Pediatric metastatic medulloblastoma: upfront biopsy followed by oncological treatment without excision of the primary tumor

Rina Dvir, MD,[1,5] Ronit Elhasid, MD,[1,5] Jonathan Roth, MD,[2,5] Shlomi Constantini, MD, MSc,[2,5] Yair Peled, MD,[1,5] Inna Ospovat, MD,[3,5] and Shelly I. Shiran, MD[4,5]

[1]Department of Pediatric Hematology/Oncology, Dana Children's Hospital, Tel Aviv Sourasky Medical Center; [2]Department of Pediatric Neurosurgery and the Pediatric Brain Center, Dana Children's Hospital, Tel Aviv Sourasky Medical Center; [3]Department of Radiation Therapy, Division of Oncology, Tel Aviv Sourasky Medical Center; [4]Pediatric Radiology, Division of Radiology, Tel Aviv Sourasky Medical Center; and [5]Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel

OBJECTIVE Advancements in medulloblastoma management have improved survival; however, high-risk metastatic cases remain challenging, with approximately 60% 5-year event-free survival and significant long-term toxicity. Standard treatment includes resection of the posterior fossa tumor, followed by multimodal oncological therapy. Yet, primary tumor resection can result in treatment delay and sometimes surgical morbidity. The aim of this study was to evaluate outcomes and assess the potential of a treatment approach that includes biopsy only followed by chemotherapy and radiation therapy as a viable alternative in selected clinical scenarios.

METHODS This retrospective study included pediatric patients (age < 18 years) who were diagnosed with metastatic medulloblastoma and underwent biopsy (with or without CSF diversion) without primary tumor resection at a tertiary pediatric center between 2010 and 2023. Clinical, surgical, pathological, molecular, and imaging data were analyzed. Tumor response was evaluated on MRI.

RESULTS During the study period, 60 patients with medulloblastoma were treated at the medical center; 12 male patients (mean age 6.5 years, range 1.1–16.1 years) with metastatic disease who were treated with the upfront biopsy-only approach met the inclusion criteria. The median follow-up duration was 3.2 years. At the time of analysis, 9 patients (75%) were alive, with an estimated 5-year survival rate of 63%, and 3 patients had died (2 with very high-risk MYC-amplified tumors and 1 with a late supratentorial relapse). No cases of posterior fossa syndrome were observed. All surviving patients showed stable or resolving residual abnormalities on MRI without progressive disease.

CONCLUSIONS In pediatric patients with metastatic medulloblastoma, primary tumor resection might be avoidable. A biopsy-based approach followed by timely multimodal therapy can preserve survival outcomes while minimizing surgical risks, as long-term prognosis is likely related to the disease subtype and prompt oncological treatment. The proposed strategy warrants further investigation and might have broader implications for medulloblastoma treatment paradigms.

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KEYWORDS medulloblastoma; metastasis; tumor resection; biopsy; pediatric; oncology

Medulloblastoma is the most common malignant brain tumor of childhood, with 20%–25% of patients presenting with metastatic disease and stratified as high risk.[1,2] This group remains a therapeutic challenge, with approximately 60% 5-year event-free survival and considerable long-term toxicities (including neurocognitive and endocrine toxicities) that are associated with high-dose radiation therapy.[2,3] Following surgery, treatment protocols for high-risk metastatic tumors generally use higher doses of radiation therapy (36 Gy craniospinal irradiation [CSI]) as opposed to lower doses in standard or low-risk tumors. Chemotherapy regimens in this group are more intensified frequently using high-dose chemotherapy with stem cell support. Infants are treated with radiation-sparing high-dose chemotherapy protocols or intensive chemotherapy with intraventricular metothrexate.[2,4,5] To date, the surgical approach to medulloblastoma aims for gross-total resection (GTR) of the posterior fossa

ABBREVIATIONS CSI = craniospinal irradiation; GTR = gross-total resection; PF = posterior fossa; PFS = PF syndrome; SHH = sonic hedgehog.

