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ORIGINAL ARTICLE

Morphometry of the Hand Knob Region and Motor Function Change in Eloquent Area Glioma Patients

Liang Jingshan[1,2] · Fang Shengyu[1,2] · Fan Xing[1,2] · Wang Zheng[1,2] · Zhang Chuanbao[1,2] · Qian Zenghui[1,2] · Liu Xing[1,2] · Sun Lihua[1,2] · Li Guanzhang[1,2] · Yang Fuqiang[1,2] · Jin Shuai[1] · Wang Yinyan[1,2] · Jiang Tao[1,2,3]

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Abstract

Purpose The hand knob area is the cortical representation of motor hand function. The current study aimed to investigate the effects of eloquent area gliomas on the morphometry of the hand motor cortex and preoperative hand motor function.

Methods A retrospective study of 320 glioma patients was conducted. Seventy-eight patients with gliomas involving motor functional area were finally enrolled. Using axial T2-weight magnetic resonance images, the width and height of the hand knob were measured in both hemispheres, and differences were compared between the affected and unaffected hemispheres. Receiver operating characteristic (ROC) curve and logistic regression analysis were used to estimate the degree of correlation between distance measurements and motor impairment.

Results The width and height of the hand knob in the affected and unaffected hemispheres were significantly different ($p < 0.0001$). The width, height and distance from the tumor to hand knob were reduced in the functionally impaired group compared to the unimpaired group ($p = 0.0003$, $p < 0.0001$, $p = 0.0005$, respectively). The three parameters were significantly correlated and remained significant in ROC and logistic regression analysis. The optimal cut-off value of width, height and distance for identifying preoperative hand muscle strength were 5.73 mm, 5.80 mm and 5.92 mm, respectively.

Conclusion The morphometry of the hand knob is often changed by the infiltration or extrusion of the tumors that were located in or near the hand knob. The width, height of hand knob and the distance from tumor to hand knob could serve as anatomic biomarkers related to preoperative neurological motor deficits.

Keywords Glioma · Hand knob region · Hand muscle strength

Liang Jingshan
neuroliang@163.com

Fang Shengyu
fangtuo1@aliyun.com

Fan Xing
xingkongyaoxiang@163.com

Wang Zheng
wangzheng1024@126.com

Zhang Chuanbao
chuanbao123@139.com

Qian Zenghui
370453167@qq.com

Liu Xing
neurosurgeonmoon@hotmail.com

Sun Lihua
sunnyshine1984@126.com

Li Guanzhang
liguanzhang122@163.com

Yang Fuqiang
13661319405@163.com

Jin Shuai
dr_king@yeah.net

✉ Wang Yinyan
tiantanyinyan@126.com

✉ Jiang Tao
taojiang1964@163.com

[1] Beijing Neurosurgical Institute, Capital Medical University, 6, Tiantanxili, 100050 Beijing, China

[2] Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

[3] Center of Brain Tumor, Beijing Institute for Brain Disorders, Beijing, China

Abbreviations

MRI Magnetic resonance imaging
ROC Receiver operating characteristic

Introduction

Structural magnetic resonance imaging (MRI) is essential for the preoperative evaluation of patients with intracranial lesions. For a successful presurgical planning, the knowledge of the spatial relationships between the lesion and the eloquent cortex is required [1]. According to the concept of "homunculus", the cortical representation of hand motor function is localized to the superior precentral gyrus [2]. Previous studies in human subjects have identified a neuroanatomical landmark referred to as the "knob" that extends from the precentral gyrus into the central sulcus. The knob has been described as exhibiting the shape of an inverted omega (Ω) or a horizontal epsilon (ε) in the axial plane and is a reliable landmark for identification of the precentral gyrus under normal and pathological conditions [3, 4].

The morphometric data of the hand knob can be used to identify central sulcus region landmarks in healthy subjects [5]. In addition, the contralateral omega sign can be reliably used to identify the topographic location of a lesion of the central sulcus since it can give a quick preoperative view of the relationships between the lesion and the precentral and post-central gyri [6]; however, the morphometry of the hand knob (axial view, Ω, ε) in the affected and unaffected hemispheres of glioma patients is poorly understood. Yousry et al. reported that the mean height and width of the hand-knob are equal between the unaffected and affected hemispheres [3]. Nevertheless, Hingwala et al. reported that when the lesion is located in the Rolandic cortex, such as the primary, premotor, and somatosensory cortex, infiltrative growth of the tumor and collateral edema can distort anatomic landmarks [7]. As the morphometry of the hand knob may be informative to preoperative planning prior to surgery to remove the glioma, a better understanding of this region in the glioma patient is desired.

