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CASE REPORT OPEN ACCESS

Metastatic Supratentorial Ependymoma: A Case Presentation and Systematic Review of the Literature

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ABSTRACT

Ependymomas are categorized based on anatomical location and specific genetic alterations, with extra-axial metastasis being a rare event, occurring in less than 1% of cases and documented sparsely in the literature. This case study details a 27-year-old male patient diagnosed with supratentorial ependymoma characterized by Zinc Finger Translocation Associated (*ZFTA*) fusion and World Health Organization (WHO) Grade 2 morphology. Additionally, a systematic review of all reported cases of extra-axial ependymoma metastases was conducted, systematically compiling clinical, morphological, and molecular data from relevant articles. Metastatic ependymoma represents a rare occurrence characterized by diagnostic and therapeutic challenges. A comprehensive review of the literature could provide valuable insights into the underlying biology and support the selection of optimal treatment strategies for such cases.

1 | Introduction

Ependymomas arise and comprise genetically distinct subgroups and more frequently affect children than adults, accounting for 1.6%–1.8% of all primary central nervous system (CNS) tumors and 10% of childhood brain tumors [1, 2]. Ependymoma is a histologically defined diagnosis characterized by ependymal differentiation with ependymal rosettes or perivascular pseudorosettes, glial fibrillary acidic protein (GFAP) and S100 cytoplasmic positivity, dot-like epithelial membrane antigen (EMA) perinuclear reactivity, and negative Olig2 nuclear reactivity [2]. The 2021 WHO CNS 5 introduced an integrated histomolecular classification of ependymal tumors across three anatomical locations: supratentorial ependymoma (STE), infratentorial/posterior fossa ependymoma (PFE), and spinal cord ependymoma (SCE). Supratentorial ependymomas are further categorized into two molecular subgroups: STE with *ZFTA* fusion and STE with yes-associated protein 1 (*YAP1*) fusion [2]. Generally, ependymomas exhibit low metastatic potential, extra-cranial metastasis being exceedingly rare and occurring in less than 1% of cases. The few reported cases of extra-axial metastases have involved dissemination to the lymph nodes, liver, lungs, peritoneum, and pleura [3]. This case report and systematic literature review aim to provide a more comprehensive insight into the underlying pathology of extra-axial metastatic ependymoma and support the selection of optimal diagnostic and treatment strategies.

Abbreviations: CDKN2A, cyclin-dependent kinase inhibitor 2A; CNS, central nervous system; CT, computed tomography; EMA, epithelial membrane antigen; FISH, fluorescence in situ hybridization; GFAP, glial fibrillary acidic protein; HPF, high power field; HSA, hepatocyte specific antigen; IHC, immunohistochemistry; INSM1, insulinoma-associated protein 1; L1CAM, L1 cell adhesion molecule; MRI, magnetic resonance imaging; NGS, next generation sequencing; PET, positron emission tomography; PFE, posterior fossa ependymoma; RELA, REL-associated protein; RNA, ribonucleic acid; SCE, spinal cord ependymoma; SRT, stereotactic radiation therapy; STE, supratentorial ependymoma; TMZ, temozolomide; VP, ventriculoperitoneal; WHO, World Health Organization; YAP1, yes-associated protein 1; ZFTA, zinc finger translocation associated.

