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Parasellar Meningiomas

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Abstract
Parasellar spaces remain particularly singular, comprising the most important neurovascular structures such as the internal carotid artery and optic, oculomotor, and trigeminal nerves. Meningiomas are one of the most frequent tumors arising from parasellar spaces. In this location, meningiomas remain mostly benign tumors with WHO grade I and a meningothelial subtype. Progestin intake should be investigated and leads mostly to conservative strategies. In the case of benign nonsymptomatic tumors, observation should be proposed. Tumor growth will lead to the proposition of surgery or radiosurgery. In the case of an uncertain diagnosis and an aggressive pattern, a precise diagnosis is required. For cavernous sinus and Meckel's cave lesions, complete removal is rarely considered, leading to the proposition of an endoscopic endonasal or transcranial biopsy. Optic nerve decompression could also be proposed via these approaches. A case-by-case discussion about the best approach is recommended. A transcranial approach remains necessary for tumor removal in most cases. Vascular injury could lead to severe complications. Cerebrospinal fluid leakage, meningitis, venous sacrifice, visual impairment, and cranial nerve palsies are more frequent complications. Pituitary dysfunctions are rare in preoperative assessment and in postoperative follow-up but should be assessed in the case of meningiomas located close to the pituitary axis. Long-term follow-up is required given the frequent incomplete tumor removal and the risk of delayed recurrence. Radiosurgery is relevant for small and well-limited meningiomas or intra-cavernous sinus postoperative residue, whereas radiation therapy and proton beam therapy are indicated for large, extended, nonoperable meningiomas. The place of the peptide receptor radionuclide therapy needs to be defined. Targeted therapy should be considered in rare, recurrent, and aggressive parasellar meningiomas.

Introduction

Meningiomas are one of the most frequent tumors arising from the parasellar spaces. The cavernous sinus (CS) and Meckel's cave are singular areas which necessitate a

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specific management. The authors propose a literature review considering the anatomy, epidemiology, neuropathology, diagnostic and therapeutic management, endocrinological assessment, postoperative complications, and follow-up modalities of parasellar meningiomas.

Anatomical Considerations

The parasellar region mostly concerns the lateral part of the turcica sellae, including the CV and Meckel's cave. The parasellar region also comprises the different areas surrounding the pituitary gland and stalk, but the precise definition of the parasellar region remains debated. The petroclival region, the optic canal, and the anterior clinoid process are part of the parasellar region. In contrast, the tuberculum sellae, the jugum sphenoidale, and the clival region are not clearly part of the parasellar region.

The specificity of this parasellar region lies in the high number of important neurovascular structures [1–3].

The CV was firstly described by Galien in the second century AD related to gladiators' injuries. In 1732 in Paris, France, Winslow described this large venous network by suggesting similarities with the corpus cavernosum of the penis. Future dissections revealed that Winslow's anatomical descriptions were probably wrong. Parkinson [4] described the CV as a large and variable extradural venous plexus, depending on each patient. Parkinson [4] preferred the term lateral sellar compartment. Nevertheless, the anatomical description of the CS remained a matter of debate for many years. Taptas [5, 6] described the concept of an interperiosteo-dural space. He defined the CS as a lodge between the intracranial periosteum which remained attached to the bone and the dura propria with its many folds. The different nerves are covered by a leptomeningeal sheath and a dural sheath [7, 8]. The CS sinus drains the blood from the ophthalmic vein the spheno-orbital sinus and the inter-CV to the petrosal sinuses and the jugular veins. The definition of plexus versus sinus remains debated [4, 5, 9]. Kehrli et al. [9, 10] concluded that the CS of the embryological and histological definition was in accordance with a sinus. Kehrli et al. [10] observed the formation of the CS resulting from embryological development of the brain and the different dural layers [11]. They concluded on the lack of a CS medial wall based on cadaveric dissection and MRI studies, suggesting a barrier constituted of connective tissue [10, 11]. These different anatomical observations facilitated surgical approaches to the CV, particularly an extradural or interdural approach [12–15].

The most important vascular structure is the internal carotid artery (ICA), which clearly impacts the endoscopic approach decision. The lateral region of the ICA remains difficult to reach via an endonasal approach, which poses the risk of oculomotor nerves and vascular lesions. The most important neurological structures for the therapeutic strategy decision are probably the optic pathway including the optic nerves (ON) and the chiasm. But the CV also comprises the different oculomotor nerves (i.e., III, IV, and VI) [7, 8]. The trigeminal nerve goes through its cisternal compartment and then to Meckel's cave. V1, V2, and V3 run, respectively, through the superior orbital fissure, the foramen rotundum, and the foramen ovale.

Epidemiologic Considerations and Location

Parasellar meningiomas represent 15% of all meningiomas [16]. They are comprised in skull base meningiomas. Precise determination of the origin of meningiomas is fundamental for therapeutic decision making and election of the surgical strategy. Parasellar meningiomas can be classified into the following different groups based on location (Fig. 1): CS, Meckel's cave, lateral wall of the CS and medial sphenoid wing, anterior clinoid, petroclival, and suprasellar (tuberculum sellae and diaphragm sellae).

Cavernous Sinus

Intra-CS meningiomas are a specific entity. The location of the tumor and its relationship to the ICA and the oculomotor nerves should be carefully analyzed. Oculomotor nerve palsy often reveals the tumor. A hazardous diagnosis is also frequent.

Meckel's Cave Meningiomas

These meningiomas are purely located in Meckel's cave and extend to the medial aspect of the cerebellopontine angle. The approach is most often different from that for CS meningiomas. Symptoms are mostly trigeminal hypoesthesia and neuralgia.

Lateral Wall of the CS and Medial Sphenoid Wing Meningiomas

Tumor extension through or arising from the lateral wall of the CS could impact the temporal cortex with edema, veins encasement, and brain invasion. Symptoms could be epilepsy, headache, and neurocognitive dysfunction, particularly language disturbances on the left side. Symptoms related to medial sphenoid wing meningiomas are similar.

