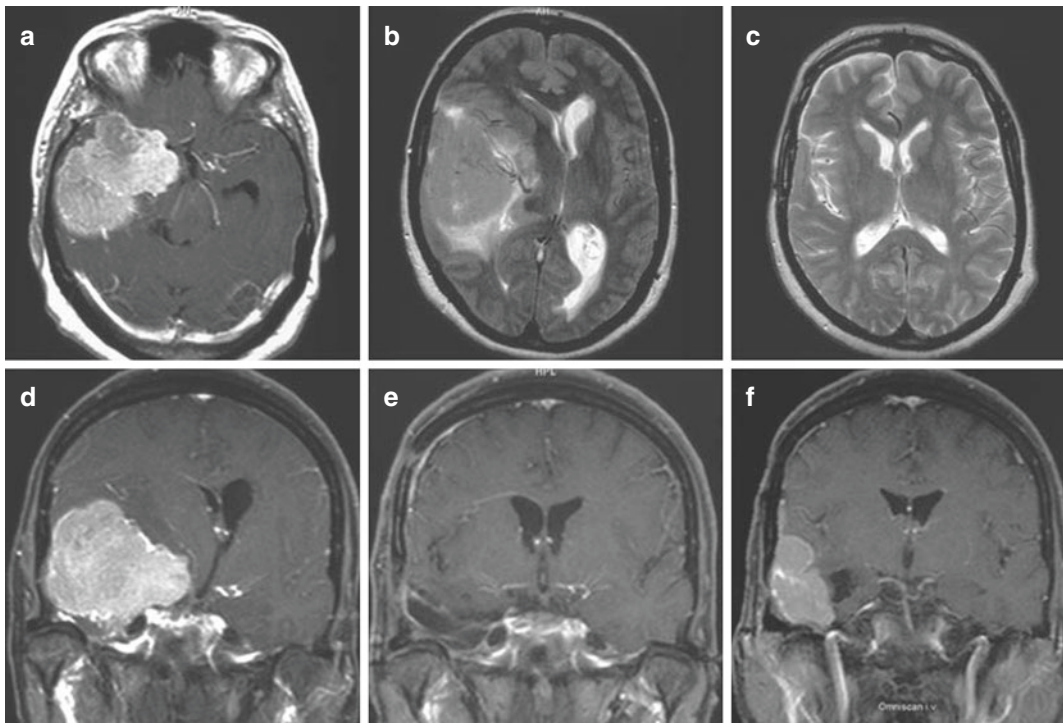

Fig. 8.2 Large temporal meningioma with impressive midline shift but no specific symptoms (**a**–**c**). The diagnosis was made after lack of concentration and inability to complete simple tasks in daily life lead to cranial imaging. Despite the appearance of encased large vessels, the tumor was completely removed without any deficits (**d**, **e**). The minimal perilesional edema was reflected by a good dissection plane over most of the tumor surface. The definitive diagnosis being an atypical meningioma, the tumor recurred with more extensive perilesional edema 4 years later (**f**)

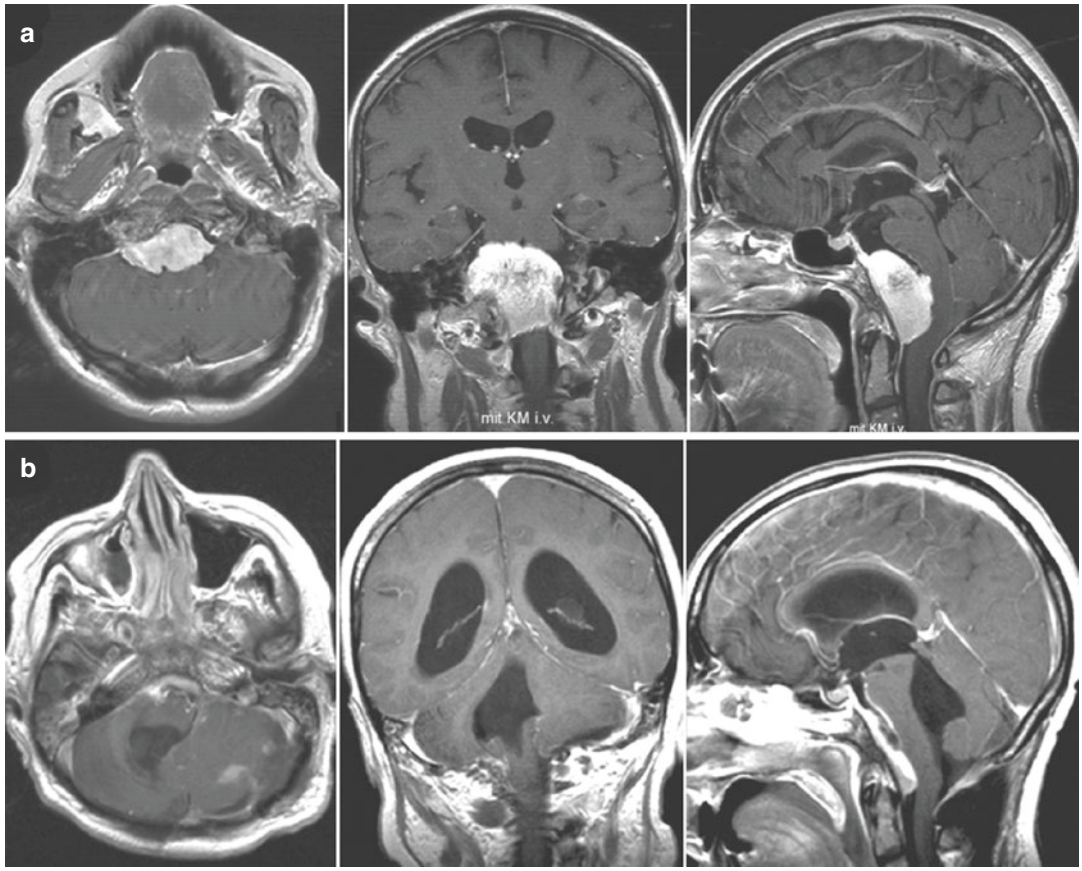

Fig. 8.3 Large meningioma of the clivus extending mostly into the right CP angle (**a**, upper panel). The removal required approaches from both sides because of encasement of the caudal cranial nerves on both sides. The dura of the clivus was completely invaded and was left in place after extensive coagulation (**b**). The course has been stable with no indication of growth of the possible extradural tumor layer seen at the level of the foramen magnum (bottom right). Postoperatively the patient developed a malresorptive hydrocephalus which required shunting

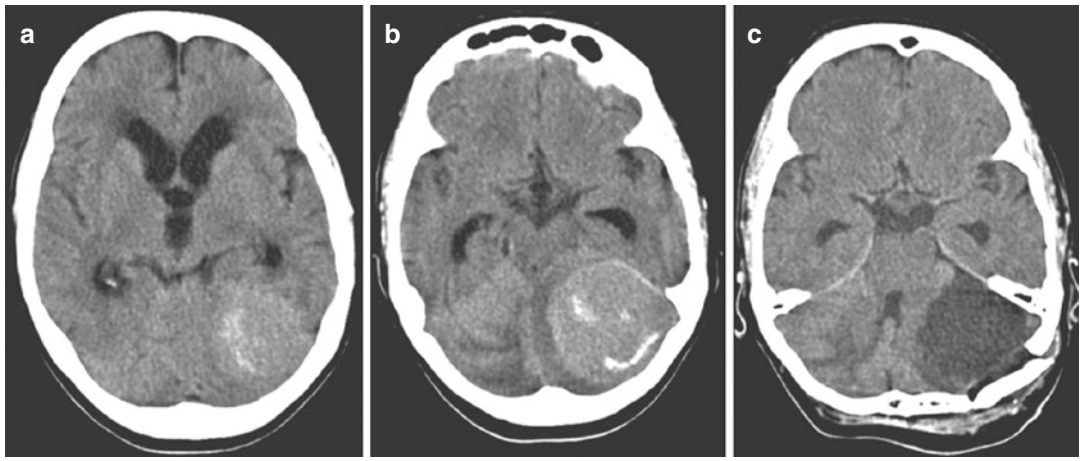

Fig. 8.4 CT of a large meningioma in the posterior fossa which has over months leads to occlusive hydrocephalus which is seen to result in distended temporal horns and periventricular capping over the frontal part of the lateral ventricles (**a**, **b**). A few days after removal, the fourth ventricle is again visible, and the temporal distension is slowly regressing (**c**)

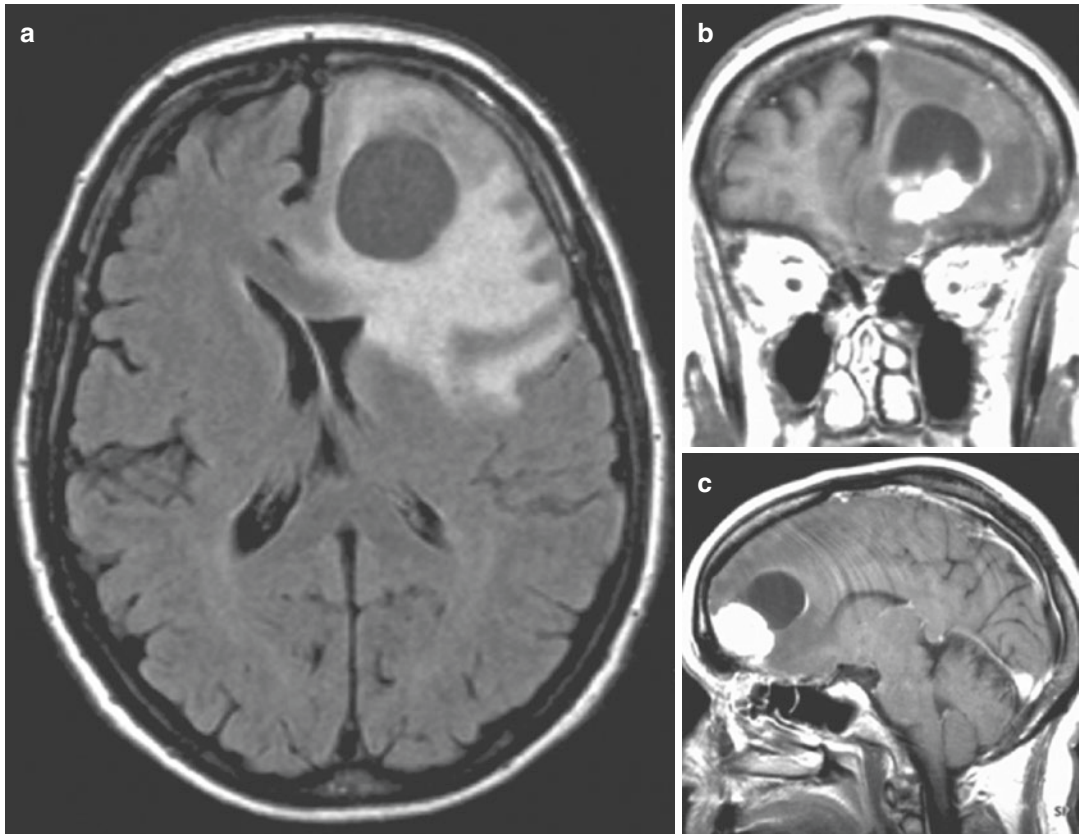

Fig. 8.5 MRI of a patient with a massive edema (**a**) resulting from a cystic meningioma of the secretory type (**b**, **c**). As seen in the T2 images (**a**), the amount of space occupation is mostly due to the edema and not so much due to the mass effect of the tumor

frequently seen that even after complete resection of a meningioma, an edema-like change in signal intensity in the MRI can remain for many years (Fig. 8.6).

It is a general rule that the risk of surgical treatment of a meningioma can be very well assessed when neurological deficits are related to edema. When appropriate treatment with steroids (see below) causes symptoms to dissappear, the surgery will be much less likely to result in additional or increased neurological deficit than when the symptoms persist despite edema resolution.

8.6 Staging and Classification

As described in the chapter on histopathology of CNS tumors, meningiomas are graded according to the WHO grading system into well-differentiated meningiomas of the WHO grade I, atypical meningiomas WHO grade II, and anaplastic meningiomas WHO grade III. According to the most recent revision of the WHO classification system, brain invasion alone qualifies for classification as WHO grade II [62]. In addition there are several subtypes of which two in themselves are equivalent to a higher grade [63]. Due to serially acquired genetic aberrations, progression from a lower grade to the next higher grade is possible [46] (Fig. 8.7a) but rare, and that is also accompanied by increasing production of angiogenic factors [47] and the late incidence of metastasis in the situation of anaplastic meningioma [39]. Meningioma may become a chronic disease in some patients spreading throughout the cranium including the skull bone and spread also to extracranial sites like the spine (Fig. 8.7b).