2 | Case Presentation

A 27-year-old male patient presented to the hospital with complaints of a headache and temporary right hemiparesis. Initial cranial computed tomography (CT) and subsequent brain magnetic resonance imaging (MRI) revealed a space-occupying lesion in the left parietal lobe (Table 1). Gross total resection was performed in November 2017, and histological examination of the tumor diagnosed a cortical ependymoma. The multidisciplinary team recommended complete neuroaxis irradiation (36 Gy to the spine and 14 Gy to the cranium) administered over 5 weeks from late January to early March 2018. Follow-up MRI scans showed mild progression with ring-like enhancement at the surgical site, and re-operation was recommended. A left parietal re-craniectomy confirmed the diagnosis of a recurring CNS WHO Grade 2 ependymoma. Post-surgical neuraxial MRI showed no intra-axial tumor spread. In September 2019, a follow-up MRI revealed a new 2–3 mm large ring-enhancing lesion, indicating yet another possible relapse. Sorafenib therapy was initiated based upon a case report, mainly because the patient wished to be treated without chemotherapy [4]. Eight months later, MR imaging indicated progression at the primary tumor site, with an increase from 5 mm to 10 mm. The patient then underwent stereotactic radiation therapy (SRT) with a total dose of 5×6 Gy. Despite the radiotherapy, subsequent follow-up MRIs confirmed further progression at the primary site (12×12×13 mm) and the development of a new lesion adjacent to the primary tumor (13×12×10 mm). Partial resection of the new lesion was performed in December 2021, and histological and fluorescence in situ hybridization (FISH) studies confirmed ependymoma with *RELA* fusion, CNS WHO Grade 3. Temozolomide (TMZ) monotherapy was started in January 2022. In May 2022, MRI of the cervical, dorsal, and lumbar spine revealed new contrast material enhancing lesions in multiple cervical and thoracic vertebrae, suggesting multiple secondary bone metastases. Neurosurgery was not recommended at this time. In June 2022, the patient presented with liver enlargement during a control visit, while full blood count showed slight eosinophilia. Abdominal ultrasound revealed multiple hepatic lesions, the largest measuring 65 mm, with suspicion for metastases. A follow-up chest/abdomen/pelvis CT showed a significantly enlarged liver with several confluent hypodense lesions, the largest in the eigth segment at 86 mm (Figure 1). Multiple sclerotic bone metastases were also noted, the largest in the thoracic vertebra at 23 mm. After ruling out possible infectious origin, a liver biopsy confirmed metastatic ependymoma, and next generation sequencing (NGS) studies led to an integrated diagnosis of supratentorial ependymoma with *ZFTA* fusion, CNS WHO Grade 3 (Figure 2). Colonoscopy and gastroscopy were done to assess for further metastases, yielding negative findings. A methionine positron emission tomography (PET) body scan was performed to identify possible further metastatic sites, confirming the previously known bone and liver metastases. No new metastatic lesions were diagnosed. Fotemustine chemotherapy was initiated as standard post-temozolomide chemotherapy for central nervous system malignancies. However, after five cycles, a follow-up CT imaging showed further progression of liver and bone metastases with the development of ascites and leg edema. Consequently, the patient was started on a combined cisplatin plus etoposide therapy. After three cycles, the patient's general condition improved greatly, with liver enzymes improving and improved appetite resulting in consequent weight gain. However, before starting the fourth cycle, an unattended scratch from a pet resulted in a septic condition, and despite these interventions, the patient died in August 2023.

TABLE 1 | Summary of clinical history.

2017 November	Finding: SOL in left parietal lobe, gross total resection of ependymoma. Management: complete neuroaxis irradiation.
2018 March	Finding: local progression with ring enhancement. Management: left parietal recraniectomy.
2019 September	Finding: local, new ring-enhancement, possible relapse. Management: sorafenib treatment.
2020 May	Finding: tumor progression at primary site. Management: stereotactic radiation therapy with a total dose of 5×6 Gy.
2021 November	Finding: further tumor progression of primary site and new lesion. Management: partial resection of new lesion. The diagnosis supratentorial ependymoma CNS WHO Grade 3 with *RELA* translocation. Themozolomide monotherapy was started.
2022 May	Finding: multiple cervical and thoracic vertebral lesions. Management: themozolomide therapy and observation of new lesions.
2022 June	Finding: liver enlargement with multiple focal lesions. Liver biopsy revealed ependymoma metastasis with *ZFTA*::*RELA* fusion. No other organ was involved. Management: fotemustin chemotherapy was initiated (five cycles) what was followed with a combination of cisplatin and etoposide due to further progression (three cycles).
2023 August	Death due to sepsis.