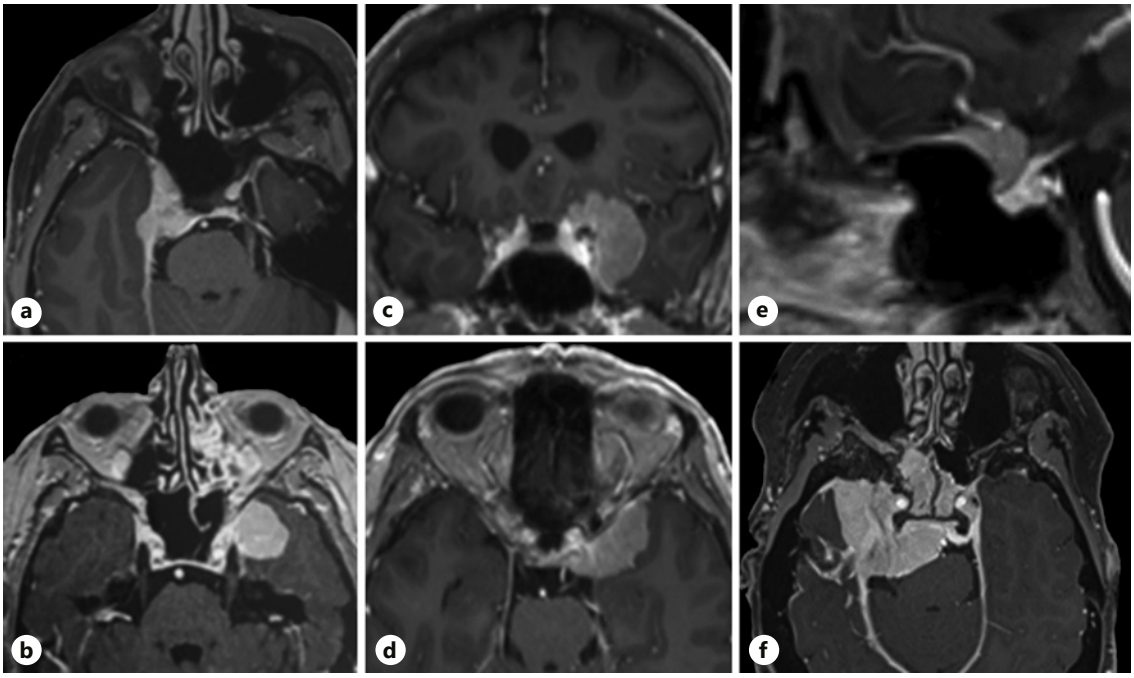

Fig. 1. Parasellar meningiomas on T1-weighted MRI with gadolinium enhancement. CS meningioma extending into Meckel's cave (**a**), CS lateral wall meningioma (**b**), meningioma arising from the CS lateral wall extending to the lateral and superior aspect of the anterior clinoid process (**c**), anterior clinoid process meningioma with osteoma of insertion (**d**), tuberculum sellae meningioma (**e**), and extensive cavernosphenopetroclival meningioma (**f**).

Anterior Clinoid Meningiomas

Anterior clinoid meningiomas are a specific entity dealing with the ICA and the ON. They were studied and classified in 1990 by Al-Mefty [17].

Group I insertion is located on the inferior face of the anterior clinoid process. ICA adventitia encasement and attachment are frequent, leading to an impossible dissection of the tumor from the ICA and then to incomplete resection.

Group II insertion is located on the superior and lateral face of the anterior clinoid process. Persistence of an arachnoid layer and the carotid cistern between the ICA and the tumor usually facilitates tumor dissection.

Group III insertion is located on the medial face of the anterior clinoid process and in the optic foramen so that extension into the optic canal is frequent, leading to ON compression and sometimes invasion. In the case of ON encasement and invasion, dissection from the tumor could be challenging and with a higher risk of postoperative visual impairment.

Petroclival Meningiomas

Pure petroclival meningiomas are classically not considered to belong to the parasellar region. However, CS meningiomas can extend to the petroclival region, which is common. But they should not be classified as petroclival. Kawase et al. [18] described different patterns of petroclival meningiomas. Large CS meningiomas extending into the petroclival region should be named cavernopetroclival or spheno-caverno-petroclival. The relation to the nerves, vascularization, and approach are different.

The tumor origin should be precisely defined to determine the best strategy and the best neurosurgical approach. In Dorello's canal invasion, nerve VI palsy is frequent. In the case of a voluminous intracisternal compartment, brain stem compression could lead to symptoms such as vertigo, dizziness, balance and walking disturbances, and weakness of the extremities [18]. Acoustic-facial nerve compression could lead to facial palsy and hearing loss, as compression of the lower cranial nerves (CN) could lead to swelling alteration. Brain stem edema indirectly suggests a subpial vascularization of the tumor, with a high risk of infarct in the case of brainstem surgical dissection. Secretory meningiomas also cause brainstem edema [19].

Suprasellar Meningiomas

The most frequent symptom for suprasellar meningiomas is visual impairment, which is often asymmetrical in comparison to pituitary adenomas. Related to their location, suprasellar meningiomas are usually of a moderate volume at diagnosis and firstly compress the ON before inducing neurocognitive dysfunction. ON compression is often superior and lateral in tuberculum sellae meningiomas and inferior and lateral in planum sphenoidale meningiomas. Different tuberculum sellae meningioma classifications are proposed in the literature [20, 21]. The most important criteria are the volume of the tumor, extension into the optic canal, and artery encasement (ICA and anterior communicating artery).

Pituitary dysfunction is rare. Hyperprolactinemia is probably the most frequent biological abnormality. Literature data on this point are poor. Mortazavi et al. [20] reported 10% preoperative pituitary dysfunction in a cohort of meningiomas operated on via a transcranial approach and a rate of 25% in a cohort of meningiomas operated on via an endoscopic approach. The difference could be related to the tumor location and its anatomical relationship with the pituitary gland and stalk.

Diaphragm sellae meningiomas were classified in 1995 depending on their precise locations [22]. They also likely compress the optic pathway. A higher rate of pituitary dysfunction was diagnosed, reaching approximately 40% in types B and C.

Neuropathology

Parasellar meningiomas are comprised in skull base meningiomas. Among the 3 WHO grades and the 15 subtypes, WHO grade I with a meningothelial subtype is the most frequently observed in parasellar meningiomas [23]. SST2 receptor expression is usually strong in the meningothelial subtype [24]. The secretory subtype is classical in this location, associated with a higher rate of peritumoral edema and seizures [19, 25]. Clear-cell meningioma could also be encountered in Meckel's cave and the petroclival region, often mimicking schwannoma, with a predilection for young women and with an aggressive pattern [26–28].

Mutational landscape mainly includes non-NF2 mutations such as *TRAF7, AKT1, SMO, PI3KCA, KLF4*, and *POLR2A* [29]. Meningothelial meningiomas are rarely *NF2* mutated (23%), with mostly *TRAF7* and *AKT1* mutations (50%) [30–32].

In their epigenomic methylome analyses, Sahm et al. [33] defined the following DNA methylation classes (MC): 3, benign MC; 2, intermediate MC; and 1, malignant MC. They demonstrated that the MC were more relevant for outcomes than the canonical WHO classification, with a better appreciation of aggressive WHO grade I and the less aggressive WHO grade II. Most parasellar meningiomas are classified as MC Ben-2, with therefore a favorable outcome. Loss of the histone H3K27me3 has also been demonstrated to be helpful in risk-of-recurrence stratification [34].

Most CS meningiomas are not inserted into bone but originate from intracavernous arachnoid granulations, which explains why they infiltrate the CN which are not protected by the arachnoid sheath anymore [13, 35–37].

Differential Diagnosis

The differential diagnosis in parasellar meningiomas should be separated into benign and malignant tumors. Considering benign tumors defined by no or slow growth and no radiographic arguments for aggressive lesions, the most frequent differential diagnosis is constituted by schwannomas. Chondrosarcomas are rare, present a benign evolution, and are easily differentiated from meningiomas. MRI tumor differentiation can sometimes be challenging. Octreotide somatostatin receptor and gallium-68 DOTATATE PET imaging could be helpful to establish the diagnosis, but they remain optional given that the therapeutic management is similar, i.e., observation followed by surgery or radiosurgery in case of progression [38–42].

In aggressive or malignant suspected tumors, the therapeutic management will change depending of the tumor type and required a precise diagnosis. Chordomas, metastases, myelomas, lymphomas, and multiple other tumors are more difficult to differentiate from meningiomas and a biopsy may be required in case of doubt. The patient's medical history, e.g., clinical symptoms, should be carefully analyzed. Acute or quickly progressive, and intense clinical symptoms should alert to the diagnosis. In the case of negative systemic explorations, a biopsy of the tumor will be required.