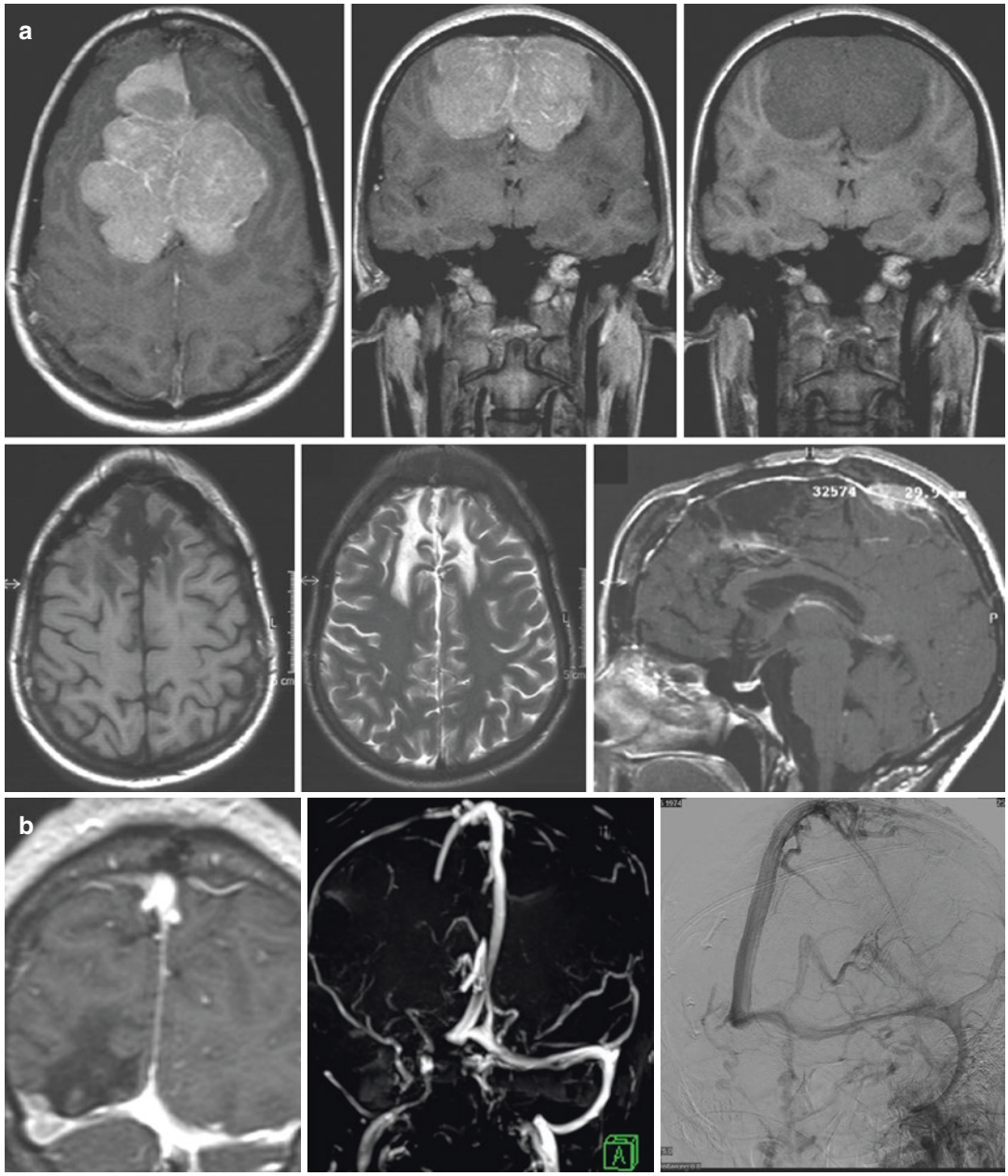

Fig. 8.6 (**a**) Very sharply demarcated bilateral falx meningioma of a 28-year-old woman who had papill-edema and developed optic nerve atrophy from constant pressure. The sinus was removed in its occluded parts. The edema which was present only in the most central aspects around the tumor was still present 5 years after follow-up (top) at which time also a recurrence was seen in the distal part of the sagittal sinus (bottom) which was eventually resected as well as further recurrences toward the frontal as well as the dorsal aspects. (**b**) Progressive meningioma of the wall of the right transverse sinus (left) which despite radiosurgery to that aspect continued to occlude the sinus which could not be removed because of stenosis and partial thrombosis of the contralateral left sinus (MR angiogram middle panel) so that eventually venous congestion as seen by the massive collaterals towards the cerebellar veins and occipital bridging veins seen upon digital subtraction angiography (right panel) became so severe that pseudotumor cerebri required permanent ventriculoperitoneal shunt

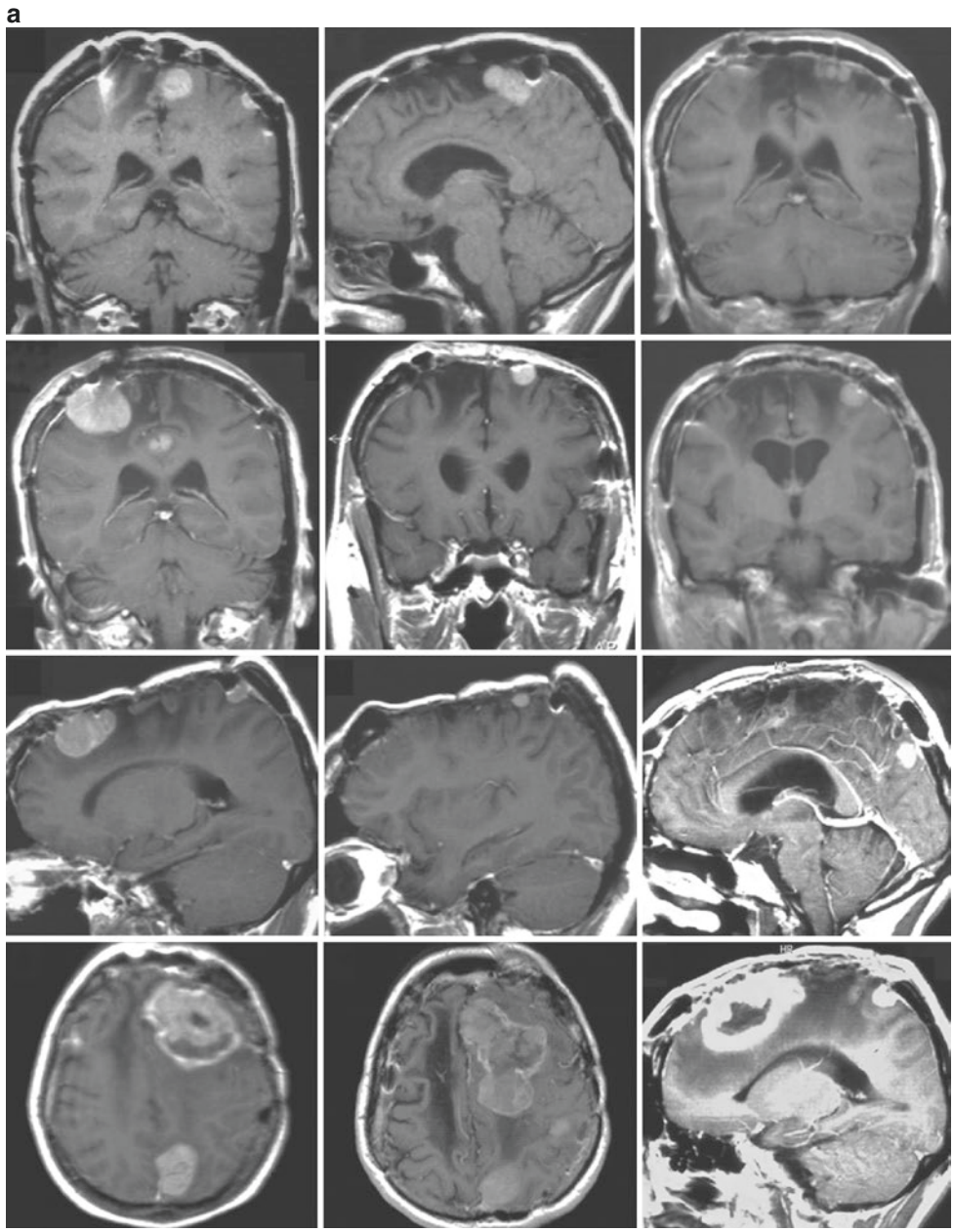

Fig. 8.7 (**a**) Progressive dedifferentiation of a meningioma which was originally operated in 1978. Altogether six operations with increasingly difficult wound conditions followed for recurrences occurring at increasingly short intervals (top two rows). This was correlated to accumulation of additional genetic alterations. After the removal of the bone flap had become necessary and a cranioplasty was placed in the context of further recurrences (third row of panels) the patient received radiosurgical treatment (fourth row) whereupon the lesions rapidly expanded with the development of a steroid dependence and with further progression and severe disability, the patient declined any further treatment in 2003, after 25 years of struggle with a clinically increasingly aggressive meningioma. (**b**) Multiple recurrences of a chronic meningioma disease in a 75-year-old female after 15 years and several resections (left two panels). Sensory and motor radicular symptoms of C7 and C8 beginning on the left side lead to the diagnosis of spinal involvement (middle panel sagittal MRI showing the extensive bone involvement) which was histologically proven to be meningioma with epidural filling of the neuroforamen (right panels) as well as bone infiltration. Due to frail health, the overall situation deteriorated rapidly, and no measures were taken beyond palliation

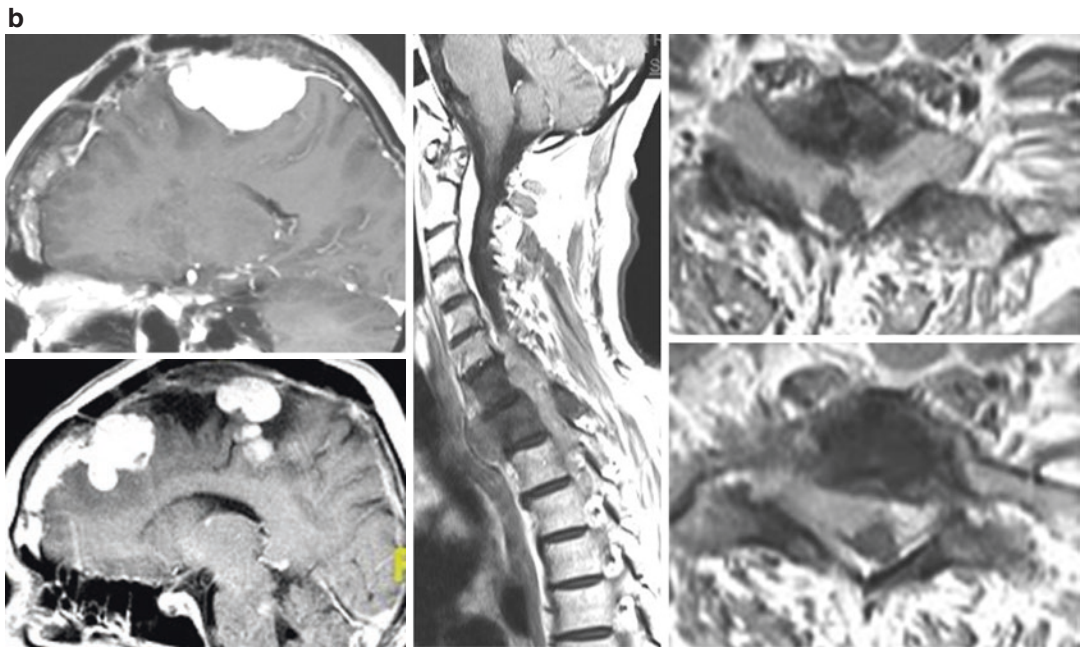

Fig. 8.7 (continued)

Although it would be desirable to clinically stage meningiomas for the extent of the disease, chronicity, or the aggressiveness of the tumor, such distinction is lacking. But there is a classification for the resection (see below). The significance of the histological grading is related to the decision-making for adjuvant therapies (see below) and the follow-up regimen. In general there is a correlation of the grades with survival but only when the tumors are in comparable locations and similar extents of resection can be achieved. On the other hand, there is a much better prognosis for a completely resected atypical meningioma (WHO grade II) of the convexities compared to a non-resectable meningioma grade WHO I of the skull base (Fig. 8.8).

8.7 Diagnostic Procedures

Many meningiomas are found incidentally because of unrelated complaints such as a dizzy spell, a transient ischemic attack, and uncharacteristic headache or because after a minor trauma, an MRI has been performed (Fig. 8.9). Otherwise any of the symptoms summarized in Table 8.2 above may have specifically led to some kind of neuroimaging. Recently, guidelines for diagnosis and therapy of meningiomas have been published [29].

Computed tomography (CT): CT shows meningiomas usually as well as described mass lesions with uniform contrast enhancement located at the surface of the brain, either at the convexity or the base of the skull. A non-enhanced scan must be obtained in the first place because it may show extensive calcification which is mostly associated with very slow growth and thus only relative indications for therapy. Especially in fronto-orbital tumors, it is important to have thin sections and a series of bone windows because that defines the borders of infiltration and resection if not even resectability. CT is the optimal modality to assess intraosseous components of frontobasal skull base meningiomas (Fig. 8.10) or to detect primary intraosseous meningiomas (Fig. 8.11). The extent of edema is shown equally well in CT and MRI.