Abbreviation: SOP, space occupying lesion.

3 | Pathological Findings

3.1 | Methods and Materials

3.1.1 | Immunohistochemistry

Formalin-fixed, paraffin-embedded tissue blocks and 4-μm thick tissue sections were used for immunohistochemical (IHC) analysis in the Department of Pathology, University of Debrecen, Hungary.

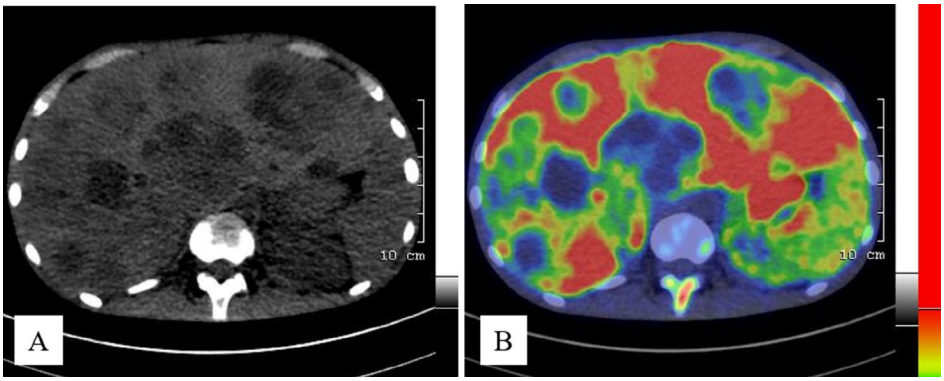

FIGURE 1 | Metastatic ependymoma with multiple hepatic nodules. (A) Axial native CT with multiple hepatic metastases. (B) Axial fusion images of PET/CT show multiple hepatic lesions.

