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QUANTITATIVE IMAGING ANALYSIS OF POSTERIOR FOSSA EPENDYMOMA LOCATION IN CHILDREN

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Abstract

Purpose—Imaging descriptions of posterior fossa ependymoma in children have focused on magnetic resonance imaging (MRI) signal and local anatomic relationships with imaging location only recently used to classify these neoplasms. We developed a quantitative method for analyzing the location of ependymoma in the posterior fossa, tested its effectiveness in distinguishing groups of tumors, and examined potential associations of distinct tumor groups with treatment and prognostic factors.

Methods—Preoperative MRI examinations of the brain for 38 children with histopathologically proven posterior fossa ependymoma were analyzed. Tumor margin contours and anatomic landmarks were manually marked and used to calculate the centroid of each tumor. Landmarks were used to calculate a transformation to align, scale, and rotate each patient's image coordinates to a common coordinate space. Hierarchical cluster analysis of the location and morphological variables was performed to detect multivariate patterns in tumor characteristics. The ependymomas were also characterized as “central” or “lateral” based on published radiological criteria. Therapeutic details and demographic, recurrence and survival information were obtained from medical records and analyzed with the tumor location and morphology to identify prognostic tumor characteristics.

Results—Cluster analysis yielded 2 distinct tumor groups based on centroid location. The cluster groups were associated with differences in PFS ($p = .044$), “central” vs. “lateral” radiological designation ($p = .035$), and marginally associated with multiple operative interventions ($p = .064$).

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Conflict of Interest

We declare that we have no conflict of interest.

Conclusions—Posterior fossa ependymoma can be objectively classified based on quantitative analysis of tumor location, and these classifications are associated with prognostic and treatment factors.

Keywords

Ependymoma; Pediatric; Image Analysis; Quantitative Imaging

Introduction

Ependymoma is one of the most common central nervous system neoplasms in children and comprises approximately 5.5% of pediatric brain tumors [1]. Roughly 90% of childhood ependymoma is intracranial and 70% occur in the posterior fossa [2]. Posterior fossa ependymoma tends to extend through foramina such as the foramina of Luschka and the foramen of Magendie [3]. The neoplasm may also encase adjacent structures in the posterior fossa such as arteries and cranial nerves. Complete surgical excision is a key prognostic factor in treating posterior fossa ependymoma as residual tumor is associated with poor outcome [4]. Characterization of posterior fossa ependymoma by neuroimaging has focused primarily on findings such as signal intensity, enhancement, relationship to blood vessels and cranial nerves and extension through posterior fossa foramina. Tumor location, as determined by imaging, has not been formally used for characterizing this lesion until recently when U-King-Im and colleagues described imaging criteria for classifying posterior fossa ependymoma that arise from an anatomical description of tumor origin, based on operative findings, proposed by Ikezaki et al [5,6]. Ikezaki and colleagues considered ependymoma that grows from the caudal half of the floor of the fourth ventricle as “midfloor-type”, tumor that originates from the inferior medullary velum as “roof-type” and lesions that arise from the lateral portion of the fourth ventricle as “lateral-type” [5].

Following the central (“midfloor-type” and “roof-type”) versus lateral distinction between posterior fossa ependymoma, U-King-Im et al.’s location-based imaging criteria relied on a radiologist’s evaluation of brainstem displacement and the appearance of the obex [6]. Ependymoma that caused anterior displacement of the brainstem and that involved the obex was considered “midfloor-type” tumor and neoplasm that shifted the brainstem laterally with sparing of the obex was designated “lateral-type”. These imaging classifications closely corresponded to surgical characterizations of the tumors as “midfloor-type” or “lateral-type”.

Midline posterior fossa ependymoma (midfloor and roof) has a better prognosis than laterally situated tumor which is associated with a larger amount of residual neoplasm following surgery than roof or midfloor neoplasm [7]. As part of a larger investigation concerning the imaging of these tumors, we analyzed posterior fossa ependymoma by imaging location, based on objective quantitative criteria, and tested whether tumor classifications arising from this quantitative technique were associated with treatment and prognostic factors. For this exploratory study, we hypothesized that imaging location is an outcome determinant in pediatric posterior fossa ependymoma and a quantitative method to

define tumor location by imaging could play an important role in characterizing these neoplasms.

