Tumors of the Skull

3

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3.1 Epidemiology

Skull tumors comprise a wide variety of entities, ranging from chronic inflammatory diseases to primary and secondary neoplasms. There are no valid data about the incidence of skull tumors in general, but the epidemiology of single entities has been assessed.

Osteoma is the most common diagnosis in benign skull neoplasms [21] and may be accompanied by Gardner's syndrome [2]. In most series, the second most common finding in benign calvarian tumors is hemangioma [8]. Benign osteoblastoma represents about 1% of all bone tumors, and a craniofacial localization is found in 15% of all osteoblastomas [2]. The most common malignant skull tumors are osteogenic sarcoma and chondrosarcoma. The former–in general–is the second most common primary malignant bone tumor after plasmocytoma. Osteogenic sarcoma occurs in all ages with a peak within the first 2 decades; 85% of osteogenic sarcoma arises before the age of 30 [23]. The main cranial locations are the maxilla and mandible, while manifestation in the calvaria is less common. In contrast, cranial chondrosarcoma arises preferentially at the skull base, accounting for 6% of all skull base tumors [9]. The highest incidence is found in the second decade; however, chondrosarcomas may be found at any age.

3.2 Symptoms and Clinical Signs

Most entities can be found in any cranial bone; therefore, the clinical presentation varies according to the site of tumor origin. Tumors involving the paranasal sinuses may present with frontal headache and recurrent sinusitis.

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Intracranial extension of large skull tumors can cause epidural compression and symptoms of elevated intracranial pressure, such as headache and nausea. Tumors of the skull base may present with cranial nerve symptoms, such as diplopia, visual or hearing loss, olfactory sensations, or impaired swallowing function. However, the most common symptom is a painless, slowly growing epicranial mass, which may vary widely in size and velocity of growth. Localized pain is a typical symptom for benign osteoid osteoma, aneurysmal bone cyst, or all types of rapidly growing malignant tumors.

3.3 Diagnostics

3.3.1 Synopsis

Simple calvarian tumors are sufficiently diagnosed by CT. The modern assessment of skull base tumors or complex calvarian tumors is multimodal: MRI is mandatory to evaluate soft-tissue structures and CT for visualizing bone alterations. In some cases, there are indications for angiography or radionuclide scans.

The basic method for diagnostics in skull tumors is still CT. It is superior to MRI in assessing the bony structures and can display bone destruction as well as bone formation or intratumoral calcification in a proper way. Similar information may also be provided by plain skull X-ray films if the tumor is localized at the calvaria. Altogether, CT may be sufficient for the diagnosis of small calvarian tumors without intracranial growth. MRI, including T2-weighted images and contrast-enhanced T1-weighted images, is important for the investigation of tumors at the skull base, where CT diagnosis of soft-tissue structures is impaired by artifacts. Involvement of cranial nerves, which are surrounded by CSF during their intradural extension, is best visualized by constructive interference in steady-state (CISS) sequences. Additionally, in case of intracranial growth of skull tumors, MRI provides more valuable information about the involvement of intracranial structures. MRI angiography may be helpful if the venous sinuses or arterial structures at the skull base are involved. Sometimes the classic invasive angiography may be indicated, particularly in cases where interventional procedures, such as embolization, are discussed. Radionuclide scans using technetium 99 (99mTc) may provide additional information in diffusely growing lesions, such as fibrous dysplasia [24].

3.4 Staging and Classification

3.4.1 Synopsis

There is a wide variety of histopathological diagnoses in tumors of the skull. These neoplasms comprise tumors of bony, cartilaginous, fibrous, histiocytic, or hematological origin. In several types of skull tumors, the tissue of origin is still a matter of debate among pathologists. This chapter does not intend to provide a complete list of all tumorous disorders of the cranium, but will concentrate on the most common and best characterized entities.

3.5 Tumors of Bony Origin

Osteomas are the most common primary tumors in the craniofacial bones. Skull osteomas are slowly growing, benign entities usually arising from the tabula externa and growing outward. Therefore, intracranial extension is rare. Two distinct subtypes can be differentiated histopathologically: the compact ("ivory") and the spongy osteoma, with the former being the more common variety. Compact osteoma consists of dense lamellar bone, whereas spongy osteoma is characterized by a trabecular architecture with a peripheral bony margin.

