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# Pathways of metastatic spread in meningiomas

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## ABSTRACT

Meningioma is a common intracranial neoplasm derived from meningothelial cells, and it is generally associated with a benign clinical course. In spite of this, the malignant behaviour of these tumours as the occurrence of extracranial meningioma metastases in different organs is described in literature: lung and pleura, spine and other bones, abdominal organs, lymph nodes or even skin. The aim of this review is to analyse the pathways of metastatic spread of the intracranial meningioma tumour cells towards different organs.

Keywords
meningioma, metastasis, malignant, WHO classification

## INTRODUCTION

Meningiomas are the most common central nervous system tumours in adults, making up approximately 30% of all the intracranial tumours, with an increasing incidence (14, 57). According to the mitotic activity and tumour differentiation, the World Health Organization (WHO) grading meningiomas as it follows: grade I, grade II and grade III, the last two being characterized by a more aggressive behaviour, a high risk of recurrence (12, 39) and even metastasis. These extracranial meningioma metastases (EMM) are more frequently associated with atypical meningiomas (Table 1) or anaplastic meningiomas (20, 27, 59). Although typical meningiomas are benign solitary intracranial neoplasms, they can cause extracranial metastasis, a rare phenomenon found only in 0.1% of cases (15, 23, 26, 35, 37). According to epidemiological data, about one in 1000 cases of meningiomas metastasize (35, 56).

The most frequent sites of EMM are: the lung (60%-70%), abdominal viscera (the liver most frequently) (30-40%), pleura (23%), lymph nodes (14-20%) and bones (10%) (3, 6, 21, 38, 42, 50, 60, 66). Other rare localizations were identified in the parotid gland (17), skin (32, 51), deep soft tissue (9, 18, 44, 48, 64, 70), kidney, spleen, thyroid and adrenal gland (64).

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Due to the rare nature of EMM, this is a challenging diagnosis for physicians and pathologists (25). Because the treatment has not yet been standardized and a management protocol has not been developed, the prognosis of these patients remains unknown (3, 42, 50).

TABLE 1. Review of publications on extracranial metastasis of atypical meningiomas

| Author | Gender, Age | Intracranial Localization | Metastasis Localization |
|---|---|---|---|
| Andric *et al.* (5) | F 52 | parasagittal | lung |
| Baek *et al*. (9) | M 44 | nasal septum | chest wall, parietal region |
| Drummond *et al.* (19) | M 66 | frontal | lung |
| Doxtader *et al*. (18) | M 8 | parasagittal | subcutaneous tissue of neck, lymph nodes |
| Kim *et al.* (41) | M 68 | parietal | skull bone |
| Lanfranchi *et al*. (43) | M 74 | not specified | lung, liver |
| Pinsker *et al*. (55) | M 76 | frontal | cervical spine |

## METASTATIC SPREAD

Although all types of meningioma, including the grade I meningiomas can metastasize, EMM is more common in the atypical (5%) and anaplastic (30%) histopathological subtypes (7). Nevertheless, some authors believe that these percentages are overestimated, firstly because some of the reported cases probably are metastatic angioblastic meningiomas and not genuine meningioma metastases. Moreover, the angioblastic meningioma is now classified as haemangiopericytoma (25, 28, 34, 46). Thus, considering all these modifications, the 5% rate of metastasis in atypical meningiomas does not coincide with the current WHO classification (25). However, the true prevalence of EMM is unknown at present (64).As for the time interval between the initial diagnosis of the meningioma and that of extracranial metastasis, it varies from 3 months to 30 years (40).

Although throughout time, some authors emphasized tumour necrosis, blood vessel invasion, high cellularity, cellular heterogeneity, high mitosis rate and nuclear pleomorphism in the occurrence of EMM (1, 20, 54), these criteria apply to malignant tumours and do not explain metastatic disease in benign meningiomas (64). In spite of this, the exact etiology of metastatic spread in meningioma is still unknown (7, 22).

Initially, the surgical resection was reported as one of the most important risk factors for iatrogenic metastasis of histologically aggressive meningiomas (2). Hence, it was hypothesised that surgery causes the seeding of the lymphatics and vascular channels (including that of the scalp), resulting in extracranial metastatic disease via haematogenous or lymphatic route (31). Besides, other studies showed that tumour cells can propagate with no previous surgery (25, 36), considering that the invasion of adjacent venous sinuses can lead to extracranial spread of meningioma, especially when there is no history of surgery (23).