Magnetic resonance imaging (MRI): MRI is the major modality for the diagnosis of meningiomas, especially as many lesions have some skull

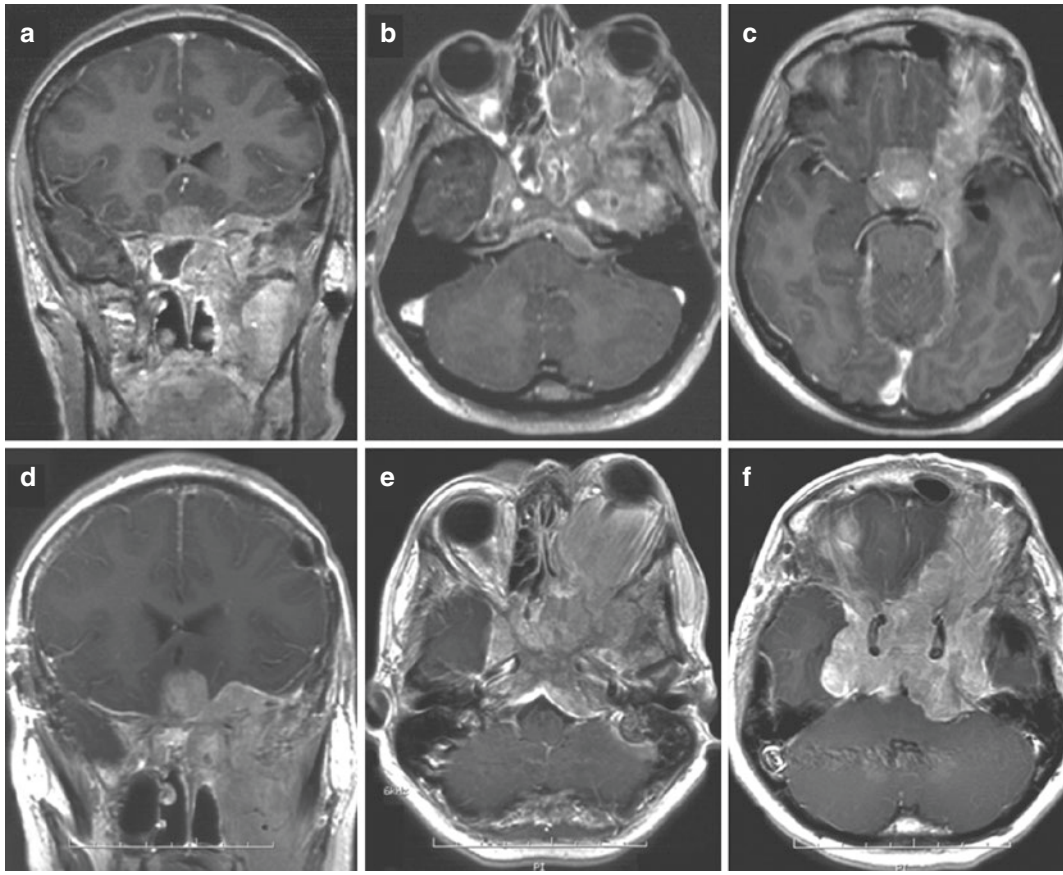

Fig. 8.8 Surgically not manageable, extensive fibrillary meningioma WHO I of the skull base (**a**–**f**) which was partially decompressed twice to save vision on the right eye. The tumor was rapidly progressive and failed radiosurgery, bromocriptine, anti-progesterone and hydroxyurea tratments

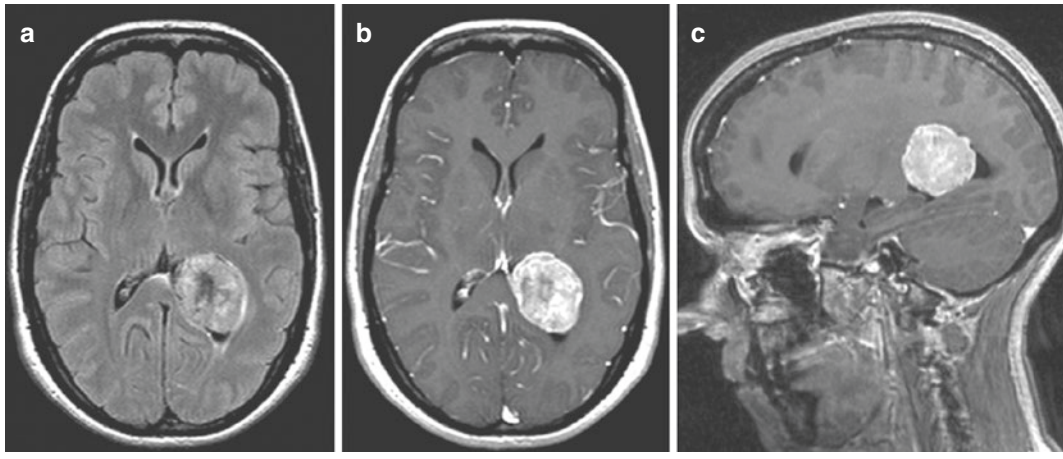

Fig. 8.9 MRI in three planes of a ventricular meningioma which was diagnosed because of intermittent headache which is completely nonreactive in the brain. The intact, non-invaded ependymal surface allowed for unrestricted CSF passage so that not even a partial hydrocephalus had developed

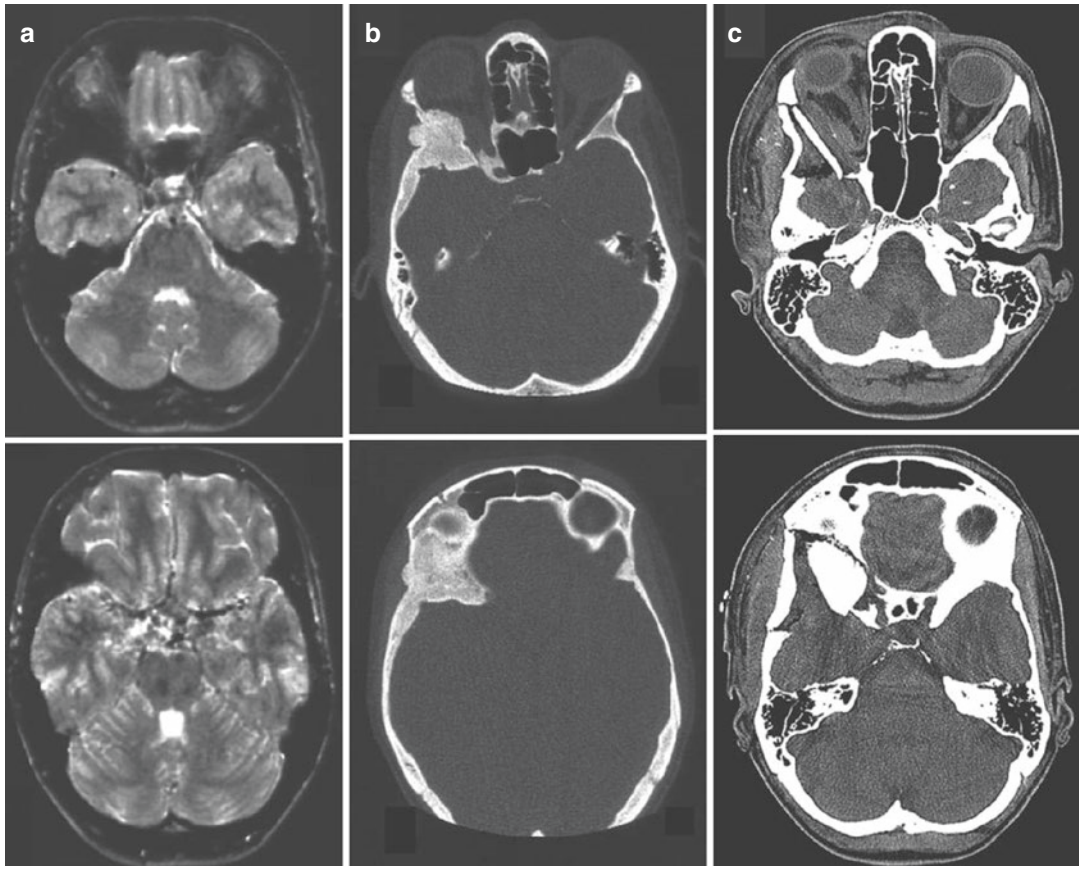

Fig. 8.10 Osseous meningioma of the lateral sphenoid wing, completely taking up the lateral wall of the orbit (**a**, **b**). No soft tissue components are present. Removal requires extensive drilling of the bone and decompression of the optic canal. The bone is reconstructed with methyl methacrylate providing an orbital roof (**c**) and a lateral wall (right bottom)

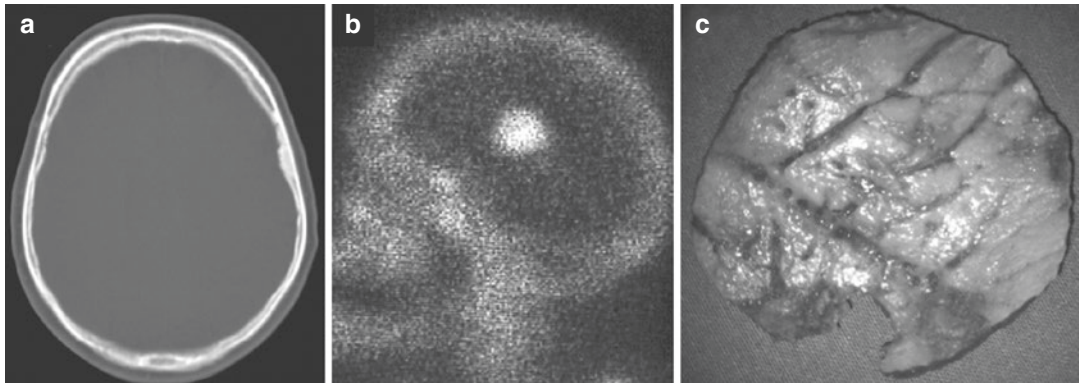

Fig. 8.11 Primary intraosseous meningioma (**a**) which was found because of a staging for prostate carcinoma involving a whole skeletal scintigraphy (**b**). The only sign of the tumor was a slight thickening of the bone and a changed bone structure. The tumor itself could be seen as pale sclerotic bone (**c**). The dura underneath the tumor was completely free of tumor and unreactive. There was no indication for any metastatic involvement

base component or extensions into compartments which are not as well visualized or differentiated in the CT. Again, the mass of the tumor will show homogeneous contrast enhancement, but also tail-like extensions in the meninges will be seen (the so-called "meningeal tail sign" (Fig. 8.12) and infiltration of neighboring structures such as the sinuses). Meningiomas of the medial skull base can be assessed whether they are limited to the cavernous sinus or, for example, can be assessed anatomically for their complex extension towards the optic canal or into the cerebellopontine angle (Figs. 8.13 and 8.14) which leads to various degrees of brain stem compression and is extensive in typical petroclival meningiomas. The carotid artery which is regularly encased by

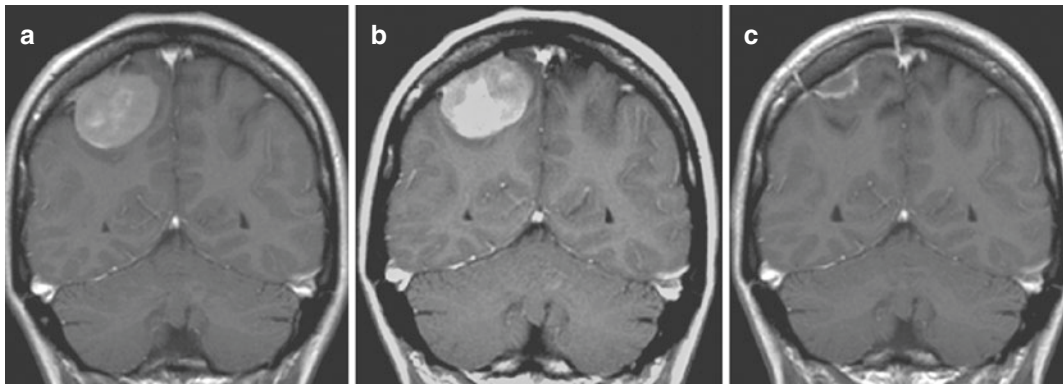

Fig. 8.12 Typical convexity meningioma with the broad dural attachment which extends further than the tumor (meningeal tail sign). Removal of the tumor (right) should include all the infiltrated zone which is to be replaced with periosteum