Osteoid osteoma is another benign lesion, which is common in the skeleton in general but is found extremely rarely within the skull. It consists of a well-defined osteolytic nidus, comprised of osteoid matrix, bony trabeculae, and vessels. The nidus is surrounded by dense cortical sclerosis [8].

Osteoblastoma is a rare, benign entity with strong histopathological similarities to osteoid osteoma. Therefore, it has also been termed "giant osteoid osteoma." Compared with osteoid osteoma, osteoblastomas are usually larger and possess more fibrous stroma, many multinucleated giant cells, extravasated blood, and less osteoid. Local recurrence after subtotal excision as well as malignant transformation has been reported; therefore, complete excision should be preferred to curettage of the nidus [11].

Osteogenic sarcoma is a highly malignant tumor occurring before the age of 30 in 85% and after the age of 60 in 10% of patients. It is the second most common bone tumor after multiple myeloma. Involvement of craniofacial bones is seen more often in elderly patients, and growth within the skull accounts for less than 1% of all osteogenic sarcomas. These tumors may grow in an osteolytic or osteoblastic pattern. The histological diagnosis is based on the identification of a malignant spindle-cell stroma that produces osteoid or immature bone. Fibroblastic, chondroblastic, and osteoblastic subtypes of osteogenic sarcoma can be distinguished, but these types do not correspond with the prognosis. In elderly patients, more than half of all osteogenic sarcomas arise secondary to fibrous dysplasia or Paget's disease [8]. Previous radiation therapy or occurrence of retinoblastoma is also a known risk factor for secondary osteosarcoma. The 500-fold increased risk of developing an osteogenic sarcoma for retinoblastoma patients might be due to a common mutation of the retinoblastoma tumor suppressor gene, which is observed in a variety of malignancies [19].

3.6 Tumors of Cartilaginous Origin

Benign, well-circumscribed *chondromas* and locally aggressive *chondroblastomas* are very rare tumors of the skull. There are only 59 cases of temporal chondroblastomas, which is the typical localization of this entity, reported in the literature [5]. Both entities may expand the cortex of the bone and typically show intralesional calcifications, which may display a pathognomonic "chicken wire" arrangement in chondroblastomas.

Chondrosarcoma is the third most common malignant tumor of bone, following multiple myeloma and osteogenic sarcoma. Patients with cranial manifestations of chondrosarcoma are usually younger (peak second decade) than patients with extracranial manifestations (peak fourth decade). Some 80% of cranial chondrosarcomas arise in the skull base, representing 6% of all skull base tumors [9]. Two subtypes can be differentiated histologically, the myxochondrosarcoma and the mesenchymal (dedifferentiated) chondrosarcoma. The former is characterized histopathologically by a myxomatous stroma and cystic degeneration, the latter by absence of cartilage lobules and presence of spindle-cell sarcomatous areas. Mesenchymal chondrosarcoma seems to have a poorer prognosis than myxochondrosarcoma; the former subtype representing 80% of recurrent chondrosarcomas after surgical resection [7]. Other prognostic factors are cellularity and nuclear atypia, stage, and presence of metastases [14].

3.7 Tumors of Histiocytotic Origin

One of the most common benign lesions found in the calvaria is *eosinophilic granuloma*. It is a proliferative disease of Langerhans-type histiocytes and may be one manifestation of histiocytosis X. Eosinophilic granuloma may present as a single lesion or as part of the Hand-Schüller-Christian syndrome, which is characterized by the triad of diabetes insipidus, exophthalmos, and bony lesions, located in the skull. Eosinophilic granuloma in general may involve any bone, but the skull is the most commonly affected site. Some 34% of patients with eosinophilic granuloma are younger than 4 years of age; 74% are younger than 20 years [8]. The radiological appearance is an osteolytic lesion without peripheral sclerosis (Fig. 3.1). Small eosinophilic granulomas may shrink or even disappear after local injection of corticosteroids, which therefore should be the first choice of therapy. If resection is performed, brownish masses are found, which may contain cysts or hemorrhagic fluid. Histiocytes are also involved in locally aggressive or malignant tumors, such as *giant-cell tumor* of the bone, *Ewing's sarcoma*, or *malignant fibrous histiocytoma*. However, skull manifestations of these entities are extremely uncommon. Thus, these tumors represent very rare differential diagnoses of skull tumors.

