Volume 4 (2014) // Issue 2 // e-ISSN 2224-3453

European Association of NeuroOncology Magazine

Neurology · Neurosurgery · Medical Oncology · Radiotherapy · Paediatric Neuro-oncology · Neuropathology · Neuroradiology · Neuroimaging · Nursing · Patient Issues

Metastatic Skull Tumours:

Diagnosis and Management

Mitsuya K, Nakasu Y

European Association of NeuroOncology Magazine 2014; 4 (2) 71-74

Homepage

www.kup.at/journals/eano/index.html

Online Database Featuring Author, Key Word and Full-Text Search

THE EUROPEAN ASSOCIATION OF NEUROONCOLOGY

Member of the DOAJ

Indexed in EMBASE

Krause & Pachernegg GmbH · VERLAG für MEDIZIN und WIRTSCHAFT · A-3003 Gablitz, Austria

Metastatic Skull Tumours: Diagnosis and Management

Koichi Mitsuya, Yoko Nakasu

Abstract: Metastases of the skull are classified into 2 anatomical groups, presenting distinct clinical features. One is calvarial metastasis, which is usually asymptomatic but may cause dural invasion, dural sinus occlusion, or cosmetic problems. The other is skull-base metastasis, which presents with cranial-nerve involvement leading to devastating symptoms. A high index of suspicion based on new-onset cranial nerve deficits or craniofacial pain in a cancer patient is important for early diagnosis and prompt management. Magnetic resonance imaging is the primary diagnostic tool. Skull metastasis is a focal lesion with a low-intensity signal on T1-weighted images. Enhanced T1-weighted images with fat-suppression show tumour, dural infiltration, and cranial nerve involvements. Irradiation is the effective and first-line therapy for most skull metastases. Chemotherapy or hormonal therapy is applied depending on tumour sensitivity. Bone resorption inhibitory drugs are used as a part of systemic therapy, and are to be studied for prevention of symptomatic skull metastasis. Surgery is indicated in selected patients with good performance status who need immediate decompression, cosmetic recovery, or histological diagnosis. **Eur Assoc NeuroOncol Mag 2014; 4 (2): 71–4.**

Key words: calvarium, cranial nerves, metastatic cancer, occipital condyle syndrome, radiation therapy, base of the skull

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 in 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].

Received on February 7, 2014; accepted after revision on February 25, 2014; Pre-Publishing Online on March 20, 2014

From the Division of Neurosurgery, Shizuoka Cancer Centre, Shizuoka, Japan

Correspondence to: Koichi Mitsuya, MD, Division of Neurosurgery, Shizuoka Cancer Centre, Naga-izumi, Shizuoka, 4118777, Japan; e-mail: k.mitsuya@scchr.jp

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].

Location and syndrome	Cranial nerves	Manifestations
Orbital	II, III, IV, V, VI	Supraorbital pain Diplopia Exophthalmos
Parasellar	III, IV, V, VI	Frontal headache Diplopia
Middle fossa (Gasserian ganglion)	V, VI, VII, VIII	Facial numbness Atypical facial pain Abducens palsy Hearing loss Facial paresis
Jugular foramen	IX, X, XI, XII	Occipital pain Dysphagia Hoarseness
Occipital condyle	XII	Occipital pain (severe) Neck stiffness Dysarthria Dysphagia

