Secondary skull tumors: Prevalence, MRI findings as a diagnostic tool, and treatment

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ABSTRACT

Background: Skull secondary tumors are malignant bone tumors which are increasing in incidence.

Objective: The objectives of this study were to present clinical features , asses the outcome of patients with secondary skull tumors ,characterize the MRI features, locations, and extent of secondary skull tumors to determine the frequency of the symptomatic disease.

Type of the study: This is a prospective study.

Methods: This is a prospective study from February 2000 to February 2008. The patients were selected from five neurosurgical centers and one oncology hospital in Baghdad/Iraq. The inclusion criteria were MRI study of the head(either as an initial radiological study or following head CT scan when secondary brain tumor is suspected , visible or palpabable skull mass is noted) that revealed either calvarial or skull base metastases were included in this study.

Results: During the period of the study 175 patients were included according the inclusion criteria. Primary sites were breast cancer (54.85%), lung cancer (14.28%), prostate cancer (6.28%), malignant lymphoma (5.14%), and others (19.42%). The mean time from primary diagnosis to skull metastasis diagnosis was 71 months for cases of breast cancer, 26 months for prostate cancer, 9 months for lung cancer, and 4 months for malignant lymphoma. Calvarial circumscribed intraosseous metastases were found most frequently (25.7%). The patients were mainly asymptomatic. However, some patients suffered from local pain or cranial nerve palsies that harmed their quality of life. Treatment, mainly for symptomatic cases, was by local or whole-skull irradiation.

Conclusion: Secondary skull tumors are not rare, and most are calvarial circumscribed intraosseous tumors. MRI contribute to understanding their type, location, and multiplicity, and their relationship to the brain, cranial nerves, and dural sinuses. Radiation therapy improved the quality of life (QOL) of patients with neurological symptoms.

Key words: Secondary skull tumor, MRI, Radiation therapy

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The cranium is the site of blood-born metastases of various malignancies including carcinoma of the lung, breast, and thyroid, renal cell carcinoma, malignant melanoma in adults, and neuroblastoma in children. Although secondary skull tumors are not rare, and can cause disabling clinical syndromes including pain, they remain neglected complications of systemic malignancies. They are manageable, but early diagnosis is crucial for selecting treatment. Although CT scan is commonly considered appropriate for bone lesion diagnosis, MRI enable screening for secondary in both skull bone and brain [1].

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MRI findings

A radiologist evaluated the images. The secondary skull tumors were described according to three criteria: first, with regard to location (either in the calvarium or in the skull base); second, with regard to distribution within the plane of the cranial bone (either ‘‘circumscribed’’, meaning confined to one bone, or ‘‘diffuse’’ and likely to spread across a suture to another bone); and third, with regard to invasion (‘‘intraosseous’’ or ‘‘invasive’’ spreading out of the bone, either out into the scalp or inward to the dura). Thus each lesion could be described by its location and by its distribution within and perpendicular to the plane of the bone..

Results

Patient characteristics

During the period of the study 175 patients were included according the inclusion criteria. Table 1 lists the clinical features of the patients. The patients' median age was 57 years (range 8-82 years). The female to male ratio was 7:3. Breast cancer (in 54.85%) was the most common primary tumor, followed by lung cancer (in 14.28%), prostate cancer (in 6.28%), malignant lymphoma (in 5.14%), and others (in 19.42%).
Fifty-two (29.71%) of all 175 patients had brain parenchymal metastases at their presentation

Table 1 Patients' characteristics

Characteristics	No. = 175
Gender	
Female	122 (69.71%)
Male	53 (30.28%)
Median age at diagnosis of skull metastases (range)	57 years (8-82 years)
Primary cancer	
Breast	96 (54.85%)
Lung	25 (14.28%)
Prostate	11 (6.28%)
Malignant lymphoma	9 (5.14%)
Gastric	7 (4.0%)
Esophagus	5 (2.85%)
Malignant melanoma	4 (2.28%)
Leukemia	4 (2.28%)
Colon	2 (1.14%)
Liver	2 (1.14%)
Orbit	1 (0.57%)
Thyroid	1 (0.57%)
Thymoma	1 (0.57%)
Intestine	1 (0.57%)
Cartinoid	1 (0.57%)
Uterus cervical	1 (0.57%)
Uterus body	1 (0.57%)
Urinary duct	1 (0.57%)
Bladder	1 (0.57%)
Unknown	1 (0.57%)

MRI findings

Secondary skull tumors were found in calvarial bones in 121 patients, and in the skull base in 97 patients, so there were 43 patients with both (Table 2).