Symptoms at Diagnosis

Impairment of the visual field and visual acuity is the most frequent symptom related to ON compression. In contrast to pituitary adenomas, the compression and related visual impairment is likely asymmetrical. ON fiber analysis via retinal nerve fiber layer and ganglion cell

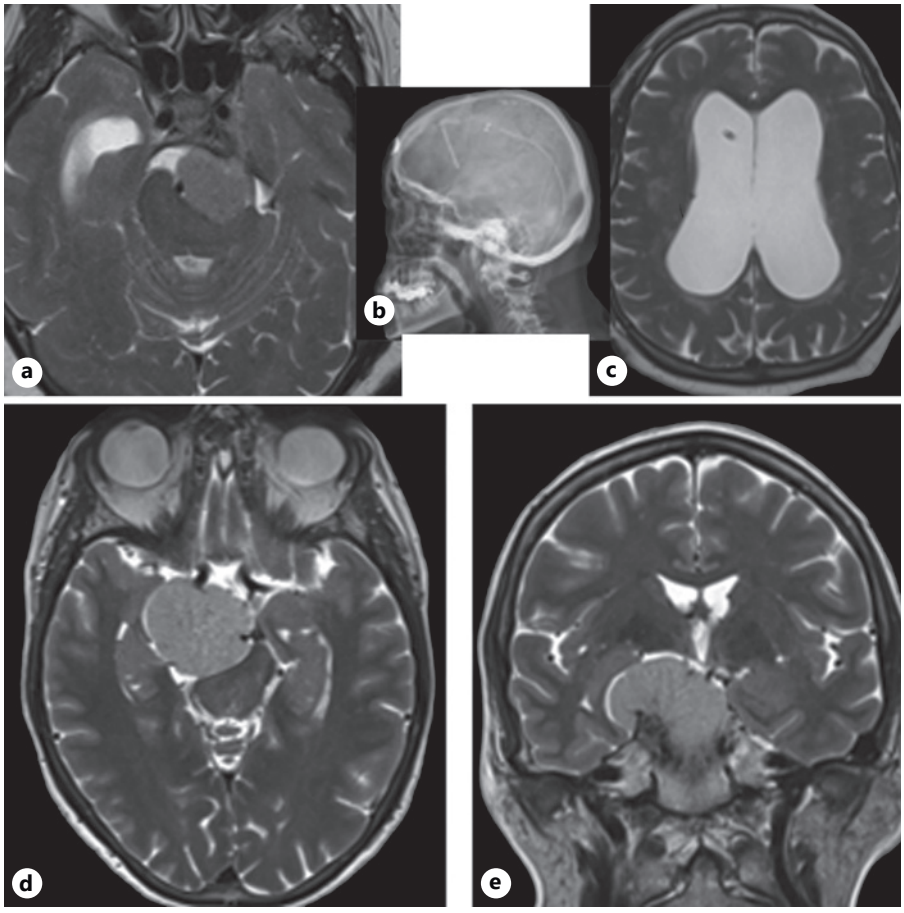

Fig. 2. Case-by-case therapeutic strategy: 2 clinical cases. Case 1: 81-year-old woman with petroclival meningioma-inducing hydrocephalus. A ventriculoperitoneal shunt was implanted and meningioma was observed. Axial (**a**) and coronal (**c**) T2-weighted MRI and skull X-ray (**b**). Case 2 (**d**, **e**): 57-years-old woman with nongrowing and nonsymptomatic petroclival meningioma (observation for 18 months). Axial (**d**) and coronal (**e**) T2-weighted MRI.

complex optical coherence tomography (OCT) has been demonstrated to be more sensitive than classical visual field and visual acuity assessment and therefore should be systematically performed to better appreciate a tight visual alteration or to assess the severity of the ON fiber lesion [43–47].

Oculomotor nerve palsy is frequent and could be assessed via the Lancaster test.

Trigeminal neuralgia, hypoesthesia, or dysesthesia should be tested, as should corneal reflex and temporal muscle motor function. Facial palsy and cochlear and vestibular dysfunctions should also be assessed but are usually observed in voluminous cerebellopontine angle lesions.

Lateral and superior tumor extension could impact brain functions inducing epilepsy, neurocognitive dysfunctions, and aphasia. Brain stem compression could generate symptoms such as vertigo, walking and balance disturbances, and rarely tetraparesia [18].

Intracranial hypertension could be observed in hydrocephalus or high-volume tumors. Hydrocephalus will require treatment initially and usually implantation of a ventriculo-peritoneal shunt (Fig. 2). In the case of intracranial hypertension related to a voluminous meningioma, corticosteroids, mannitol, and tumor removal will be required.

Preoperative Assessment

Cerebral MRI is indispensable. A 3-T T2 coronal sequence is of high interest, particularly in suprasellar meningiomas, to precisely localize the optic apparatus (Fig. 3). Millimetric CISS or FIESTA sequences are also valuable to identify the different CN trajectory. Different techniques of tractography are currently in development and will probably be available for clinical practice in the midterm [48]. Gadolinium enhancement is required to delineate the tumor, except in the pregnant women, when the nonenhanced MRI is usually considered sufficient for diagnosis.

A CT scan is required for the preoperative bone status assessment. The CT scan is also particularly helpful to