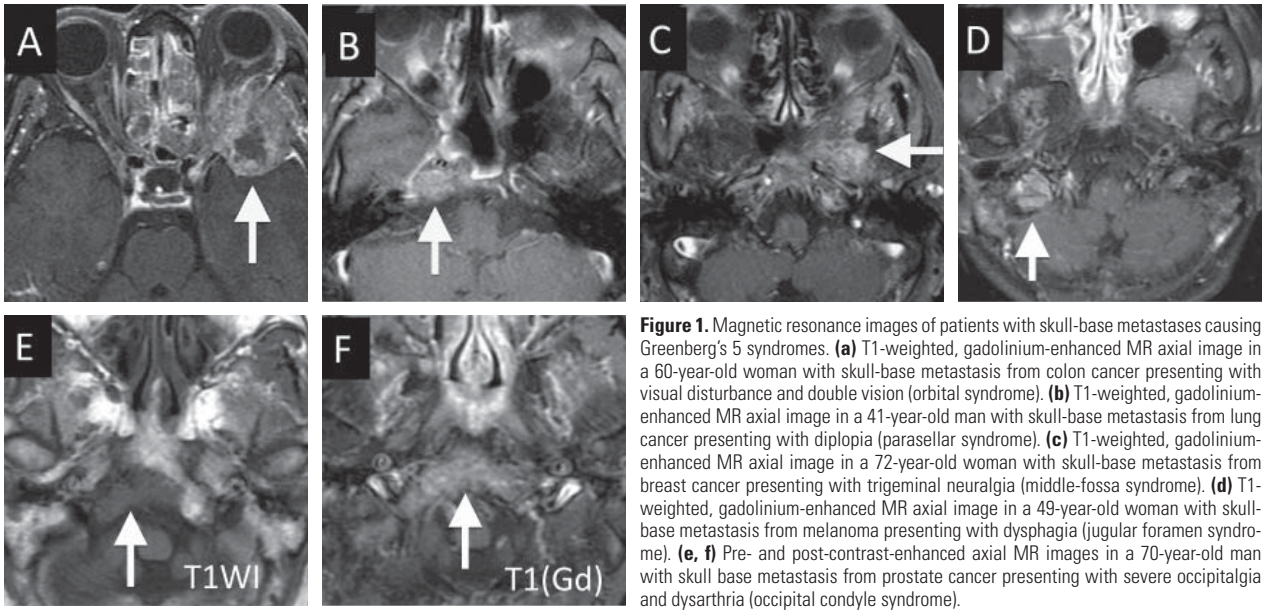

Figure 1. Magnetic resonance images of patients with skull-base metastases causing Greenberg's 5 syndromes. **(a)** T1-weighted, gadolinium-enhanced MR axial image in a 60-year-old woman with skull-base metastasis from colon cancer presenting with visual disturbance and double vision (orbital syndrome). **(b)** T1-weighted, gadolinium-enhanced MR axial image in a 41-year-old man with skull-base metastasis from lung cancer presenting with diplopia (parasellar syndrome). **(c)** T1-weighted, gadolinium-enhanced MR axial image in a 72-year-old woman with skull-base metastasis from breast cancer presenting with trigeminal neuralgia (middle-fossa syndrome). **(d)** T1-weighted, gadolinium-enhanced MR axial image in a 49-year-old woman with skull-base metastasis from melanoma presenting with dysphagia (jugular foramen syndrome). **(e, f)** Pre- and post-contrast-enhanced axial MR images in a 70-year-old man with skull base metastasis from prostate cancer presenting with severe occipitalgia and dysarthria (occipital condyle syndrome).

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].

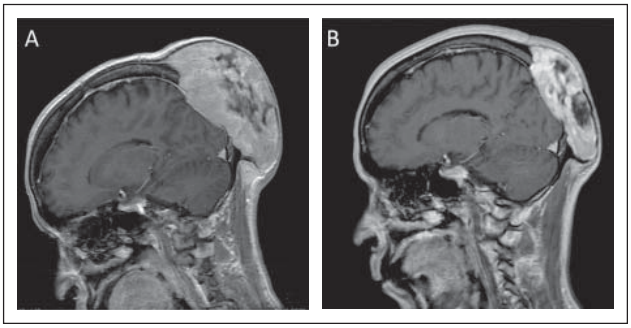

Figure 2. T1-weighted, gadolinium-enhanced sagittal MR images of a 57-year-old woman with calvarial metastasis from thyroid cancer. **(a)** Pre- and **(b)** 3 months post-irradiation 40 Gy per 20 fractions.

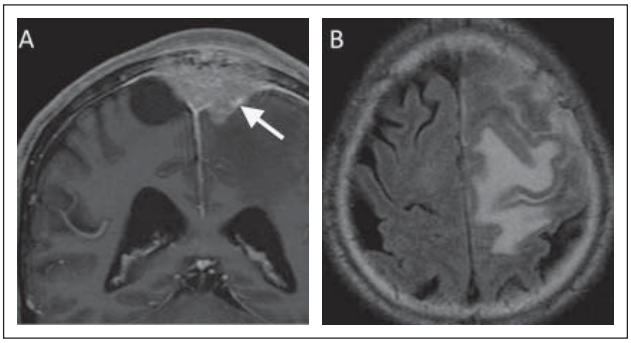

Figure 3. MR images of a 72-year-old man with calvarial metastasis from cholangiocarcinoma presenting with hemiparesis and partial seizures. **(a)** Coronal, T1-weighted, gadolinium-enhanced MR image demonstrating dural invasion and occlusion of the superior sagittal sinus (white arrow). **(b)** Axial FLAIR image demonstrating diffuse brain oedema in the left hemisphere.

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].

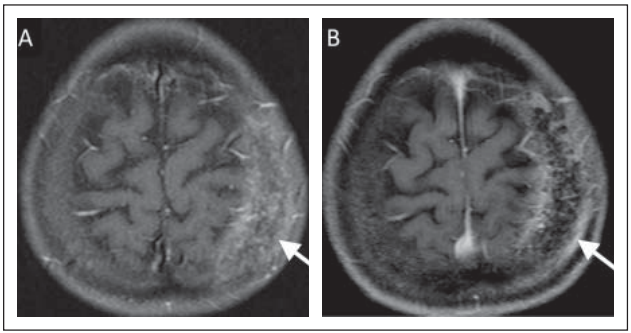

Figure 4. (a) T1-weighted, gadolinium-enhanced MR axial images of a 58-year-old woman with calvarial metastasis from breast cancer presenting with headache. **(b)** The tumour became less enhanced 3 years after 40 Gy per 20 fractions radiation therapy.