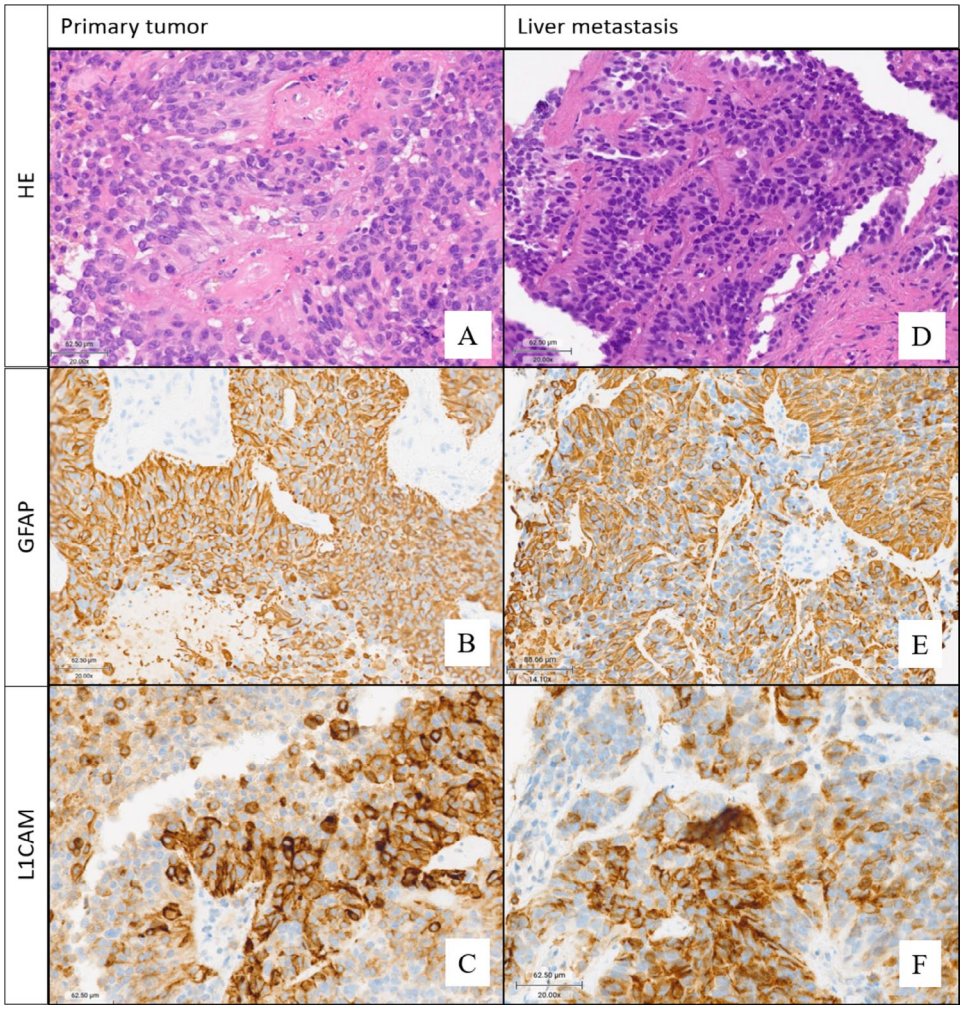

FIGURE 2 | Histopathological findings of primary and metastatic ependymoma. Primary tumor (A–C): Hematoxylin and eosin staining of the primary tumor sample shows a cell-rich tumor composed of ependymal cells with monomorphic round nuclei and perivascular pseudorosettes. GFAP and L1CAM immunohistochemical staining of the primary tumor shows diffuse positivity. Hepatic metastasis (D–F): HE staining of the metastasized tumor sample shows a similar picture of abundant tumor cells with perivascular pseudorosettes; positive GFAP and L1CAM IHC staining of the metastasis confirms ependymal origin of the tumor.

The most relevant immunohistochemical stains were the following: antibody against L1 cell adhesion molecule (L1CAM) (monoclonal mouse, clone UJ127.11; Merck Life Science Ltd., Darmstadt, Germany; 1:500), antibody against Cyclin D1 (rabbit monoclonal, clone SP4-R; Roche Diagnostics, Budapest, Hungary; RTU), antibody against EMA (mouse monoclonal, clone E29; Kromat Ltd., DAKO, Torokbalint, Hungary; 1:300), antibody against GFAP (mouse monoclonal, clone 6F2; Kromat Ltd., DAKO, Torokbalint, Hungary; 1:500). All immunohistochemical reactions were performed according to the manufacturer's instructions.

3.1.2 | Next-Generation Sequencing

NGS was performed from liver biopsy in the Department of Pathology, University of Debrecen, Hungary. For NGS library preparation from tumor tissue-derived ribonucleic acid (RNA) and peripheral blood cell-free RNA samples, an RNA-based Archer FusionPlex custom gene panel (Archer DX, Boulder, CO, USA) was applied to identify the SNVs, indels, and gene fusions. The final libraries were quantified with a KAPA library quantification kit (Roche, Basel, Switzerland), diluted to a final concentration of 4 nM, and pooled by equal molarity. For sequencing on the MiSeq System (MiSeq Reagent kit, version 3, 600 cycles), the libraries were denatured using 0.2 nM NaOH and diluted to 40 pM with hybridization buffer (Illumina, San Diego, CA, USA). The final loading concentration was 8 pM libraries and 5% PhiX. Captured libraries were sequenced in a multiplexed fashion with a paired-end run to obtain 2 × 150 bp reads, with a depth of coverage of at least 500×. Trimmed FASTQ files were generated using the MiSeq reporter (Illumina, San Diego, CA, USA) and were uploaded to the Archer Analysis v7 website (Archer DX, Boulder, CO, USA). For alignment, the human reference genome GRCh38 (equivalent UCSC version hg38) was built. A 5% variant allele frequency was used as the cut-off value.