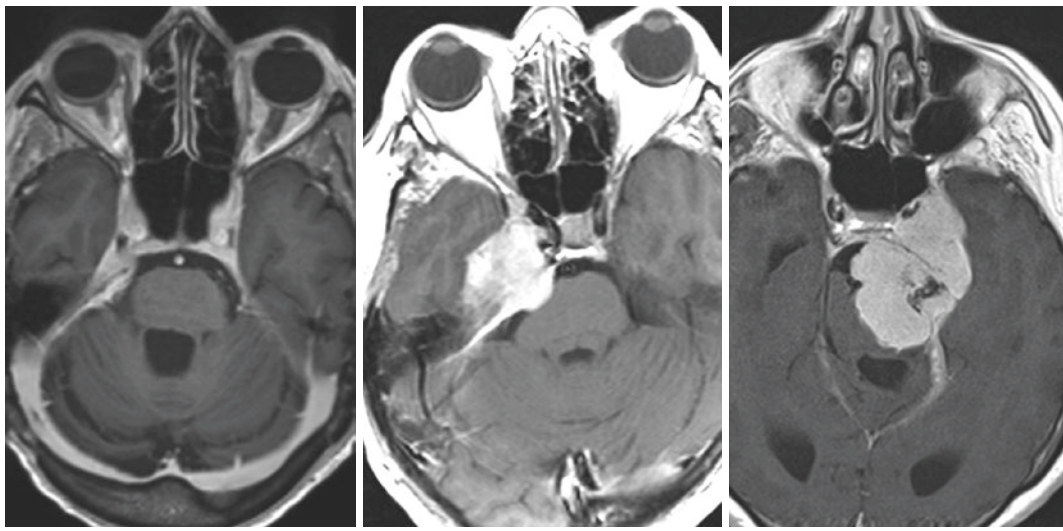

Fig. 8.13 Three examples of meningiomas involving the cavernous sinus. The lesion limited to the cavernous sinus (left) is an a priori nonsurgical lesion and will only be considered for radiation therapy when symptomatic and when discovered incidentally be followed with MRI. A lesion extending into the middle and posterior fossa (middle panel) will require treatment because of cranial nerve symptoms and affection of the brain stem. The strategy can be a combination of reductive surgery and radiation (Fig. 8.14). When expanding for a long time (right panel), the petroclival aspect warrants extensive resection to decompress the brainstem

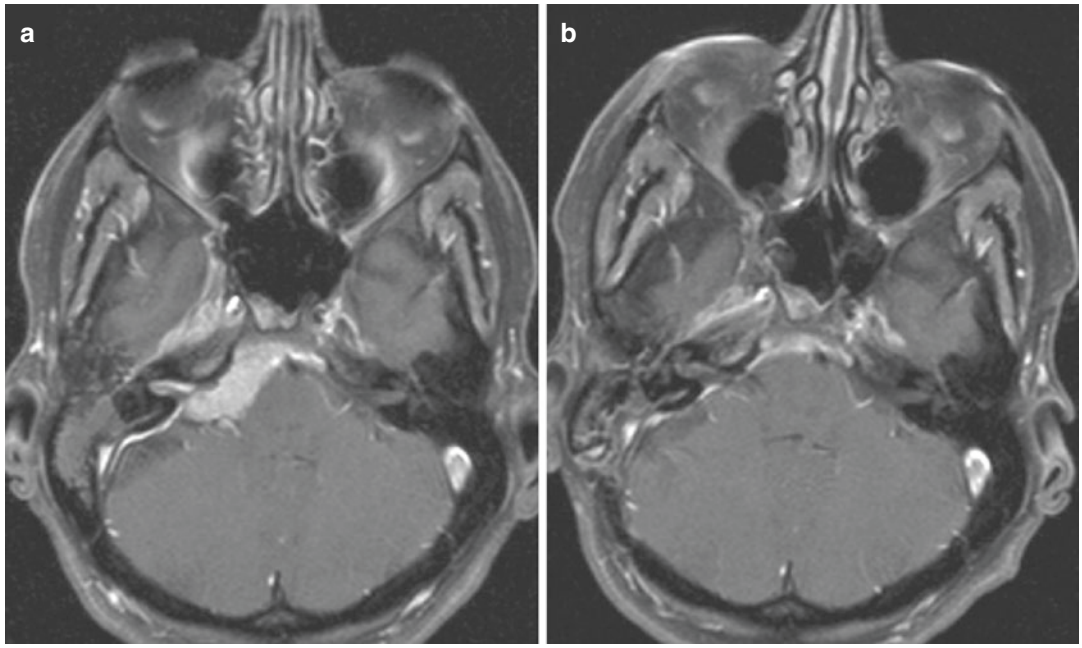

Fig. 8.14 (**a**) Extensive, non-resectable meningioma of the clivus, CP angle, cavernous sinus, sellar lumen, and jugular foramen with extracranial extension (partially not shown). (**b**) Removal of the intracranial parts to decompress the brainstem and free the cranial nerves together with coagulation of the clival and posterior petrosal dura was performed, and the whole residual has been irradiated by fractionated stereotactic radiation

petroclival meningiomas can be judged for its width and shape and patency. When considerable narrowing is present, a "time to peak" analysis after gadolinium application comparing the timing of gadolinium arrival in the two hemispheres already allows to estimate the hemodynamic relevance of the stenosis and indication for bypass surgery (Fig. 8.15). Frontobasal meningiomas are occasionally not much more than a thin layer of contrast enhancement and that is especially true for optic sheath meningiomas which other than on thin-sliced MRI with special attention to all three planes will be missed (Fig. 8.16). When close to a sinus or originating from a sinus wall, extension of the tumor into the sinus or patency of the sinus can be seen on T2-weighted images and MR angiography (Fig. 8.17).

Some differential diagnosis at first imaging is to be considered. In the first place, meningiomas may be taken for a solid metastatic lesion because the age groups with the peak incidence overlap. Clues to decide for meningioma would be the extent of dural involvement and especially a reaction of the bone-like hyperostosis (Fig. 8.18). Meningiomas may also occur in multiple locations in the same patient (Fig. 8.19), but multiplicity is much more common in metastasis, and for three metastatic lesions, it would be very unusual to have all of them on the surface of the brain. Metastases also tend to be cystic from necrosis after a certain size. In patients with a known neoplastic disease, direct metastasis to the meningioma is possible and has to qualify any reservation about surgery in an incidental finding. Most common intrameningiomatous metastases are from mammary carcinoma [77] and second most are from the lung [69].

In tumors over 1 cm^3, MR spectroscopy is an additional tool which shows a characteristic spectrum of metabolites which can provide an increasingly reliable estimate of the nature of the lesion [26]. Diagnostic pitfalls are the rare cystic meningiomas which are from their appearance like a pilocytic astrocytoma or a cystic metastasis (Fig. 8.5).

Angiography: This diagnostic tool is only used to answer specific questions related to the

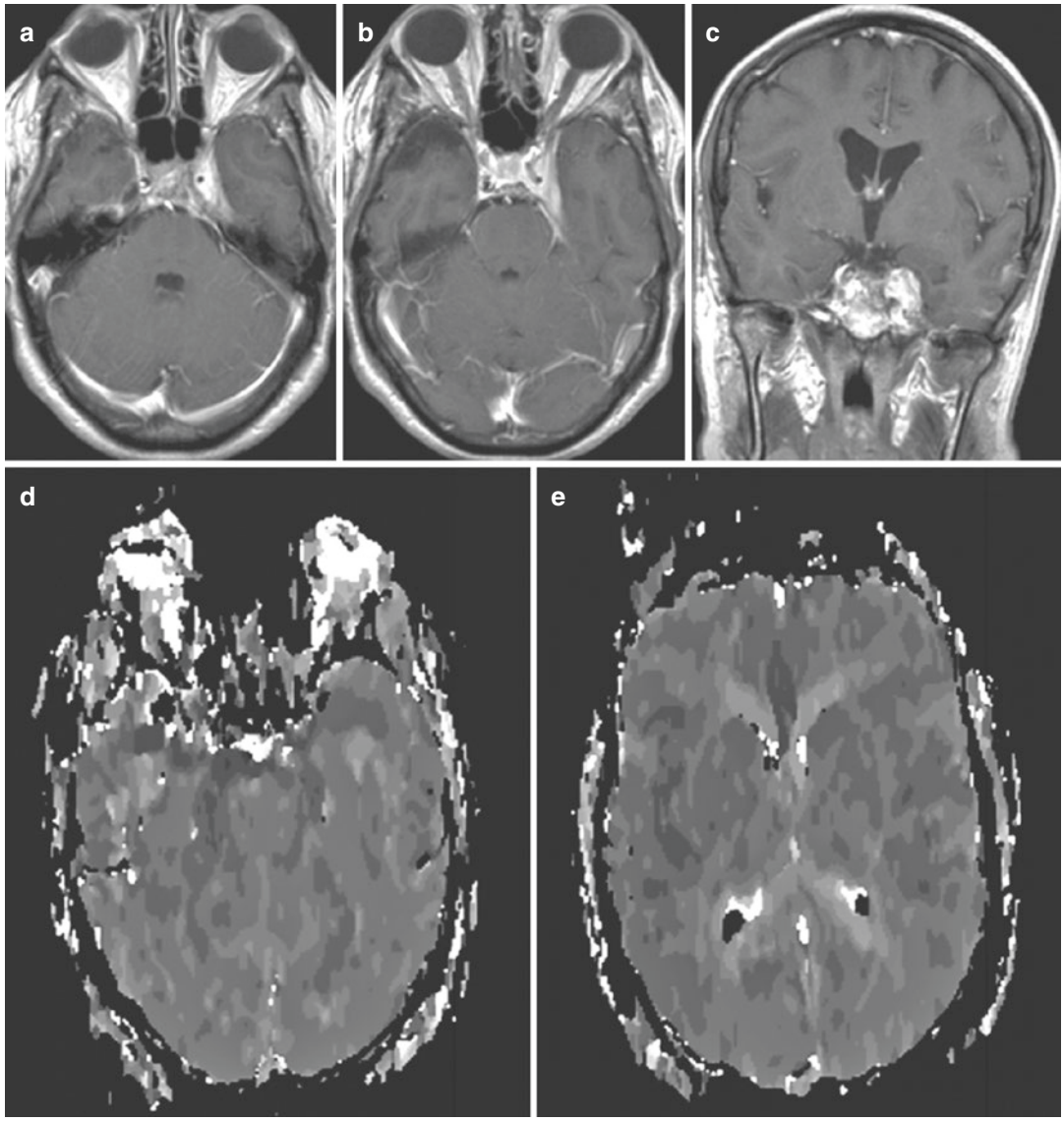

Fig. 8.15 Very compact meningioma of the anterior part of the cavernous sinus with significant narrowing of the left carotid but no symptoms of ischemia (**a**–**c**). In these situations further progression of the tumor or the sequelae of radiosurgery may lead to "silent" occlusion of the carotid in case of sufficient collateralization. To assess the risk, a very easy screening method is the so-called "time to peak" measurement of the gadolinium distribution in both hemispheres in perfusion-weighted MRI (**d**, **e**). In case the peaks are reached simultaneously, there is no hemodynamic relevance of the stenosis, and bypass surgery is not indicated

surgical strategy and has no use in the diagnosis itself. It is indicated to answer the question of patency of sinuses, collateralizations, and the hemodynamic relevance of a stenosis within a sinus. It provides a good overview of the vascularization (Fig. 8.20) and in some cases will provide an opportunity for preoperative embolization, especially when there is major blood supply from tentorial or mastoidal meningeal arteries which during surgery will be caught only later during the procedure.