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(PF) primary tumor, regardless of metastatic status. However, the prognostic value of resection extent in metastatic cases remains unclear, with studies reporting that residual tumor > 1.5 cm^2 does not consistently correlate with worse outcomes,[6,7] leading the European Society for Paediatric Oncology to recommend standard-risk therapy in such cases when no other high-risk features are present.[8] In addition, resection of PF tumor carries a substantial risk of cerebellar mutism, reported in 15%–48% of cases across centers.[9]

Some high-risk patients with metastatic disease present with acute complications such as cord compression or hydrocephalus. In such cases, a minimal surgical approach—biopsy of the most accessible lesion and CSF diversion—might be preferable, enabling rapid initiation of oncological therapy and minimizing surgical morbidity. This aligns with neoadjuvant strategies increasingly adopted in pediatric neuro-oncology, with recent North American data supporting neoadjuvant chemotherapy as a safe and effective preresection strategy.[10]

In this study, we aimed to evaluate outcomes and assess the potential of an approach that includes biopsy only followed by chemotherapy and radiation therapy as a viable alternative in selected clinical scenarios for the management of metastatic medulloblastoma in pediatric patients.

Methods

Following approval by the institutional ethics committee, we conducted a retrospective review using the electronic medical records of a university-affiliated pediatric tertiary medical center. The database was searched for pediatric patients who were diagnosed with and treated for medulloblastoma between 2010 and 2023. Inclusion criteria were: 1) metastatic medulloblastoma with at least one solid metastasis, 2) age younger than 18 years at diagnosis, and 3) a treatment protocol based on biopsy of any lesion (with or without CSF diversion, as clinically indicated). Data retrieved from medical records included patient age, sex, clinical presentation, surgical approach, histopathological and molecular subgroups, treatment protocols, and clinical outcomes.

Baseline MRI was retrospectively reviewed by a senior pediatric neuroradiologist to characterize the primary tumor, including the tumor volume (calculated using the ellipsoid formula based on three-plane measurements), tumor-to-PF area ratio (Fig. 1), metastatic distribution, mass effect, and presence of hydrocephalus. Follow-up MRI studies were evaluated at two time points: 1) after completion of initial treatment (CSI or chemotherapy, per protocol), prior to initiation of high-dose chemotherapy with stem cell support (n = 11) or conventional high-dose chemotherapy (n = 1); and 2) at the end of treatment. Follow-up MRI was assessed for changes in primary tumor volume and the presence or absence of metastatic disease.

Statistical Analysis

Categorical variables are reported as counts and percentages, while continuous variables are reported as means ± standard deviations or medians with interquartile ranges. The Wilcoxon signed-rank test was used to compare tumor volumes across time points. Survival during the follow-up period was analyzed using Kaplan-Meier curves. The median follow-up duration was estimated using the reverse Kaplan-Meier method. Statistical analyses were performed using IBM SPSS Statistics (version 29), with $p < 0.05$ considered as statistically significant.

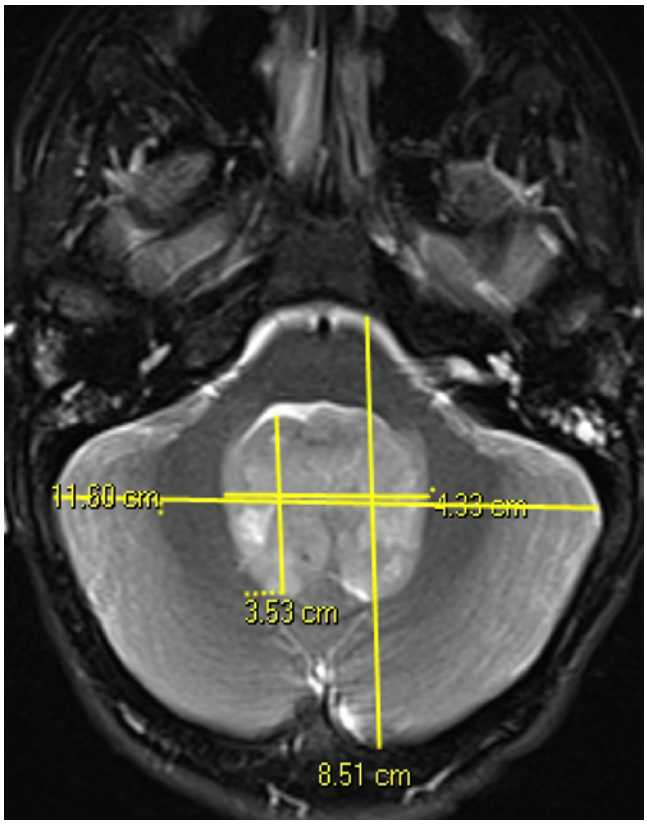

FIG. 1. Patient 8. Axial T2-weighted MR image of the brain obtained in a 16-year-old patient with metastatic medulloblastoma. The tumor-to-PF area ratio of 0.15 was calculated by measuring the maximum anteroposterior and transverse diameters of both the tumor and the PF, and dividing the tumor dimensions by the PF dimensions.

Results

Demographic Data

Between 2010 and 2023, 60 patients with medulloblastoma were treated at our medical center. Ten patients (2 with metastatic and 8 with nonmetastatic disease at presentation) were initially treated at outside institutions and excluded due to incomplete data. Of the remaining 50 patients (35 male, 70%), 16 patients (32%) presented with gross metastatic disease (15 male, 94%). Four patients (3 male and 1 female) underwent GTR and thus were excluded (3 had inaccessible small PF metastasis and 1 presented prior to implementation of the upfront biopsy approach). Therefore, 12 patients, all male, who underwent the upfront biopsy-only approach without primary tumor resection were included in this analysis (Table 1). The age at diagnosis ranged from 1.1 to 16.1 years (mean 6.5 years, SD 4.96 years).

TABLE 1. Demographics, treatment protocols, and outcomes for patients with metastatic medulloblastoma who underwent biopsy without primary tumor resection

Pt No.	Age at Diagnosis, yrs	M Stage	Biopsy Site	Tumor Type	Oncology Protocol	FU Duration, yrs	Outcome	2nd Biopsy
1	2.1	3	Spine	SHH	ACNS0334	3.15	Alive	
2	1.2	3	Spine	SHH	ACNS0334	12.04	Alive	From spine residual, equivocal
3	8.4	3	Spine		SJMB03	5.12	Dead	
4	9.7	3	Spine		SJMB03	13.21	Alive	
5	4.2	2	Supratentorial	SHH	SJMB03	6.16	Alive	
6	3.5	3	Spine	Group 3	SJMB03	0.59	Dead	
7	1.1	2	PF	SHH	ACNS0334	3.32	Alive	
8	16.1	3	Supratentorial	Group 4	SJMB03	3	Alive	
9	5.9	3	Spine	Group 3	ACNS0332	2.62	Alive	From PF residual, scar tissue
10	5.1	3	Spine	Group 3	SJMB03	2.63	Alive	From spine residual, scar tissue
11	6.1	3	Supratentorial	Group 3	SJMB03	1.21	Dead	
12	15	3	Supratentorial	Group 4	SJMB03	1.75	Alive	

FU = follow-up; M = metastasis; pt = patient.

Clinical Presentation and Staging

Eight patients (67%) presented with symptoms of increased intracranial pressure and 4 patients (33%) exhibited signs of spinal cord compression. According to the Chang staging system,[11] 2 patients (17%) were classified as having M2 disease (intracranial metastases only) and 10 patients (83%) as having M3 disease (combined intracranial and spinal metastases).

Radiological Characteristics at Presentation

All patients had PF tumors. Tumor volumes ranged from 4.6 to 62.5 cm^3 (median 19.4, IQR 8.4–45.5 cm^3). The tumor-to-PF area ratio ranged from 0.06 to 0.25 (median 0.14, IQR 0.1–0.19). Hydrocephalus was present in 10 patients (83%).

Surgical Procedures and Complications

The surgical approach was based on targeting a lesion that had optimal surgical accessibility with minimal surgical morbidity. Biopsy approaches were spinal laminectomy in 7 patients (58%), supratentorial endoscopic ventricular biopsies from the suprasellar and third ventricle region in 4 patients (33%), and infratentorial PF stereotactic biopsy in 1 patient (8%). The aim of biopsy was to achieve a sufficient tissue sample for diagnostics, not reducing tumor burden. All 10 patients with hydrocephalus received a ventriculoperitoneal shunt at the time of biopsy. Postoperative wound infections occurred in 2 patients (17%), with no other immediate surgical complications. No cases of PF syndrome (PFS) or upward herniation were observed. Two patients (17%) required late shunt revisions, which occurred at 3 and 11 years postoperatively.

Pathology

Nine patients (75%) had classic medulloblastoma, 2 (17%) had desmoplastic/nodular medulloblastoma, and 1 (8%) had large-cell medulloblastoma. Molecular subtyping was available for 10 patients (83%). Full molecular subgrouping was performed using NanoString gene expression profiling and fluorescence in situ hybridization in 7 patients: 4 (33%) had group 3 tumors (2 with MYC amplification), 2 (17%) had group 4 tumors, and 1 had sonic hedgehog (SHH) medulloblastoma. Three additional SHH cases were diagnosed via immunohistochemistry (GAB1-positive, β-catenin–negative). None of the SHH tumors showed tumor protein P53 gene (TP53) positivity.

Treatment Protocols

The time interval from biopsy to initiation of oncological treatment ranged from 2 to 27 days (median 12, IQR 4.5–18.75 days). The 4 patients who presented with cord compression started treatment with steroids and oncological treatment was initiated promptly within 2 days (patient 1), within 4 days (patients 3 and 10), and within 9 days (patient 4).

Three patients (25%) under the age of 3 years were treated per the ACNS0334 protocol and received induction chemotherapy (vincristine, cyclophosphamide, etoposide, and cisplatin) without methotrexate followed by high-dose chemotherapy (thiothepa and carboplatin) with autologous stem cell rescue, without radiation therapy. Eight patients (67%) received treatment per the SJMB03 protocol, which included CSI followed by 4 cycles of high-dose chemotherapy (cyclophosphamide, vincristine, and cisplatin) with stem cell support. One patient (8%) with group 3 disease was treated per ACNS0332, including CSI with concomitant carboplatin and vincristine, followed by 6 cycles of consolidation chemotherapy (cyclophosphamide, vincristine, and cisplatin). All patients older than 3 years of age received photon CSI at a high-risk dose (36 Gy), with a boost to the primary tumor and any bulky metastases.

Stem cell harvesting was successful in all 11 patients who received bone marrow transplant. Stem cells were collected from 3 patients after the first chemotherapy

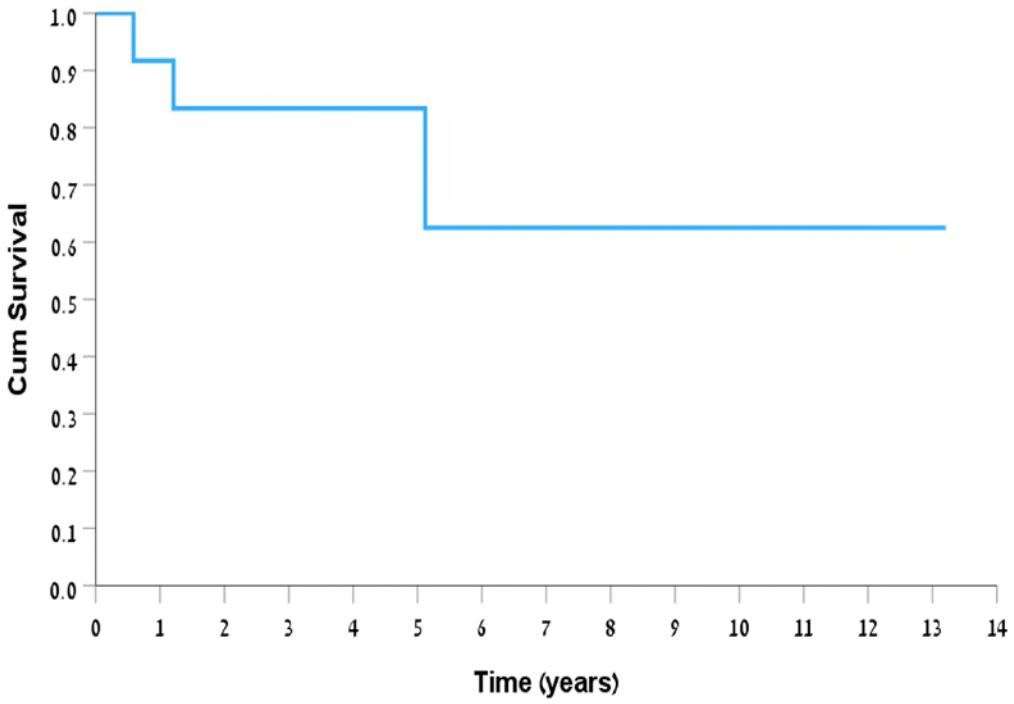

FIG. 2. Kaplan-Meier curve showing cumulative (cum) survival following biopsy and oncological treatment.

cycle. Of 8 patients treated with upfront radiation therapy, stem cells were collected from 3 patients beforehand, while 5 required plerixafor and filgrastim following radiation therapy.

Radiological Characteristics at Follow-Up

All patients demonstrated a reduction in primary tumor volume following initial oncological therapy (volume range 0–27.8 cm^3; median 3.2, IQR 1.3–11.7 cm^3), with persistent metastatic findings. At the end of treatment, residual masses were observed in 11 patients (92%), with volumes ranging from 0.1 to 14.5 cm^3 (median 0.95, IQR 0.58–2.28 cm^3). Changes consistent with prior metastatic lesions were present in 6 patients (50%). Tumor volume reduction from baseline was statistically significant ($p = 0.002$).

Survival and Outcomes

No patients were lost to follow-up. The follow-up duration for the overall cohort ranged from 0.6 to 13.2 years (median 3.2 years). At the time of analysis, 9 patients (75%) were alive and 3 (25%) had died. Kaplan-Meier analysis estimated a 63% 5-year survival rate (Fig. 2). The early deaths included 2 patients with very high-risk MYC-amplified group 3 tumors (patients 6 and 11) and 1 patient (patient 3) with a late supratentorial relapse (unknown subgrouping).

Among the 9 surviving patients, 3 underwent secondary biopsies of residual lesions, either at the end of therapy or before the final chemotherapy course, according to physician preference. Biopsy revealed scar tissue in 2 patients (patients 9 and 10) and was inconclusive in 1 patient (patient 2). The final patient received an additional year of maintenance treatment with oral temozolomide and remains a long-term survivor (Fig. 3).

Neurologically, 8 patients were fully ambulatory. One patient, who presented with triplegia, remained wheelchair-dependent. Neurocognitive sequelae were noted in 6 patients: 3 with mild learning disabilities and 3 requiring special education, including 1 diagnosed with autism spectrum disorder. Endocrine disorders were present in 4 patients: 2 with panhypopituitarism (both long-term survivors, 1 underwent biopsy from a spinal metastasis and 1 underwent biopsy from a suprasellar metastasis), 1 with hypothyroidism, and 1 with precocious puberty. Seven patients were diagnosed with hearing loss, 2 of whom required hearing aids. No secondary malignancies or kidney, heart, or lung complications were documented.

Discussion

This retrospective cohort study highlights the feasibility and potential advantages of a biopsy-only approach followed by chemotherapy and radiation therapy for pediatric metastatic medulloblastoma, omitting resection of the primary tumor. Despite conventional emphasis on maximum safe resection, our data suggest that initial biopsy combined with prompt oncological treatment can yield survival outcomes comparable with more aggressive surgical strategies while avoiding surgical morbidity. A previous study reported upfront biopsy followed by oncological treatment, pursuing PF primary tumor resection when the patient's clinical status allowed.[12] Our approach differs by not pursuing complete tumor resection.

Traditionally, high-risk medulloblastoma is defined by

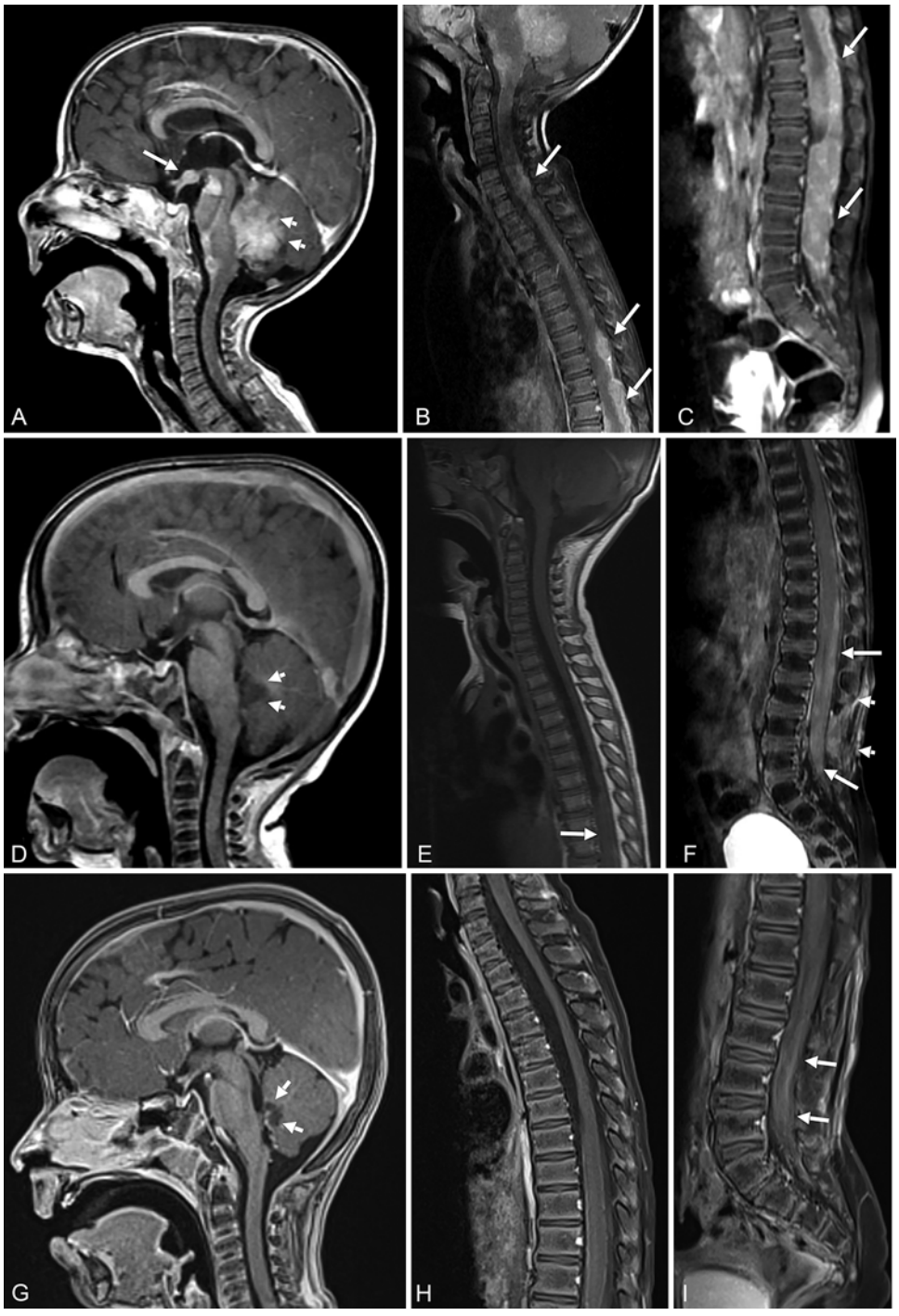

FIG. 3. Patient 2. **A–C:** Midline sagittal postcontrast T1-weighted MR images of the brain (A) and spine (B and C) obtained at presentation in a 1-year-old patient with an M3 metastatic medulloblastoma showing a PF-enhancing tumor mass centered in the fourth ventricle (*short arrows*, A) and diffuse metastatic lesions, including a suprasellar metastasis (*long arrow*, A) and extensive thecal sac tumor masses (*arrows*, B and C). **D–F:** Midline sagittal postcontrast T1-weighted MR images of the brain (D) and spine (E and F) obtained at the end of treatment showing a small nonenhancing residual lesion in the PF (*arrows*, D) and complete resolution of intracranial metastasis. Postsurgical changes are seen at the laminectomy site, with enhancing scar tissue (*short arrows*, F). There is decreased size of extensive tumor metastasis in the thecal sac but without complete resolution (*long arrows*, E and F). Due to the extent of residual disease, a biopsy was performed, which was inconclusive. The patient continued maintenance therapy with oral temozolomide for an additional year. Due to stable imaging, no further treatment was pursued. **G–I:** Midline sagittal postcontrast T1-weighted MR images of the brain (G) and spine (H and I) obtained at the 5-year follow-up showing a small nonenhancing residual change at the PF tumor bed (*arrows*, G) and a continuous decrease in size of persistent mildly enhancing changes within the lumbar thecal sac (*arrows*, H and I). This patient remains a long-term survivor and was 13 years of age at the time of the study.

metastatic disease and subtotal resection. Additional molecular markers, including MYC amplification in all patients and MYCN amplification in SHH tumors, are also associated with poor prognosis. Advances in molecular profiling have led to the classification of medulloblastoma into four major subgroups: WNT-activated, SHH-activated, group 3, and group 4, with additional subclassifications emerging.[13] These distinctions challenge previous assumptions in risk stratification and management.

A large single-center cohort study that assessed the correlation between metastatic disease imaging profiles and medulloblastoma subgroups demonstrated that the location, morphology, and imaging characteristics of metastatic medulloblastoma differ across molecular subgroups, with implications for diagnosis and management.[14] For example, group 3 patients tended to have smaller primary tumors and metastases were more laminar compared with a more nodular pattern in group 4 patients. Another important observation was that WNT-activated tumors had a favorable prognosis even with a metastatic presentation, whereas poor prognosis groups, such as SHH tumors with P53 mutation, had unfavorable prognosis regardless of the metastatic status at presentation.[14]

It is important to acknowledge that the high-risk category of medulloblastoma is further divided into high-risk and very high-risk groups based on metastatic status and cytogenetic biomarkers. The high-risk group (50%–75% survival) includes patients with SHH tumors that are either metastatic and/or with MYCN amplification and those with group 4 metastatic tumors. The very high-risk group (< 50% survival) includes patients with TP53-mutated SHH tumors (regardless of metastatic status) and those with metastatic group 3 tumors with or without MYC amplification and isochromosome 17q.[3,15] The outcome for the very high-risk group is dismal as there is poor response to current chemotherapy and radiation therapy protocols, leading to difficulty in interpreting major treatment protocol study results related to these subgroups.[16] Based on these criteria, in our high-risk medulloblastoma cohort, 4 patients were considered at very high risk and 2 of those patients did not survive.

While maximum resection is still a surgical goal, recent studies cast doubt on its benefit, even in nonmetastatic tumors and especially in the molecular era. A multicenter study of more than 700 medulloblastoma cases showed that the survival benefit of GTR was significantly diminished once the molecular subgroup was considered.[7] The authors showed that although maximum safe resection should remain the standard of care, surgical removal of small residual portions of medulloblastoma is not recommended when the likelihood of neurological morbidity is high as there is no definitive benefit to GTR over near-total resection.[7]

PFS is one of the most severe complications following PF surgery, affecting 10%–40% of patients.[17] A European multicenter study reported a 27% incidence of PFS in children who underwent medulloblastoma resection.[18] Symptoms included mutism, ataxia, and emotional lability, with growing evidence of long-term neurocognitive deficits.[19,20] Rare but fatal cases of diffuse cerebellar swelling following tumor resection have also been reported in patients with metastatic anaplastic medulloblastoma.[21–23] In light of such risks, an initial conservative surgical approach, especially in very high-risk patients, might be warranted.[17,23]

Our biopsy-based strategy resulted in no PFS or cerebellar swelling in any patient. CSF diversion was performed safely when hydrocephalus was present, with no complications, which occur in approximately 2.3% of patients undergoing shunt placement before PF surgery.[24] This suggests that a minimal surgical approach is not only feasible but also safer in select cases.

The rationale for aggressive resection becomes questionable in the metastatic setting in which numerous untreated lesions remain. Furthermore, surgery-related complications might delay timely initiation of oncological therapy, which should begin within 28–40 days postoperatively.[25] Delays can be particularly detrimental when metastases are progressing. In our study, the upfront biopsy-only approach facilitated early initiation of treatment, which ranged from 2 to 27 days (median 12 days); this was crucial, especially for patients presenting with cord compression who were able to receive urgent treatment within several days.

Neoadjuvant strategies are well established for other pediatric solid tumors (e.g., osteosarcoma and Ewing sarcoma) and offer benefits such as early treatment of micrometastases and reduced tumor burden.[26,27] A recent systematic review confirmed the safety and efficacy of preoperative chemotherapy in pediatric neuro-oncology, including medulloblastoma.[10,12] In a single-center study of 92 children with metastatic medulloblastoma, 2 therapeutic strategies were retrospectively compared; 59% of the cohort underwent upfront surgery aiming at complete resection and 41% were assigned preoperative chemotherapy with carboplatin and etoposide. Neoadjuvant chemotherapy yielded lower surgical morbidity, improved resection rates, and had similar survival compared with upfront surgery.[28]

Unlike neoadjuvant approaches, our approach differs because the treatment protocol was initiated following upfront biopsy without tumor resection. To date, 75% of our patients are still alive, with a 63% estimated 5-year survival rate calculated using Kaplan-Meier analysis. This result is comparable to the reported survival rates (68% in the neoadjuvant group and 60% in the initial tumor resection group) that were described by Guerrini-Rousseau et al.[28] Although our cohort had comparable survival rates, residual tissue changes were present on follow-up MRI in most patients.

Persistent residual lesions following treatment have been reported without indicating active disease. In a small retrospective study, patients with residual medulloblastoma lesions remained disease-free for 7–13 years.[29] Case reports have even described maturation of residual medulloblastoma into benign gangliocytoma or ganglioglioma.[30,31] A recent study of 84 patients with residual lesions on MRI found no benefit from additional therapy after first-line chemotherapy, supporting a watch-and-wait approach.[32] This is particularly relevant for metastatic cases for which residual lesions are more common.

In our cohort, 11 of 12 patients (92%) had residual lesions in the PF, with volumes ranging from 0.1 to 14.5 cm^3

(median 0.95 cm^3). Six patients (50%) had residual tissue in metastatic locations. Among the surviving patients, follow-up imaging did not demonstrate any growth of residual lesions. Three patients underwent second biopsies at the physician's discretion (2 showed scar tissue and 1 was inconclusive); all 3 are long-term survivors, including 1 with 12 years of stable residual lesions without resection.

Among the 3 patients who relapsed or progressed and did not survive, 2 had very high-risk disease characterized by group 3 tumors with MYC amplification, a known poor prognostic factor. One patient progressed with therapy and died soon after, and the second patient progressed after ending therapy and died despite a secondary removal of the progressive PF tumor. The third patient had a late supratentorial relapse, without evidence of disease in the primary tumor site. These cases emphasize the importance of molecular subgrouping in tailoring treatment strategies and prognostication.

This study had limitations, including its retrospective design, small cohort size, and lack of a control group. Molecular data were incomplete for 2 patients, limiting subgroup analysis. The follow-up duration varied (median 3.2 years), making it difficult to assess late recurrences and long-term toxicities.

Conclusions

Our findings support the feasibility of an upfront biopsy-only approach followed by intensive oncological treatment in pediatric patients with metastatic medulloblastoma. A 63% estimated 5-year survival rate and minimal surgical morbidity suggest that this might be a viable strategy, especially for patients with high surgical risk or diffuse metastatic disease. Further prospective multicenter studies with molecular stratification and long-term follow-up are warranted to validate and refine this treatment model.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: all authors. Acquisition of data: Dvir, Elhasid, Roth, Constantini, Peled, Shiran. Analysis and interpretation of data: Dvir, Elhasid, Constantini, Shiran. Drafting the article: Dvir, Elhasid, Roth, Constantini, Peled, Shiran. Critically revising the article: all authors. Reviewed submitted version of manuscript: Dvir, Elhasid, Roth, Constantini, Ospovat, Shiran. Approved the final version of the manuscript on behalf of all authors: Dvir. Statistical analysis: Constantini. Administrative/technical/material support: Roth, Constantini. Study supervision: Elhasid, Roth, Constantini.

Correspondence

Rina Dvir: Dana Children's Hospital, Tel Aviv Medical Center, Tel Aviv, Israel. rinad@tlvmc.gov.il.