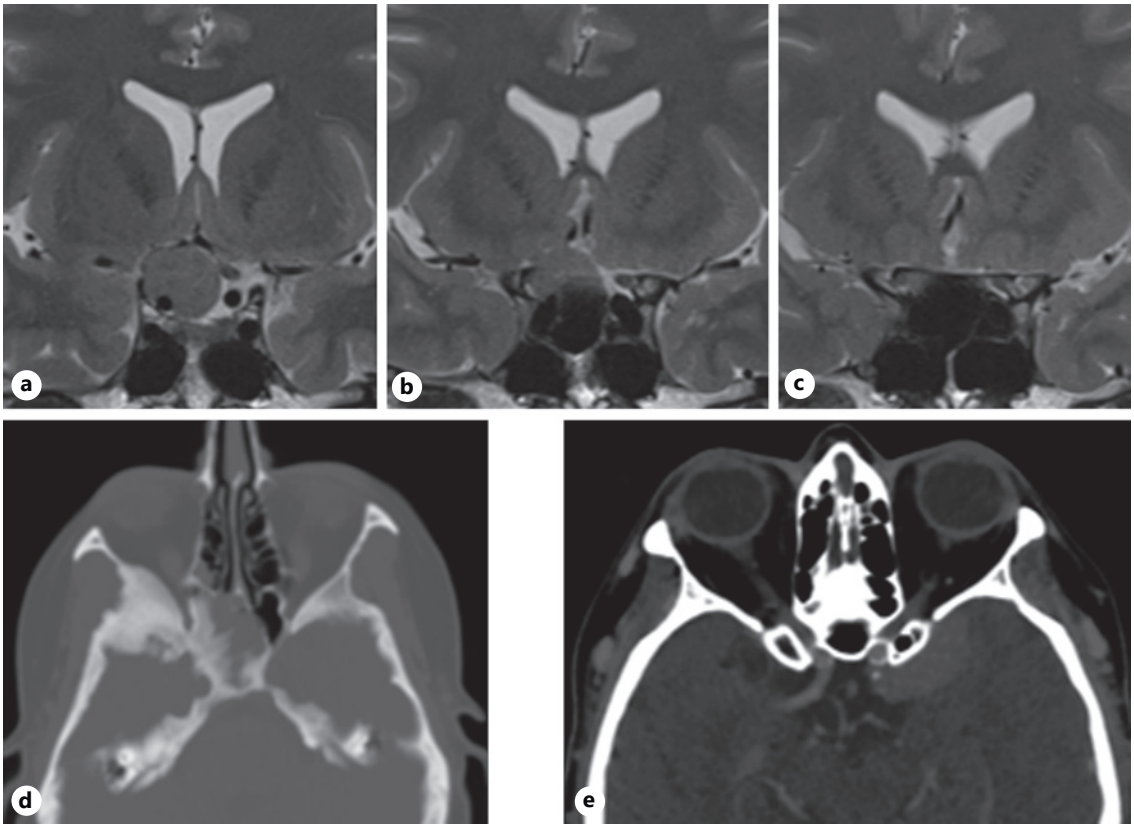

Fig. 3. Interest of 3-T T2-weighted coronal MRI (**a–c**) showing the relationship between tuberculum sellae meningiomas, ON, and optic canal invasion. Preoperative CT scan displaying an osteoma (**d**) as pneumatization of the anterior clinoid process and the different sinuses (**e**).

analyze the sinuses and anterior clinoid process pneumatization (Fig. 3). As previously recommended, visual examination should include visual acuity, the visual field (using standard Goldman perimetry techniques), and OCT assessment including the retinal nerve fiber layer + ganglion cell complex [43, 44, 46, 47]. The VIS (visual impairment score; guidelines of the German Ophthalmological Society) is an objective scoring system that could be used to precisely assess visual outcome and homogenize visual outcome results to compare patient series [49, 50].

Arteriography and embolization are rarely required in meningiomas and the indications are team dependent. In parasellar and particularly petroclival meningiomas, preoperative embolization could limit the peroperative bleeding, particularly in voluminous and complex cases.

Endocrinological assessment is not systematically performed in clinical practice and no clear recommendations exist, but the literature supports a systematic and complete preoperative assessment, particularly in tumors

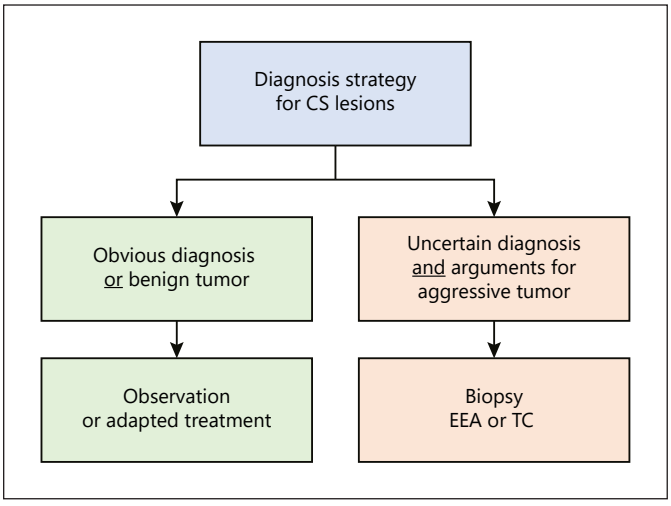

Fig. 4. Indication of biopsy for CS lesions. EEA, endoscopic endonasal approach; TC, transcranial approach.

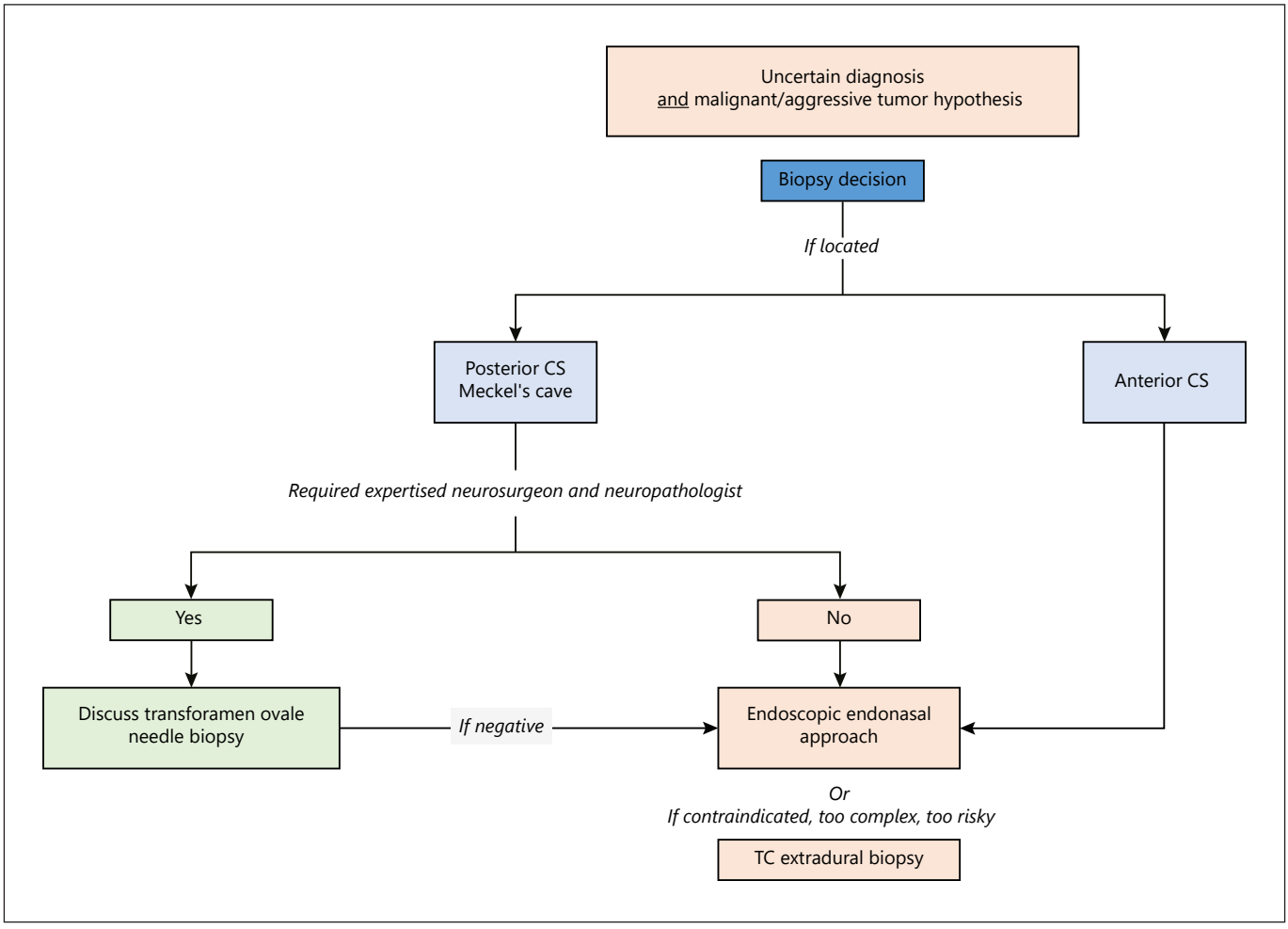

Fig. 5. Biopsy strategy for CS and Meckel's cave lesions suspected to be aggressive or malignant and with an uncertain diagnosis.

located close to the pituitary gland or the pituitary stalk as in case of pituitary dislocation [50, 51]. Hyperprolactinemia is probably the most frequently encountered endocrinological disturbance; hypopituitarism remains rare and cases of diabetes insipidus (DI) or syndrome of inappropriate secretion of ADH (SIADH) at diagnosis remain exceptional [52–56].