The aim of this study was to use preoperative MRI to explore the influence of gliomas located in or near the motor area on hand knob morphometry and hand motor function. In our interpretation of the data, we assumed that the occurrence of neurological deficits indicated a limitation in the neural reorganization in response to the tumor. We therefore assessed the distance from the tumor to the hand knob and the neurological state of the corresponding hand in order to identify the association between morphometric changes in the hand motor cortex and the neurological deficit.

Materials and Methods

Patients

A total of 320 consecutive low grade glioma patients (WHO grade II–III) who underwent surgical resection between August 2010 and May 2012 at the Glioma Therapy Center of Beijing Tiantan Hospital were systematically reviewed. The inclusion criteria included: (1) >18 years of age, (2) no history of brain surgery or biopsy and (3) pathologically confirmed lower grade glioma. The exclusion criteria: (1) misty images of preoperative MRI, (2) tumor lesion located far from the primary motor cortex (distance from the tumor to the hand knob ≥20 mm). Finally, 78 patients were enrolled in this study. The study was approved by the Ethics Committee of Beijing, Tiantan Hospital. Written informed consent was obtained from all patients. Their demographic and clinical information are listed in Table 1.

Muscle Strength Assessment

Muscle strength was assessed according to the British Medical Research Council (BMRC) scale [8]. Patients included in the study were divided into two groups according to their preoperative state of hand muscle strength. The unimpaired group with normal hand strength was defined by a muscle strength of BMRC grade 5, and the functionally impaired group was defined by a muscle strength of BMRC grades 0 to 4.

Magnetic Resonance Imaging

The MR imaging scans were performed before surgery in all patients with a 3 T MRI scanner with an 8-channel phased array head coil (Siemens, Erlangen, Germany). Structural imaging of the entire brain volume was obtained with a T2-weighted sequence. The parameters were as follows: TR = 5500 ms; TE = 120 ms; FOV = $240 \times 240\ mm^2$; section thickness = 5 mm; slice gap = 1 mm; and flip angle = 150°. All images were obtained by using a matrix of 512 × 512 voxels and a voxel size of $0.47 \times 0.47 \times 6.0\ mm^3$.

Morphometry of the Hand Knob and Distance from the Tumor to the Hand Knob

According to the axial MRI T2-weighted sequence and the MRIcron database (http://www.nitrc.org/projects/mricron), we started with a Z value of 1 and gradually increased the value of Z as the image plane increased. For each patient, the analysis of the axial plane in which the hand knob and the tumor appeared at the same time in the affected hemisphere was decided independently by two board certified neuroradiologists (Fig. 1). If the analysis plane was not the

Table 1 Demographic and clinical data of the 78 patients

Characteristics	Value
Age (years, mean±SD)	42.7 ± 12.1
Sex	
Male	51 (65.4%)
Female	27 (34.6%)
Handedness	
Left	0 (0%)
Right	78 (100%)
Hemisphere of lesion	
Left	44 (56.4%)
Right	34 (43.6%)
Tumor histopathology	
WHO grade II	41 (52.6%)
WHO grade III	37 (47.4%)
BMRC scale	
5 (Normal)	53 (67.9%)
4	18 (23.1%)
3	7 (9.0%)
2	0 (0%)
1	0 (0%)

BMRC scale British Medical Research Council scale for muscle strength assessment

Table 2 Patient information of the unimpaired and impaired group

Characteristics	Unimpaired group	Impaired group	*P*-value
Mean age (years)	41.57 ± 10.20	45.04 ± 15.33	0.239[a]
Gender			
Male	31	20	0.077[b]
Female	22	5	
Histology			
WHO grade II	31	10	0.127[b]
WHO grade III	22	15	
M1 infiltration	12	22	<0.001[b]
PMC infiltration	17	10	0.492[b]
SMA infiltration	27	10	0.366[b]

