Abstract
Extraneural metastases of primary central nervous system malignancies are rare and challenging pathologies, with unknown metastatic mechanism and no consensus regarding the best treatment regimen. Herein, we have reviewed the literature to help elucidate characteristics, prognostic factors, and treatment outcomes of patients with metastatic primary brain tumours.

Keywords: glioblastoma; extra-neural metastasis; extracranial metastasis; medulloblastoma; ventriculoperitoneal shunt

Introduction
Extra-neural metastasis (ENM) of primary brain tumours is rare. In 1926, Bailey and Cushing stated that gliomas practically never metastasize outside the central nervous system (CNS). The claim, however, was disproved two years later, when the first case of ENM was published. Following this, incontrovertible evidence now exists of true systemic metastasis occurring in the setting of medulloblastoma, astrocytoma, oligodendrogliaoma and glioblastoma, among other primary brain tumours. The rarity of ENM is attributed to the short survival period in primary brain malignancies, as well as the presence of the blood-brain barrier (BBB), and lack of a classic lymphatic drainage system.

Possible mechanisms leading to ENM remain unclear. However, extracranial metastasis are most commonly found in patients with prior invasive surgery or biopsy, which create iatrogenic access to extracranial structures. Metastatic primary brain malignancies thus occur by migration of tumour cells through shunts to the peritoneum or peritoneal cavity, or direct seeding to soft tissues through craniotomy defects. Endogenous factors may also be responsible, such as breach of BBB that occur in the setting of most high-grade gliomas. This, added to the effect of BBB disruption on peri-tumoural oedema, tumour development and progression, might also be one of the factors leading to ENM. Cancer cell escape via haematogenous or lymphatic routes is, however, infrequent.

Based on this, we have herein reviewed and evaluated the characteristics, prognostic factors, and survival outcomes in patients with metastatic primary brain malignancies.

Review of literature
Hoffman and Duffner in 1985, published 282 cases with ENM of CNS tumours. They focused on differences between children and adults and found that in children particularly, medulloblastoma spread outside the CNS (65 medulloblastomas and 11 astrocytoma/glioblastoma). In adults, on the other hand, gliomas were the most common brain tumours to metastasize extracranially (68 astrocytoma/glioma and 22 medulloblastoma). Of the 79 patients with gliomas, 70 (88%) patients received a craniotomy, which, according to them, played an important part in the metastases, along with cerebrospinal fluid (CSF) diversion. The authors also proposed the use of chemotherapy as a measure of both palliation and improving quality of life and survival. Maeda et al., reported a case of a 51-year-old female, presenting with a temporal gliosarcoma with ENM post-resection. Highly proliferative nature of the tumour due to the high MiB-1 index of the sarcomatous component of the lesion on histopathology, as well as craniotomy with partial excision of the dura were the proposed mechanisms of ENM.

Young et al., carried out a 20-year-long retrospective analysis, and identified 14 patients with ENM secondary to medulloblastoma in their institutional database. The median age at initial diagnosis was 16.3 years and the most common subtype was desmoplastic (n=6). After initial GTR, most patients received radiation therapy alone. None of the patients underwent ventriculoperitoneal shunting (VPS) prior their diagnosis of ENM. Metastasis to bone were most common (n=11) followed by metastasis to bone marrow (n=6), usually of the spine. The median time from initial diagnosis to ENM was 1.5 years, and the median OS from ENM to death was 3.3 years. The 5-year survival estimate after ENM were diagnosed, was 40%. The authors suggested whole-body MRI in high-risk patients, due to the proclivity of medulloblastoma to metastasize to the spine, to enable timely diagnosis that may potentially improve survival.

Narayan et al., reported a case of a 7-year-old boy, who developed abdominal metastases, secondary to a left thalamic glioblastoma. The patient developed progressive abdominal distention, 7 months and 2 weeks after the...
placement of right and left occipital VPS catheters respectively for obstructive hydrocephalus, and a computed tomography (CT) scan of the abdomen showed diffuse ascites with evidence of carcinomatosis. Additional work-up also revealed extensive leptomeningeal carcinomatosis involving the cord and cauda equina. The authors further reviewed the literature for peritoneal ENM in paediatric brain tumours, that yielded 22 cases of ENM secondary to VPS placement in tumours including medulloblastoma, pineal germinoma, and pilocytic astrocytoma.