Diagnosis Management

In the benign tumors without any argument for aggressiveness or malignancy, diagnostic certainty is not required. Surgical removal or stereotactic radiosurgery (SRS) treatment could be proposed in case of growth. In contrast, in case of an uncertain diagnosis and aggressive or malignant features, surgical removal is recommended. But in specific locations such as the CS and Meckel's cave, where complete tumor removal is considered as usually nonreasonable, a biopsy is recommended. The indications for biopsy are summarized in the Figure 4. The biopsy strategy is described in Figure 5. Transforamen ovale needle biopsy could be an option for Meckel's cave and posterior CS lesions, but it requires an expert couple (neurosurgeon-neuropathologist) given the delicate approach and the small size of the tumoral sample [57]. The endoscopic endonasal approach is really of interest in anterior CS lesions or when a transforamen ovale biopsy is non-feasible or negative for Meckel's cave or posterior CS lesions [58–61]. The ICA trajectory should be carefully analyzed. Transcranial extradural biopsy is also a valuable alternative when endoscopic endonasal biopsy is considered complex or high risk. A transcranial minipterional approach could be proposed with a reasonable risk as illustrated in Figure 6.

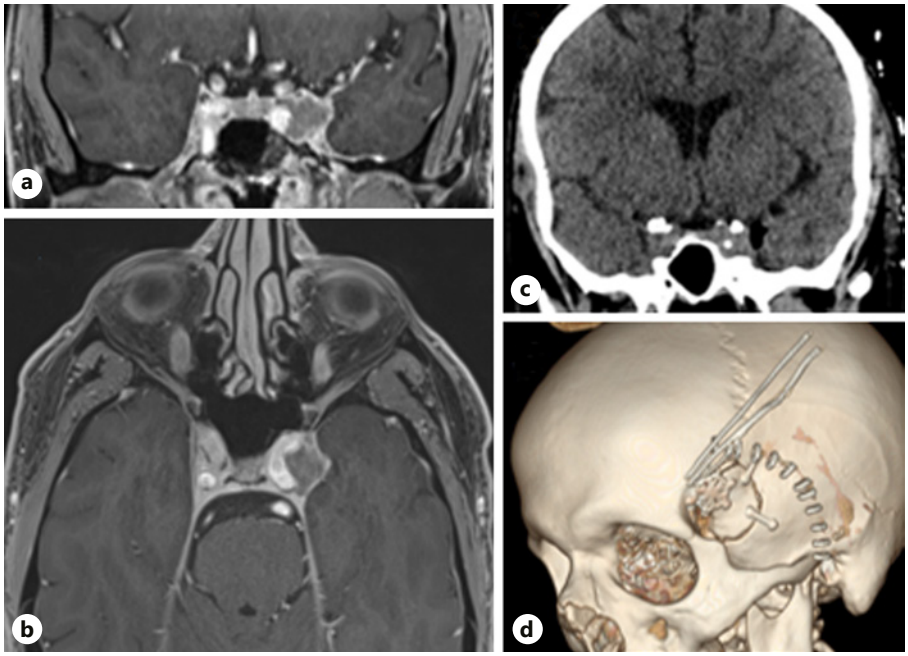

Fig. 6. Trancranial extradural CS biopsy. Case of a 55-year-old man with a history of myeloma with long-term remission. The clinical presentation included nerve III palsy and intense retroorbital headache. Diagnoses of myeloma, meningioma, and neurinoma were supected. Transcranial CS biopsy via a minipterional approach confirmed the diagnosis of myeloma. Preoperative T1-weighetd MRI with gadolinium enhancement (**a**, **b**). Postoperative CT scan (**c**) with 3-D bone reconstruction (**d**).

Therapeutic Management

Generalities

Intra-CS and Meckel's cave meningiomas are considered mostly nonsurgical. Amelot et al. [62] analyzed 53 patients with CS meningiomas. The median follow-up was 10.8 ± 5.5 years. One hundred percent of the patients with incidental findings remained nonsymptomatic at the end of follow-up. Eighty percent of all of the patients were nonsymptomatic at the end of the follow-up, and 83% of all of the patients did not show any tumor growth. This study shows that most CS meningiomas are nongrowing with a benign outcome even in oculomotor nerve palsy, suggesting observation as the initial strategy in most cases.

Lateral wall of the CS, medial sphenoidal wing, clinoidal, large petroclival, and suprasellar meningiomas are mostly surgically related to their location. Nevertheless, nongrowing and nonsymptomatic features likely lead us to propose observation, even in oculomotor nerve palsy.

Surgery remains the treatment of reference in meningiomas, but the surgical risks should not be underestimated. A clear explanation of the surgical risks and the balance of benefits versus risks should be provided to the patient. ON compression is probably the most formal symptom which leads to surgery. Tumoral impact on the cortex or the brainstem is also a formal surgical indication.

Growing and size-limited (small to medium) meningiomas could be treated by surgery or radiosurgery. The classical criterion of a tumor diameter ≤3cm for radiosurgery indication is currently not up to date; the final optimal treatment decision should be based on the tumor location, the proximity to the optic pathway and different critical structures, the peritumoral edema, the general medical status, the patient's age, and the patient's will. The safety and efficacy of SRS are high for small lesions and tend to decrease with tumor size. Pollock et al. [63] demonstrated a similar effect, comparing small to medium size Simpson grade I resected meningiomas. Therefore, SRS could be proposed for small to medium, well-limited and growing meningiomas with no or minimal symptoms and no optic pathway compression that are far from the optic pathways.

Radiation therapy (RT) indications would be proposed for large and poorly limited skull base tumors, with radiological and/or clinical progression, without any surgical or SRS alternative.