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.

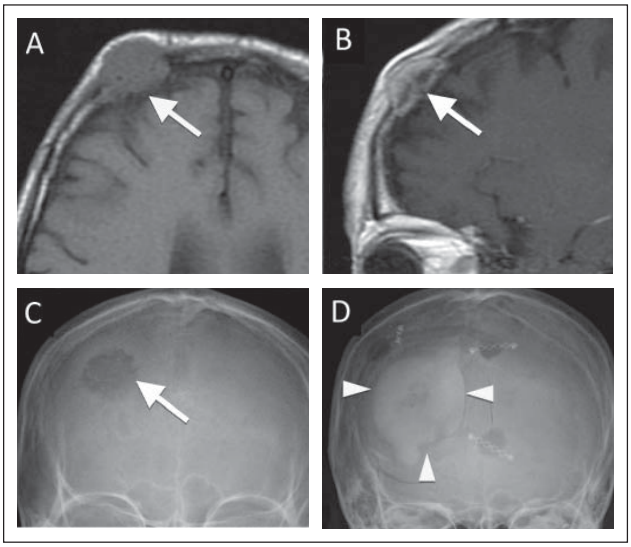

Figure 5. A 70-year-old woman with calvarial metastasis from lung cancer presenting with cosmetic problem in the forehead. **(a)** Pre-enhanced axial and **(b)** post-enhanced sagittal MR images demonstrating a mass lesion with focal invasion into the skin and dura mater. **(c)** Skull X-rays showing an osteolytic lesion (white arrow), and **(d)** surgical results of resection with a wide margin and reconstruction in the frontal bone (arrow heads).

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.

Acknowledgements

The authors would like to thank Satoshi Nakasu, MD, and Nakamasa Hayashi, MD, for valuable discussion, and Mr Piers Vigers for editorial support.

Conflict of Interest

None.

References:

1. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res 2006; 12 (Suppl): 3243s–3249s.

2. Mitsuya K, Nakasu Y, Horiguchi S, et al. Metastatic skull tumors: MRI features and a new conventional classification. J Neurooncol 2011; 104: 239–45.

3. Michael CB, Gokaslan ZL, DeMonte F, et al. Surgical resection of calvarial metastases overlying dural sinuses. Neurosurgery 2001; 48: 745–55.

4. Laigle-Donadey F, Taillibert S, Martin-Duverneuil N, et al. Skull-base metastases. J Neurooncol 2005; 75: 63–9.

5. Greenberg HS, Deck MD, Vikram B, et al. Metastasis to the base of the skull: clinical findings in 43 patients. Neurology 1981; 31: 530–7.

6. Hanbali F, DeMonte F. Metastatic tumors of the skull base. In: Sawaya R (ed). Intracranial Metastases: Current Management Strategies. Blackwell Futura, Malden, 2004; 415–29.

7. Maroldi R, Ambrosi C, Farina D. Metastatic disease of the brain; extra-axial metastases (skull, dura, leptomeningeal) and tumour spread. Eur Radiol 2005; 15: 617–26.

8. Vikram B, Chu FC. Radiation therapy for metastases to the base of the skull. Radiology 1979; 130: 465–8.

9. Hong B, Herman EJ, Klein R, et al. Surgical resection of osteolytic calvarial lesions: Clinicopathological features. Clin Neurol Neurosurg 2010; 112: 865–9.

10. Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol 2007; 25: 1423–36.

11. Chamoun RB, DeMonte F. Management of skull base metastases. Neurosurg Clin N Am 2011; 22: 61–6.

12. Mori Y, Hashizume C, Kobayashi T, et al. Stereotactic radiotherapy using Novalis for skull base metastases developing with cranial nerve symptoms. J Neurooncol 2010; 98: 213–9.

13. Lipton A, Fizazi K, Stopeck AT, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomized, phase 3 trials. Eur J Cancer 2012; 48: 3082–92.

14. Saad F, Brown JE, Van Poznak C, et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Ann Oncol 2012; 23: 1341–7.

15. Chamoun RB, Suki D, DeMonte F. Surgical management of cranial base metastases. Neurosurgery 2012; 70: 802–9.

16. Stark AM, Eichmann T, Mehdorn HM. Skull metastases: clinical features, differential diagnosis, and review of the literature. Surg Neurol 2003; 60: 219–26.