Bridges et al., described a case of ENM in a patient with haemangiopericytoma (HPC), secondary to VPS placement. The authors presented a case of a 34-year-old man, who, 10 years after his initial diagnosis of an intracranial HPC, that was treated with multiple surgeries and adjuvant therapy through-out, and 7 years after VPS placement, presented with rapid onset urinary retention. CT of the abdomen and pelvis revealed a retro-prostatic mass with histopathology consistent with HPC. Despite adjuvant radiation and an aggressive treatment course of the extracranial lesion, the patient kept presenting with new extracranial lesions every year – in the mesentery adjacent to the caecum, the chest wall, right distal humerus, and para-aortic abdomen, all consistent with HPC on biopsy. The authors suggested patients with intracranial HPC requiring permanent CSF diversion to be considered foremost for ETV over VPS placement, to minimize risk for ENM. Stephens et al., reported the case of a 4-year-old female, who presented with a diffuse midline glioma H3 K27M-mutant (astrocytoma) centered on the suprasellar cistern and metachronous spinal metastatic lesions. The patient developed further metastatic lesions to the peritoneum 14 months after bilateral VPS placement for the initial lesions, implicating VPS to be the cause of metastases.

Of all the gliomas, oligodendroglioma (OG) are the least likely to metastasize outside the CNS. In 2019, Singh et al., described a case of a young male, who developed metastases to the bone marrow, six months after being diagnosed with anaplastic OG, and treated with sub-total resection (STR) with adjuvant chemotherapy with temozolomide (TMZ). Follow-up imaging revealed further metastases to the liver and retroperitoneal lymph nodes, and the patient passed away within a year of initial diagnosis. Another case and literature review of anaplastic ependymoma metastasizing extracranially, was published by Umbach et al., in 2020. Fifteen cases of anaplastic ependymoma with ENM, including the presented case were included, and the mean age at diagnosis was 15 years. The initial tumour location was predominantly supratentorial (93.3%) and all cases demonstrated leptomeningeal seeding before ENM, predominantly to the cervical lymph nodes, bone, lung, and scalp. Two cases, including the author's case, showed metastases to the parotid gland. Mean survival from initial diagnosis was 4.5 years.

Extracranial metastasis of GBM is rare, with a reported incidence of about 0.4% to 2.0%, and mainly occurring in adults, particularly men. The prognosis of metastatic GBM is poor, with a median overall survival (OS) of 6 months from diagnosis of metastasis. A recent meta-analysis on GBM ENM by Cunha et al., involved 110 cases of glioblastoma and 5 cases of gliosarcoma. The mean age of patients was 38.2 years, with 70.4% males in the cohort. The time elapsed between the identification of the metastasis and death was significantly increased in patients undergoing surgery (p=0.019), whereas the time from the diagnosis of the primary tumour to death was significantly increased in patients receiving radiation therapy (p=0.050). The time elapsed from metastasis to death and diagnosis to death was significantly longer in patients receiving chemotherapy (p<0.001 and p=0.027, respectively). The liver was the metastatic site associated with the shortest overall survival. The authors emphasized upon the importance of the extent of surgical resection and application of adjuvant chemo- and radiation therapies for prolonged survival. Liu et al., published a case of a 46-year-old man with primary GBM who developed scalp metastasis and subsequent multiple pulmonary metastases, 6 and 18 months after the primary diagnosis, respectively. Despite salvage chemotherapy and targeted therapy for the scalp metastasis, the patient eventually died of respiratory failure due to multiple pulmonary metastases, 20 months after the initial diagnosis. The authors highlighted the need for rigorous follow-up, including serial brain MRI, and prompt relevant examinations secondary to the occurrence of extracranial symptoms. Prophylactic craniospinal irradiation was also proposed for patients at high risk of CSF seeding, if the ventricles were opened during surgery or if the tumour was in close contact with the CSF.

**Conclusion**

Extra-neural metastasis, especially of the bone and lung, are rare and fatal sequelae of primary CNS malignancies. Prompt diagnoses, aggressive management and judicious use of CSF diversion methods is required to improve both the quality and duration of life.

**References**