3.1.3 | Fluorescent in Situ Hybridization

FISH was performed on 5 μm-thick sections of the formalin-fixed, paraffin-embedded block, with RELA break apart probe (Empire Genomics, Williamsville, NY USA). Slide and probe co-denaturation was carried out at 75°C for 10 min, while hybridization was at 37°C in a moist chamber for 18 h (StatSpin ThermoBrite, Abbott Molecular, Des Plaines, IL, USA). After washing, the nuclei were counterstained with 4′-6′ diamidino-2-phenylindole (DAPI, MetaSystems, Altlussheim, Germany). The images were analyzed using ISIS software v.5.5.4. (MetaSystems, Altlussheim, Germany).

3.1.4 | Systemic Literature Review

For the systematic literature review, articles published in PubMed, Web of Science, and Google Scholar using the keywords “metastasis” “metastatic” and “ependymoma” were selected. The inclusion criteria were as follows: articles published between 2000 and 2023, articles written in English, and articles containing information about the primary tumor location, metastasis location, age, and gender of the patient. The exclusion criteria were duplicate articles across different databases, studies conducted on animals, and articles on other ependymoma subtypes, such as myxopapillary ependymoma and subependymoma. Finally, we cross-checked all references to identify any additional studies that met our criteria. The first 500 findings were included for Google Scholar. A total of 807 full-text studies published in English from 2000 to 2023 were screened, and based on our criteria, 22 articles were selected. After cross-checking with all articles from the reference list, one additional study was included [4–27] (Figure 3) The original tumor grade provided in publications was used for further analysis.

3.2 | Histopathological Findings

The initial histological examination of the left parietal tumor resection revealed a cell-rich tumor composed of ependymal cells, characterized by monomorphic round nuclei with speckled chromatin, focal atypia, and a mitosis index of 0/10 high power field (HPF). Classic true ependymal and perivascular pseudorosettes were dispersed throughout the tumor. Immunohistochemical (IHC) analysis showed a diffuse GFAP and dot-like EMA expression indicative of a CNS WHO Grade 2 ependymoma. Cyclin D1 and L1CAM were positive.

The second biopsy, taken after radiation therapy, displayed signs of prior irradiation (hemosiderin, hyaline vascular changes), an increased mitosis index of 4/10 HPF, and a Ki-67/MIB-1 labeling index of 10% (focally 30%). Further IHC analysis revealed GFAP+, OLIG2-, EMA+ (dot-like), D2-40+ (dot-like), Cyclin D1+, and L1CAM+ immunophenotype confirming a diagnosis of CNS WHO Grade 3 ependymoma. FISH revealed the presence of a *RELA* translocation, and NGS confirmed the presence of *ZFTA* fusion, further classifying the tumor as supratentorial ependymoma, *ZFTA* fusion-positive.

Following hepatic metastasis, a liver biopsy was performed and microscopic analysis showed a cell-rich tumor with perivascular pseudorosettes and salt-and-pepper chromatin. IHC studies confirmed the diagnosis of metastatic ependymoma with a characteristic immunophenotype: GFAP+, perinuclear dot-like EMA+, cyclinD1+. Further stains (panCK−, CK8/18−, Hepatocyte Specific Antigen (HSA)−, Insulinoma associated protein 1 (INSM1)−, chromogranin-A−) were performed to exclude carcinoma (Figure 2).

3.3 | Molecular Findings

The diagnosis of supratentorial ependymoma with *ZFTA* fusion was confirmed by the presence of a *ZFTA::RELA* fusion. The detection of these alterations was achieved using both NGS and FISH analysis of the primary tumor and the hepatic metastasis.

3.4 | Systematic Literature Review Findings

The systematic review revealed that the most common location for primary tumors was the supratentorial region of the brain (16 out of 23 cases), consistent with the fact that this subtype is the most frequent ependymoma. Most tumors that metastasized were CNS WHO Grade 3 (17 out of 19 cases with known grade); however, Grade 2 ependymomas are much more frequent in general. We also found that the patient's sex did not affect primary tumor metastasis, with a male-to-female ratio of 11:12. The primary treatments were resection (21 out of 23 cases) and radiotherapy (19 out of 23 cases), while chemotherapy was mainly used for treating metastases (16 out of 23 cases). The three most common metastatic sites were the lymph nodes, lungs, and integumentary system, with many cases involving multiple organs (17 out of 23 cases). Notably, two out of four cases with ventriculoperitoneal (VP) shunt placement showed metastasis to the peritoneum. The overall 5-year survival rate of

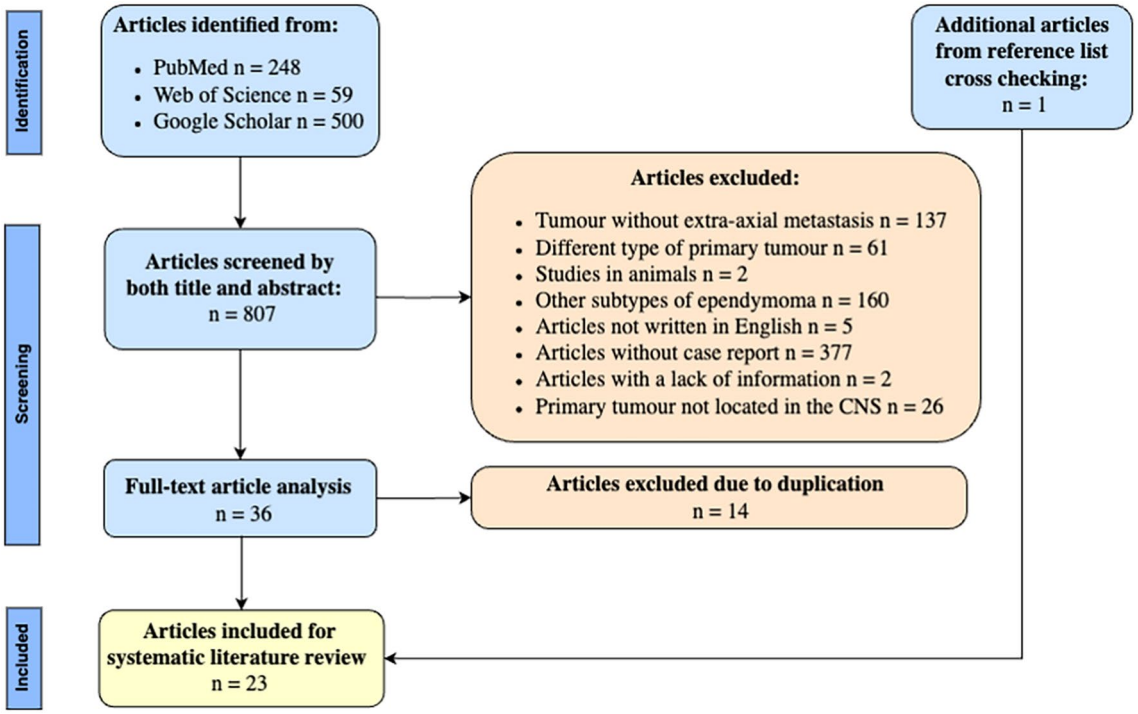

FIGURE 3 | Flowchart of the systematic literature review process. Initially, 807 articles were identified from various sources (PubMed, Web of Science, Google Scholar) and screened by their titles and abstracts. Irrelevant articles were excluded, leaving 36 articles for full-text analysis. Finally, after the exclusion of duplicates and the addition of one article from reference list cross-checking, 23 articles were included in the systematic literature review.

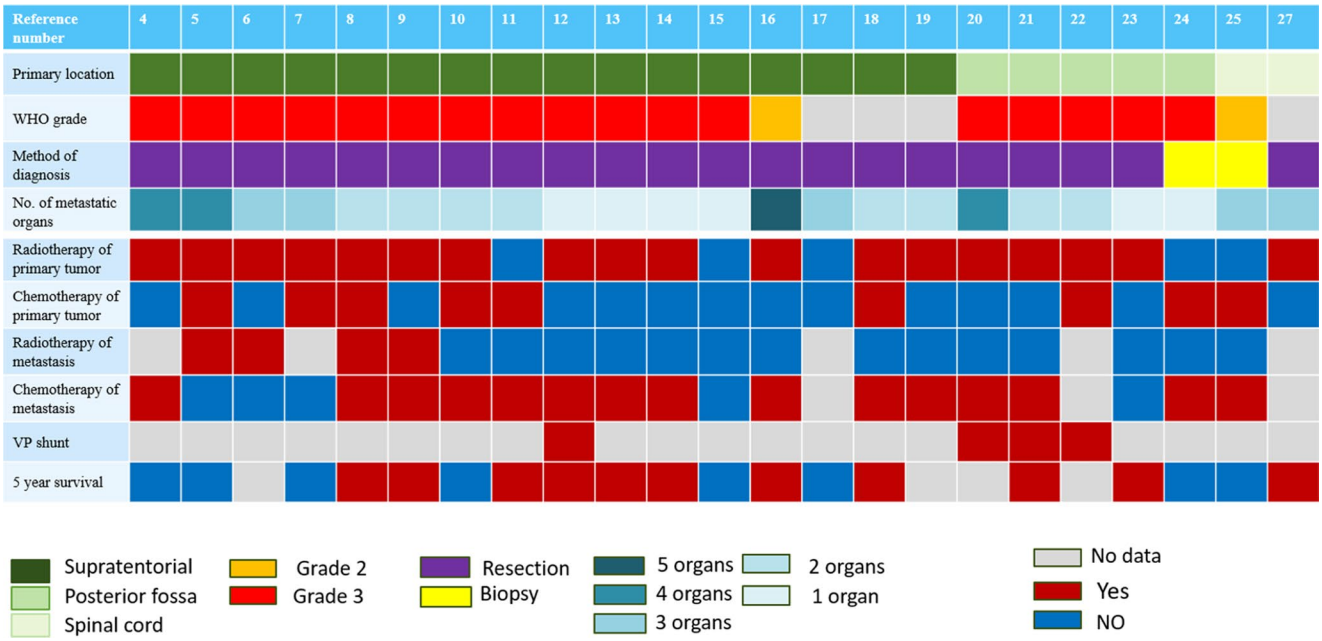

FIGURE 4 | Heatmap showcasing the results of the systematic literature review. Primary location: 16 cases were primarily supratentorial, five cases were found in the posterior fossa, and two cases occurred in the spinal cord. CNS WHO Grade: 17 cases were given a CNS WHO Grade 3, two cases were CNS WHO Grade 2, and four cases had no CNS WHO grading. Method of diagnosis: 21 cases were diagnosed by tumor resection, and only two cases were diagnosed via biopsy. Number of metastatic organs: one case involved ≥ 5 organs, three cases involved 4 organs, three other cases involved 3 organs, 10 cases involved 2 organs, and six cases involved 1 organ. Radiotherapy of primary tumor: in 21 of the 23 cases, radiotherapy of the primary tumor was performed. Chemotherapy of primary tumor: in 10 of the 23 cases, chemotherapy for the primary tumor was administered. Radiotherapy of metastasis: in four cases, radiotherapy of the metastasis was performed; in 14 cases, it was not performed, and in five cases there was no data available. Chemotherapy of metastasis: in 16 cases, chemotherapy was given to treat the metastasis; in four cases, it was not administered, and in three cases there was no available data. Ventriculoperitoneal (VP) shunt: in four cases a VP shunt had been placed; the remaining 19 cases had no relevant data. Five-year survival: 10 cases had a 5-year survival, eight cases did not have a 5-year survival, and in five cases survival data was not available.

the patients was approximately 55.55% (10 out of 18 cases); not all articles provided complete details on outcome post-treatment [4–27] (Figure 4).

