Brain metastases in paediatric patients – characteristics of a patient series and review of the literature

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Abstract
In contrast to the occurrence of brain metastases advanced malignant tumours in adult cancer patients, the dissemination of solid tumours to the brains of paediatric cancer patients is very uncommon. We present a neuropathological and clinical study of a group of children and adolescents with brain metastases (BM) from extracranial solid malignancies. The analysed patients were diagnosed with soft tissue sarcomas (three), germ cell tumours (three), or osteosarcoma, neuroblastoma, clear cell sarcoma of the kidney, or pleuropulmonary blastoma (one each). In our series, BM frequently coexisted with pulmonary metastases. Three different metastatic patterns were discernible: a solitary tumour, multiple lesions and diffuse parenchymal dissemination. Two cases showed haemorrhagic presentation. Most of the children died due to BM progression, while children with germ cell tumours showed the best prognosis. The histopathological pictures of BM can be different from the primary tumour, showing dedifferentiation or a diverse neoplastic component. The autopsy examination can still be helpful in the final diagnosis of certain cases with atypical clinical presentations.

Key words: brain metastases, children, paediatric oncology, solid tumours.

Introduction
Metastases are the most common tumours of the central nervous system (CNS) in adults, constituting approximately 30% of all intracranial neoplasms [2,4,16]. In approximately 10% of cases, the CNS is the only site of secondary spread, and in up to 15%

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Brain metastases of solid tumours are rarely observed in children with cancer. Interestingly, the CNS, liver, kidneys and lymph nodes are the most common sites of extramedullary spread in leukaemia [11,12]. Data regarding BM in paediatric solid tumour patients are limited, but clinical reports suggest that their frequency is 1.5-4.9% [3,8,18], and autopsy studies suggest a 6-13% frequency [7,26]. The most common types of cancer in children include soft tissue and osteogenic sarcomas (STS, OSA), neuroblastic tumours (NBL), nephroblastoma, and germ cell tumours (GCT) [23]. Brain metastases are occasionally present in patients with NBL, OSA and STS (mainly in alveolar rhabdomyosarcoma 2.4-8%), but are uncommon in children with Wilms’ tumour (1%) [3,10,13,17,18]. In contrast, they are often a feature of very rare tumours such as pleuropulmonary blastoma (PPB) (25%) [20], alveolar soft part sarcoma (15-29%) [27] and melanoma (18%) [21].

In recent years, long-term survival rates in paediatric patients treated for malignant solid tumours have gradually increased, while the risk of BM has risen. Brain metastases may be present at the initial diagnosis, but in most cases, they develop later, during disease progression or relapse. The median time from initial diagnosis to BM development is 13-22 months [3,5,8]. The results of treatment of CNS metastases are particularly poor, as most of the children die due to disease progression [3,8,18].

The aim of the current study was to characterise the clinical and pathological picture of a series of unique metastatic brain tumours in paediatric patients.

**Material and methods**

We performed a retrospective analysis of medical records of children and adolescents (up to 18 years of age) treated for malignant extracranial solid tumours between 1992 and 2010 in two paediatric oncological clinics at the Medical University of Gdańsk (Department of Paediatrics, Haematology, Oncology and Endocrinology and Department of Paediatrics, Paediatric Gastroenterology, Hepatology and Nutrition). Patients with intracranial secondary foci were selected, but cases involving direct extension of the tumour from the skull or dura mater were excluded. Finally, only patients with brain metastases (BM) were analysed in detail.

The clinical data included the age of patients at the time of BM diagnosis, the presence of systemic metastases at cancer diagnosis, time from primary diagnosis to BM detection, symptoms and localisation of BM, number of foci and their size (diameter), type of treatment and outcome. The MRI and CT neuroimaging records were reviewed again in all the cases.