M1 primary motor cortex, *PMC* premotor cortex, *SMA* supplemental motor area
[a]Result of t-statistical test
[b]Result of χ^2-test

same, a final decision was made in an imaging meeting of board certified neuroradiologists and neurosurgeons. To calculate the morphometry of the hand knob, the endpoints of the hand knob were labeled A and B, according to the corresponding coordinates in MRIcron, and the coordinates of C were calculated as the midpoint of A and B. The highest point of the hand knob was termed as D (Fig. 1a). According to the coordinates, values were then calculated for the distance between A and B and between C and D, which were defined as the width (d_1) and height (d_2) of the hand knob, respectively. If the hand knob of the affected hemisphere could not be observed due to the influence of the tumor, the width and height were set to zero. To determine the distance (d) from the hand knob to the tumor (Fig. 1b), the same method was used to calculate the coordinates of C, then a boundary was drawn around the tumor. Point E was determined as the point closest to C along the boundary of the tumor. According to their coordinates, the distance between the C and E were calculated to determine the value of d.

Statistical Analysis

A χ^2-test was performed to test the distribution of several attributes. The logistic regression analysis was used for analyzing normal muscle strength based on clinical (gender, age and grade) and radiographic characteristics (width, height and distance). Pearson analysis was used to test the correlation of width, height and distance. A Student's *t*-test (for parametric data) was used for analysis of the differences between the two patient groups. All results are presented as mean ± standard deviation (GraphPad Prism 6.0c, La Jolla, CA, USA). The receiver operating characteristic (ROC) curve was generated with the pROC package of R language. The level of significance was 0.05 for each statistical test (two-sided).

Results

Clinical Characteristics of Patients

Patients were divided into two groups according to the grade of hand muscle strength. Of the patients 25 with reduced preoperative hand muscle strength were included in the functionally impaired group. The remaining 53 patients with normal hand muscle strength comprised the unimpaired group. The mean age, sex, histology, side of lesion, supplemental motor area (SMA) and premotor cortex (PMC) infiltration were comparable in both groups, with no statistically significant differences; however, significant difference was found between the two groups in primary motor cortex (M1) infiltration ($p < 0.001$, χ^2-test), which suggested that patients with M1 infiltrated lesions were more likely to have reduced hand muscle strength (Table 1 and 2).

Hand Knob Morphometry

Across all subjects, the mean height and width of the hand knob in the glioma affected hemispheres were 4.49 ± 3.53 mm and 6.83 ± 5.04 mm, respectively. In the unaffected hemispheres, the mean height and width of the hand knob were 7.02 ± 1.84 mm and 11.43 ± 3.45 mm,