Surgical Approaches

CS, lateral Wall of the CS, and Clinoid Meningiomas Approaches

A pterional approach is usually required to access to the lateral wall of the CS. A fronto-orbitozygomatic approach improves the exposition of the CS. Dedoubling of the CS lateral wall is required to access to the tumor. In

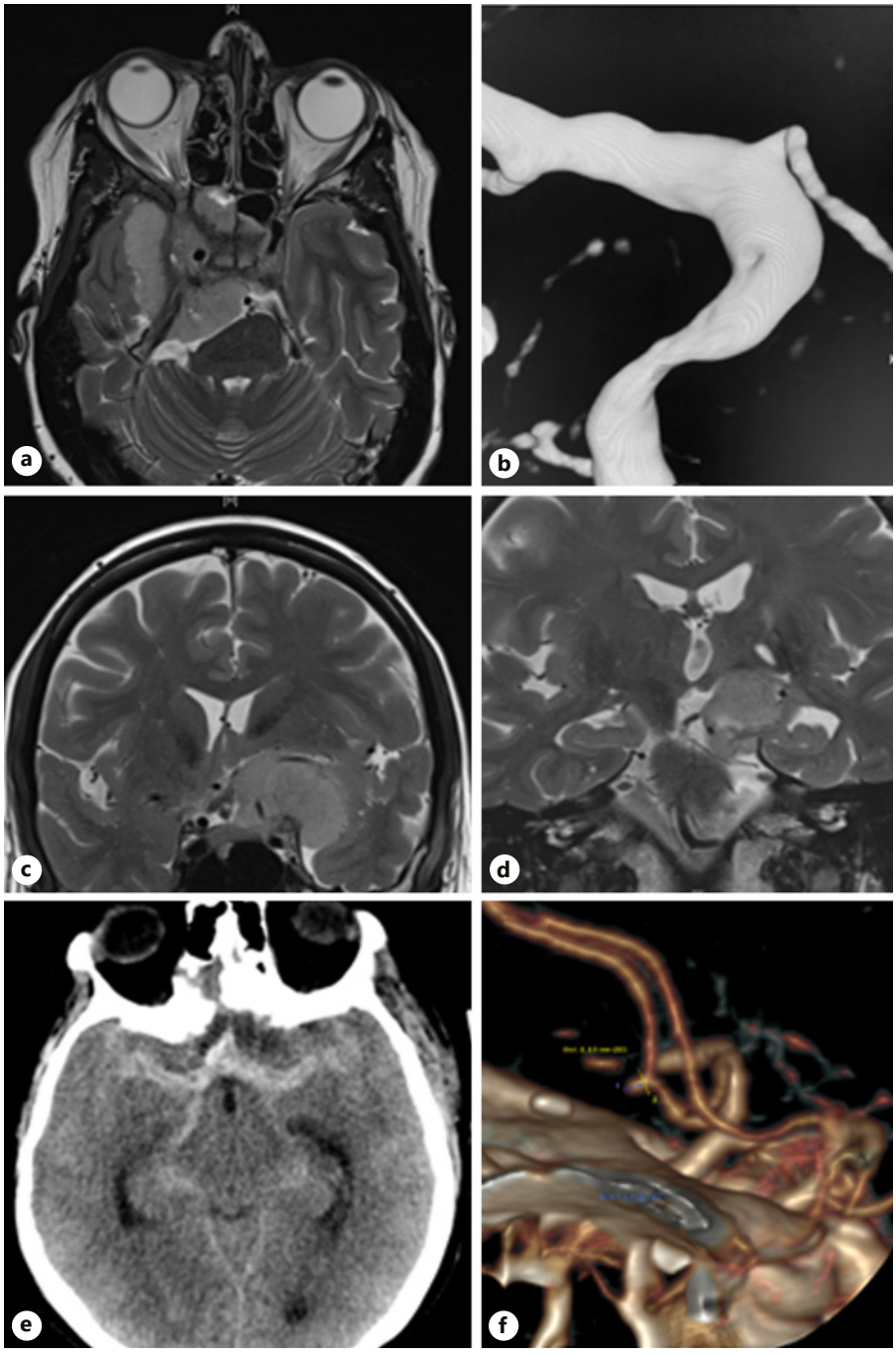

Fig. 7. Vascular surgery complications. Case 1: preoperative ICA lesion during ON decompression; preoperative repair; postoperative arteriography showing a defect on the ICA wall. ICA occlusion was performed with a favorable outcome. Preoperative axial T2-weighted (**a**) and T1-weighted MRI with gadolinium (**b**) enhancement and postoperative 3-D angiography (**c**). Case 2: anterior clinoid meningioma with ICA invasion and partial tumor removal. The patient presented a transient postoperative hemiparesia. The outcome was quickly favorable. MRI showed a limited brain infarct. Pre- (**d**) and postoperative (**e**) coronal T2-weighted MRI. Case 3: preoperative bleeding and brain swelling during meningioma surgery. Postoperative CT scan showing a subarachnoid hemorrhage with pseudo aneurysm on anterior cerebral artery A2. Postoperative CT scan (**f**) and 3-D angio-CT scan.

CS lateral wall meniniomas, only the exophytic lateral expansion is usually removed [64]. In anterior clinoid meningiomas, a clinoidectomy is required to expose the ICA and the ON, and it allows tumor devascularization and desinsertion [65, 66]. The first objective is to decompress the ON in case of preoperative visual impairment. ICA is the main concern during this surgery. Early exposition of the ICA is suggested to improve surgery safety and facilitate tumor dissection. In cases of supraclinoid ICA adventitia invasion, tumor removal will be incomplete [17]. Lesions of the ICA or perforating arteries arising from the the ICA could lead to dramatic hemorrhagic or ischemic consequences (Fig. 7). ON decompression could be performed by EEA or TC depending on the tumor and ON

compression side: medial compression of the ON will tend to result in proposal of EEA; conversely, lateral compression will tend to result in proposal of TC with clinoidectomy [67–69]. A case-by-case analysis is usually required.

CS decompression aims to improve the functional outcome and avoid aggressive surgical removal. EEA and TC approaches could be proposed depending on the location of the tumor, the compression, and the team habits, but the expected benefits for the patient remain uncertain. Literature data are poor and not sufficient to support systematic CS decompression in current clinical practice. The TC extradural approach has been previously described [64, 70, 71]. More recently, an endonasal approach was reported, providing interesting results on CN palsy but also an uncertain clinically relevant benefit for pituitary function [72–74].

Petroclival and Meckel's Cave Approaches

Different approaches could be proposed and combined as an anterior and/or posterior petrosectomy, retrosigmoid approach [75]. The best approach is a case-by-case decision. Insertion of the tumor, CN trajectory, venous configuration, tumor volume and expansion, and brainstem edema should be carefully preoperatively analyzed.

Tuberculum Sellae, Planum, and Diaphragm Sellae Meningiomas

The decision for a tuberculum sellae meningioma approach remains particularly debated. In the 20 last years, many approaches have been described. The transcranial approach was the first historically performed, but recent advances in endoscopic endonasal surgery have opened new perspectives. There is still a debate regarding the best approach, with different transcranial approaches including: the classical pterional approach; the key hole approach; subfrontal unilateral, supra orbital, interhemispheric approaches; and the endoscopic endonasal approach [50, 76–79]. Recent studies have demonstrated better visual outcomes after the endoscopic endonasal approach but, in contrast, a higher postoperative rate of cerebrospinal fluid leakage and a higher rate of arterial lesion [52, 80–83]. EEA could be an interesting option in the specific case of diaphragm sellae meningioma type C [54].

Today, the transcranial approach remains the most consensual and the most used approach in the neurosurgical community [50]. Considering the transcranial approach, selection of the best side approach also remains the subject of debate [84, 85]. Recent developments in mini-invasive surgery have led to decreased skin incisions, temporal muscle retraction, and bone flap size in proposed eyebrow or eyelid incision. For instance, the eyebrow approach is commonly used for tuberculum sellae meningiomas. However, the neurosurgeon should adapt the skin incision to the patient's cosmetic appearance and hairline and, at the same time, be careful to preserve the angle of work around the tumor and the ON. Transcranial endoscopy-assisted surgery could be an alternative to improve the quality of tumor resection, particularly in the blind area of the tuberculum sellae and avoiding complications related to an endonasal approach [86]. A precise preoperative case analysis and a case-by-case decision remain required.