MR findings	Incidence (%)[b]	Symptom	Symptomatic cases (%)[c]
Calvaria (No. = 121[a])			
Circumscribed			
Intraosseous	25.7% (45/175)	None	0% (0/45)
Invasive	20.57% (36/175)	Pain Cosmetic problem	13.88% (5/36) 8.33% (3/36)
Diffuse			
Intraosseous	5.71% (10/175)	None	0% (0/10)
Invasive	17.14% (30/175)	Meningeal irritation Disorientation	10% (3/30) 10% (3/30)
Skull base (No. =97[a])			
Circumscribed			
Intraosseous	0.28% (18/175)	Pain	11.11% (2/18)
Invasive	14.85% (26/175)	Cranial nerve sign Pain Direct compression on the orbit	26.92% (7/26) 15.38% (4/26) 11.53% (3/26)
Diffuse			
Intraosseous	8% (14/175)	Pain	21.42% (3/14)
Invasive	22.28% (39/175)	Cranial nerve sign Pain	33.33% (13/39) 10.25% (4/39)

a : Numbers of cases; 43 patients presented with both
b: Incidence (%) in 175 patients
c : Frequency (%) in each type

MRI signals varied; there were low to iso-intensity signals on T1-weighted, and low to iso-intensity signals on T2-weighted images. Skull metastases were enhanced by gadolinium to different degrees; most lesions showed nearly homogenous enhancement, but one of the lesions showed only rim enhancement.

Examples of calvarial metastases are presented on Fig.1, and skull-base metastases in Fig. 2.

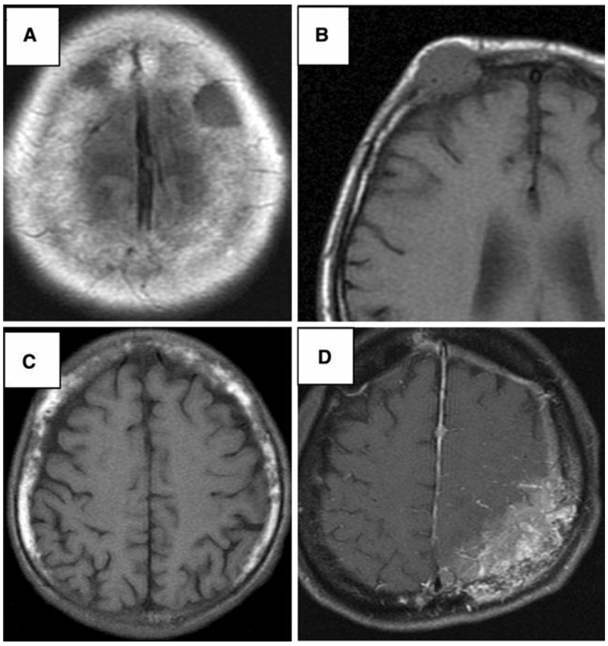

Fig. 1 MRI images show four types of calvarial metastasis. a T1-weighted image shows a lesion of low-intensity signal with clear margin; circumscribed intraosseous type. b T1-weighted image shows an oval lesion of isointensity signal invading to the dura; circumscribed invasive type. c T1-weighted image shows heterogeneous bone marrow; diffuse intraosseous type. d T1-weight image with contrast media shows heterogeneous enhancement of the parietal bone, dura and the cortical sulci; diffuse invasive type.

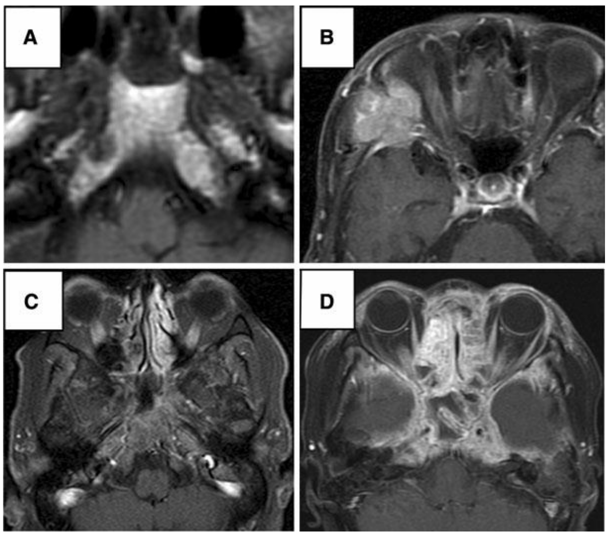

Fig. 2 MRI images show four types of skull-base metastasis. a T1-weighted image shows a lesion of low-intensity signal with clear margin in the right pyramid apex; circumscribed intraosseous type. b T1-weighted image with contrast media shows a multilobulated lesion in the sphenoid bone invading the temporal muscle and the dura; circumscribed invasive type. c T1-weighted image with contrast media and fat suppression shows diffuse enhancement of the clivus and pyramis apex; diffuse intraosseous type. d T1-weighted image with contrast media and fat suppression shows heterogeneous enhancement of the skull base and the dura of the middle fossa; diffuse invasive type.