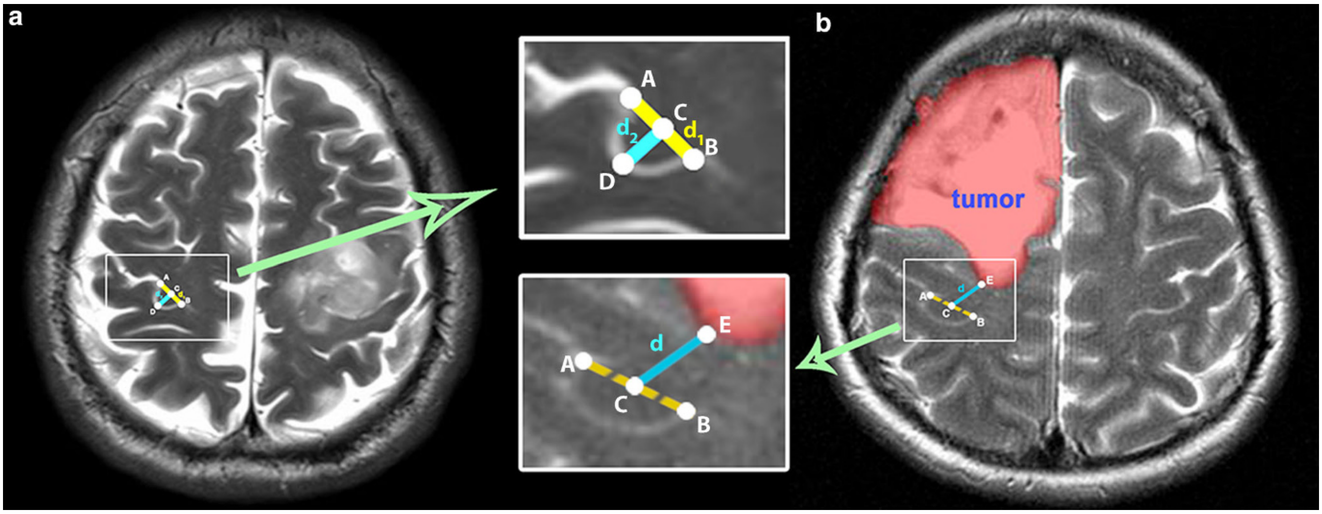

Fig. 1 Assessment of the hand knob and the distance from the tumor to the hand knob. **a** The morphometry of the hand knob. The boxed region is enlarged in the inset. *Inset: A* and *B* are the two endpoints of the hand knob, *C* is the midpoint of *A* and *B*, and *D* is the top of the hand knob gyrus. The width of the hand knob (d_1) was defined as the distance between *A* and *B*; the height of hand knob (d_2) was defined as the distance between *C* and *D*. **b** The calculation of the distance from the tumor to the hand knob. The boxed region is shown enlarged in the inset. *Inset*: *E* is the location on the tumor border that is closest to *C*. The distance (*d*) from the tumor to the hand knob was defined as the distance between *C* and *E*

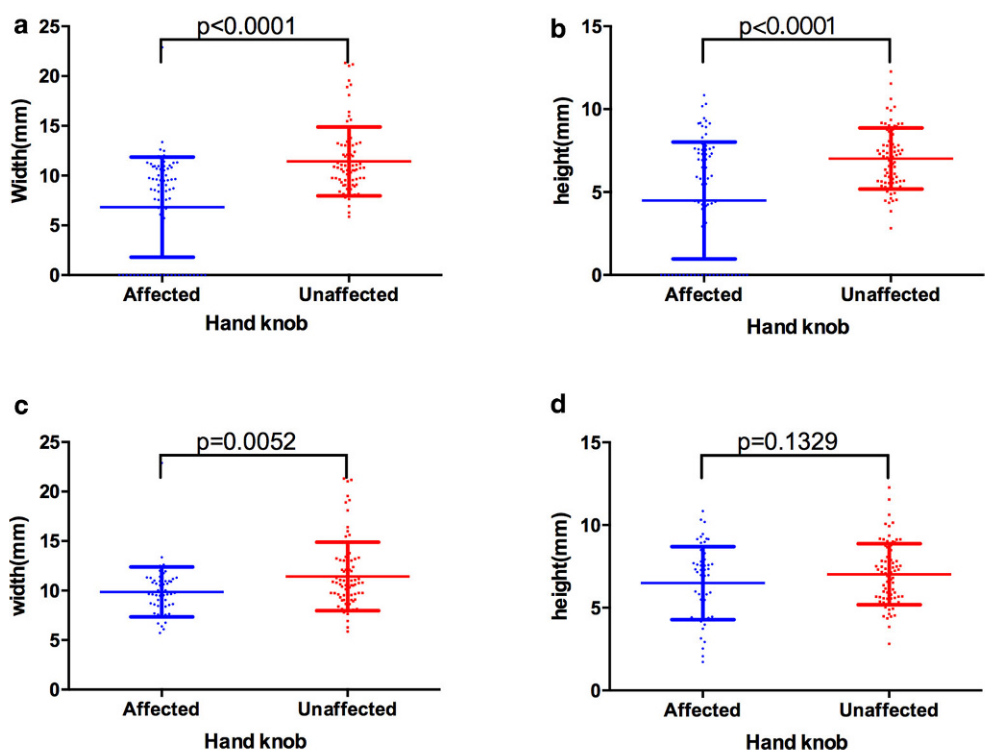

Fig. 2 A comparison of the width and height of the hand knob in the affected and unaffected hemispheres. **a** In all patients, the difference of width between affected and unaffected hemispheres was statistically significant ($p < 0.0001$). **b** Similar results were obtained for height of hand knob ($p < 0.0001$). **c** After removing the cases in which the hand knob could not be observed, the width remained to be significantly different ($p = 0.0052$) but **d** there was not a significant difference of height ($p = 0.1329$)

respectively. The differences between hemispheres were statistically significant ($p < 0.0001$; Fig. 2a, b).

When we removed the cases in which the hand knob could not be observed (height = 0 and width = 0), the mean height and width of hand knob were 6.49 ± 2.20 mm and 9.86 ± 2.52 mm, respectively, in the affected hemisphere. The differences in the width of the hand knob in the unaffected and affected hemispheres were statistically significant ($p = 0.0052$, Fig. 2c) but the height of the hand knob in the two hemispheres was not statistically different ($p = 0.1329$, Fig. 2d).