Meningiomas have been found to have several interesting hormone receptors, none of which however have led to targeted therapeutics except

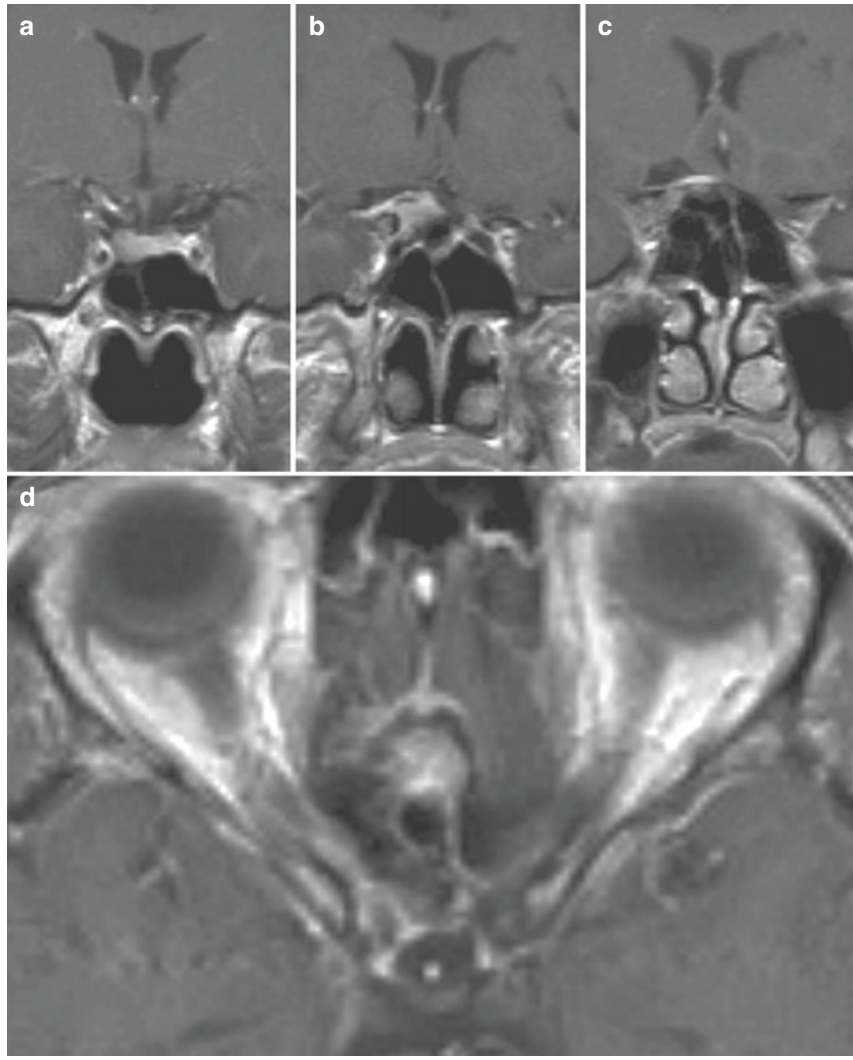

Fig. 8.16 Very small meningioma of the right optic nerve which has led to visual impairment. Only in the coronal view one can see the enhancement which is minimal in the other planes (**d**). The only option is decompression of the optic canal

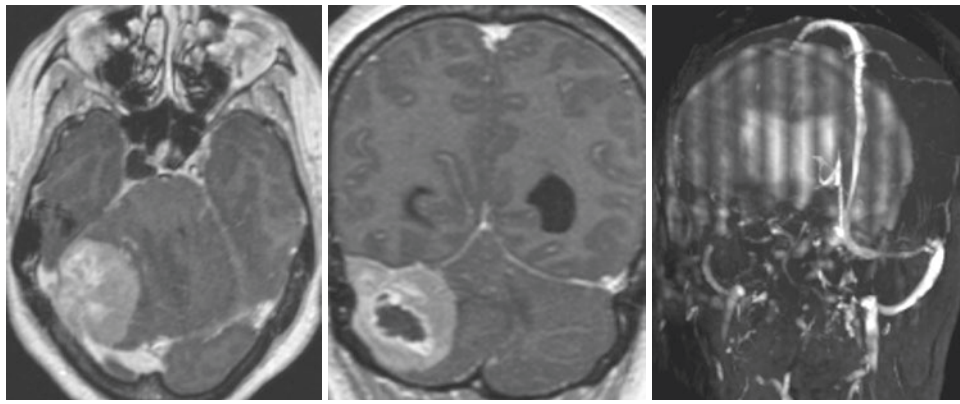

Fig. 8.17 Posterior fossa meningioma which has invaded the sinus and completely fills the niche of the transverse/sigmoid junction, and MR angiography (right panel) confirms the complete obliteration

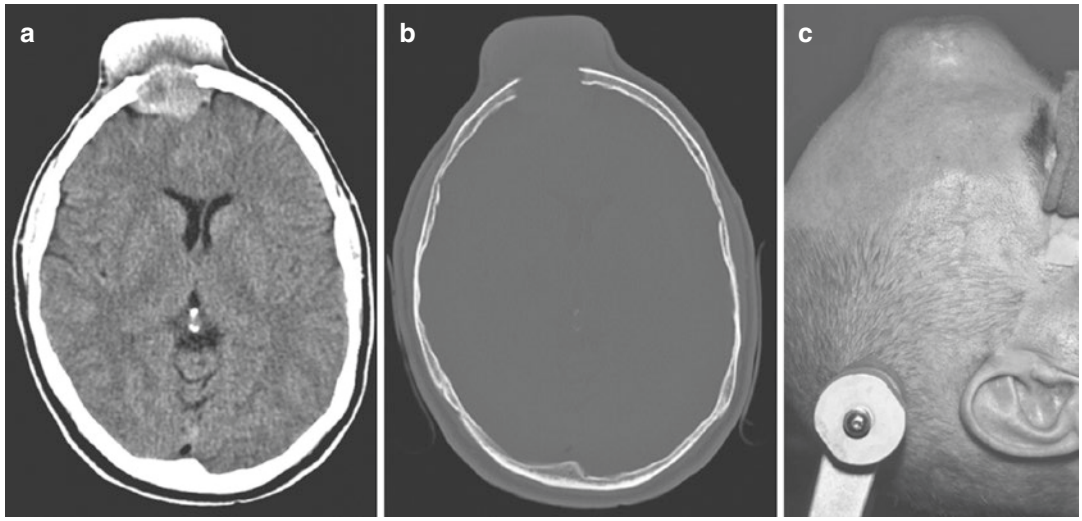

Fig. 8.18 Meningioma which has grown through the bone and can be seen extracranially as a deformity of the skull

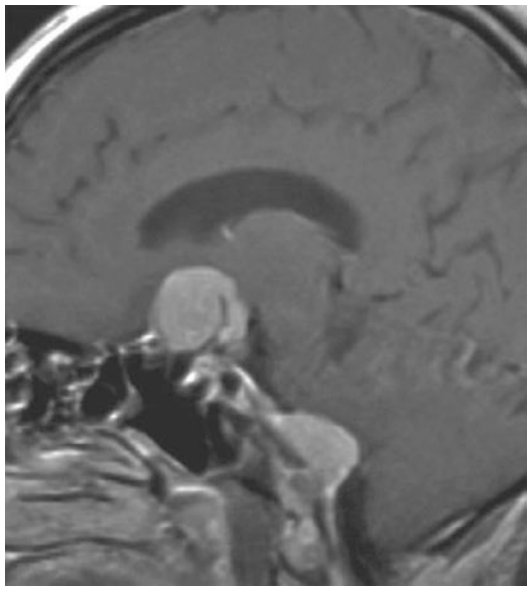

Fig. 8.19 Multiple meningiomas of a patient who was seen because of visual problems on the right eye as a result of a suprasellar meningioma. The MRI revealed a second, non-connected lesion in the right CP angle which was removed in a separate session

for the somatostatin receptor type 2 (SSTR2) [23], which is explored for radiotherapy (see below) or imaging. To determine in cases of inoperable tumors, residuals, or recurrence of the optimal treatment volumes for radiotherapy, a radiolabeled compound, ^{68}Ga-DOTATATE, a positron emitter, is used to delineate active tumor and follow treatment effects (Fig. 8.21) [67]. The place for PET imaging in meningiomas is currently being defined by its increasing use [27].

8.8 Therapy

8.8.1 Surgery

Therapy of meningiomas generally involves surgery [1, 2]. Especially for the skull base locations, over the last decade, it has become more interdisciplinary [32] with additional treatment opportunities also for radiotherapists and neuroradiologists with their improving tools [41]. The refinement of microsurgical approaches offers a resective option, at least partial for almost all locations of meningiomas [1, 2]. Again, as for the symptoms, there are different strategies of surgical management according to location.

The most important question is whether a meningioma needs to be treated at all or can be left to observation, keeping in mind that many lesions are found incidentally. Especially with incidental, calcified meningiomas in the elderly, a repeated imaging within 6 months or even a year is justified, and when no increase in size is

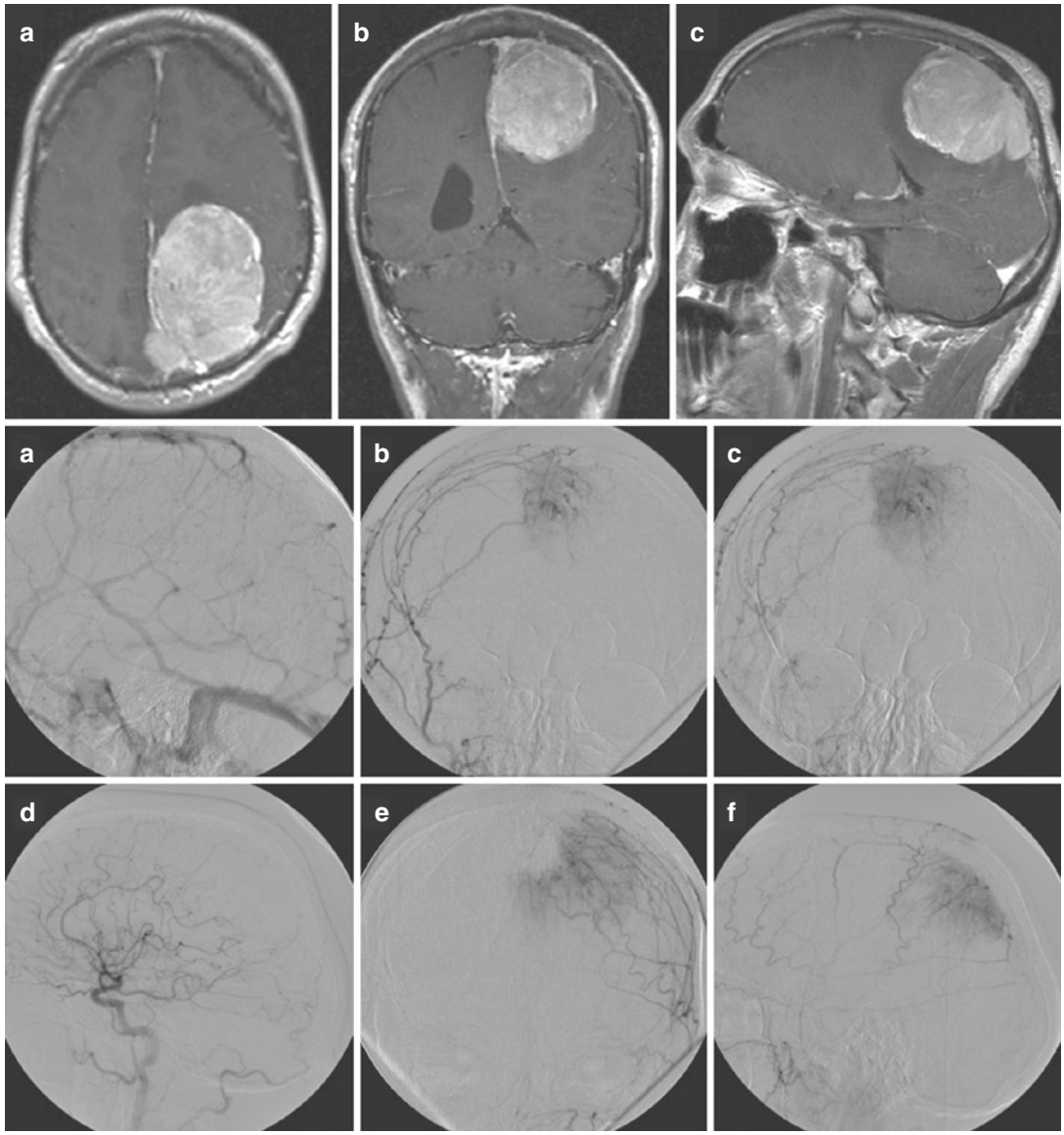

Fig. 8.20 Large bilateral meningioma of the falx which has occluded the sinus and results in pronounced edema (**a**–**c**) which was the cause of the neurological deficit and which completely resolved within a week of surgery. The vascularization is exclusively via the external carotid artery (**a**–**c**, **e**, **f**) and is completely eliminated when performing the dural circumcision as the first part of the surgery. Consequently, this tumor was an avascular mass during the removal without preoperative embolization. There is no contribution from the internal carotid (**d**)

seen, the lesion is left to observation. In a recent survey, the observation periods to decide for treatment were even 5–10 years [54]. Calcification in CT as such does not indicate a priori slow growth as the tumor upon resection may still be well vascularized and vital and all the hyperdensity due to microcalcification (Fig. 8.22). Tumors may even change their growth characteristics over time. A tumor may recur or a residual may slowly grow in higher age and then slow down and remain constant for many years (Fig. 8.23).