The Notion of Incomplete Removal

As described by the Simpson [87] classification in 1957, complete tumor removal including the tumor insertion significantly decreases the risk of recurrence. In contrast, the particularity of skull base meningiomas is clearly the balance between the frequent benign meningioma feature and the potential morbidity of complete tumor removal. Incomplete removal is therefore frequent in skull base meningiomas, suggesting an increase in the risk of delayed recurrence and the interest of long-term follow-up.

Postoperative CN Outcome

In the case of preoperative ON compression and visual impairment, visual improvement is frequent, but the visual outcome is clearly related to the severity of impairment as determined by the preoperative visual assessment [50, 88]. In the case of ON tumoral invasion, the risk of postoperative visual impairment is high.

Surgery rarely improves oculomotor nerve palsy, and new postoperative CN palsy is frequent, particularly in complex CS or petroclival meningiomas [75]. In the case of meningioma intracavernous resection, the risk of postoperative worsening of the oculomotor function is particularly high [36]. The risk is also higher in CS meningiomas with petroclival extension. Complete oculomotor dysfunction can lead to a nonfunctional eye and impact the patient's quality-of-life.

Trigeminal neuralgia could be improved by decompression but it is rarely improved in the Meckel's cave and

nerve V invasion. Trigeminal nerve injury can also occur when peeling the lateral wall of the CS. In these situations the risk of a deafferentation lesion should be considered and carefully avoided. In V1 dysfunction, the loss of a corneal reflex severely increases the risk of keratitis. In anterior petrosectomy, preservation of the great petrous nerves is preferable to avoid dry eye syndrome.

Surgical Complications

Peroperative ICA lesions rarely occur but they remain a major concern in parasellar meningioma surgery given the severity of the hemorrhagic and neurological complications. The risk of ICA lesions is mostly higher in cases of caverno-clinoidal meningiomas that surround the ICA. In those cases, preoperative angiogram is necessary and balloon test occlusion should be discussed.

In peroperative vascular lesions, repair remains challenging and the long-term efficacy of the repair is uncertain, with the risk of postoperative pseudoaneurysm [89] (Fig. 7). A postoperative angiogram is usually required, and ICA occlusion is proposed in the case of a functional Willis circle. Delayed pseudoaneurysm could be treated by endovascular procedures but the endovascular possibilities are limited in early postopeperative pseudoaneurysm related to the need for double antiaggregation therapy [89]. Surgical ICA manipulation and lesions also increase the risk of stroke due to perforating artery lesions or embolic mechanisms.

Visual impairment is a classical complication. Drilling close to the ON should be carefully performed under a microscope with high irrigation to avoid ON thermic injury [90].

Postoperative CN complications were discussed in the previous paragraph.

Venous complications are probably the most frequent complications in meningioma surgery and could lead to edema and hematoma. The preoperative venous configuration should be carefully studied. Determination of the principal venous drainage of the temporal lobe as the Labbé vein location is required and could impact the approach decision as in posterior petrosectomy and sigmoid sinus transposition [91, 92].

Meningitis is a rare complication but early diagnosis is important. Exceptionally, severe and fulminant meningitis could lead to dramatic outcomes.

Postoperative Assessment

Postoperative CT and MRI are usually required in the first postoperative days. We propose a postoperative MRI follow-up at 3 months, 9 months, and then every year, which could be adapted in a case-by-case manner. Recommendations have been proposed by the EANO group depending on the WHO grade, with annual follow-up for WHO grade I and biannual follow-up for WHO grade II [93]. Postoperative visual assessment is required if the patient complains of impairment. In other cases, an early visual assessment is facultative. The most important visual assessment is at 3 months and 1 year, and then on a case-by-case basis.

A complete endocrine assessment is recommended during the first postoperative week (with intake and urinary output quantification) and at 3 months in cases of surgery close to the hypothalamus and the pituitary axis. Postoperative rates of partial or complete hypopituitarism and DI or SIADH are variable but remain very low [49, 55, 94–96]. Nevertheless, endocrinological complications are unpredictable, could be life-threatening, and are important to diagnose.

Long-Term Follow-Up and Outcome

The outcome is usually favorable, but rare aggressive multirecurrent cases could be challenging.

Long-term follow-up is required related to the risk of delayed recurrence. In contrast, long-term endocrine follow-up is of limited interest in the case of a normal postoperative assessment, except if the patient has undergone RT or SRS.

Complementary Therapies

RT and Proton Beam Therapy

Different RT modalities are currently available to treat postoperative parasellar meningioma residues. Systematic radiation therapy treatment is proposed to treat a residue of WHO grade II meningioma (including clear-cell meningioma) or WHO grade I with aggressive features. WHO grade I meningioma residues are amenable to observation [93, 97].

Fractionated RT including conventional radiotherapy and proton beam therapy remains a relevant option for large and poorly limited lesions [98, 99], but long-term tumoral control and the risk of malignant transformation