The available archival BM slides and tissue material embedded in paraffin blocks were reviewed and additional immunostaining was performed. Monoclonal antibodies (DAKO) raised against glial fibrillary acid protein (GFAP, 1 : 50), CD68 (1 : 50), leucocyte common antigen (LCA, 1 : 50), CD34 (1 : 50), and Ki67 (1 : 50) were used in all cases. In addition, primary tumour type-specific antibodies were used, including alpha fetoprotein (AFP, 1 : 100), desmin (1 : 50), cytokeratin AE1/AE3 (1 : 50), S100 (1 : 100), epithelial membrane antigen (EMA, 1 : 50), beta chorioneprotein (BHCG, 1 : 200), CD30 (1 : 100), synaptophysin (1 : 100), and Novocastra antibody against placental alkaline phosphatase (PLAP, 1 : 25). The slides were stained manually with DAKO and Novocastra reagents. Appropriate positive and negative controls (omission of the primary antibody) were carried out for every antibody. Diaminobenzidine was the chromogen in all reactions, and En Vision (DAKO) was used for visualisation.

The histology of BM and neuropathological changes in the surrounding brain tissue were examined in detail. Furthermore, the histology of the primary and metastatic tumours was compared.

**Results**

The analysed clinical material included 511 oncological paediatric patients with malignant neoplasms excluding primary CNS tumours. In this cohort, only ten patients (2%) had brain metastases. These included three STS – two rhabdomyosarcoma (RMS) and one angiosarcoma (ASA); three GCT – two testicular and one extragonadal; and single cases of...
OSA, NBL, clear cell sarcoma of the kidney (CCSK) and PPB. The clinical characteristics of the patients are presented in Table I.

Mean age at the diagnosis of BM was 10.6 years (median 13.8 years). Two patients (p. 8 and 10) were diagnosed with BM at the initial time of cancer diagnosis. In the remaining patients, metastases were detected 1 to 32 months (median 8 months) after the first manifestation of disease. In three cases, the brain was the only site of metastatic disease at the time of BM diagnosis (p. 2, 5, and 6).

The most common initial signs and symptoms of BM were headaches (5), vomiting (4), hemiparesis or muscle weakness in the extremities (3), speech disorders (2), seizures (1), gait and balance problems (1), extrapyramidal symptoms and chorea (1). Two patients were asymptomatic, including a GCT patient, who underwent brain imaging due to increasing AFP serum levels, and an OSA patient with an abnormal positron emission tomography (PET) scan.

All patients underwent CT/MRI imaging of the brain. Solitary lesions were recognised in five children, while two patients had bifocal lesions. Neuroimaging revealed typical contrast enhancing lesions, with adjacent brain oedema. The size (diameter) of the lesions varied between 9 and 78 mm. All BM were supratentorial, located in the parietal (4), temporal (3) and frontal lobes (1). Three patients had multiple foci localised bilaterally in the cerebral hemispheres. One child presented with signs of tumour haemorrhage – on MRI scans, blood at the stage of methaemoglobin and haemosiderin was visible (Figs. 1A-B). One child had a large lesion in the frontal-parietal region, with concomitant infiltration of the meninges (Fig. 2). One case showing bilateral subdural haematoma was finally diagnosed with BM at the autopsy (Fig. 3).

Patient management varied according to the type of cancer and the clinical course of the disease. Two patients were treated with chemotherapy alone (one GCT, one STS), and in two cases (STS), only symptomatic treatment was used. Six patients underwent surgical resection of metastatic lesions, including two patients who underwent two operations. Four of these patients subsequently received adjuvant chemo- and radiotherapy.

Three GCT patients lived with remission for 1, 3 and 16 years after completing the oncolgical treatment. Five patients died 2-12 months after diagnosis of BM due to disease progression. Two patients (with OSA and NBL) died after successful BM therapy due to systemic cancer dissemination.

**Characteristics of the cases analysed**

**Soft tissue sarcomas**

Tissue slides were available from the autopsy of an alveolar RMS case (p. 5). This child developed bilateral subdural haematoma and died due to progression of neurological symptoms. The post-mortem gross neuropathological findings included occipital invagination, brain oedema, haemorrhages in the dura mater and subacute subdural haematomas in the tempo-ro-occipital regions. Histological examination showed disseminated neoplastic infiltrations in the haematoma capsule, made of small spindle desmin-positive cells. Moreover, neoplastic dissemination was present in the perivascular areas in all sections of the brain taken and was the most intense in the occipital lobes (Fig. 4A).