The classical, typical meningioma of the convexity or lateral sphenoid wing will be resected including its origin, likewise meningiomas of the

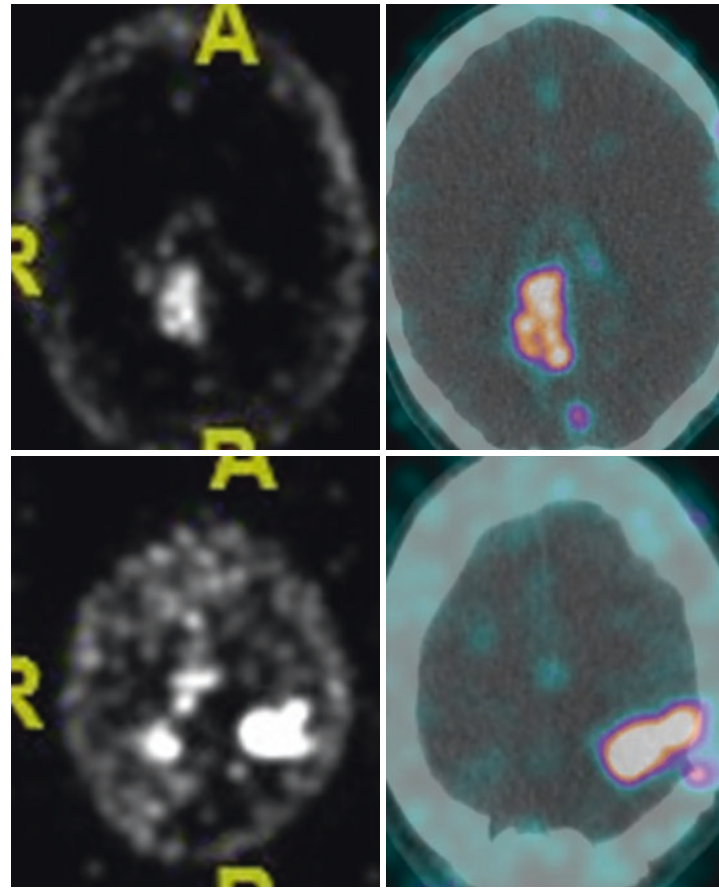

Fig. 8.21 Recurrent multifocal meningioma in a chronic course where anaplastic transformation took place and a pre-resection DOTATATE-PET was performed to find out whether the tumor cells of all foci actively label with the tracer so that after resection a radioisotope therapy is possible. Two manifestations of the tumor show strong enhancement

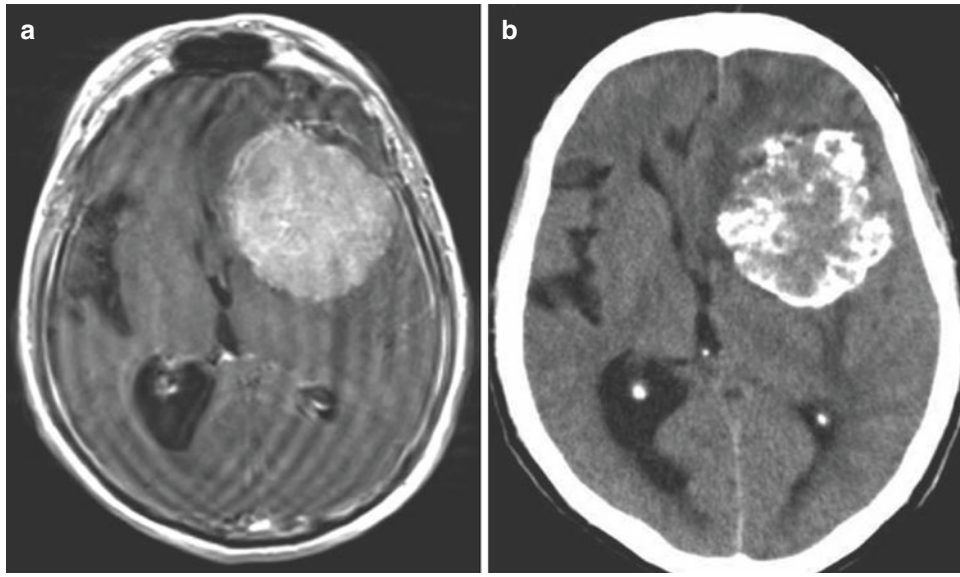

Fig. 8.22 Large sphenoid wing meningioma hyperdense on CT suggesting extensive calcification (**a**). The enhancement on MRI (**b**) already indicates that the tumor may consist mostly of vital tissue, and indeed this was a soft meningioma in which the calcification apparently was microscopic

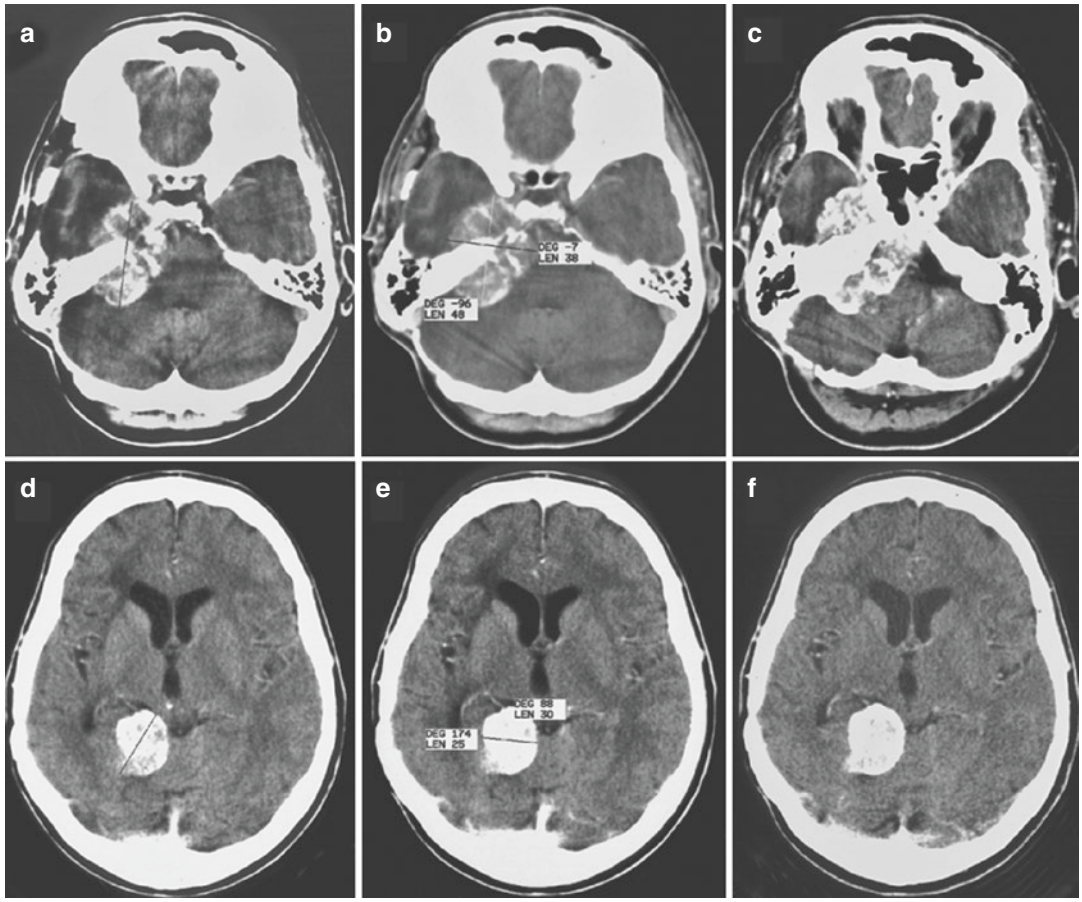

Fig. 8.23 Residuals of a meningioma which was operated 10 years before the first CT scan seen in this follow-up (**a**, **d**). The patient felt no symptoms at the time and had other health problems which resulted in the decision to remain in follow-up without any surgical therapy. Further follow-up at 2 years (**b**, **e**) and after 5 years (**c**, **f**) showed that there was almost no further growth and the patient remained in stable condition without neurological deficits and passed of unrelated cause 5 more years later

falx or the frontal skull base. Excision of the dura should be performed as far as the preoperative imaging showed any enhancement (meningeal tail sign). In most cases there will be sufficient periosteum to substitute the resected dura. If not, artificial materials exist which may be used instead. When the bone appears to be affected, it might be drilled out at the suspicious site, and if it is completely infiltrated, it has to be replaced as well. Thus, in some cases the reconstruction is more laborious than the resection itself, especially in fronto-orbital meningiomas or olfactory grove meningiomas where it may be necessary to close a bony destruction of the frontal skull base with split bone and periosteum [11].

Involvement of sinuses pose a specific problem. When the sagittal sinus in its frontal part is involved or a transverse sinus which has hemodynamically become irrelevant and is compensated by the other side, it can be sacrificed for the sake of a radical resection as there are good collaterals. If the sagittal sinus in its parietal aspect or the confluens or a dominant transverse sinus is involved and still patent and infiltrated to an extent which is beyond what can be easily patched during surgery, the wall and any intrasinusoidal part should be left. It can be irradiated or left to slowly grow on and slowly occlude the sinus while forming collaterals which usually happens over years and as a rule goes unnoticed.

Then the whole residual can be removed in one block if there are sufficient symptoms or growth over time to justify surgery. There are reports about sinus repair, but the rates of complication exceed that of this "wait and see" and "second look" approach [81] although it is advocated to attempt a venous repair after radical resection if not too risky, which means in selected individual cases [82]. Many reports about focal irradiation have now emerged which state that local control is achieved in a high percentage (see below) either arresting the tumor or leading to a longer delay until the sinus is closed.

The use of preoperative embolization has not become standard [6, 66]. Although many meningiomas would lend themselves to this approach, it is an unnecessary risk for the patient because with most tumors, the surgical approach to the lesion already involves extensive devascularization and achieves the same result as embolization. A large series reports a low complication rate of 3.7% and reduced necessity of blood transfusions, but there is no mention of conversion of an inoperable case to a surgical case [9]. Fibrin glue and particles have been used mostly as embolic materials, and this leads to necrosis in the tumor which can make histopathological classification more difficult. Also there may be swelling with ensuing neurological deficits necessitating more urgent surgical intervention than anticipated. The indication for preoperative embolization should be very strict and limited to cases where there is a clear surgical advantage or a situation in which blood transfusions are anticipated but cannot be done for medical or nonmedical reasons [71]. In one small series, the lesion shrunk considerably so that surgery was delayed for several months or canceled [57].

8.8.2 Radiation

Radiation therapy has a long history as part of meningioma management, either as external beam fractionated radiotherapy (RT) or stereotactic radiation of small volumes with high intensity either as single dose or in very few fractions (stereotactic radiosurgery, SRS). The inclusion of radiosurgery has been the most consequential new therapeutic development over the last decades.

For several tumor locations the treatment paradigms over the last years have shifted and the extensive skull base approaches with bypass surgery and cranial nerve interpositions have been left in favor of a radiosurgical treatment component (Figs. 8.14 and 8.24). It is now common to approach large skull base meningiomas which involve the whole cavernous sinus or parts opportunistically. That applies to petroclival meningiomas and some lesions of the clivus and cerebellopontine angle or fronto-orbital meningiomas where remnants may be left behind deliberately in critical areas to be then treated with preconceived radiotherapy [88]. Any exophytic parts will be aggressively removed and the tumor reduced to the part containing encased cranial nerves and blood vessels which will be left. That part can then be treated with conformal fractionated radiation or radiosurgery with any of the radiosurgical tools [32]. With growing experience the possible risks of radiosurgery become apparent [22, 56] and lead to the conclusion that radical surgery should really be attempted wherever possible so that radiation treatment is only applied when surgical risks are too high. In particular the possibility of an accelerated aggressive growth after radiotherapy is troublesome [22].

Recently, somatostatin receptor-targeted radionuclide therapy has been shown to be quite effective in a multi-institutional series of heavily pretreated progressive meningiomas [79], but further confirmatory studies are pending.