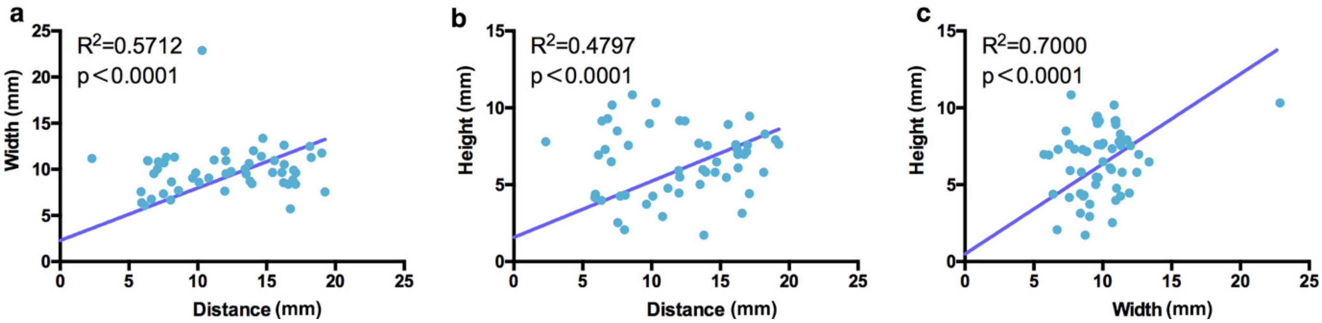

Fig. 3 Correlation of width, height and distance. Pearson correlation analysis showed that width and height of hand knob and tumor to hand knob distance were all significantly correlated: $p < 0.0001$, for width and distance (**a**); $p < 0.0001$, for height and distance (**b**); $p < 0.0001$, for height and width (**c**)

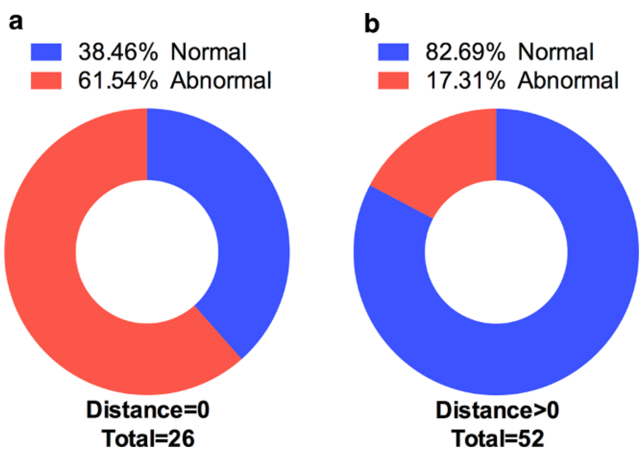

Fig. 4 Distribution of patients with normal or abnormal hand strength in two groups. Patients were divided into two groups according to the distance from the tumor to the hand knob (**a** group 1, distance = 0, 26 patients, abnormal rate = 64.51% [16/26]; **b** group 2, distance >0, 52 patients, abnormal rate = 17.31% [9/52]). Both groups contained patients with normal and reduced (abnormal) hand muscle strength. The proportion of each group representing patients with reduced hand strength was significantly different between the two groups ($p < 0.0001$, χ^2-test)

Width, Height and Distance were Correlated

To investigate the correlation of width, height and distance, we applied Pearson correlation analysis (Fig. 3). The width of the hand knob and distance of the tumor to the hand-knob were significantly correlated ($R^2 = 0.5712$, $p < 0.0001$, Fig. 3a). Similarly, height of hand knob and distance, width and height of hand knob were all significantly correlated ($R^2 = 0.4797$, $p < 0.0001$, Fig. 3b; $R^2 = 0.7000$, $p < 0.0001$, Fig. 3c).

Glioma Nearer to the Hand Knob was More Likely to Affect Hand Muscle Strength

Of the 78 patients 26 had tumors that involved the hand knob. For these, the distance from the tumor to the hand-knob was set to zero. Among these 26 patients, 16 patients showed a reduction in preoperative hand muscle strength. For the other 52 patients, the distance from the tumor to the hand knob was between 0 and 20 mm. In these patients and 9 out of 52 showed reduced preoperative hand muscle strength. The proportion of patients with reduced hand strength was significantly different between the two groups ($p < 0.0001$, χ^2-test, Fig. 4).

