Metastatic Skull Tumours:
Diagnosis and Management

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Introduction

Advances in oncology have extended survival for cancer patients, leading to a larger population at risk for complication of metastases. Skull metastases have rarely been clinically diagnosed, but are frequently found in autopsy and head magnetic resonance (MR) imaging for staging in cancer patients [1, 2]. Skull metastasis has received limited neuro-oncological attention. Clinical studies for comparative treatment options or evidence-based practice guidelines are not available. The aim of this review is to present clinical features of and treatment strategies for patients with haematogenous skull metastases located at either the calvarium or the skull base.

Epidemiology

At post mortem examination, up to 70 % of patients dying of prostate or breast cancer have skeletal metastases. In patients with prostate cancer, 10 % have bone metastases at presentation [1]. Carcinomas of the thyroid, kidney, and lung also commonly give rise to bone metastases, with an incidence at post mortem examination of 30–40 % [1].

The true incidence of skull metastasis is not known. Reports have described skull metastases from all types of primary cancers, most commonly from breast, lung, prostate, and thyroid cancers [2, 3]. As for skull-base metastases, Laigle-Donadey reported that the most frequent primary neoplasms were prostate cancer (38 %) and breast cancer (20.5 %) in 279 patients in the literature [4]. Many other neoplasms affected the skull base: lung, colon, renal, thyroid cancers, lymphoma, melanoma, multiple myeloma, and neuroblastoma. Metastatic skull tumours are a late event in the course of cancer at a stage in which many patients already have disseminated disease, particularly other bone metastases [5]. However, skull-base involvement constituted the first sign of malignant tumours in 28 % of 279 patients [4].

Pathophysiology

Haematogenous spread to the skull or the meninges is the most frequent cause, particularly from a lung metastasis from a primary tumour. A postulated possible mechanism might be retrograde seeding through the Batson’s valveless venous plexus from pelvic structures to the basilar plexus of veins without transiting through the lungs [6]. Direct extension or migration along the cranial nerves or perivascular structures from contiguous head and neck tumours are less common [7].

Clinical Presentation

Skull metastasis is basically in the class of systemic bone metastases, but it never causes pathologic fracture which is prominent in skeletal metastasis morbidity. Calvarial metastases are mostly asymptomatic, until they invade into dura mater, compress dural sinuses, or form a mass sufficient to cause cosmetic problems [3]. On the other hand, skull-base metastases frequently cause progressive ipsilateral involve-

Table 1. Tumour location and clinical syndromes in skull-base metastases. From [5].

<table>
<thead>
<tr>
<th>Location and syndrome</th>
<th>Cranial nerves</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orbital</td>
<td>II, III, IV, V, VI</td>
<td>Supraorbital pain, Diplopia, Exophthalmos</td>
</tr>
<tr>
<td>Parasellar</td>
<td>III, IV, V, VI</td>
<td>Frontal headache, Diplopia</td>
</tr>
<tr>
<td>Middle fossa (Gas-serian ganglion)</td>
<td>V, VI, VII, VIII</td>
<td>Facial numbness, Atypical facial pain, Abducens palsy, Hearing loss, Facial paresis</td>
</tr>
<tr>
<td>Jugular foramen</td>
<td>IX, X, XI, XII</td>
<td>Occipital pain, Dysphagia, Hoarseness</td>
</tr>
<tr>
<td>Occipital condyle</td>
<td>XII</td>
<td>Occipital pain (severe), Neck stiffness, Dysarthria, Dysphagia</td>
</tr>
</tbody>
</table>
ment of cranial nerves, pain, or increased intracranial pressure resulting in poor quality of life (QoL). Especially dysphagia, diplopia, trigeminal and occipital neuralgia are seriously disabling symptoms and are alarming signs of skull-base involvement in cancer patients. For a high index of suspicion and for prompt diagnosis to lead to personalized treatment of the patients, 5 significant syndromes have been identified according to the metastatic site: the orbital, parasellar, middle-fossa, jugular foramen, and occipital condyle syndromes (Table 1) [5]. Cases representative of the 5 syndromes are shown in Figure 1.

The overall prognosis is poor, with a median survival of about 2.5 years in 279 patients between 1963 and 2003 [4]. Survival time after diagnosis of skull metastases mainly depends on the prognosis of the primary cancers [4, 8].