Another specific situation occurs in optic sheath meningiomas (Fig. 8.25a, b) [58]. These meningiomas are usually very difficult to treat and pose a major dilemma. In an attempt to temporarily stabilize the disease, surgery may for some cases be limited to decompression of the optic nerve canal and splitting of the sheath as much as the tumor infiltration allows (Fig. 8.25b). Attempts at resection almost always result in severe immediate deterioration of vision. With decompression only, visual loss will come gradually and may be

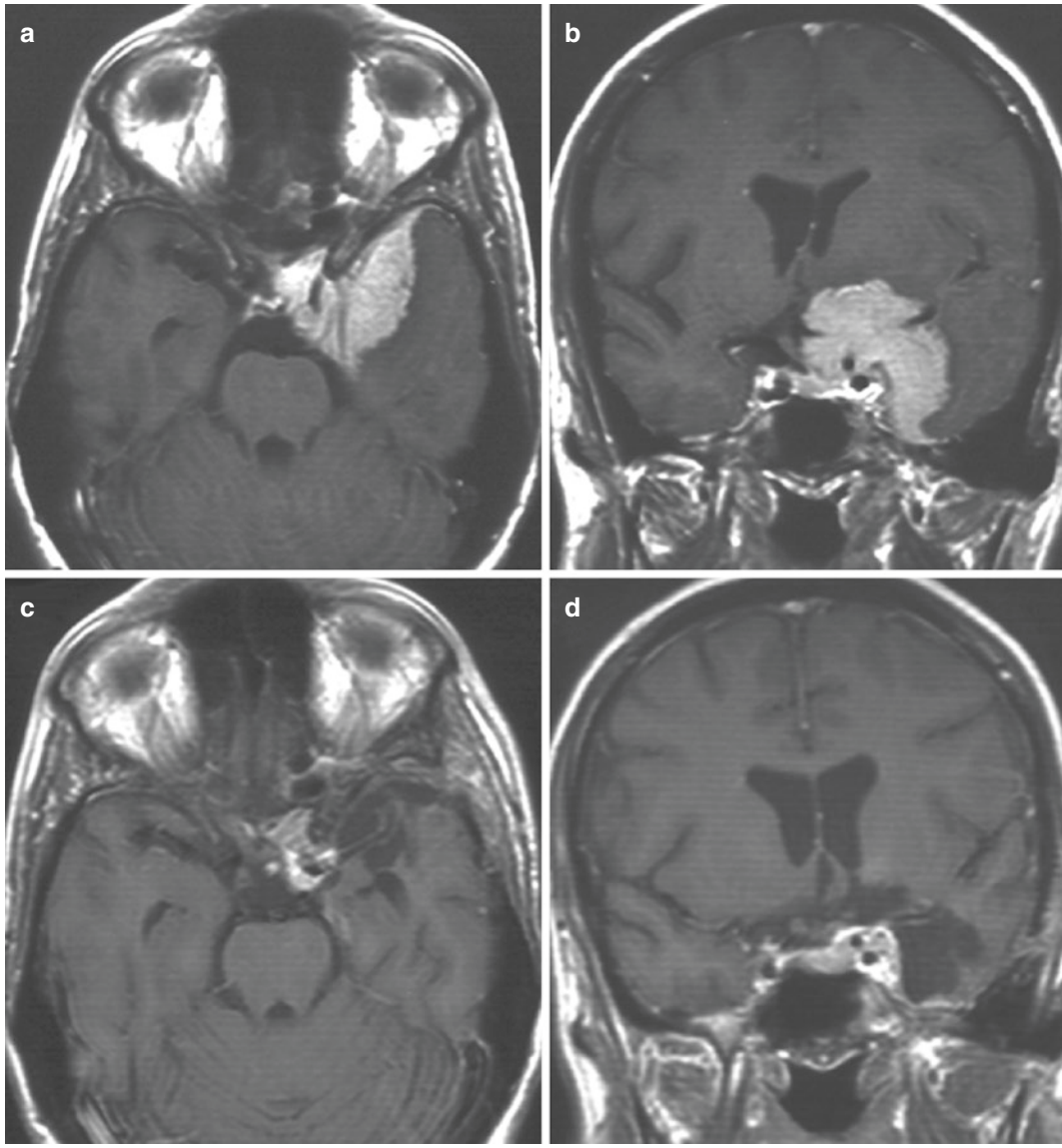

Fig. 8.24 Exophytic meningioma of the anterior clinoid process extending into the cavernous sinus and around the optic canal (**a**, **b**). Small residuals of the tumor were left (**c**), and at the first sign of progressive growth (bottom right), fractionated stereotactic surgery was indicated

postponed for a long time. There are reports about radiosurgery, and these show that in the majority of cases, stable disease can be secured, although long-term results over several decades are not available yet [5]. Whatever therapy is selected, care should be taken that it is administered only to patients with progressive disease because the course can be stable without treatment for many years [25]. For these reasons, it is advocated to intervene early with exploratory surgery in medial sphenoid wing meningiomas as tumor may extend into the optic canal before that is detectable on MRI, and direct surgical inspection is the most sensitive technique to detect such extensions, and resection eliminates the need for radiation, at least until recurrence can be documented.

Radiosurgery as a *primary* modality is reserved to cases in which surgical manipulation

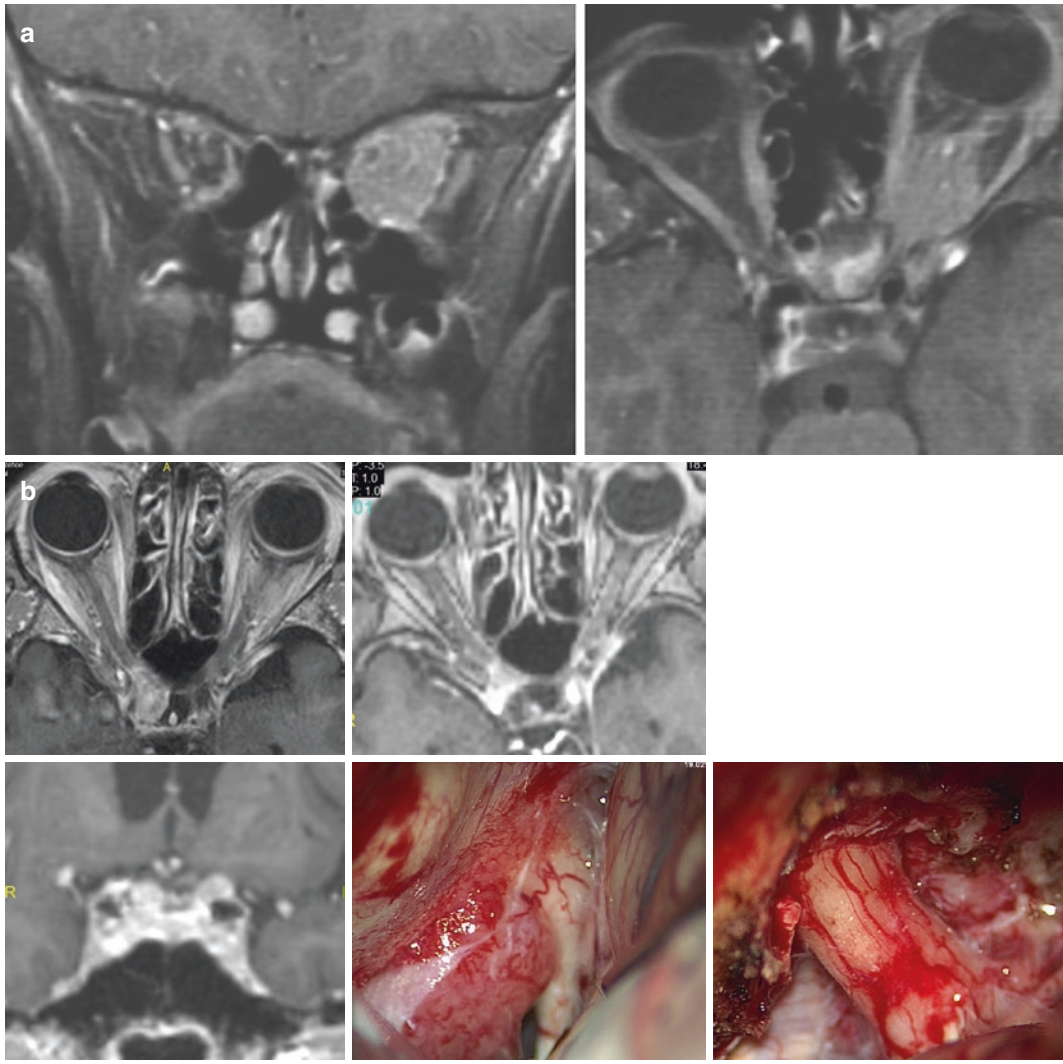

Fig. 8.25 (**a**) Biopsy proven meningioma of the optic nerve in a young boy, which upon inspection proved to be unseparable from the nerve and thus cannot be removed without risking blindness which in this case was not yet present. The optic canal was decompressed, and an intracranial extension was removed to prevent spread to the other side; eventually after years of progression and loss of vision, the whole orbit was decompressed and cosmetically reconstructed with an epithesis. (**b**) Two cases of encased optic nerves where in the top row, the canal was opened, and all exophytic tumor removed but a remnant had to be left on the infiltrated nerve (left pre- and right postsurgery). The case in the bottom row presented with an engulfed optic nerve (intraoperative micrograph middle panel) which however was only overlapping allowing for complete removal and decompression (bottom right panel)

is associated with presently unacceptable morbidity and the likelihood of only subradical resection. As with the meningiomas which have a radiosurgical component in the interdisciplinary strategy, the locations are mostly at the skull base with true intracavernous meningiomas being the largest group but also locations in the cerebellopontine angle and the perisellar region. In addition to location, age, comorbidities, and general status of health have to be included into the decision-making. The results of larger series show that disease control can be achieved in the majority of cases with acceptable morbidity which, however, is not negligible [31]. Total

remissions, however, are rare which is expected when the induction of fibrous changes and stable disease is the major goal in these rather slowly proliferating lesions [41]. The issue of radiation as such, be it RT or SRS, is heavily debated and extensively reviewed [53, 70], and while a clear benefit shown in many series is acknowledged, the uniform application is still seen controversial, and the rates for tumor control, regression, and side effects vary widely most likely reflecting discordant histological gradings due to retrospective series and changing WHO guidelines. The inclusion of RT and SRS or the use of SRS instead of resection has to follow an individual evaluation of histology, grade of resection, risk of radiation damage, and risk of recurrence/progression.

Chemotherapy has never played a major role in the treatment of meningiomas. Even in anaplastic meningiomas, there is only limited experience and limited efficacy for the classical chemotherapeutic agents [13, 14, 43]. Hope has for a long time rested with the discoveries about the cell biology of meningiomas and the possibility to develop targeted approaches which in the context of meningioma hold only limited promise [59]. The intriguing presence of progesterone receptors has eventually been explored in a phase III clinical trial for non-resectable meningiomas, but no efficacy was seen for the synthetic antiprogestin mifepristone [36]. Also the detection of dopamine receptors [12] has not translated into therapeutic opportunities despite phase II clinical trials [30]. Because of their abundant vasculature, anti-angiogenic therapy has been explored, and there are early clinical indications that the small molecule tyrosine kinase inhibitor sunitinib may be active in atypical and anaplastic meningiomas when the vascular endothelial growth factor receptor 2 was present in the tumors [38]. The most widely used chemotherapeutic option with some limited efficacy comes from drawing an analogy to chronic lymphatic leukemia which also is a slowly proliferating disorder. Hydroxyurea which is effective in that disorder has shown a therapeutic effect also in some patients [50, 52], but a large randomized prospective phase III trial is still unavailable. Also when used in combination with imatinib, a tyrosine kinase inhibitor, the efficacy is described as modest in a phase II trial [68].

Immunotherapy has become a major component in oncology but is still under evaluation for intrinsic brain tumors and not established for meningiomas. The analysis of components of the immune system which seem to be prerequisite for effective immune checkpoint inhibition has shown that potentially that approach is worth exploring but mainly for anaplastic meningiomas and clinical trials are outstanding [8].

8.9 Prognosis

The prognosis of meningiomas depends on their grade and their location. It can only be determined in the individual patient from regular follow-up. It has been difficult to find prognostic parameters based on histological markers except for grade and subtype. All other markers do not seem to have prognostic relevance. Based on the resection, the completeness of removal has been classified and basically distinguishes between a radical resection including the origin (Simpson grade 1), resection with coagulation of the origin (Simpson grade 2), partial resection (Simpson grade 3), and a mere biopsy (Simpson grade 4) [80].

Evidently there is better prognosis with more radical resection, but that may need to be revisited with the now widespread use of radiotherapeutic techniques for residual tumors. As a rule of thumb, one can expect permanent cure of a convexity meningioma grade WHO I or II which is fully resected in over 90% of the cases. Skull base meningiomas even when completely reduced to their site of origin will recur in 50% of the cases.

Anaplastic meningiomas have a poor prognosis and will eventually even metastasize.

To quote any numbers for average survival when facing patients is meaningless for the most part as there is no uniformity in the diagnosis of meningioma as such and the term “benign” is counterproductive in large unresectable skull base tumors (Fig. 8.8).

8.10 Follow-Up

Patients with resected meningiomas need to be followed regularly after treatment, and the scheduling includes WHO grade and degree of resection. After complete resection (Simpson grade 1) and WHO grade 1, first follow-up by MRI after the immediate post-op imaging should be at 1 year and, when that scan is clear, in intervals increasing from 2 to 3 years thereafter. In atypical meningiomas WHO grade II, the schedule should be 6 months for the first follow-up and then yearly for 3 years increasing to 2 years thereafter. For anaplastic meningiomas WHO grade III, the follow-up will be as for high-grade gliomas. Recurrent meningiomas when recapitulating the original tumor underlie the same considerations about resection, partial safe resection, and additional treatment with radiation or re-irradiation [87].

For resection Simpson grade 2 and above, the schedule depends on the dynamics of the residual. In some cases regrowth or increase in size cannot be detected for years even without treatment, and in some, growth detectible at 6 months will determine what kind of additional therapy is recommended. MRI is generally the best modality, but in cases of bone involvement at the skull base, CT may need to be done as well. Because imaging changes may be subtle in some patients, other interdisciplinary monitoring modalities may need to be included like regular ophthalmological assessment or audiograms when the tumor was in the area of the respective compromised cranial nerves and recurrence/progression impairing their function is feared. As it has been reported that patients with radiosurgical treatment for residual tumor may experience sudden aggressive growth with years of delay, special attention must be given to patients with such combined treatments.