Methods

After approval by our institution's institutional review board, preoperative magnetic resonance imaging (MRI) examinations of the brain, performed at outside institutions, of 107 pediatric patients with histopathologically proven posterior fossa ependymoma were reviewed by a neuroradiologist with a certificate of advanced qualification in neuroradiology and over 10 years practice experience (NS). Patients were imaged between 1997 and 2010, and scope and quality of the MRI examinations were heterogeneous. Most of the presurgical imaging studies were only available on printed film and were not suitable for our analysis. Other studies were excluded because image resolution was not sufficient to reliably identify the tumor margin. A total of 39 studies were identified as suitable for quantitative analysis. Diffusion-weighted imaging (DWI) was not available for 6 of the children and for another 6, ADC maps were not available. The remainder of the DWI was of heterogeneous quality and was not analyzed further.

During the review of the MRI examinations, the tumors were characterized as “central” or “lateral” based on the criteria described by U-King-Im et al. [6]. No “roof-type” tumors were seen in that previous investigation and that study did not provide imaging criteria for distinguishing the Ikezaki “midfloor” and “roof-type” lesions. We, therefore, used the term “central-type” to describe ependymoma matching the criteria provided by U-King-Im et al. for “midfloor-type” ependymoma to potentially capture tumors that may have arisen from the roof of the fourth ventricle.

Extent of tumor resection was based on review of postoperative MRI examinations. When a patient had undergone multiple surgical interventions for tumor removal, extent of tumor resection for each subject was determined after the child's final operation. All patients had received cranial radiation therapy (RT) for their posterior fossa ependymoma. Therapeutic details and demographic, recurrence and survival information, including the time from diagnosis to RT, were obtained from patient medical records.

The margins of each tumor were outlined on multiple axial image sections by a neuroradiologist (NS) and a biomedical engineer with over 20 years' experience in neuroimaging research and imaging neuroanatomy (RO). The contouring of each tumor was performed on the axial pulse sequence for each subject that provided the best delineation of lesion margins (Supplementary Table 1). During tumor contouring, all available image data was used to cross-reference and guide the tumor evaluation. The nasion, tip of the clivus and both external auditory canals were identified on each patient's MRI as anatomic landmarks for coregistration across the group. Image analysis and visualization were performed with the Fiji distribution [8] of the ImageJ software package [9].

The 3 dimensional surface of each tumor was estimated from the manually delineated 2 dimensional tumor contours [10] and then used to determine the volume, compactity (normalized ratio of volume to surface area, with value 1 for a sphere), and centroid of each

tumor [11]. Subsequent processing and analysis of the morphometric data was performed with R [12]. The anatomic landmarks were used to calculate a rigid transformation to align, scale, and rotate each patient's image coordinates to a common coordinate space [10]. Hierarchical cluster analysis [13] of the location and morphological variables was performed to detect multivariate patterns in the tumor morphological characteristics.

Clinical factors were categorized as follows and analyzed in relation to the image-based tumor findings: extent of lesion resection (gross total or no gross total), pathologic grade (II vs. III), progression free survival (PFS), overall survival (OS), "central" versus "lateral" tumor designation, single versus multiple surgeries, pre-RT chemotherapy, time lapse from diagnosis to the start of RT and, when applicable, pattern of metastasis. Associations between clinical factors were also explored. PFS is defined as the time interval from the radiation start date to the date of progression, or to the date of last MRI for patients without disease progression at the end of study. OS is defined as the time interval from the radiation start date to the date of death, or to the date of last MRI for patients who were alive at the end of study. Cox proportional hazards models were built to investigate the relationship between PFS/OS distributions and cluster groups, as well as clinical factors. Chi-square or Fisher's exact test were performed to test the association between categorical variables. Two sample t-test or Wilcoxon rank sum tests were used to determine whether continuous variables were different between groups. A p-value ≤ 0.05 was considered statistically significant, and values up to 0.06 were considered marginally significant. Due to the exploratory nature of this study, multiple testing corrections were not performed in the statistical analyses. All statistical analyses were performed using SAS 9.3 software.

Results

Demographic and treatment information are summarized in Table 1. One patient had recurrent tumor before presenting for RT and had a much longer time lapse between diagnosis and RT (1707 days) than the other subjects (maximum 418 days). This child was excluded from further analysis. No patient had metastatic disease at diagnosis. Thirty-six tumors enhanced, one did not enhance and one subject had no post-contrast imaging available on the pre-operative MRI.

Tumor delineation and segmentation was successful in all patients. Coregistration of the skeletal landmarks, and summary statistics of the tumor morphological parameters are summarized in Table 2. Cluster analysis of the tumor morphological characteristics showed that only the centroid location yielded detectable systematic differences between groups of tumors (Figs 1 and 2). One cluster group of ependymoma was located more anteriorly and inferiorly in the posterior fossa (Group AI) than the other more posterior and superior group (Group PS). Figure 3 shows tumor examples from each cluster group to illustrate the tumor segmentation and relative location in the posterior fossa.

There was a statistically significant difference in PFS, adjusted for time lapse between diagnosis and RT, and for multiple tumor resections, between centroid cluster groups ($p=0.044$) with Group PS demonstrating 2.7 times the hazard of developing progressive disease than Group AI. The time lapses between diagnosis and RT for the cluster groups was

significantly different with Group AI having a shorter time lapse than Group PS ($p=.016$). There was no significant correlation between the centroid cluster groups and OS, tumor volume, compactity, extent of lesion resection, tumor histopathology, pattern of metastasis, radiation dose, age at diagnosis or gender. Tumor volume and compactity were not significantly associated with PFS, OS, pattern of metastasis, pathologic grade or RT dose.

The cluster groups were associated with the administration of pre-RT chemotherapy ($p=.006$). More children received pre-RT chemotherapy in the PS group (7/14) than in the AI group (2/24). Pre-RT chemotherapy was also significantly associated with “central” vs. “lateral” tumor designation ($p=.040$) (3/25 “central” group, 6/13 “lateral” group). By itself, pre-RT chemotherapy was significantly associated with PFS as children who received chemotherapy had a 4.7 times greater hazard of disease progression than those who did not ($p=.002$). Subjects who were treated with pre-RT chemotherapy also had a 4.5 greater hazard of death than those who were not ($p=.010$).

There was a marginally significant difference between the cluster groups as to the need for multiple surgical interventions for ependymoma resection with 9/14 PS patients needing more than 1 operation compared with 8/24 AI children ($p=.064$). Although the need for multiple surgeries, by itself, was not significantly correlated with PFS, its correlation with OS was significant ($p=0.027$) with patients undergoing multiple resections having a 4.4 times greater hazard of death than those who received one operation.

“Central” vs. “lateral” tumor designation was significantly associated with cluster group assignment ($p=.035$) as 8/14 ependymomas in Group PS were designated “lateral” compared with 5/24 in Group AI. There was no significant association, however, between “central”/“lateral” tumor location and PFS, OS, tumor volume, compactity, extent of lesion resection, pathologic grade, pattern of metastasis, radiation dose, time lapse from diagnosis to the start of RT, age at diagnosis, gender or whether multiple surgeries were needed for ependymoma removal.

Discussion

Posterior fossa ependymoma arising from or centered in the lateral recess of the fourth ventricle or foramen of Luschka is often associated with a worse prognosis than centrally located tumors [14–16]. The difference in prognosis has been attributed to the greater technical difficulty of obtaining complete surgical resection of lateral ependymoma [4]. Ikezaki, and colleagues noted that “lateral-type” ependymoma is more difficult to completely resect and were associated with a lower survival time and rate than the “midfloor-type” and “roof-type” lesions [5]. Beyond the technical challenges of resecting laterally located tumors, some studies report a worse prognosis for lateral tumors even with gross total resection [17,14,16]. A reliable imaging-based method for distinguishing posterior fossa ependymoma by location may help identify tumors that will be particularly challenging to resect and may assist in establishing disease prognosis.

To our knowledge, the study by U-King-Im et al. is the only previous investigation concerning the use of imaging to classify posterior fossa ependymoma by location. By using

criteria focused on brainstem displacement and tumor involvement of the obex, that study identified 2 groups of posterior fossa ependymoma that corresponded to the “midfloor” and “lateral-type” tumors described by Ikezaki and colleague [6]. The investigators determined that their preoperative classification system closely agreed with surgical findings as to site of tumor origin.

Our posterior fossa ependymoma classification approach builds on the concept, proposed by U-King-Im et al., that the locations of these tumors may provide clues as to their origin and, potentially, prognosis. By using a quantitative method for characterizing posterior fossa ependymoma in 38 patients, we have identified two distinct groups of lesions based on cluster analysis of their centroids with respect to defined anatomic landmarks. Statistical clustering based on objective, quantitative tumor characteristics identified one group of lesions (Group PS) that were located more superiorly and posteriorly in the posterior fossa than the other (Group AI). The coordinates of the tumor centroids allow the posterior fossa ependymomas to be objectively compared in 3-dimensional space, rather than by radiologist-assigned location or presumed tumor origin based on location.

The location of the tumor centroid may predict the difficulty in treating a posterior fossa ependymoma and the risk of tumor progression. The use of pre-RT chemotherapy was highly associated with the centroid-based cluster groups, with chemotherapy more frequently used for Group PS tumors than for Group AI lesions. Pre-RT chemotherapy was, by itself, associated with an increased hazard for progressive disease and death, supporting the concept that Group PS lesions may be more prone to disease and treatment complications than Group AI. There was also a marginal association between cluster groups and multiple operations for ependymoma resection with Group PS lesions more often requiring more than one attempt at resection. Group PS tumors also had a longer time lapse between ependymoma diagnosis and beginning RT than Group AI subjects which may also reflect difficulty in obtaining complete lesion resection and treatment complexity. Finally, Group PS tumors were associated with a greater risk of disease progression than Group AI ependymoma. These findings suggest that Group PS lesions pose a greater treatment challenge than those in Group AI.

Quantitative morphological analysis of posterior fossa ependymoma extends location-based imaging evaluation of these tumors, introduced by U-King-Im and colleagues. Although we did not attempt to use lesion centroids to predict anatomic site of tumor origin, we did detect a correlation between the centroid cluster groups and the “central” vs. “lateral” tumor designations that were based on the radiological criteria of U-King-Im, et al. We also found that, unlike “central” vs. “lateral” tumor designation, the cluster groups were associated with PFS and marginally associated with the need for multiple attempts at lesion resection. Although the use of pre-RT chemotherapy was associated with “central” vs. “lateral” tumor designation, it was more strongly associated with the cluster group assignments. These additional statistical relationships support the idea that metric analysis of posterior fossa ependymoma centroid location detects differences between tumors that affect treatment and prognosis beyond the classification system of U-King-Im and colleagues. Additional research is needed with a larger posterior fossa ependymoma cohort to test the strength of the cluster group associations with factors that may affect PFS.

Age and tumor grade, which have been associated with prognosis for posterior fossa ependymoma in children [18–20], were not associated with centroid cluster groups or “central” vs. “lateral” tumor designation, suggesting that these disease characteristics are independent of tumor location. The cluster groups and “central” vs. “lateral” designation were also not associated with OS.

Limitations to our investigation include variability in the clinical characteristics of the patients and the heterogeneity of the pre-surgical image data. The use of pre-RT chemotherapy, RT dose, and number of attempts at tumor resection varied across the patient cohort. Some of these differences led to variations in the time between disease diagnosis and RT treatment. All of these variables may affect PFS and OS, although we attempted to control for these factors in our analysis. The scope and quality of imaging techniques used for the pre-surgical diagnostic MRI examinations also varied across the cohort. The examinations differed in pulse sequences and sequence parameters (e.g., slice thickness, slice gap, in-plane resolution). We excluded otherwise eligible patients, however, whose MRI examinations were inadequate for determination of tumor margins. Subjectivity may have been introduced into the study during the process of outlining tumor margins for centroid analysis, however, we had already only chosen tumors that had imaging sufficient for lesion delineation and any questions we had concerning lesion boundaries were resolved by consensus between the neuroradiologist and biomedical engineer specializing in neuroimaging research.