3.8 Fibrous Dysplasia

Fibrous dysplasia is characterized by the presence of woven bone that has not transformed to lamellar bone during normal evolutionary development. The etiology of fibrous dysplasia has not been explored yet; it occurs spontaneously, and there is no evidence for Mendelian inheritance. A mutation of the G(s) alpha subunit and activation of *C-FOS* and other proto-oncogenes have been observed, representing possible etiologic mechanisms [16]. Fibrous dysplasia occurs in the monostotic form or polyostotic form involving multiple bone sites.

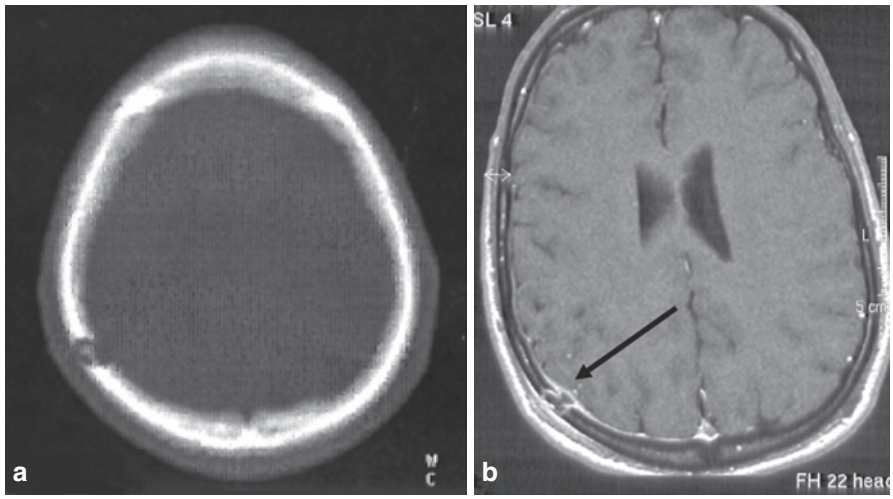

Fig. 3.1 (**a**) CT scan of a parietal eosinophilic granuloma showing a small, osteolytic lesion without any space-occupying effect or any sclerotic reaction. (**b**) T1-weighted MRI of the same patient showing slight contrast enhancement around the lesion (*arrow*)

Of all patients with fibrous dysplasia, 3% have McCune–Albright syndrome, which is characterized by precocious puberty, hyperpigmented maculae, and polyostotic fibrous dysplasia. The typical histological appearance of fibrous dysplasia is anvil-shaped trabeculae of woven bone surrounded by swirls of abundant fibrous tissue. The radiological appearance may be cystic, sclerotic, or mixed. The cystic form is usually present in the calvaria with a thinned and bulged outer table and a thickened, but preserved inner table. The sclerotic form is typical for fibrous dysplasia of the skull base, mostly present in the anterior and middle fossa, ignoring any suture lines. The mixed form, which is also called "pagetoid" form, is found in patients older than 30 years of age, whereas the other forms are observed in younger individuals. Therefore, the pagetoid form is considered a natural progression of the cystic and sclerotic form. Patients with fibrous dysplasia are considered to have a 400-fold increased risk of developing malignant bone tumors, with osteogenic sarcoma being the most common entity in this patient population [4]. *Paget's disease* is an important differential diagnosis to fibrous dysplasia. Paget's disease is a premalignant condition with increased bone resorption and bone formation [10]. Woven bone replaces lamellar bone in contrast to fibrous dysplasia where not even lamellar bone develops. Paget's disease occurs in elderly patients, and malignant transformation into osteogenic sarcoma (50%), fibrosarcoma (30%), chondrosarcoma (16%), or other malignancies occurs in about 2% of patients [8].

3.9 Miscellaneous

Besides tumors of well-defined, bony, chondroid, or histiocytic origin, a variety of tumors arise from connective tissue or poorly differentiated mesenchymal structures. Tumors arising from vascular structures are found in the calvaria as well, such as the most common malignant neoplasm of the bone in adults, plasmocytoma.