Width, Height and Distance were Associated with Hand Muscle Strength

For the group of 25 patients with reduced preoperative hand muscle strength, the mean width, height and distance were 3.90 ± 4.95 mm, 2.30 ± 3.04 mm and 4.28 ± 6.21 mm, respectively. For the remaining 53 patients with normal hand muscle strength, the mean width, height and distance were 8.21 ± 4.49 mm, 5.53 ± 3.28 mm and 9.73 ± 6.22 mm, respectively. The three parameters were all significantly different between the two groups ($p = 0.0003$, Fig. 5a; $p < 0.0001$, Fig. 5c; $p = 0.0005$, Fig. 5e).

A ROC curve analysis was conducted to assess the optimal cut-off value of width, height and distance for differentiating the motor status of the patients. The ROC curve showed that width = 5.73 mm, height = 5.80 and distance = 5.92 mm were the best cut-off values, and the areas under the curve were 0.71, 0.76 and 0.73, respectively (Fig. 5b, d, f).

Hand Muscle Strength Associated Factors Assessed by Logistic Regression Analysis

To identify factors associated with presurgical hand muscle strength, we applied the logistic regression analysis including clinical (gender, age, grade) and radiographic (width, height, distance) characteristics. The three radiographic characteristics were strongly associated with presurgical hand muscle strength. Low width, low height and short distance were risk factors for a higher incidence of abnormal

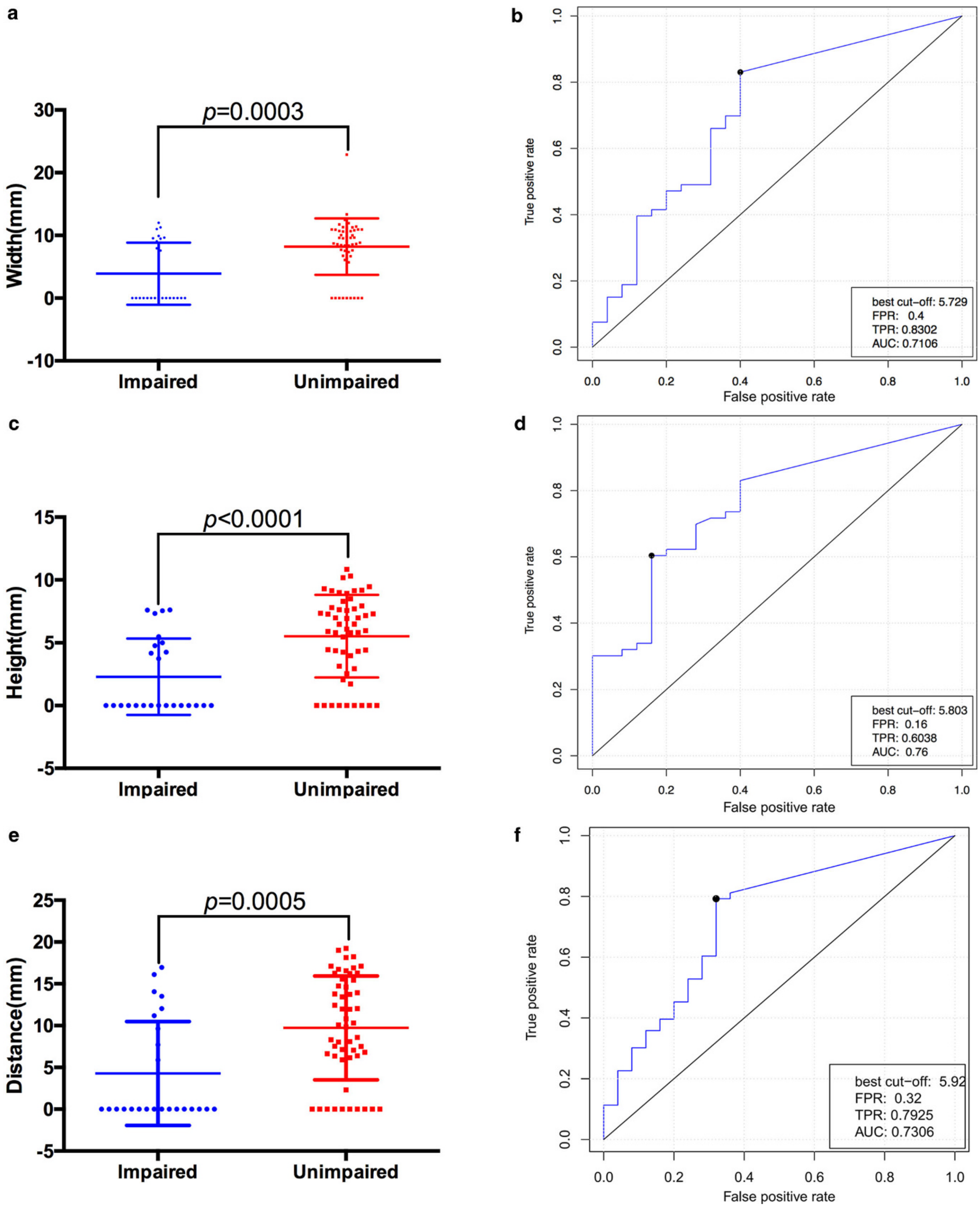

Fig. 5 Width, height and distance were associated with hand muscle strength. **a**, **c**, **e** The width and height of hand knob and distances from the tumor to the hand knob were significantly different between the impaired and unimpaired groups, respectively ($p = 0.0003$, $p < 0.0001$, $p = 0.0005$, *t*-test). **b**, **d**, **e** ROC curve predicting the motor state using the width, height and distance. The areas under the curve were 0.71, 0.76 and 0.73, respectively

Table 3 The prediction of normal muscle strength based on clinical and radiographic characteristics by the logistic regression analysis

Characteristics	OR	95% CI	*P*-value
Gender	0.352	0.115–1.082	0.068
Age	0.976	0.938–1.016	0.237
Grade	0.572	0.322–1.015	0.056
Distance	1.148	1.055–1.250	0.001
Width	1.208	1.084–1.347	0.001
Height	1.344	1.142–1.582	<0.001

presurgical hand muscle strength (*P*-values, odds ratios, and 95% confidence intervals are shown in Table 3).

Discussion

Gliomas that involve the primary motor area can lead to morphometric changes of the hand knob and consequently induce weakness in the contralateral hand. The current study aimed to quantitatively assess the distortion of the hand knob in patients with gliomas and further identify the association between morphometric changes in the hand knob and the impairment in muscle strength.

Glioma Affected the Morphometry of Hand Knob

Up to now, the morphometric analysis of the hand knob in glioma patients, especially for cases in which tumors are located in or near the primary motor cortex has been rarely investigated. In our study, the mean height and width of the hand knob in affected hemispheres were found to be significantly lower than those in unaffected hemisphere (4.49 mm versus 7.02 mm and 6.83 mm versus 11.43 mm for height and width, respectively). For further correction, we excluded patients whose hand knob could not be observed by tumor infiltration or extrusion, since the height and width of these hand knobs were calculated as zero. As the results show, in the affected hemisphere the mean height and width of the hand knob were 6.49 and 9.86 mm, respectively. The width of the hand knob between affected and the unaffected hemispheres remained statistically significant, while the height no longer differed. It might indicate that the gliomas would obviously affect the width of hand knob more than the height. In addition, we found that the height and width of the hand knob were smaller than previous studies [3, 5, 6]. These differences were related to different axial planes of measurement. Previously, studies used the hand knob to measure at the site of maximum visibility of the hand knob; however, the measurement at the axial slice was where the distance between tumor and hand knob was least in this study. Because of this the axial slice could ensure that the hand knob and tumor appeared simultaneously s that the data of the height and width of hand knob were decreased.

Width, Height and Distance were Associated with Hand Muscle Strength

Gliomas that are located in or near the eloquent areas can lead to neurological deficits [9]. A large distance (>19 mm) between the functional cortex and the tumor, identified by using functional MRI, was suggested to significantly reducing the risk of postoperative dysfunction [10]. Further, a lesion to activation distance of less than 5 mm was found to be associated with a higher risk of neurological deterioration; within a 10 mm range cortical stimulation should be performed [11]. Motor deficits increased linearly as the distance from the tumor to the primary sensorimotor cortex decreased, and the threshold was different depending on the lesion to activation distance [12, 13]; however, other authors held the opposite view, reporting that the lesion to activation distance and the degree of tract involvement on diffusion tensor imaging were predictive factors for preoperative neurological deficits but not for postoperative deficits [14]. Whether using functional MRI or diffusion tensor imaging to research how the glioma impaired motor functions, there are always some factors to affect the accuracy of the results, such as the neurovascular uncoupling in blood oxygen level dependent functional MRI [15] and massive effects for white matters signals in diffusion tensor images [16]. Hence, to research the relationship between factors in basic MRI sequence and motor impairment is important.

Little is known about the detailed distance that could lead to preoperative motor functional impairment, especially for glioma patients. The ultimate goal of this approach was to enable a preoperative assessment of the risk of inducing neurological deficiency during surgery by establishing the distance between the tumor margin and the eloquent or essential functional areas as an index of pre-existing motor deficiency. In the current study, we measured the shortest distance from the tumor to the hand knob. Our results showed that when the distance from glioma to the hand knob was shorter than 5.92 mm, the hand motor function would be more likely impaired. It corresponded to previous studies that less than 10 mm between the functional MRI activation areas and the tumor results in a greater risk of permanent neurological deficiency [11, 14].

The height and width of the hand knob in the lesion hemisphere could reflect the degree of glioma infiltration or extrusion. In the present study, they were also found to be related to hand motor impairment. The ROC curve analysis was conducted to determine the cut-off value for the width, height and tumor to hand knob distance for differentiating hand function. The ideal cut-off values in terms of sensitivity and specificity were 5.73 mm and 5.80 mm and indicated that the height and width of hand knob would be anatomic biomarkers for preoperative motor deficits. In the current study, we calculated the maximum value of height and width in the axial slice where the distance between tumor and hand knob was least and calculated them by their coordinates. Hence, we believe that our data are reliable. Besides, we also found the three factors were well correlated and remained significant in the logistic regression analysis when taking both clinical and radiographic factors into consideration. In addition, tumors that involved the hand knob area led to a higher risk (16/26) of motor deficits compared with tumors that were near the hand knob area (between 0 and 20 mm, 9/52; $p < 0.0001$). This result indicated that the shorter the distance of tumor to hand knob and the lower the width or height of hand knob was, the greater the risks of impairment of muscle strength on the contralateral hand.

Several studies have reported the functional reorganization of the motor cortex, which could result in shift of the functional area [17–20]. Although the hand knob has not been confirmed as the motor area cortex by functional MRI or electronic stimulation in these glioma patients, we found that the width and height of the hand knob and distance of the tumor to hand knob were associated with hand muscle strength. The three parameters are easily measured by structural MRI in clinical practice.

The main limitation of this study is that the morphometry of the hand knob and the tumor to hand knob distance were evaluated only in the axial plane. Nevertheless, the axial plane is the most commonly used plane by clinicians and neuroscientists and the one in which they have the most experience. In this study, the spatial resolution of T2-W images was 0.5 mm × 0.5 mm on the axial plane, and we believe the resolution is high enough for quantitative analysis. There are several segmentation algorithms which was widely used to segment grey matter and white matter of the brain (such as algorithms provided by Freesurfer or SPM12); however, there algorithms fit well for healthy subjects, but not that well for brains with tumors. In addition, the muscle strength describes the movement ability of the limbs. The fine motor skills can be used to evaluate the quality of life of the patients. Clinical data about fine motor function should be added to our future research, we believe that they are of great significance and will further improve glioma treatment. In the future, adding more data about fine motor skills to the research will provide more important help for glioma treatment.

Conclusion

Anatomical changes may indicate functional alterations in brain tumor cases. The current study identified the association between morphometric changes in the hand-knob area and a functional disorder. The width and height of hand knob and the shortest distance from tumor to hand knob were three anatomic biomarkers that were associated with preoperative motor functional impairment. These findings may help develop customized treatment for glioma patients and provide further knowledge regarding the occurrence and limitations in the neuroplasticity caused by tumor involvement.

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Compliance with ethical guidelines

Conflict of interest L. Jingshan, F. Shengyu, F. Xing, W. Zheng, Z. Chuanbao, Q Zenghui, L. Xing, S. Lihua, L. Guanzhang, Y. Fuqiang, J. Shuai, W. Yinyan and J. Tao declare that they have no competing interests.

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors. Informed consent was obtained from all patients identifiable from images or other information within the manuscript. In the case of underage patients, consent was obtained from a parent or legal guardian.

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