Potential differences in the experience of neurosurgeons in the resection of posterior fossa ependymoma in children may affect treatment outcomes [4]. At our institution, where neurosurgeons have much experience in the resection of complex posterior fossa pediatric ependymomas, an aggressive attempt is always made to achieve gross total resection which may account for the lack of association of “central” vs. “lateral” tumor designation with extent of resection. Patient positioning may affect visibility of tumor which could account for the need for multiple surgical inventions for PS lesions which may be more difficult to completely visualize when the child is in the prone or sitting position. In our investigation, the need for multiple resection attempts in some cases and the presence of residual tumor may have been avoided if the initial operative intervention had been performed by a surgeon with greater expertise in the complete removal of complex ependymoma. The effect of lesser surgical experience, however, would likely be most prominent for lesions that presented the greatest operative challenge which is related to the idea that tumor location and configuration are associated with the difficulty in treating some posterior fossa ependymoma. Additional studies on the use of centroid analysis for operative planning and for the prospective identification of lesions that may be more difficult to treat may help establish the usefulness of this imaging technique in the management of posterior fossa ependymoma in children.

Conclusions

Posterior fossa ependymoma can be classified based on location and these classifications may be associated with prognostic and treatment factors. Quantitative imaging-based measurement of tumor centroid provided 2 distinct cluster groups of posterior fossa

ependymoma that were, in turn, associated with the administration of pre-RT chemotherapy, PFS and “central” vs. “lateral” tumor designation, a distinction that was based on the criteria of U-King-Im and colleagues, the only previous work focused on imaging-based classification of posterior fossa ependymoma. The tumors with more superior and posterior centroids were associated with factors that suggest they pose a greater therapeutic challenge. The proposed method for quantitative analysis of pediatric posterior fossa ependymoma location may add another layer to pretreatment risk stratification for this tumor. Prospective research, with standardized treatment, is needed to validate the use of tumor centroid and other morphological characteristics for classification of posterior fossa ependymoma, and to test the prognostic and treatment-related associations detected in this investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Hierarchical clustering analysis of tumor centroid coordinates identifies two groups. One group is distributed relatively more anteriorly and inferiorly (Group AI) and the other relatively more posteriorly and superiorly (Group PS). The columns represent coordinates and rows represent individual tumors. The color scale indicates the relative location of tumor centroid along the coordinate axis.

Fig. 2.

(a–c) Centroid coordinates for the AI and PS cluster groups. There is no difference in tumor volume (d) or tumor compactness (e) between the cluster groups. f) Landmark coordinates after coregistration show that the differences in cluster coordinates are much greater than errors in coregistration. (AI=Group AI, PS=Group PS, EAC=external auditory canal)

Fig. 3.

Examples of tumors from each cluster group. Top row: Unenhanced axial T2-weighted, sagittal T1-weighted and coronal T2-weighted images (left to right) demonstrate a Group AI tumor. Bottom row: Unenhanced fat saturated axial T2-weighted, sagittal T1-weighted and fat saturated coronal T2-weighted images (left to right) show one of the Group PS ependymomas. The images on the far right illustrate the results of tumor delineation and segmentation, and display the relative distribution of tumor mass (red) for each lesion. (AI – Group AI, PS – Group PS)

Table 1

Demographic and Treatment Summary (N = 38)

Variable	Value
Age (years) ^a	3.0 [0.6–16.8]
Gender (male)	21 (55)
Single surgery	21 (55)
Multiple surgeries	17 (45)
Gross Total Resection	32 (84)
Near Total or Subtotal Resection	6 (16)
Anaplastic Histopathology (WHO Grade III)	22 (58)
Pre-RT chemotherapy	9 (24)
Cranial RT (59.4 Gy)	34 (89)
Cranial RT (54 Gy)	4 (11)

Notes: RT indicates radiation therapy, Gy indicates radiation dose in Gray, WHO indicates World Health Organization.

^aValues for Age indicate median and range. For all other variables, the values indicate the number with percentage in parentheses.

Table 2

Summary statistics for tumor location and morphological parameters

Variable	N	Mean	Median	Standard Deviation	Minimum	Maximum
TCx	38	21.5	15.5	21.1	0.6	68.3
TCy	38	-51.2	-53.7	33.55	-120.5	20.5
TCz	38	-41.9	-41.9	20.66	-70.2	-1.9
VOL	38	28.7	27.5	11.9	6.7	59.6
COMP	38	0.08	0.04	0.07	0.01	0.37

Notes: TC indicates tumor centroid coordinates (x, y, z), VOL indicates tumor volume, COMP indicates compactity (normalized volume to surface-area ratio).