Plasmocytoma, also known as multiple myeloma, may involve any bone, but the vertebral bodies, ribs, pelvic bones, and skull are most frequently involved. Plasmocytoma usually produces multiple osteolytic lesions that may be pathognomonic on skull X-ray. These lesions are highly vascularized, with the blood supply derived from scalp arteries. Solitary plasmocytoma of the skull is an extremely rare lesion representing a single mass of plasma cells without any sign of systemic disease.

Hemangioma is the second most common skull tumor–after osteoma–in several series comprising 10% of benign skull neoplasms [6, 20]. The incidence of calvarian hemangioma increases with age, with a peak between the 4th and sixth decade. Two distinct subtypes are differentiated: the more common sessile hemangioma, which causes an expansion of the diploe and represents a well-demarcated, lytic lesion, and the globular type, which arises from the skull base and acts like a space-occupying lesion. Remnants of the bony trabecular structure are usually seen in

hemangioma, but the pathognomonic bony "sunburst" striations occur in only 10–15% of hemangiomas. Hemangiomas are classified according to their vessel size, with cavernous hemangiomas being the most common entity within the skull. Important differential diagnoses for hemangioma are giant-cell tumor and–in particular–*aneurysmal bone cyst***.** The latter entity is characterized by a multiloculated, painful swelling and a thin-walled bone cyst filled with unclotted blood.

One of the most common neoplasms within the skull is *intraosseous meningioma*, which usually grows in an osteoplastic pattern and arises within the anterior fossa. This entity is described in detail elsewhere in this textbook.

An important differential diagnosis to any primary bone tumor is *metastatic carcinoma*. These lesions, derived from breast, prostate, ovarian, or many other types of cancer, may arise in any bone and have to be treated within a comprehensive treatment concept (Fig. 3.2).

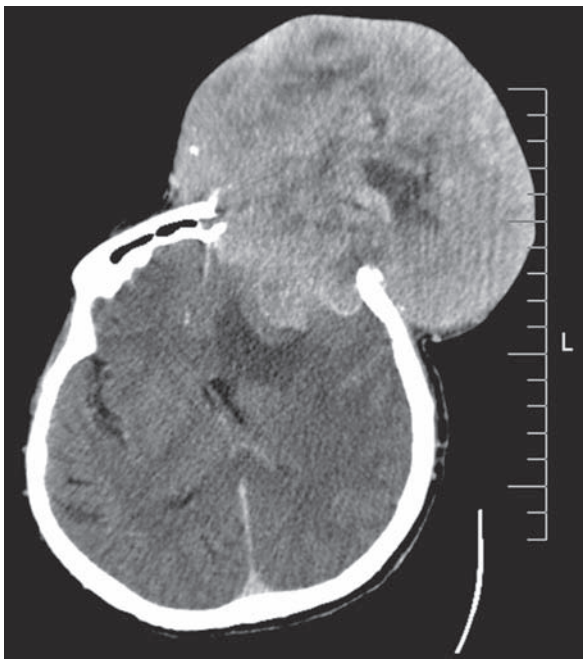

Fig. 3.2 CT scan of a skull metastasis from ovarian cancer. This mass lesion has been growing for more than 6 months in parallel to systemic bone metastases. The tumor displays a sharp demarcation towards the brain, significant perifocal edema, and no evidence of intratumoral sclerosis

3.10 Treatment

3.10.1 Synopsis

Total surgical resection is the standard treatment for benign and most malignant tumors of the skull. Radiation and chemotherapy may be indicated as adjuvant options in case of metastatic or incompletely resected tumors. Local injection of corticosteroids should be considered in the case of small eosinophilic granuloma.