**Germ cell tumours**

Two cases were suitable for pathological examination. The first (p. 9) was a 2.5-year-old girl with sacrococcygeal mixed GCT (immature teratoma mixed with yolk sac tumour) with a single BM excised from a parietal lobe. Histologically, BM consisted of a yolk sac tumour component made of delicate tubular structures. The neoplastic tissue showed confluent multinodular growth. Immunohistochemically, the neoplastic cells were positive for CK, AFP, and PLAP, and negative for EMA and CD30 (Figs. 4B-C).

The second case (p. 7) concerned an adolescent boy with a testicular tumour and a focus in a parietal lobe detected in parallel with pulmonary lesions a month after admission. The testicular tumour showed features of a mature teratoma with a microfocus of cytotoxicoblasts (Fig. 4D). Interestingly, its metastatic foci were consistent with pure choriocarcinoma, as it was composed of malignant syncytio- and cytotoxicoblasts with necrotic and haemorrhagic foci. The neoplastic cells were positive for CK, BHC, EMA, PLAP (focally) and negative for AFP (Fig. 4E).

**The other tumours**

In a girl with CCSK (p. 1), BM was composed of the most aggressive component of the tumour. In this case, the differential diagnosis included the
### Table 1. Clinical characteristics of patients with malignant solid tumours with brain metastases

<table>
<thead>
<tr>
<th>No.</th>
<th>Patient (sex, age [years])</th>
<th>Primary tumour</th>
<th>Systemic metastases at diagnosis</th>
<th>Time from diagnosis to BM detection [months]</th>
<th>Symptoms of BM</th>
<th>Localization of BM (number of foci)</th>
<th>Treatment of BM</th>
<th>Outcome (survival) from BM diagnosis [months]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>BI (F), 7.8</td>
<td>CCSK – right kidney</td>
<td>Right lung</td>
<td>11</td>
<td>Facial-brachial paresis, speech disorders</td>
<td>Left parietal lobe, right parietal lobe (2)/3 × 4</td>
<td>CHT 2 surgical resections</td>
<td>DOD (6)</td>
</tr>
<tr>
<td>2.</td>
<td>TO (M), 4.2</td>
<td>PPB type IV/III – right lung</td>
<td>None</td>
<td>13</td>
<td>Headaches, vomiting, disturbances of consciousness</td>
<td>Right frontal lobe (1)/5</td>
<td>2 surgical resections</td>
<td>DOD (12)</td>
</tr>
<tr>
<td>3.</td>
<td>MM (M), 14.5</td>
<td>RME – primary disseminated</td>
<td>Generalized lymphadenopathy, pleura, peritoneum, subcutaneous tissue</td>
<td>6</td>
<td>Headaches, extrapyramidal symptoms, chorea, gait ataxia, dysarthria, muscular tremor</td>
<td>Numerous foci in the cortex in both hemispheres of the brain</td>
<td>CHT</td>
<td>DOD (3)</td>
</tr>
<tr>
<td>4.</td>
<td>TM (F), 13.8</td>
<td>ASA – heart</td>
<td>Lungs/multiple</td>
<td>8</td>
<td>Headaches, vomiting</td>
<td>Numerous foci in both hemispheres of the brain</td>
<td>Symptomatic treatment</td>
<td>DOD (3)</td>
</tr>
<tr>
<td>5.</td>
<td>SD (M), 4.4</td>
<td>RMA – perimandibular region</td>
<td>None</td>
<td>4</td>
<td>Headaches, vomiting, drowsiness, bilateral Babinski, progressive para paresis, impaired consciousness, coma</td>
<td>In autopsy: numerous infiltrations of neoplastic cells surrounding the vessels, haematoma within neoplastic infiltration of dura mater</td>
<td>Symptomatic treatment</td>
<td>DOD (2)</td>
</tr>
<tr>
<td>6.</td>
<td>SA (F), 5.2</td>
<td>NB poorly differentiated, Schwannian stroma poor – left suprarenal gland</td>
<td>Bones, bone marrow/multiple</td>
<td>32</td>
<td>Headaches, vomiting</td>
<td>Left temporal lobe (1)/3.5 × 3.8</td>
<td>CHT Surgical resection RTX Maintenance oral CHT Cis-retinoic acid therapy</td>
<td>DOD (39) (due to bone metastases)</td>
</tr>
<tr>
<td>7.</td>
<td>KM (M), 17.7</td>
<td>GCT (mixed germ cell tumour) – right testis</td>
<td>Lungs, spleen, lymph nodes/multiple</td>
<td>1</td>
<td>Right-sided paresis</td>
<td>Left parietal lobe (1)/17 × 18</td>
<td>Surgical resection CHT</td>
<td>Alive (17)</td>
</tr>
</tbody>
</table>
blastematos component of nephroblastoma because this case was initially diagnosed as Wilms’ tumour. Fast local recurrence of the tumour and BM forced a re-diagnosis of this case. The pattern of a primary renal tumour was nested and microcystic, but BM showed a solid cellular pattern with a very high mitotic activity, focal anaplasia and formation of an abortive rosette. The BM tissues from the first and the second neurosurgical resection showed a similar picture (Figs. 5A-B).