**Diagnosis**

MR imaging is the best method to detect skull metastases [4], which appear as focal lesions of low-intensity signal on pre-contrast T1-weighted MR images. Contrast-enhanced fat-saturated sequence is important to demarcate the lesions in bone marrow fat [2]. MR imaging demonstrates tumour invasion into the dura mater, brain surface, or cranial nerves better than any other imaging modality. On X-ray film and CT scan, calvarial metastases are focal osteolytic or osteoblastic lesions of both the inner and the outer table. Radionuclide bone studies are still valuable screening tests to detect bone metastases [7]. Metastasis to the calvarium is easy to detect, but skull-base metastases that involve the ethmoid and sphenoid bones, clivus, and pyramids remain underestimated because their clinical expression is inconstant and because these regions are difficult to explore, even at autopsy [4]. When a cancer patient presents with headache, pain, or cranial nerve signs, a skull-base metastasis must be included in the differential diagnosis process. Prompt diagnosis is crucial for appropriate management to relieve symptoms of skull-base metastases.

Differential diagnosis consists of haemangioma, epidermoid cyst, meningioma, fibrous dysplasia, histiocytosis, neuroblastoma, primary sarcomas, haematologic malignancies, and others. In a surgical case series of osteolytic calvarial lesions, Hong reported that the most common pathological diagnosis was metastatic tumour in 25% of 36 patients [9].
### Treatment

#### Radiation Therapy

For patients with painful bone metastases, palliative radiotherapy gave an overall response rate for pain at 60% in 5000 patients in a total of 16 randomized trials [10].

For patients with symptomatic skull-base metastases, Vikram et al reported that local radiotherapy relieved symptoms in 78% of 46 patients, with improvement lasting until death in 81% of the responders [8]. One must note that the likelihood of response dropped sharply if treatment was delayed. Improvement was observed in 87% of patients with symptoms lasting < 1 month, while in only 25% of patients with symptoms > 3 months. Therefore, they insisted that radiation therapy should not be withheld for patients with suspected skull-base metastases even if radiographic investigation is negative [8].

Figure 2 shows MR images of a patient with a huge calvarial metastasis from thyroid cancer with good response to radiation therapy. Radiation therapy is indicated even for asymptomatic skull metastases when they pose impending risks of dural sinus occlusion or mass effect with rapid growth (Figure 3).

Stereotactic radiosurgery (SRS) is a minimally invasive palliative option for primary management as well as for treatment of postsurgical or post-radiotherapeutic residual or recurrent skull-base metastases [11]. Response rates vary between 65% and 90% [11]. The main limitation of SRS is related to the size of the lesions. Patients with larger lesions near sensitive structures or in previously irradiated fields might benefit from fractionated stereotactic radiation techniques [12].

#### Chemotherapy

Patients with both skull and systemic bone metastases or with symptomatic skull metastases may undergo chemotherapy and hormonal therapy based on specific tumour types in addition to radiotherapy (Figure 4).

Much progress has been accomplished for the treatment of bone metastasis with bone resorption-inhibitory drugs. A human monoclonal antibody-inhibiting RANK ligand, denosumab, proved superior to bisphosphonate zoledronic acid in preventing skeletal-related events in patients with breast and prostate cancers, or achieved non-inferior effects in patients with other solid tumours in phase-III trials [13]. Osteonecrosis of the jaw is the most important side effect of both compounds [14]. Potential major roles for antiresorptive agents are the prevention of bone metastases and improvement in survival in specific cancers. The contribution of these agents for patients with skull metastasis alone is to be examined.

#### Surgery

The goal of surgery for skull metastases is to provide rapid symptom relief and to preserve function with low morbidity. Surgery should be considered for the sake of histological diagnosis or for palliative decompression of radiotherapy-resistant tumours with worsening neurological deficits. Patients should be critically selected based on their clinical and functional status and also on supposed surgical morbidity. Michael et al reported that only 27 of 900 patients with calvarial metastases underwent surgery between 1993 and 1999 [3], and Chamoun reported that another 27 patients with skull-base metastases underwent surgery between 1996 and 2009 [15] at the MD Anderson Cancer Centre.

To achieve total removal, a wide resection of the lesion should be performed with removal of marginal bone tissue as well as resection of any infiltrated dura mater or skin [9] (Figure 5). Median survival times after cranial surgery have been reported as 8–11.4 months [3, 15, 16].

#### Conclusion

Patients with skull-base metastases present with syndromes of cranial neuropathies and headache or pain, and patients with calvarial metastases may have dural sinus occlusion or cosmetic problems. Patients can benefit from early diagnosis of the tumour and surrounding neurovascular structures on MR imaging and radiation therapy.
Metastatic Skull Tumours

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Conflict of Interest

None.

References: