

Pediatric cancer pathology review from a single institution: Neuropathology expert opinion is essential for accurate diagnosis of pediatric brain tumors

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Abstract

Background and objectives: Second pathology review has been reported to improve accuracy in oncologic diagnoses, including pediatric malignancies. We assessed the impact of second review on the diagnosis of pediatric malignancies at a tertiary care referral center in Beirut, Lebanon.

Methods: Pathology reports of patients treated at the Children's Cancer Institute in Lebanon were retrospectively reviewed for the period 2008–2016 and compared with same samples' diagnoses at St. Jude Children's Research Hospital. Diagnostic disagreements were divided into major, minor, and none based on their effect on diagnosis and/or patient management.

Results: Second review was requested for 171 cases, accounting for 19% of all cases during that period. Second opinion was mostly requested for brain tumors (62% of all brain tumor cases) and neuroblastoma for NMYC testing (65% of all neuroblastoma), while hematologic malignancies had the fewest referrals (3% of all hematologic cases). Major disagreements in second review occurred in 20 cases (12% of total), and minor disagreements in 21 cases (12% of total). The largest proportion of major disagreements (71%) occurred in pediatric brain tumors, and novel molecular tests contributed to the diagnosis in 55% of these cases.

Conclusions: The availability of a specialized pediatric neuropathologist and a basic panel of relevant molecular testing are essential for appropriate diagnosis of pediatric brain tumors. Centers that do not have the available infrastructure in place can benefit greatly from second review referrals for this challenging subset of tumors.

KEYWORDS

neuropathology, pathology, pediatric cancer, second opinion

1 | INTRODUCTION

Correct histologic diagnosis is a cornerstone in the proper allocation of treatment in malignancies in general and childhood malignancies in particular. Discrepancies and errors in diagnostic pathology interpretation can have significant implications on patient care and appropriate treatment planning, and eventually patient outcome.^{1,2} Reasons

for such discrepancies are multiple and include lack of sufficient experience and expertise in the histologic evaluation of these rare tumors, and lack of certain immunohistochemical or molecular diagnostic techniques, especially in smaller hospitals. Second opinion in pathology by expert subspecialists can therefore be very beneficial in confirming the diagnosis in rare cancers. Even beyond direct improvement in diagnostic accuracy, such second reviews can be used to identify specific gaps in the diagnostic infrastructure locally, and help in proper resource allocation and building of local expertise. Herein, we report the results of such an experience, which led to the identification and prioritization of areas of need, specifically in pediatric neuropathology.

Abbreviations: AUBMC, American University of Beirut Medical Center; CCI, Children's Cancer Institute; HICs, high-income countries; IHC, immunohistochemistry; SJCRH, St. Jude Children's Research Hospital

The Children's Cancer Institute (CCI), at the American University of Beirut Medical Center (AUBMC), is a tertiary care center that treats patients with childhood malignancies in Lebanon and the Middle East. The CCI has a close affiliation with St. Jude Children's Research Hospital (SJCRH) in Memphis, Tennessee, through its International Outreach Program, which serves to assist in development of specific medical programs and quality improvement projects that directly contribute to improved patient outcome and clinical care. One such program is the review of histologic diagnoses for difficult or unclear cases, as needed. Thus, the local pediatric oncology team identifies cases that would benefit from a second opinion regarding histologic diagnosis, and those specimens are then sent to SJCRH—a National Cancer Institute designated Cancer Center—for second review. Patient treatment is initiated in most cases prior to the results of the second opinion, and once the review is received, the cases are rediscussed locally, and treatment plans adjusted when needed. In this study, we have evaluated the discrepancy rate between the local pathology diagnosis and the second opinion diagnosis performed at SJCRH, and attempted to clarify reasons for the identified discrepancies and their impact on clinical care.

2 | MATERIALS AND METHODS

A retrospective data analysis was performed for all pathology reports that were reviewed at SJCRH for patients treated at the CCI between January 2008 and December 2016. The local pathology reports are generated following examination of samples at AUBMC by American Board certified pathologists, who order and interpret available immunohistochemistry (IHC) and molecular studies as needed. All cases are then discussed in a multidisciplinary team meeting, and difficult and/or unclear cases are sent for second opinion at SJCRH, by decision of the multidisciplinary team including the pathologist and pediatric treating oncologist. A brief history comprising the age, sex, lesion's anatomic and radiologic characteristics, and the relevant diagnostic techniques performed at AUBMC is sent with the referred pathology material. Additional IHC, molecular or cytogenetic testing performed at SJCRH, is ordered by the SJCRH reviewer, if applicable. From January 2008 to June 2014, a single experienced pediatric St. Jude pathologist—regardless of the anatomic location of the lesion—performed the histopathologic review of all cases submitted by CCI. After July 2014, a subspecialized review process was implemented at SJCRH and the referred cases were then analyzed by different surgical pathologists, hematopathologists, and/or neuropathologists,

as needed for each case, according to the tumor type. In some cases, more than one pathologist contributed to the final diagnosis.

The pathology reports issued by AUBMC and SJCRH were compared across different tumor categories to identify areas and rates of discrepancy. Discordances were considered major if they resulted in a complete change in histologic diagnosis, or if they impacted treatment plans or patient outcome. Minor discordances were those with either changes in grading that did not impact treatment plan, or those that provided extra information that did not impact therapy. The review was deemed by the AUBMC Institutional Review Board to be exempt research.

3 | RESULTS

Among 846 pediatric oncology patients treated at the CCI between January 2008 and December 2016, we identified 171 records where a second pathology review was performed. Reasons for referral included uncertain diagnosis, need for further molecular testing, and tumors with unusual characteristics or poor agreement with clinical diagnosis. These included brain tumors ($n = 78$), neuroblastoma ($n = 35$), sarcoma ($n = 19$), hematologic malignancies ($n = 10$), and other tumor types ($n = 29$). Thus, the highest number of cases referred for pathology second opinion was for brain tumors, which represented 46% of total cases. The relative proportion of cases sent for second review varied by subtype, with the highest for neuroblastoma (65%; 35 of 54 seen cases) and brain tumors (62%; 78 of 126 seen brain tumors), and ranging from 3 to 20% for other tumor types, as shown in Table 1. For neuroblastoma, the main reason for second opinion was for *N-MYC* amplification testing, which is not available locally. Overall, second opinion was requested for 19% of total cases seen during the studied period, and 17% when excluding neuroblastoma cases sent essentially for *N-MYC* testing.

There was an overall agreement between the local diagnosis and the reviewed diagnosis in 130 of the 171 reviewed cases (76%), with minor disagreements in 21 cases (12%) and major disagreements in 20 cases (12%), as detailed in Table 1. Brain tumors accounted for the majority of the tumors reviewed ($n = 78$, 46% of total). This group had major disagreements in 14 out of 78 reviewed cases (18%), and the majority of all identified major disagreements ($n = 14$ out of total of 21 major disagreements, 67%) (Table 1). This discordance in brain tumor pathology was found across multiple diagnoses (Table 2). To identify whether the subspecialty pathology review implemented after July

TABLE 1 Number, distribution, and diagnosis agreement rate in reviewed cases

Tumor type	Total number	Reviewed (%)	Number with major disagreement (%)	Number with minor disagreement (%)
Brain	126	78 (62)	14 (18)	12 (15)
Neuroblastoma	54	35 (65)	1 (3)	0 (0)
Sarcoma	129	19 (15)	1 (5)	4 (21)
Hematologic	393	10 (3)	1 (10)	0 (0)
Other	144	29 (20)	3 (10)	5 (17)
Total	846	171 (19)	20 (12)	21 (12)

TABLE 2 Major discrepancy diagnoses in brain tumors

Initial diagnosis	Second opinion diagnosis						
	MBL	GBM	PCA	EP	AC Grade II	ABL	GM
PNET				1			
HGG					1		
CPC		1				1	
EP	1						
NC			2				
Mixed glial + PNET			1				
AC Grade II			3	1			
GG					1		
Hypophysitis							1
Total	1	1	6	2	2	1	1

MBL, medulloblastoma; GBM, glioblastoma multiforme; PCA, pilocytic astrocytoma; EP, ependymoma; LGG, low-grade glioma; AC, astrocytoma; ABL, astroblastoma; GM, germinoma; PNET, primitive neuroectodermal tumor; HGG, high-grade glioma; CPC, choroid plexus carcinoma; PMA, pilomyxoid astrocytoma; NC, neurocytoma; GG, ganglioglioma.

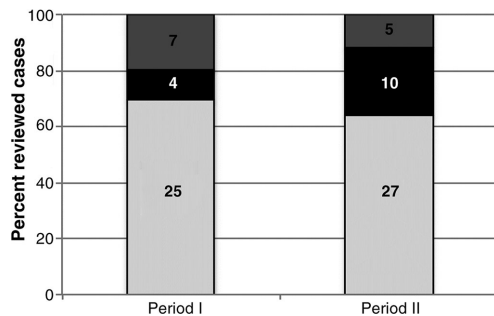


FIGURE 1 Percent disagreement rates in brain tumors diagnosed before (Period I) and after (Period II) implementation of pathology subspecialty review by neuropathologist at SJCRH. Numbers of the reviewed cases in the different categories are shown on the graph in the respective columns. Light grey denotes cases with agreement, black denotes those with major discrepancy, and dark grey denotes those with minor discrepancy

2014 at SJCRH influenced the rate of discordance, we investigated the discordance rate in brain tumor diagnoses before and after July 2014. Indeed, we found a higher rate of major discordance during the second period (Fig. 1). Notably, different interpretation of histologic findings was described in 12 of the 14 cases (86%) of brain tumors with major discrepancies, and novel molecular stains contributed to the altered diagnosis in 10 (71%) brain tumors (Table 3).

TABLE 3 Findings contributing to major disagreements in histologic diagnosis

	Brain (n = 14)	Hematologic (n = 1)	Neuronal (n = 1)	Sarcoma (n = 1)	Other (n = 3)	Total
Different interpretation	2		1		1	4
Molecular tests	3			1		4
Immunostains					1	1
Immunostains + different interpretation	2	1			1	4
Molecular tests + different interpretation	3					3
Molecular tests + immunostains + different interpretation	4					4

Importantly, 38% of the total brain tumor cases seen during the study period were not submitted for second review of pathology. Specifically, of the total number of 126 brain tumors seen during the study period, 48 were not sent for pathology review. These included 15 medulloblastoma, seven pilocytic astrocytoma, six low-grade glioma, five craniopharyngioma, four ependymoma, three supratentorial primitive neuroectodermal tumor, three choroid plexus carcinoma, two pineoblastoma, two atypical teratoid rhabdoid tumor, and one glioblastoma. Thus, in retrospect, it is possible that our review underestimates the percent of potential discrepancies in brain tumor diagnoses.

On the other end of the spectrum, 10 hematologic malignancies were sent for review but only one (10%) had major disagreement. Neuroblastoma comprised 20% of the total reviewed cases; only one of 35 cases (3%) had a major discrepancy with a change in diagnosis from ganglioneuroma to ganglioneuroblastoma. All remaining neuroblastoma cases had the original diagnosis confirmed but the second opinion provided additional essential information by offering *N-MYC* amplification testing, which is not available locally and is essential for patient stratification and risk-allocated therapy decisions. For sarcomas, there was one major diagnosis change among 19 reviewed cases (5%), with a change of diagnosis from “soft tissue sarcoma” to “primitive myxoid mesenchymal tumor of infancy”. Finally, the group of “other” tumor types included lesions such as Wilms tumor and clear cell sarcoma of the kidney (n = 5), undifferentiated small round cell tumor (n = 4), fibromatosis and myofibroblastic tumors (n = 3),

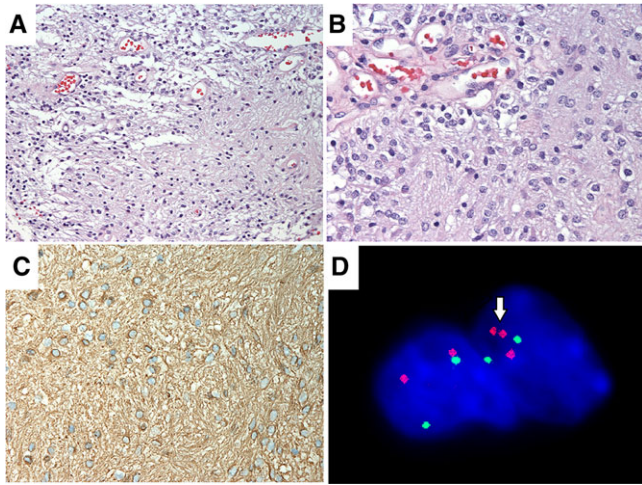


FIGURE 2 Representative example of discordant diagnosis. Seven-year-old male child with a mixed cystic and solid enhancing mass in the cerebellar vermis initially diagnosed as astrocytoma (WHO grade II) and reclassified after pathology review as pilocytic astrocytoma (WHO grade I). (A) Compact tissue composed of piloid cells and microcystic areas (hematoxylin & eosin, 200 \times). (B) Vascular proliferation with wickerwork-like pattern (hematoxylin & eosin, 400 \times). (C) The tumor cells are diffusely positive for glial fibrillary acidic protein (immunohistochemistry, 400 \times). (D) FISH revealed *BRAF* duplication (Locus 7q34, red signal, arrow). KIAA1549-*BRAF* fusion transcript was detected by PCR (not shown)

carcinoma ($n = 3$), teratoma ($n = 3$), rhabdoid tumor ($n = 3$), retinoblastoma ($n = 2$), lymphohistiocytic lesion ($n = 1$), melanoma ($n = 1$), giant cell tumor ($n = 1$), Sertoli-Leyding cell tumor ($n = 1$), neuroendocrine tumors ($n = 1$), and melanotic neuroectodermal tumor of infancy ($n = 1$). In this group, three cases (10%) had major disagreement, corresponding to final diagnoses of inflammatory myofibroblastic tumor, rhabdoid tumor, and retinal atrophy/fibrosis.

Altogether, second review resulted in a change of diagnosis from one type of malignant tumor to another in 16 cases, from benign to malignant tumor in two cases, from malignant to benign tumor in one case, and from one type of benign tumor to another in one case. For all discrepancies, cases were rediscussed in multidisciplinary tumor board at the institution, and the pathology results and discrepancies reviewed. For all cases, the second review diagnosis made at SJCRH was adopted. Of the 20 major discrepancies, 14 (70%) resulted in a change of treatment, and the remaining six (30%) had a change in final diagnosis (these six cases were all glial tumors, shown in Table 2).

New immunohistochemical (IHC) markers, molecular testing, discordant IHC results, or different interpretation of similar results all contributed to the major disagreement cases. The findings contributing to the altered diagnosis are detailed in Table 3, with molecular studies contributing to altered diagnosis in 11 of the 20 cases (55%). Notably, IHC stains that were performed on second review, but were not available locally, included mainly integrase interactor 1/BAF-47, GRB2-associated binding protein 1, Yes-associated protein 1, and transducin like enhancer of split 1. Molecular tests that were not performed locally but most commonly contributed to the final diagnosis included rearrangement of C11orf 95, *BRAF* duplication, isochromosome 17q, and *N-MYC* amplification (Fig. 2).

4 | DISCUSSION

It has long been recognized that pediatric tumor pathology is an area where discordances in histologic diagnosis are not uncommon, and where subspecialty training in pediatric tumor diagnosis is recommended due to the rare nature of these tumors, peculiarities of grading, and detailed subclassification specific to some pediatric entities.³ In this review, 19% of all pediatric oncology cases seen at our hospital were sent for second pathology opinion. If neuroblastoma cases, sent primarily for *N-MYC* testing, are excluded, the referral rate becomes 17%. The rate of referrals as a proportion of total cases seen at the primary site was lowest for hematologic tumors, representing about 3% of hematologic cases seen, and highest in the brain tumors, with 62% of brain tumor cases submitted for review. Reasons for referrals included difficult cases as determined by the local pathologist, unusual diagnoses, or discordance between clinical presentation and histologic diagnosis. Another important factor in the high percentage of neuropathology cases sent for consultation is the reliance of the most recent classification of brain tumors on molecular testing, most of which have yet to be introduced to our laboratory operation.

The observed major and minor discordance rates in our study were 12% each. A previous retrospective review from SJCRH for the years 2009–2011 showed that of 705 cases referred for second review from 37 countries, 25% had major disagreement in diagnosis, and an additional 14% had minor disagreements.⁴ Our definition of major discrepancy included cases where the change in diagnosis would directly affect treatment decisions, as well as change to a diagnosis that reflects a different entity, even if the eventual treatment and outcome may be unaffected. Thus, in brain tumors, a change in diagnosis from one distinct entity in the WHO classification to another was considered a major discrepancy.

In this study, brain tumor cases sent for second opinion had the highest major discordance rate (18%, 14 of 78 reviewed cases). Notably, a high rate of discordance has also been reported upon central pathology review and subtyping of brain tumors in children when enrolled in collaborative clinical trials. For example, a review of the North American Children's Cancer Group CCG-945 study showed discordance in diagnosis in 51 of 172 patients (29%) with high-grade glioma, accounting for 30% of all reviewed cases.⁵ In our review, the most commonly misdiagnosed entities within brain tumors were pilocytic astrocytoma and anaplastic ependymoma. This reflects the need for continued international collaboration in pediatric neuropathology, where subspecialty expertise is essential in these relatively rare tumors.

Also, molecular testing is quickly becoming the standard of care in diagnosis of brain tumors, while technology adaptation to hospitals in low- and middle-income countries continues to lag behind those available at referral centers in high-income countries (HICs). The recently updated World Health Organization classification of tumors of the central nervous system now includes, for the first time, molecular parameters for the accurate diagnosis and definition of both adult and pediatric brain tumors.⁶ Indeed, in our study, the discordance rate was higher after subspecialty neuropathology review of referred cases was initiated at SJCRH in 2014, reflecting the value of subspecialty review

of these rare tumors, where novel diagnostic techniques and classifications continue to evolve.

Referral and discordance rates were low for hematologic malignancies that reflect the availability of specialized hematopathologists in our institution, as well as the accessibility to most of the needed immunostains, flow cytometry, and molecular tests for this disease category. Much higher discordance rates are reported in countries where such expertise is not available; for example, a study in children diagnosed with lymphoma in Uganda showed a very low concordance rate of only 36% when evaluated by a second pathology review in the Netherlands.⁷ The results for adult lymphoma samples reviewed at Memorial Sloan Kettering Cancer Center showed an 18–21% rate of major discrepancies, even in samples referred within HICs.⁸

As for the remaining referred cases (sarcoma and other tumor types), major discordance rates were at 5% and 10%, respectively, which are comparable to that reported within centers in HICs.^{9–14} A review from Mayo Clinic showed a total rate of 29% of disagreement for referred pediatric bone and soft tissue tumors,⁹ and in the European pediatric neuroblastoma studies, rates of discordance ranged from 3.5% to 17%.¹⁵ In adult sarcoma cases reviewed by experts within three regions in France and Italy, 117 of 1,463 cases (8%) showed major discordance and 35% (n = 512) showed minor disagreements (due to difference in grading or histologic subtype).¹⁰ Another study from the United Kingdom found a major discrepancy of 16.4% among 286 patients with confirmed or suspected soft tissue tumors, where only 10% of the referred cases originated from overseas.¹¹

Discrepancies upon second review in pathology can be attributed to many reasons, including the lack of expertise in oncologic pathology, the rarity of some types of malignancies, and the limited laboratory infrastructure and nonavailability of special immunohistochemical, cytogenetic, and/or molecular testing that are considered essential in differentiating microscopically similar tumors. In our study, we found that rates of concordance were similar to those seen for pediatric cancer diagnoses within HICs, and we identified pediatric neuropathology as an area of need for continuing second review, pending the development of specialized local pediatric neuropathology expertise, and local availability of a panel of essential immunostains and molecular studies that can contribute to further improvement in diagnostic accuracy. In addition, development of focused online meetings (telepathology) for continued education with specific case discussion would be a useful strategy to enhance expertise across distances.^{16–18}

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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