A 4-year-old boy (p. 2) with PPB type II (solid-cystic PPB of the right lung) (Fig. 5C) developed BM with a diameter of 5 cm approximately four months after completion of the first-line treatment. He was operated on twice – at the moment of BM diagnosis, and 10 months later. Histologically, the metastatic tumour was solid, consistent with type III PPB. It was composed of rhabdomyosarcomatous, spindle sarcomatous component, blastemal areas and fields with early chondroid differentiation (Fig. 5D). Immunohistochemically, the tumour was cytokeratin-negative and focally positive for desmin and S-100.

The female patient with adrenal neuroblastoma (p. 6) (neuroblastoma poorly differentiated, Schwannian stroma poor) was initially diagnosed as stage IV, with bone and bone marrow metastases. After a few months of chemotherapy, the residual primary tumour was excised and showed differentiation of up to ganglioneuroma maturation (Schwannian stroma predominant). Eight months after completion of the primary line of therapy, the girl developed a solitary BM in the temporal lobe. The tumour was subtotally resected. Histologically, it showed small round blue cell tumour morphology with neuropile islands, consistent with a Schwannian stroma poor neuroblastoma. Immunohistochemically, the neoplastic cells were positive for synaptophysin and negative for desmin, CK and LCA.

The BM of a patient with osteosarcoma (p. 10) had histology indicative of osteoblastic OSA, similar to his primary bone tumour. It was composed of malignant polymorphic hyperchromatic osteoblastic cells with focal osteoid production in the stroma. In the neuropathological examination, the neoplastic growth was quite well delineated or nodular in GCT and NBL. CCSK and PPB BM had widely infiltrative borders. The proliferative index differed between the primary tumour and BM in three cases. It was approximately 20% higher in BM of CCSK, PPB and diffuse infiltrating RMS. In all cases, the changes in the surrounding nervous tissue

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<table>
<thead>
<tr>
<th>No.</th>
<th>Patient</th>
<th>Primary Tumour</th>
<th>Metastases</th>
<th>Death Cause</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Time of BM</th>
<th>BM Site</th>
<th>Treatment</th>
<th>Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>WM (M)</td>
<td>17/3</td>
<td>GCT (Kc)</td>
<td>Alive (43)</td>
<td>17</td>
<td>M</td>
<td>1/0.8</td>
<td>Left temporal lobe</td>
<td>CHT, RTX</td>
<td>17.3</td>
</tr>
<tr>
<td>9</td>
<td>LP (F)</td>
<td>2.6</td>
<td>OSA – femoris</td>
<td>Surgical resection</td>
<td>10</td>
<td>F</td>
<td>1/0.9</td>
<td>Left temporal lobe</td>
<td>CHT</td>
<td>2.6</td>
</tr>
<tr>
<td>10</td>
<td>NT (M)</td>
<td>16.5</td>
<td>– femoris</td>
<td>Died of disease (11), months; systemic disease progression</td>
<td>16.5</td>
<td>M</td>
<td>1/0.9</td>
<td>Right lung, brain, skin, bones, skull, temporal lobe, and meninges</td>
<td>CHT, RTX, chemotherapy, RTX</td>
<td>16.5</td>
</tr>
</tbody>
</table>
Axial T1-weighted MR images show brain metastases from angiosarcoma in both hemispheres. Signs of haemorrhage are visible (high signal from methaemoglobin). T2-weighted MR image shows heterogeneous brain metastasis from angiosarcoma in the right hemisphere, with a large adjacent region of oedema.

Contrast-enhanced T1-weighted MR image shows intensive enhancement of two intracranial metastases. A larger lesion is located in the brain parenchyma with an infiltration of dura matter. A second lesion is visible in the dura of the cerebral falx.

Native CT scan shows bilateral subdural haematomas with generalised brain oedema.
Brain metastases in paediatric patients – characteristics of a patient series and review of the literature

Fig. 4. Pathology of selected tumours (RMS and GCT). A) BM of RMS with wide perivascular invasion and astroglial reaction in the surrounding tissue (HE, 200×). B) BM of mixed sacral GCT composed of yolk sac tumour component. The well-defined borders of the tumour can be observed (HE, 100×). C) AFP immunopositivity of neoplastic cells and intraluminal product (AFP, 400×). D) Primary testicular tumour predominantly composed of mature teratoma (HE, 100×). E) BM composed of choriocarcinoma (HE, 200×). F) Intensive astrogliosis surrounding yolk sac tumour BM (GFAP, 100×).
**Fig. 5. Pathology of selected tumours (PPB, CCSK).**

**A)** Primary renal tumour – clear cell sarcoma of the kidney (CCSK) (HE, 200×). **B)** BM of CCSK from the first resection composed of solid anaplastic component (HE, 200×). **C)** Primary focus of pleuro-pulmonary blastoma (PPB) with areas of diverse differentiation components (HE, 200×). **D)** PPB BM composed of small blue cells with aggressive perivascular invasion of the nervous tissue (HE, 200×). **E)** Vasogenic brain oedema and lymphocytic perivascular infiltrates in peritumoural brain tissue (HE, 100×). **F)** Microglial reaction with ramified and foamy cell forms accompanying BM (CD68, 200×).
included significant vasogenic oedema, prominent astrogliosis (cellular and fibrous) and inflammatory response. A vascular reaction in the form of proliferation of small blood vessels (angiogenesis) and vascular dilatations was present in the cerebral tissue. The immunological reaction to the BM was observed in the form of macrophage infiltrates (positive for LCA and CD68) with ramified forms, foamy cells or haemosiderin-laden macrophages as well as lymphocytic perivascular infiltrates (Fig. 4F, 5E, 5F).

Discussion

Brain metastases constitute a rare complication in paediatric tumours. The reasons for the difference between paediatric and adult tumours in this regard are not fully understood. One possible explanation involves the histological spectrum of paediatric tumours. The rarity of BM in paediatric cancer patients can also be explained by the different therapeutic oncological approaches used compared to those used for adults. Most paediatric malignancies are chemosensitive and are treated aggressively, and it is possible that the less mature blood-brain barrier in children enables penetration of the drugs into the cerebral parenchyma. However, most systemic treatments can transiently weaken the blood-brain barrier and allow neoplastic cells to be seeded in the CNS, so the brain may be a “sanctuary site”, that is, a place where neoplastic cells may persist [10]. In general, there are two main pathophysiological hypotheses for BM development that involve either haemodynamics or “molecular recognition”. Roughly 20% of the cardiac output goes to the brain, so it is obvious why lung tumours, both primary and secondary, are a frequent source of BM. The molecular recognition hypothesis involves an affinity between tumour cells and the host tissue. An example is the predilection of breast cancer with a HER2 amplification to generate BM, which can be explained by the fact that HER2 ligands (heregulins) are widely expressed in brain tissue [6].

Some of the current treatment protocols used in paediatric oncology practice recommend performing brain imaging studies at the time of cancer diagnosis and later on at certain phases of treatment. Imaging studies that are useful for BM detection include CT and MR. In a non-enhanced phase, metastases may have different densities as found by CT examination. Hypodense foci indicate necrosis while hyperdense ones may reflect intratumoural bleeding or calcifications. Contrast-enhanced CT usually reveals peripheral enhancement and a surrounding oedema. Contrast-enhanced MRI detects two to three times as many lesions as contrast-enhanced CT, especially lesions smaller than 5 mm in diameter. In T2-weighted images, BM have elevated signals, while in T1-weighted images, their signal is reduced or not visible. Intratumoural bleeding during the methaemoglobin phase is visible as a hyperintensity in T1-weighted images. The characteristic oedema surrounding the metastatic foci is most visible in T2-weighted images and FLAIR sequences [14]. Neuroimaging findings in our series of patients were typical for BM, except from a case of RMS with subdural haematomas. The haemorrhagic picture of the metastases is quite typical for choriocarcinoma, which is angioinvasive, as it is devoid of blood vessels [9,24].