4 | Discussion

According to a study published in 2022, the incident rate of ependymoma is about 0.29–0.6 per 100 000, comprising only 1.6%–1.8% of the primary CNS tumors [2]. Based on the cohort study performed by Korshunov, Andrey et al. in 2004, only 2% of the cases show extraneural metastasis (5/258 cases), highlighting the rarity of extra-axial metastasis ependymoma [28]. Consequently, there are many difficulties in the proper diagnosis and treatment of such patients. Hence, it is important to conduct a systematic literature review to study the characteristics of the disease and the patient outcome in order to provide a comprehensive, evidence-based analysis of this rare condition.

Current primary treatment for ependymoma involves gross total resection followed by 59.4 Gy radiation therapy. While chemotherapy may sometimes be considered due to concerns about radiation toxicity, its effectiveness has not been well established. Despite the use of postoperative chemo-radiotherapy, many cases still show tumor recurrence [2]. A study by Zacharoulis, Stergios, et al. reported a 5-year overall survival rate of approximately 40% (17/40 cases) [3].

In alignment with the WHO database, our study also found that most primary tumors are located in the supratentorial region (16 out of 23 cases), with the majority of patients (14 out of 23 cases) being under 18 years of age [1]. However, while most ependymoma cases recorded in the WHO database were Grade 2 tumors, our study revealed that most ependymomas leading to extra-axial metastases were CNS WHO Grade 3. This suggests that more anaplastic cells exhibit more aggressive behavior. Our systematic review identified the main sites of metastases as the lymph nodes, lungs, and integumentary system. However, no correlation was found between the primary tumor location and the metastatic sites. Among the cases reviewed, four involved ventriculoperitoneal (VP) shunt placement; three of these were for primary tumors located in the posterior fossa region. Interestingly, two of these cases exhibited metastasis to the peritoneum, suggesting that the VP shunt might play a role in tumor dissemination. This aligns with findings from an article, indicating that patients with VP shunts may require closer monitoring for distant metastasis of the tumor [29].

Characteristic histological features such as rosettes or pseudorosettes with positive immunohistochemical staining for GFAP, EMA remain a reliable confirmation of ependymoma, while cyclinD1 and L1CAM expression correlates with the presence of *ZFTA* fusion. The most recent 2021 WHO classification of ependymoma emphasized the growing importance of molecular alterations in the diagnosis and prognosis of patients [1]. Unfortunately, many reported case reports of ependymoma did not provide data on pathological molecular alterations. One exception is the case report by Kim et al., which demonstrated that the *ZFTA::RELA* fusion leads to more aggressive ependymoma behavior, with metastases to five different organs [19]. In our patient, multiple distant metastases to the osseous system and liver occurred eight months after detecting the *RELA* translocation. Both cases showed poor prognosis associated with the *ZFTA*::*RELA* gene translocation, as indicated in the new WHO classification of CNS tumors. Additionally, studies by Pachella et al. [23], and Zhou, Mading, et al. mentioned the deletion mutation of the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) tumor suppressor gene [7]. However, the correlation between this mutation and ependymoma behavior is not well established.

In conclusion, ependymomas with extra-axial metastasis are an exceedingly rare occurrence. Due to the limited studies available, it remains challenging to fully understand the correlation between molecular alterations and their impact on the behavior of the tumor. Consequently, determining whether specific mutations influence disease progression and patient prognosis is difficult. However, our study confirms that supratentorial ependymomas with *ZFTA*::*RELA* fusion often exhibit more aggressive behavior; therefore, detecting this mutation may be important for establishing an appropriate treatment plan for patients.

Ethics Statement

Approval of the research protocol: This study was approved by the ethical committees of the University of Debrecen, Hungary (IRB reference number: IV/8465-3/2021/EKU).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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