3.10.2 Surgery

The standard treatment for benign skull tumors or tumors of unknown etiology is total surgical resection. Most calvarian tumors are palpable, and therefore, a straight skin incision above the tumor can be made depending on the size of the tumor. In small, nonpalpable tumors, neuronavigation or marking of the lesion during CT scanning may be useful to ensure a minimal approach. If a complete resection is accomplished, the bone defect should be covered by cranioplasty, e.g., by artificial polymers. Skull base tumors still represent a major surgical challenge in many cases. Even locally aggressive or malignant tumors like chondrosarcomas may be cured by total excision [14]. Therefore, transfrontal, transsphenoidal, midfacial, pterional, or transzygomatic approaches to the anterior skull base may be used for en bloc resection of these tumors. The risk of cranial nerve impairment or even sacrifice of one carotid artery to enable complete removal has to be discussed with the patient before the procedure (please see Chap. 17). In large skull base neoplasms or bone-forming conditions like fibrous dysplasia, decompression of single cranial nerves may be indicated to improve or prevent nerve dysfunctions, such as visual loss or trigeminal neuralgia [3, 17].

3.10.3 Radiotherapy

The vast majority of skull tumors are cured by surgery alone. However, radiotherapy may be indicated in malignant tumors of the skull after incomplete resection. In large skull base tumors, commonly

chondrosarcomas, which often are nonresectable despite sophisticated skull base approaches, a combined treatment regime consisting of surgery and radiation may be the therapy of choice. In particular, radiosurgery by gamma knife [12] or cyber knife techniques seems to be a valuable adjunct to surgery for chordomas and chondrosarcomas. In premalignant bone-forming conditions, such as Paget's disease or fibrous dysplasia, radiation is even contraindicated, since radiation increases the risk of secondary malignancies [13].

3.10.4 Chemotherapy/Medical Therapy

There are only a few indications for chemotherapy in the treatment of skull tumors. High-dose chemotherapeutic regimes combined with autologous stem-cell transplantation and currently anti-angiogenic therapy are standard treatment for plasmocytoma. Metastatic malignancies primarily located at the skull, such as osteogenic sarcoma or Ewing's sarcoma, also have to be treated by chemotherapy within a multimodality concept. Medical treatment is required in conditions with increased bone turnover, such as fibrous dysplasia, and–even more–Paget's disease. Second- or third-generation bisphosphonates have been shown to inhibit bone turnover in these conditions effectively [10]. However, in general the majority of tumors of the skull are successfully treated by surgical resection and do not need any adjunctive therapy.

3.11 Prognosis/Quality of Life

The prognosis of skull base tumors is defined by the tumor entity. All benign, totally removed tumors have an excellent prognosis. The same is true for locally aggressive or malignant nonmetastatic tumors that have been resected completely. In metastatic tumors, the prognosis depends on the systemic control of the disease. Quality of life may be impaired by the degree of resection, particularly in the frontal or skull base area. Cranial nerve dysfunction may lead to a significant worsening in the quality of life. Cosmetic alterations due to large bone defects should be avoided by adequate plastic techniques, e.g., polymer plastic in calvarian defects or autologous bone grafts in skull base surgery.

3.12 Follow-Up/Specific Problems and Measures

If a benign tumor of the skull is excised completely, as documented by postoperative imaging, no further follow-up is mandatory. However, an intense local and systemic follow-up has to be performed in possibly metastatic or incompletely resected malignant skull tumors. In incompletely resected chondrosarcomas, MRI and CT are recommended every 6 months; highly malignant tumors, such as osteogenic sarcoma, need local checks every 3 months for the first 2 years, followed by further checks twice a year.

3.13 Future Perspectives

Modern skull base surgery has already provided the chance to cure even complex processes by total resection or to improve local control of these lesions. Improving imaging modalities based on MRI, CT, or radionuclide scans will allow better demarcation of skull base processes. Implementation of this imaging information in modern neuronavigation systems will provide the basis for more extensive curative surgical approaches. On the other hand, future developments in radiation protocols based on proton beam or carbon ion techniques may enhance the chance of local control of nonresectable neoplasms [15, 18]. Sparing functional structures, such as cranial nerves, by a sharp delineation of the radiation target will be extremely important in the radiotherapeutic treatment of these patients. Therefore, LINAC-, gamma knife- or cyber knife-based radiosurgery is also a rapidly developing field in the therapy of skull base tumors [9]. Highly vascular skull base tumors may be treated with increasing frequency by interventional neuroradiology employing different embolization techniques [22]. Currently, these procedures are performed preoperatively to decrease blood loss; however, many tumors may be completely controlled by these techniques alone [1].

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