Neuropathological studies on BM in children are very few [7,26]. In the current study, the frequency of BM in children with malignant solid tumours was 2%. All lesions were located in the supratentorial region of the brain, as in the report by Matthay et al. [14]. In six of our patients, the pulmonary metastases or pulmonary tumour locations coexisted with BM, which was also found in other reports [3,8,18]. This suggests that the haemodynamic hypothesis of metastatic processes is more suitable in paediatric cancer.

The optimal treatment for patients with BM depends on the tumour type, the number of brain lesions and the presence of other systemic metastases. For patients with solitary metastases and no systemic disease, surgery followed by radiotherapy and/or chemotherapy may be the best treatment [3,8]. It is recommended to use high-dose radiotherapy ± surgery in such patients [5]. For patients with multiple BM, chemotherapy and radiotherapy only, without surgery, may be of value [18].

It is generally acknowledged that the prognosis of patients with extracranial solid tumours with BM is poor. The majority of children die from disease progression even if the brain lesions remain under control [18]. In the present group of patients, seven died, all due to disease progression. In five cases, CNS involvement was the direct cause of death. Three patients are still alive, all diagnosed with GCT.

Our series includes three children with STS and BM. A 14-year-old girl with angiosarcoma of the right
atrium and ventricle of the heart developed rapid and direct spread of cancer to the lungs and brain. In the patient with alveolar RMS, neurological signs due to bilateral subdural haematomas occurred during pancytopenia after chemotherapy. Massive neoplastic perivascular infiltration of the CNS was detected histologically in the autopsy sections. The third STS patient primarily had disseminated RMS with disseminated intravascular coagulation, and multiple cortical BM were also present in this unusual course of disease [1].

In GCT patients, BM are most common in extragonadal tumours, in advanced stages of the disease [24] and in tumours with choriocarcinoma elements [8,24]. Previously, the frequency of brain involvement in GCT was estimated at 3.7%, but in recent years this level has gradually begun to drop. This decrease is a result of both intensive multi-drug chemotherapy protocols and accurate monitoring of the course of the disease using BHC G and/or AFP levels [24]. In our series, there were three GCT cases with BM – two testicular tumours in adolescents and one extragonadal tumour in a young girl. Two of these GCT were mixed tumours, and the third case was a pure choriocarcinoma.

Over 50% of NBL cases are diagnosed with disseminated disease at the time of initial diagnosis. A high frequency of haematogenous bone, liver and bone marrow metastases is in contrast to infrequent BM, constituting only 5% in a large dataset [14]. In the course of NBL, CNS invasion usually results from direct extension of the disease from the foci in the adjacent cranial bones and orbital metastases [10,14,18]. One of our patients had a solitary metastatic relapse in the brain. She underwent subtotal surgical resection of the brain lesion and received multimodal oncological treatment. Permanent CNS remission was achieved; however, the patient died from bone metastases 39 months after BM diagnosis. Similarly, a boy with OSA with totally resected BM died 11 months after chemotherapy showed a mature histology. However, it relapsed in the form of a single BM, which showed immature morphology. It seems that this tumour was derived from a residual chemoresistant immature neuroblastic cell population that may have been dormant in the CNS “niche”. Furthermore, in three cases, we observed that BM metastatic foci can differ histologically from the primary tumour [25]. These histological differences are detected in mature teratomas, which can create secondary foci of immature germ cell components, for instance, in the case of choriocarcinoma. Another rare possibility is a “burnt out” gonadal GCT with metastases of choriocarcinoma tissue [24,25]. This is connected with the specific biology and differentiation pathways in this group of tumours. One of our patients had testicular mature teratoma and metastases composed of choriocarcinoma tissue. In
another patient, the metastatic component from mixed GCT consisted of yolk sac tumour.

In conclusion, our study confirms that BM in paediatric solid tumour patients are rarely encountered. The best prognosis occurs in children with GCT. The histopathological picture of BM can be different from that of the primary tumour, showing dedifferentiation or a diverse neoplastic component. An autopsy examination can still be helpful in the establishment of the final diagnosis in certain cases with an atypical clinical presentation.

References