Only when after 10 years there is no evidence for any activity of the disease, patients can be dismissed from regular follow-up. Bearing in mind that tumors may alter their growth characteristics over the years, patients can be advised that not each indication of a new tumor activity needs to be treated right away because it may not cause any symptoms and might be safely watched for some time. On the other hand, it must be pointed out that exactly because of the usually slow-growing nature, regular follow-up is important because symptoms from a recurrent or progressing lesion may arise only late and then optimal therapeutic opportunities may have been missed. There are no blood tests yet which would allow monitoring of tumor activity, but the development of detection techniques for tumor constituents in plasma such as extracellular vesicles may revolutionize the whole follow-up regimens.

8.11 Future Perspectives

Optimal definition of the treatment modalities in an interdisciplinary setting and evaluation of that concept in larger series with meticulous follow-up will make treatment of meningiomas safer and more efficacious on a much more individualized basis. Given the absence of any pharmacological treatment option and lack of perspective of such in the near future, therapy will for a long time rest on surgery and radiation. It is to be hoped that refined and meticulously clinically correlated gene expression analyses will lead to the definition of candidate genes for truly targeted therapies.

8.12 Other Meningeal Tumors

The 2016 WHO contains now a chapter of mesenchymal, non-meningothelial tumors [4]. According to this, *Haemangiopericytoma* which comprises about 2% of meningeal tumors [34] is now used synonymously with solitary fibrous tumor (SFT) which is the preferred terminology in the WHO classification. These tumors tend to occur at a younger age than the meningiomas with a peak incidence in the fourth and fifth decade. Also, there appears to be a slight prevalence for the male sex. By WHO grading they are allocated to the grades II and III, but the parameters distinguishing the two still need to be fully validated. The genetic alterations are different from meningioma with alterations of the chromosome 22 absent. Most alterations are found on chromosome 12q13 and 6p21.

As for clinical signs and symptoms, there is no difference between meningiomas and hemangiopericytomas. The neuroradiological features may be identical to meningioma (Fig. 8.26) but are somewhat different from meningiomas in respect to bone. The tumors tend to cause lytic lesions in bone and do not grow through the bone like the meningiomas which with rare exceptions either cause hyperostosis or just distend the bone without completely destroying it. The tumors are highly vascularized and upon angiography show a wealth of pathological vessels (Fig. 8.26), [51]. In contrast to meningiomas, calcifications are rare.

Treatment of hemangiopericytoma is more complex than that of the average meningioma. The tumors should be removed as completely as possible, and then there is a consensus that the region needs to be irradiated [3] because otherwise the rate of recurrence is 91% [89]. Especially with anaplastic tumors, the prognosis is bad without radical removal and radiation, but when achieved and completed, 5-year overall survival may be 90% [93]. Also, these tumors have a tendency to metastasize, primarily into bone [83]. No chemotherapeutic regimen has emerged as an effective standard [24]. Corresponding to the

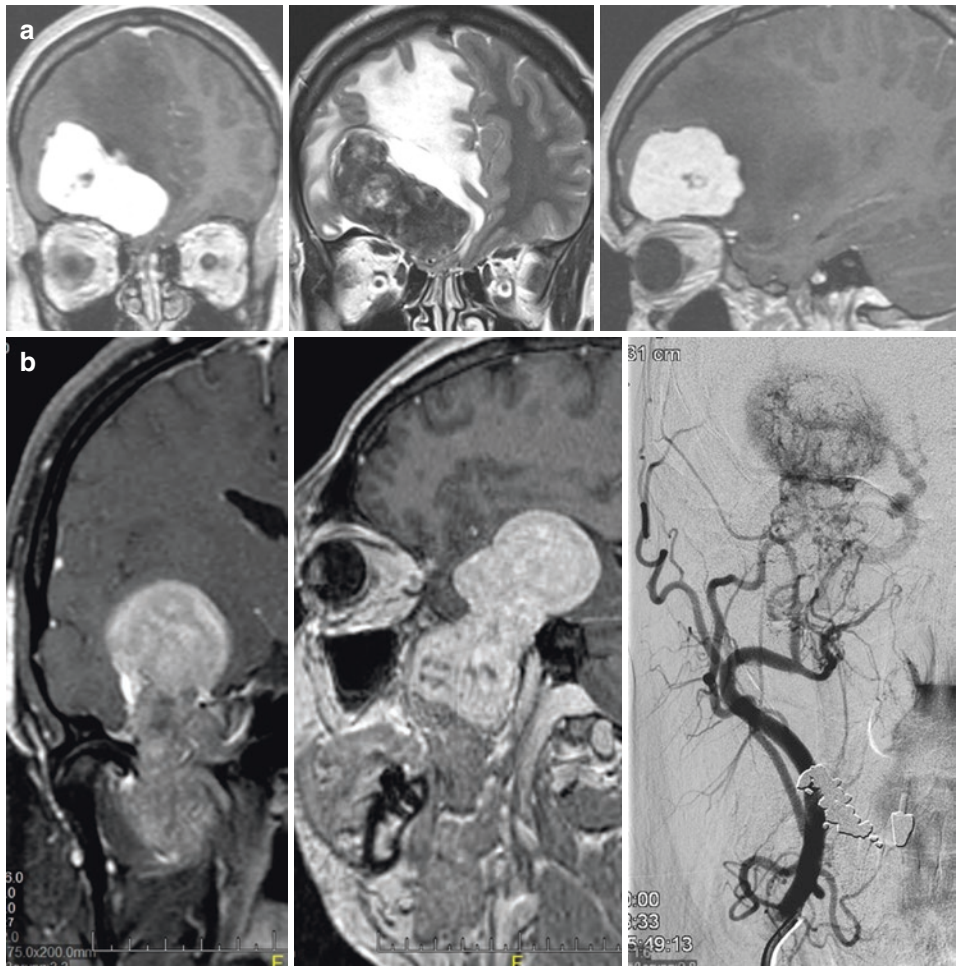

Fig. 8.26 Solitary fibrous tumor/hemangiopericytoma. (**a**) Frontobasal solitary fibrous tumor with massive edema but no infiltration to the brain and a very clean plane of dissection. The origin was a very small area of dural and bony infiltration at the orbital roof. (**b**) Large highly vascularized tumor growing destructively trough the temporal skull base which after partial embolization could be removed completely and is free from recurrence after 6 years

aggressiveness of the disease, patients need to be followed closely, especially to detect metastases. The high rate of recurrence and metastases is the cause for mortality, and despite aggressive treatment, up to 60% of the patients may have succumbed to the disease by 15 years [89].

8.12.1 Dural Lymphoma

Dural lymphomas present as contrast-enhancing lesions with an extension like a subdural hematoma, like a nodular meningioma with a dural tail, like an en plaque meningioma, or just as dural hypertrophy. Particularly suspicious is an extension deep into the arachnoid spaces and sulci (Fig. 8.26). Primary dural lymphomas are rare and not to be mistaken for primary CNS lymphoma (see Schlegel, this volume). They are mostly of the MALT type [28, 72] although other kinds and regular Hodgkin's disease have been reported [37]. They seem to have a better prognosis than PCNSL and respond well to cranial radiation [7]. Many of the reported dural lymphomas were unexpected, and therefore, some were resected like en plaque meningiomas. Cranial radiation is to be recommended even after resection but certainly after biopsy.

8.12.2 Dural Metastases

Metastatic disease to the brain is seen with increasing frequency, but in comparison with the parenchymal or leptomeningeal variants, purely dural involvement is rare and is detected most frequently in the context of suspected meningioma [44, 86]. Whereas in intracranial disease, a metastasis is more readily suspected because of imaging characteristics and has a known primary in about 80% [92]; the diagnosis of a dural metastasis is made much more frequently when the primary tumor is still unknown [86]. This can be partially explained by the fact that dural metastases may occur in any type of cancer but show a spectrum which is different from intracranial disease. A large combined surgical and autoptic series showed a surprisingly broad spectrum including the expected high numbers of breast cancer as primary but an even higher number of underlying prostate cancer which can have extensive manifestation (Fig. 8.27) and also

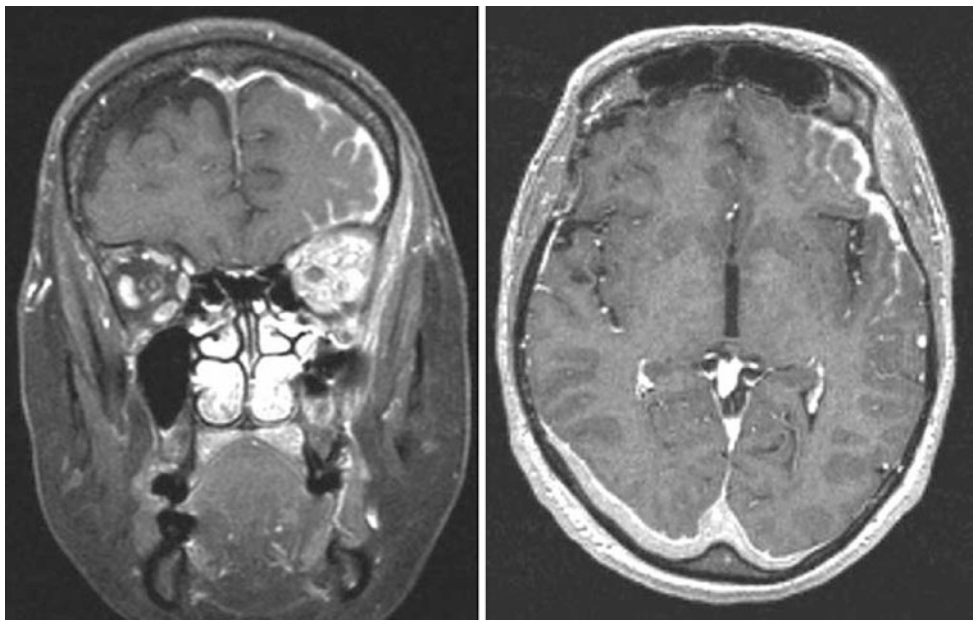

Fig. 8.27 Gd-enhanced MRI of a left frontal lesion which was observed for 5 years with deteriorating vision where the patient decidedly declined all offers for a biopsy. Because of an increasing exophthalmos, the lesion was biopsied, and it turned out to be the metastasis of a slowly growing lymphoma of which a cervical manifestation had been treated 7 years ago

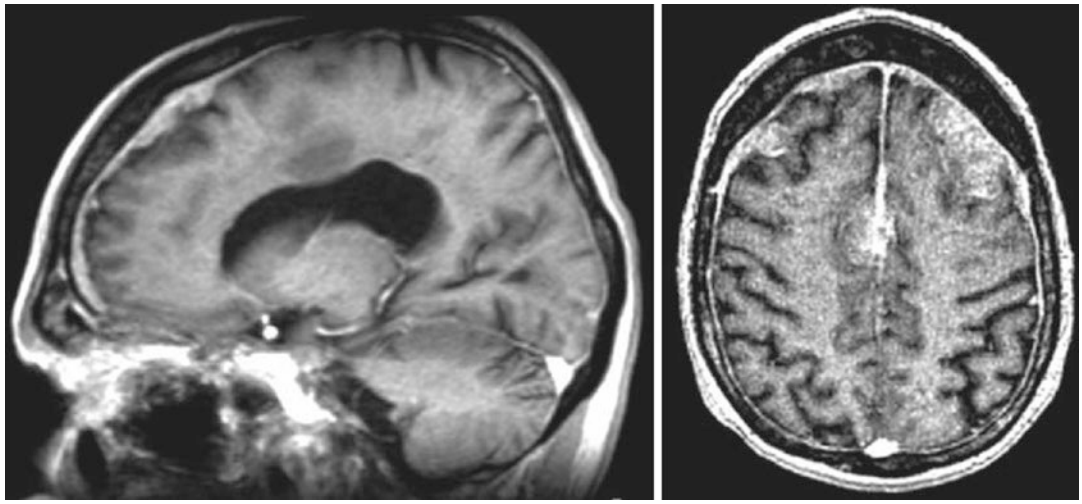

Fig. 8.28 Bihemispheric, mostly frontal en plaque, and nodular manifestation of a prostate carcinoma known for 6 years treated only with endocrine therapy. The patient presented with beginning signs of disorientation. No treatment was given because of rapid deterioration

such primaries as the larynx, gall bladder, and stomach, which otherwise rarely metastasize to brain [40].

When purely dural and an appearance like meningioma, the differential diagnosis is close to impossible without a tissue diagnosis because the neuroradiological techniques may not provide sufficient parameters for differentiation [42]. The tumors may be dural with a flat spread, be nodular, or show a combination of subdural-dural-skull extension. Depending on the context of the overall status of the patient, there may be an indication for resection, especially when the differential diagnosis toward meningioma cannot be made without histology and there is no known primary. As the spectrum of histological origins is very heterogeneous, there are no published series about the role of radiotherapy or chemotherapy as there are for leptomeningeal metastatic disease. How to proceed after histological verification of a dural metastasis will depend on the established treatment paradigms for the primary tumor and has to be determined in an interdisciplinary tumor board (Fig. 8.28).

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