The distribution of metastases according to the above description is shown in Table 2. The most common type was calvarial circumscribed intraosseous metastases (25.7%), followed by skull base diffuse invasive (22.28%) then calvarial circumscribed invasive metastases (20.57%). Metastases from breast cancer most frequently presented as calvarial circumscribed intraosseous tumors (30 of 96 patients), followed by calvarial diffuse invasive metastases (25 of 96 patients). Metastases from lung cancer (like those from breast cancer) most frequently presented as calvarial circumscribed intraosseous lesions (7 of 25 patients), followed by calvarial circumscribed invasive metastases (6 of 25 patients). Calvarial circumscribed intraosseous lesions were the commonest skull-bone metastases in cases of both breast cancer (30 of 96 breast-cancer patients) and lung-cancer (7 of 25 lung-cancer patients). Calvarial circumscribed invasive lesions were the second commonest skull-bone metastases in cases of lung-cancer (6 of 25 lung-cancer patients). Calvarial diffuse invasive lesions were the second-commonest skull-bone metastases in cases of breast cancer (25 of 96 lung-cancer patients).

Clinical manifestations (Table 2)

Patients with calvarial circumscribed intraosseous metastases had no symptoms. Calvarial circumscribed invasive metastases caused local pain in five patients (4.13%). Three patients (2.47%) with calvarial diffuse invasive metastases suffered from headache and nausea because of dural and subdural invasion. As demonstrated in Table 2, the most common symptom in our patients with skull-base metastasis was cranial nerve signs (20.61%), followed by pain (13.4%). Of 20 patients with cranial nerve signs, 11 (55%) presented with diplopia, 4 (20%) with trigeminal nerve sign, 4 (20%) with hypoglossal nerve dysfunction, and 1 (5%) with facial nerve palsy.

The median interval between diagnosis of the primary tumors and detection of secondary skull tumors was 4 years (mean 6 years; range 0-16 years 5 months). The mean survival time from skull metastasis in the 175 patients was 19.5 months (median 9 months; range 3-65 months). The time from primary diagnosis to secondary skull tumors was 71 months for cases with breast cancer, 26 months for prostate cancer, 9 months for lung cancer, and 4 months for malignant lymphoma[2] (Table 3).

Table 3 Primary cancer and intervals from diagnosis of primary malignancy to skull metastases

Primary tumor	No.	Median time (*M*, range)
Breast	96 (54.85%)	71 (1-197)
Lung	25 (14.28%)	9 (0-40)
Prostate	11 (6.28%)	26 (0-132)
Lymphoma	9 (5.14%)	4 (0-8)
Miscellaneous	34 (19.42%)	7 (1-61)
Total	175	17 (0-197)

Treatment

Patients with asymptomatic secondary skull tumors and without brain metastases were followed up with regular MRI. Sixty-three (36%) of our patients underwent radiation therapy. Thirty-five (55.55%) of those 63 patients had simultaneous brain parenchymal metastases, and needed whole brain radiation. Another 28 patients were symptomatic because of skull metastases: 23 (82.14%) patients showed improvement of their symptoms or stable disease after local or whole cranial radiation. Overall survival from diagnosis of metastatic skull tumor was 23 months for patients with prostate cancer, 15 months for breast cancer, 6 months for malignant lymphoma, and 5 months for lung cancer.

Discussion

Incidence and general consideration

Our study showed breast cancer is the most frequent source of secondary skull tumors both for calvarial (of 122 patients) and for skull-base (of 97 patients). This contributed to the large preponderance of female vs male patients (7:3) in our study. We found no significant difference in primary cancer between calvarial and skull-base metastases. There has been no study of large series of secondary calvarial tumors. However, a meta-analysis of 279 cases with secondary skull-base tumors demonstrated the most frequent primary tumor was prostate cancer (38.5%) followed by breast (20.5%) and lymphoma (8%). Prostate cancer may cause symptomatic secondary skull-base tumors more frequently than do other malignancies. Also one might overlook secondary skull tumors from prostate cancer, because the patients seldom undergo brain MRI for screening[3].