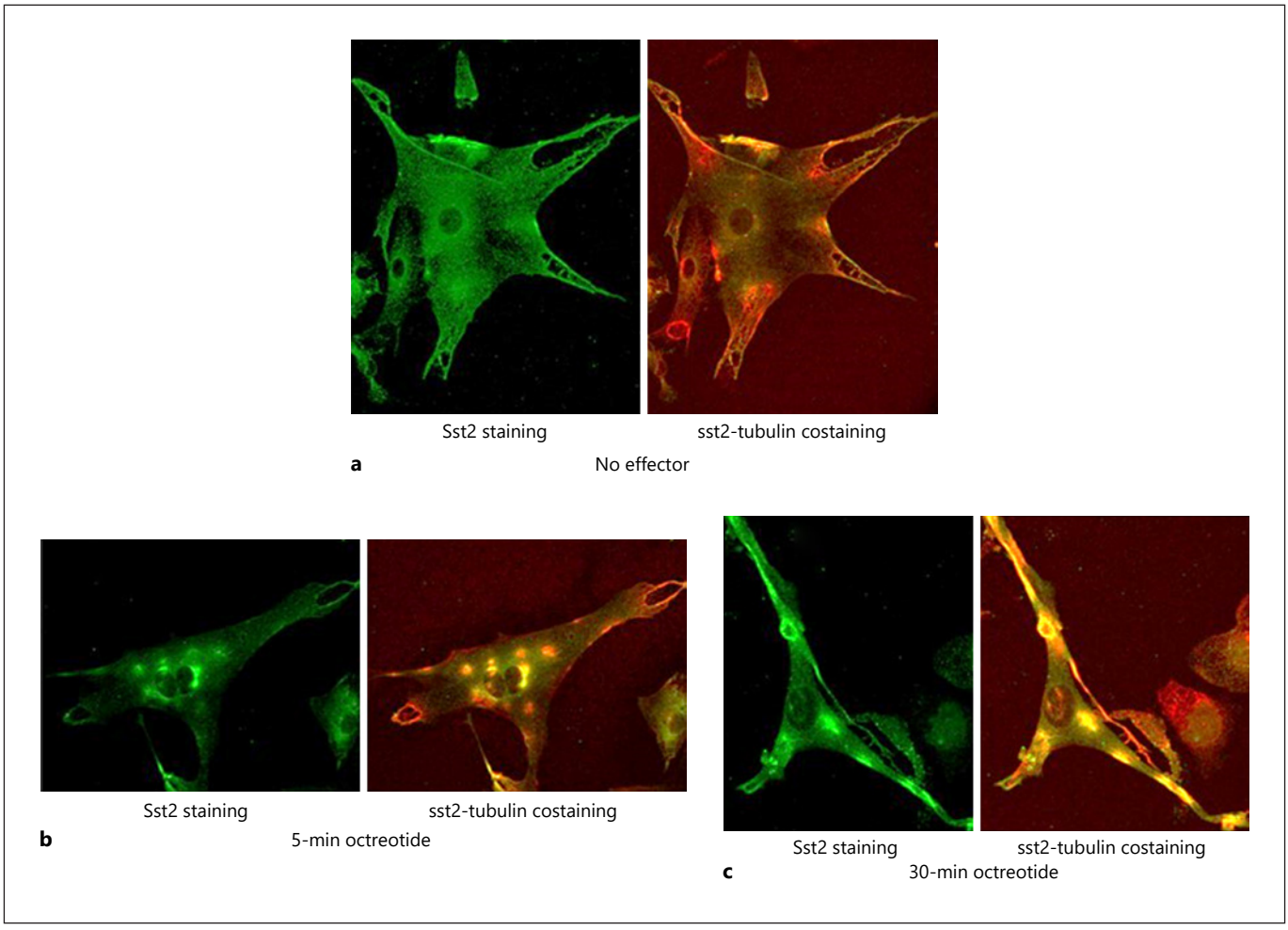

Fig. 8. In vitro study of SST2 receptor internalization under Octreotide in meningioma cells by immunostaining (from the DIP-NET team, MMG, France) without octreotide (**a**) and then after 5 (**b**) and 30 min (**c**) of octreotide impregnation.

remain unclear. Proton beam therapy is particularly adapted to parasellar lesions, but adverse events and the occurrence of radiation necrosis remain difficult to predict. The tumor recurrence or progression rate remains similar when comparing the different radiation technics, but SRS provides 2-fold higher rate of tumor volume regression versus fractionated RT [100–102].

Stereotactic Radiosurgery

SRS is mostly proposed for meningiomas located in the CS or Meckel's cave. The tumor or the postoperative residue should be small to medium sized, well limited, and distant from the ON. SRS could be hypofractionated in the case of proximity to the optic pathway [100, 103, 104]. In WHO grade I parasellar meningiomas, the outcome of radiosurgery is favorable [105–109]. The long-term recurrence rate also appears to be favorable but remains uncertain [110]. The risk of remote recurrence is persistent, whereas the risk of tumor transformation remains uncertain. Complications such as new nerve palsy or radiation necrosis are rare [107–111].

Medical Therapies

Medical therapies are rarely necessary in this location. For aggressive multirecurrent meningiomas, the combination of everolimus and octreotide as anti-VEGF drugs are of interest [112–114]. Somatostatine alone could be relevant for nonresectable skull base slowly growing meningiomas [24, 115]. Targeted therapy adapted to the non-*NF2* tumor mutations is also an option, particularly for parasellar meningiomas as reported in this case of invasive and metastasis skull base meningioma with a me-

ningothelial subtype and AKT1 mutation. Treatment with AKT inhibitor AZD5363 provides tumor control [116]. Immunotherapy seems more adapted to high-grade meningiomas [117–119].

Peptide Receptor Radionuclide Therapy

Peptide receptor radionuclide therapy (PRRT) with somatostatins could be a relevant alternative to extended skull base meningiomas (Fig 8). The aim of the therapy is to target SST2RA with a nuclear agent such as yttrium-90-DOTATOC or lutetium-177-DOTATATE. SST2RA expression is strong in most meningiomas and higher in the meningothelial subtype [24]. PRRT is already being used with success in clinical practice for gastropancreatic neuroendocrine tumors, which present a similar pattern of growth than low-grade meningiomas. The literature results are promising for low-grade meningiomas [120–124]. The hematologic and renal toxicity seems acceptable. The place of PRRT in meningiomas remain to be defined but these conclusions suggest that PRRT could be, in the near future, an alternative to conventional RT in extended skull base meningiomas with a low growth rate. In recurrent high-grade meningiomas, the literature results are disappointing [125].

Progestin-Associated/-Induced Meningiomas: Considerations and Management

Progestin intake should be investigated in each case at diagnosis, particularly for cyproterone acetate. The parasellar area is a classical location for progestin-associated meningiomas [126, 127]. An anterior and medial skull base location represents approximately 70% of progestin-associated meningiomas in our experience.

The French agency "Agence Nationale de Sécurité du Médicament et des Produits de Santé" performed a French epidemiologic study correlating the risk of operation or treatment with of meningioma by radiotherapy with the CPA intake. In conclusion, it highlights an increased risk (7-fold) of meningioma with a high dose of CPA versus a low dose, reaching ×20 if the cumulated dose exceeds 60 g.

Progestin discontinuation is required. Surgery is only recommended in cases of severe visual acuity impairment or threatening intracranial hypertension. However, in most cases, progestin discontinuation is sufficient to provide a tumoral volume decrease and clinical improvement. The long-term outcome seems favorable but remains uncertain, requiring long-term follow-up.

In our experience, tumoral growth is observed in approximately 5% of cases despite CPA discontinuation.

Pregnancy and Parasellar Meningiomas

Parasellar meningiomas are the most frequently diagnosed meningiomas during pregnancy [128–131]. This is related to the proximity to the optic pathway. The context of a high progesterone plasmatic level can lead to an increase in meningioma volume during pregnancy. This volume increase is usually reversible [132–134], which is not the case in severe visual disturbances. Therefore, in the case of severe visual impairment, meningioma surgical removal should be considered [128–131]. If there is moderate visual field impairment, tight observation could be proposed until the delivery, and the surgical decision should be discussed postpartum. The decision in each case should be multidisciplinary, made on a case-by-case basis, and adapted to the delivery term [132, 135].

Conclusion

Parasellar meningiomas remain mostly benign tumors with WHO grade I and a meningothelial subtype. Progestin intake should be investigated. The therapeutic strategy should be adapted to the tumor location and growth. "Wait and see" could be a (good) option. Endoscopy is a reliable alternative to conventional transcranial approaches for diagnosis of CS and Meckel's cave meningiomas and for ON decompression, but a case-by-case discussion about the best approach is recommended. A transcranial approach remains necessary for tumor removal in most cases. Long-term follow-up is required given the frequent incomplete tumor removal and the risk of delayed recurrence.

Radiosurgery is relevant for small and well-limited meningiomas, whereas RT and proton beam therapy are indicated for large extended nonoperable meningiomas. The place of the PPRT needs to be defined. Targeted therapy should be considered in rare recurrent and aggressive parasellar meningiomas.

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Statements of Ethics

This study was approved by the Aix-Marseille University Institutional Review Board.

Conflict of Interest Statement

The authors have no conflict of interests to declare.

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Author Contributions

Conceptualization: T.G. and T.B. Methodology: T.G., H.D., and M.B. Formal analysis: T.G. Investigation: A.B., J.R., and T.G. Resources and support: H.D. and M.B. Original draft preparation: T.G. Review and Editing: T.G., M.B., H.D., and J.R. Supervision: T.B., M.B., and H.D.

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