Lung metastasis. As mentioned before, the lung is the most common site of the EMM. In these cases, the seeded tumour cells access dural venous sinuses and cranial veins, then diffuse through the azygos system into pulmonary circulation and then they can reach either the lung or the pleura (21, 32, 40). Most EMM were found along the jugular vascular drainage, such as in the cervical lymph nodes, parotid and thyroid gland and finally in lung and pleura (64).

Bone metastasis. Bone is one of the least common sites of meningioma metastasis (38, 60). In a review of meningioma metastasis in the bone, Khan et al. found out that half of the patients had multiple areas of bone metastatic disease, while the

other half had solitary bone involvement (40). The most common region was the axial skeleton, namely the thoracolumbar spine and sacrum (40), while metastases in the extra-axial bone were rarely identified (22). The most common involvement of the spine can be explained by the connection between the dural venous sinuses and the vertebral venous system (10). This route via the paravertebral venous plexus may also play a role in the metastatic spread across the kidney or adrenal glands (64).

Of the non-axial skeleton, the femur was the most common long bone site of involvement (40), and this metastasis location is more difficult to explain, even if some authors suggested the extension of the tumour via arterial spread (68). The bone metastatic disease is a lytic bone lesion and may result in pathological fractures or collapse of the vertebral bodies (40).

Liver metastasis. As far as the dissemination pathways for hepatic metastasis are concerned, some authors believe that this lies in the dissemination through the vertebral venous system connected with the veins of the thoracoabdominal wall or dissemination of tumour cells of the bone metastasis to the liver (24, 25). The liver can be involved whether the metastases pass through the right atrium towards the inferior vena cava and further into the hepatic veins (64). In literature, cases of hepatic metastasis of meningioma via a ventriculoperitoneal shunt through the cerebrospinal fluid route were cited (51).

Scalp metastasis. Surgical seeding of tumour cells in meningioma surgery is a rare entity and it usually involves soft tissues near the craniotomy site (8). In literature, 19 such cases of scalp metastasis of intracranial meningiomas were reported (8).

Scalp metastasis of meningioma were firstly reported by Harvey Cushing, with an incidence of 1.21% cases in a cohort of 313 patients, which results in 4 patients suffering from this condition. In all of these cases, scalp metastases were found in surgical scar many years after the first surgery (4, 30, 49, 69). Different series reported percentages of 3% in a cohort of 119 patients with WHO grade II and III meningiomas (53) and others of 1.2% (8).

The suggested mechanism is intraoperative seeding and it may apply to all histological grades of meningiomas. Avecillas-Chasin et al. considers that immunosuppression, radiation therapy, CSF fistulae and multiple reoperations with subsequent surgical wounds problems (8). Nevertheless, the reason for extracranial tissue invasions is still unclear.

Carrying out multiple interventions can be a risk factor for the extracranial spreading of intracranial tumours, in that surgical bone deteriorates the natural barriers for intracranial tumour dissemination, providing access to the blood vessels and lymphatic system (8, 63). The higher-grade histopathological meningioma also contributes to this in case of tumours which have the tendency to produce greater levels of vascular endothelial growth factor and angiogenesis, thus favouring vascular invasion and metastatic behaviour (29).

Piecemeal resection was also presented as a risk factor of extracranial dissemination of tumour cells in WHO grade III meningiomas (8). Although initially, it was suggested that the latency period of meningioma metastasis is influenced by the histological grade (2), the significant variability over this la-tency period proved that this is not related only to the histological grade of meningioma (2, 16, 30, 45, 47, 52, 61, 62, 65, 67, 69).

With regard to preventing the spread of tumour cells, some authors recommended: air-tight closure of dura mater, changing the gloves and surgical instruments for wound closure after the intracranial phase, replacing the bone flap and saline irrigation, wound abundance before the closure (4, 33).

Treatment strategies. The treatment for meningioma metastasis has yet to be set out. In spite of this, metastectomy seems to improve the prognosis, especially when the tumour is a low-grade meningioma. As for the chemotherapy with hydroxyurea, vincristine, cyclophosphamide and doxorubicin, this has a limited efficiency with progression under chemotherapy (25). Moreover, some immunotherapies with interferon-α and somatostatin analogue were tested lately, but with limited effects (11, 58). Nonetheless, the choice treatment in meningiomas remains the gross total resection and adjuvant radiotherapy (13).

## Conclusions

Because of the fact that EMM were rarely reported, there are no guidelines regarding the staging or treatment of EMM. Metastatic spread remains a therapeutic challenge and the treatment must be multidisciplinary evaluated. In addition, this data highlights the fact that metastatic dissemination of meningiomas is possible even under conditions of

benign histopathological grades and thus organ donation should be considered.

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