Sensitivity of MRI

Cancer cells may metastasize to bone marrow, where MRI is very sensitive. The normal pattern of fat distribution in the diploic space and marrow of the skull base was symmetric. Gross asymmetry of the diploic space alone is highly suggestive of calvarial disease on pre-contrast and post-contrast images. MRI using T2 and T1-weighted sequences before and after intravenous gadolinium administration is the best way to detect skull metastases. Fat suppression in combination with gadolinium infusion is particularly important. The main finding in skull metastases consists of substitution of the usual hyperintense fat sign by a hypointense lesion on non-enhanced T1-weighted images with a variable appearance on T2-weighted images. T1-weighted sequences with fat suppression show variable enhancement after gadolinium infusion [3]. MRI is particularly useful to show any invasion into the dura or cranial nerves. Careful comparison of T2-weighted, T1-weighted, and enhanced images is crucial for detection of subtle intradiploic metastases. A normal adult skull base shows low and high-intensity signals mixed in T1-weighted images and iso-intensity with the pons in T2-weighted images. Typical MRI findings of skull-base lymphoma are iso-intense with the grey matter on T1-weighted images, but giving high-intensity signal on T2-weighted images, and homogenous gadolinium enhancement [4, 5]. CT-scan with bone windows is a useful method to show lytic bone lesions. However, CT scan does not clearly show boundaries and degrees of dural invasion by bone metastasis. It has poorer spatial resolution for concomitant brain metastasis than does MRI. Radionuclide bone scan offers relatively poor sensitivity in detecting purely osteolytic bone metastases [6], because this technique requires enhanced remodeling of bone to become positive. Also, bone scintigraphy may be negative when MRI is positive [7].

Clinical presentation and symptoms

Secondary skull tumors are clinically important for patients' quality of life, although they may not directly influence survival time. Secondary calvarial tumors may cause superficial focal pain and cosmetic problems [8], and once secondary calvarial tumors invade into the dura and intradural space, patients suffer from increased intracranial pressure, meningeal irritation, and focal neurological signs. Secondary skull-base tumors usually cause various combinations of cranial nerve signs. Lower cranial nerve involvements are serious clinical manifestations, sometimes causing aspiration pneumonia. Five syndromes enable convenient understanding of the anatomical features of skull-base tumors (Table 4). The five syndromes listed in table 4 illustrate the clinical features of skull-base tumors [2]. Among those five syndromes, occipital condyle syndrome is of particular importance in differential diagnosis for patients with unilateral severe occipital headache. Cancers can metastasize to the condyle, causing severe pain and deviation of the protruded tongue toward the side of the pain; metastases from prostatic, colon, and other cancers have recently been reported [9, 10]. Initial imaging may be within normal limits in occipital condyle syndrome, however, patients should be followed up closely [9]. In our study, orbital and parasellar syndromes were frequently seen, although other syndromes were rare.

Table 4 Clinical syndromes associated with skull-base metastases

Clinical syndrome	This study	Greenberg et al.[2]
Orbital syndrome	4 (20%)	3 (7%)
Parasellar syndrome	7 (35%)	7 (16%)
Middle fossa (Gasserian ganglion) syndrome	4 (20%)	15 (35%)
Jugular foramen syndrome	3 (15%)	9 (21%)
Occipital condyle syndrome	2 (10%)	9 (21%)
Total	20	43

Treatment of skull metastases

Four modalities were used for patients with skull metastasis: irradiation, chemotherapy, endocrinological therapy, and surgical removal.

Conventional fractionated radiation therapy remains the primary treatment. Vikram and Chu reported that radiation had better effects for patients presenting with symptoms of short duration; response rate was 87% for patients with less than 1 month history, 69% for patients with 1-3 months history, however, 25% for those with more than 3 months history [11].

Radiosurgery provides good tumor control, with side effects comparable with those of standard radiation therapy [2].

Patients with larger lesions near sensitive structures or in a previously irradiated field might benefit from the fractionated stereotactic radiation technique. Small-cell lung carcinomas, breast cancers, and prostate cancers are sensitive to radiation therapy and chemotherapy or hormone therapy. Renal cell carcinoma or melanoma is relatively radio-resistant. Only a minority of patients with secondary skull tumors are candidates for surgical resection. Michael et al. reported that 13 patients with metastases overlying dural sinus underwent surgical resection. Renal cell carcinoma and sarcoma were the most common primary malignancies [12].

Overall median actual survival was 16.5 months. Recent advances in chemotherapy have contributed in treatment of secondary skull tumors and systemic bone metastasis. Bisphosphonates (BPs) are effective as a palliative treatment for painful secondary bone tumors and other bone complications [13]. Zoledronate, a BP, has been increasingly used for patients because of improved convenience in clinical application. However, long-term treatment with BPs may cause mandibular necrosis; patients are advised to consult an oral surgeon before undergoing treatment with BPs [14]. Other new bone-specific medications which may contribute to improving clinical manifestations and survival are an isotope, 89Sr, and an antibody for receptor activator of NF-kappa B (RANKL), denosumab [15].

Conclusion

Secondary skull tumors are found in calvarial bones more than the skull base bones.

Breast cancer is the most frequent source of secondary skull tumors both for calvarial and skull base. Skull metastases can be diagnosed by use of routine head MRI acquired for screening or assessing brain metastases. Secondary skull tumors are clinically important for patients' quality of life, although they may not directly influence survival time. Early diagnosis then treatment with irradiation can give patients a better quality of life.

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